UNIVERSITÉ DE STRASBOURG

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES, UMR 7509

EDSC
Ecole Doctorale des Sciences Chimiques

COMENIUS UNIVERSITY IN BRATISLAVA

SCIENTIFIC FACULTY, Departmet of Organic Chemistry

THESIS

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defended : **27th Septembre 2013**

for degree of : **Docteur de l'université de Strasbourg,**

Doctor of Comenius University in Bratislava

Discipline/ Speciality : Chemistry

Development of VEGFR-2 Inhibitors by Ynamide-Based Click Chemistry

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. . . to my parents. . .

Resume in English

Despite to the intensively research, cancer is still a leading cause of death worldwide. There are still developed new active compounds for cancer treatment. We have decided to prepare new antiangiogenic drugs based on already clinically tested AAZ from PDB complex 1Y6A. The *in Silico*-designed 1,2,3-triazole analogues of AAZ were prepared using a Click chemistry approach. In order to accomplish Click reactions two key building blocks: ynamides and azides were mandatory to synthetize.

The chemistry of ynamides has exploded just in the last decade. In fact, ynamides represent the right balance between reactivity and stability of a nitrogen-atom conjugated to a triple bond. Based on wide bibliographical study and experimental experiences, we have prepared two target ynamides with different electron-withdrawing groups. The second synthetical goal was preparation of several azides as partners of prepared ynamides for Click chemistry reaction. Copper catalyzed Click reactions were performed in very mild condition with quantitative regioselectivity.

Five predicted triazolic compounds were prepared and sent for VEGFR-2 biologicall assays. Three of them modulate VEGFR-2 tyrosine kinase activity and two of them are inactive. Although the activities of triazolic compounds are significantly lower than the activities of their oxazolic isosters these compounds deliver structural novelty to IP crowded space of tyrosine kinase inhibitors.

Résumé en français

Malgré d'intenses recherches, le cancer reste une des causes principales de mortalité dans le monde. Le développement de nouveaux produits actifs pour le traitement des cancers est de plus en plus nécessaire. Nous avons décidé de préparer de nouveaux composés anti-angiogéniques dérivés du composé **III.1** (ligand du complexe PDB : 1Y6A) dores et déjà testé cliniquement. Sept composés issus d'un remplacement bioisostèrique du noyau oxazole de **III.1** en noyau 1,2,3-triazole par design *in silico* ont été planifiés. Cinq d'entres eux ont pu être synthétisés en utilisant une réaction Click entre un ynamide et un azide.

La chimie des ynamides a littéralement explosé pendant les dix dernières années car la mise en place d'un groupement électroattracteur (carboxylate, sulfonate) a permis de stabiliser et de développer de nombreuses réaction d'amines directement liées à une triple liaison. Après une revue bibliographique sur la chimie des ynamides, nous avons pu préparer deux ynamides précurseurs des triazoles cibles possédant deux groupement protecteur différents avec d'excellents rendements. Nous avons ensuite préparé différents azides aryliques comme partenaire de la réaction Click envisagée. Enfin, la réaction Click catalysée au cuivre a permis de préparer cinq de nos 1,2,3-triazole cibles avec une excellente régiosélectivité.

L'activité inhibitrice de VEGFR-2 kinase a été évaluée pour chacun de ces cinq produits. Bien que l'activité de ces composés soit bien moins importante que celle du composé oxazolique **III.1** dont elles sont dérivées, nous avons montré qu'ils sont des ligands spécifiques de VEGFR-2 kinase et qu'elles représentent une nouveauté structurale intéressante dans lespace très protégé des inhibiteurs de tyrosine kinases.

Resumé v slovenskom jazyku

Napriek intenzívnemu výskumu, rakovina stále patrí k najčastejším príčinám úmrtia na svete. Neustále sú vyvíjané nové aktívne látky na liečbu rakoviny. Rozhodli sme sa pripraviť nové antiangiogenetické liečivá na základe klinicky testovaného AAZ z PDB komplexu 1Y6A. *In Silico* navrhnuté 1,2,3-triazolové AAZ analógy boli pripravené prostredníctvom Click chémie. Za účelom uskutočnenia Click reakcie, bolo nevyhnutné pripraviť dva kľúčové stavebné jednotky: ínamidy a azidy.

Chémia ínamidov sa rozrástla v poslednej dekáde. V skutočnosti ínamidy predstavujú správnu rovnováhu medzi reaktivitou a stabilitou dusíkového atómu naviazaného na trojitú väzbu. Na základe rozsiahlej bibliografickej rešerše a experimentálnych skúseností, boli pripravené dva cieľové ínamidy s rozdielnymi elektón-akceptornými skupinami. Druhým syntetickým cieľom bola príprava rôznych azidov ako partnerov ínamidov pre Click reakcie. Meďou katalyzované Click reakcie boli uskutočnené vo veľmi jemných podmienkach s kvantitatívnou regioselektivitou.

Bolo pripravených päť nových triazolových látok, ktoré boli zaslané na VEGFR-2 biologické testy. Tri z nich majú vplyv na aktivitu VEGFR-2 tyrozín kinázy a dve z nich nie sú aktívne. Aj keď sú aktivity triazolových derivátov výrazne nižšie ako aktivity oxazolvých izostérov, tak tieto zlúčeniny vnášajú do oblasti tyrozín kinázových inhibítorov, ktorá obsahuje už rôznorodé látky, štruktúrnu originalitu.

Acknowledgement

Foremost, I would like to thank to the members of committee for agreeing to read and evaluate this thesis: Prof Daniele Pasarrella, Prof. Milan Remko, Prof. Philippe Compain, Prof. Céline Tarnus, Dr. Pavol Koiš, Assoc. Prof. Vladimír Frecer and Dr. Thierry Langer.

I'd like to address a huge thank to my supervisors: Dr. Gilles Hanquet and Assoc. Prof. Andrej Boháč for creating this bilateral cooperation between Université de Strasbourg and Comenius University in Bratislava and welcoming me in their research teams. I am thankful for their professional advices, help, patience, valuable discussions, support and enthusiasm during all my doctoral study. Also thank you for the freedom and confidence granted me for my research!

In the beginning of the collaboration was my Erasmus assignment in the laboratory of Dr. Gilles Hanquet in 2006. During this stage I was deeply motivated in chemical research by Dr. Don Antoine Lanfranchi and in this time I have decided to apply for PhD study. One special thank for you, Don Antoine!

I would like to thank to the permanent stuff at ECPM – Prof. Françoise Colobert, Dr. Sabine Choppin and Dr. Frédéric Leroux for all their professional advices. Special thanks to the most recent permanent member Dr. Armen Panossian, who helped to me a lot, mainly in the last period of my study. I cannot forget to thank to our security technician – always in positive state of mind - Arlette Klein, to our secretary Bouchra El Fahssi and to technician Didier Boettger. Special thanks to Matthieu Chessé for his help in the subject of analytical chemistry (HPLC, LCMS, IR …).

Special thanks to Dr. Michel Schmitt and the team of Dr. Branislav Horváth for their help during NMR analysis during day, night and weekends. Also I'm very grateful for several analyses of Université de Strasbourg and Comenius University.

Undoubtedly, I'm also thankful to the permanent stuff at Department of Organic Chemistry at Comenius University in Bratislava.

I will never forget about my colleagues from ECPM – Dr. Christophe, Dr. Irene, Dr. Mercedes, Dr. Marie, Dr. Thomas, Dr. Thibault, Elena, Boubacar, Dr. Nicolas, Bruno, Pierre-Antoine, Anaïs, D. Gregory, Dr. Stephany and many others, for their friendly approach and unconditional help from professional point of view. I'm deeply grateful to my colleagues from Bratislava Lucia L., Dr. Lucia K., Dr. Marcela and technician Miroslava, who have helped me to cover my administration duties during my absence at Faculty in Bratislava.

Last but not least, I would like to thank to my parents for supporting me both emotionally and economically throughout my life and study. I'm also thankful to my friends from Košice and

Strassbourg for supporting me and help me to pass various problems and keeping me smiling in every situation ☺

I am very thankful for financial support to Comenius University, French Embassy in Bratislava and COST STSM CM 0602.

Abbreviations

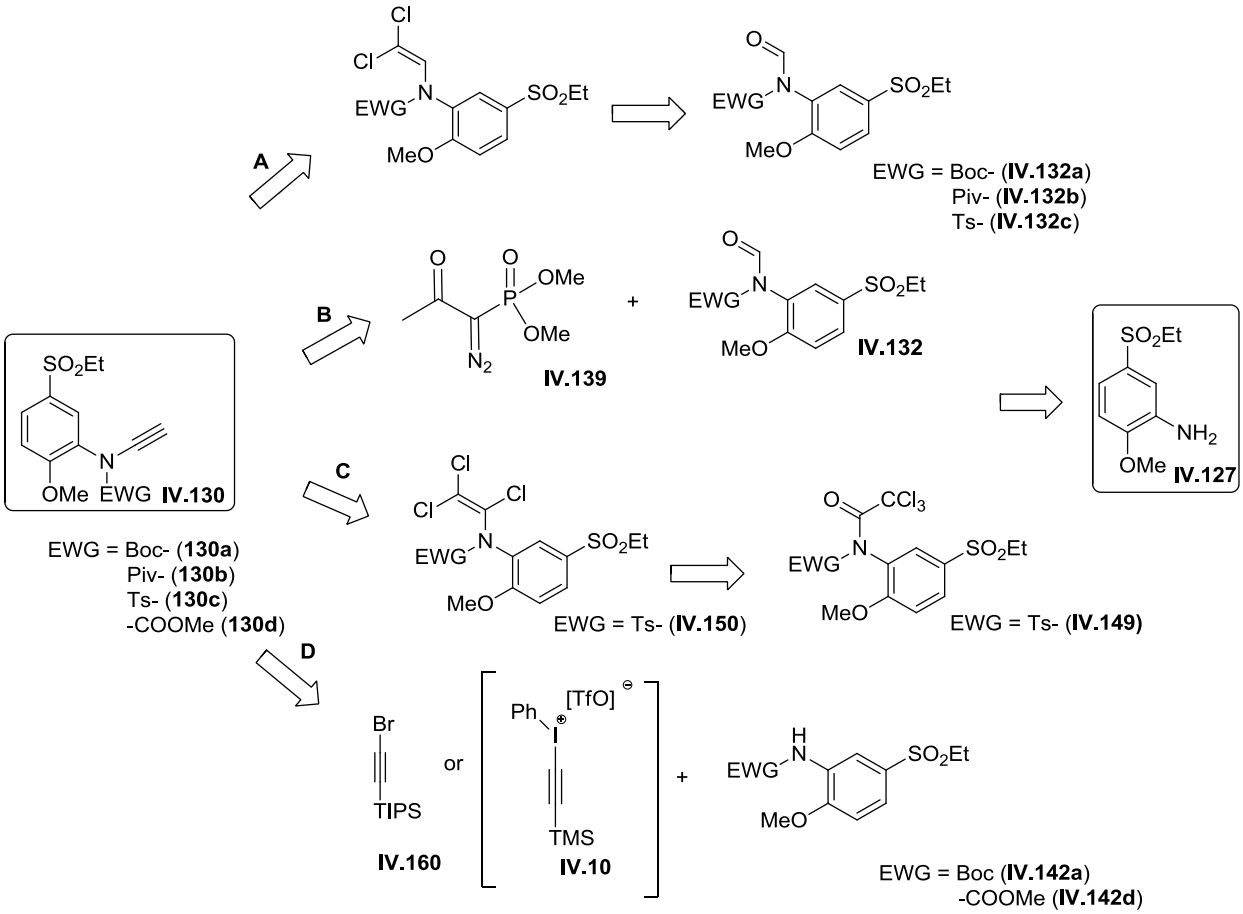
AAZ	*N*-aryl-5-aryloxazol-2-amine ligand
BtCHO	Benzotriazole aldehyde
Boc	*tert*-butyloxycarbonyl
CDI	carbonyldiimidazole
conc.	Concentration
CRAAC	Core Restriction Additive Attraction Compensation
CSCs	Cancer Stem Cells
CuAAC	Copper Alkyne-Azide Cycloaddition
Cy	cyclohexane
δ	chemical shift
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
decomp.	decomposition
DMED	*N,N'*-dimethylethylenediamine
DMF	*N,N'*-dimethylformamide
equiv.	equivalent
ESI	electron spray ionization
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FDA	Food and Drug Administration
FW	Formula Weight
h	hour(s)
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
IC_{50}	50 % inhibitory concentration
J	coupling constant
kDA	kilodalton
KDR	Kinase Domain Receptor
LDA	lithium diisopropylamide
µL	microliter
M	molarity
m	multiplet
m.p.	melting point
Me	methyl
MeI	methyl iodide
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute(s)
mmol	millimole
MS	mass spectroscopy
MW	molecular weight
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
PDB	Protein Data Bank
pH	potential hydrogen
Ph	phenyl

ppm	parts per million
R_f	retention factor
RuAAc	Ruthenium Azide-Alkyne Cycloaddition
rt	room temperature
s	singlet, second
SAR	structure activity relationship
sat.	saturated
t	triplet
TBME	methyl *tert*-butyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TK	tyrosine kinase
TLC	thin layer chromatography
TMSI	trimethylsilyl iodide
Ts	*para*-toluensulfonyl
UV	ultraviolet
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organisation

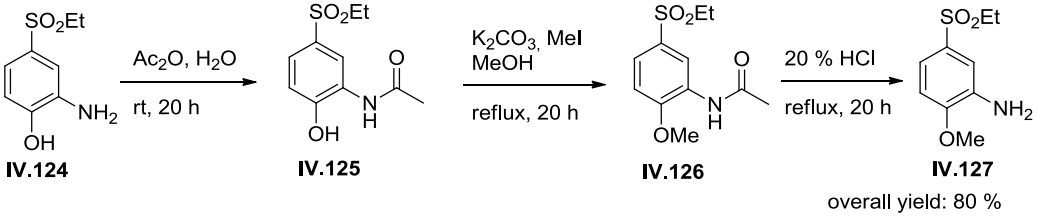
Graphical abstract of reactions

Synthetical preparation of ynamides

- *Retrosynthetic plan towards target ynamide **IV.130**.*

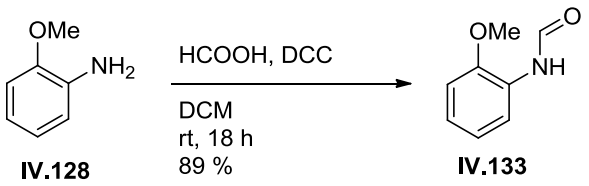


- *Preparation of 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** from commercially available phenol **IV.124**.*



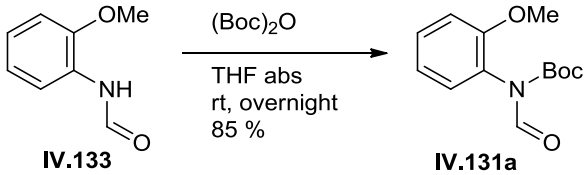
Preparation of model ynamide

- *Preparation of N-formylated o-anisidine* ***IV.133****.*



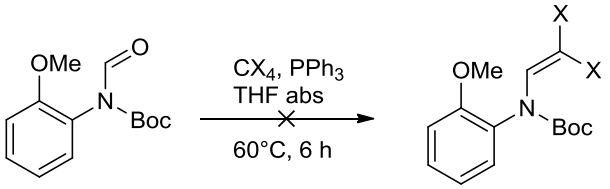
IV.128 **IV.133**

- *Preparation of N-Boc protected formamide* ***IV.131a****.*



IV.133 **IV.131a**

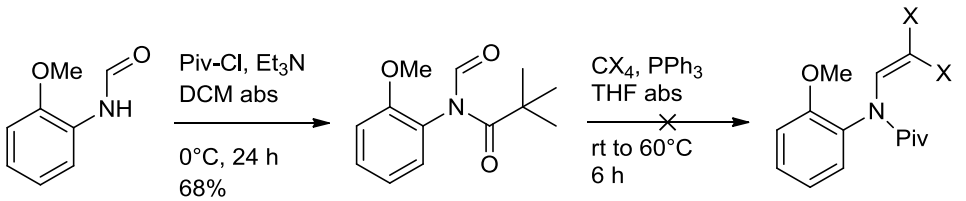
- *Unsuccessful dihalogenovinylation of N-tert-*butyloxylcarbonyl *protected formamide* ***IV.131a****.*



IV.131a **IV.135a**

X=Cl or Br

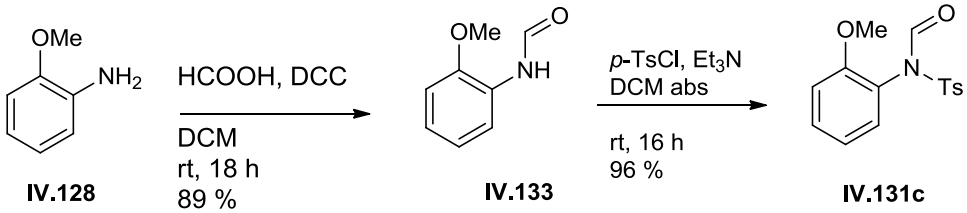
- *Protection of N-formamide* ***IV.133*** *with pivaloyl protecting group and unsuccessful dichloromethylation. Expected product* ***IV.135b*** *was not observed.*



IV.133 **IV.131b** **IV.135b**

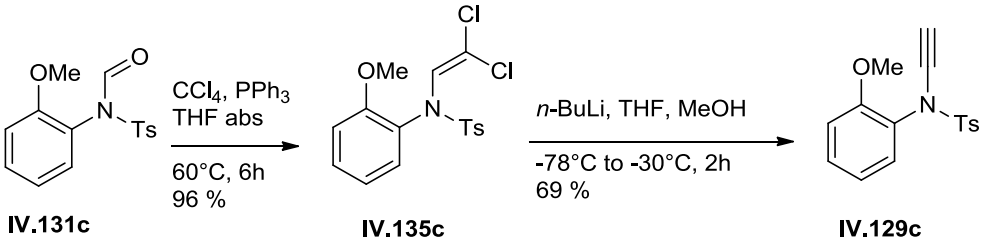
X = Cl *or* Br *not observed*

- *Preparation of N-tosylated formamide* ***IV.131c****.*



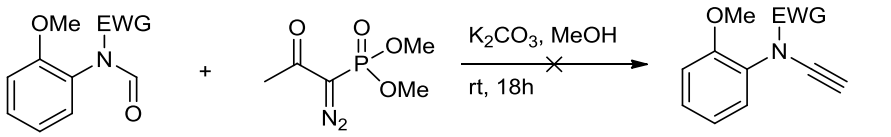
IV.128 **IV.133** **IV.131c**

- *Preparation of N-tosylated ynamide **IV.129c** from formamide **IV.131c**.*



IV.131c **IV.135c** **IV.129c**

- *Performed Bestmann-Ohira reactions on substrate **IV.131a,b,c**.*



EWG = Boc- (**IV.131a**)
Piv- (**IV.131b**)
Ts- (**IV.131c**)

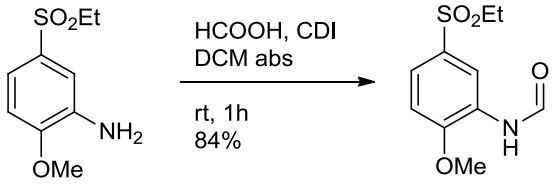
IV.139

EWG = Boc- (**IV.129a**)
Piv- (**IV.129b**)
Ts- (**IV.129c**)

Preparation of target ynamide

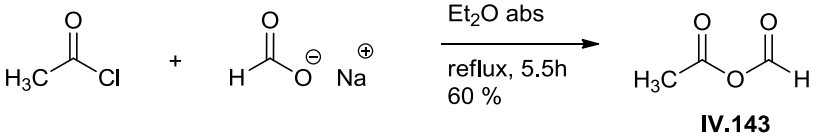
Corey-Fuchs approach (pathway A)

- *Preparation of N-(5-(ethylsulfonyl)-2-methoxyphenyl)formamide **IV.141**.*



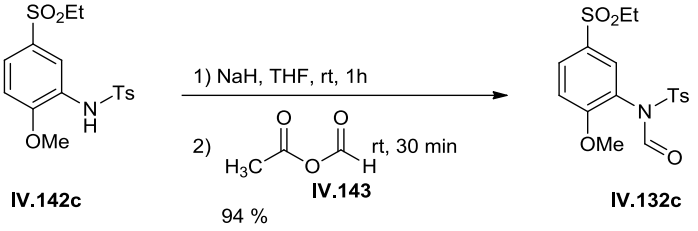
IV.127 **IV.141**

- *Preparation of acetic formic anhydride **IV.143**.*

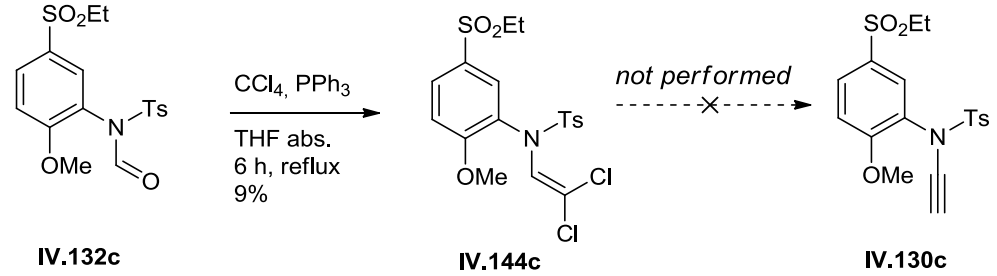


IV.143

➢ *Preparation of N-tosyl formamide* ***IV.132c*** *using acetic formic anhydride* ***IV.143***.

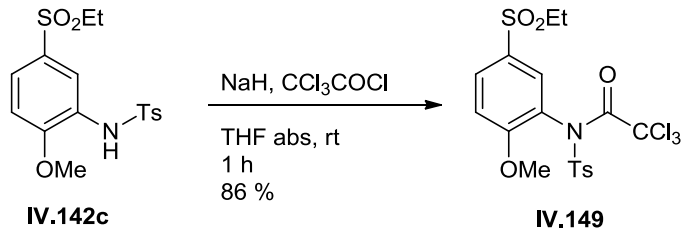


➢ *Preparation of 1,1-dichlorovinyl* ***IV.144c*** *from Corey-Fuchs precursor* ***IV.132c***.

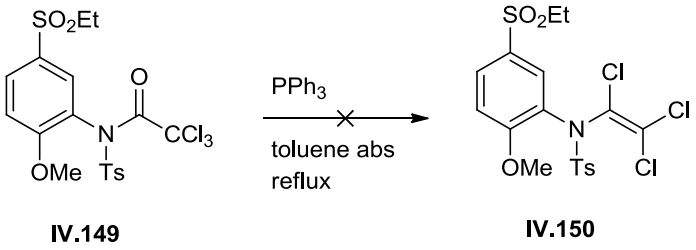


Transformation of *N*-trichloroacetales to ynamides (pathway C)

➢ *Preparation of N-tosylated trichloroacetyl* ***IV.149***.

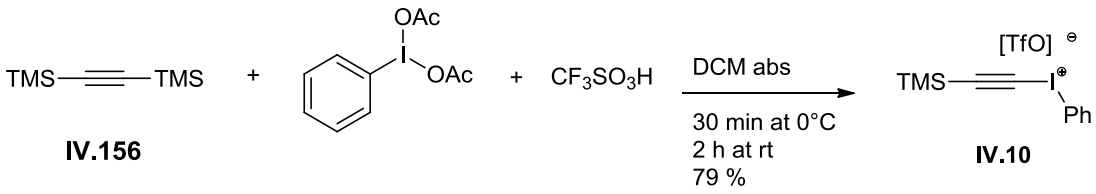


➢ *Unsuccessful transformation of* ***IV.149*** *to trichlorovinyl* ***IV.150***.

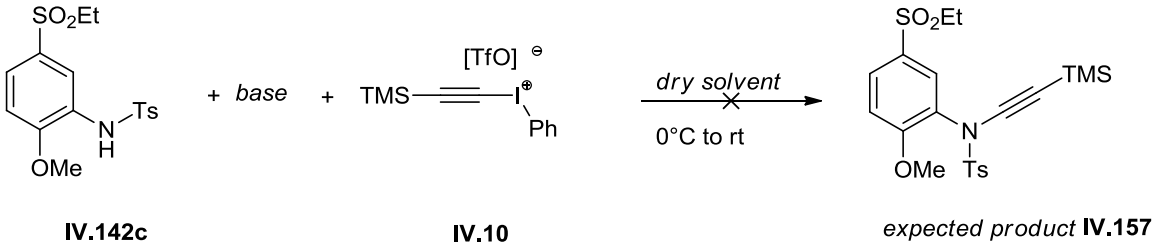


Direct *N*-alkynylation of arylamines (pathway D)

- *Preparation of phenyl(trimethylsilyl)iodonium triflate (**IV.10**).*

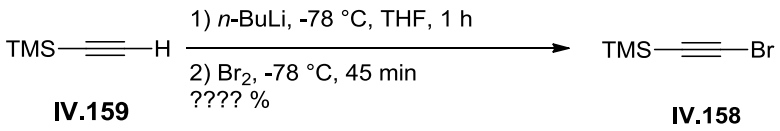


- *Unsuccessful preparation of ynamide **IV.157** via direct N-alkynylation with alkynyliodonium salt **IV.10**.*

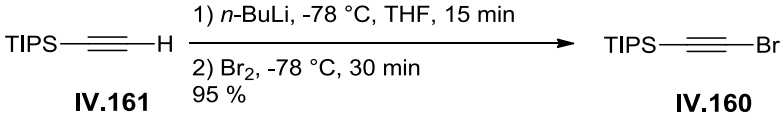


base: *n*-BuLi, KHMDS, LiHMDS
solvent: THF, PhMe

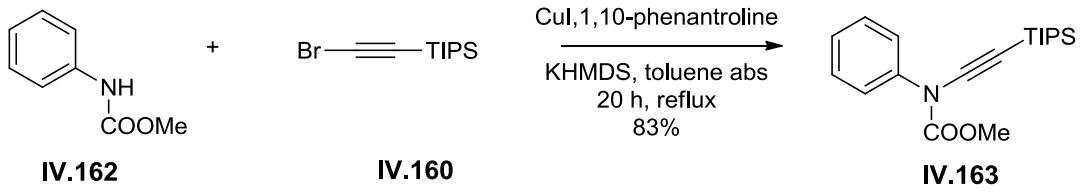
- *Preparation of (bromoacetylene)trimethylsilane **IV.158**.*



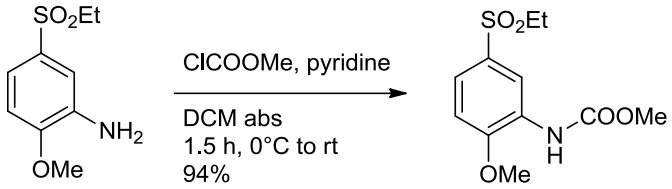
- *Preparation of brominated triisopropylylsilane **IV.160.***



- *Verification of Tam's protocol used N-COOMe protected aniline **IV.162.***

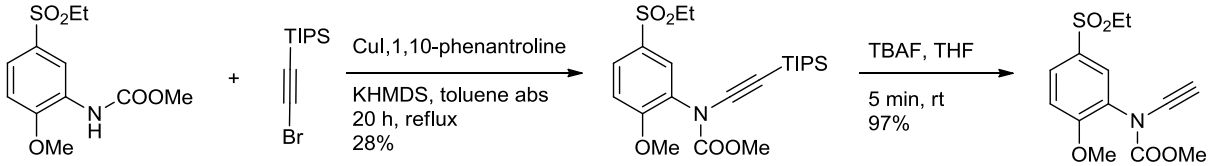


- *Introduction of methoxycarbonyl protecting group.*



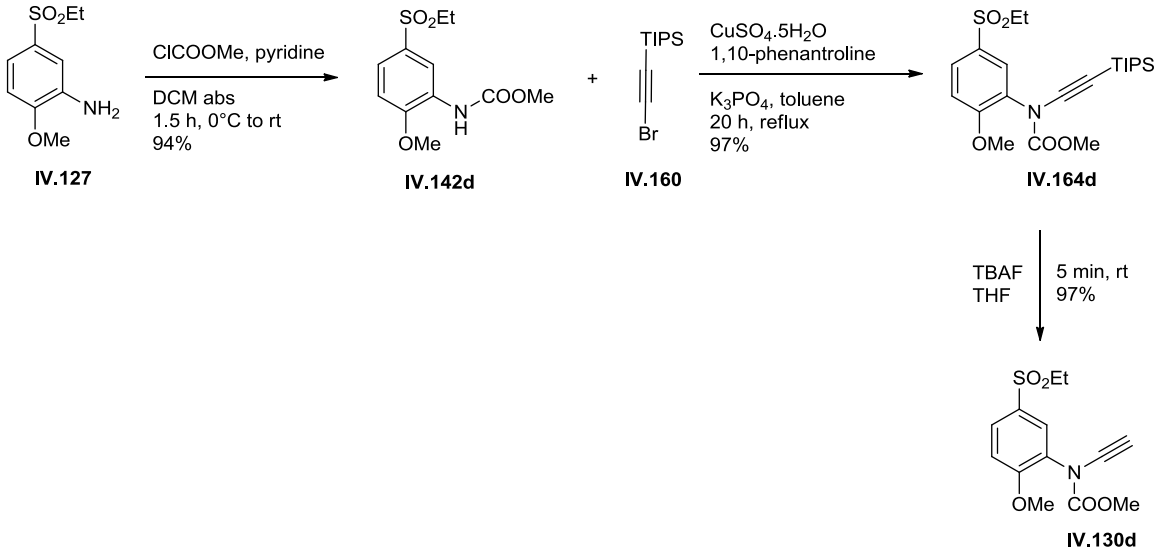
IV.127 **IV.142d**

- *Preparation of desired ynamide **IV.130d** through the N-direct alkynylation using Tam's protocol.*



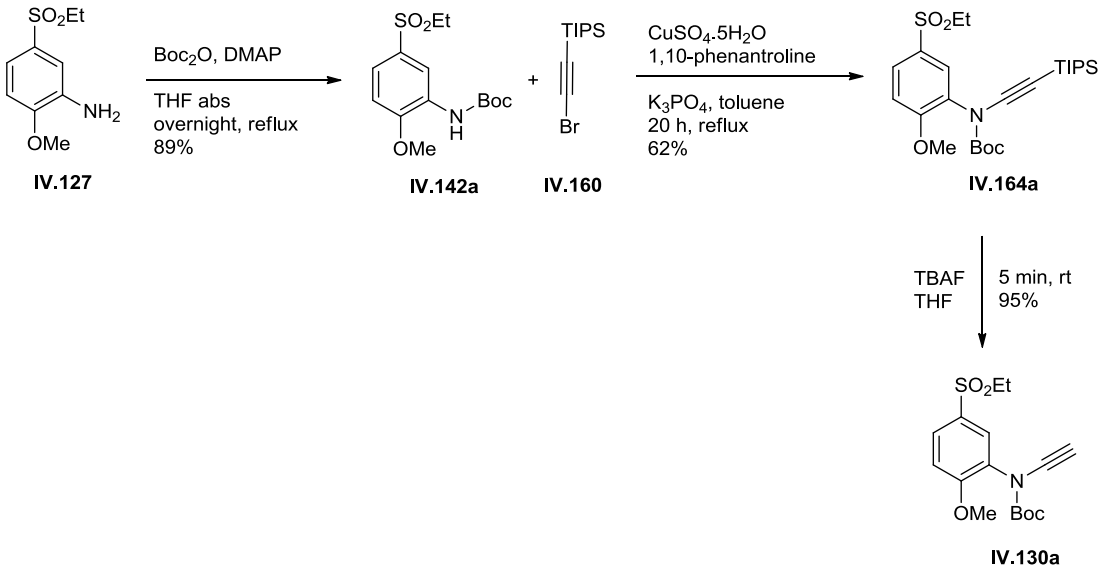
IV.142d **IV.160** **IV.164d** **IV.130d**

- *Preparation of ynamide **IV.130d** through the direct N-alkynylation using the protocol of Skrydstrup et al.*



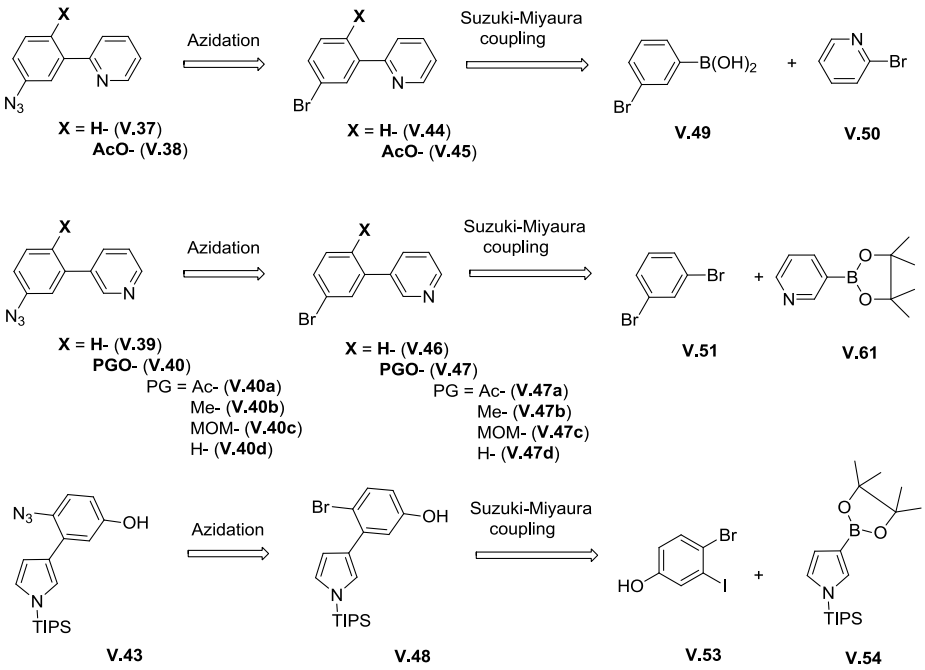
IV.127 **IV.142d** **IV.160** **IV.164d** **IV.130d**

- *Preparation of ynamide **IV.130a** through the N-direct alkynylation using the protocol of Skrydstrup et al.*

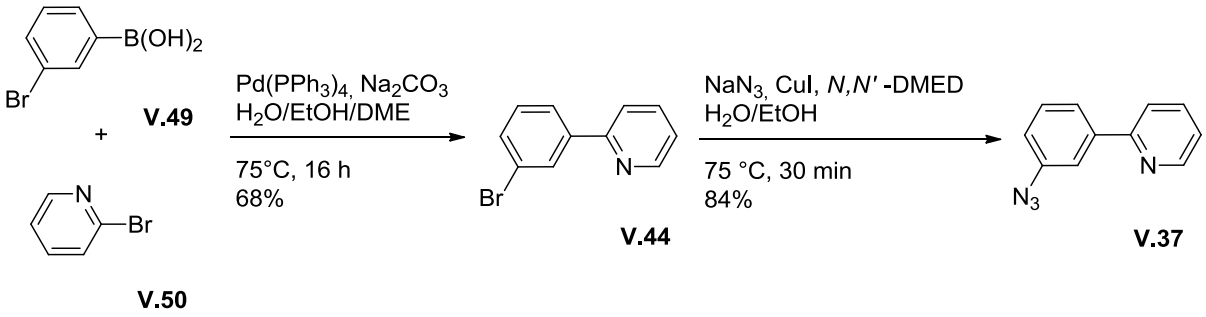


Synthetical preparation azides

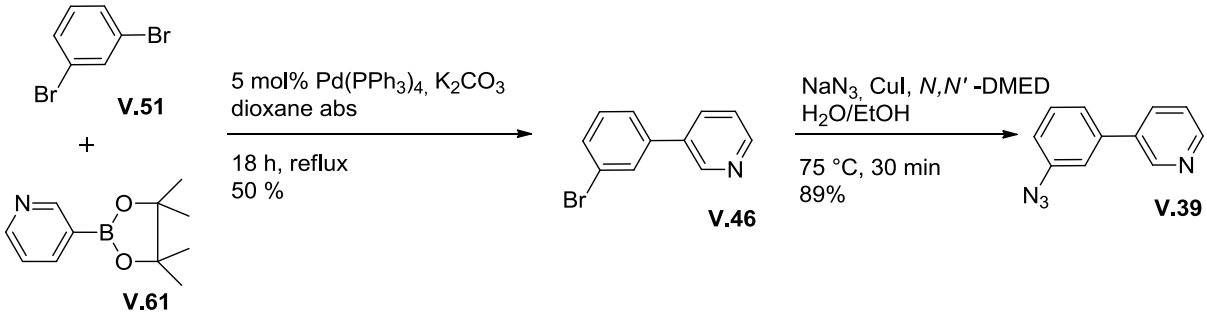
- *General access to biarylic azides **V.37**, **V.38**, **V.39**, **V.40** and **V.43** via Suzuki-Miyaura cross-coupling.*



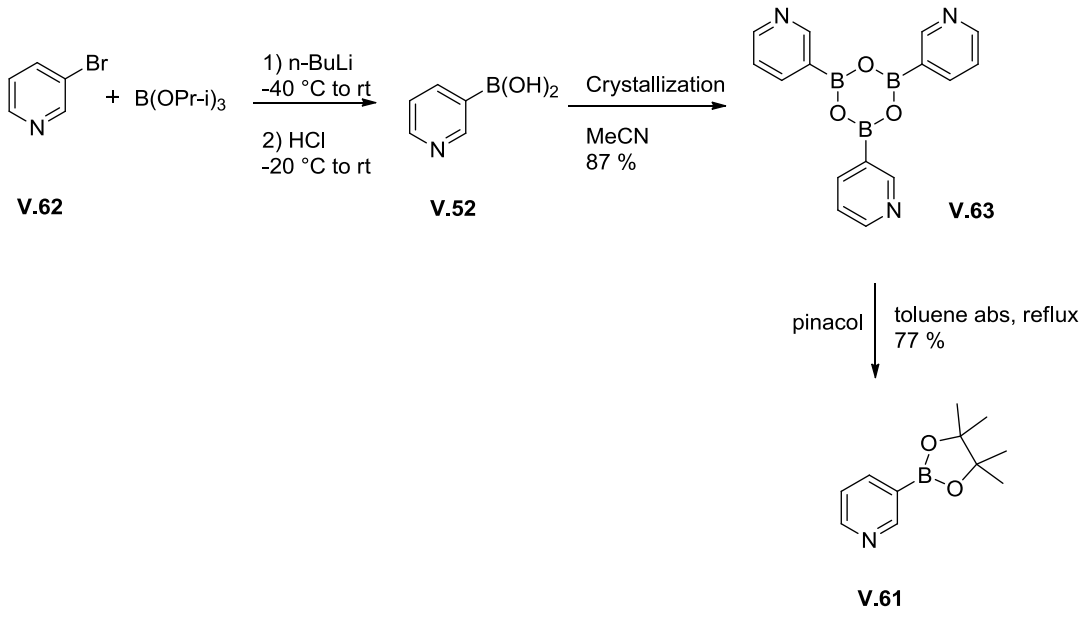
- *Preparation of azide biaryl ligand **V.37**.*



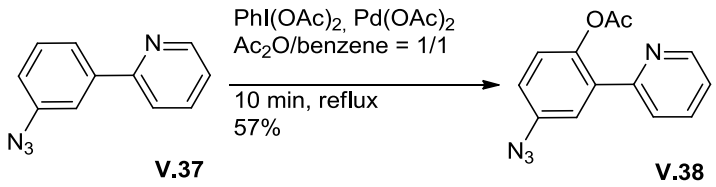
- *Preparation of azide **V.39**.*



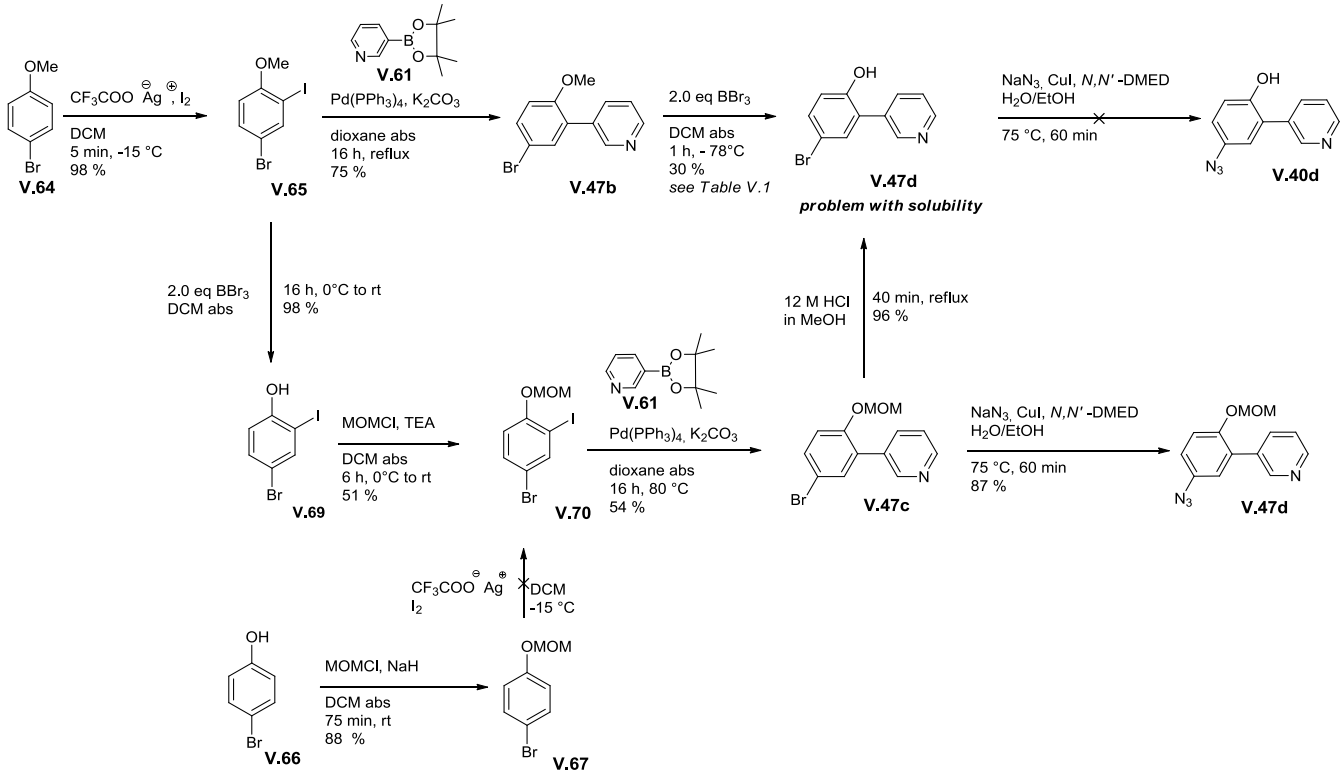
- *Synthesis of pinacol boronic ester **V.61**.*



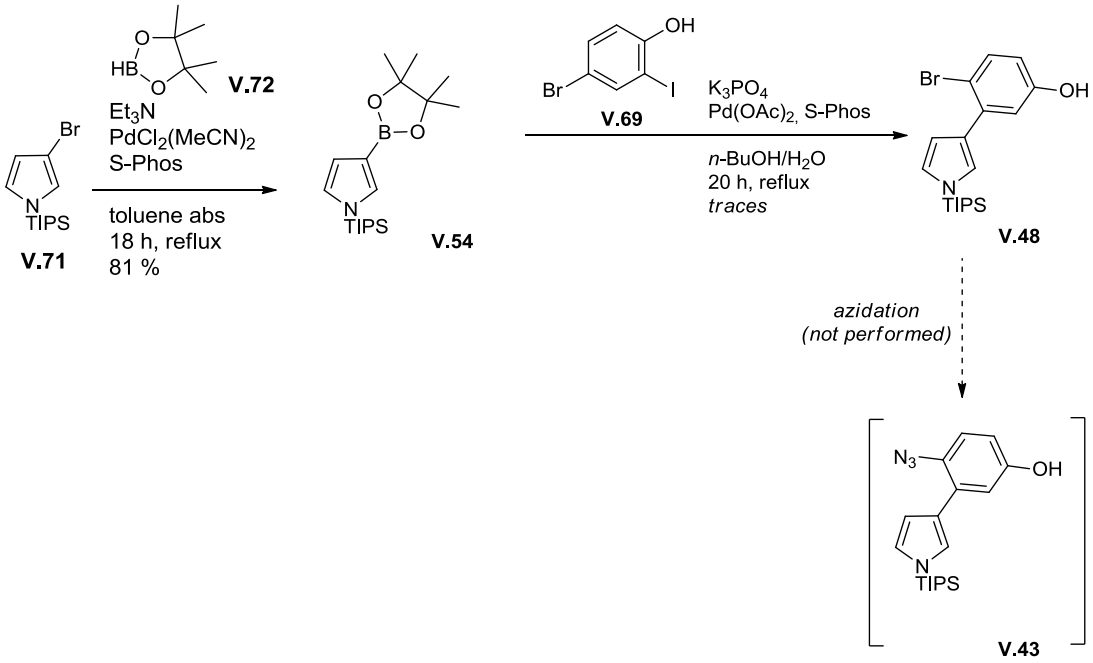
- *The C-H palladium activated acetoxylation - preparation of azide **V.38**.*



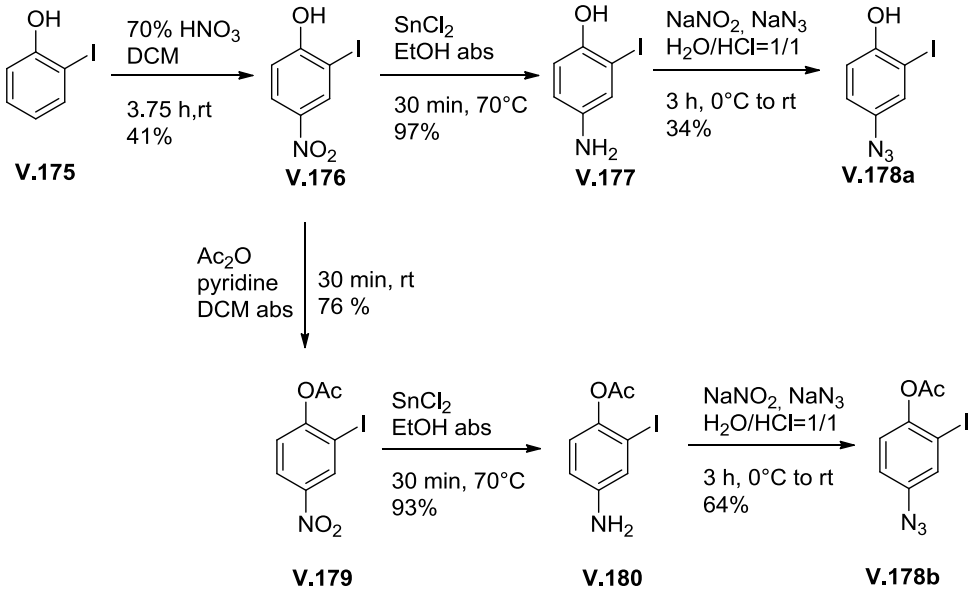
- *Synthesis of azide **V.47d** and unsuccessful preparation of azide **V.40d** as precursors of triazole **III.23.***



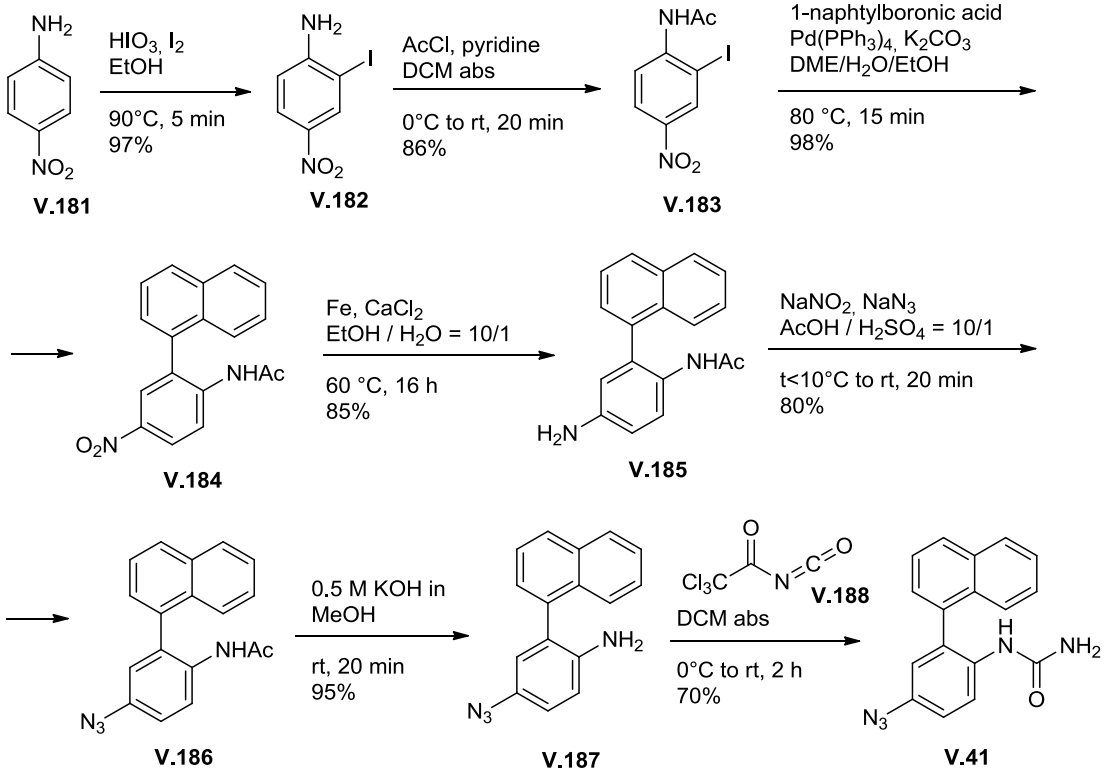
- *Proposed preparation of azide **V.43**.*



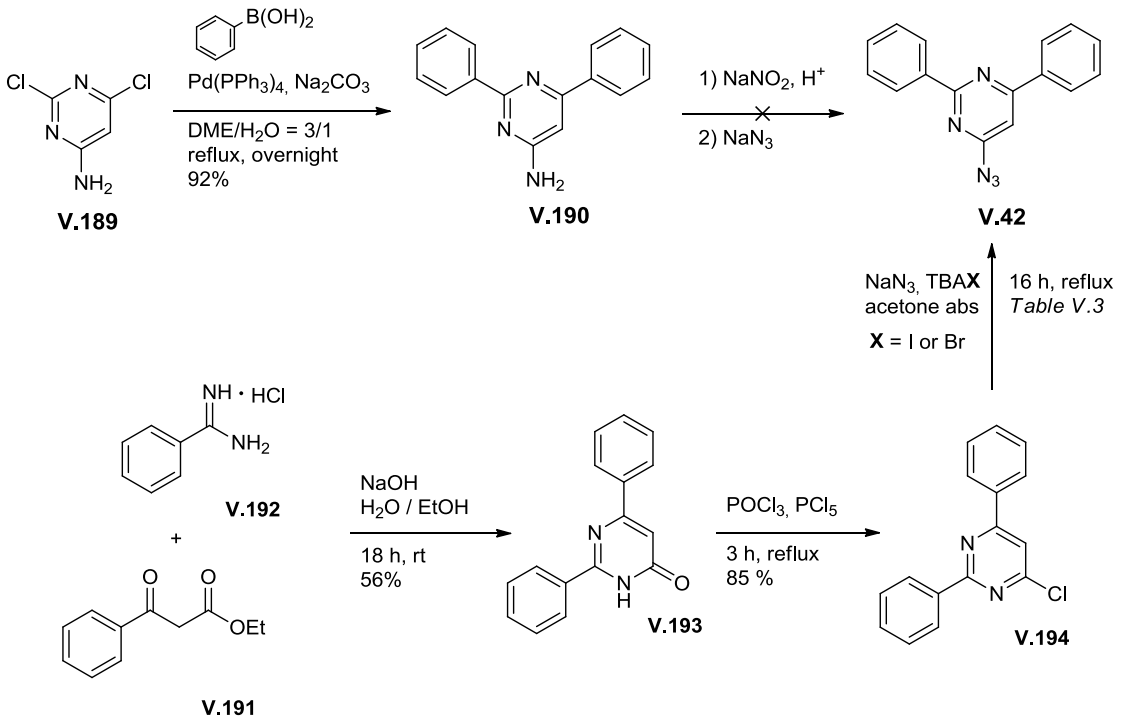
- *Preparation of azide **V.178a** and **V.178b**.*



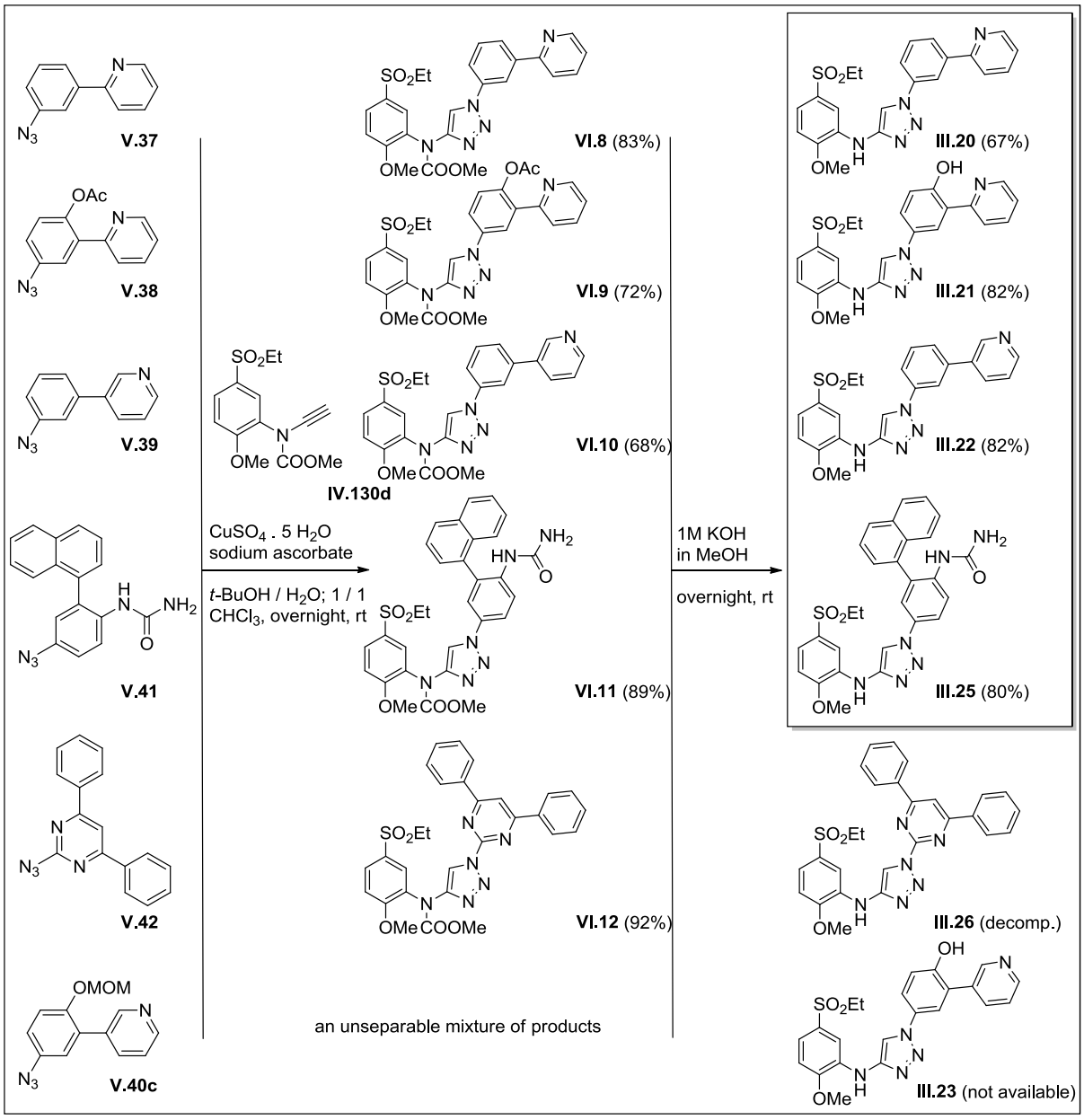
➢ *Preparation of urea azide **V.41** from p-nitroaniline **V.181**.*



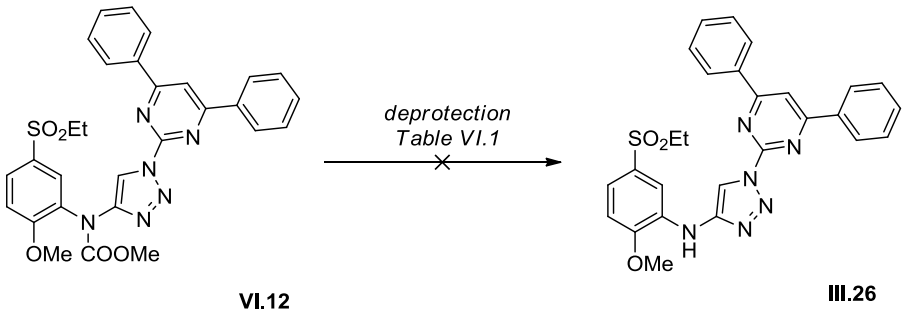
➢ *Proposed preparation of azido-pyrimidine **V.42.***



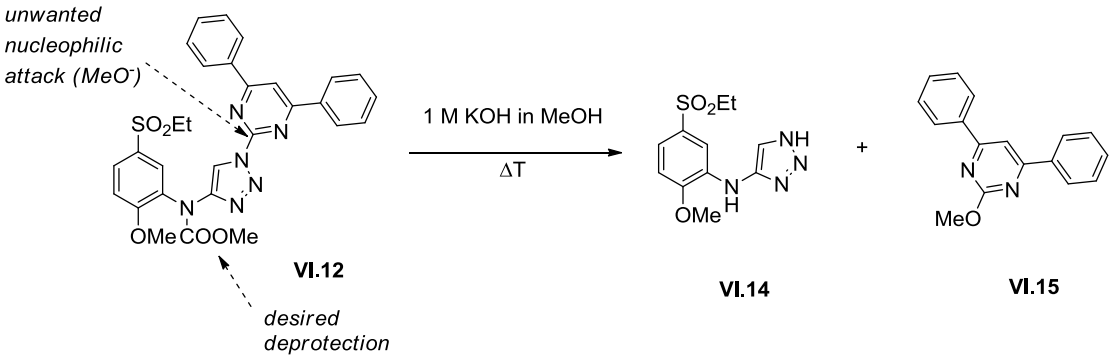
- *Preparation of proposed target molecules* ***III.20, III.21, III.22, III.25*** *and* ***III.26*** *via Click chemistry approach.*



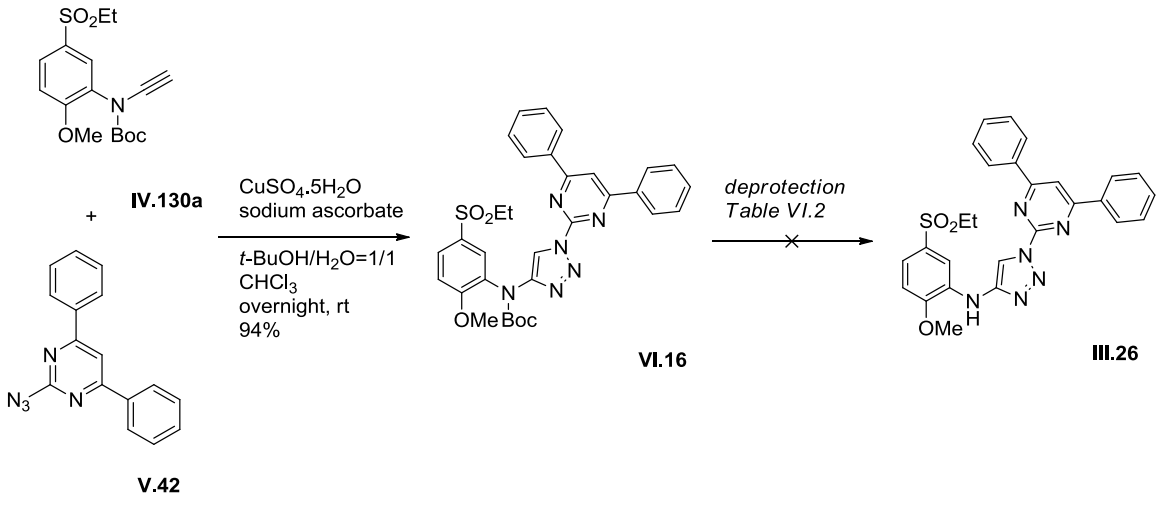
- *Unsuccessful deprotection of –COOMe group from pyrimidine triazole* ***VI.12****.*



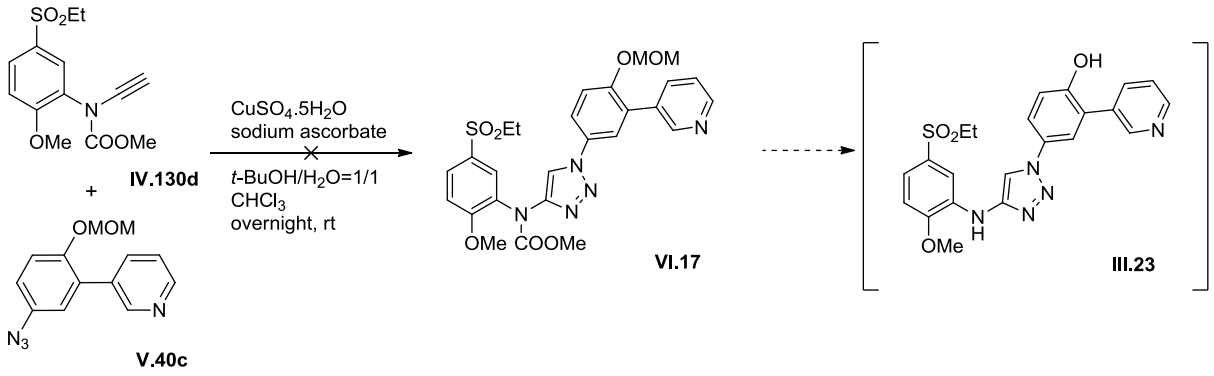
- *Products of decomposition* ***VI.14*** *and* ***VI.15*** *during the deprotection of –COOMe from triazole* ***VI.12*** *in basic condition under reflux.*



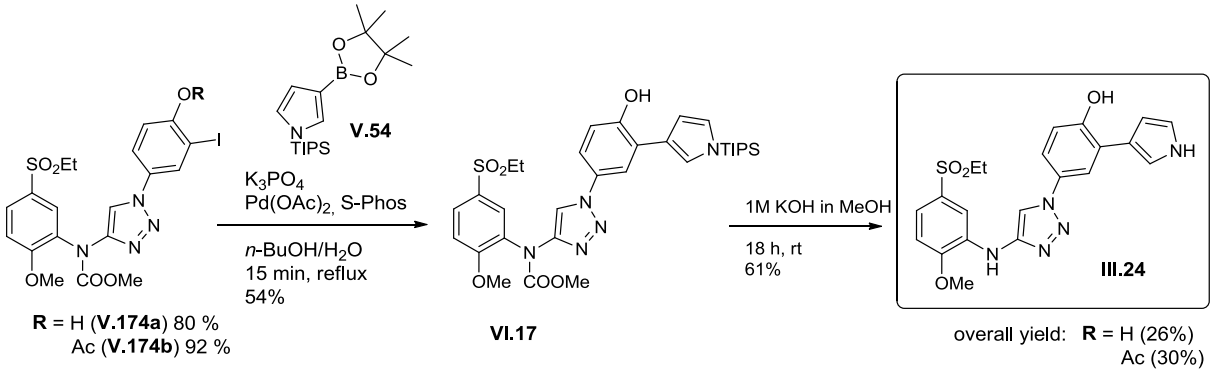
- *Preparation of Boc-protected triazole* ***VI.16*** *and its deprotection.*



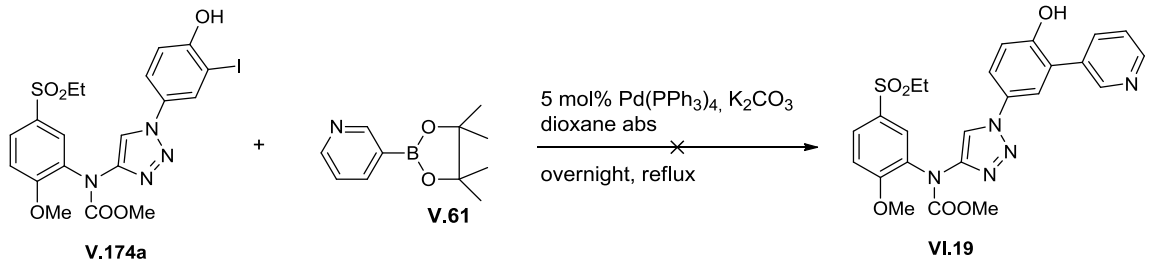
➢ *The Click reaction in order to get precursor **VI.17** of desired triazole **III.23**.*



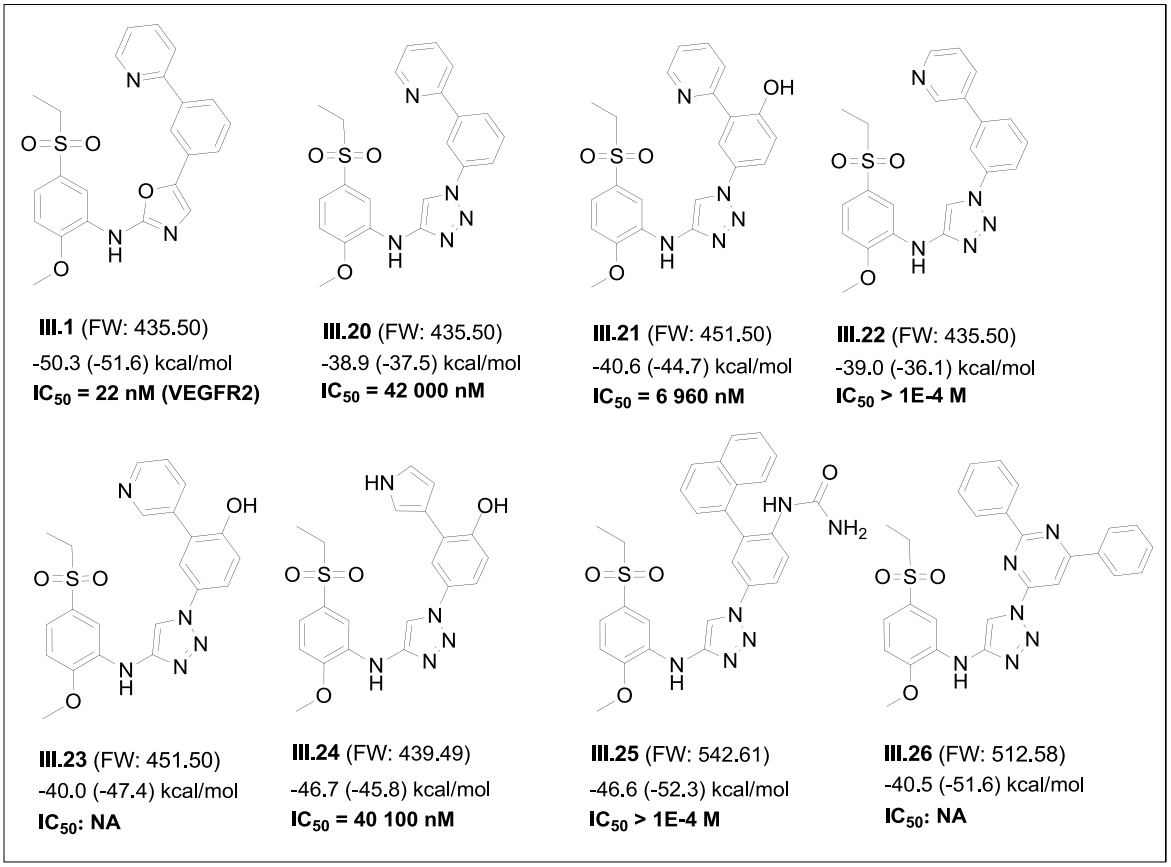
➢ *Preparation of triazole **III.24**.*



➢ *Unsuccessful preparation of triazole **VI.19** via alternative procedure.*



- *The structures of oxazolic inhibitor **III.1** and its 1,2,3-triazolic analogues **III.20** – **III.26** with their score and determined IC_{50} (VEGFR2) activity, if stated. NA: the compound was not available.*



Summary

Chapter 1. **Introduction**

The WHO´s definition of cancer is: *"Cancer is the uncontrolled growth and spread of cells."*[1]

In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous; benign tumors do not invade neighboring tissues and do not spread throughout the body. There are over 200 different known cancers that afflict humans.[2]

Cancer can develop from almost any type of cell in the body. There is usually more than one type of cancer that can develop in any one part of the body. Often though, one type of cancer will be much more common in a particular organ. Cancers are classified by the type of cell that the tumor cells ressembles and is therefore presumed to be the origin of the tumor. These types include:

- *Carcinoma*: Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged, and include nearly all those developing in the breast, prostate, lung, pancreas, and colon.
- *Sarcoma*: Cancers arising from connective tissue (*i.e.* bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.
- *Lymphoma and leukemia*: These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukemia is the most common type of cancer in children accounting for about 30%.
- *Germ cell tumor*: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).
- *Blastoma*: Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults.3

Cancers are primarily an environmental disease with 90–95 % of cases attributed to environmental factors and 5–10% due to genetics. Environmental, as used by cancer researchers, means any cause that is not inherited genetically, not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%),

[1] http://www.who.int/topics/cancer/en/ (visited 12.5.2013)
[2] http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/how-many-different-types-of-cancer-are-there (visited 23.5.2013)

infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants.[3]

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy and surgery. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age. In 2007, cancer caused about 13 % of all human deaths worldwide (7.9 million). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world.

Chemotherapy (often abbreviated to *chemo*) is the treatment of cancer with one or more cytotoxic antineoplastic drugs ("chemotherapeutic agents") as part of a standardized regimen. Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of most cancer cells. Medicinal chemistry considers also this type of research. Organic chemistry and molecular biology affords the new types of anti-cancer compounds. The newest trends in medicinal chemistry prefer target design of new potential drugs based on modern methodologies, using the chemoinformatic and predictive calculation tools (*In Silico*). The more specific treatment of cancer can bring better activity and also decrease side effects. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. The new blood vessels provide nutrients and oxygen for tumor growing, and it is a possible way also for formation of metastasis. The influence of growing of new blood vessels is the new way in the area of cancer treatment. Inhibitors of angiogenesis in combination with chemotherapy are suitable therapeutics using for slow-downing and stopping of tumor growth.

[3] Kravchenko, J.; Akushevich, I.; Manton, K. G. *Cancer mortality and morbidity patterns in the U. S. population: an interdisciplinary approach*. Berlin, Springer, 2009.

Chapter 2. **Angiogenesis**

2.1 Definition of angiogenesis

Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels.[4,5] Angiogenesis is a normal and vital process in growth and development. Physiological angiogenesis occurs during wound healing, the reproduction cycle and pregnancy, and produces well ordered vascular structures with mature, functional blood vessels.[6] Pathological angiogenesis is associated with tumor growth (Figure II.1) and several other diseases (*e.g.* psoriasis, diabetic retinopathies, mascular degeneration, arthrosis, ...). The new blood vessels provide nutrients and oxygen for tumor growth, and it is a possible way also for formation of metastasis.

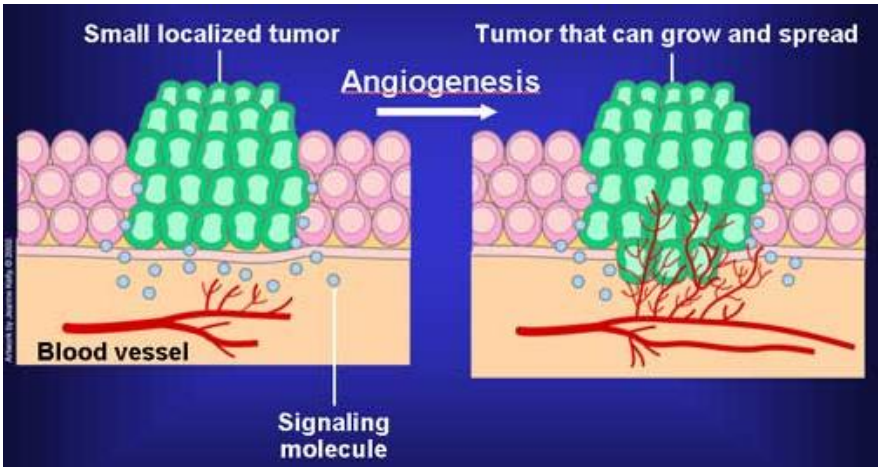


Figure II.1. *Tumor angiogenesis.*[7]

Angiogenesis is facilitated by a number of growth factors – signal proteins (*e.g.* VEGF, b-FGF) binding to appropriate receptors localized on the surface of endothelial cells. These ligands bind, in an overlapping pattern, to three different, but structurally related, VEGF-receptor tyrosine kinases (VEGFR-1 – 3). VEGFR-1 is critical for haematopoietic cell development, VEGFR-2 is critical for vascular endothelial cell development and VEGFR-3 critical for lymphatic endothelial cell development. Vascular endothelial growth factor (VEGF) represents a family of homodimeric glycoproteins which are critical or the embryonic development of the blood vascular system (vasculogenesis), lymphatic system lymphangiogenesis) and in the formation of new blood vessels

[4] Folkman, *J. Nat. Rev. Drug. Disc.* **2007**, *6*, 273.
[2] Nagakawa, T.; Tohyama, O.; Yamaguchi, A.; Matsushima, T.; Takahashi, K.; Funasaka, S.; Shirotori, S.; Asada, M.; Obaishi, H. *Cancer Science* **2010**, *1*, 210.
[6] Madhusadan, S.; Ganesan, T. *Clin. Biochem.* **2004**, *37*, 618.
[7] http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis/page3 (visited 18.5.2013)

from pre-existing vessels (angiogenesis). VEGF-A was first described as a tumor-secreted vascular-permeability factor (VPF).[8]

2.1.1 Function of Vascular endothelial growth factor receptor 2

VEGFR-2 (Flk-1/KDR) is expressed on vascular endothelial cells and lymphatic endothelial cells. It is a type III transmembrane kinase receptor with full-length of 1356 amino acids.[9] It consists of an extracellular region composed of seven immunoglobulin (Ig-like) domains, a short transmembrane domain, and an intracellular region containing a tyrosine kinase domain, split by a 70- amino-acid insert. (Figure II.2) VEGF-A binds to the second and third extracellular Ig-like domains of VEGFR-2. Ligand binding induces receptor dimerisation and autophosphorylation. Binding of the dimeric VEGF ligand, to the Ig-like domains 2 and 3 of one receptor monomer, increases the probability that a second receptor monomer binds the already tethered ligand. (Figure II.3) Phosphorylation of specific tyrosine residues in the receptor creates a consensus sequence for the recruitment of specific intracellular proteins.

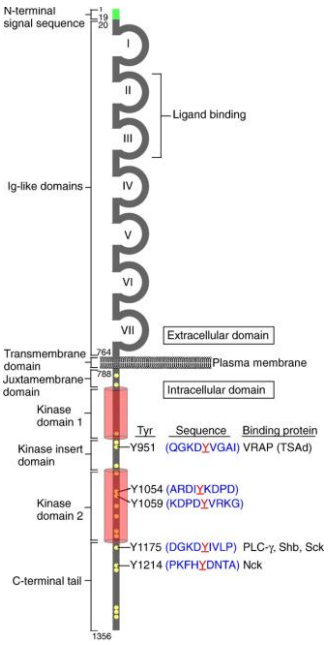


Figure II.2. *Structure and phosphorylation sites of human VEGFR-2.*

[8] Senger, D. F.; Galli, S. J.; Dvorak, A. M.; Perruzzi, C. A.; Harvey, V. S; Dvorak, H. F. *Science* **1983**, *219*, 983.
[9] Sait, S. N.; Dougher-Vermazen, M.; Shows, T. B.; Terman, B. I. *Cytogenet. Cell. Genet*. **1995**, *70*, 145.

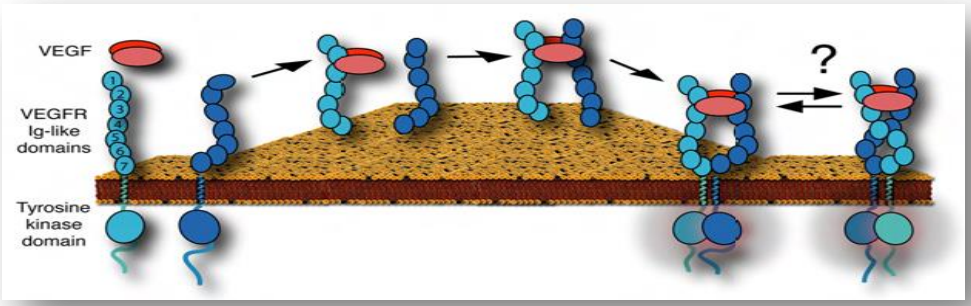


Figure II.3. *Mechanism of VEGFR-2 receptor activation by VEGF ligand.*7

VEGFR-2 is the principal mediator of several physiological and pathological effects of VEGF-A on endothelial cells. These include proliferation, migration, survival and permeability.

Angiogenesis plays a role in a number of pathological conditions, with VEGFR-2 signalling implicated in both tumour angiogenesis, and diabetic retinopathy.[10] Angiogenesis is crucial for tumor development as cancer cells have a relatively high metabolic demand for oxygen and nutrients to continue growing. In 1971, Folkman first proposed the theory that inhibition of angiogenesis may result in the arrest of tumor growth.[11]

2.2 The most important antiangiogenic drugs

The development of angiogenesis inhibitors usually follows three directions, including the inhibition of tumor cell synthesis of angiogenic proteins, the neutralization of angiogenic proteins by antibodies or traps, and the inhibition of endothelial cell binding to angiogenic proteins or direct induction of endothelial cell apoptosis.[12] (Figure II.4)

[10] Folkman, *J. Pediatr. Surg*. **2007**, *42*, 1.
[11] Folkman, J. *N. Engl. J. Med.* **1971**, *285 (21)*, 1182.
[12] Wu, H.-W.; Huang, C.-T.; Chang, D.-K. *J. Cancer Mol.* **2008**, *4,* 37.

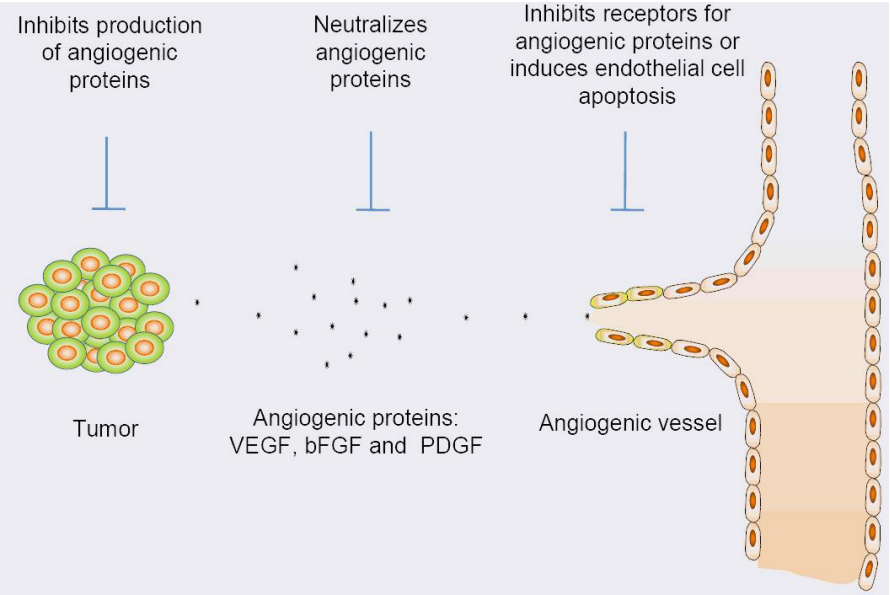
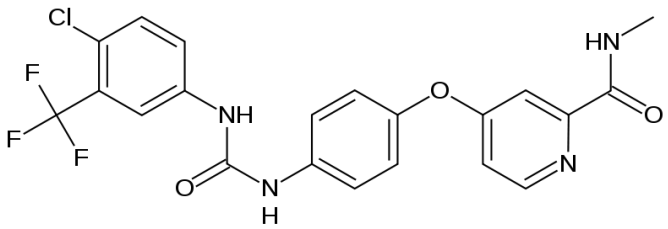


Figure II.4. *Strategies for inhibition of tumor growth by anti-angiogenic therapeutic drugs.*[12]

Recently, several low-molecular inhibitors of VEGFR-2 are known, *e.g.* Nexavar®, Sutent®, Votrient®, Afinitor®.

Nexavar® [13,14] possesing active compound Sorafenib (2005, Bayer) is an antiangiogenic drug used to treat advanced renal cell carcinoma, and a certain type of liver cancer known as hepatocellular carcinoma.

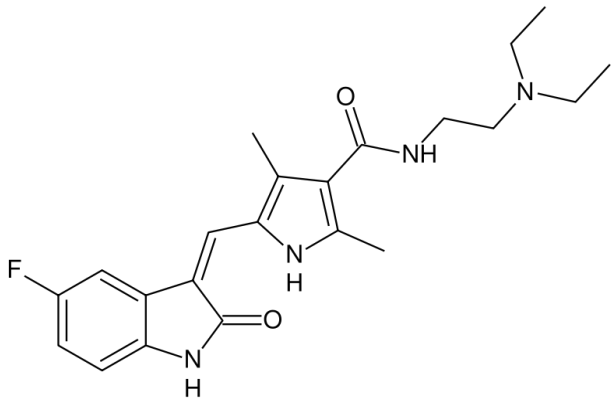


Nexavar® *(Sorafenib)*

Sutent®[15,16] with active part called Sunitinib (2006, Pfizer) is an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor that was approved by the FDA for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor (GIST). Sunitinib was the first

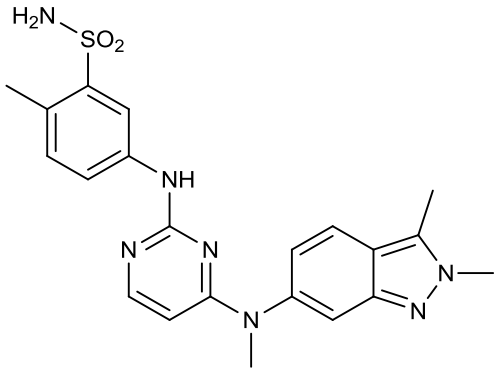
[13] http://www.nexavar.com/scripts/pages/en/index.php (visited 25.5.2013)
[14] Wilhelm, S. M.; Adnane, L.; Newell, P.; Villanueva, A.; Llovet, J. M.; Lynch, M. *Mol. Cancer Ther.* **2008**, *10*, 3129.
[15] http://www.sutent.com/ (visited 25.5.2013)
[16] Quek, R.; George, S. *Hematol. Oncol. Clin. North Am.* **2009,** *23*, 69.

cancer drug simultaneously approved for two different indications. In November 2010 Sutent® gained approval from the European Commission for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults.



Sutent® *(Sunitinib)*

Votrient® [17,18] (with active part known as Pazopanib) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β, and c-kit that blocks tumor growth and inhibits angiogenesis. It has been approved for renal cell carcinoma by the FDA (U.S. Food and Drug Administration). Pazopanib may also be active in ovarian cancer and soft tissue sarcoma. Pazopanib also appears effective in the treatment of non-small cell lung carcinoma.



Votrient® *(Pazopanib)*

Avastin®[19,20] (active compound Bevacizumab, FW~149 kDa)) is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A). Bevacizumab was the first

[17] Sleijfer, S.; Ray-Coquard, I.; Papai, Z.; Le Cesne, A.; Scurr, M.; Schoffski, P.; Collin, F.; Pandite, L. *J. Clin. Onc.,* **2009**, *27*, 3126.
[18] http://en.wikipedia.org/wiki/Pazopanib (visited 25.5.2013)
[19] Los, M.; Roodhart, J. M. L.; Voest, E. E. *The Oncologist* **2007**, *12*, 443.
[20] http://en.wikipedia.org/wiki/Bevacizumab (visited 25.5.2013)

clinically available angiogenesis inhibitor in the United States. Bevacizumab was approved by FDA for certain metastatic cancers. It received its first approval in 2004, for combination use with standard chemotherapy for metastatic colon cancer. It has since been approved for use in certain lung cancers, renal cancers, and glioblastoma multiforme of the brain.

Plan of the manuscript:

In the first two chapters of this pHD work we have presented a brief state of the art and described concisely the biological background of low molecular weight inhibitors of VEGFR-2 tyrosinkinase such as **III.1** (from complex PDB:1Y6A).

In the third chapter we will present the aim of the project which deals with a 1,3-oxazole / 1,2,3-triazole replacement of **III.1** to obtain more stable and synthetically more available VEGFR-2 inhibitors. Interaction analysis, molecular modeling and docking will be used for prediction of seven 1,2,3- triazolic analogues **III.20** – **III.26** derived from oxazolic inhibitor **III.1** (from complex PDB: 1Y6A)

Chapters IV, V and VI will describe our synthetic efforts to prepare target molecules which would be available via a cycloaddition (chapt. VI) between a key ynamide (chapt. IV) and different azides (chapt. V).

In chapter VII, we will present the biological activity of the different 1,2,3-triazoles we have prepared on VEGFR-2 tyrosinkinase.

The last part will expose and general conclusion.

Chapter 3. **Aim of the project**

VEGFR-2 receptor is considered a key mediator for VEGF signal transduction in angiogenesis (neovascularisation).[21] VEGFR-2 was recently predicted to influence in part also the fate of glioma cancer stem cells.[22] Cancer stem cells (CSCs) representing the most tumorigenic population from tumor cells responsible for metastasis, tumor recruitment and drug resistance. CSCs also called the root of tumors are considered to be a new promising anticancer target. Therefore VEGFR-2 inhibitors are important compounds reducing angiogenesis and interfering with CSCs resistance.

The Protein Data Bank (PDB) contains VEGFR-2 tyrosinkinase (TK) complex 1Y6A possessing *N*-aryl-5-aryloxazol-2-amine ligand **III.1** determined as powerful VEGFR-2 inhibitor (IC_{50} = 22 nM). (Figure III.1)

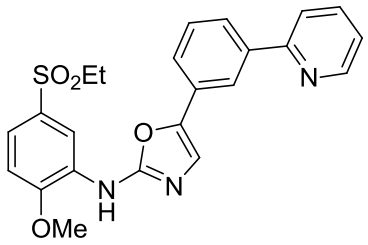


Figure III.1. *Structure of N-aryl-5-aryloxazol-2-amine ligand **III.1**.*

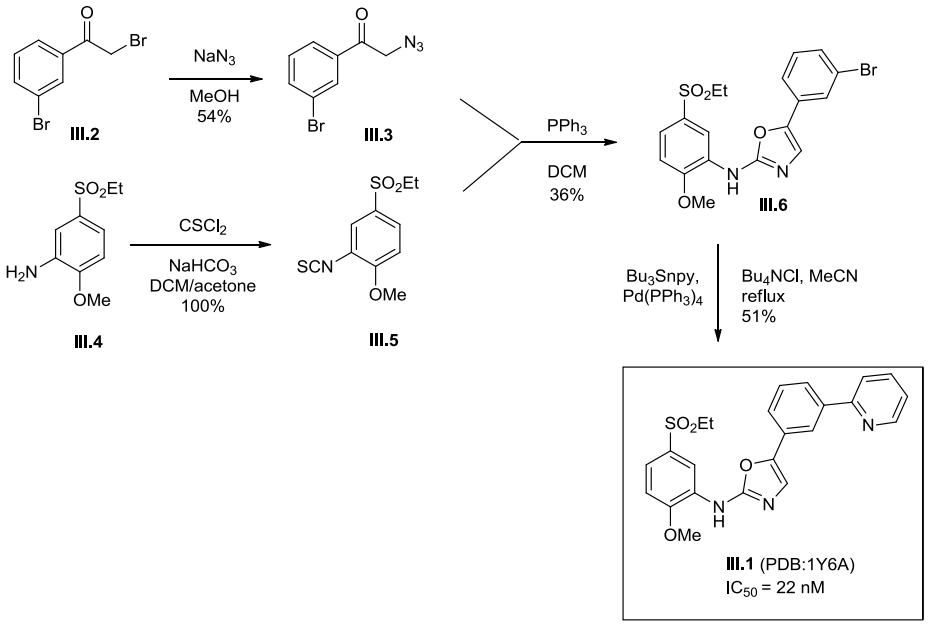
Ligand **III.1** was prepared in five steps in a low ca 10 % yield mostly due to the problematic oxazole-2-amine core formation step.[23,24] (Scheme III.1)

[21] Carmeliet, P. *Oncology* **2005**, *69*, 4.

[22] Hamerlik, P.; Lathia, J. D.; Rasmussen, R.; Wu, Q.; Bartkova, J.; Lee, M.; Moudry, P.; Bartek, J. Jr.; Fischer, W.; Lukas, J.; Rich, J. N.; Bartek, J.; *J. Exp. Med.* **2012**, *209*, 507.

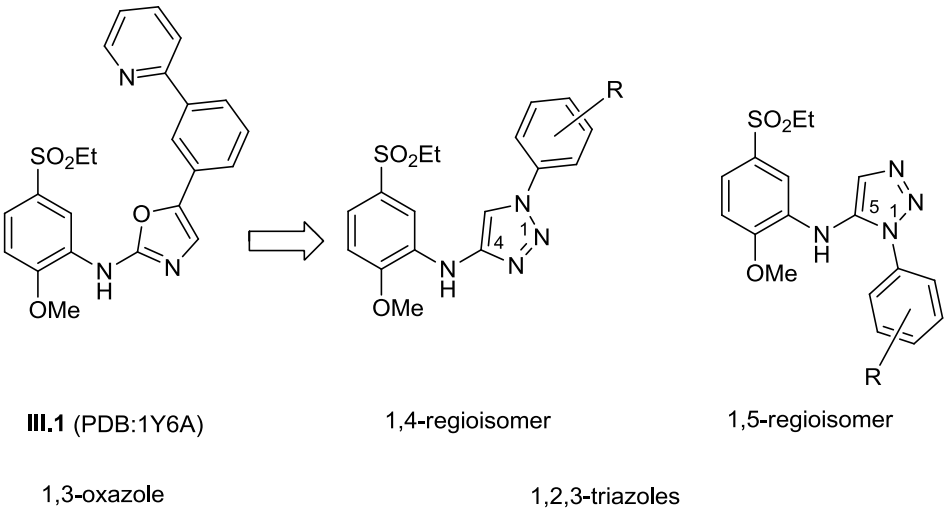
[23] Harris, P. A.; Cheung, M.; Hunter, R. N.; Brown, M. L.; Veal, J. M.; Nolte, R. T.; Wang, L.; Liu, W.; Crosby, R. M.; Johnson, J. H.; Epperly, A. H.; Kumar, R.; Luttrell, D. K.; Stafford, J. A. *J. Med. Chem.* **2005**, *48*, 1610.

[24] Lintnerová, L.; Kováčiková, L.; Hanquet, G.; Boháč, A. *J. Heterocyc. Chem.* **2013**, in press.



Scheme III.1. *Preparation of ligand **III.1**.*[23]

Compound **III.1** was prepared in low yield and contains a sensitive *N*-aryloxazol-2-amine functionality.[25] Therefore we decided to develop novel, more stable and synthetically more available VEGFR-2 inhibitors based on 1,3-oxazole / 1,2,3-triazole replacement (also known as *me-too* or *me-better* methodology). (Scheme III.2)



Scheme III.2. *1,2,3-triazole ligands based on 1,3-oxazole **III.1** (PDB:1Y6A).*

[25] unpublished results

Exchange of heterocyclic core in the structure of already described inhibitor AAZ from PDB: 1Y6A can lead to improvement in:

- activity and/or selectivity
- higher stability
- synthetic feasibility
- better physical and chemical properties for biovalability
- lower toxicity
- inhibitor novelty.

3.1 Described 1,2,3-triazole VEGFR-2 inhibitors

In literature are described only few 1,2,3-triazole VEGFR-2 active inhibitors (6 inhibitors - $IC_{50} < 50$ nM; 10 compounds - $IC_{50} < 100$ nM; 19 compounds - $IC_{50} \leq 200$ nM).[26] Structures and activities of the most active triazole inhibitors are depicted in Figure III.2. The above mentioned VEGFR-2 inhibitors **III.7**-**III.12** content triazole core in the *external* part of molecule. In this case, the triazole core is probably responsible for better pharmacokinetic properties (*e.g.* solubility) of inhibitors and this part is not directly contributing to an affinity of inhibitor to the receptor.

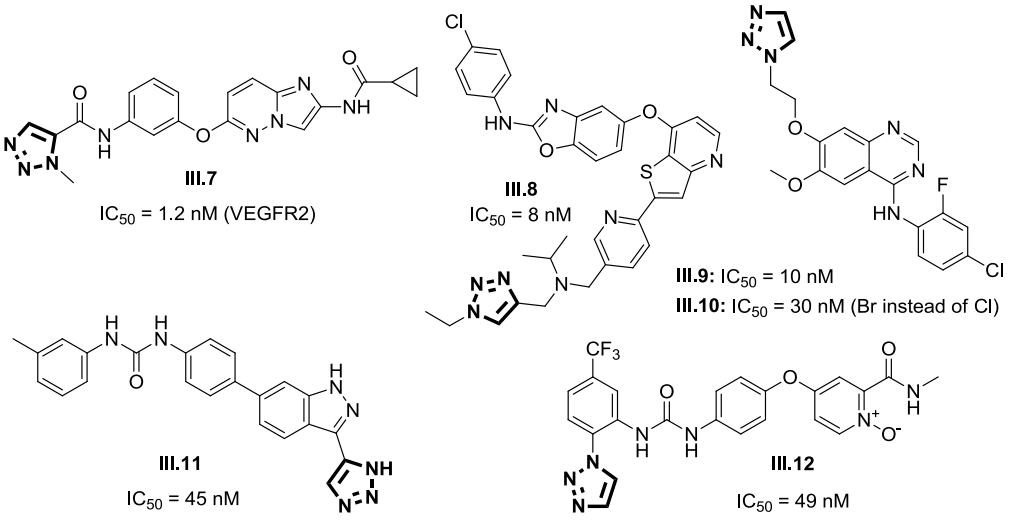


Figure III.2. *Structures of described VEGFR-2 inhibitors **III.7**-**III.12** containing 1,2,3-triazole core with $IC_{50} < 50$ nM.*

[26] Database REAXYS https://www.reaxys.com/ (last visited 28.06.2013).

Only few VEGFR-2 inhibitors possessing internal 1,2,3-triazole core were found.[27] Staurosporin mimicking inhibitor **III.16** inhibits VEGFR-2 (IC_{50} = 200 nM).[28] (Figure III.3)

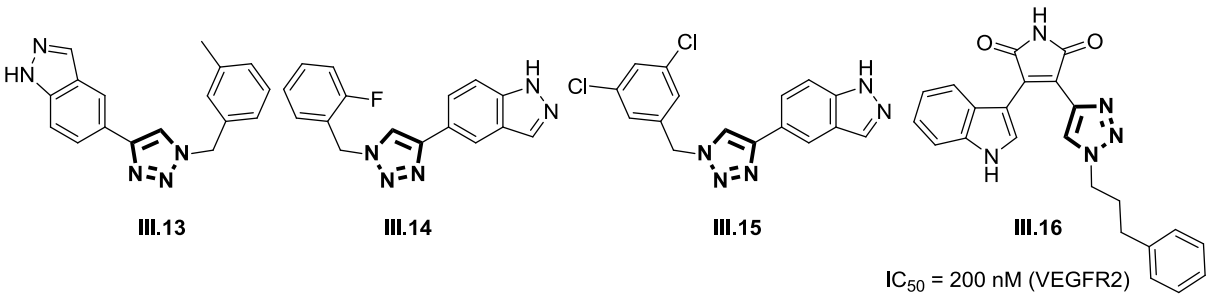


Figure III.3. *VEGFR-2 modulators **III.13-III.16** possessing 1,2,3-triazolic core.*

Up today, only one literature[29] describes highly active VEGFR-2 inhibitors **AB12 – AB14** (IC_{50}: 51 - 87 nM) possessing internal 1,2,3-triazol core. The active compounds are interesting even more when considering their relatively low molecular weight (MW: 395 – 411 g/mol). (Figure III.4)

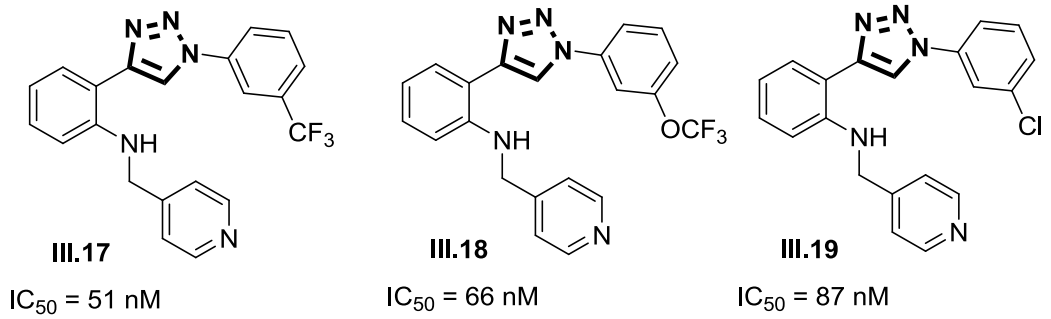


Figure III.4. *Potent VEGFR-2 inhibitors **III.17-III.19** possessing internal 1,2,3-triazole core.*

[27] Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21,* 1476.

[28] Gu, G.; Wang, H.; Liu, P.; Fu, C.; Li, Z.; Cao, X.; Li, Y.; Fang, Q.; Xu, F.; Shen, J.; Wang, P. G. *Chem. Commun.* **2012**, *48,* 2788.

[29] Kiselyov, A. S.; Semenova, M.; Semenov, V. V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1344.

3.2 Predicted potential 1,2,3-triazole VEGFR-2 inhibitors and synthetical approach

Interaction analysis, molecular modelling, docking were used for development of seven 1,2,3-triazolic analogues **III.20-III.26** derived from oxazolic VEGFR-2 inhibitor **III.1** (from complex PDB: 1Y6A).[30]

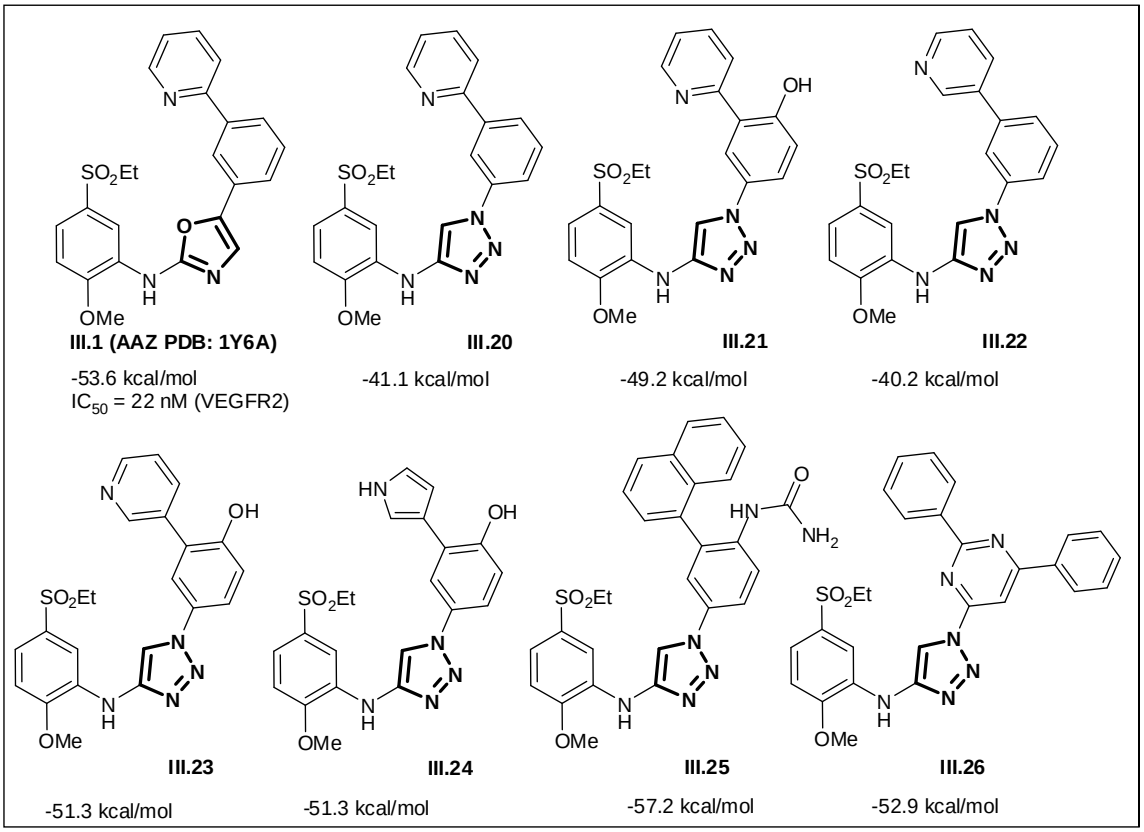
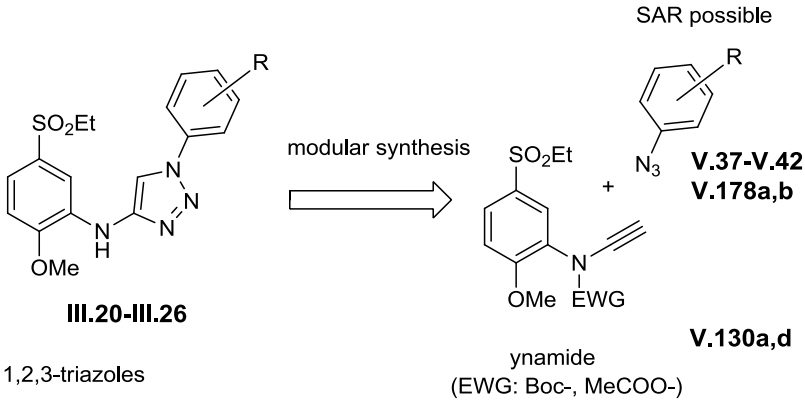


Figure III.5. *Predicted potential 1,2,3-triazolic modulators of VEGFR-2 TK.*

Synthesis of **III.20** – **III.26** was proposed by copper-catalyzed azide alkyne cycloaddition (CuAAC) of a key ynamides **IV.130a**,**d** with appropriate organic azides **V.37**-**V.42** and **V.178a**,**b**. (Scheme III.3) Oxazole - triazole isosteric replacement and Click chemistry allow us to obtain stable compounds possessing novel skeleton easily prepared by modular synthesis. Click chemistry step introduced also the possibility to broaden the amount of prepared products by its capacity to produce selectively either 1,4- (Cu(I)

[30] http://www.rcsb.org/pdb/home/home.do

catalysed) or 1,5- disubstituted (Ru(II) catalysed) regioisomers of 1,2,3-triazoles. (Figure III.5 and 6)



Scheme III.3. *Retrosynthetic approach to obtain 1,2,3-triazoles **III.20-III.26** via Click chemistry.*

In order to predict also 1,5-regioisomeric 1,2,3-triazolic analogues of **III.20B - III.25B**, the *in Silico* calculations were done. However, docking scores of predicted 1,5-regioisomers were much more less interesting as their 1,4-regioisomers. Therefore we did not plane to prepare 1,5-regioisomers. (Figure III.6)

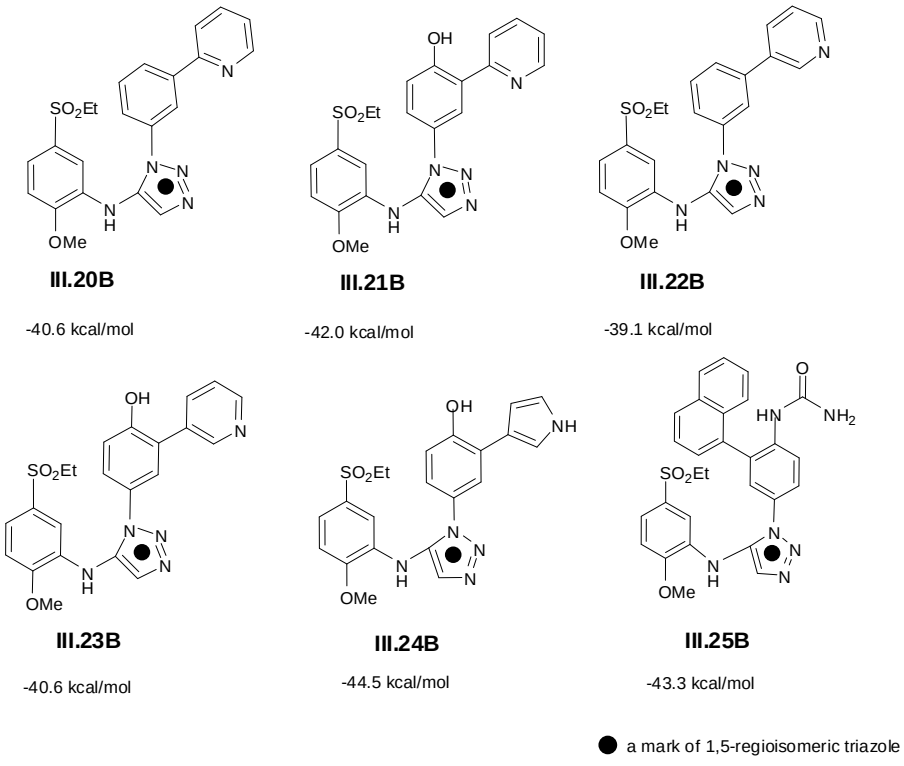


Figure III.6. *Predicted 1,5-regiosiomeric analogues **III.20B-III.25B** derived from III.1 (AAZ) ligand (PDB: 1Y6A) and their docking scores.*

Analysis of predicted 1,2,3-triazoles **III.20-III.26** and their possible interactions with VEGFR-2 tyrosinkinase protein (in protein taken from complex PDB:1Y6A) was made in Discovery Studio Visualizer 3.5 software.[31] Also drug-like properties for structures **III.20-III.26** were estimated by freely available prediction toolkit Molinspiration.[32] According to the mentioned *in Silico* predictions we got several informations about predicted structures based on Lipinski's rules of five and other predictive rules.[33] The parameters of drug-like properties are depicted in Table III.1.

Table III.1. Parameters of drug-like properties.

Entry	Parameter	Abbreviation of parameter	Range
1	formula weight	FW	≤ 500
2	coefficient of lipophilicity	miLogP	≤ 5
3	topological polar surface area	TPSA	≤ 140 Å
4	number of H-acceptors	nON	≤ 10
5	number of H-donors	nOHNH	≤ 5
6	number of rotatable bonds	NRB	≤ 10

The ligand **III.1** was found to be present in PDB: 1Y6A complex in form of two conformers ("U-shaped" and "S-shaped"). After docking its skeleton possess a score -53.6 kcal/mol. (Figure III.7)

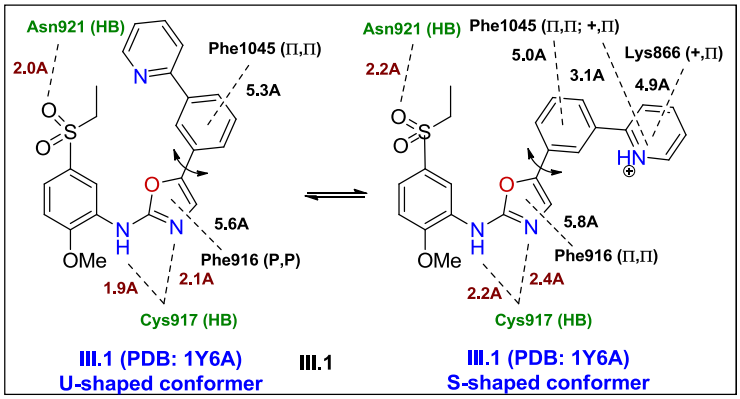


Figure III.7. *Two observed conformers of original ligand **III.1** in PDB:1Y6A complex.*

[31] http://accelrys.com/products/discovery-studio/visualization-download.php (visited 29th June 2013)
[32] Molinspiration Property Calculation Service http://www.molinspiration.com/cgi-bin/properties (visited 29th June 2013)
[33] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3.

Phenylurea **III.25** has got the best docking score (-52.1 kcal/mol). **III.25** is a drug-like compound except for small excess of molecular weight (FW: 542.62, miLogP: 4.70, TPSA: 141.2, nON: 10, nOHNH: 4, NRB: 8). (Figure III.8)

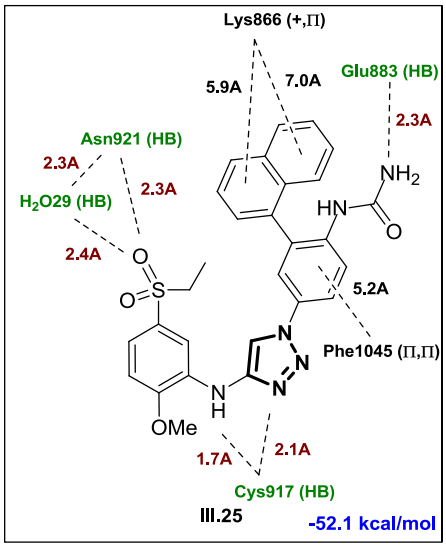


Figure III.8. *Interaction map of predicted triazole **III.25** with VEGFR-2.*

Predicted compound **III.26** posseses docking score -51.5 kcal/mol. (Figure III.9) Compound **III.26** slightly exceeds 2 parameters of drug-like properties: molecular weight and parameter of lipophilicity (FW: 512.60, miLogP: 5.10, TPSA: 111.9, nON: 9, nOHNH: 1, NRB: 8). Compound **III.23** has docking score -47.4 kcal/mol and its structure is in accordance with drug-like properties (FW: 452.52, miLogP: 3.12, TPSA: 119.2, nON: 9, nOHNH: 2, NRB: 7). Proposed intermolecular properties of III.26 and III.23 are depicted in Figure III.9.

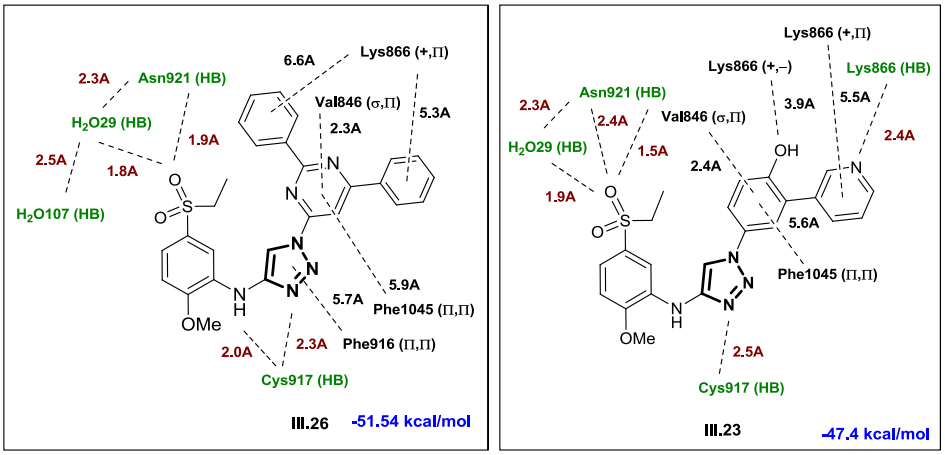


Figure III.9. *Interaction maps of predicted triazoless **III.26** and **III.23** with VEGFR-2 kinase.*

Compound **III.24** has docking score -45.1 kcal/mol (Figure III.10) and its structure fulfils drug-like rules (FW: 439.50, miLogP: 3.03, TPSA: 122.1, nON: 9, nOHNH: 3, NRB: 7). Compound **III.21** has docking score -44.7 kcal/mol and this compound is in accordance with predictive drug-like properties (FW: 451.51, miLogP: 3.04, TPSA: 119.2, nON: 9, nOHNH: 2, NRB: 7). Interaction analysis for both structures are depicted in Figure III.10.

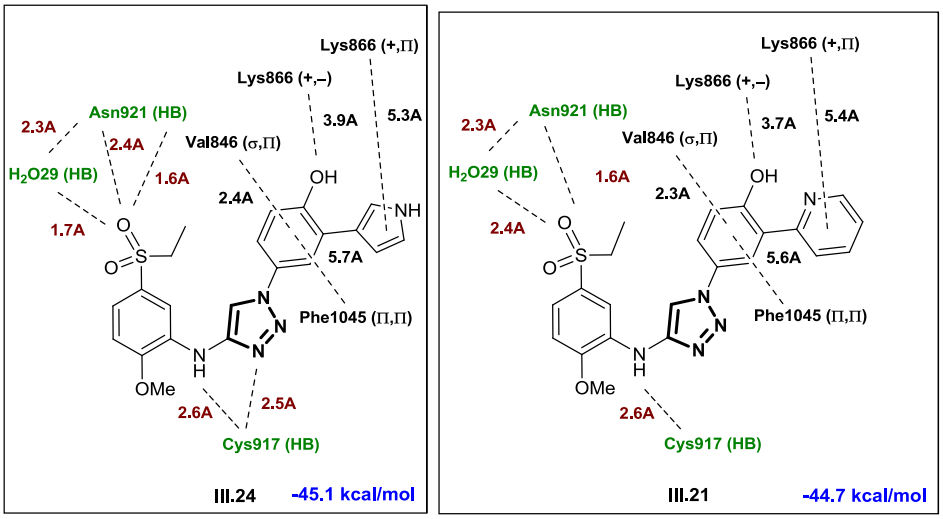


Figure III.10. *Interaction maps of predicted triazoles **III.24** and **III.21** with VEGFR-2 kinase.*

Structure **III.20** is an isosteric analogue of oxazolic inhibitor **III.1**. Compound **III.20** is in accordance with predicted drug-like properties (FW: 435.51, miLogP: 3.31, TPSA: 99.0, nON: 8, nOHNH: 1, NRB: 7). Structure of **III.20** obtained docking score -37.9 kcal/mol. Its VEGFR-2 IC_{50} activity was determined to be 42.2 uM that is 1 918 times less compare to its 1,3-oxazolic analogue **III.1** (IC_{50}: 22 nM). Compound **III.22** is in accordance with drug-like selection rules (FW: 435.51, miLogP: 3.39, TPSA: 99.0, nON: 8, nOHNH: 1, NRB: 7). Interaction analyses for both compounds are depicted on Figure III.11.

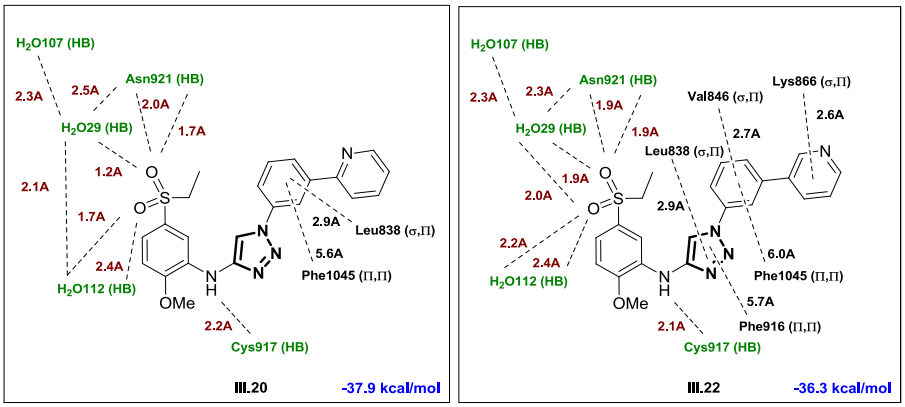
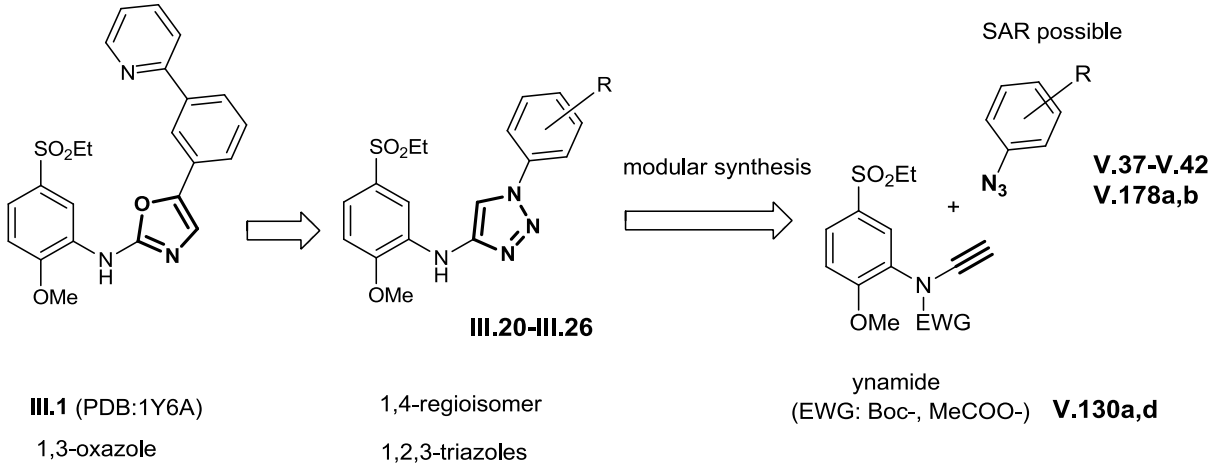


Figure III.11. *Interaction maps of predicted triazoles **III.20** and **III.22** with VEGFR-2 kinase.*

An oxazole / triazole isosteric replacement is an important novel point to determine whether it is possible to develop compounds that have enough affinity to modulate VEGFR2 kinase despite that the triazolic core is much less attracted to VGEFR2 receptor **III.1** binding place compare to the 1,3-oxazolic ring. Weaker affinity was found by *in Silico* predictions and experimentally confirmed by the first enzymatic IC_{50} activity determination. The well designed functional groups on the skeleton of 1,2,3-triazoles could be a compensation of the oxazole / triazol affinity disadvantage. We would call this as a **CRAAC** effect (**C**ore **R**estriction **A**dditive **A**ttraction **C**ompensation). Molecules possessing lower affinity of lead skeleton compensated by functional group interaction can be termed as CRAAC molecules (or spider-like molecules). An advantage of CRAAC molecules rests in development of novel inhibitors possessing skeletons out of the crowded kinase IP space. Other advantage of triazolic CRAAC molecules is their chemical stability, the synthetic feasibility and production of many derivatives by Click chemistry reaction with different azidic fragments.

Chapter 4. **Study towards target ynamides**

Construction of the predicted triazoles can be envisioned to proceed *via* Click cycloaddition of ynamide with different azides. This disconnection is depicted in Scheme IV.1.



Scheme IV.1. *General retrosynthetic approach in order to prepare triazolic analogue of PDB:1Y6A ligand **III.1** via Click chemistry.*

4.1 Literature background of ynamides

In the last decade, the chemistry of ynamides has exploded. In fact, ynamides represent the right balance between reactivity and stability of a nitrogen-atom conjugated to a triple bond and can be employed in a wide spectrum of reactions forbidden so far with the corresponding ynamines.

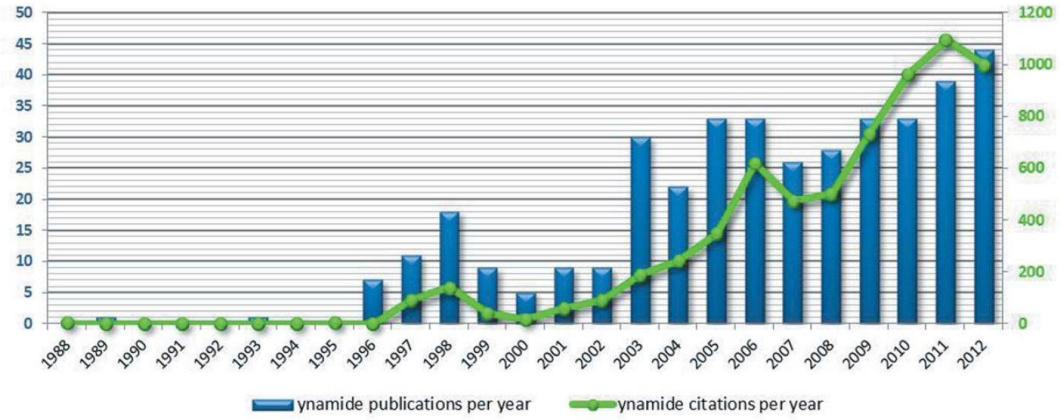


Figure IV.1. *Ynamide publications and citations per year – the "ynamides boom" (source: Web of Science®, 22nd November 2012).*[34]

4.1.1 General characterization

Heteroatom-substituted alkynes probably represent the most versatile class of alkynes. An especially useful subgroup is the one containing a nitrogen atom directly attached to the triple bond: **ynamines** and **ynamides**. The first report on ynamines (Figure IV.2) was published by Bode in 1892.[35]

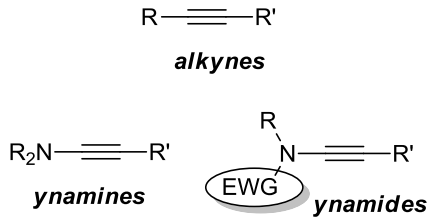
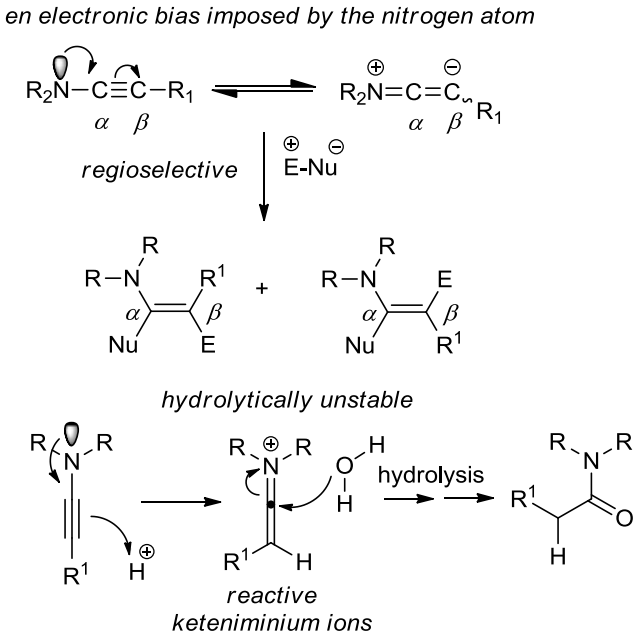


Figure IV.2. *General structure of alkynes, ynamines and ynamides.*

The pioneering characterizations of ynamines were published in 1958 by Zaugg *et al.*[36] and in 1960 by Wolf and Kowitz.[37] In 1963 was reported the first practical synthesis by Viehe.[38] Afterwards, more

[34] Evano, G. ; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17.
[35] Bode, J. *Liebigs Ann. Chem.* **1892**, *267*, 268.

reviews and works about ynamines were published – by Viehe in 1967[39] and 1969[40], Ficini in 1976[41], Pitacco and Valentin in 1979[42], Collard-Motte and Janousek in 1985,[43] and more recently in 1993 by Himbert.[44] Ynamines have limitation in synthetic application because of the difficulty of preparation and handling. Generally, ynamines are readily hydrolyzed due to the ability of the nitrogen atom to push its lone pair to the alkynyl moiety. (Scheme IV.2)



Scheme IV.2. *Reactivity of ynamines and their instability toward hydrolysis.*[45]

Diminishing the electron-donating ability by substituting the nitrogen atom with an electron-withdrawing group (EWG) should improve ynamides stability. The ynamides are in the fact the stable variant of ynamines and are bringing an exciting future to the chemistry of ynamines. (Figure IV.3) During the last 20 years, the chemistry of interesting "push-pull" ynamines was described.

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[36] Zaugg, H. E. ; Swett, L. R. ; Stone, G. R. *J. Org. Chem.* **1958***, 23*, 1389.
[37] Wolf, V. ; Kowitz, F. *Liebigs Ann. Chem.* **1960**, *638*, 33.
[38] Viehe, H. G. *Angew. Chem. Int. Ed.* **1963**, *2*, 477.
[39] Viehe, H. G. *Angew. Chem. Int. Ed.* **1967**, *6*, 767.
[40] Viehe, H. G. *Chemistry of Acetylenes ;* Marcel Dekker: New York, 1969; Chapter 12, pp 861.
[41] Ficini, J. *Tetrahedron* **1976**, *32*, 448.
[42] Pitacco, G. ; Valentin, E. *Enamines, Ynamines.* In : *The Chemistry of Functional Groups ;* Patai, S., John Wiley & Sons: New York, 1979; Chapter 15, pp 623.
[43] Collard-Motte, J. ; Janousek, Z. *Top. Curr. Chem.* **1985**, *130*, 89.
[44] Himbert, G. *Methoden Der Organischen Chemie*, Kropf, H., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1993; pp 3267.
[45] DeKorver, K. A.; Li, H. ; Lohse, A. G. ; Hayashi, R. ; Lu, Z. ; Zhang, Y. ; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

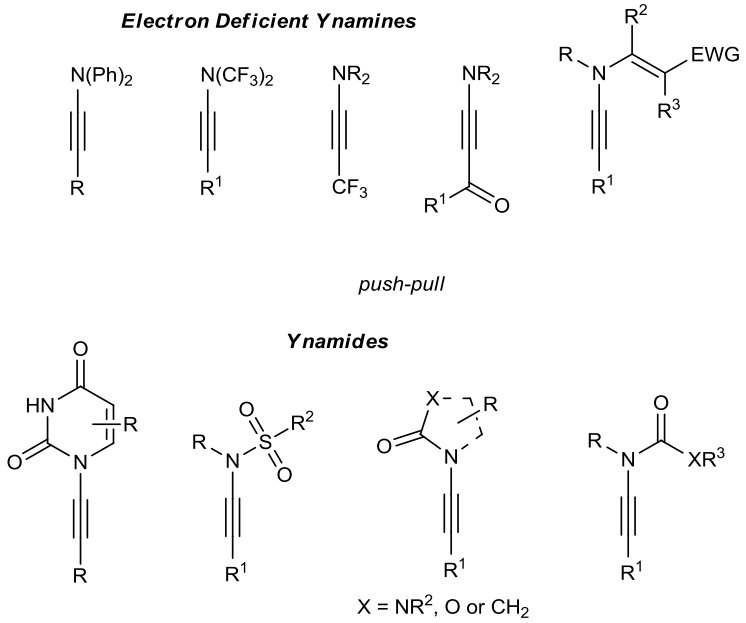
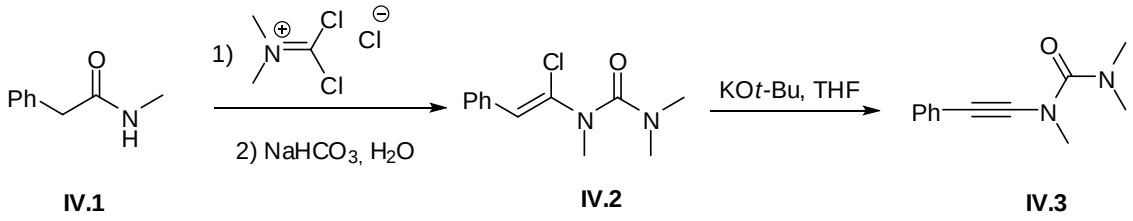


Figure IV.3. *Several types of electron deficient ynamines and ynamides.*[46]

4.1.2 Preparation of ynamides

The very first synthesis of an ynamide was reported in 1972 by Viehe, [47] some fourteen years after the first isolation of a nitrogen-substituted alkyne by Zaugg and co-workers. The synthesis of yne-urea **IV.3** was based on the base-induced elimination of the corresponding α-chloroenamide **IV.2**, itself obtained from reaction of *N*-methyl-2-phenylacetamide (**IV.1**) with an excess of Viehe's salt followed by hydrolysis. (Scheme IV.3)



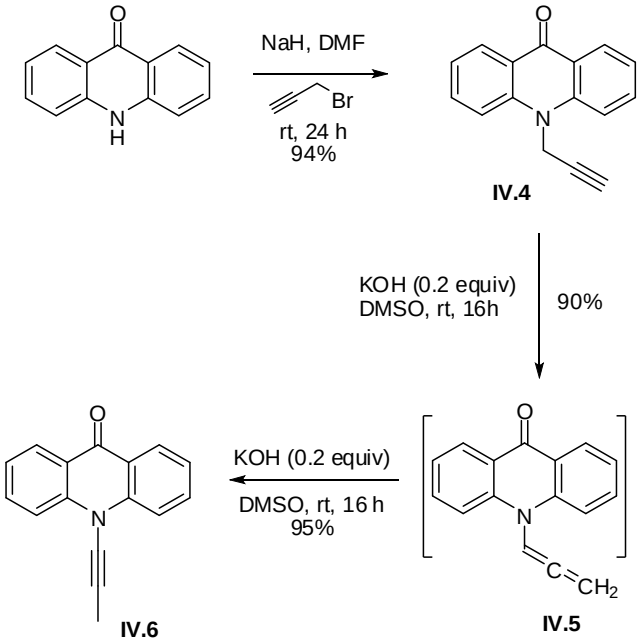
IV.1 **IV.2** **IV.3**

Scheme IV.3. *First ynamide synthesis by Viehe.*[47]

Zaugg's electron-deficient ynamine[36] **IV.6** has been prepared by Galy in 1979. (Scheme IV.4) Subsequently, series of efforts[48,49] for the synthesis of the electron-deficient ynamine **IV.6** *via* base-induced isomerisation protocols have been done. Isomerisation of the propargyl amine **IV.5** to

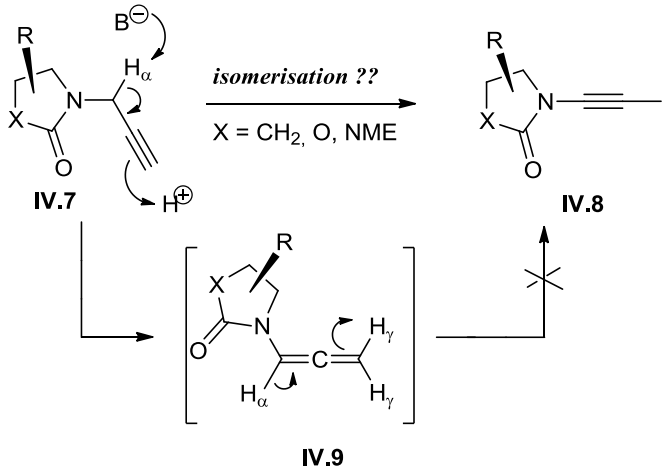
[46] Mulder, J. A., Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, *10*, 1379.
[47] Janousek, Z. ; Collard, J. ; Viehe, H. G. *Angew. Chem. Int. Ed.* **1972**, *11*, 917.
[48] Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.
[49] Majumdar, K. C.; Ghosh, S. K. *Synth. Commun.* **1994**, *24*, 217.

isomeric ynamine **IV.6** *via* an intermediate allenamine **IV.5** was accomplished in 80 % overall yield using 20 mol % of KOH in DMSO.[50]



Scheme IV.4. *Preparation of electron-deficient ynamine **IV.6** via base-induced isomerisation.*[36]

Hsung and co-workers[51] tried a base-induced isomerisation of propargyl amides **IV.7**. They observed that desired ynamides **IV.8** were not formed because the isomerisation was stopped at the allenic intermediates. (Scheme IV.5)

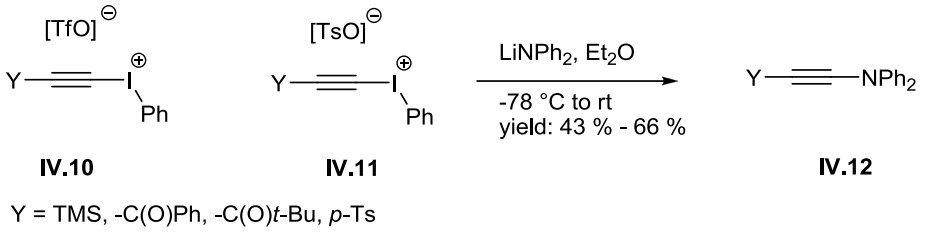


Scheme IV.5. *Failed attempt to get ynamide **IV.8** via base-promoted isomerisation.*[51]

In 1994, Zhdankin and Stang developed a new method for the synthesis of ynamines that involved reactions of alkynyl iodonium triflate salts[52,53] **IV.10** or tosylate salts[54,55] **IV.11** with lithium

[50] Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903.
[51] Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.;Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

amides. A variety of ynamines **IV.12** (Scheme IV.6) were thereby prepared. This alkyne formation is believed to proceed *via* β-addition to the iodine to generate iodobenzene and a vinyl carbene, which then undergoes a 1,2- shift to form the acetylide.[52,53]



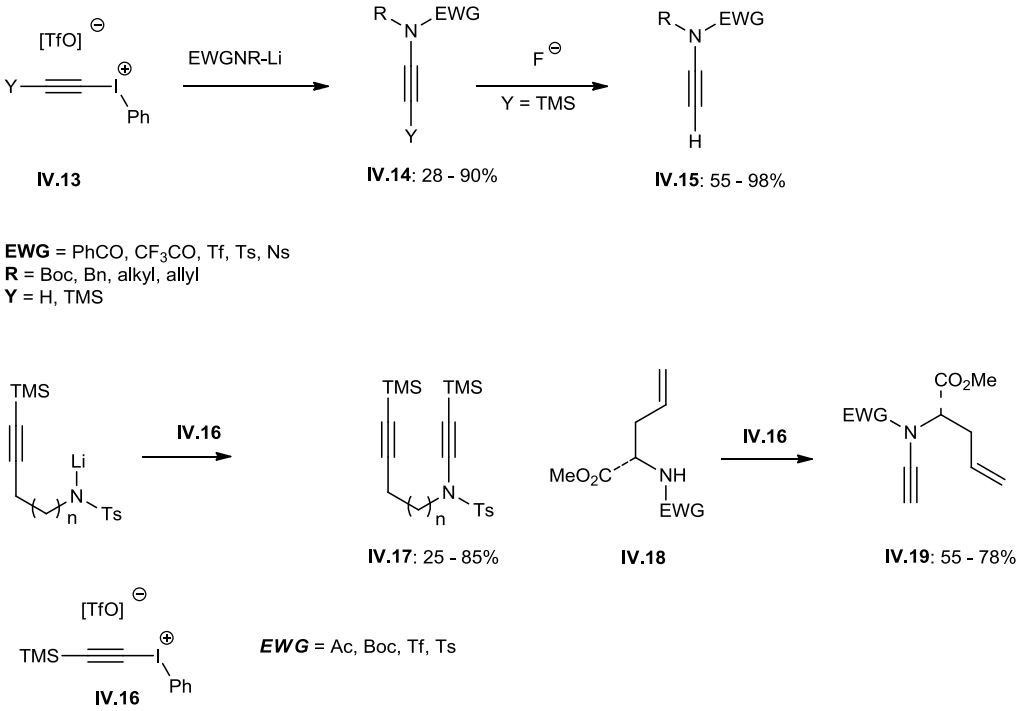
IV.10 **IV.11** **IV.12**

Y = TMS, -C(O)Ph, -C(O)*t*-Bu, *p*-Ts

Scheme IV.6. *Preparation of ynamines **IV.12** using alkynyl iodonium triflate salts **IV.10** and tosylate salts **IV.11** with lithium amides.*[52,53,54 ,55]

This new methodology led to an exciting expansion in chemistry of ynamides. Both the Witulski[56,57,58,59,60] and Rainier[61,62] working groups utilized alkynyl iodonium triflate salt **IV.13** and **IV.16** in reactions with various amides to prepare ynamides such as **IV.14** and **IV.15**, diyne ynamides **IV.17**, and enyne ynamides **IV.19**. (Scheme IV.7)

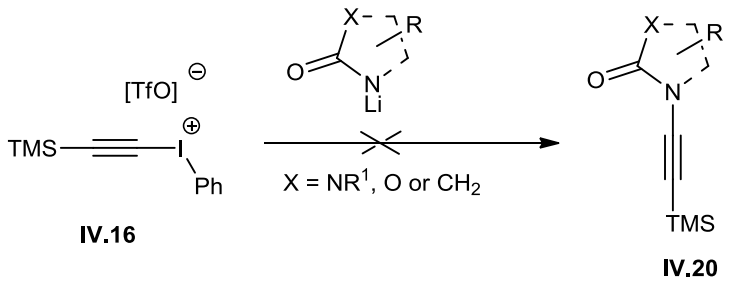
[52] Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**,1255.
[53] Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927.
[54] Kitamura, T.; Tashi, N.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 3787.
[55] Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y. *Heterocycles* **2000**, *52*, 303.
[56] Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489.
[57] Witulski, B.; Gößmann, M. *Synlett* **2000**, 1793.
[58] Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *38*, 2426.
[59] Witulski, B.; Stengel, T.; Fernandez-Hernandez, J.M. *Chem. Commun.* **2000**, 1965.
[60] Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281.
[61] Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272.
[62] Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037.



Scheme IV.7. *Preparation of various types of ynamides **IV.14, IV.15, IV.17, IV.19** using alkynyl iodonium salts **IV.14** and **IV.16** by Witulski and Rainer.*[56-62]

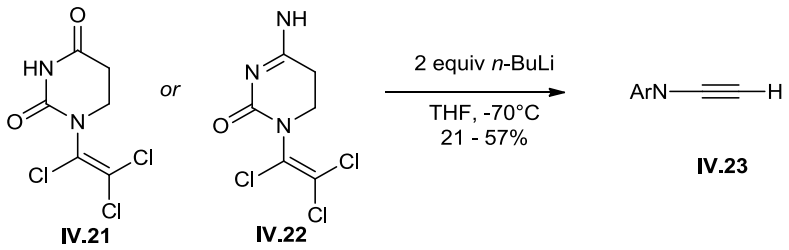
Particularly, Witulski[56,57] was able to prepare ynamides **IV.14** where, desilylation using tetra-*n*-butyl ammonium fluoride (TBAF) yielded the terminally unsubstituted sulfonyl substituted ynamides **IV.15**.

Hsung *et al.*[46] presented in their review the limitation of using iodonium triflate salt **IV.16**. It was not possible to carry out the prudent transformation toward ynamide **IV.20** using lithiated lactams, imidazolidinones or oxazolidinones. (Scheme IV.8) They concluded that the alkynyl iodonium salt protocol could be best applicable for sulfonamides.



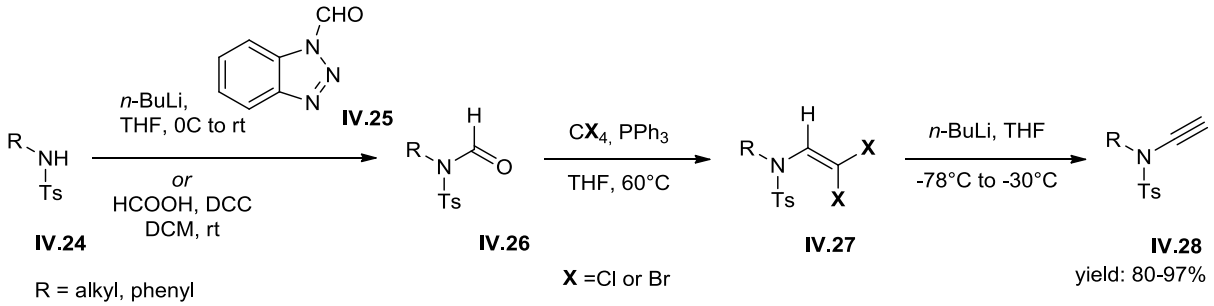
Scheme IV.8. *Unsuccessful attempts to prepare ynamide of **IV.20** using iodonium triflate salt **IV.16**.*[46]

Zemlicka[63] had prepared numerous ynamides **IV.23** as shown in Scheme IV.9 *via* lithium–halogen exchange. Treatment of trichloro enamides **IV.21** or **IV.22** with *n*-BuLi at low temperature afforded the ynamines **IV.23** in 21–57% yields.



Scheme IV.9. *Preparation of ynamides **IV.23** via lithium-halogen exchange by Zemlicka*.[63]

In 2000, Brückner[64,65] also confirmed the potential of such a promising protocol in his preparation of ynamides **IV.28** from corresponding fomamides **IV.26**. (Scheme IV.10) The benefits of this method include its amenability to scale-up and the avoidance of potentially explosive alkynyl iodonium triflate salts.

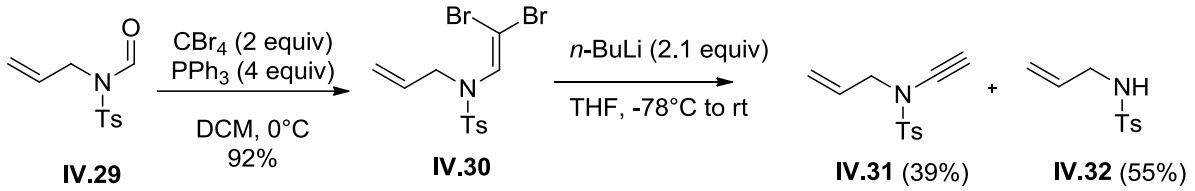


Scheme IV.10. *Preparation of ynamides **IV.28** from formamides **IV.26** via lithium-halogen exchange by Brückner.*[64,65]

Formamides **IV.26** were prepared from *N*-tosyl-amines *via* deprotonation and treatment with formyl benzotriazole, or DCC coupling with formic acid. (Scheme IV.10) The formation of the 1,1-dihaloolefins **IV.27** *via* phosphine-dihalogenoethylenes was originally discovered by Desai and McKelvie.[66] The second step using a lithium base (*n*-BuLi, LDA) generates a haloalkyne intermediate *via* dehydrohalogenation, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne **IV.28** upon a work-up. (Scheme IV.10)

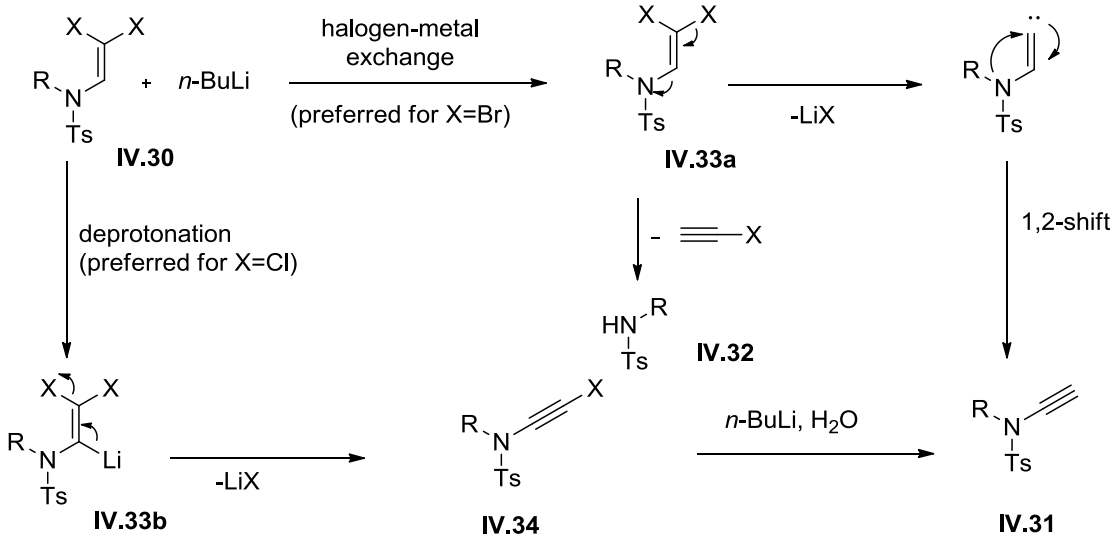
[63] Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans.1* **1994**, 1089.
[64] Brückner, D. *Synlett* **2000**, 1402.
[65] Brückner,D. *Tetrahedron* **2006**, *62*, 3809.
[66] Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

Reaction of **IV.29** with triphenylphosphine and CBr_4 afforded the dibromoenamide **IV.30** in very good yield. However, the following step—treatment with *n*-butyllithium—resulted in a mixture of the desired ynamide **IV.31** and tosylamide **IV.32**. (Scheme IV.11)



Scheme IV.11. *Synthesis of ynamide **IV.31** via dibromovinylamides **IV.30**.*[65]

A possible explanation of this result is given in Scheme IV.12. The initial bromo–lithium exchange leading to **IV.33a** is followed by two competing eliminations, that of lithiumbromide or of bromoacetylene, respectively, resulting in a mixture of **IV.31** and **IV.32**. But a second reaction sequence is conceivable as well. If the initial step is a deprotonation, intermediate **IV.33b** should be formed and an elimination of lithium halogenide should follow leading to the triple bond formation. A cleavage of the C–N bond appears to be unlikely here. The chlorine-lithium exchange is significantly slower.

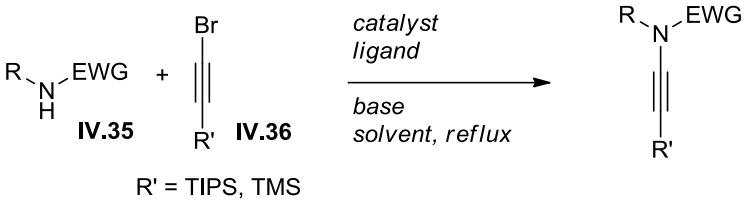


Scheme IV.12. *Proposed mechanism of the reaction of dihalovinylamide **IV.30** with n-BuLi.*[65]

N-alkynylation of amines **IV.35** *via* direct C-N bond-formation using bromoalkynes **IV.36**[67] represents a facile route to synthesis of ynamides, extensively utilized in medicinal chemistry. (Scheme IV.13) Despite significant improvements in the palladium-catalyzed *N*-arylation of amines,[68,69,70] some limitations still remain: the high cost of palladium species, removal of palladium

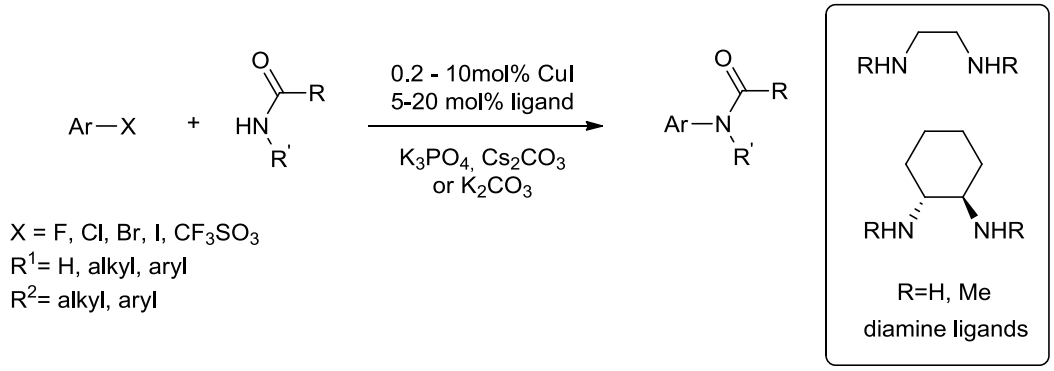
[67] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
[68] Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805.

residues from reaction products, particularly in the late stages of the synthesis of a pharmaceutical substances. Applications of Ullman reaction[71,72]and Goldberg reaction[73] are very well documented, but still not enough developed (*e.g.* the necessity to use high temperatures, highly polar solvents, large amount of copper reagent…).



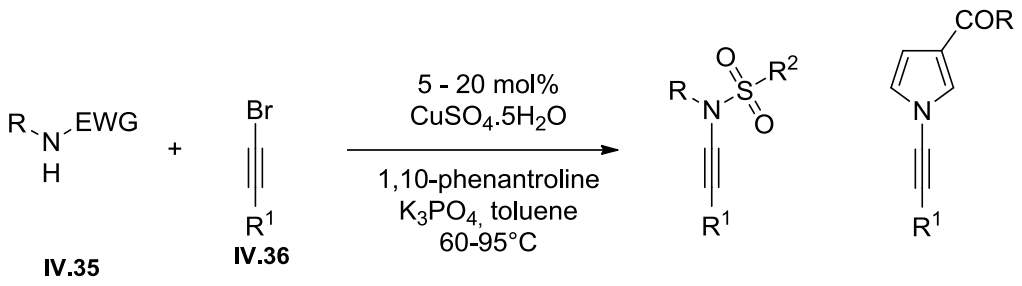
Scheme IV.13. *General example of N-direct alkynylation of amide **IV.35**.*

Inspired by Buchwald's copper-catalyzed *N*-arylations of amides,[74] practical cross-coupling was developed using copper salts ($CuSO_4$. $5H_2O$,[75] CuI, Cu_2O, $Cu(OAc)_2$) or simple copper powder. (Scheme IV.14, Scheme IV.15)



Scheme IV.14. *General Buchwald's copper-catalyzed N-arylations of amides.*[74]

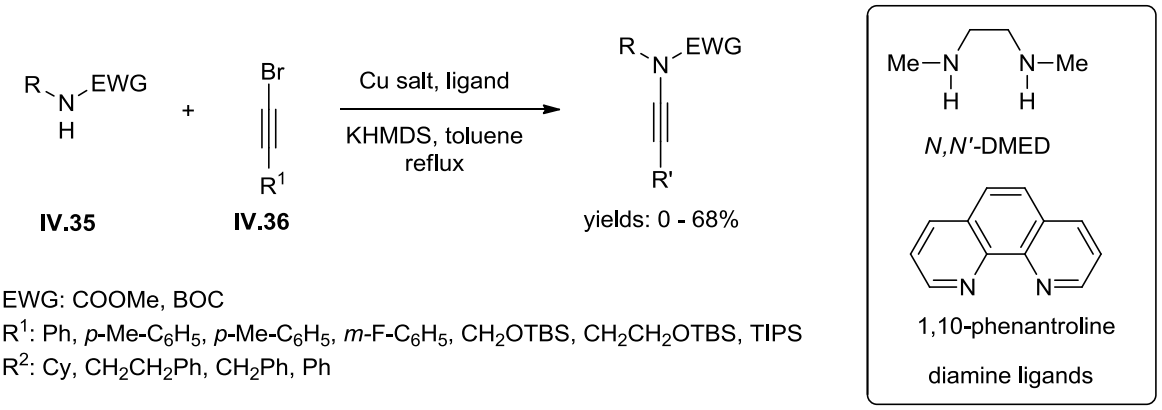
[69] Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046.
[70] Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
[71] Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382.
[72] Gauthier, S.; Fréchet, J. M. J. *Synthesis* **1987**, 383.
[73] Freeman, H. S.; Butler, J. R.; Freedman, L. D. *J. Org. Chem.* **1978**, *43*, 4975.
[74] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
[75] Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.



R: Ph, TIPS, $(CH_2)_4OTBS$, Me, H
R_1: Bn, $PhCH_2CH_2$, $CH_2CH{=}CH_2$, CH_2CH_2OTBS
R_2: Ph, 2-MeO-Ph, *n*-hex, $CH_2OTBDPS$, TIPS, Ph, Me, tolyl

Scheme IV.15. *Preparation of ynamides using the Hsung's protocol.*[75]

In 1996 Tam[76] significantly improved the yield of ynamides by using modified reaction conditions (0.2–0.3 equiv of CuI, 0.22–0.36 mol equiv of 1,10-phenanthroline (ligand), and adding 1.2 equiv of the base KHMDS slowly over 3–4 h in toluene at 90 °C. (Scheme IV.16)

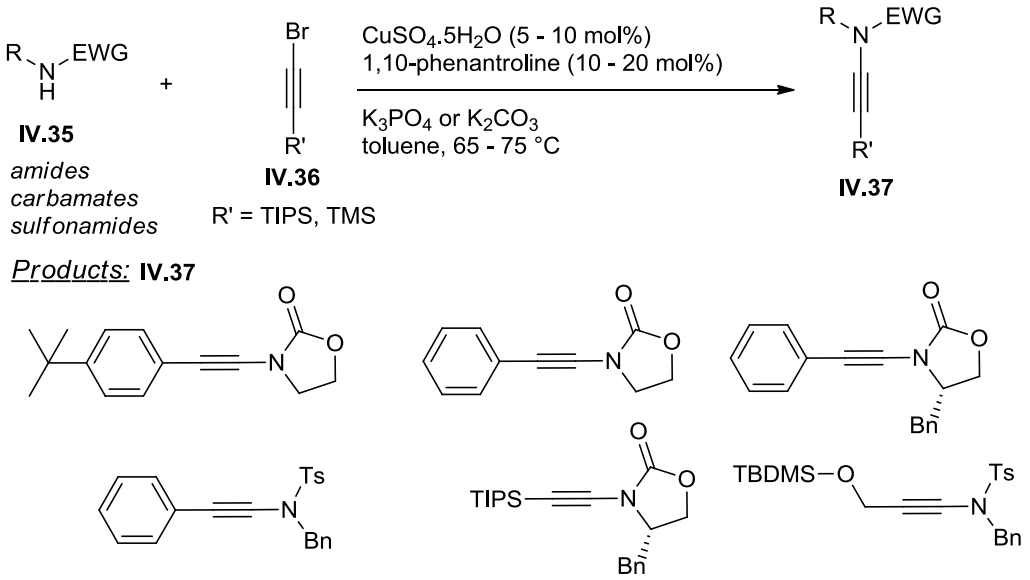


EWG: COOMe, BOC
R^1: Ph, *p*-Me-C_6H_5, *p*-Me-C_6H_5, *m*-F-C_6H_5, CH_2OTBS, CH_2CH_2OTBS, TIPS
R^2: Cy, CH_2CH_2Ph, CH_2Ph, Ph

Scheme IV.16. *Direct N-alkynylation performed by the group of Tam.*[76]

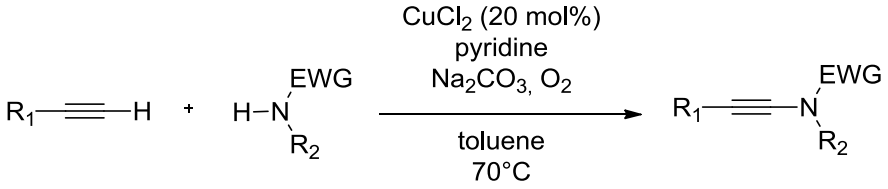
In 2008 Skrydstrup *et al.*[77] published a second generation of the Hsung's protocol. (Scheme IV.17) Potassium phosphate or potassium carbonate was used as mild base substituents of KHMDS. The yields of ynamides **IV.37** depend on the quality of K_3PO_4 used as base. Pure anhydrous K_3PO_4 provides higher ynamides yields (52 – 91 %) in comparison to samples contaminated with hydrates.

[76] Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62*, 3823.
[77] Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T.*J. Org. Chem.* **2008**, *73*, 9447.



Scheme IV.17. *The Hsung's second generation protocol.*[77]

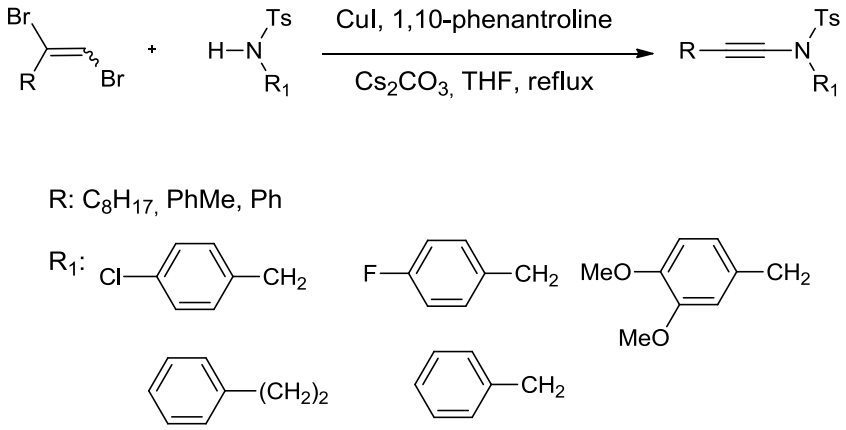
In 2008, the direct aerobic amination of alkynes was reported by the Stahl group[78] inspired on two early works of Peterson[79] and Balsamo and Domiano.[80] They developed an efficient catalytic system based on copper(II) chloride in combination with pyridine, sodium carbonate, and oxygen as the terminal oxidant in toluene at 70 °C to accomplish the direct cross-coupling between terminal alkynes and oxazolidinones, lactams, imidazolidinones *etc*. (Scheme IV.18)



Scheme IV.18. *Synthesis of ynamides by copper-catalyzed oxidative amination of terminal alkynes.*[78]

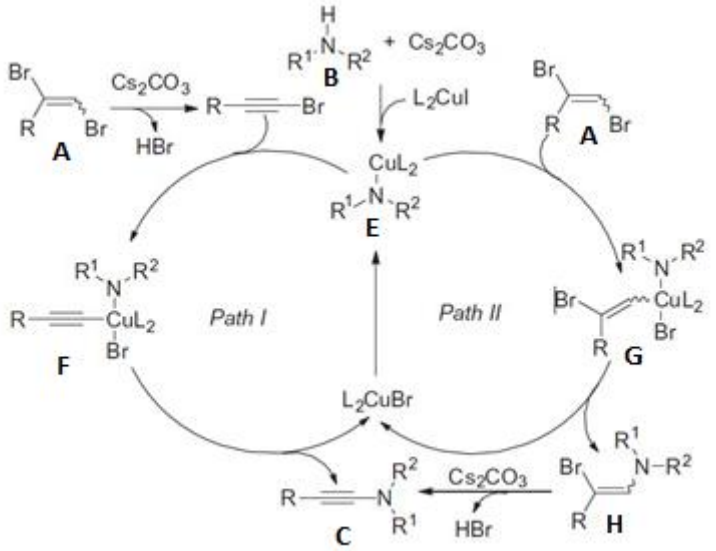
In 2009, Evano's group[81] and three years later Liang's group[82] published another efficient preparation of ynamides through copper-catalyzed coupling reaction. In the presence of copper iodide, 1,10-phenanthroline, and Cs_2CO_3. Coupling reaction of 1,2-dibromo-1-styrenes with sulfonamides proceeded smoothly and generated the corresponding products with excellent isolated yields. (Scheme IV.19)

[78] Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.
[79] Peterson, L. I.; Britton, E. C. *Tetrahedron Lett.* **1968**, *9*, 5357.
[80] Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Domiano, P. *Tetrahedron Lett.* **1985**, *26*, 4141.
[81] Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381.
[82] Yang, Y.; Zhang, X.; Liang,Y. *Tetrahedron Lett.* **2012**, *53*, 6557.



Scheme IV.19. *Copper-catalyzed coupling of 1,2-dibromo-1-styrenes with sulfonamides for ynamides preparation.*[82]

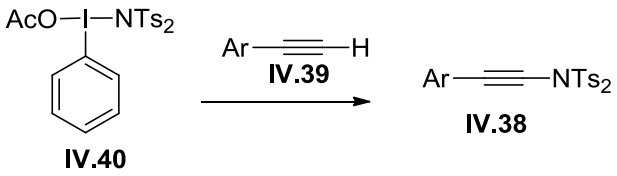
A proposed catalytic cycle for the formation of ynamides **C** from **A** and **B** is given in Scheme IV.20. First, dehydrobromination of the starting 1,2-dibromo-1-alkenes **A** would generate intermediate alkynyl bromides. Then, oxidative addition of **E** to the alkynyl bromides presumably generates a copper(III) intermediate **F**. Finally, reductive elimination of **F** would furnish the desired ynamides and regenerate the active Cu(I) species for the catalytic cycle (Path I). According to Evano's work,[81] another mechanism involving the formation of β-bromoenamide by amination of the starting 1,2-dibromo-1-alkenes **A** and its subsequent dehydrobromination to form ynamides could also account for the formation of ynamides **C** from 1,2-dibromo-1-alkenes **A**.



Scheme IV.20. *A proposed catalytic cycle for the formation of ynamides.*[81,82]

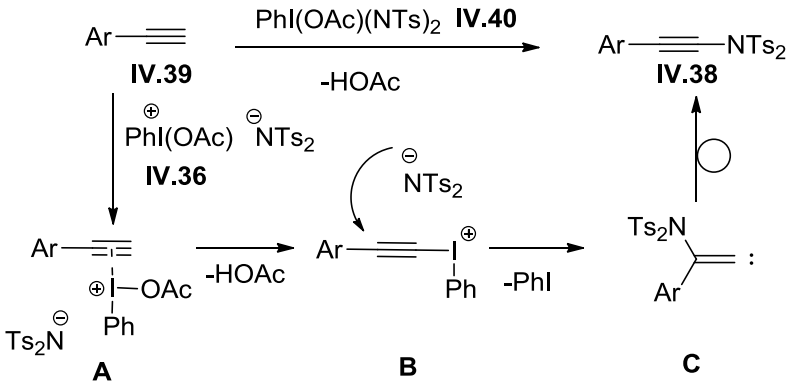
In 2012, a direct metal-free amination of arylalkynes leading to ynamide **IV.38** has been developed, which proceeds by reaction of the terminal alkyne **IV.39** with the hypervalent iodine

reagent PhI(OAc)NTs_2 **IV.40** within a single-step operation.[83] (Scheme IV.21) This unprecedented intermolecular C–H to C–N bond conversion provides rapid access to the important class of ynamides.



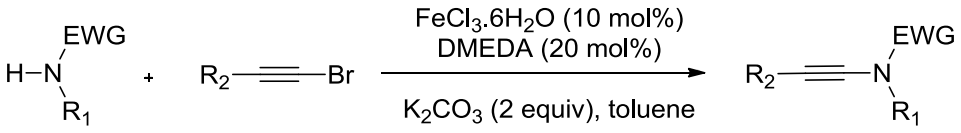
Scheme IV.21. *Direct metal-free amination of arylalkynes **IV.39** published by Muniz et al.*[83]

A rational was proposed based on literature precedents and started from dissociation of reagent **IV.40** followed by reversible coordination of the electrophilic iodine(III) to the aryl acetylene **IV.39**. The resulting complex **A** further acidifies the alkyne C–H bond, leading to internal deprotonation and loss of acetic acid to form a σ- alkynyl iodine(III) **B**.[83] (Scheme IV.22)



Scheme IV.22. *The reaction mechanism proposal of metal-free amination of arylalkynes **IV.39** using hypervalent iodine reagent PhI(OAc)NTs_2 (**IV.40**)*.[83]

Another alternative in order to obtain ynamides in high yields was described by Zhang *et al.* in 2009.[84] The products were achieved through the iron catalyzed C-N coupling reaction of amides with alkynyl bromides in the presence of 20 mol % of *N*,*N*'-dimethylethane- 1,2-diamine (DMEDA). (Scheme IV.23)



R_2: Aryl, Alkyl, TIPS, CH_2OH

Scheme IV.23. *The iron catalyzed C-N coupling of amides with alkynyl bromides.*[84]

[83] Souto, J. A.; Becker, P.; Iglesias, A.; Muniz, K. *J. Am. Chem. Soc.* **2012**, 2497.
[84] Yao, B.; Liang, Z.; Niu, T. ; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630.

4.1.3 Reactivity and synthetical utilization of ynamides

During the last decade, the number of publications dealing with the use of ynamides has increased exponentially. In the next chapter, some synthetic applications of ynamides will be shown. The general reactivity of ynamides is depicted in Figure IV.4. The classification of the addition reactions is based on the first substituent introduced on the ynamide. There is also a possible chelation of the reagent with the electron-withdrawing groups (*vide infra*).[85]

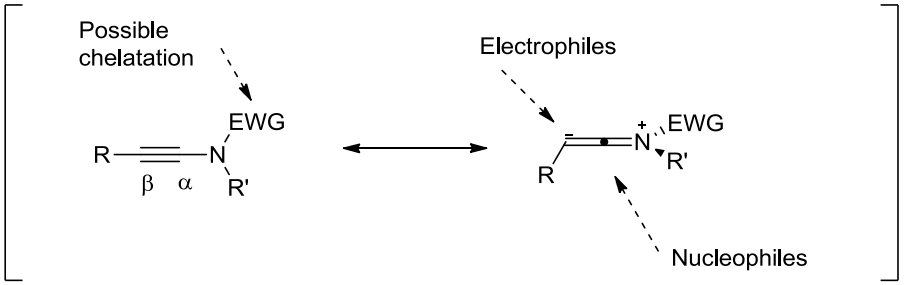
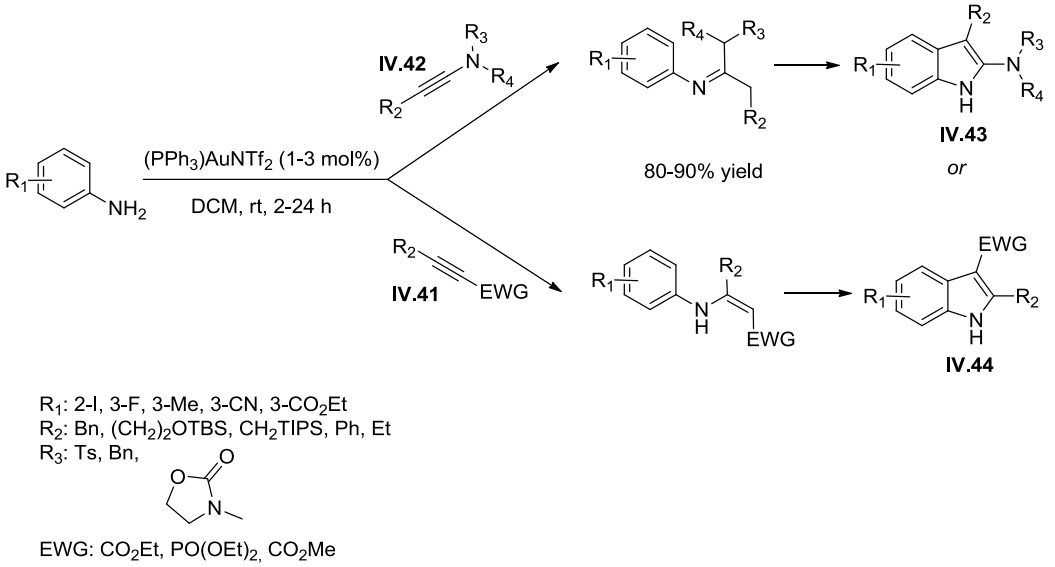


Figure IV.4. *General reactivity of ynamides.*[97]

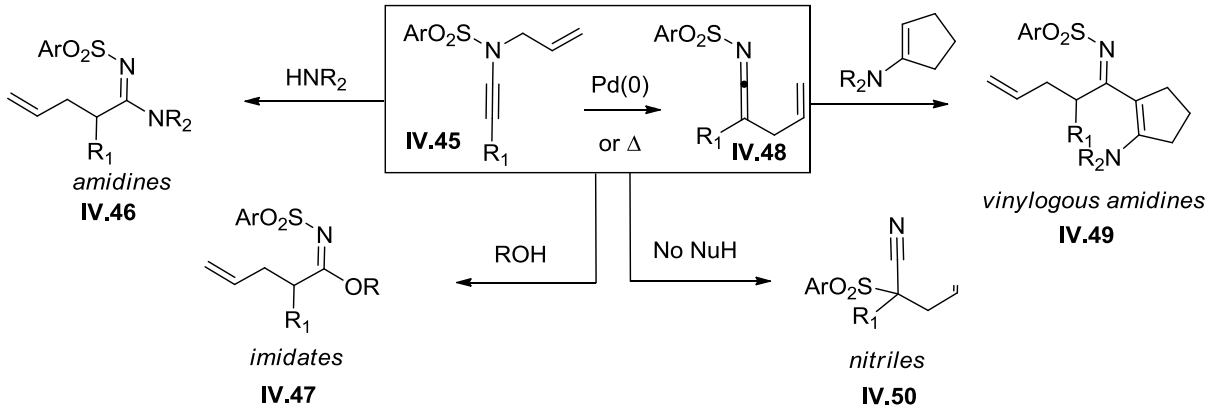
In 2009, Skrydstrup *et al.*[86] published a highly regioselective hydroamination of unsymmetrical electron-poor **VI.41** and electron-rich **VI.42** alkynes with anilines catalyzed by Au(I) under mild conditions leading to indoles (**IV.43**, **IV.44**). (Scheme IV.24)



Scheme IV.24. *Regioselective Au(I)-catalyzed hydroamination of alkynes (**IV.41**, **IV.42**) with anilines.*[86]

[85] Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *10*, 2840.
[86] Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottlander, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

A detailed study of amidine **IV.46** or vinylogous amidine **IV.49** synthesis from *N*-allyl-*N*-sulfonyl ynamides **IV.45** has been described by Hsung and Zhang group.[87] (Scheme IV.25) This reaction is consisting of diverging pathways that could lead to deallylation or allyl transfer depending on the oxidation state of palladium catalysts, the nucleophilicity of amines, and the nature of the ligands. It essentially constitutes a Pd(0)-catalyzed aza-Claisen rearrangement of *N*-allyl ynamides leading to ketenimine **IV.48**, which can also be accomplished thermally. An observation of *N*-to-C 1,3-sulfonyl shift was made when examining these aza-Claisen rearrangements thermally. This represents a useful approach to nitrile synthesis **IV.50**. While attempts to render this 1,3-sulfonyl shift stereoselective failed, they covered another set of tandem sigmatropic rearrangements, leading to vinyl imidate **IV.47** formation. This work shows cases of the rich array of chemistry one can discover using these ynamides.

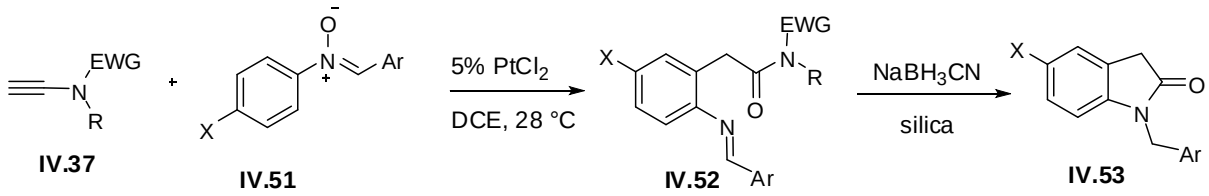


Scheme IV.25. *N-Allyl-N-sulfonyl ynamides **IV.45** as synthetic precursors to amidines (**IV.46**) and vinylogous amidines (**IV.49**).*[87]

In 2012, Liu *et al.* published a new platinum-catalyzed oxoarylation of ynamides **IV.35** with nitrones **IV.51**.[88] Cascade sequences for the synthesis of indolin-2-ones **IV.53** *via in situ* $NaBH_3CN$ reduction of the initially formed oxoarylation products **IV.52** were also developed. (Scheme IV.26)

[87] DeKorver, K.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092.

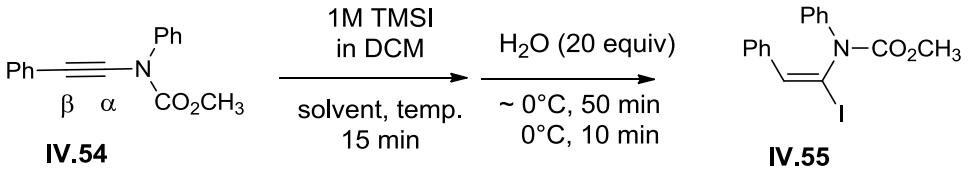
[88] Bhunia, S.; Chang, C.-J.; Liu, R.-S. *Org. Lett.* **2012**, *14,* 5522.



EWG = Ms, Ts
X = F, Cl, Me, MeO

Scheme IV.26. *Platinum-catalyzed oxoarylations of ynamides **IV.35** with nitrones **IV.51**.*[88]

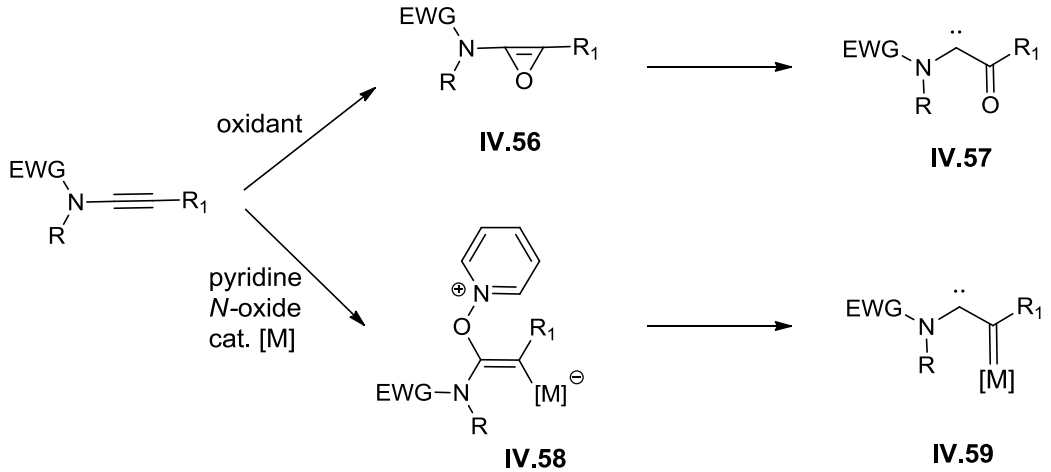
A facile approach to *(E)*-α-haloenamide moieties **IV.55** from ynamides **IV.54** using bromo- or iodotrimethylsilane was described by Iwasawa *et al*.[89] The simple protocol enables a regio- and stereospecific hydrohalogenation of the triple bond in gram-scale and provides a general entry for synthesis of novel enamide analogues. (Scheme IV.27)



Scheme IV.27. *Synthesis of (E)-α-iodoenamide **IV.55** from ynamide **IV.54** via iodotrimethylsilane-mediated hydroiodation.*[89]

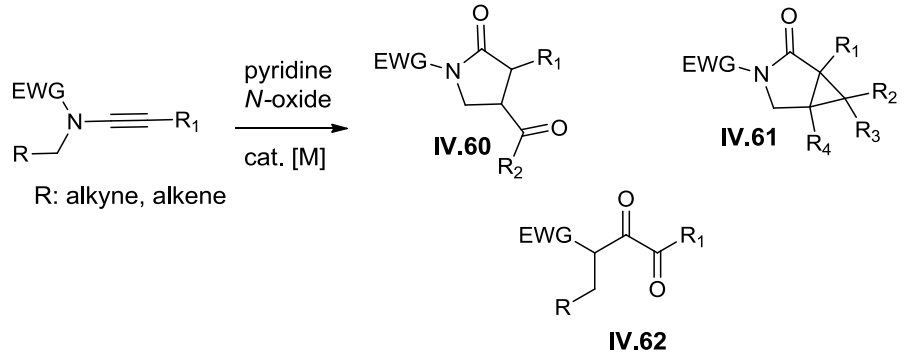
In 2013, generation of Rh(I)-carbenes from readily available ynamides **IV.37** has been described.[90] Oxidation of ynamides by dimethyl dioxirane (DMDO) or other oxidants was shown to afford the push−pull α-oxo carbenes **IV.57** through oxirene intermediates **IV.56**. Interestingly, complementary α-oxo gold carbenes **IV.59** (M = Au) were formed via intermediates **IV.58** in the presence of gold catalysts and mild external oxidants (*e.g*. pyridine *N*-oxide). (Scheme IV.28)

[89] Sato, A. H.; Ohashi, K.; Iwasawa, T. *Tetrahedron Lett.* **2013**, *54*, 1309.
[90] Liu, R.; Winston-McPherson, G. N.; Yang, Z.-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 8201.



Scheme IV.28. *Complementary carbenes from ynamides **IV.37**.*[90]

It was envisioned that the choice of metal catalyst and ligand would have a significant impact on the reactivity of carbene **IV.59**. It was reported that α-oxo Rh(I) carbenes **IV.59** (M = Rh) can be generated from ynamides and then react with the tethered alkyne or alkene to afford heterocycles **IV.60** and **IV.61**, respectively. In contrast, keto imide **IV.62** was often the predominant product observed by the authors and others in the presence of gold(I) catalysts.(Scheme IV.29)

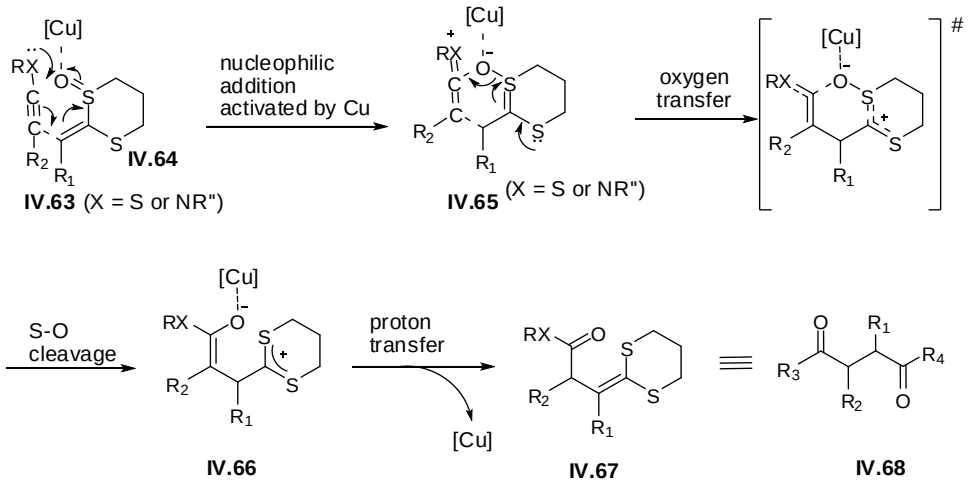


Scheme IV.29. *Reactivity of Rh(I)-generated carbenes from ynamides.*[90]

The first examples of metal-catalyzed extended Pummerer reactions through the activation of sulfoxides have been described recently.[91] (Scheme IV.30) The copper-catalyzed reactions of ketene dithioacetal monoxides **IV.64** with alkynyl sulfides and ynamides (**IV.63**) provided a wide

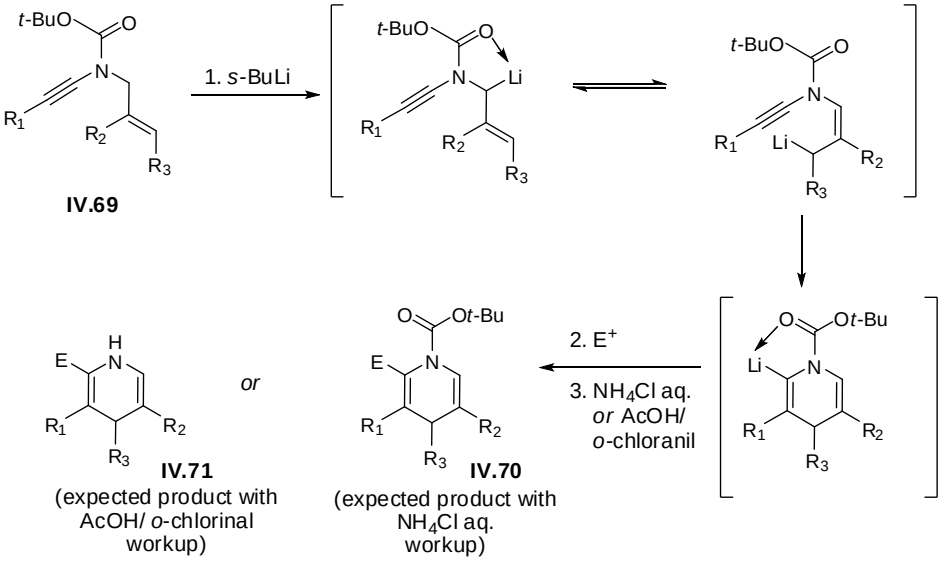
[91] Murakami,K.; Imoto, J.; Matsubara, H.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2013**, *19*, 5625.

variety of γ,γ-disulfanyl-β,γ-unsaturated carbonyl compounds **IV.67** with an accompanying oxygen rearrangement. The products were easily converted into 1,4-dicarbonyl compounds **IV.68** and substituted heteroaromatics.



Scheme IV.30. *Proposed mechanism for the copper-catalyzed Pummerer reactions with alkynyl sulfides and ynamides* ***IV.63***.[91]

In 2012, Evano's group published a full paper,[92] which described a general synthesis of polysubstituted 1,4-dihydropyridines and pyridines (**IV.70**, **IV.71**) based on a highly regioselective lithiation/ intramolecular carbolithiation from readily available *N*-allyl-ynamides **IV.69**. (Scheme IV.31)

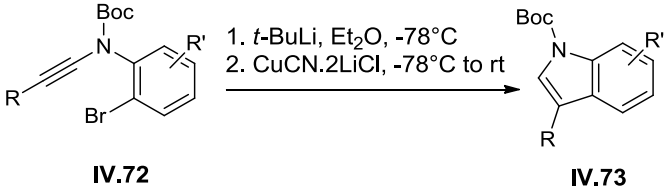


Scheme IV.31. *Strategy for the synthesis of (1,4-dihydro)pyridines* (**IV.70**, **IV.71**) *by deprotonation/intramolecular carbolithiation.*[92]

[92] Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012,** *8,* 2214.

This reaction, which has been successfully applied to the formal synthesis of the anti dyskinesia agent Sarizotan, extended the use of ynamides in organic synthesis and further demonstrated the synthetic efficiency of carbometallation reactions.

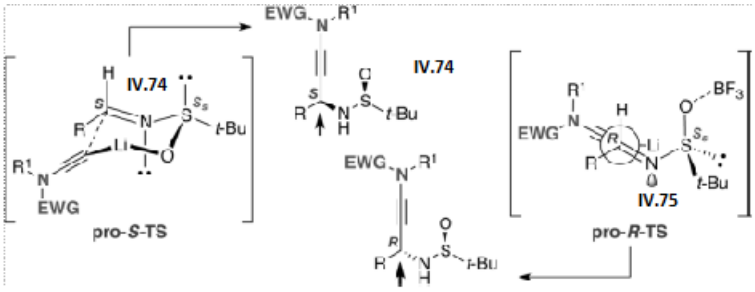
In 2013 Evano's group reported a modular indole synthesis based on an intramolecular carbocupration starting from readily available *N*-aryl-ynamides **IV.72**.[93] (IV.32) A variety of ynamides were converted to indoles **IV.73** in moderate to good yields and with varying substitution pattern on the indole ring. This further extends the synthetic utility of ynamides in organic synthesis and provides additional insights on the use of intramolecular carbometalation reactions.



IV.72 **IV.73**

Scheme IV.32. *Intramolecular carbocupration of N-Aryl-ynamides (**IV.72**) - modular indole synthesis.*[93]

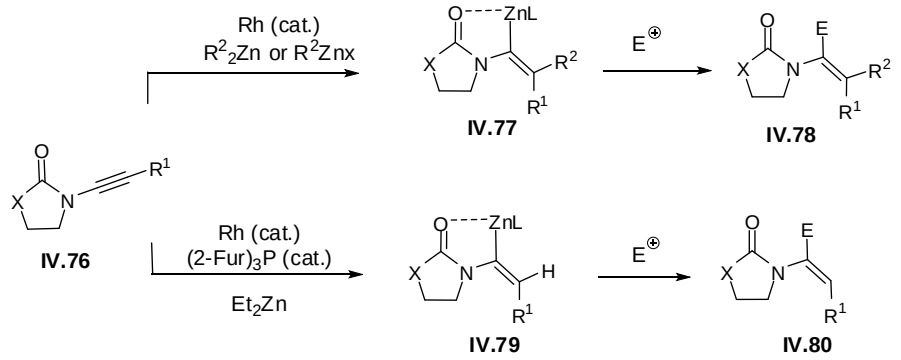
Hsung *et al.*[94] described a highly diastereoselective addition of lithiated ynamides to Ellman-Davis chiral imines **IV.74**. (Scheme IV.33) While additions of *N*-sulfonyl ynamides deliver ynamides **IV.75** with high enantioselectivity even without Lewis acids, the use of BF_3-OEt_2 completely reversed the stereoselectivity. In addition, oxazolidinone-substituted ynamides behaved differently and functioned better with BF_3-OEt_2, chirality of the oxazolidinone ring exerting no impact on the selectivity.



Scheme IV.33. *A highly diastereoselective addition of lithiated ynamides to Ellman-Davis chiral imines **IV.74**.*[94]

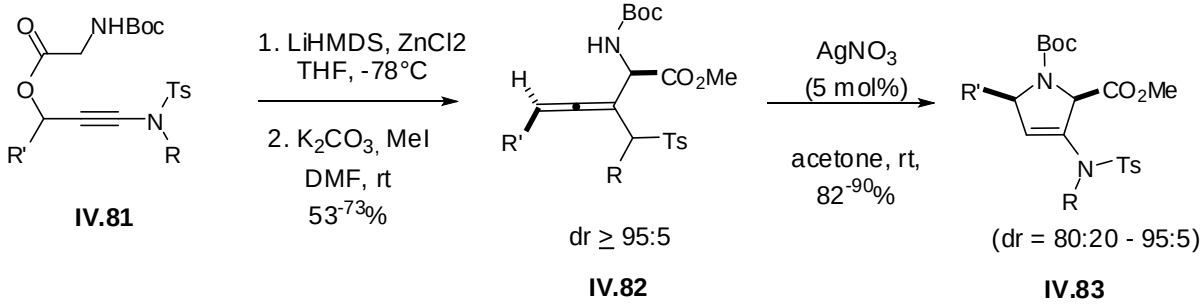
[93] Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013**, *15,* 3122.
[94] Wang, X.-N.; Hsung, R. P.; Qi, R.; Fox, S. K.; Lv, M. C. *Org. Lett.* **2013**, *15,* 2514.

In 2009, Lam *et al.*[95] described rhodium-catalyzed carbozincation of ynamides **IV.76** using diorganozinc reagents or functionalized organozinc halides. (Scheme IV.34) Using a tri-(2-furyl)phosphine-modified rhodium catalyst, the reaction course is altered to hydrozincation when diethylzinc is employed as the organozinc reagent. Trapping of the alkenylzinc intermediates (**IV.77**, **IV.79**) is possible. Collectively, these processes enable access to a range of multisubstituted enamides in regiocontrolled fashion (**IV.78**, **IV.80**).



Scheme IV.34. *Preparation of multisubstituted enamides via rhodium-catalyzed carbozincation and hydrozincation of ynamides **IV.76**.*[95]

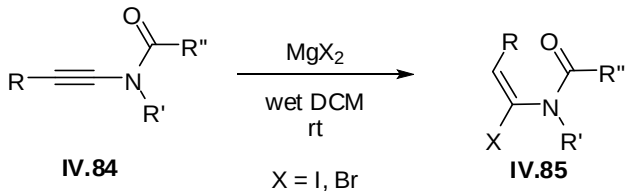
In 2013, the Claisen rearrangement of *N*-Boc glycinates **IV.81** derived from ynamido-alcohols was published and afforded an efficient and stereoselective access to highly functionalized allenamides **IV.82**.[96] (Scheme IV.35) These compounds undergo silver-catalyzed cyclization to 3-pyrrolines which are useful precursors for the synthesis of substituted pyrrolidines **IV.83**.



Scheme IV.35. *Synthesis of functionalized allenamides **IV.82** from ynamides **IV.81** by enolate Claisen rearrangement.*[96]

[95] Gourdet, B.; Rudkin, M. E.; Watts, C. A.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 7849.
[96] Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2013**, *15,* 1626.

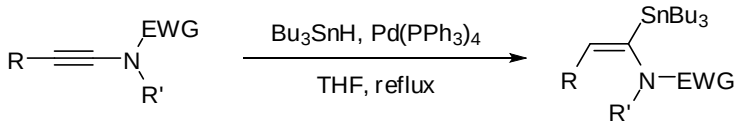
In 2003, Hsung and co-workers[97] published a stereoselective hydrohalogenation of ynamides **IV.84** with $MgBr_2$ or MgI_2 in wet dichloromethane affording enamides **IV.85**. (Scheme IV.35) This hydrohalogenation was obtained in excellent yield and good selectivity. The presence of water was necessary, due to *in situ* generation of HBr or HI from magnesium salt and water.



IV.84 **IV.85**

Scheme IV.36. *Stereoselective hydrohalogenation of ynamides **IV.84**.*[97]

The second example of α-addition of ynamides is hydrostannylation. Ynamides are very good substrates for transition-metal-catalyzed transformations due to their polarization by the nitrogen atom and the possible chelation with the electron-withdrawing group. Based on these facts, Buissonneaud and Cintrat[98] published a highly regiocontrolled synthesis of α-stannyl-enamides **IV.87** by hydrostannylation of ynamides **IV.86**. (Scheme IV.36)

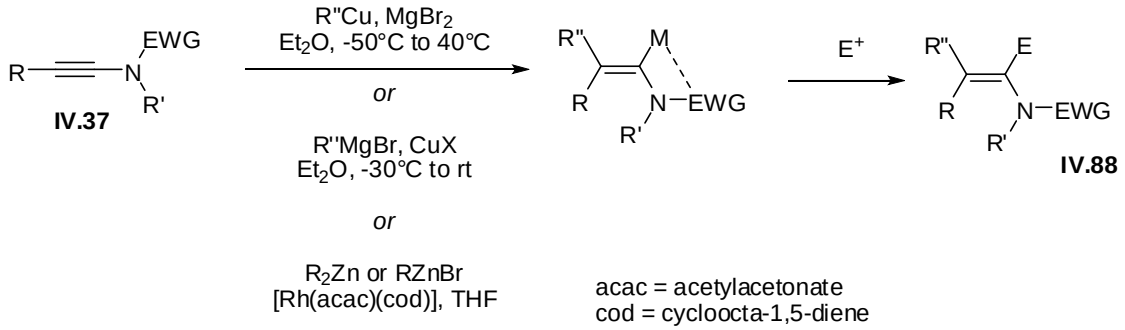


IV.86 **IV.87**

Scheme IV.37. *Hydrostannylation of ynamides.*[98]

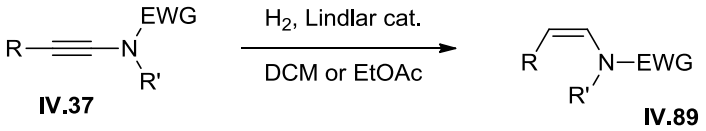
An example of addition at the β-position of ynamides leading to enamides **IV.88** is the carbometalation reactions with ynamides **IV.37** studied by Marek and co-workers.[99] (Scheme IV.38) Chelation with the electron-withdrawing group acts as regiodirecting group. The reaction is highly regioselective due to the carbocupration and copper-catalyzed carbomagnesiation of ynamides The reaction belongs to the β-addition of ynamides.

[97] Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C.A. *Org. Lett.* **2003**, *5*, 1547.
[98] Buissonneaud, D.; Cintrat, J. C. *Tetrahedron Lett.* **2006**, *47*, 3139.
[99] Checkik-lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098.



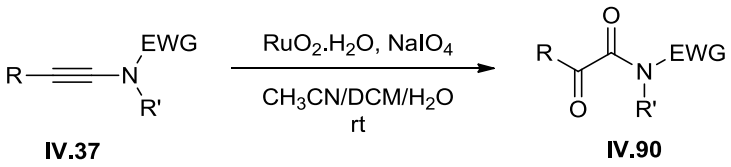
Scheme IV.38. *Carbometalation of ynamides **IV.37**.*[99]

In 2006, Hsung and co-workers[100] reported the strategy, which enables the selective preparation of *Z*-enamides **IV.89** (except when bulky substituents are attached to the ynamide). (Scheme IV.39) For this transformation they have used Lindlar-type hydrogenation. (Scheme IV.39)



Scheme IV.39. *Lindlar-type hydrogenation of ynamides **IV.37**.*[100]

The preparation of α-ketoimides **IV.90** by the oxidation of ynamides was published in 2008 by Hsung's group.[101] (Scheme IV.40) They screened several conditions for oxidation, where $RuO_2/NaIO_4$ as well as 3,3-dimethyldioxirane were found as the most efficient systems.



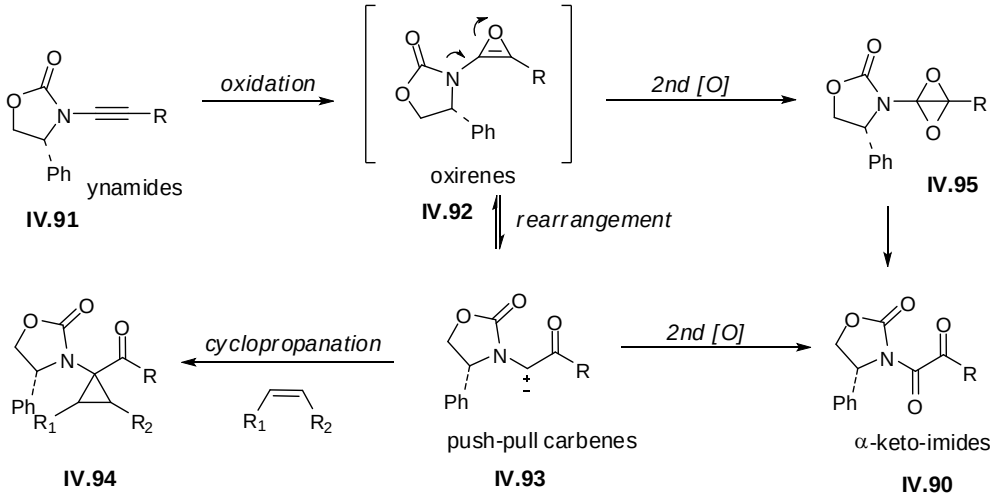
Scheme IV.40. *Oxidation of ynamides **IV.37**.*[101]

A more consistent entry to α-keto-imides from ynamides became apparent during the exploration of the dimethyldioxirane (DMDO) oxidation of ynamides **IV.91**. (Scheme IV.41) It was probing the possibility of arriving at push-pull carbenes **IV.93** derived from the oxidation of ynamides through the rearrangement of presumed oxirenes **IV.92**. This event was confirmed by the isolation of push-pull carbene-derived cyclopropanes **IV.94**. The formation of α-keto-imides **IV.90** was often a competing

[100] Zhang, X.; Zhang, Y.; Huang, J. ; Hsung, R. P., Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170.

[101] Al-Rhashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780.

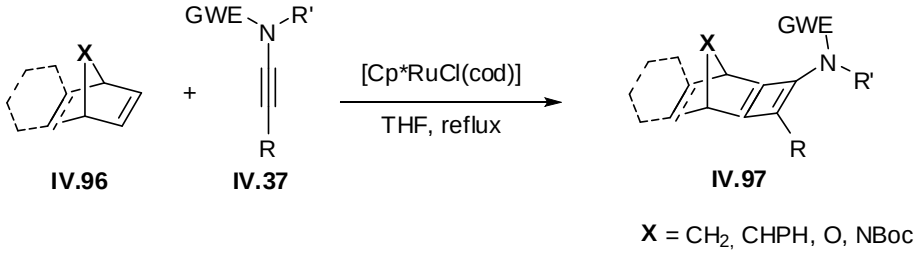
outcome of these reactions, presumably resulting from a second oxidation of the carbenes **IV.93**, although oxidation of oxirenes **IV.92** to 1,3-dioxabicyclobutanes **IV.95** followed by rearrangement to α-keto-imides **IV.90** cannot be ruled out.[101]



Scheme IV.41. *DMDO oxidation of ynamides **IV.91**.*[101]

Ynamides are widely used in all kinds of cycloadditions and similar reactions. The most common are [2+2], [4+2], [3+2], [2+2+1] and [2+2+2] cycloaditions.

Tam and co-workers[102,103] studied the ruthenium-catalyzed [2+2]-cycloadditions of bicyclic and tricyclic alkenes **IV.96** with ynamides **IV.37** affording cycloadducts **IV.97**. (Scheme IV.42)

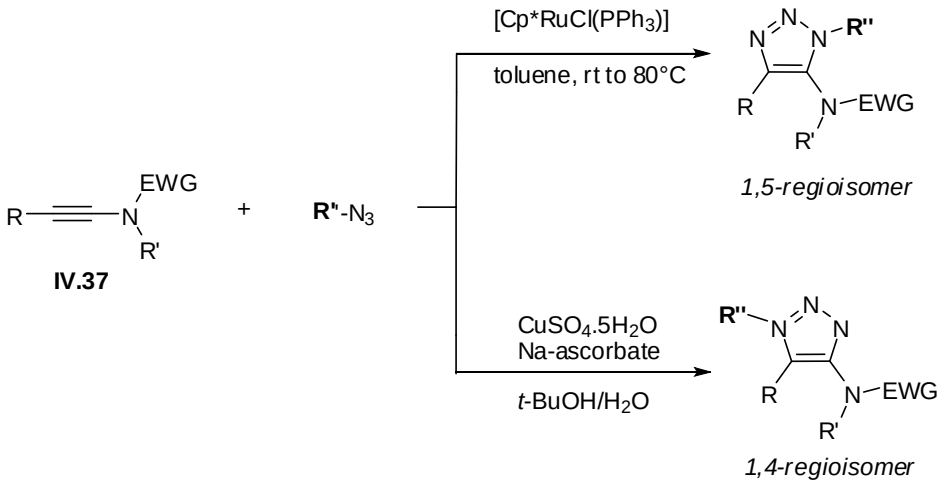


Scheme IV.42. *[2+2]-cycloadditions of ynamides **IV.37**.*[102,103]

Hsung and co-workers[104] reported dipolar [3+2]-cycloadditions between ynamides **IV.37**and azides. (Scheme IV.43) The dipolar [3+2] cycloadditions between ynamides and azides were also published by Ijsselstijn and Cintrat.[105] More details about this type of cycloaddition are written in Chapter VI. dealing with Click chemistry. The cycloaddition is highly regioselective and catalyst

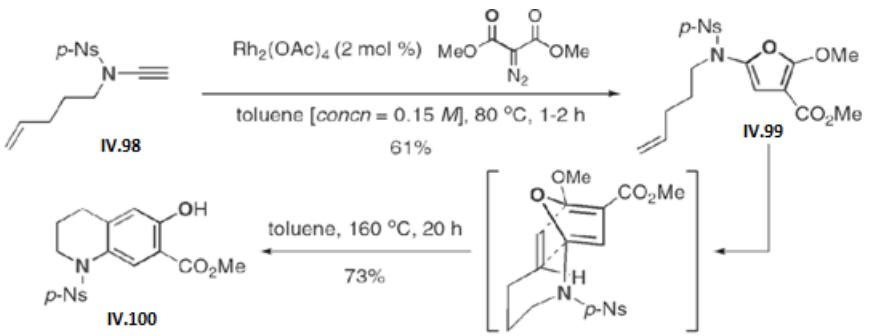
[102] Riddell, N.; Villeneuve, K.; Tam, W. *Tetrahedron* **2005***, 7*, 3681.
[103] Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62*, 3823.
[104] Zhang, X.; Hsung, R. P.; You, L. *Org. Biomol. Chem.*. **2006**, *4,* 2679.
[105] Ijsselstijn, M.; Cintrat, J.-C. *Tetrahedron* **2006**, *62*, 3837.

dependant affording 1,4-regioisomer (copper catalyst) or 1,5-regioisomer (ruthenium catalyst). (Scheme IV.43)



Scheme IV.43.*The Huisgen metal-catalyzed [3+2]-cycloadditions between ynamides **IV.37** and azides.*[104]

In 2009, Li and Hsung[106] described Rh(II)-catalyzed cyclopropenations of ynamides **IV.98**. (Scheme IV.44) Although an actual amido-cyclopropene intermediate may not be involved, these reactions provide a facile entry to highly substituted 2-amido-furans **IV.99**, thereby formerly constituting a [3+2]-cycloaddition. An application of these *de novo* 2-amido-furans in *N*-tethered intramolecular [4+2]-cycloadditions is also illustrated, leading to tetrahydroquinolines (**IV.100**).

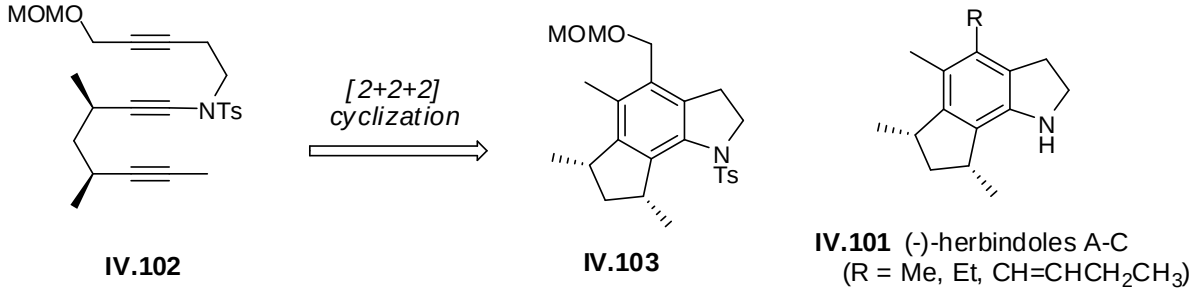


Scheme IV.44. *Highly substituted 2-amido-furans **IV.99** from Rh(II)-catalyzed cyclopropenations of ynamides.*[106]

The total syntheses of naturally occurring (-)-Herbindoles A, B, and C **IV.101** were accomplished for the first time through transition-metal catalyzed intramolecular [2+2+2]-cyclization

[106] Li, H.; Hsung, R. P. *Org. Lett.* **2009**, *11,* 4462.

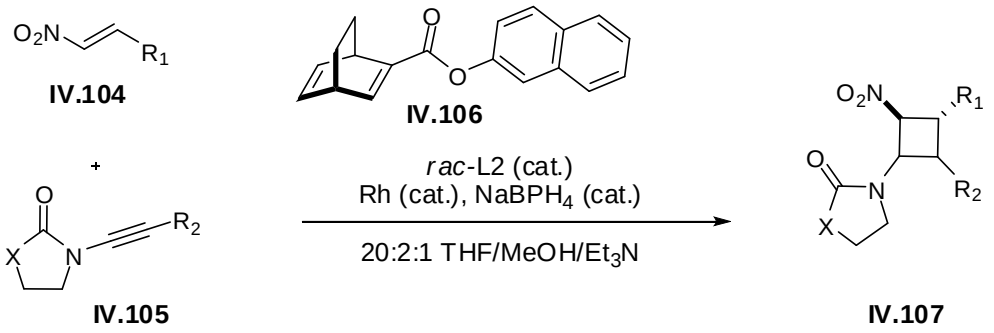
between ynamide and diynes of **IV.102**.[107] (Scheme IV.45) This strategy provided a highly efficient synthetic route to all three herbindoles indoline precursors **IV.103**.



IV.102 **IV.103** **IV.101** (-)-herbindoles A-C (R = Me, Et, $CH=CHCH_2CH_3$)

Scheme IV.45. *Total synthesis of (-)-Herbindoles **IV.101** via transition metal catalyzed intramolecular [2+2+2]-cyclization between ynamide and diynes.*[107]

In the presence of a diene-ligated rhodium complex, ynamides **IV.105** and nitroalkenes **IV.104** undergo catalytic [2+2]-cycloadditions to provide cyclobutenamides **IV.107** in the presence of ligand **IV.106**.[108] (Scheme IV.46) The presence of sodium tetraphenylborate was found to be crucial for the reactions to proceed efficiently.

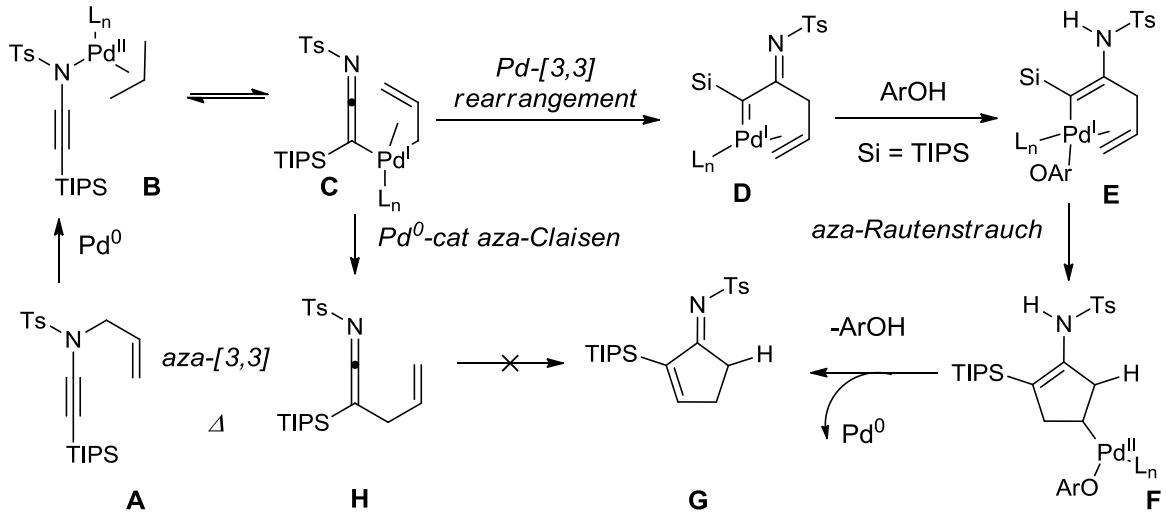


IV.104 **IV.106** **IV.105** **IV.107**

Scheme IV.46. *Rhodium-catalyzed [2+2]-cycloaddition of ynamides **IV.105** with nitroalkenes **IV.104**.*[108]

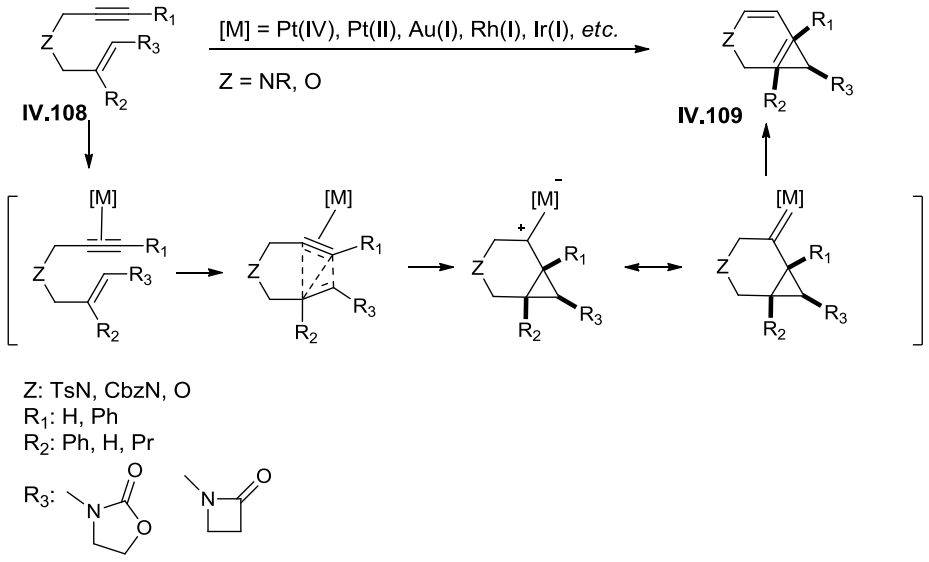
The group of Hsung described[109] a fascinating mechanistic study of ynamido-palladium-π-allyl complexes **B** that features isolation of a unique silyl ketenimine **H** *via* aza-Claisen rearrangement. which can be accompanied by an unusual thermal *N*-to-C 1,3-Ts shift in the formation of a novel cyclopentenimine **F** formation *via* a palladium-catalyzed aza-Rautenstrauch-type cyclization pathway. (Scheme IV.47)

[107] Saito, N.; Ichimaru, T.; Sato, Y. *Org. Lett.* **2012**, *14,* 1914.
[108] Smith, D. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, *14,* 4934.
[109] DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12,* 1840.



Scheme IV.47. *Pd(0)-catalyzed aza-Claisen rearrangement and aza-Rautenstrauch type cyclization of N-allyl ynamides **A**.*[109]

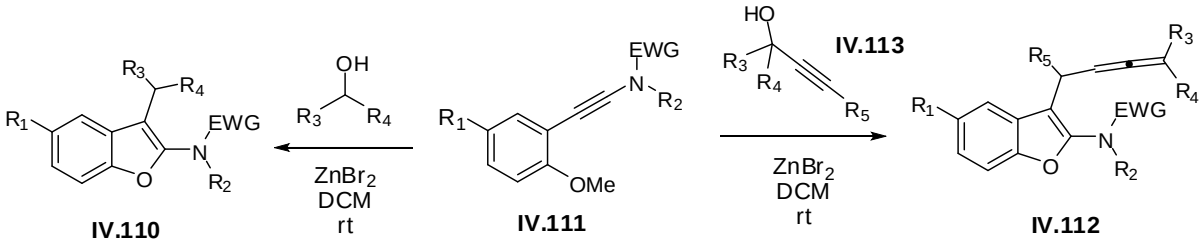
Recently was published the rhodium-catalyzed asymmetric cycloisomerization[110] of heteroatom-bridged 1,6-ene-ynamides **IV.108** giving high yields of functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives **IV.109** with high enantioselectivity, which was achieved by use of a rhodium/chiral diene catalyst. (Scheme IV.48) The 1,6-ene-ynamides substituted with 2-oxazolidinone and 2-azetidinone moieties at the alkyne terminus were found to display high reactivity towards the rhodium/chiral diene catalyst, where the chelate coordination of the alkyne moiety and the carbonyl oxygen of the eneynamides might be responsible for the high catalytic activity.



Scheme IV.48. *Cycloisomerization of heteroatom-bridged 1,6-enynes **IV.108**.*[110]

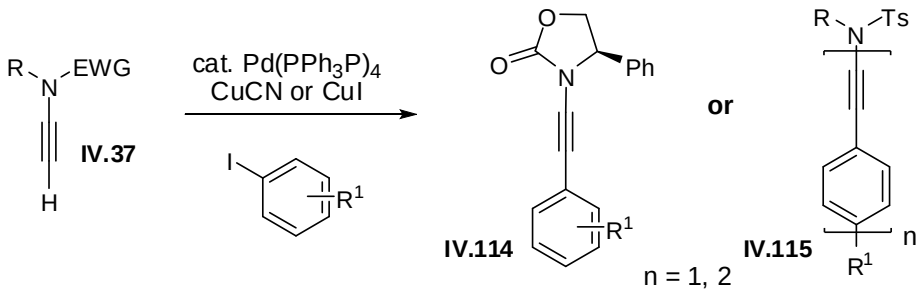
[110] Nishimura, T.; Takiguchi, Y.; Maeda, Y.; Hayashi, T. *Adv. Synth. Catal.* **2013**, *355*, 1374.

Cao *et al.*[111] developed a facile carbocation-induced electrophilic cyclization reaction for the synthesis of 3-alkyl- or 3-allenyl-2-amidobenzofurans (**IV.110**, **IV.112**) from *o*-anisole-substituted ynamides **IV.111** and diarylmethanol or 1,1-diarylprop-2-yn-1-ol **IV.113**. (Scheme IV.49)



Scheme IV.49. *Synthesis of 3-alkyl- (**IV.110**) or 3-allenyl-2-amidobenzourans (**IV.112**) via electrophilic cyclization of o-anisole substituted ynamides **IV.111** with carbocations.*[111]

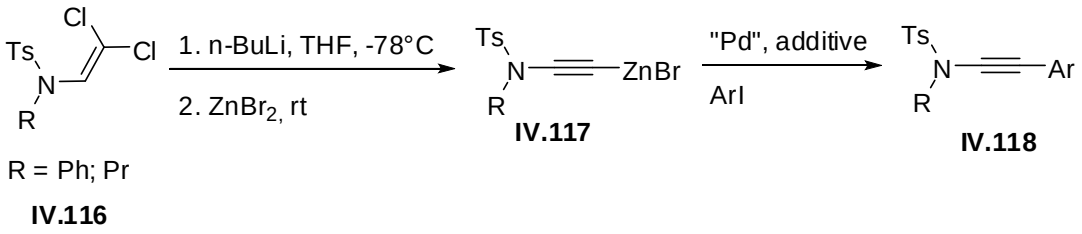
The metalated ynamides have been shown to be excellent partners in Sonogashira and Negishi coupling reaction. (Scheme IV.50). The first successful Sonogashira coupling of ynamides **IV.37** with aryl and vinyl iodides was described by Hsung *et al*. [112] This study resolves the problem of the competing pathway involving homocoupling of ynamides and provides a practical entry to novel urethane- **IV.114** or sulfonamide- **IV.115** terminated conjugated phenylacetylenic systems. (Scheme IV.50)



Scheme IV.50. *The Sonogashira coupling of ynamides **IV.37** with aryl iodides.*[112]

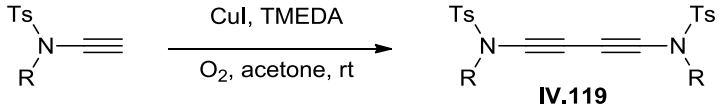
The transmetalation of dichlorovinyl **IV.116** with zinc bromide and a further Negishi coupling reaction of **IV.117** intermediate allows for preparation of aryl-substituted ynamide **IV.118**. [113] (Scheme IV.51)

[111] Kong, Y.; Jiang, K.;Cao, J.;Fu, L.; Yu, L.; Lai, C.;Cui, C.; Hu, Z.; Wang, G. *Org. Lett.* **2013**, *15,* 422.
[112] Tracey, M. R.; Zhang, Y. ; Frederick, M. O.; Mulder, J. A.; Hsung, R.P. *Org. Lett.* **2004**, *6,* 2209.
[113] Martinez-Esperon, M. F.; Rodriguez, D. ; castedo, L. ; Saa, C. *Tetrahedron* **2006**, *62*, 3843.



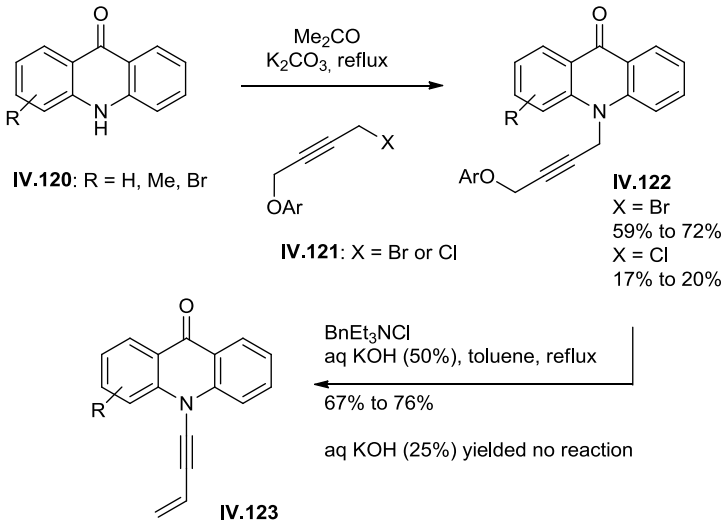
Scheme IV.51. *Preparation of N-aryl and N-alkyl arylynamides **IV.118** by Negishi coupling.*[113]

Ynamides can be also homocoupled to bisynamides **IV.119** upon treatment with copper(I) iodide and *N,N,N',N'*-tetramethylethylenediamine in acetone under oxygen atmosphere.[113] (Scheme IV.52)



Scheme IV.52. *Homocoupling of terminal ynamides.*[113]

The work on the biologically interesting acridone system was made by Majundar.[114] The substituted acridones **IV.120** were alkylated with propargyl halides **IV.121** in order to get propargylated acridones **IV.122**. The vinylogous enynamides **IV.123** were prepared by isomerisation of the propargyl group affected by KOH. (Scheme IV.53)



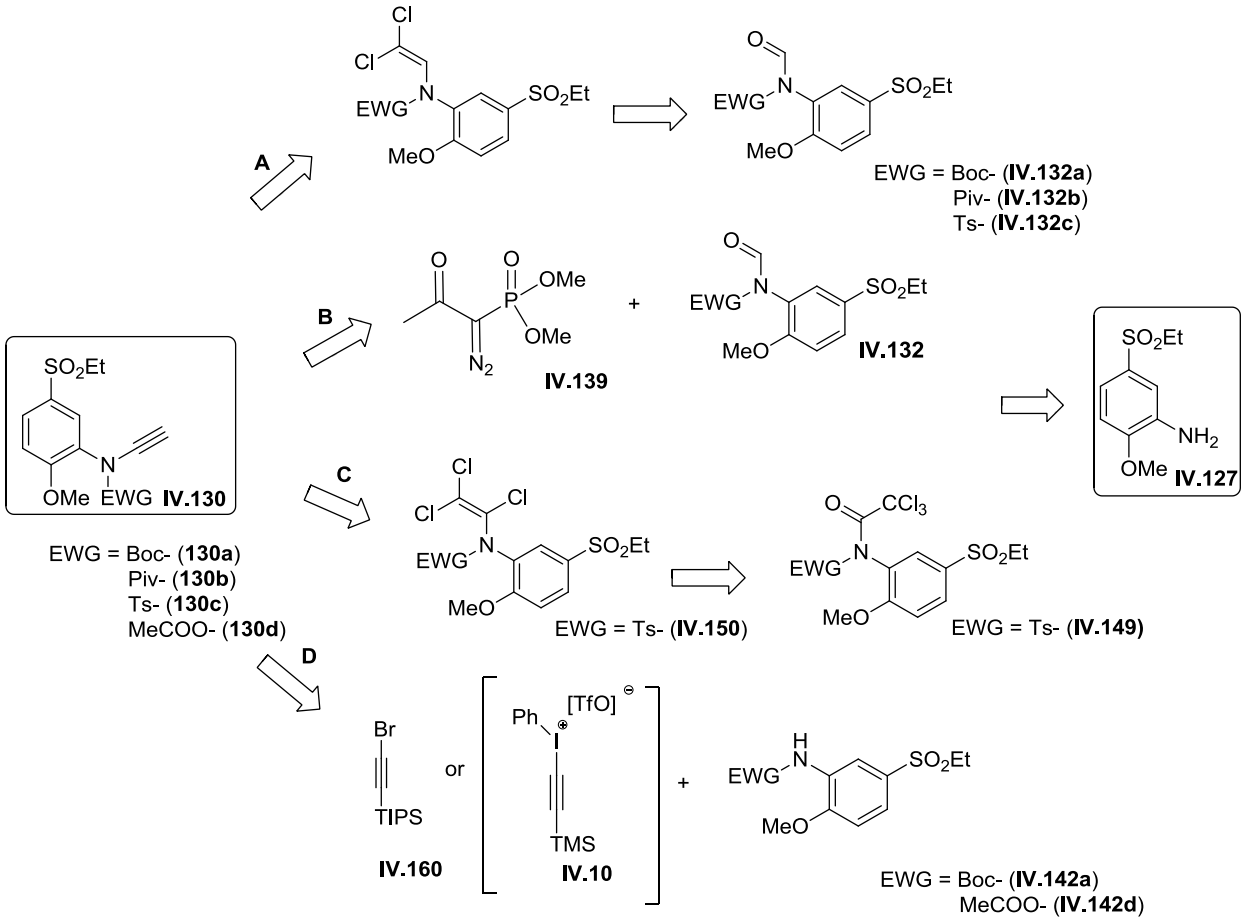
Scheme IV.53. *Preparation of acridone systems **IV.123**.*[114]

[114] Majumdar, K. C. ; Ghosh, S. K. *Synth. Commun.* **1994**, *24*, 217.

In the fact, ynamide is a quite recent functional group in organic chemistry. However, based on the wide literature study of several reviews and journals, we obtained sufficient information about reactivity and chemical properties of ynamides. Upon it, we were able to propose retrosynthetical approach in order to prepare ynamides as one of the partner for Click chemistry reaction.

4.2 Proposed synthesis of ynamides

Ynamides are one of the key intermediates of our project. Access to ynamide has been reviewed several times[34,45,46] and can be summarized by the four main possible pathways (A, B, C, D) depicted in Scheme IV.54. Methods are exposed in this report according to our synthetical progress.

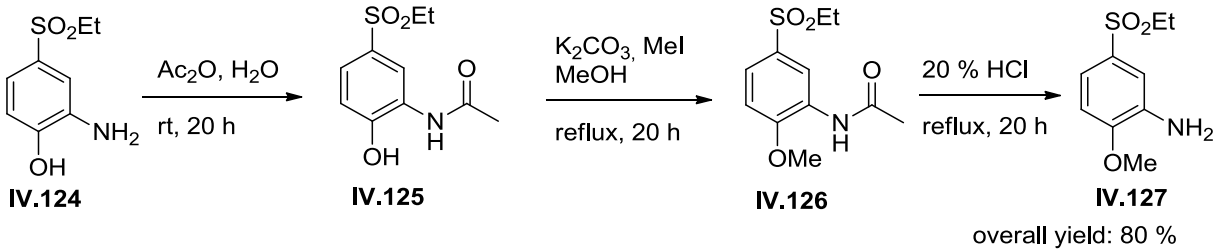


Scheme IV.54. *Retrosynthetic plan towards target ynamide **IV.130**.*

Pathway A and B correspond to a homologation of a formamide to an ynamide using Corey-Fuchs or Bestmann-Ohira protocols, the latter representing a shortcut to ynamide **IV.130**. Pathway C uses the transformation of trichloroacetales to ynamides, and finally pathway D is the direct alkynylation of anilines using trifluoro alkynyl iodonium salt **IV.10** or bromoacetylene **IV.160**.

Starting 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** was prepared from commercially available 2-amino-4-(ethylsulfonyl)phenol **IV.124** in 3 steps and 80 % overall yield.[115]

[115] *unpublished results*



Scheme IV.55. *Preparation of 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** from commercially available phenol **IV.124**.*[115]

Because **IV.124** was discontinued within our research and 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** is rather expensive (1g ~ 22 €), *o*-anisidine *o*-anisidine **IV.128** was chosen as model starting material amine to find the best reaction conditions towards the corresponding ynamide **IV.129**. (Figure IV.5)

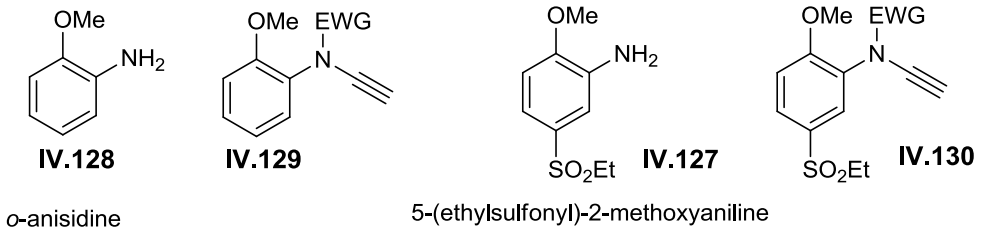


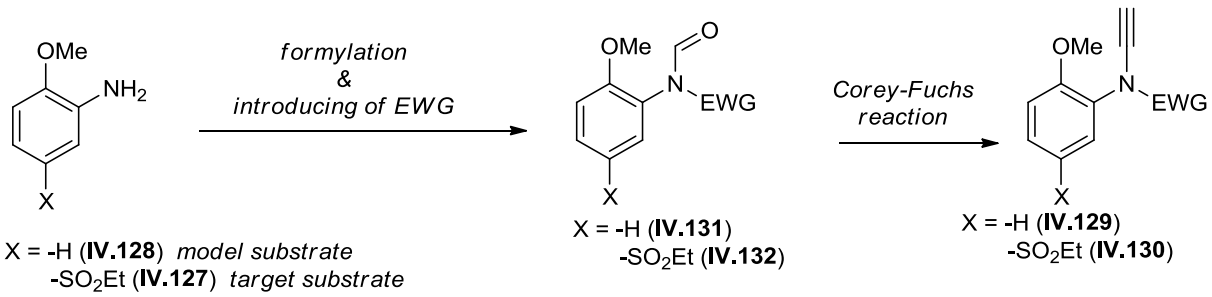
Figure IV.5. *Model molecule o-anisidine **IV.128**, 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** and corresponding ynamides **IV.129** and **IV.130**.*

4.2.1 Preparation of model ynamide

The first synthetical strategy (Scheme IV.54, Pathway A) we proposed deals with Corey-Fuchs reaction[116] as known transformation of aldehydes to alkynes. (Chapter 4.1.2) The transformation of *N*-formylated tosylamides to ynamides *via* dihalovinylamides was described in the work of David Brückner.[64,65]

Starting from **IV.128**, we tested the sequence depicted in Scheme IV.56. The problem was the selection of the suitable EWG group and to find the best conditions to prepare formamide **IV.131**.

[116] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

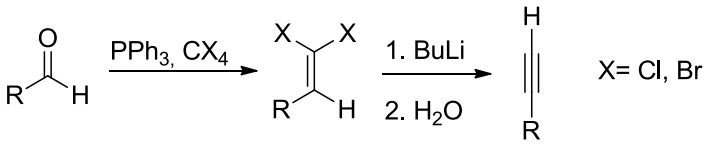


Scheme IV.56. *Strategy for application of Corey-Fuchs methodology on model (**IV.128**) and target substrate (**IV.127**).*

4.2.1.1 Corey-Fuchs approach

Characterization of the Corey-Fuchs reaction:

- two step methodology that allows the preparation of terminal alkynes by one-carbon homologation of an aldehyde.[117,118,119] (Scheme IV.57)

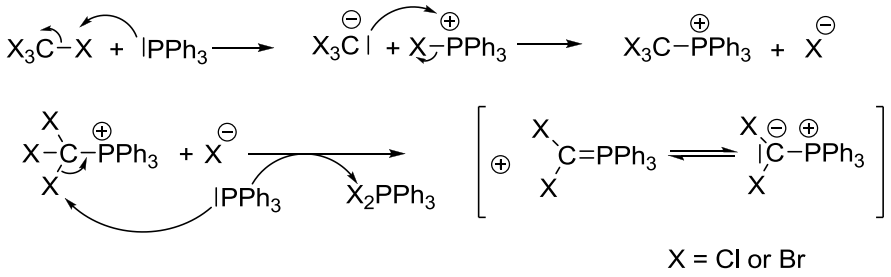


Scheme IV.57. *The conditions Corey-Fuchs reaction.*

- the first step is comparable to Wittig Reaction and leads to a dihaloalkene derivate (was originally discovered by Desai and McKelvie[120])
- formed dihaloalkenic intermediate with a lithium base (*n*-BuLi, LDA) generates *via* dehydrohalogenation a haloalkyne intermediate, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne upon a work-up

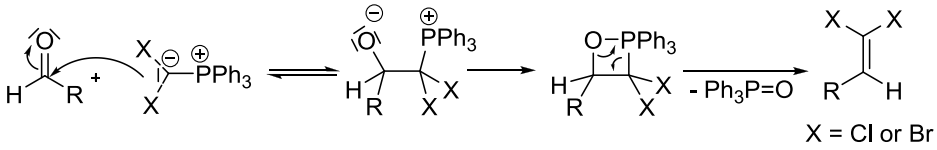
Mechanism of Corey-Fuchs reaction: During the ylide formation from CX_4, two equivalents of triphenylphosphine are used. One equivalent of PPh_3 forms ylide while the other one acts as halogene scavenger. (Scheme IV.58)

[117] Mori, M.; Tonogaki, K.; Kinoshita, A. *Org. Synth.* **2005** *81*, 1.
[118] Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005**, *81*, 157.
[119] http://en.wikipedia.org/wiki/Corey-Fuchs_reaction (visited 20.5.2013)
[120] Desai, N. B.; McKelvie, N. *J. of Am. Chem. Soc.* **1962**, *84*, 1745.



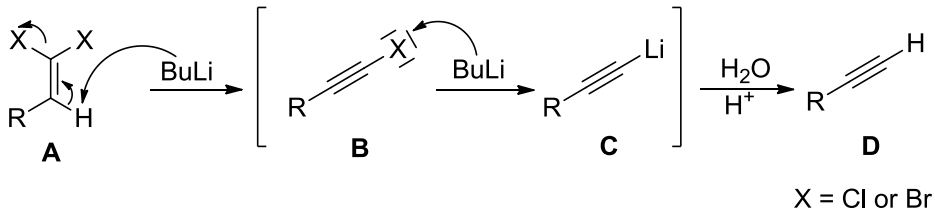
Scheme IV.58. *Initial ylide formation during the 1st step of Corey-Fuchs reaction.*

The prepared ylide consequently undergoes a Wittig Reaction when exposed to an aldehyde. (Scheme IV.59)



Scheme IV.59. *The general reaction mechanism of the dihaloylide with aldehyde.*

Deprotonation of the weakly acidic olefinic proton from dihaloalkene intermediate **A** by treatment of *n*-BuLi rises to a lithio-olefinic species which undergo a β-elimination and yielded the haloalkyne compound **B**. Further treatment with *n*-BuLi allows a lithium-halogen exchange and the formed organometalic intermediate **C** is transformed to the required alkyne **D** by reaction with water during a reaction work up. (Scheme IV.60)

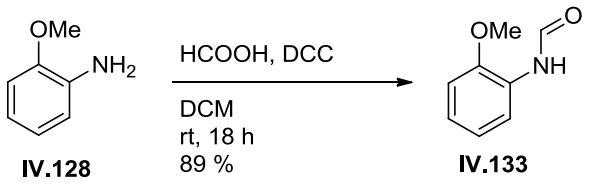


Scheme IV.60. *The treatment of 1,1-dihalovinyl **A** with excess of n-BuLi.*[65]

4.2.1.1.1 Preparation of formamides

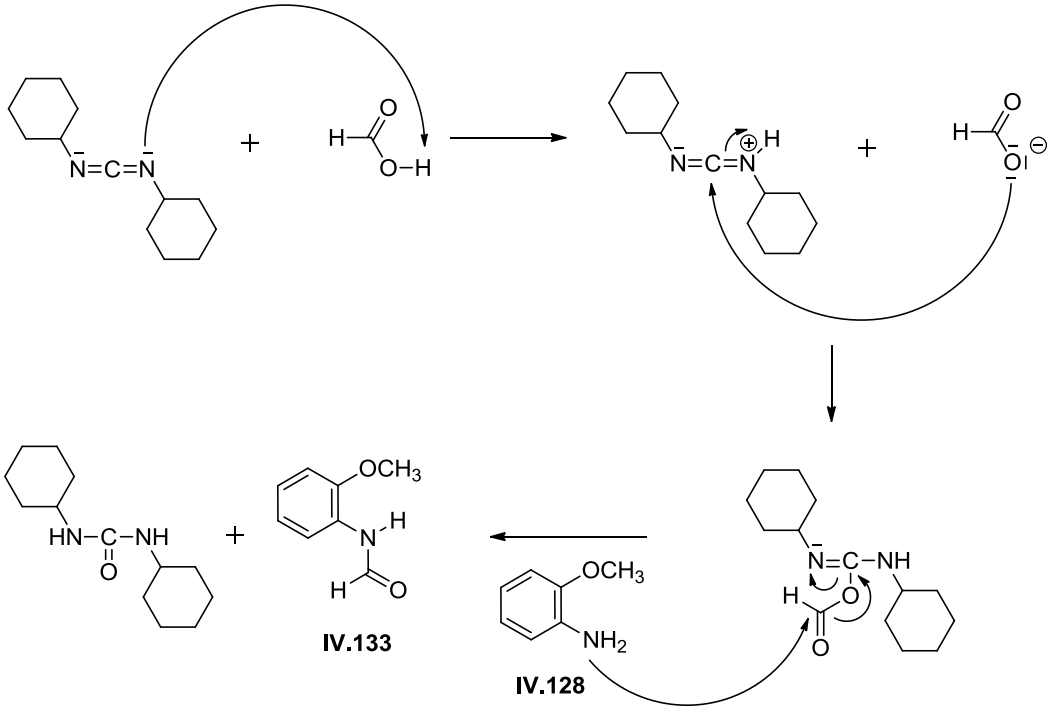
According to the Brückner's work, we choose first to perform *N*-formylation of **IV.128**. *N*-formyl group was intended to transform to ynamidic group in the next steps

For *N*-formylation we used the same conditions as was described by Brückner's protocol[64,65] (DCC, HCOOH in DCM). (Scheme IV.61) The reaction was performed on *o*-anisidine **IV.128 and** proceeded with high conversion, but separation of **IV.133** from dicyclohexylurea side product was quite difficult. The product **IV.133** was isolated in 89 % yield.



Scheme IV.61. *Preparation of N-formylated o-anisidine **IV.133**.*

In order to increase the reaction rate, the electrophilicity of carboxylate group was enhanced. (Scheme IV.62) *N,N'*-Dicyclohexylcarbodiimide (DCC) was used for this purpose as the most common coupling reagent. The negatively charged oxygen was acting as a nucleophile, attacking the central carbon in DCC. (Scheme IV.62) The poor soluble dicyclohexylurea was filtrated throught the short pad of silica gel.



Scheme IV.62. *Mechanism of formylation of o-anisidine **IV.128** by HCOOH and DCC.*

4.2.1.1.2 Introducing of EWG protecting group and Corey-Fuchs reaction

As already described in general characterization of ynamides, the electron-withdrawing group (EWG) is mandatory for the ynamide stabilization. For this purpose we were looking for protecting group with electron-withdrawing ability. The most suitable aniline protecting groups are Boc- (*tert*-butyloxycarbonyl), Piv- (pivaloyl) or Ts- (*para*-toluensulfonyl).

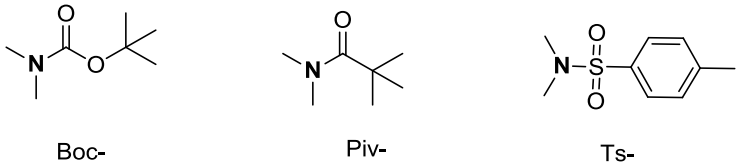
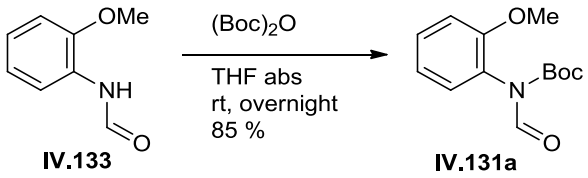


Figure IV.6. *Protecting groups with electron-withdrawing properties.*

4.2.1.1.2.1 Corey-Fuchs reaction with Boc- protected formamide **IV.131a**

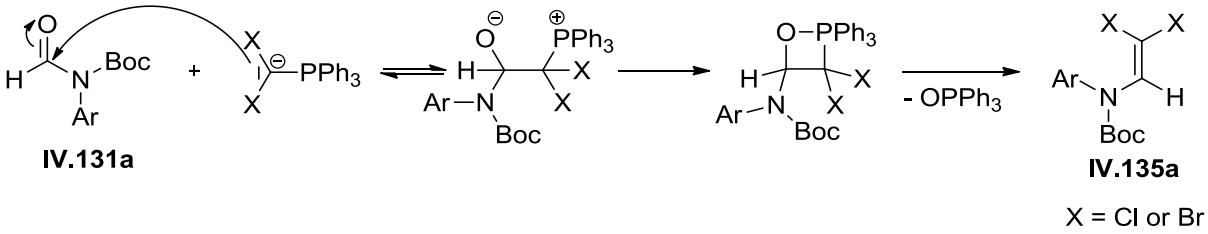
Introduction of a convenient EWG on formamide **IV.133** was the second step of the preparation of the Corey-Fuchs precursor. As our target molecule posseses an ethylsulfonyl group on aromatic part, it was necessary to select a protecting group, which does not contain a sulfonyl group (Ts-, Ms-, …) to avoid a potential unwanted cleavage of ethylsulfonyl group during the deprotection step. Boc- protection of formylated *o*-anisidine **IV.133** with di-*tert*-butyl dicarbonate afforded 85 % of *N*-formyl-*N*-Boc *o*-anisidine **IV.131a**. (Scheme IV.63)



Scheme IV.63. *Preparation of N-Boc protected formamide **IV.131a**.*

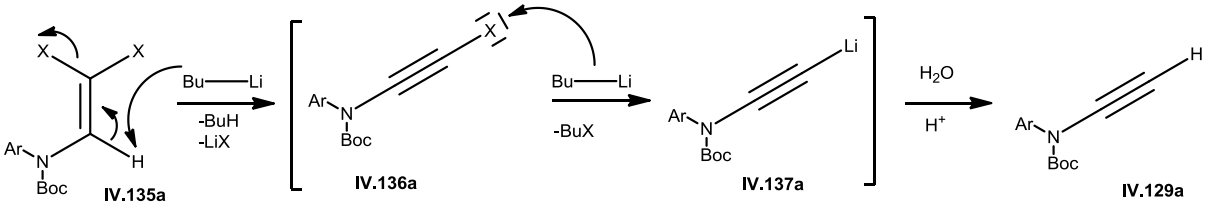
The *N*-Boc protected formamide **IV.131a** in hands, we tried to prepare the corresponding ynamide **IV.129a** using Corey-Fuchs homologation.[64,65]

We tried to prepare the corresponding ynamide IV.129a from *N*-Boc protected formamide **IV.131a** by Corey-Fuchs homologation.[64,65] The starting ylide was prepared by reaction of CCl_4 and two equivalents of PPh_3 in THF at 60°C within 6 hours. (Scheme IV.64). Subsequently formamide **IV.131a** was added to afford dihalogenovinyl derivates **IV.135a**. (Scheme 4)



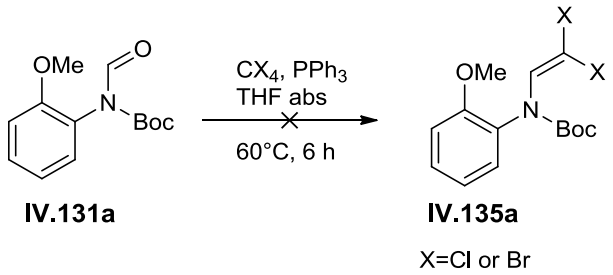
Scheme IV.64. *Mechanism of ylide attack on formamide **IV.131a**.*

Deprotonation of the weakly acidic olefinic proton from **IV.135a** by *n*-BuLi could give species that should undergo a β-elimination yielding haloalkyne intermediate **IV.136a**. Further treatment of **IV.136a** with excess of *n*-BuLi allows a lithium-halogen exchange and after quenching with an electrophile, such as water or MeOH, to get ynamide **IV.129a**. (Scheme IV.65) But in this reaction the vinylic intermediate **IV.135a** was not obtained because the Boc- group was cleaved within the reaction conditions.



Scheme IV.65. *Deprotonation of an olefinic proton with n-BuLi. Vinylic product **IV.135a** was not observed due to Boc- deprotection.*

Unfortunately, no ynamide **IV.129a** formation was observed (Scheme IV.66), and subsequent analysis revealed that Boc- deprotection occurred during the reaction.



Scheme IV.66. *Unsuccessful dihalogenovinylation of N-tert-*butyloxylcarbonyl *protected formamide **IV.131a**.*

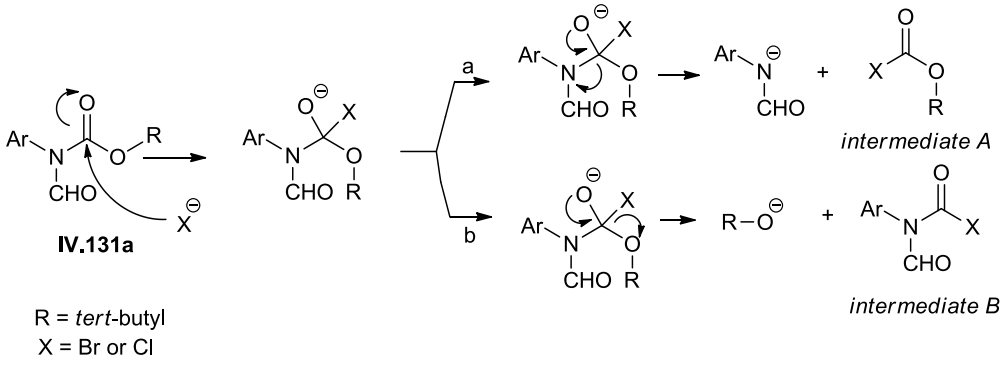
The reactions were repeated several times with the same results. (Table IV.1) The expected halovinyl intermediates **IV.135a** were not obtained in any case and the *N*-formamide **IV.133** was recovered. (Table IV.1)

Table IV.1. *Corey-Fuchs reaction with BOC- protected formamide **IV.131a**.*

Entry	Conditions	Results
1	10 eq CCl_4*, 3 eq PPh_3, THF, 60°C, 6 h	cleavage of Boc-, **IV.133** observed
2	2 eq CBr_4**, 4 eq PPh_3, THF, 60°C, 6 h	cleavage of Boc-, **IV.133** observed
3	10 eq CCl_4, 3 eq PPh_3, without solvent, 60°C, 6 h	cleavage of Boc-, **IV.133** observed

**Carbon tetrachloride was distilled under argon atmosphere, **carbon tetrabromide was purified by sublimation.*

We suppose that unwanted cleavage of Boc- protected group came from the presence of the bromide anion generated during the formation of ylide. (Scheme IV.67) The deprotection of *tert*-butyl carbamaoyl group on pyrole and primary and secondary aromatic amines by TBAF in THF was already reported by U. Jacquemard *et al.*[121] Cleavage of *tert*-butyl carbamates using TBAB in THF has been also described.[3] We suppose that bromide attacks the carboxyl group of Boc- to form a tetrahedric intermediate which can give intermediates A or B by two possible pathways as depicted in Scheme IV.67. *N*-arylformamide **IV.133** was only isolated in our case confirming the first pathway of mechanism (Scheme IV.67)

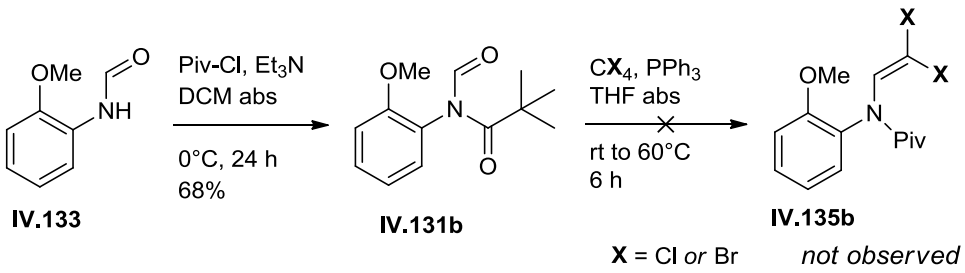


Scheme IV.67. *Proposed BOC- group cleavage during the Corey-Fuchs reaction.*[121]

[121] Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J. Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.

4.2.1.1.2.2 Corey-Fuchs reaction with pivaloyl- protected formamide **IV.131b**

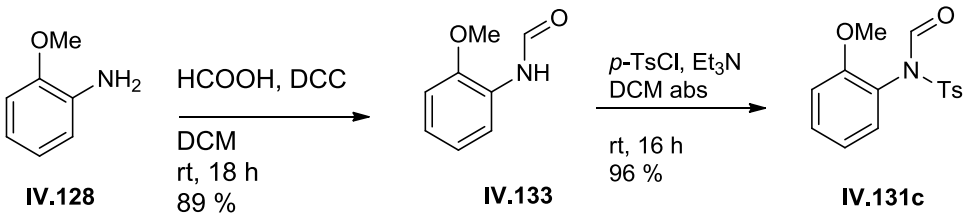
As Boc- group deprotection occured during the Corey-Fuchs homologation of the corresponding formamide, we prepared the more stable pivaloyl protected one **IV.131b**. (Scheme IV.68) Unfortunately, we observed in this case the pivaloyl cleavage leading again to *N*-arylformamide **IV.133**.



Scheme IV.68. *Pivaloyl chloride protection of N-formamide **IV.133** unsuccessful dihalomethylation.*

4.2.1.1.2.3 Corey-Fuchs reaction with *p*-toluensulfonyl protected formamide

According to literature,[122,123] which describes the selective cleavage of *N*-SO_2 bond in the presence of C aromatic-SO_2R bond, we decided to use a *p*-toluensulfonyl as *N*-protecting group. Such protecting group was utilized in Brückner's protocol.[64,65] As depicted in Scheme IV.69, *N*-formamide **IV.133** was protected with *p*-toluensulfonyl chloride in good yield. (Scheme IV.69)



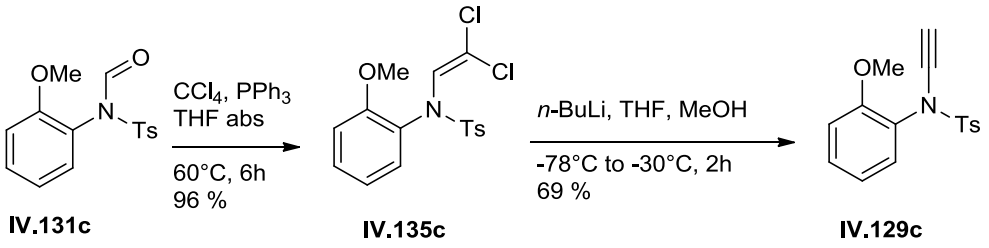
Scheme IV.69. *Preparation of N-tosylated formamide **IV.131c**.*

Reaction of **IV.131c** with CCl_4 and PPh_3 afforded dichloroenamide **IV.135c** at 60°C in very good yield. (Scheme IV.70) No detosylation reaction was observed in this case. It confirmed our

[122] Adams, R.; Nair, M. D. *J. Am. Chem. Soc.*, **1956**, *78*, 5932.

[123] Carril, M., Sanmartin, R., Churruca, F.; Tellitu, I., Domínguez, E. *Org. Lett.*, **2005**, *7*, 4787.

hypothesis of nucleophilic attack of bromide on the carboxyl group of Boc-, or Piv- groups in the previous cases. Treatment of **IV.135c** with *n*-BuLi resulted in ynamide **IV.129c** in 69 % yield. The structure of **IV.129c** was proven by ^{1}H NMR, ^{13}C NMR and LCMS analyses.



Scheme IV.70. *Preparation of N-tosylated formamide **IV.131c**.*

4.2.2.1 Bestmann-Ohira approach

The Seyferth-Gilbert homologation[124,125,126] is the base-promoted reaction of dimethyl (diazomethyl)phosphonate **IV.138** with aldehydes or arylketones at low temperatures, and provides a synthesis of alkynes from aldehydes in one step. The Bestmann-Ohira modification using dimethyl 1-diazo-2-oxopropylphosphonate **IV.139** allows the conversion of base-labile substrates (*e.g.* enolizable aldehydes, which would tend to undergo aldol condensation) under the Seyferth-Gilbert conditions.

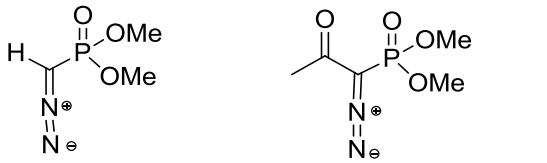
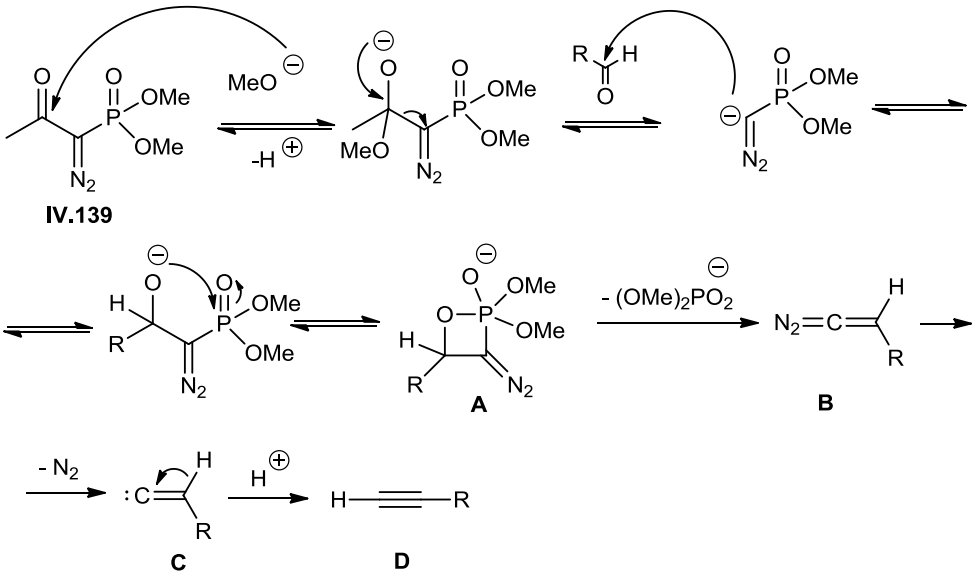


Figure IV.7. *The Seyferth-Gilbert and Bestmann-Ohira reagent.*

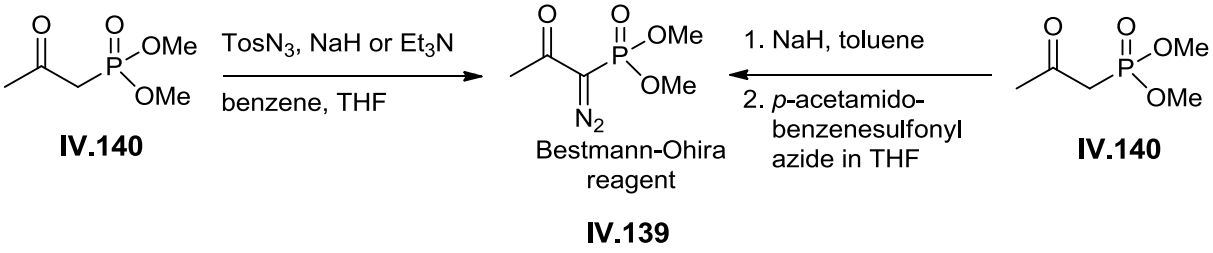
Mechanism of Bestmann-Ohira reaction: Treatment of reagent **IV.139** with base gives an anion, which reacts with the ketone or aldehyde to form the oxaphosphatane **A**. Elimination of dimethylphosphate gives the vinyl diazo-intermediate **B**. The generation of nitrogen gas gives a vinyl carbene **C**, which via a 1,2-migration forms the desired alkyne **D**.[126] (Scheme IV.71)

[124] Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, *1,* 59.
[125] Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
[126] Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.*, **1982**, *47*, 1837.



Scheme IV.71. *The mechanism of the Bestmann-Ohira reaction.*[126]

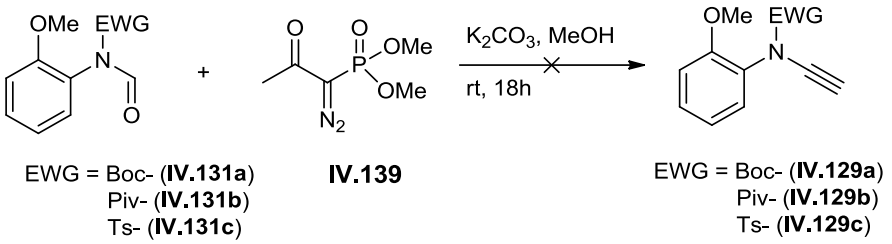
Bestmann-Ohira reagent **IV.139** is problematically available. It can also be prepared from dimethyl-2-oxopropylphosphonate **IV.140** with tosylazide or *p*-acetamidobenzenesulfonyl azide in the presence of base.[127] (Scheme IV.72)



Scheme IV.72. *Preparation of Bestmann-Ohira reagent **IV.139**.*

After unsuccessful conversion of *N*-Boc or *N*-Piv formamides **IV.131a** and **IV.131b** to the corresponding ynamides *via* Corey-Fuchs approach, we decided to perform Bestmann-Ohira reaction as alternative method to afford directly ynamide **IV.129a** and **IV.129b** in one-step reaction as depicted in Scheme IV.73. Unfortunately, deformylation of starting materials **IV.131a**, **b, c** occurred and expected products **IV.129a** and **IV.129b** were not observed. In every case, the starting substrates **IV.131a**, **IV.131b**, **IV.131c** were converted to deformylated derivates.

[127] Patil, U. D. *Synlett* **2009**, *17*, 2880.



Scheme IV.73. *Bestmann-Ohira reactions performed on substrate **IV.131a,b,c**.*

4.2.2 Preparation of target ynamide

4.2.2.1 Corey-Fuchs approach (pathway A)

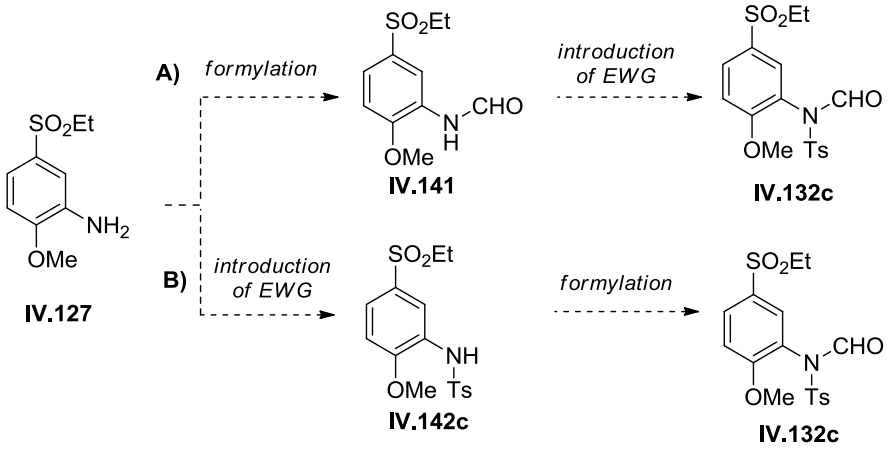
Among the different EWG protected *o*-anisidines **IV.131** tested, only tosyl group was compatible with the Corey-Fuchs conditions leading to ynamides **IV.129c**. We apply these reaction conditions starting from aniline **IV.127**. Our first goal was the preparation of *N*-tosylformamide **IV.132c**.

4.2.2.1.1 Preparation of N-tosylformamide IV.132c precursor for Corey-Fuchs reaction

There are two possible ways for the preparation of **IV.132c**. (Scheme IV.74)

A) Preparation of *N*-formamide **IV.141** *and* subsequent introduction of tosyl group, which was successful with our model **IV.128**

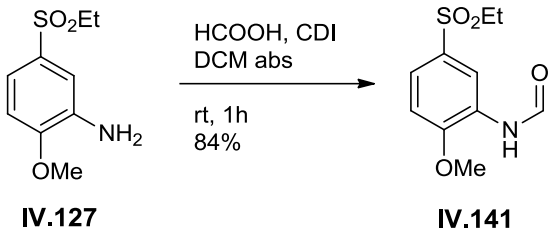
B) Introduction of tosyl group *and* subsequent formylation of *N*-protected aniline **IV.142c**. (Scheme IV.74)



Scheme IV.74. *Two possible pathways for preparation of the Corey-Fuchs precursor **IV.132c**.*

✓ **Pathway A:**

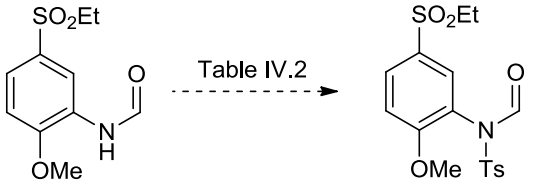
The formylation of 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** was performed with formic acid and 1,1'-carbonyldiimidazole (CDI). Required *N*-(5-(ethylsulfonyl)-2-methoxyphenyl)formamide **IV.141** was obtained in 84 % yield.



IV.127 **IV.141**

Scheme IV.75. *Preparation of N-(5-(ethylsulfonyl)-2-methoxyphenyl)formamide **IV.141**.*

Subsequent introduction of Ts protecting group on **IV.141** was unsuccessful due to the lower nucleophilicity of the nitrogen atom from **IV.141** compare to anisidine analogue **IV.133**.



IV.141 **IV.132c**

Scheme IV.76. *The proposed preparation of N-(5-(ethylsulfonyl)-2-methoxyphenyl)-N-tosylformamide **IV.132c**.*

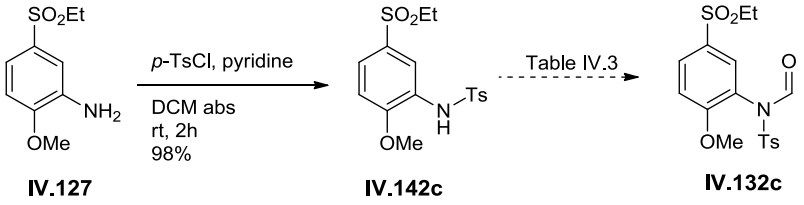
We have tried different conditions of tosylation of formamide **IV.141** which are listed in Table IV.2. Initially, due to the high reactivity of *p*-toluenesulfonyl chloride we tried to introduce tosyl group without basic catalysis. Regarding to the unsuccessful attempts (Table IV.2, Entry 1, 2), we used weak bases (Et_3N, pyridine), but no reaction occured in general basic catalysis conditions and starting material was recovered. In order to deprotonate nitrogen atom of formamide **IV.141**, we used stronger bases (NaH, *n*-BuLi). Unfortunately, in this case deformylation was observed and only *N*-tosylated aniline **IV.142** was obtained (Table IV.2, Entry 7, 8).

Table IV.2. *Conditions and results of performed tosylation reactions perfomed on formamide **IV.141**.*

Entry	Reagents (1.1 equiv) & Conditions	Base (1.1 equiv)	Results
1	*p*-TsCl, THF, rt	---	starting material **IV.141**
2	*p*-TsCl, THF, 60°C	---	starting material **IV.141**
3	*p*-TsCl, THF, rt	pyridine	starting material **IV.141**
4	*p*-TsCl, THF, 60°C	pyridine	starting material **IV.141**
5	*p*-TsCl, THF, rt	Et_3N	starting material **IV.141**
6	*p*-TsCl, THF, 60°C	Et_3N	starting material **IV.141**
7	*p*-TsCl, THF, rt	NaH	side product **IV.142c**
8	*p*-TsCl, THF, rt	*n*-BuLi	side product **IV.142c**

✓ **Pathway B:**

As pathway A delivered negative results, we decided to perform tosylation of aniline **IV.127** prior to its formylation. Required *N*-tosylated sulfonylanisidine **IV.142c** has been prepared using classical conditions and the subsequent formylation has been studied. (Scheme IV.77)



IV.127 **IV.142c** **IV.132c**

Scheme IV.77. *An alternative strategy for preparation of **IV.132c**.*

In order to get desired product **IV.132c** we selected several formylating conditions (Table IV.3, Scheme IV.77):

- activation of formic acid using DCC[128] (*N,N'*-dicyclohexylcarbodiimide), CDI[129] (1,1'-carbonyldiimidazole), BtCHO (1H-Benzotriazole-1-carboxaldehyde) without or in the presence of bases to deprotonate the starting *N*-tosylated aniline (Table IV.3, Entries 1-5)
- use of HCOOEt (ethyl ester of formic acid) (Table IV.3, Entries 6-9)
- Vilsmeier-Haack formylation (Table IV.3, Entry 10)
- use of Eschenmoser salt (Table IV.3, Entry 11)
- use of acetic-formic anhydride (Table IV.3, Entry 12).

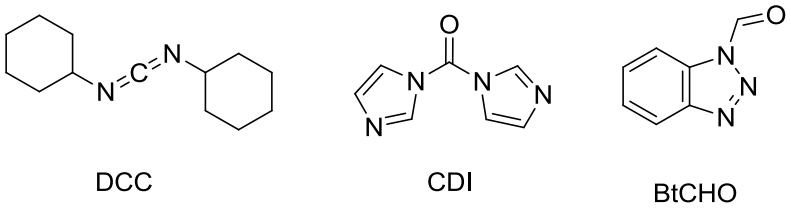


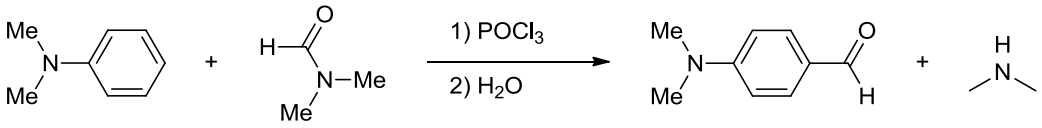
Figure IV.8.*Structures of used formylating agents.*

Table IV.3. *The reactions performed in order to perform formylaltion of N-tosylamide* ***IV.142c****.*

Entry	Reagents	Conditions	Results
1	HCOOH, CDI	DCM, 0°C to rt, 18 h	Starting material **IV.142c**
2	HCOOH, DCC	DCM, 0°C to rt, 22 h	
3	HCOOH, CDI, NaH	THF, 0°C to rt o 70°C, 20 h	
4	BtCHO	THF, rt, 20 h	
5	BtCHO, *n*-BuLi	THF, 0°C to rt, 18 h	
6	HCOOEt, NaH	rt, 18 h	
7	HCOOEt, *t*-BOK	DMF, rt to 50°C, 18 h	
8	HCOOEt, LDA	THF, -78°C to rt to 50°C, 20 h	
9	HCOOEt, *n*-BuLi	THF, -78°C to rt, 20 h	
10	DMF, $POCl_3$	0°C to rt, 15 h	
11	$Me_2N^+=CH_2$ Cl^-, Et_3N	DCM, rt to 50°C	
12	Acetic formic anhydride **IV.143**, NaH	THF, 0°C to rt, 1.5 h	desired product **IV.132c**, 94 % yield

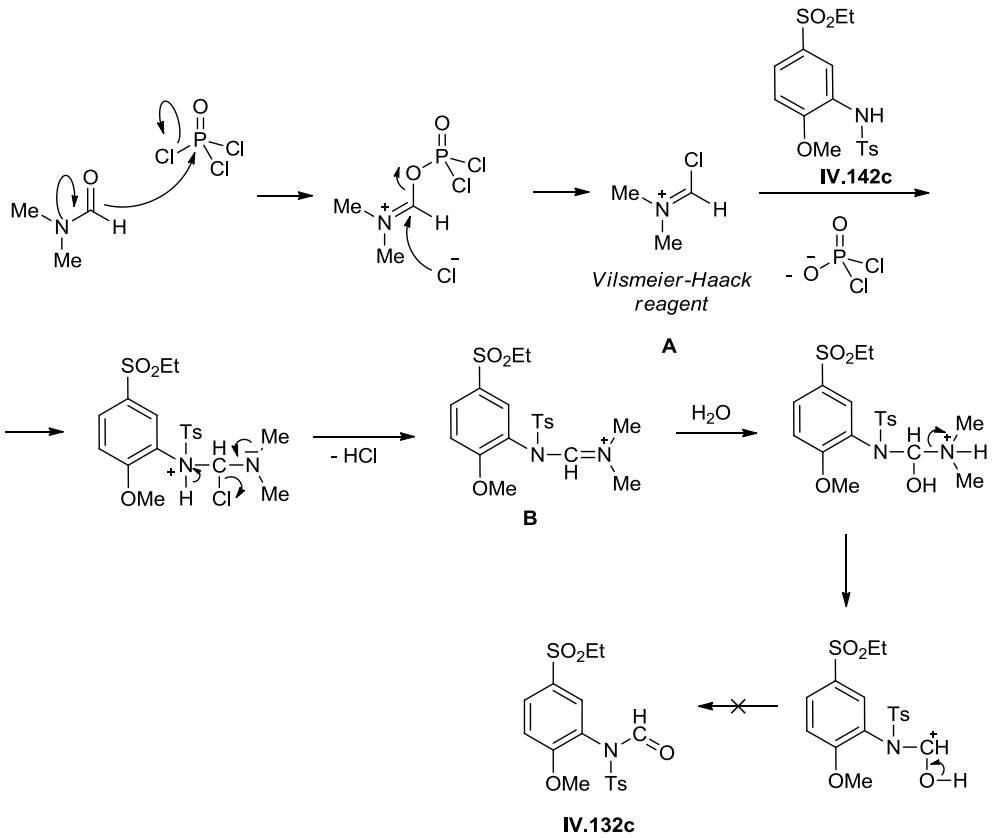
[128] Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671.
[129] Walz, A. J.; Miller, M. J. *Org. Lett.* **2002**, *12*, 2047.

Many assays carried out formylation of **IV.142c** failed. (Table IV.3, Entry 1-9) Afterwards, Vilsmeier-Haack reaction has been tested.[130] (Table IV.3, Entry 10) Vilsmeier-Haack reaction (Scheme IV.78) is usually successfully applied for electron-rich arenes to produce the corresponding aryl ketones or aryl aldehydes and we decided to use this approach for compound **IV.142c**.



Scheme IV.78. *The preparation of 4-(dimethylamino)benzaldehyde from N,N-dimethylaniline via Vilsmeier-Haack reaction.*

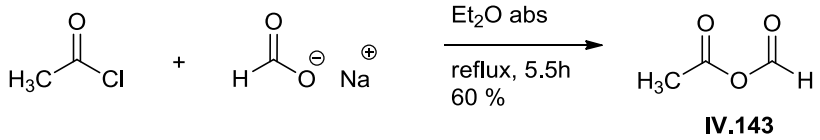
Vilsmeier-Haack reagent is formed *in situ* from DMF (or another substituted amide) and phosphorus oxychlorid or oxalyl chloride.[131] (Scheme IV.79) The reaction of DMF with phosphorus oxychloride produces an electrophilic iminium cation **A**. The subsequent electrophilic addition produces an iminium ion intermediate **B**, which is hydrolyzed to give the desired product **132c**. Unfortunately, these conditions failed in our case. (Table IV.3, Entry 10)



Scheme IV.79. *An attempt to prepare N-tosylated substrate **IV.132c** via Vilsmeier-Haack reaction.*

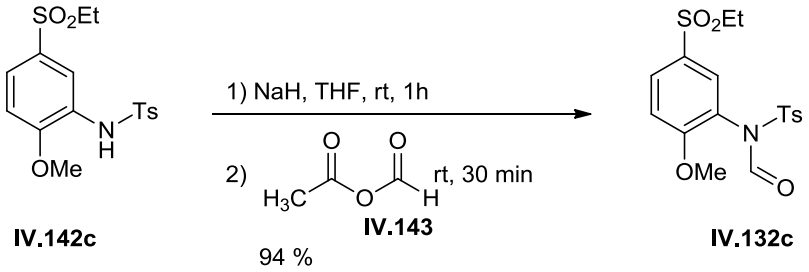
[130] Campaigne, E. ; Archer, W. L. *Org. Synth.* **1963**, *4*, 331.
[131] Mikhaleva, A. I.; Ivanov, A. V.; Skitaltseva, E. V.; Ushakov, I. A.; Vasiltsov, A. M.; Trofimov; B. A. **2009**, *4*, 587.

We decided to try formylation of *N*-tosylamide **IV.142c** using the freshly prepared mixed anhydride of formic and acetic acid **IV.143**. (Table IV.3, Entry 12) The acetic formic anhydride was prepared according to the protocol published by Krimen[132] in 1970 from acetylchloride and sodium formate in 60 % yield.



Scheme IV.80. *Preparation of acetic formic anhydride **IV.143**.*

Mixed acetic formic anhydride **IV.143** is sensitive to the air. Fortunately, deprotonation of *N*-tosylated aniline **IV.142c** using sodium hydride, followed by addition of mixed anhydride **IV.143** afforded *N*-tosyl formamide **IV.132c** in 94 % yield. (Scheme IV.81, Table IV.3, Entry 12)

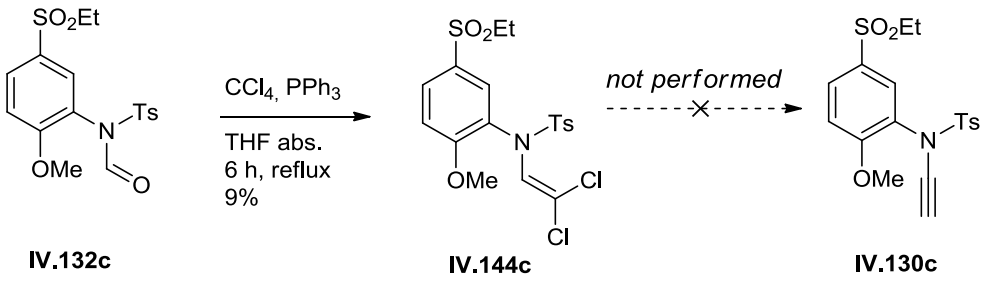


Scheme IV.81. *Preparation of N-tosyl formamide **IV.132c** using acetic formic anhydride **IV.143**.*

4.2.2.1.2 The Corey-Fuchs reaction

We tried conversion of *N*-tosyl formamide **IV.132c** to the corresponding 1,1-dichlorovinyl **IV.144c** using the conditions selected from model *o*-anisidine study. Unfortunately, the yield of the reaction was very poor (9 %). In order to prepare ynamide **IV.130c** we decided to select synthetic pathways C or D (Scheme IV.82).

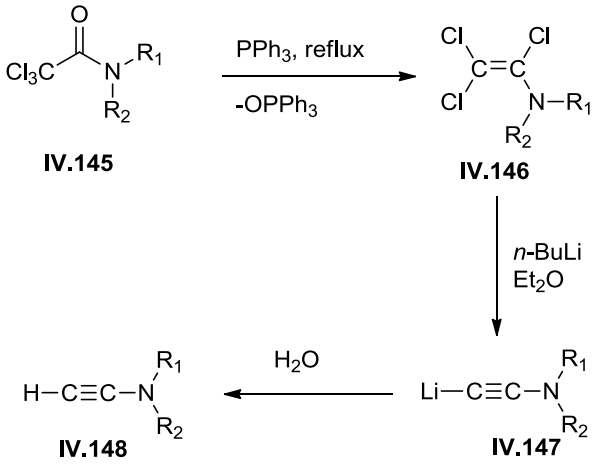
[132] Krimen, L. I. *Org. Synth.* **1970**, *50*, 1.



Scheme IV.82. *The preparation of 1,1-dichlorovinyl **IV.144c** from Corey-Fuchs precursor **IV.132c**.*

4.2.2.2 Transformation of trichloroacetamides to ynamides (pathway C)

The transformation of trichloroacetates to ynamines were described by Speziale and Smith in 1962.[133] In 1972, the same methodology for preparation of ynamines **IV.148** was published by Himbert and Regitz.[134] The key step is the preparation of trichloroenamine **IV.146** and its subsequent conversion to lithiated ynamine **IV.147** by action by *n*-BuLi. (Scheme IV.83)



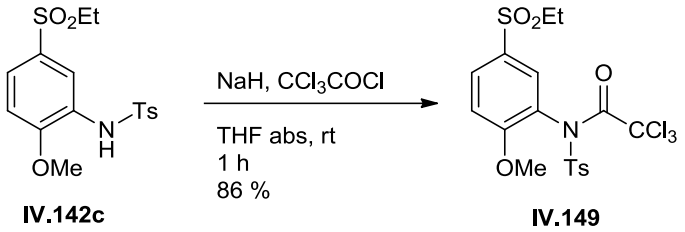
R_1	C_2H_5	CH_3	C_2H_5	$CH(CH_3)_2$	CH_2Ph	Ph
R_2	C_2H_5	Ph	Ph	Ph	Ph	Ph

Scheme IV.83. *The preparation of ynamines **IV.148** from N-alkyl-trichloroacetyl anilide **IV.145** as is described by Himbert and Regitz.[134]*

For this purpose trichloroacetylation of *N*-tosylated sulfonylanisidine **IV.142c** by CCl_3COCl was performed. (Scheme IV.84)

[133] Speziale, A. J.; Smith, L. R. *J. Am. Chem. Soc.* **1962**, *84*, 1868.

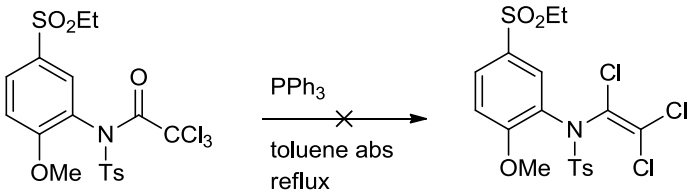
[134] Himbert, G.; Regitz, M. *Chemische Berichte* **1972**, *105*, 2963.



IV.142c **IV.149**

Scheme IV.84. *Preparation of N-tosylated trichloroacetyl **IV.149**.*

Treatment of **IV.149** with triphenylphosphine in refluxing toluene did not afford trichlorovinyl intermediate **IV.150**. (Scheme IV.85) During the reaction, cleavage of trichloroacetyl group was observed. The intermediate **IV.149** seemed to be unstable and the same cleavage was observed upon its storage at room temperature.



IV.149 **IV.150**

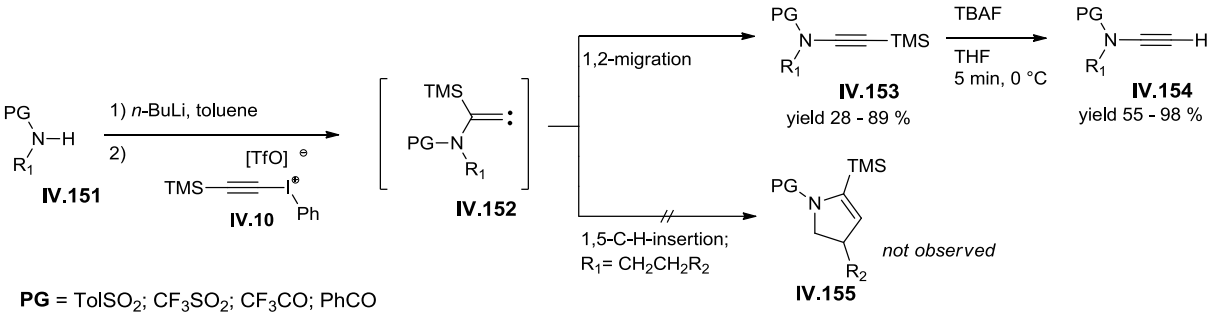
Scheme IV.85. *Unsuccessful transformation of **IV.149** to trichlorovinyl **IV.150**.*

4.2.2.3 Direct N-alkynylation of arylamines (pathway D)

4.2.2.3.1 Direct N-alkynylation of arylamines by alkynyliodonium triflate salts

Direct *N*-alkynylation using alkynyliodonium triflate salts **IV.10** belongs to the one of the recent developed methodologies for preparation of ynamides. The key step of the synthesis is an ethynylation of the amide with the trimethylsilylethynyliodonium triflate **IV.10**.[135] Addition of nitrogen nucleophiles to alkynyliodonium salts were reported by Feldman *et al.*[136] With respect to the cases studied herein, and in accordance with a very high aptitude of silyl group for 1,2-migrations towards carbenoid centers such as in **IV.152**,[137] preferential formation of 1-alkynylamides is expected. The proposed mechanism is shown in Scheme IV.86. Indeed the alkynes **IV.153** were obtained as single products after deprotonation of **IV.151** with *n*-butyllithium followed by addition of **IV.10** at laboratory temperature.[56] Desilylation with *n*-tetrabutylammonium fluoride (TBAF) yields the desired functionalized ynamides **IV.154**.

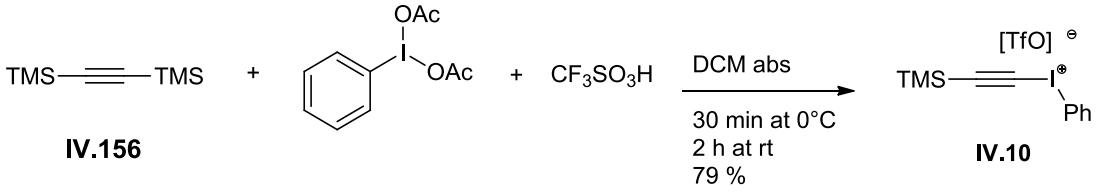
[135] Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.
[136] Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.
[137] Kirmse, W. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1164.



Scheme IV.86. *Synthesis of functionalized ynamides **IV.154** as is published in work by Witulski and Stengel.*[56]

*Preparation of trimethylethynyliodonium triflate salt **IV.10***

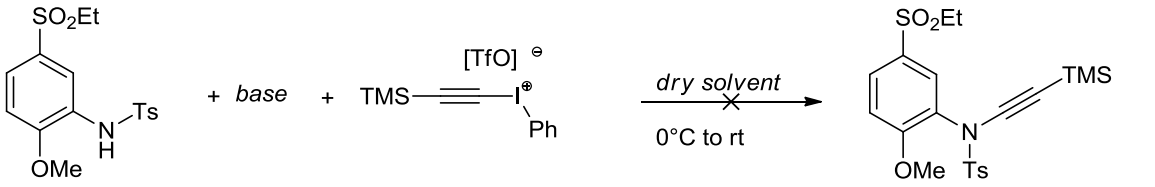
The first synthesis of trimethylethynyliodonium salt **IV.10** was described by Stang in 1995.[138] The compound **IV.10** belongs to the organic polyvalent iodine compounds (Iodine (III) possessing two carbon ligands). An important study about the organic polyvalent iodine compounds[135] and alkynyliodonium salts in organic synthesis were published by Zhdankin and Stang. [53] The synthesis started from commercially available bis(trimethylsilyl)acetylene **IV.156**. Treatment of **IV.156** with $PhI(OAc)_2$ and CF_3SO_3H furnished (trimethylsilyl)ethynyliodonium salt **IV.10** in 79 % yield. (Scheme IV.87) [139] Analytical data of prepared **IV.10** were consistent with literature.[139]



Scheme IV.87. *Preparation of phenyl(trimethylsilyl)iodonium triflate (**IV.10**).*[139]

Freshly prepared **IV.10** was directly used in the next step of synthesis. Amide **IV.142c** was deprotonated with strong base and triflate salt **IV.10** was added dropwise at low temperature. Despite several strong bases (*n*-BuLi,[56] KHMDS,[139] LiHMDS[140]) were tested, we did not reach positive results and only starting material **IV.142c** was observed. (Scheme IV.88)

[138] Stang, P. J. *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F.; Eds.; Wiley-VCH: Weinheim **1995**, 67.
[139] Tanaka, K.; Takeishi, K. *Synthesis* **2007**, *18*, 2920.
[140] Kerwin, S.; Nadipuram, A. *Synlett* **2004**, 1404.



IV.142c **IV.10** *expected product* **IV.157**

base: *n*-BuLi, KHMDS, LiHMDS
solvent: THF, PhMe

Scheme IV.88. *Unsuccessful preparation of ynamide **IV.157** via direct N-alkynylation with alkynyliodonium salt **IV.10**.*

4.2.2.3.2 Direct N-alkynylation of arylamines by acetylene bromides

In front of the negative results obtained by iodonium triflate mediated *N*-alkynylation and the potential explosive properties of hypervalent iodine in **IV.10**, we decided to turn our attention to transition metal mediated *N*-direct alkynylation using bromoacetylenes **IV.158**, **IV.160**.

Silyl group was mandatory for protection of acetylenes. The most common commercially available silylated acetylenes were ethynyltrimethylsilane **IV.159** and ethynyl-(triisopropyl)-silane **IV.161**. (Figure IV.9)

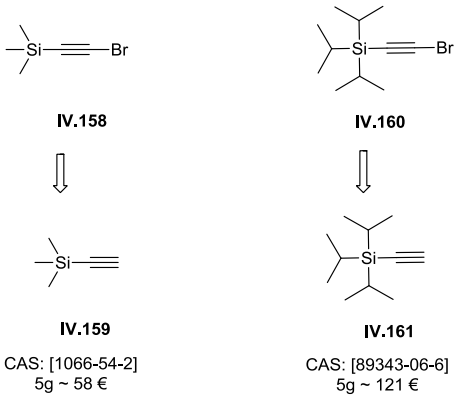
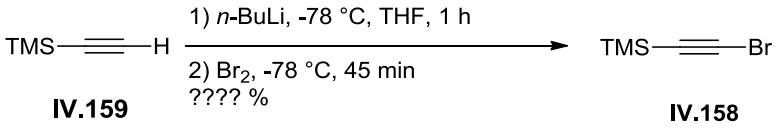


Figure IV.9. *Bromoacetylenes **IV.158** and **IV.160** and their commercial availability.*

As already mentioned in our bibliographical part (Chapter 4.1.2), *N*-alkynylation of anilines *via* direct C-N bond-formation[141] represents a facile route to synthesis of ynamides, extensively utilized in medicinal chemistry.

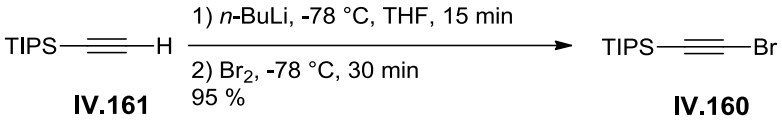
[141] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

Firstly, the terminal bromoalkyne **IV.158** was prepared as alkynylation precursor. (Scheme IV.89) Bromination of alkyne **IV.159** was performed according to the published procedure.[142] However, the resulting product **IV.158** had a low boiling point and was not easy to purify leading to low and irreproducible yields.



Scheme IV.89. *Preparation of (bromoacetylene)-trimethylsilane **IV.158**.*

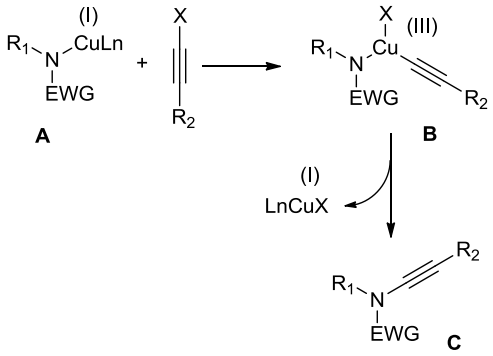
Alternatively, terminal bromoalkyne **IV.160** was prepared from commercially available TIPS-acetylene **IV.161** in 95 % yield (Scheme IV.90)[143] after treatment with *n*-BuLi.



Scheme IV.90. *Preparation of brominated triisopropylylsilane **IV.160**.*

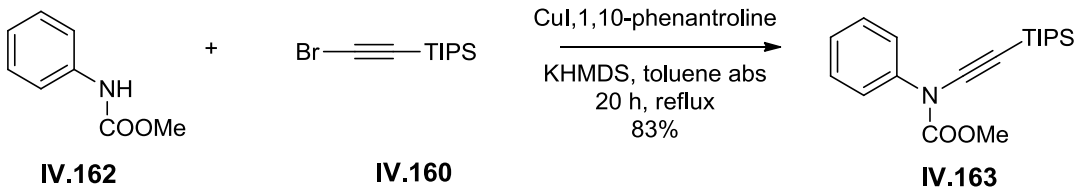
With bromide **IV.160** in our hands, we turned our attention to the coupling reaction with the protected anilines. Tam and co-workers used 0.2 equiv of CuI, 0.25 equiv of 1,10-phenanthroline ligand, and added 1.2 equiv of the base KHMDS slowly over 3–4 h in toluene at 90°C to perform such coupling reaction. As outlined in the Scheme IV.91, oxidative addition of **A** to the alkynyl halide generated a copper(III) intermediate **B**, which then furnished the desired ynamide by reductive elimination. The formation of copper amide intermediate **B** favored the reaction with the alkynyl halide and minimized the competitive reaction of the alkynyl halide with copper salts to "homodimer" byproducts.

[142] Fox, M. A.; Cameron, A. M.; Low, P. J.; Paterson, M. A. J.; Batsanov, A. S.; Goeta, A. E.; Rankin, D. W. H.; Robertson, H. E.; Schirlin, J. T. *Dalton Trans.* **2006**, 3544.
[143] Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359.



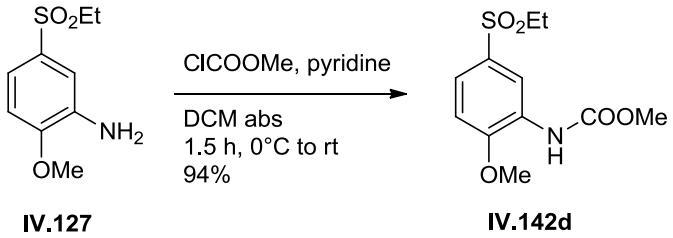
Scheme IV.91. *Mechanism of copper- catalyzed N-alkynylation of anilines (R_1: Ar).*[144]

Tam's protocol[76] was tested on model aniline **IV.162**. Inspirated by Tam's procedure, methoxycarbonyl (-COOMe) was chosen as electron-withdrawing group for stabilization of target ynamide **IV.163**. To our delight, protected ynamide **IV.163** was produced in very good yield (83 %). (Scheme IV.92)



Scheme IV.92. *Verification of Tam's protocol used N-COOMe protected aniline **IV.162**.*

Upon the above results, the Tam's procedure was applied on 5-(ethylsulfonyl)-2-methoxyaniline **IV.127**. Methoxycarbonyl (-COOMe) was chosen as alternative suitable electron-withdrawing protecting group. (Scheme IV.93)

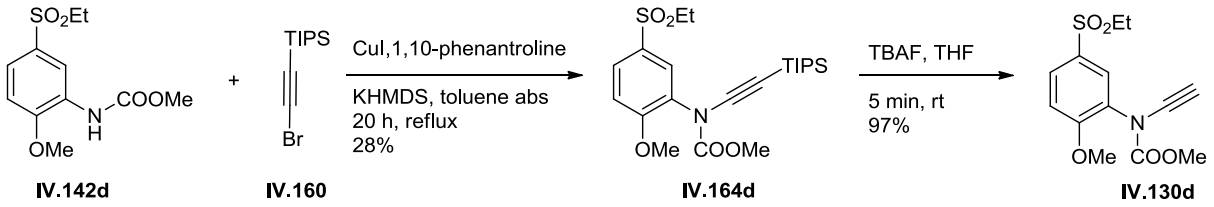


Scheme IV.93. *Introduction of methoxycarbonyl protecting group.*

The direct *N*-alkynylation of protected aniline **IV.142d** afforded the expected ynamide **IV.164d** in only 28 % yield and mostly starting material **IV.142d** was recovered from reaction mixture. (Scheme IV.94) Conversion of starting material **IV.142d** to product **IV.164d** stayed in the same range even if the reaction was prolonged and if bigger quantity of bromoacetylene **IV.160** (2.0 equiv) and

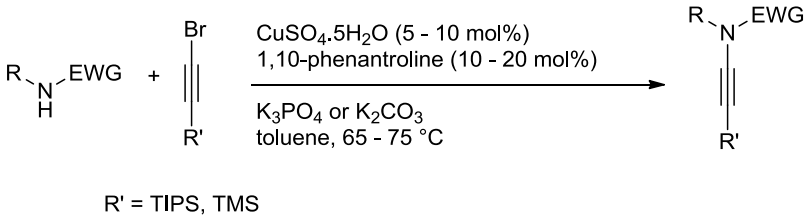
[144] Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *21*, 4011.

base KHMDS were used (3.0 equiv). The TIPS- protecting group was removed by the fluoride anione (TBAF) in quantitative yield 97 %. Compound **IV.130d** was isolated in 26 % overall yield over 3 steps from aniline **IV.127**.



Scheme IV.94. *Preparation of desired ynamide **IV.130d** through the N-direct alkynylation using Tam's conditions.*[76]

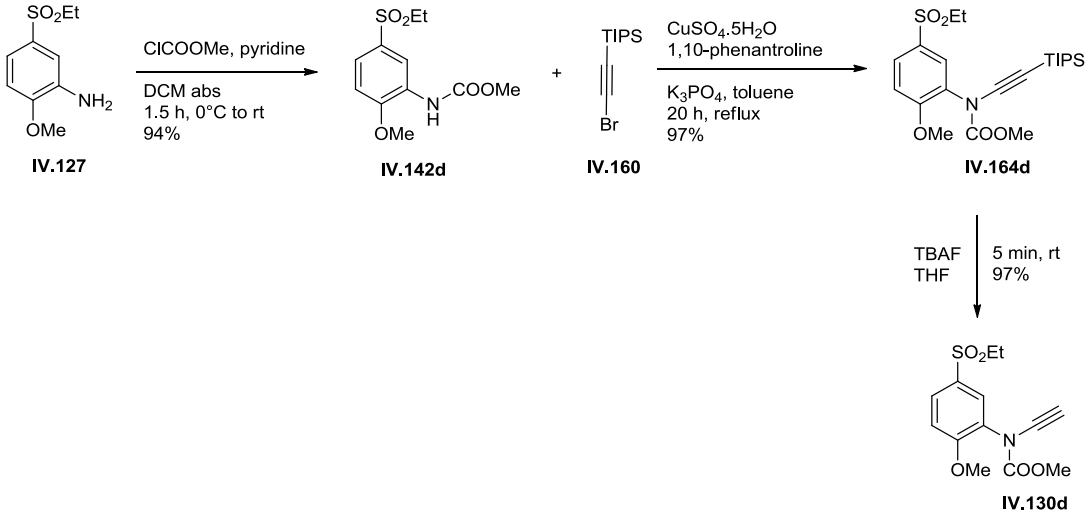
In 2008, Skrydstrup *et al.*[145] described the Hsung's second generation protocol. (Scheme IV.95) Yields of ynamides depended on the quality of K_3PO_4 used as base. The anhydrous K_3PO_4 provided higher ynamides yields (52 – 91 %) in comparison to samples contaminated with hydrates.



Scheme IV.95. *Hsung's second generation protocol.*[145]

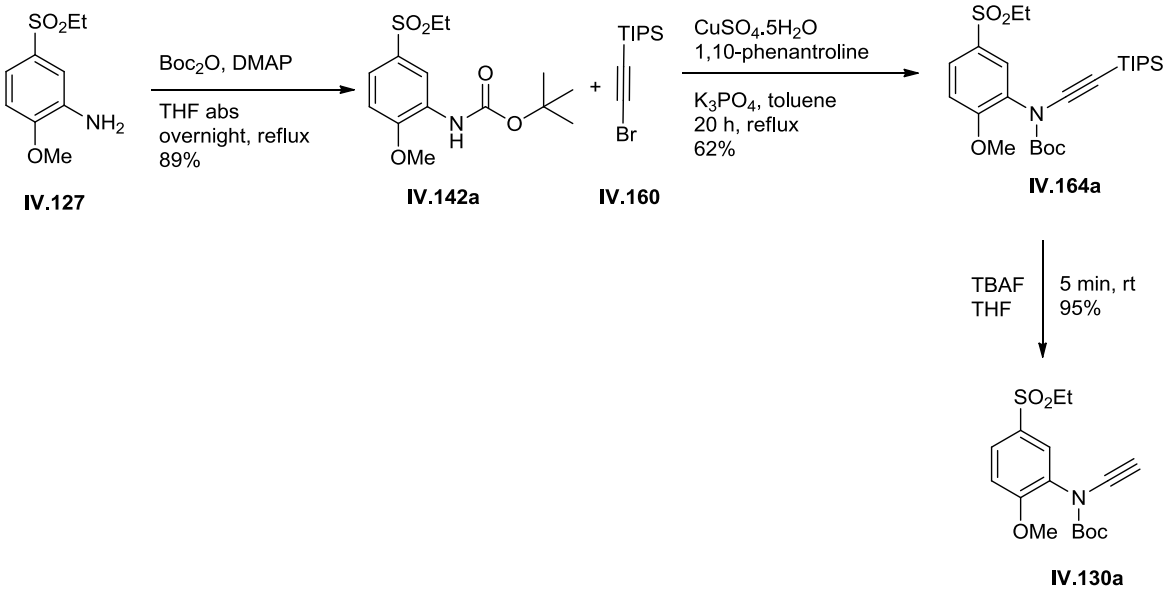
The poor yield obtained with Tam's protocol (28 %) encouraged us to test the Skrydstrup modified procedure. The use of mild conditions (K_3PO_4 as base and $CuSO_4.5H_2O$ as catalyst) was another motivation for testing this protocol. Finally, the reaction afforded an exceptional 97 % yield of **IV.164d** (after purification on silica gel). (Scheme IV.96) Cleavage of TIPS- protecting group afforded ynamide **IV.130d** 88 % overall yield over 3 steps from aniline **IV.127**, which represented a spectacular improvement of the previous procedure (26 %).

[145] Skrydstrup., T. ; Dooleweerdt, K. ; Birkedal, H. ; Ruhland, T. *J. Org. Chem.* **2008**, *73*, 9447.



Scheme IV.96. *Preparation of ynamide **IV.130d** through the direct N-alkynylation using the protocol of Skrydstrup et al.*

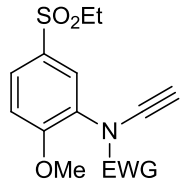
N-COOMe protecting group is generally cleaved under basic conditions. In order to have in hands as possible acid mediated cleavage of triazole adducts resulting from click chemistry, we prepared *N*-Boc protected ynamide **IV.130a**. Boc- protection of aniline **IV.127** was performed in 89 % yield with di-*tert*-butyl dicarbonate using the catalytic amount of 4-dimethylaminopyridine under reflux in THF overnight. (Scheme IV.97) Afterwards, reaction according Skrydstrup's protocol lead to Boc- protected ynamide **IV.164a** in 62 % yield. Subsequent TIPS- deprotection using TBAF afforded the new ynamide **IV.130**. The overall yield of synthesis over 3 steps is 52 %.



Scheme IV.97. *The preparation of ynamide **IV.130a** through the N-direct alkynylation using the protocol of* Skrydstrup *et al.*

4.3 Conclusion of ynamides preparations

In order to realize Click reaction, it was necessary to prepare the key synthon – ynamide **IV.130**.



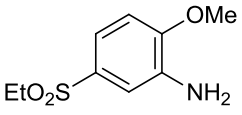
IV.130

target ynamide

We started by reviewing the chemistry of ynamides and detailing their preparation, properties and reactivity. Ynamides are very recent and still intensively studied functions in organic syntheses. The first forerunners of ynamides were ynamines, which are unstable and very sensitive to hydrolysis. (Scheme IV.2) The pioneering work dealing with ynamines was written by Bode in 1892. The hydrolytic instability has caused much difficulty in the experimental preparation and general handling of ynamines. To improve the stability of ynamines and revitalize their synthetical utility, dimishing the electron density by substituting the nitrogen atom with electronegative elements have appeared to be a logical solution. (Figure IV.3) The very first synthesis of ynamides was reported by Viehe in 1972. (Scheme IV.3)[47]

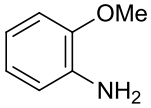
The restrosynthetic strategy proposed for our purposes is depicted in Scheme IV.54 and was based on extensive literature study.

When we have started the synthesis, the target substrate 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** was not commercially available. Lately, we have found the commercial source, but the availability and price was not suitable. Upon this, we have decided to use *o*-aniside **IV.128** as a suitable and cheap model substrate.



IV.127

target substrate

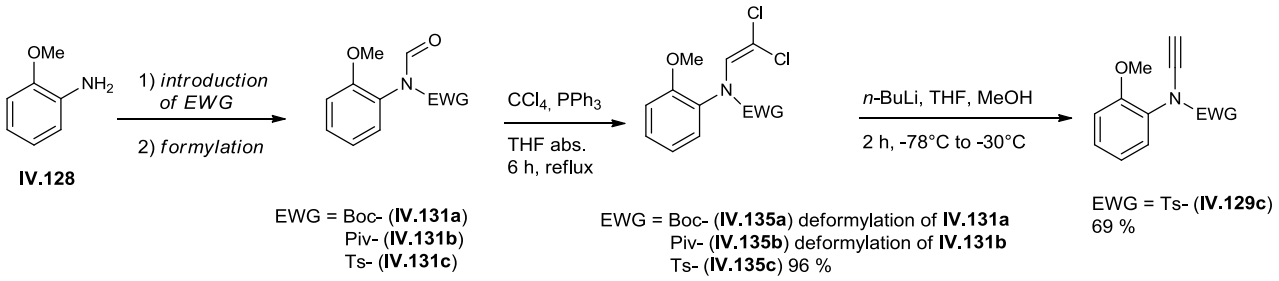


IV.128

model substrate

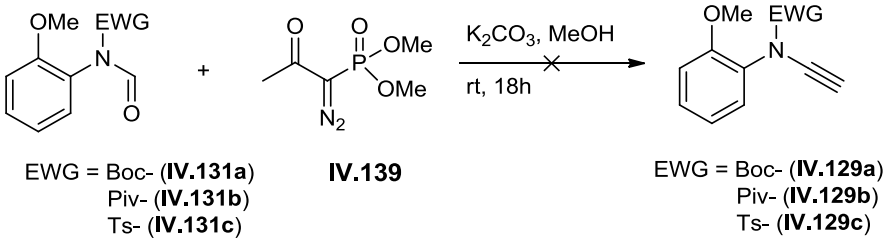
The first protocol in the hand was the two-steps synthesis - Corey-Fuchs approach (Pathway A) published by Brückner.[64,65] The first problems we met was the right selection of the

electron-withdrawing group. Reactions performed with *tert*-butyloxycarbonyl (Boc-) and pivaloyl (Piv-) protected formamides **IV.131a** and **IV.131b** failed. Alternatively, *p*-toluenesulfonyl as EWG (Ts-) furnished in desired model ynamide **IV.129c** in 66 % yield over two steps. (Scheme IV.70 and IV.98)



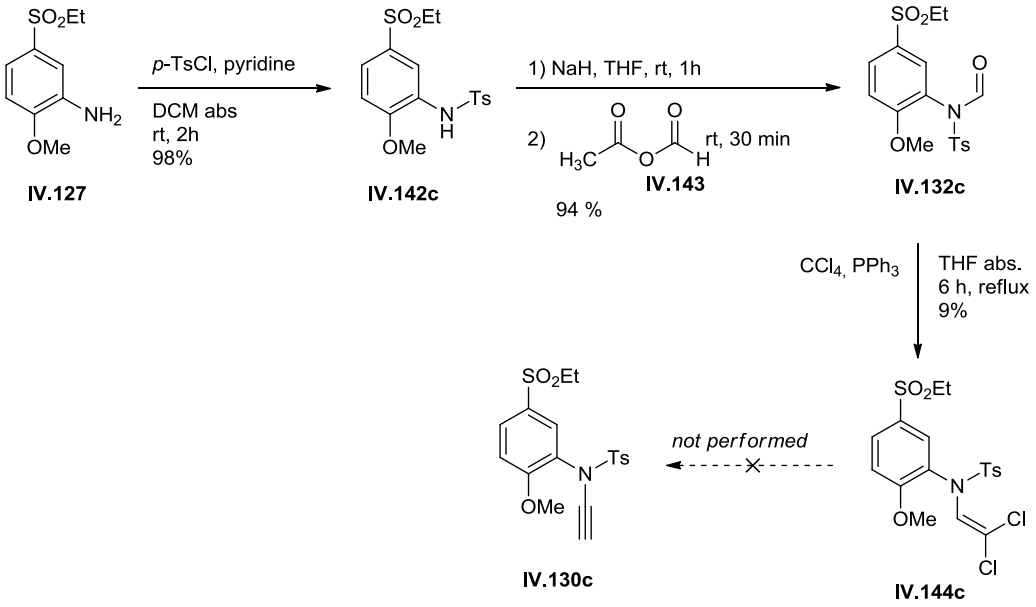
Scheme IV.98. *The Corey-Fuchs approach leading to the model ynamide **IV.129c**.*

As alternative to Corey-Fuchs reaction we examined the one-step Bestmann-Ohira reaction (Pathway B) by **IV.139** for preparation of *N*-Boc or *N*-Piv protected ynamides **IV.129a**,**b.** But all these attempts failed.



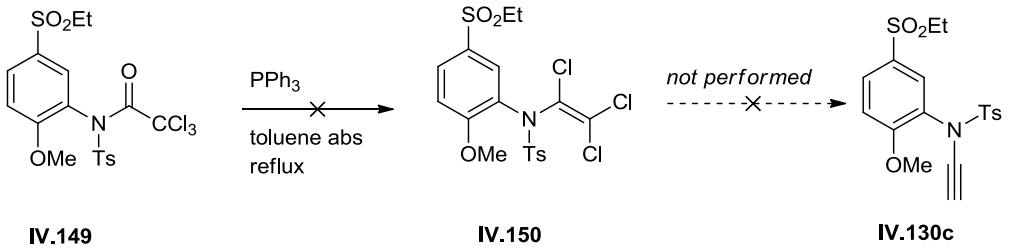
Scheme IV.73. *Performed Bestmann-Ohira reactions on substrate **IV.131a,b,c**.*

The positive results obtained *via* Corey-Fuchs reaction on model molecule producing ynamide **IV.129c** motivated us to apply the same conditions on target substrate **IV.127**. We focused our effort for preparation of *N*-formylated substrate protected with *p*-toluensulfonyl electron-withdrawing group **IV.132c**. Its synthesis was difficult. We met lot of problems to introduce the second functional group on the nitrogen atom due to the low nucleophily of the nitrogen caused by $EtSO_2$- substituent present on aromatic ring of aniline **IV.127**. Finally, introduction of the Ts- group prior to formylation was successfully performed. (Scheme IV.99) Unfortunately, preparation of 1,1-dichlorovinyl **IV.144c** from **IV.132c** did not give satisfactory yield (9 %). (Scheme IV.99) Consequently, we abandoned this pathway.



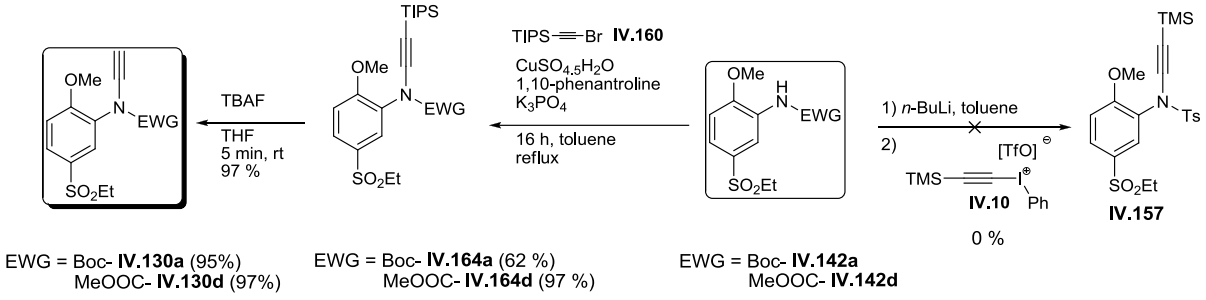
Scheme IV.99. *Application of Corey-Fuchs approach on tosylated N-formamide **IV.132c**.*

The third proposed pathway C was conversion of trichloroacetamides **IV.149** to ynamides inspirited by the protocol of Speziale and Smith[133], and by Himbert and Regitz.[134] One more time this procedure was not adapted to our substrate and failed. (Scheme IV.100)



Scheme IV.100. *Conversion of of trichloroacetamide **IV.149** to ynamide.*

The last proposed pathway D was direct *N*-alkynylation of target substrate equipped with EWG. Direct *N*-alkynylation using alkynyliodonium salt **IV.10** was examinated, but failed. (Scheme IV.101) Alternatively, *N*-direct alkynylation using bromoalkyne **IV.160** gave excellent results using Skrydstrup's procedure. *N*-COOMe and *N*-Boc protected ynamides **IV.142a** and **IV.142d** were obtained in excellent 97 % and 62 % yield respectively. Subsequent desilylation was almost quantitative and each ynamide **IV.130a** and **IV.130d** were obtained in 88 and 58 % overall yield starting from aniline **IV.127** over 3 steps.



EWG = Boc- **IV.130a** (95%)
MeOOC- **IV.130d** (97%)

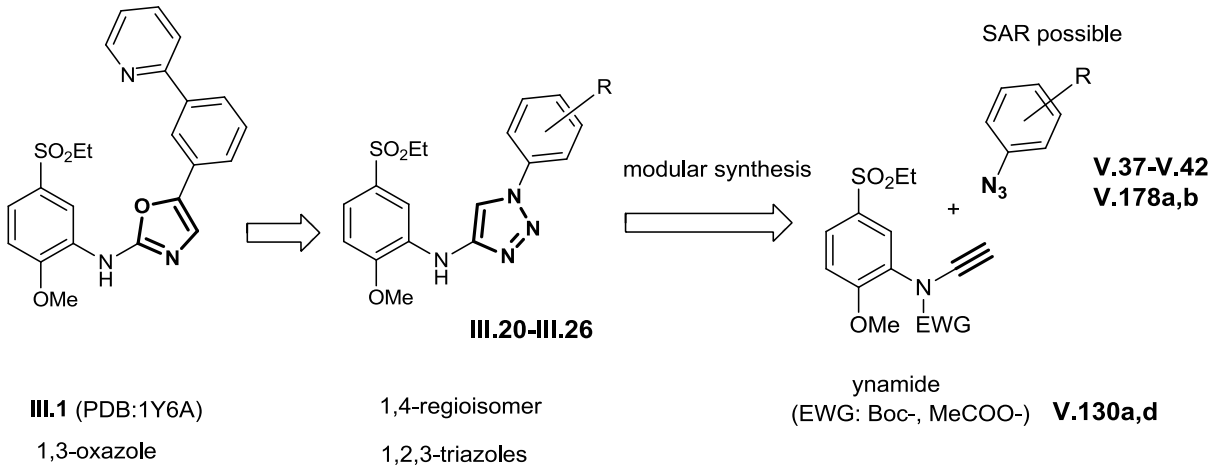
EWG = Boc- **IV.164a** (62 %)
MeOOC- **IV.164d** (97 %)

EWG = Boc- **IV.142a**
MeOOC- **IV.142d**

Scheme IV.101. *Preparation of ynamides **IV.130a** and **IV.130d** via N-direct alkynytation of N-EWG protected aniline **IV.164a** with bromoalkyne **IV.160** and alkynyliodonium triflate salt **IV.10**.*

Chapter 5. **Azides**

The next synthetical goal of our project was the preparation of several aromatic azides **V.37-V.42** and **V.178a,b** as partners of ynamides **IV.130a** and **IV.130d** for Click chemistry reaction. (Scheme V.1)



Scheme V.1. *General retrosynthetic approach in order to prepare triazolic isostere ofAAZ ligand known from PDB complex 1Y6A using Click chemistry.*

5.1 General characterization, properties and reactivity of azides

Since the discovery of organic azides by Peter Grieß more than 140 years ago[146], numerous syntheses of these energy-rich molecules have been developed. In more recent times in particular, completely new perspectives have been developed for their use in peptide chemistry, combinatorial chemistry, and heterocyclic synthesis. Organic azides have assumed an important position at the interface between chemistry, biology, medicine, and materials science.[147]

5.1.1 Structure and properties

The structural determination of azides originates from the initial postulation of Curtis and Hantzsch, who had suggested a cyclic *1H*-triazirine structure,[148,152,153] that was, however, rapidly revised in favor of the linear structure. (Figure V.1) Aromatic azides are stabilized by conjugation with the aromatic system.

[146] Grieß, P. *Justus Liebigs Ann. Chem.* **1865**, *135*, 131.
[147] Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.
[148] Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1349.

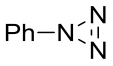


Figure V.1. *1-phenyl-1-H-triazinine*

A basis for the chemical diversity of azides comes from the physicochemical properties of azides. Some of the physicochemical properties of the organic azides can be explained by a consideration of polar mesomeric structures. (Figure V.2) The dipolar structures of type **V.1c** and **V.1d** (proposed by Pauling[149]) also explained the facile decomposition into the corresponding nitrene and dinitrogen as well as the reactivity as a 1,3-dipole. The regioselectivity of their reactions with electrophiles and nucleophiles is explained on the basis of the mesomeric structure **V.1d** (attack on N^3 by nucleophiles, and electrophiles are attacked by N^1).

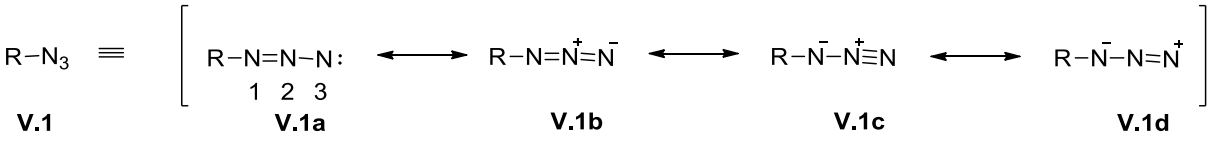


Figure V.2. *Polar mesomeric structures **V.1a**-**V.1d** of azide **V.1.***

Like hydrogen azide most other azides are also explosive substances that decompose with the release of nitrogen through the slightest input of external energy, for example pressure, impact, or heat. The heavy-metal azides are used, for example, in explosives technology, in which they serve as detonators. Sodium azide is applied in airbags. Organic azides, particularly methyl azide, often decompose explosively.[147]

Since the preparation of the first organic azide, phenyl azide, by Peter Grieß in 1864 these energy-rich and flexible intermediates have enjoyed considerable interest.[150,151] A few years later Curtius developed hydrogen azide and discovered the rearrangement of acyl azides to the corresponding isocyanates (Curtius rearrangement).[152,153] The organic azides received considerable attention in the 1950s and 1960s[154,155] with new applications in the chemistry of the acyl, aryl, and alkyl azides. Industrial interest in organic azide compounds began with the use of azides for the synthesis of heterocycles such as triazoles and tetrazoles as well as with their use as blowing agents

[149] Pauling, L.; Brockway, L. O. *J. Am. Chem. Soc.* **1937**, *59*, 13.
[150] Scriven, E. F. V.; Turnbull, K. *Chem. Rev*. **1988**, *88*, 297.
[151] Grieß, P. Philos. *Trans. R. Soc. London* **1864**, *13*, 377.
[152] Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023.
[153] Curtius, T. *J. Prakt. Chem.* **1894**, *50*, 275.
[154] Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
[155] Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1.

and as functional groups in pharmaceuticals. Thus, for example, azidonucleosides attract international interest in the treatment of AIDS.[156]

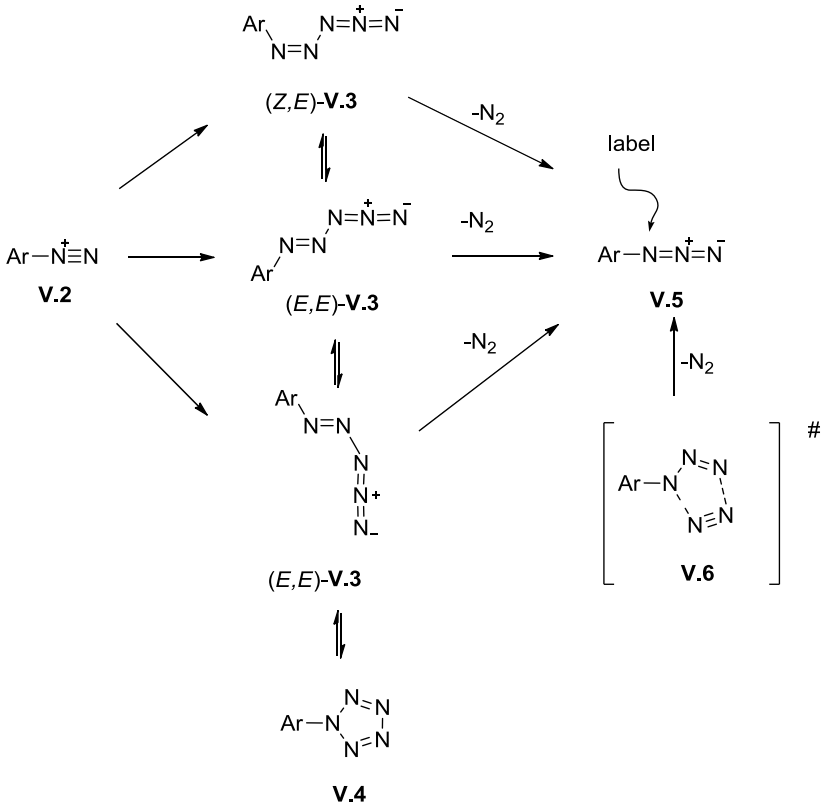
5.1.2 Synthesis of aryl azides

Aryl azides are widely used because of their relatively high stability in comparison with aliphatic ones.

5.1.2.1 Preparation of aryl azides from diazonium salts

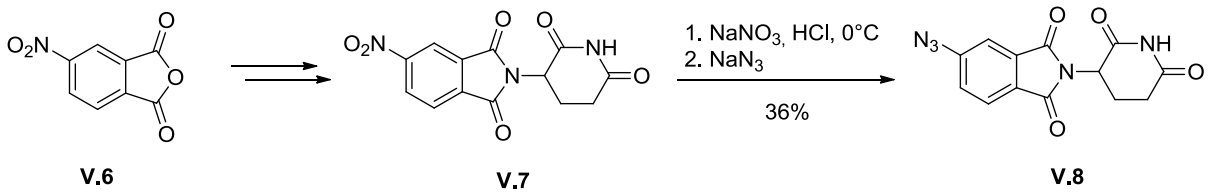
In the meantime, some convenient conversions of aryl diazonium salts **V.2** into aryl azides **V.5** have been developped. Aryl diazonium salts **V.2** react directly with azide ions without catalysts to give the corresponding aryl azides **V.5**.[157]Alkali azides or trimethylsilyl azides act as source. Unlike the Sandmeyer reaction, this reaction does not take place with cleavage of the C– heteroatom bond but occurs with attack of the azide on the diazonium ion with formation of aryl pentazoles **V.6** and its subsequent products.[158] (Scheme V.2) A pentazole structure was established for the first time by X-ray crystal-structure analysis in 1983.[159] A British group[158] investigated this reaction spectroscopically by ^{1}H and ^{15}N NMR spectroscopy of three isomeric aryl pentazenes **V.3** (*Z, E*), (*E, E*) and (*E, Z*) isomers.

[156] Lin, T. S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109.
[157] Biffin, M. E. C.; Miller, J.; Paul, D. B. *The Chemistry of the Azido Group* (Ed.: S. Patai),Wiley, New York, **1971**, 147.
[158] Butler, R.N.; Fox, A.; Collier, S.; Burke, L. A. *J. Chem. Soc. Perkin Trans. 2* **1998**, 2243.
[159] Wallis, J. D.; Dunitz, J. D. *J. Chem. Soc. Chem. Commun.* **1983**, 910.



Scheme V.2. *Mechanism of conversion of diazonium ions **V.2** into azide **V.5**.*[158]

A more recent example of the decomposition of diazonium salts into the corresponding aryl azides is illustrated by the synthesis of azido-thalidomide **V.8**.[160] (Scheme V.3)

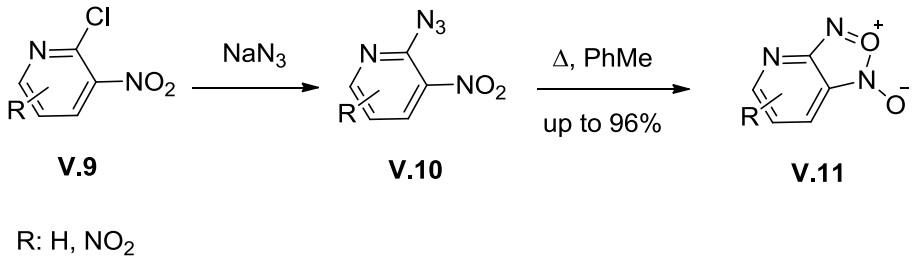


Scheme V.3. *Synthesis of azido-thalidomide **V.8**.*[160]

5.1.2.2 Nucleophilic Aromatic Substitutions

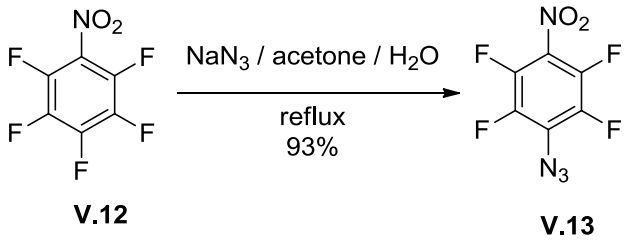
Activated aromatic systems such as fluoro- and chloronitroarenes **V.9** and a few heteroaromatic systems[161] can undergo nucleophilic substitution by azide ions. (Scheme V.4) They are generally sufficiently nucleophilic to produce aryl azides in good yields.

[160] Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Org. Lett.* **2003**, *5*, 2865.
[161] Miller, D. R.; Svenson, D. C.; Gillan, E. G. *J. Am. Chem. Soc.* **2004**, *126*, 5372.



Scheme V.4. *An example of aromatic substitution in order to prepare aryl azides **V.10** from aryl chloride **V.9**.*[162]

Commercially available pentafluoronitrobenzene **V.12** was converted into 4-azidotetrafluoronitrobenzene **V.13** by nucleophilic aromatic substitution with NaN_3 in 93% yield. (Scheme V.5) No *ortho* isomer was detected in the crude reaction mixture. [163]



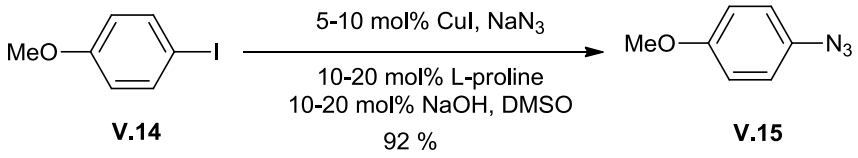
Scheme V.5. *An example of aromatic substitution in order to prepare aryl azides from aryl fluoride **V.12**.*[163]

5.1.2.3 Synthesis of aryl azides from non-activated aromatic halides using copper catalyst

Although aryl azides and vinyl azides have shown increasing importance in many aspects, synthetic studies toward these compounds are rare.[164] The preparation methods for aryl azides are based mainly on the replacement of diazonium salts or some activated aryl halide with sodium azide.[165] Direct coupling of inactivated aryl halides with sodium azide catalyzed by CuI were reported with low yields, mainly because completion of the reaction needed a higher reaction temperature, which caused decomposition of the aryl azides.[166]

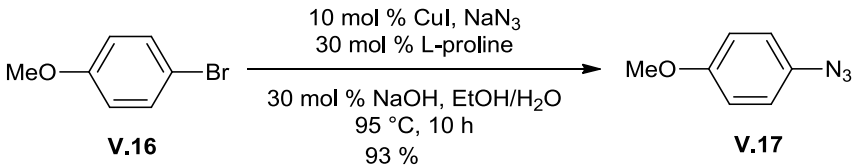
[162] Lowe-Ma, C. K.; Nissan, R. A.; Wilson, W. S. *J. Org. Chem*. **1990**, *55*, 3755.
[163] Chehade, K. A. H.; Spielmann, H. P. *J. Org. Chem.* **2000**, *65*, 4949.
[164] Scriven, E. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 351.
[165] Liu, Q.; Tor, Y. *Org. Lett.*, **2003**, *5*, 2571.
[166] Suzuki, H.; Miyoshi, K.; Shinoda, M. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1765.

In 2004, Ma and Zhu published a work,[167] which described easy copper-catalyzed conversion of aryl iodides and aryl bromides into aryl azides. They have demonstrated that amino acids, as the additives, could promote Ullmann-type couplings thereby decreasing the reaction temperature. As an extension of this work, they reported here a proline-promoted, CuI-catalyzed coupling reaction of aryl halides **V.14** or vinyl halides with sodium azide, which provided a variety of aryl azides and vinyl azides.



Scheme V.6. *Preparation of aryl azide **V.15** from aryl iodide **V.14** via proline promoted CuI-catalyzed coupling reaction.*[167]

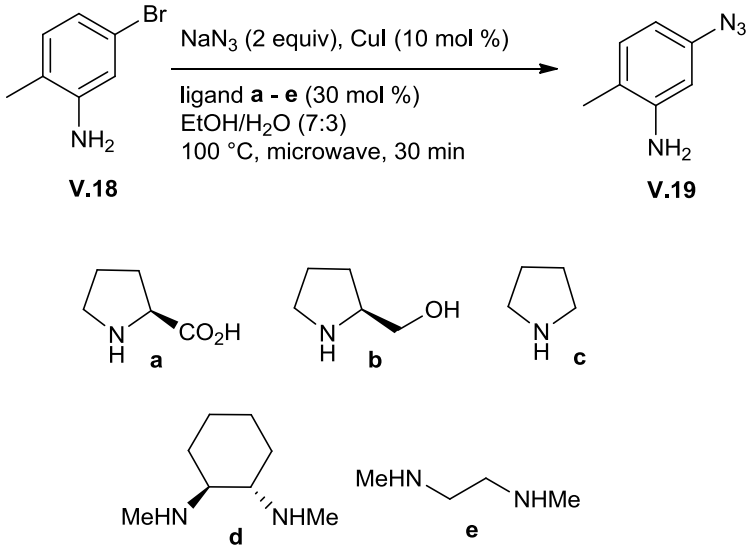
It was found that under the action of 10 mol % CuI, 20 mol % L-proline, and 20 % NaOH in DMSO the reaction gave 4-methoxyphenyl azide **V.15** in 92 % yield at 60 °C. (Scheme V.6) Without addition of NaOH the reaction gave only 64 % yield within the same reaction time. In the absence of L-proline or its sodium salt, the reaction gave only 9 % yield, which indicated that L-proline plays an essential role in this reaction. In addition, they noticed that other amino acids such as *N*-methylglycine and *N*,*N*-dimethylglycine also worked as additive for this reaction but gave lower yields. Further investigations indicated that aryl bromides did not work for the above reaction conditions because only a trace of coupling product was isolated, even when the reaction temperature increased. After some attempts it was found that if a mixed solvent (7 : 3 = EtOH : H_2O) was used, the coupling reaction of 4-bromoanisole **V.16** with sodium azide provided 4-azidoanisole **V.17** in 93% yield under the catalysis of 10 mol % CuI and 30 mol % L-proline at 95 °C. (Scheme V.7)



Scheme V.7. *Preparation of aryl azide from aryl bromide* via *proline promoted CuI-catalyzed coupling reaction.*[167]

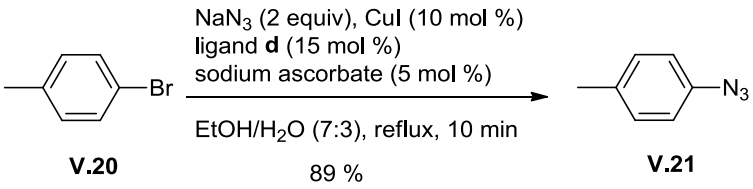
[167] Zhu, W.; Ma, D. *Chem. Comm.* **2004**, 888.

In 2005, Liang and co-workers published an article,[168] where the preparation of aryl azides **V.19** was described from corresponding aryl halides under very mild conditions using CuI / diamine as catalyst. Sodium ascorbate was found to have a positive effect on stabilization of the catalytic system. Five ligands **a**-**e** for azidation of 5-bromo-2-methylaniline **V.18** under microwave irradiation were examined. (Scheme V.8)



Scheme V.8. *Ligand screening for azidation of 5-bromo-2-methylaniline **V.18**.*[168]

Two diamine ligands **d** and **e** efficiently accelerated this reaction. Afterwards, they examined the solvent system using ligand **e**. In contrast to Ma's work, in which only traces of coupling product were isolated, 55 % yield was observed when DMSO was used as solvent. However, no solvent systems were as good as EtOH : H_2O (7 : 3). They also studied the microwave influence on the reaction rate. Conventional heating gave full conversion within 40 minutes, suggesting that the high reaction rate was not due to microwave effect. Similar reaction needs 24 hours for completion using proline



Scheme V.9. *Conversion of aryl bromide **V.20** to aryl azide **V.21** under very mild conditions catalyzed by CuI/diamine.*[168]

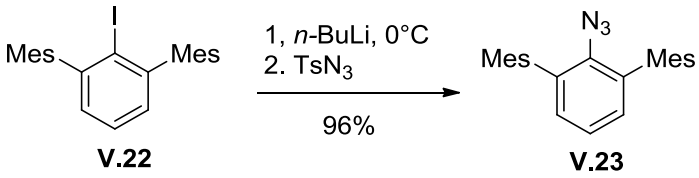
[168] Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005,** *14,* 2209.

as ligand. For example, conversion of **V.20** to corresponding azide **V.21** was accomplished under the action of 2 equiv sodium azide, 10 mol % copper iodide, 15 mol % of ligand **d** and 5 mol % sodium ascorbate in the mixture of EtOH / H_2O (7 : 3) within 10 min in 89 % yield. (Scheme V.9)

In addition, it was shown that conversion of aryl iodides to the corresponding azides is easy to perform even at room temperature.

5.1.2.4 Synthesis of aryl azides from organometallic reagents

Recently, numerous methods for the preparation of aryl azides with organometallic reagents have been developed.[169] For example, tosyl azide reacts with Grignard or lithium reagents— depending on the corresponding aryl halide **V.22**— to form novel aryl azides. In Scheme V.10 is depicted an example of this approach leading to aryl azide **V.23**.

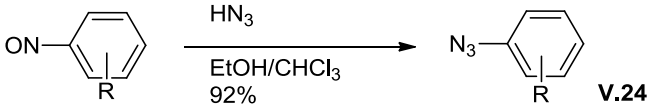


V.22 **V.23**

Scheme V.10. *Preparation of aryl azide **V.23** according to Tilley and co-workers.*[169]

5.1.2.5 Synthesis of aryl azides from nitrosoarenes

The reaction of nitrosoarenes with hydrogen azide leads to aryl azides **V.24** in good yields.[170] (Scheme V.11) However, the diazonium ions must first be formed and then treated with azide ions as the second step - 2 equivalents of the explosive acid are required.



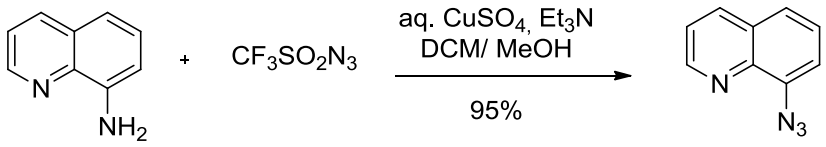
V.24

Scheme V.11. *Preparation of azide **V.24** from nitrosoarene.*[170]

[169] Gavenonis, J.; Tilley, T. D. *Organometallics* **2002**, *21*, 5549.
[170] Maffei, S.; Rivolta, A. M. *Gazz. Chim. Ital.* **1954**, *84*, 750.

5.1.2.6 Preparation of aryl azides by diazo transfer

Aryl azides and heteroaryl azides may be prepared by the reaction of anilines with triflyl azide **V.26**.[171] The mild reaction conditions and very high yields make these transformations the method of choice for the preparation of numerous aromatic azides. In a typical reaction (Scheme V.12) freshly prepared **V.26** is treated with 8-aminoquinoline **V.25** at room temperature in a mixture of dichloromethane/methanol and the presence of triethylamine and copper sulfate to deliver compound **V.27**.

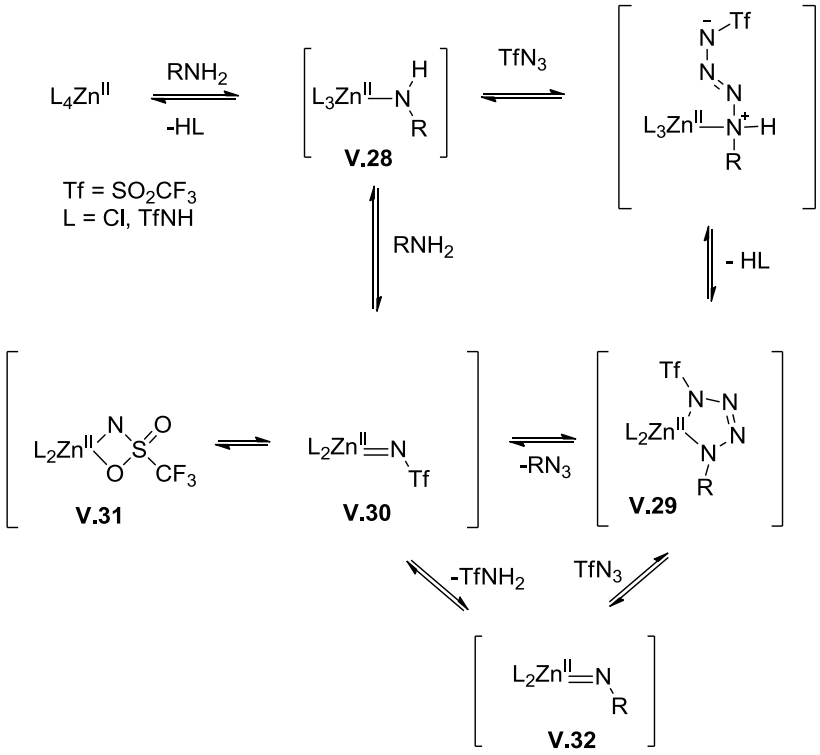


V.25 **V.26** **V.27**

Scheme V.12. *Conversion of aromatic amines **V.25** into aryl azides **V.27** according to Tor and co-workers.*[171]

Mechanism for the metal-catalyzed diazo transfer for the aliphatic amine-to-azide interconversion has been proposed by Wong *et al.* [172] (Scheme V.13) Amine complexation to the zinc catalyst, under basic conditions, may provide **V.28**. Owing to the extreme electrophilicity of triflyl azide **V.26**, nucleophilic attack by the amine of **V.28** on the highly electrophilic triflyl azide, followed by deprotonation, form the zinc-stabilized mixed tetrazene **V.29**. The breakdown of **V.29**, possibly *via* a reverse [3+2]-dipolar cycloaddition, would produce the product azide and zinc-triflyl imido complex **V.30**. This complex could be in equilibrium with **V.32**. From here, two possible pathways could be operative. Amine complexation, followed by the transfer of a proton, would provide **V.30**, with one of the ligands being triflamide. The other mechanism is the transimination of **V.31** to yield the transient zinc-imido complex **V.32**. The imido-metal complex could be engaged with triflyl azide in a [3+2]-dipolar cycloaddition to alternatively provide **V.29**.

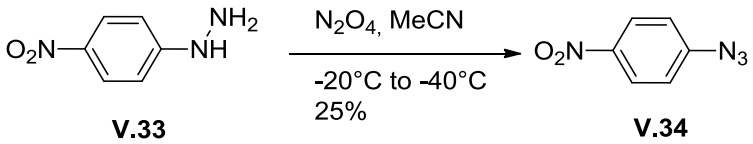
[171] Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571.
[172] Wong. See: Nyffeler, P. T.; Liang, C. H.; Koeller, K. M.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 10773.



Scheme V.13. *Possible mechanism for the transition metal-catalyzed diazotransfer reaction releasing RN_3 product (mentioned under the reaction arrow).*[172]

5.1.2.7 Diazotation of hydrazines

The next type of procedure suitable for the preparation of different aromatic and aliphatic or aryl azides, acyl azides, and sulfonyl azides is the reaction of hydrazines such as **V.33** with nitrosyl ions or their precursors (N_2O_4,[173] mixtures of nitrogen oxide/oxygen,[174] nitrosyl salts,[175] and sodium nitrite[176]) leading to azide **V.34**.



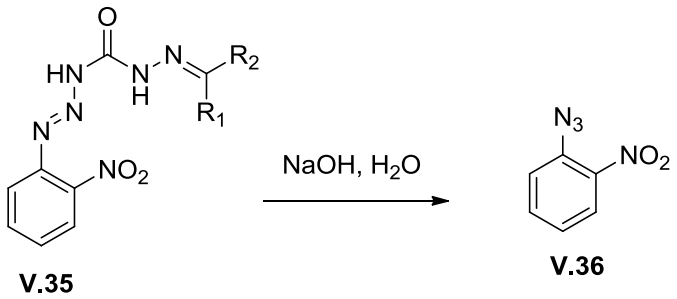
Scheme V.14. *Conversion of the aromatic hydrazine **V.33** into aryl azide **V.34** according to Kim et al.*[173]

[173] Kim, Y. H.; Kim, K.; Shim, S. B. *Tetrahedron Lett.* **1986**, *27*, 4749.
[174] Matsuya, Y. I. T.; Nagata, K.; Ohsawa, A. *Tetrahedron* **1997**, *53*, 15701.
[175] Pozsgay, V.; Jennings, H. *Tetrahedron Lett*. **1987**, *28*, 5091.
[176] Wamhoff, H.; Wambach, W. *Chem.-Ztg.* **1989**, *113*, 11.

The reaction temperature must be controlled at lower than -20°C. While, *p*-nitrophenyl- and phenyl-azides appear to rearrange to the heterocycles due their instability at high temperature.

5.1.2.8 Modification of triazenes and related compounds

The rearrangement of triazenes into azides belongs to the older methodologies for preparation of aryl azides.[177] In particular, the base-induced cleavage of semicarbazones **V.35** can be used for the preparation of azides **V.36**. (Scheme V.15)



V.35 **V.36**

Scheme V.15. *Synthesis of aryl azide **V.36** from semicarbazone **V.35**.*[177]

[177] Forster, M. O. *J. Chem. Soc.* **1906**, 233.

5.2 Preparation of target azides for Click chemistry synthesis

Prediction studies selected several triazoles **III.20** - **III.26** (Chapter 3, Figure III.5) differing in their upper aromatic parts in order to observe different interactions in an active site of VEGFR-2.

The structures of appropriate azides **V.37** – **V.43** are depicted (Figure V.3). They were selected for synthesis in order to obtain the predicted triazolic analogues of AAZ ligand (**III.1**) from complex PDB: 1Y6A.

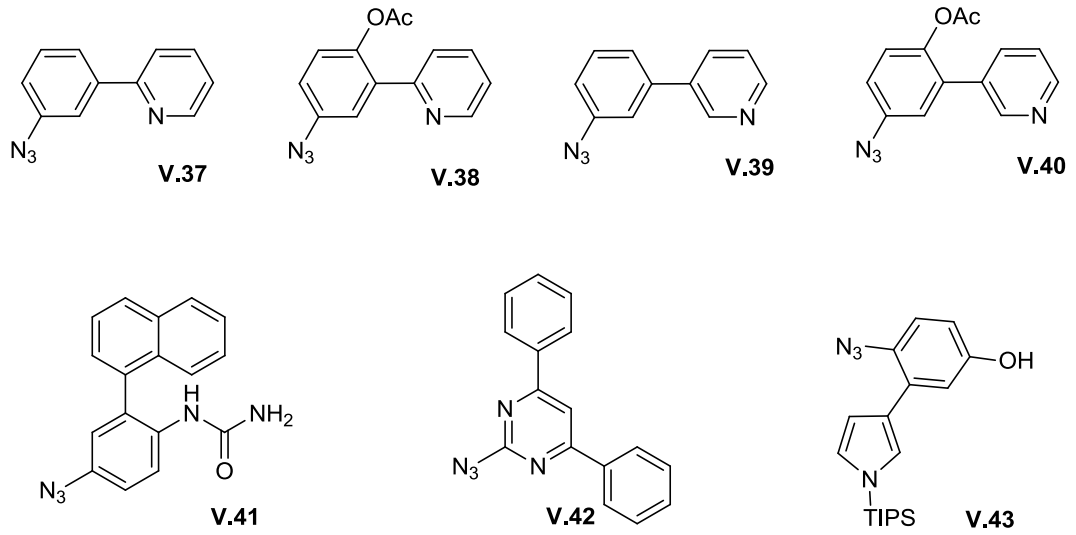
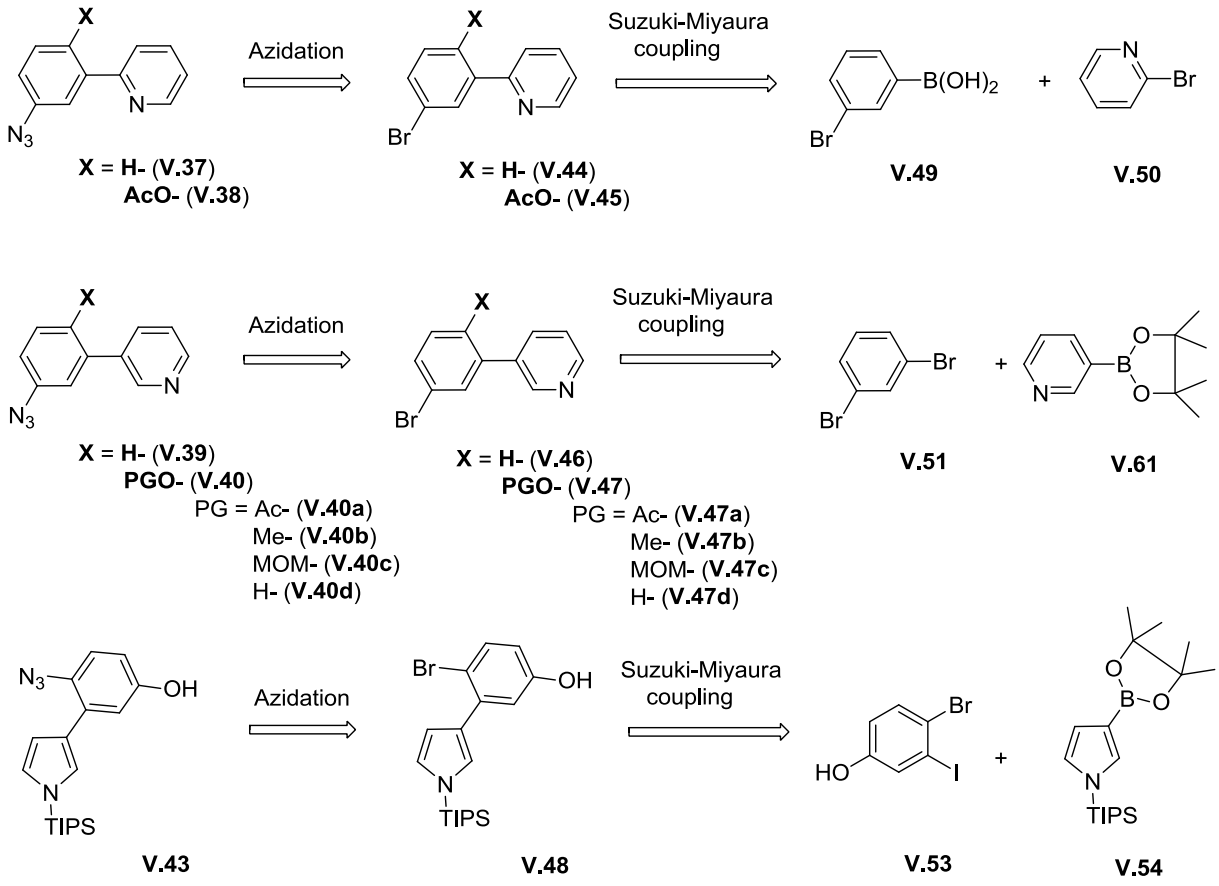


Figure V.3. *Azides corresponding to predicted aromatic parts of proposed triazolic analogues of **III.1**.*

Concerning azides **V.37**, **V.38**, **V.39**, **V.40** and **V.43**, we tried first the general strategy depicted in Scheme V.16 which consisted on the preparation of the corresponding brominated derivatives **V.44** – **V.48** resulting from a Suzuki-Miyaura coupling reactions.



Scheme V.16. *General access to biarylic azides **V.37, V.38, V.39, V.40** and **V.43** via Suzuki-Miyaura cross-coupling.*

Azides **V.41** and **V.42** were prepared using specific strategies which will be developed later.

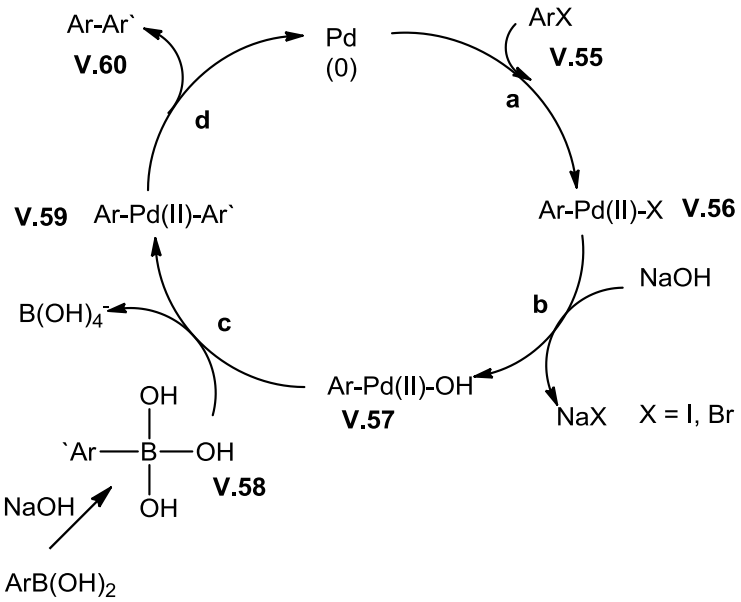
Suzuki-Miyaura cross-coupling

Suzuki-Miyaura cross-coupling is one of the crucial step used for the preparation of azides **V.37** – **V.40** and **V.43**.

- the coupling of an aryl- or vinyl- boronic acid with an aryl- or vinyl halide catalyzed by a palladium(0) complex is known as Suzuki reaction
- the original article on cross-coupling with an organoborane compound was published by Suzuki *et al.* in 1979[178]

[178] Miyaura, N.; Yamada, K.; Suzuki, A., *Tetrahedron Lett.* **1979**, *36*, 3437.

- the reaction is widely used to synthetize polyolefins, styrenes, and substituted biphenyls, and has been extended to incorporate alkyl bromides
- in 2010 Nobel Prize in Chemistry was awarded to Suzuki for his discovery and development of this reaction
- in many publications this reaction is also called Suzuki-Miyaura reaction or Suzuki coupling



Scheme V.17. *Mechanism of Suzuki-Miyaura cross-coupling.*[179]

The first step in the Suzuki cross-coupling is *oxidative addition* (a) of palladium to the halide **V.55** forming intermediate **V.56**. Reaction with base gives intermediate **V.57** in a step (b). Its *transmetallation* (c) with boronate complex **V.58** forms the organopalladium species **V.59**. The last step (d) represents a *reductive elimination* which results in the product **V.60** and regeneration of the Pd (0) catalyst.[179] (Scheme V.17)

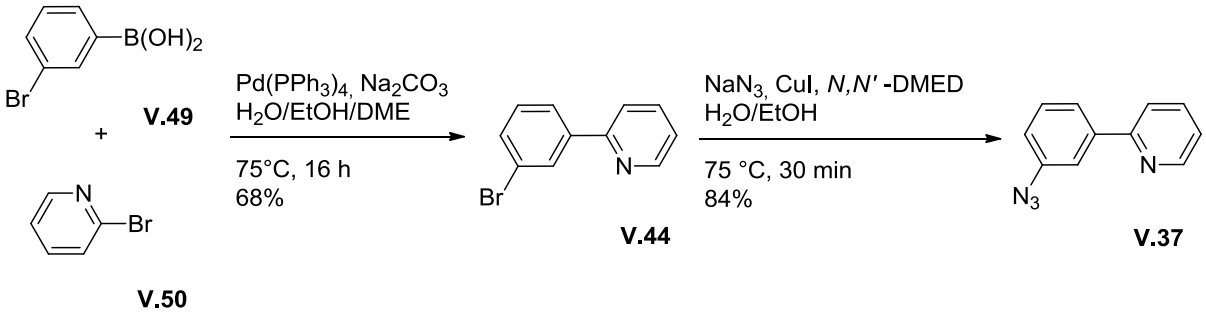
The oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in the order of **I > OTf > Br >> Cl**. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups, thus allowing the use of chlorides such as 3-chloroenone for the cross-coupling reaction. A very wide range of palladium(0) catalysts or precursors can be used for cross-coupling reaction. $Pd(PPh_3)_4$ is most commonly used, but $PdCl_2$(PPh3) and $Pd(0Ac)_2$ in the presence of PPh3 or

[179] Kürti, L.; Czakó, B., *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: London, **2005**.

other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complexes by organometallics or phosphines used for the cross-coupling.[180,181,182,183]

5.2.1 Preparation of azide V.37

The bromobiaryl **V.44** was prepared by Suzuki coupling reaction between commercially available 3-bromophenyl boronic acid **V.49** and 2-bromopyridine **V.50**.[184,185] The transformation of bromobiaryl **V.44** to azide **V.37** was performed using sodium azide, catalytic amount of copper iodide and *N,N'*-DMED according to the methodology published by Liang and co-workers in 2005.[168]



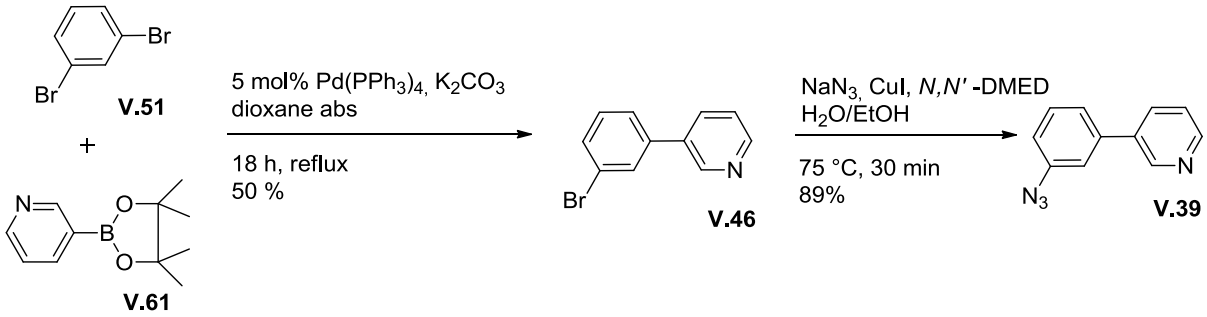
Scheme V.18. *Preparation of azide biaryl ligand **V.37**.*

Azide **V.37** was isolated in 57 % overall yield for 2 steps reaction.

5.2.2 Preparation of azide V.39

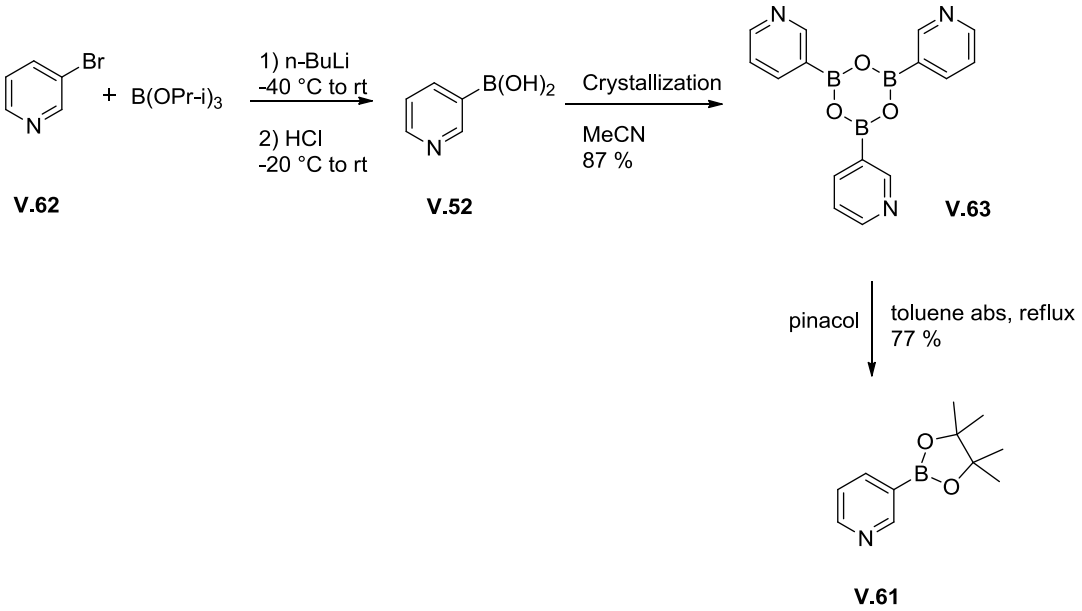
Azide **V.39** differs from **V.37** by the *meta*-subtitution of the pyridyl cycle. 3-(3-Bromophenyl)-pyridine **V.46** was prepared by Suzuki-Miyaura cross-coupling[186] between 1,3-dibromophenyl **V.51** and pinacol boronic ester **V.61** in 50 % yield after purification. (Scheme V.19) Finally, the bromine was substituted by azide functional group by copper catalyzed substitution in 89 % yield.

[180] McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J.; Stephanson, D. K. *J. Chem. Res.* **1984**, 360**.**
[181] Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992,** *11***,** 3009**.**
[182] Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177**.**
[183] Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.
[184] Trokowski, R.; Akine, S.; Nabeshima, T. *Dalton Trans.* **2009**, *46,* 10359.
[185] Mongin, F.; Rebstock, A. S. ; Trécourt, F. ; Quéguiner, G. ; Marsais, F. *J. Org. Chem.* **2004**, *69*, 6766.
[186] Trokowski, R.; Akine, S.; Nabeshima, T. *Dalton Trans.* **2009**, *46,* 10 359.



Scheme V.19. *Preparation of azide **V.39**.*

The pinacol boronic ester **V.61** was prepared from 3-bromopyridine **V.62** *via* boroxin **V.63** in 65 % overall yield.[187] (Scheme V.20)



Scheme V.20. *Synthesis of pinacol boronic ester **V.61**.*

5.2.3 Preparation of azide V.38

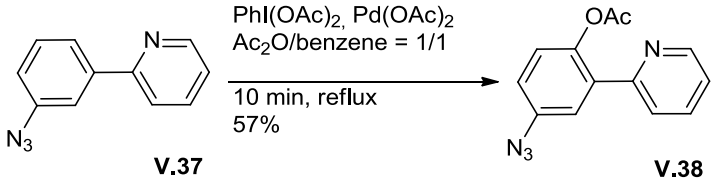
Recently, Pd^{II}-catalyzed methods for the heteroatom-directed functionalization of arene and alkane C-H bonds have been reported.[188] These transformations offer several advantages:

- they generally do not require the use of strong acids/bases or expensive ancillary ligands,
- they are tolerant of ambient air and moisture,

[187] Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D; Larsen, R. D. *Org. Synth.* **2005**, *11*, 393.
[188] Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

- they can be used to install carbon-oxygen,[189,190] carbon-halogen,[191] and carbon-carbon bonds,[192,193] and
- they proceed with very high levels of *ortho*-regioselectivity.

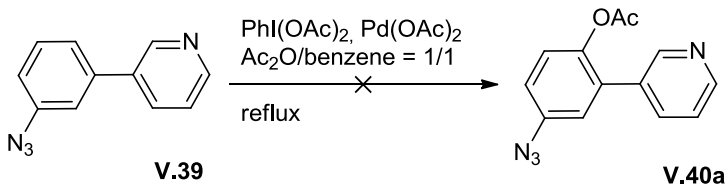
The recent development of metal catalyzed acetoxylation of arene C-H bonds has facilitated the preparation of azide **V.38**. Azide **V.37** was treated with phenyliodine diacetate ($PhI(OAc)_2$) and catalytic amount of $Pd(OAc)_2$ in acetic anhydride.[194] (Scheme V.21) The deacetylation of azide **V.38** was planned to be perform after Click reaction.



Scheme V.21. *The C-H palladium activated acetoxylation - preparation of azide **V.38**.*

5.2.4 Preparation of azide V.40

In order to prepare azide **V.40a**, we could not use the palladium-catalyzed acetoxylation as used for preparation of azide **V.38** from azide **V.37**. It was not possible to activate the C-H bond in ortho position of the phenyl group of a 3-substituted pyridine. (Scheme V.22)

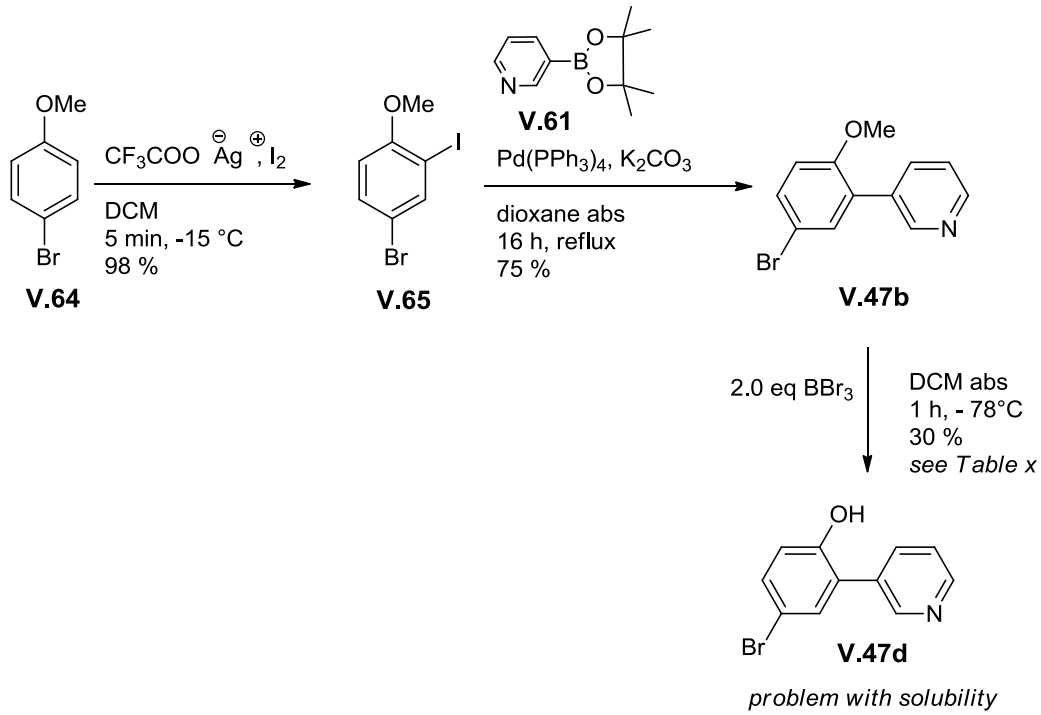


Scheme V.22. *The unsuccessful C-H palladium activated acetoxylation of azide **V.39**.*

This drawback leads us to propose an alternative pathway for the synthesis of azide **V.40b** through selective Suzuki-Miyaura coupling. (Scheme V.23) The synthesis started from cheap, commercially available *p*-bromoanisole **V.64**, which was selectively iodinated in *ortho* position by

[189] Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.
[190] Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
[191] Daugulis, O.; Zaitsev, V. G. *J. Am. Chem. Soc.* **2005**, *127*, 4156.
[192] Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.
[193] Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.
[194] Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

silver trifluoroacetat and iodine at -15°C within 5 minutes in almost quantitative yield 98 %. The next step – Suzuki-Miyaura cross-coupling, was performed using already described conditions with pinacol boronic 3-pyridyl ester **V.61**. Substituted bromobiaryl **V.47b** was obtained in 75 % yield. Deprotection of methoxy group from bromobiaryl **V.47b** was performed using the Lewis acid boron tribromide (BBr_3). This approach was described as a versatile methodology for deprotection of methoxy group.[195] The best result (30 %) of expected product **V.47d** was obtained using 2 equivalents of BBr_3 (Table V.1, Entry 2). Isolation of biaryl **V.47d** was very difficult due to its low solubility. (Scheme V.23)



Scheme V.23. *Preparation of bromo biaryl **V.47d** via selective Suzuki-Miyaura cross-coupling.*

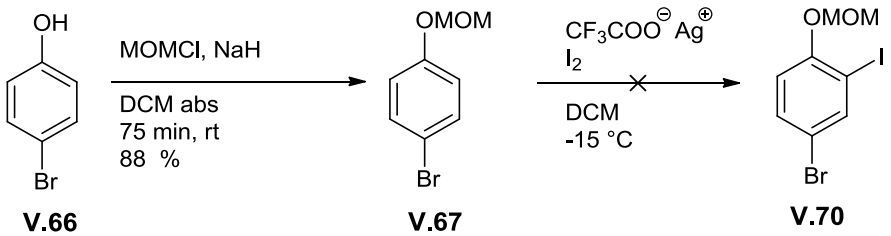
In front of these difficulties, we decided to study different conditions of deprotection. (Table V.1, Entries 4-10) Unfortunately, no reaction or decomposition of starting material **V.47b** were observed in all conditions tested.

[195] Doyagüez, E. S. *Synlett* **2005**, *10*, 1636.

Table V.1. *Deprotection of methoxy group from bromo biaryl **V.47b**.*

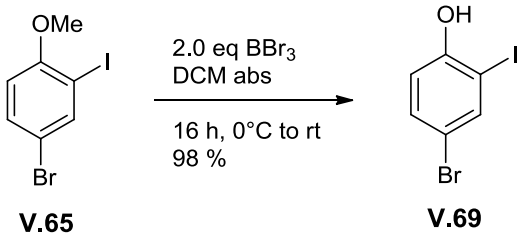
Entry	Reagents/Reaction conditions	Results
1	1.0 equiv BBr_3/DCM abs/ -78°C to rt/3 h	80 % starting material **V.47b** + 20 % expected product **V.47d** (conversion)
2	2.0 equiv BBr_3/DCM abs/ -78°C to rt/3 h	expected product **V.47d** (30 % yield) + decomposition products
3	3.0 equiv BBr_3/DCM abs/ -78°C to rt/3 h	expected product **V.47d** + decomposition products
4	1.5 equiv NaI/1.5 equivTMSCl in MeCN abs/0°C to rt	starting material **V.47b**
5	1.5 equiv NaI/1.5 equivTMSCl in MeCN abs/0°C to rt to reflux	starting material **V.47b**
6	2.0 equiv $AlCl_3$ in MeCN abs/rt	starting material **V.47b**
7	2.0 equiv $AlCl_3$ in MeCN abs/reflux	starting material **V.47b**
8	1.0 equiv TFA (protection) /1.2 equiv BBr_3/DCM/-15°C to rt	starting material **V.47b**
9	1.0 equiv 47 % HBr in AcOH/rt	decomposition
10	1.0 equiv 47 % HBr in AcOH/reflux	starting material **V.47b** + decomposition products

To circumvent the difficulties with deprotection of stable methyl group, we decided to change the protecting group and to choose methoxymethyl group which is easily removed in acidic conditions. *p*-Bromophenol **V.66** was reacted with MOMCl after deprotonation with NaH (Scheme V.24) and the resulting MOM- protected *p*-bromophenol **V.67** was submitted to iodination already used on *p*-bromoanisol **V.64**. However, the expected iodinated substrate **V.70** was not observed. We have just isolated the starting material **V.67**.



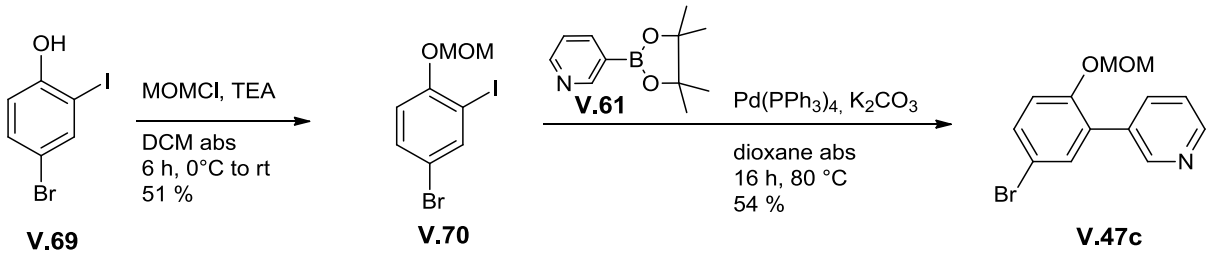
Scheme V.24. *Unsuccessful preparation of compound **V.70**.*

Since we had previously prepared the iodinated *p*-bromoanisole **V.65** in large quantity, we decided to cleave the methyl group in order to obtain 4-bromo-2-iodo phenol **V.69** which could be subsequently protected as MOM ether. (Schemes V.23 and V.25) Deprotection was performed with BBr_3 affording the desired substituted phenol **V.69** in 98 % yield. This excellent result showed that the presence of the nitrogen atom in bromo biaryl **V.47b** was problematic in the Lewis acid conditions used for methyl deprotection. Difficulties during the demethylation of aza-heterocyclic methyl ethers were already published.[196]



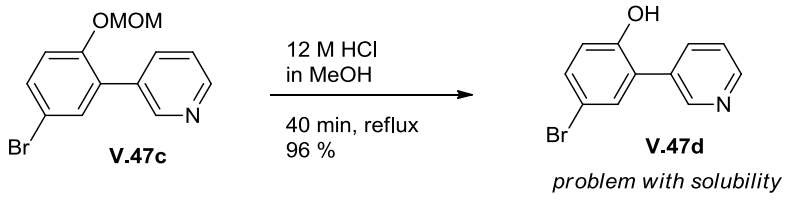
Scheme V.25. *Deprotection of 4-bromo-2-iodo anisole **V.65**.*

Protection of phenol **V.69** with MOMCl was subsequently accomplished. (Scheme V.26) Suzuki-Miyaura cross-coupling of pinacol boronic ester **V.61** with the resulting MOM arylether **V.70** afforded bromobiaryl **V.47c** in 54 % yield.



Scheme V.26. *Preparation of bromobiaryl **V.47c** via Suzuki-Miyaura cross-coupling.*

Finally, MOM deprotection of **V.47c** was performed in acidic medium affording bromobiaryl **V.47d** in 96 % yield.

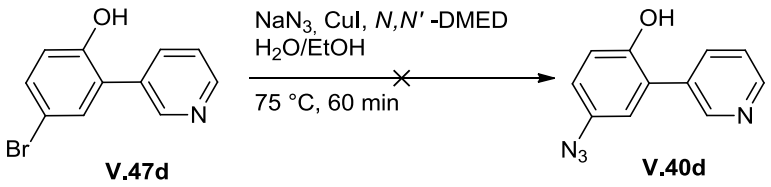


Scheme V.27. *MOM-deprotection of protected bromobiaryl **V.47c**.*

[196] Soni, A.; Dutt, A.; Sattigeri, V.; Cliffe, I. A. *Synth. Commun.* **2011**, *41*, 1852.

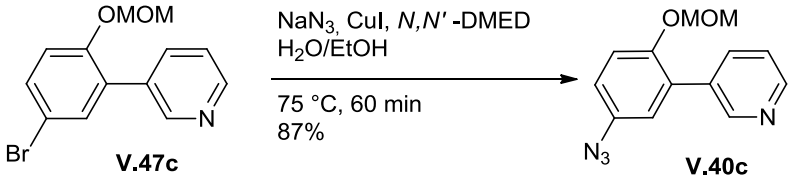
Bromobiaryl **V.47d** was obtained from *p*-bromoanisole **V.64** in 22 % over 3 steps using directly the methoxy substituent as protecting group and in 25 % over 5 steps *via* conversion of the methoxy substituent to the corresponding MOM ether.

As already mentioned bromobiaryl **V.47d** is poorly soluble in almost all solvents tested and its further transformation into the corresponding azide **V.40d** using Liang's procedure[168] failed (Scheme V.28)



Scheme V.28. *Unsuccessful synthesis of azide **V.47d**.*

We decided to build the triazole ring prior to MOM deprotection, and we prepared azide **V.40c** from bromobiaryl **V.47c** in 87 % yield using the copper catalyzed reaction. (Scheme V.29) The MOM protecting group could be selectively removed from final triazole in acidic conditions.

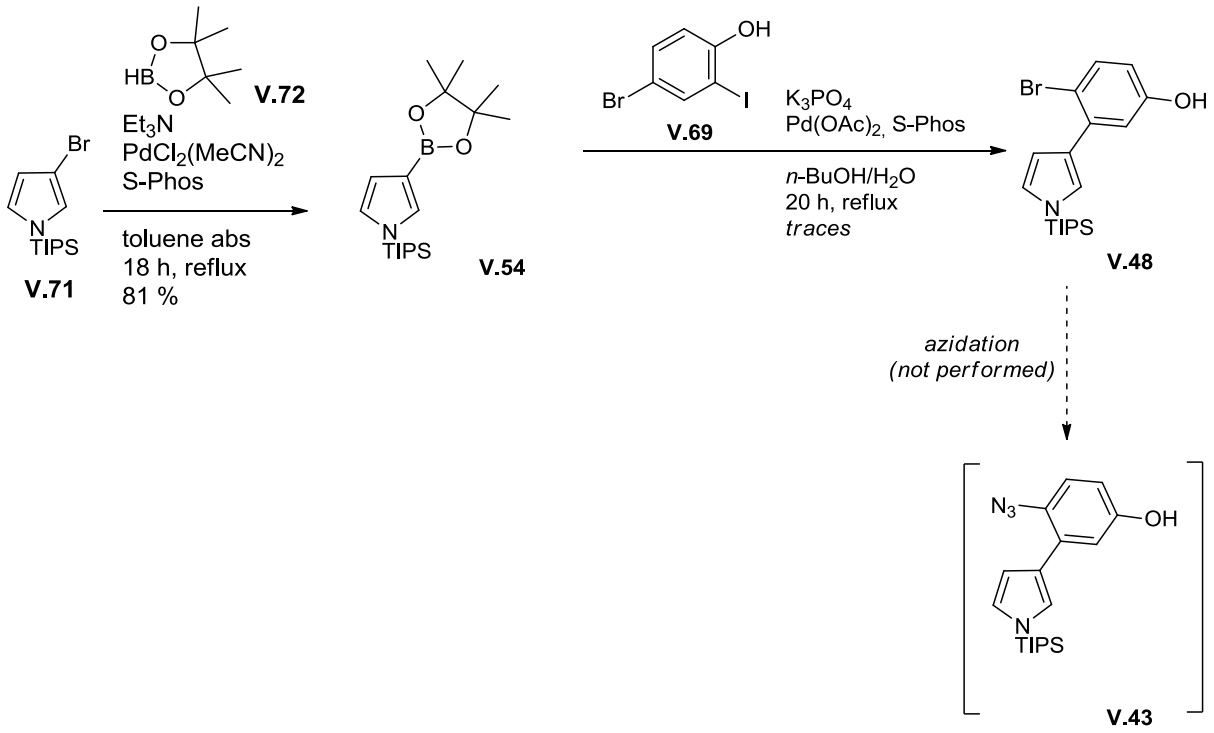


Scheme V.29. *Preparation of azide **V.40c**.*

5.2.5 Preparation of pyrrole azide V.43

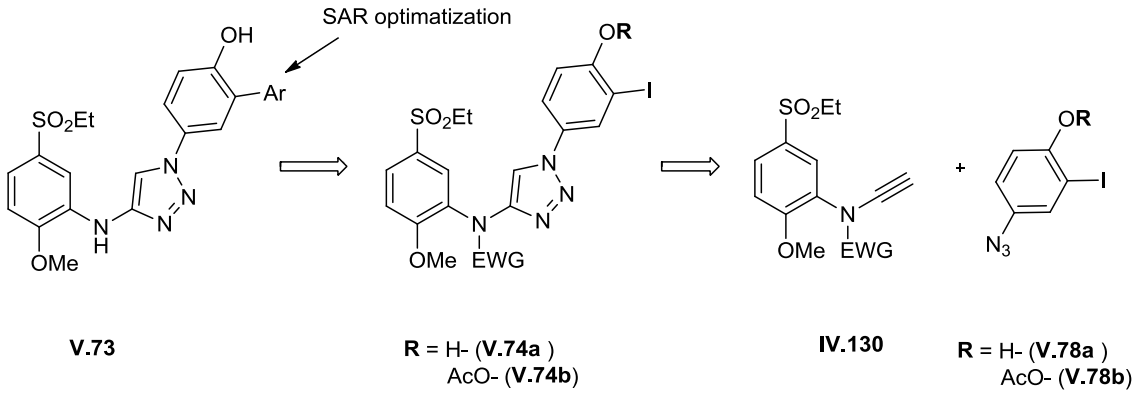
Preparation of pyrrole boronic ester **V.54** from commercially available 3-bromo-*N*-triisopropylsilylpyrrole **V.71** has been performed using pinacolborane **V.72** in the presence of a catalytic amount of bis-(acetonitrile)palladium dichloride and S-Phos.[197] (Scheme V.30) The Suzuki-Miyaura cross-coupling[198,199] between **V.54** and the dihalogenated phenol **V.69** following described conditions lead to some traces of expected biarylic compound **V.48** detected by LCMS analysis. This negative result led us to consider another pathway and prompted us to perform the coupling reaction after the click reaction.

[197] Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.
[198] Gu, Z. ; Zakarian, A. *Org. Lett.* **2010**, *12,* 4224.
[199] Morrison, M. D. ; Hanthorn, J. J. ; Pratt, D. A. *Org. Lett.* **2009**, *11,* 1051.



Scheme V.30. *Proposed preparation of azide **V.43**.*

We designed new retrosynthesis approach which consisted on performing Click reaction prior to Suzuki-Miyaura cross-coupling. (Scheme V.31)

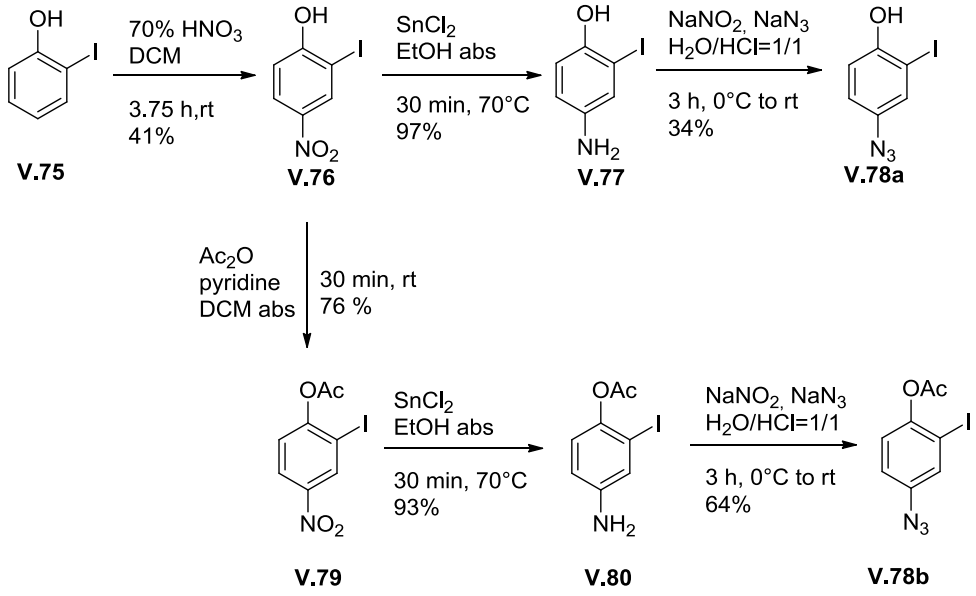


Scheme V.31. *New proposed retrosynthetic strategy for preparation of triazole library.*

Considering this new synthetic pathway, (Scheme V.31) we had to prepare azides **V.78a,b** (R=H, AcO) which could result from commercially available *o*-iodo phenol **V.175**. (Scheme V.32) Nitrophenol **V.76**, the pivotal intermediate for the synthesis of both azides, is commercially available, but very expensive (1 g ~ 170 €). Consequently, we decided to prepare nitrophenol **V.76** by simple nitration of *o*-iodo phenol using a 70 % solution of nitric acid.[200] Reduction of nitrophenol **V.76** to the

[200] Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445.

corresponding aniline **V.77** was performed by $SnCl_2$ in dry ethanol.[201] The resulting aminophenol **V.77** was submitted to diazotation and azide nucleophilic substitution using NaN_3 to afford azide **V.78a** in 34 % yield. Azide **V.78a** was obtained in 14 % overall yield over 3-steps. A prior acetylation of nitrophenol **V.76** led to azide **V.78b** in 19 % overall yield over 4 steps-synthesis using the same sequence.



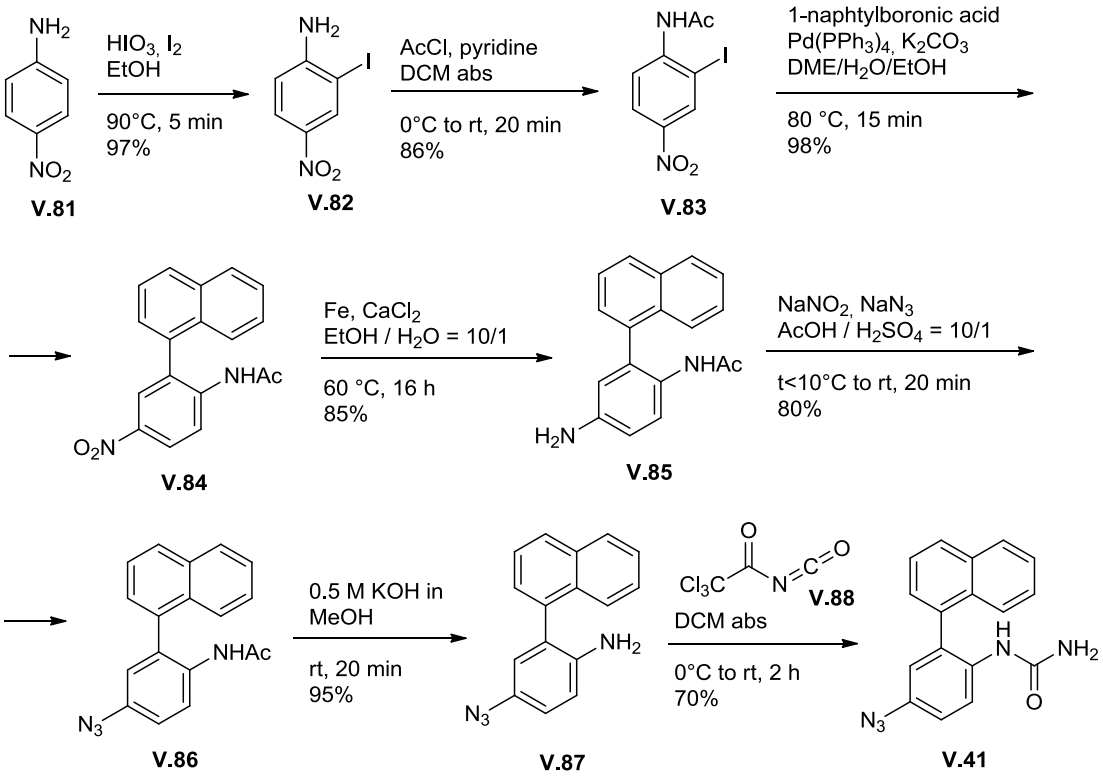
Scheme V.32. *Preparation of azide **V.78a** and **V.78b**.*

5.2.6 Preparation of urea azide V.41

Synthesis of urea azide **V.41** was initiated *via* previously described iodination[202] of *p*-nitroaniline **V.181** and subsequent acetylation of the free amino group.[203] Introduction of the naphtyl part was realized using a Suzuki-Miyaura cross-coupling.[204] The coupling of highly reactive *o*-iodoacetanilide derivate **V.83** and 1-naphtylboronic acid afforded the intermediate **V.84** in quantitative yield 98 %. Transformation of the nitro derivative **V.84** into the corresponding azido derivative **V.41** was performed in 2 steps *via* reduction using powder iron in the presence of calcium chloride and subsequent diazotation[205,206]. (Scheme V.33) Deacetylation of **V.86** was performed in basic conditions affording the free amine **V.87** required for urea preparation. Among the methods of urea synthesis, one of the most versatile is the addition of isocyanate to aniline. Unfortunately, all

[201] Bellamy, F. D.; Ou, K. *Tetrahedron Lett.*, *25*, **1984**, 839.
[202] Shinde, A. T.; Zangade, S. B.; Chavan, S. B.; Vibhute, A. Y.; Nalwar, Y. S.; Vibhute, Y. B. *Synth. Commun.* **2010**, *40*, 3506.
[203] Kotha, S.; Shah, V. R. *Eur. J. Org. Chem.* **2008**, 1054.
[204] Ganesh, T.; Thepchatri, P.; Du, L. L. Y.; Fu, H; Snyder, J. P.; Sun, A. *Bio. Med. Chem. Lett.* **2008**, 4982.
[205] Chandrappa, S.; Vinaya, T.; Ramakrishnappa, T.; Rangappa, K. S. *Synlett* **2010**, 3019.
[206] Walton, R.; Lahti, P.M. *Synth. Commun.* **1998**, *28*, 1087.

attempts using KNCO as isocyanatation reagent failed. Finally, the urea derivate **V.41** was prepared from unstable amino azide **V.87** using trichloroacetyl isocyanate **V.88** in dry dichloromethane followed by basic work up.[207] Desired urea azide **V.41** was prepared from cheap *p*-nitroaniline with 37 % overall yield in seven steps.

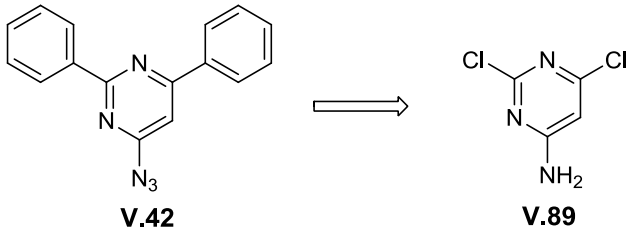


Scheme V.33. *Preparation of urea azide **V.41** from p-nitroaniline **V.81**.*

5.2.7 Preparation of pyrimidine azide V.42

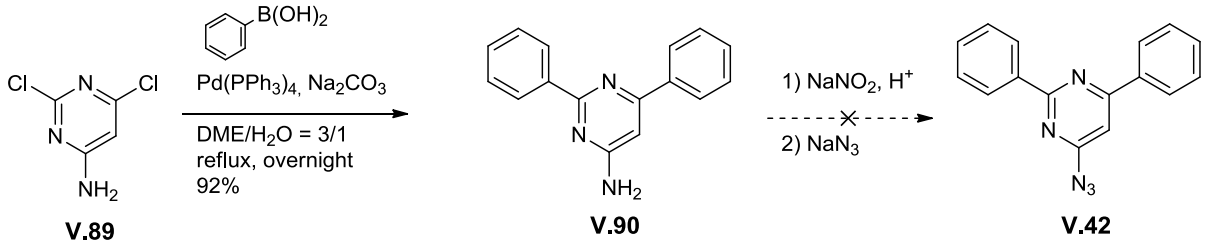
Firstly, we have suggested a simple retrosynthetic strategy (Scheme V.34) in order to prepare pyrimidine azide **V.42** starting from commercially available 2,6-dichloro-4-pyrimidinamine **V.89** (5 g ~ 56 €).

[207] Deng, Q. H.; Wang, J. C.; Xu, Z. J.; Zhou, C. Y.; Che, C. M. *Synthesis* **2011**, *18*, 2959.



Scheme V.34. *Retrosynthetic strategy azide **V.42** from pyrimidine **V.89**.*

We have started the synthesis with already described double Suzuki-Miyaura cross-coupling to prepare 2,6-diphenylpyrimidin-4-amine **V.90**.[208] Coupling reaction has been performed using the easily available phenylboronic acid. (Scheme V.35) The desired diphenyl pyrimidine **V.90** was obtained in 92 % yield after purification.



Scheme V.35. *Proposed preparation of azide **V.42** from 2,6-dichloro-4-pyrimidinamine **V.189.***

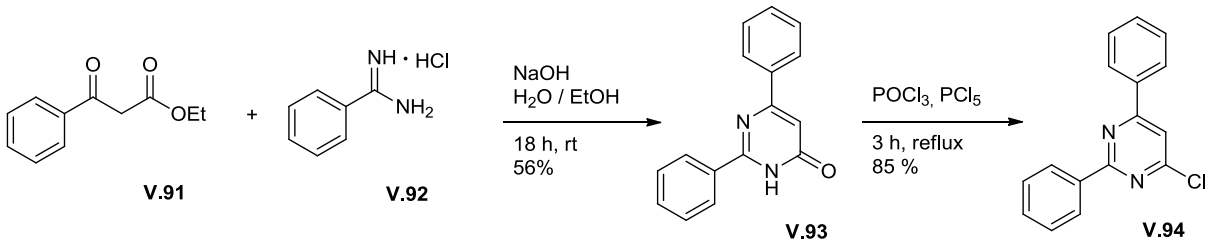
The last step was the transformation of amino group of **V.90** into azido group using the widely described diazotation by sodium nitrate ($NaNO_2$) in acidic medium and subsequent substitution by NaN_3. This reaction has not been described on substrate **V.90** so far. Since this procedure was successful for preparation of amine **V.85** (Scheme V.33), we applied the conditions on substrate **V.90**. Unfortunately, we did not observe the desired azide **V.42**. (Table V.2, Entry 1) We increased the stoechiometry of reagent and prolonged the reaction time, but starting material was recovered quantitatively. (Table V.2, Entry 2) As amine **V.90** was poorly soluble, we decided to use a co-solvent (toluene, THF). (Table V.2, Entry 3,4) but one more time with unsuccessful results.

[208] Yaziji, V,; Rodriguez, D.; Guierrez-de-Terran, H.; Coehlo, A. ; Caamano, O. ; Garcia-Mera, X. ; Brea, J. ; Loza, M. I. ; Cadavid, M. I. ; Sotelo, E. *J. Med. Chem.* **2011**, *54*, 457.

Table V.2. *Reaction conditions tried for preparation of pyrimidine azide **V.42** from amine **V.90**.*

Entry	Reagents/Reaction conditions	Results
1	1.0 equiv $NaNO_2$, 1.05 equiv NaN_3, $AcOH/H_2SO_4$, t<10°C to rt, 2 h	starting material **V.90**
2	2.0 equiv $NaNO_2$, 2.1 equiv NaN_3, $AcOH/H_2SO_4$, t<10°C to rt, 4 h	starting material **V.90**
3	1.0 equiv $NaNO_2$, 1.05 equiv NaN_3, $AcOH/H_2SO_4$, toluene t<10°C to rt, 4 h	starting material **V.90**
4	1.0 equiv $NaNO_2$, 1.05 equiv NaN_3, $AcOH/H_2SO_4$, toluene t<10°C to rt, 4 h	starting material **V.90**

Due to the problematic transformation of amino pyrimidine **V.90** to the corresponding azide **V.42**, we selected another procedure. Pyrimidine azide **V.42** was prepared from pyrimidine ketone **V.93**. According to an American Patent,[209] condensation of benzamidine hydrochloride **V.92** on β-keto ethyl ester **V.91** afforded pyrimidinone **V.193** in 56 % yield. (Scheme V.36) Chlorination of **V.93** was performed in refluxing $POCl_3$ and PCl_5 during 3 hours and yielded product V.194 in 85 % (Scheme V.36).



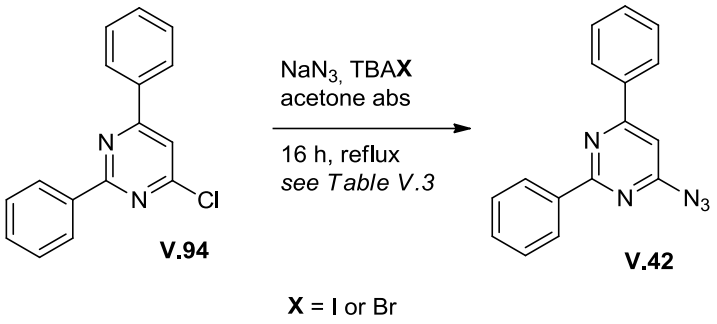
V.91 **V.92** **V.93** **V.94**

Scheme V.36. *Preparation of pyrimidine chloride **V.94**.*

Chloride substitution of **V.94** by azido group was performed using sodium azide and tetra-*n*-butylammonium bromide (TBAB), which facilitates the reaction (Table V.3, Entry 2 and 3).[210] (Scheme V.37) Without TBAB, the reaction was very slow and only starting material **V.94** was observed after several hours (Table V.3, Entry 1). In order to get better conversion, we tried tetra-*n*-butylammonium iodide (TBAI), but conversion into pyrimidine azide **V.42** was not improved. (Table V.3, Entry 4) Isolation of **V.42** was impossible in our hands and azide **V.42** was used without

[209] Chang, L. C. W.; Ijzerman, A. P.; Brussee, J. Oct. 1, 2004, United States Patent US 2007/0032510.
[210] Ye, C.; Gao, H.; Boatz,Drake, G. W.; Twamley, B.; Shreeve, J. M. *Angew. Chem. Int. Ed.* **2006**, p. 7262.

purification in the following step. We suppose, chlorine next to nitrogen is less reactive due to the presence of two phenyl groups in positions 2 and 6.



Scheme V.37. *Substitution of chloride **V.94** to azide **V.42**.*

Table V.3. *Substitution of chloride **V.94** to azide **V.42**.*

Entry	Conditions*	Results
1	NaN_3	starting material **V.94**
2	NaN_3, TBAB (cat.)	86% yield
3	NaN_3, TBAB (equiv)	87% yield
4	NaN_3, TBAI (equiv)	87% yield

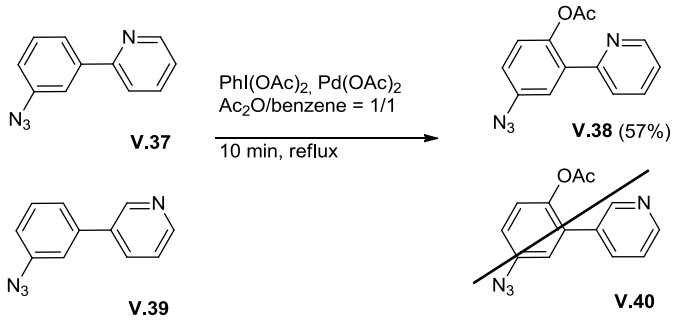
**reactions performed with 2 equiv of NaN_3 in dry acetone under reflux, 16 h*

The desired azide **V.42** was prepared in 41 % overall yield in 3 steps-synthesis.

5.3 Conclusion for required azides preparations

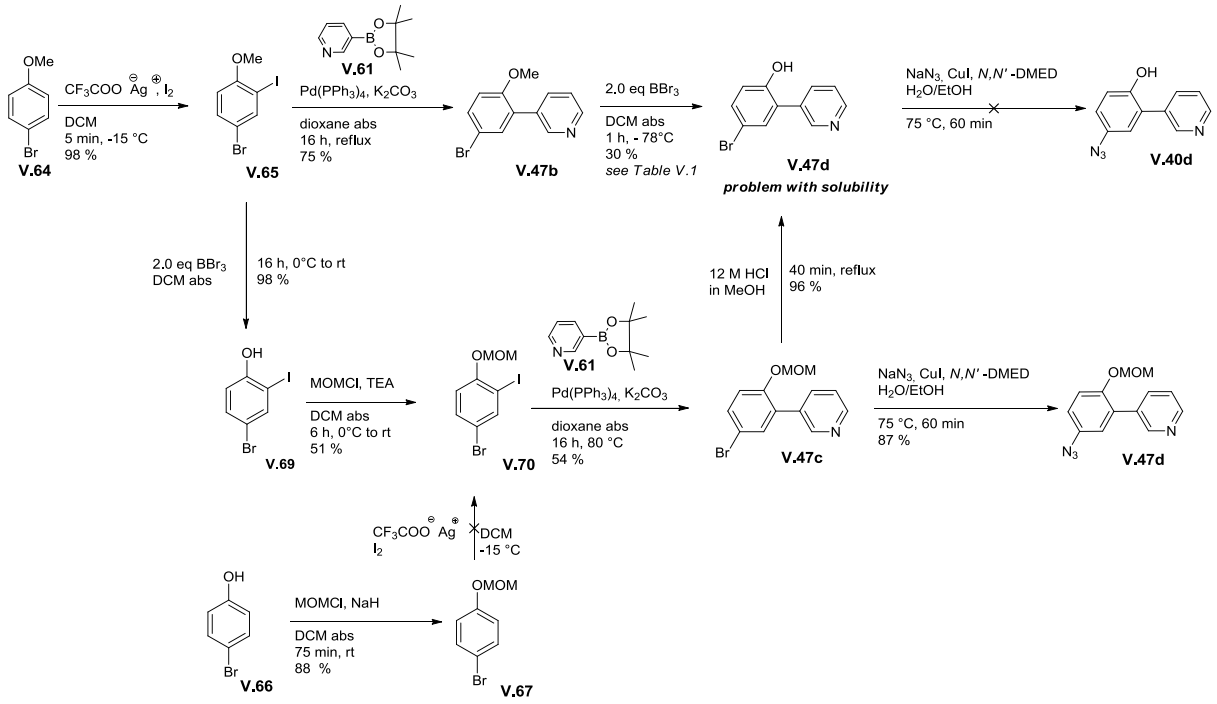
In order to perform click reaction towards designed triazolic analogues **III.20** – **III.26** of **III.1** ligand from complex PDB: 1Y6A, the corresponding **V.37**-**V.42** and **V.178a**,**b** were prepared. (Figure V.4)

First, we prepared biaryl bromides **V.44** and **V.46** using a described procedure which were converted to the corresponding azides **V.37** and **V.39** *via* copper catalyzed reaction with sodium azide.[168] Azide **V.37** was subsequently converted to acetylated azide **V.38** *via* palladium-catalyzed C-H activation.[194] Palladium(II) activated the C-H bond in *ortho* position. Using this methodology it was not possible to prepare acetylated azide **V.40a**, due to the substitution of pyridyl ring at C3 position. (Scheme V.38)



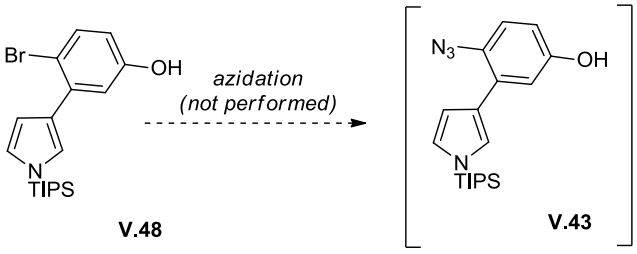
Scheme V.38. *The C-H palladium activated acetoxylation - preparation of azide **V.38**, and unsuccessful preparation of azide **V.40**.*

As alternative towards azide **V.42**, Suzuki-Miyaura coupling reaction between methyl- (**V.65**) and methoxymethyl- (**V.70**) protected 4-bromo-2-iodo phenol **V.69** has been performed. Cleavage of methoxy group was difficult leading to poorly soluble bromobiaryl **V.47d** in low yield which was impossible to be converted into the desired azidobiaryl **V.40d**. (Scheme V.39) Finally, we have prepared azide **V.47d** *via* a MOM- protection of phenol which was planned to be cleaved after the construction of the triazole ring.



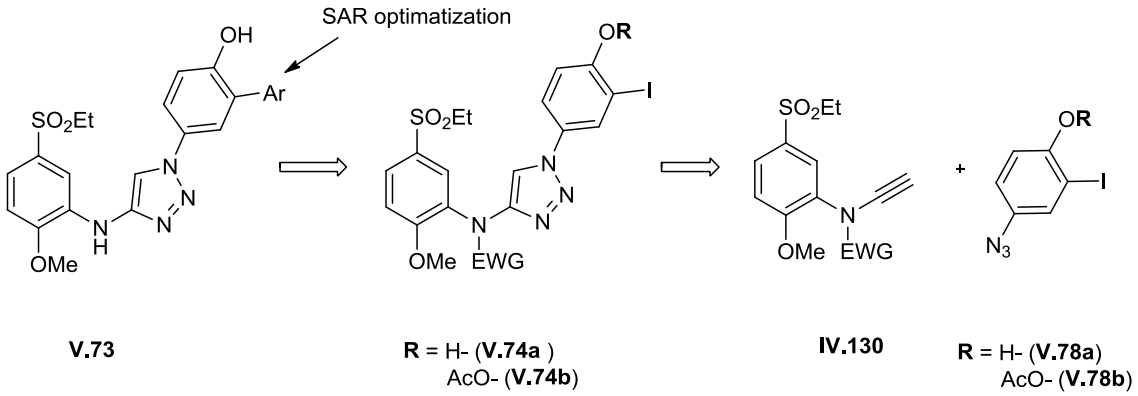
Scheme V.39. *Preparation of MOM- protected azidobiaryl **V.47c** and unsuccessful preparation of hydroxylated azidobiaryl **V.40d** from p-bromoanisole **V.64**.*

Pyrrole bromide **V.48** has been prepared in very poor yield by selective Suzuki-Miyaura cross-coupling. Therefore the next step containing its azidation was omitted. (Scheme V.40)



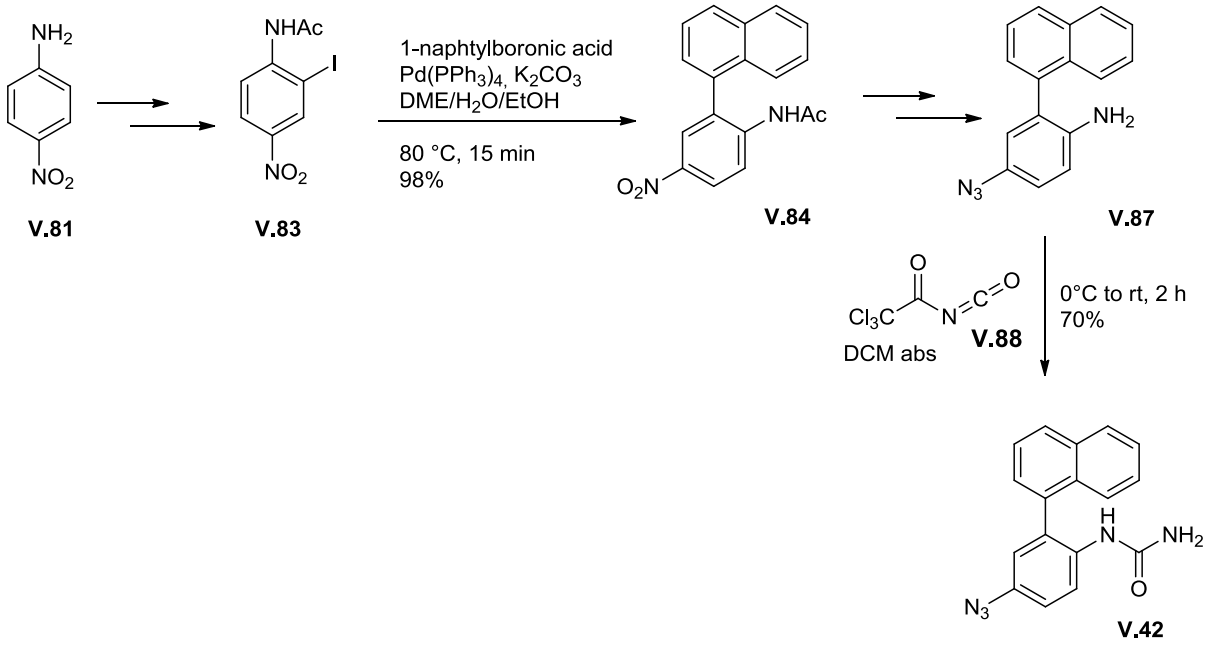
Scheme V.40. *Prepared bromobiaryl **V.48** and not performed azidation.*

According to the difficulties met during the preparation azide **V.40** and **V.43**, we proposed a new approach for which preparation of azide **V.78a** or acetylated azide **V.78b** was necessary. (Scheme V.31)



Scheme V.31. *New proposed retrosynthetic strategy for the preparation of the triazole library.*

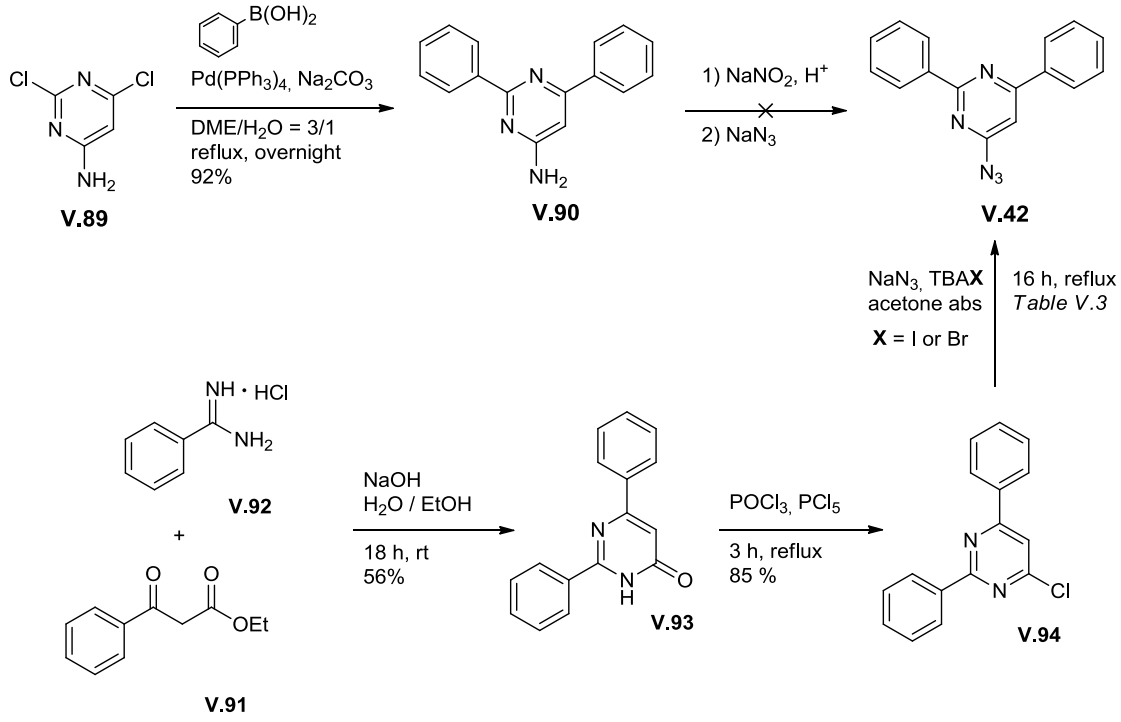
Urea azide **V.41** was prepared without any notable difficulties from *p*-nitroaniline with 37 % overall yield in 7 steps. (Scheme V.41) Efficient introduction of urea functional group using trichloacetylisocyanate followed by basic treatment has to be highlighted.[207]



Scheme V.41. *Preparation of urea azide **V.42** from p-nitroaniline*.

The first attempt for preparation of pyrimidine azide **V.42** was a double Suzuki-Miyaura cross-coupling using 2,6-dichloropyrimidinamine **V.89** and phenolboronic acid. Unfortunately, the resulting diphenylpyrimidine amine **V.90** was not conveniently transformed into the desired pyrimidine azide **V.42** due to the low solubility of amine **V.90**. (Scheme V.42) Alternatively, we prepared ketone **V.93** using a previously described procedure which was transformed into chloride

and finally into the desired pyrimidine azide **V.42**. The latter was prepared in 41 % overall yield in 3 steps.



Scheme V.42. *Preparation of azido pyrimidine **V.42**.*

In summary we have prepared 8 azides **V.37** – **V.42** and **V.78a,b** (Figure V.4) suitable for Click chemistry reaction in order to synthesize predicted triazolic modulators.The Click reactions will be presented in the next Chapter.

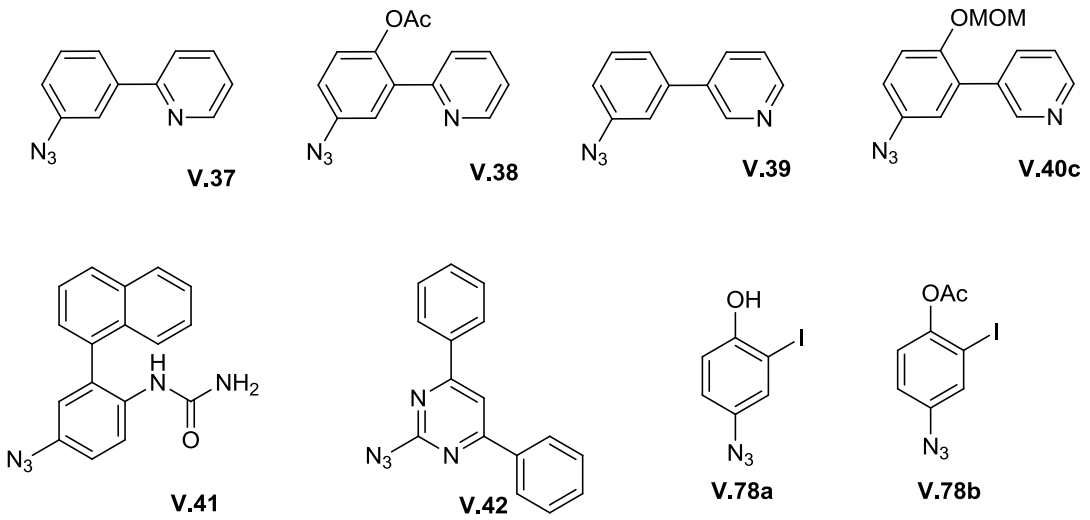


Figure V.4. *Prepared azides **V.37**-**V.42** and **V.78a,b** suitable for Click chemistry reaction*

Chapter 6. **Click chemistry**

6.1 Literature background

Click chemistry is more and more involved in the demanding world of medicinal chemistry, either by development of new inhibitors or easy production of screening libraries. The reliability of the Click reactions, means that compounds can be screened directly from the reaction mixture. This was demonstrated, by Wong *et al.*[211] in a paper wherein the Cu(I) catalysed Huisgen reaction was utilized in the development of high throughput methodology which led to the discovery of a novel and selective Inhibitor of Human r-1,3-Fucosyltransferase (Fuc-T).

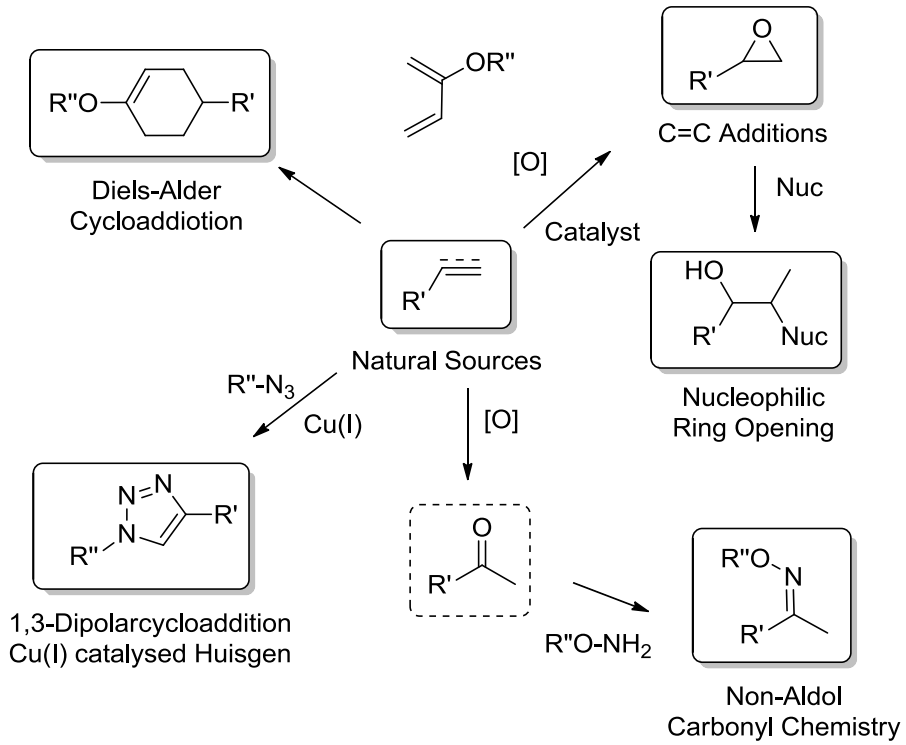
Click chemistry was introduced by Barry Sharpless and co-workers in 2001.[212] This concept was developed in parallel with the interest within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research. The requirements for click chemistry defined by Sharpless are listed below:[213]

- modular and wide in scope
- highly efficient and give high yields
- no or inoffensive by-products
- stereospecific
- readily available starting materials and reagents
- no solvent or a benign solvent
- simple purification non-chromatographic techniques

Although meeting the requirements of a Click reaction is a tall order, several processes have been identified which step up to the mark (Scheme VI.1):

- nucleophilic ring opening reactions: epoxides, aziridines, aziridinium ions *etc.*
- non-aldol carbonyl chemistry: formation of ureas, oximes and hydrazones *etc.*
- additions to carbon–carbon multiple bonds: especially oxidative addition, and Michael additions of Nu–H reactants
- cycloaddition reactions: especially 1,3-dipolar cycloaddition reactions, but also the Diels–Alder reaction.

[211] Detz, R. J.; Heras, S. A.; Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227.
[212] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[213] Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 4900.



Scheme VI.1. *A selection of reactions which match the Click Chemistry criteria.*[214]

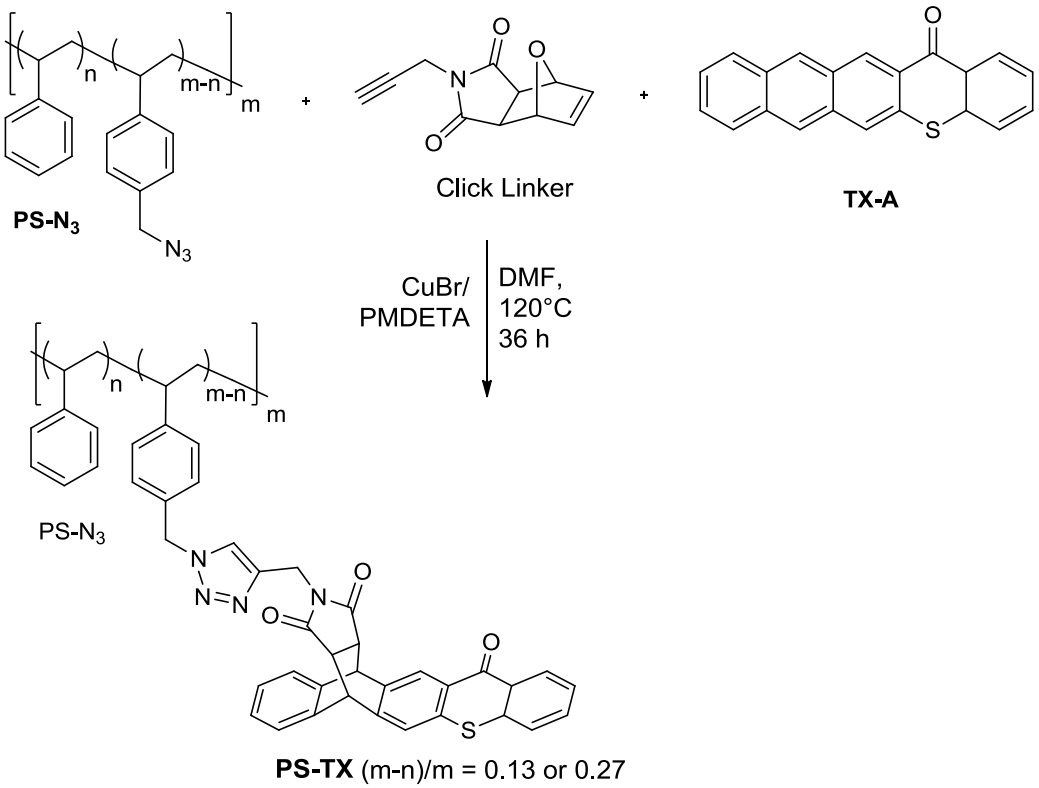
Diels–Alder reactions were first documented in 1928[215] and they are amongst the most fascinating organic reactions, in terms of both their synthetic potential and reaction mechanism. Diels–Alder reactions involve the simultaneous formation and destruction of carbon–carbon bonds.[216] This reaction requires very little energy, and thus can be successful even below room temperature. There are several reports on Diels–Alder click reactions,[217] and here we highlight some recently published examples based on bioconjugates and macromolecules. (Scheme VI.2)

[214] Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.

[215] Otto Paul Hermann Diels and Kurt Alder first documented the reaction in 1928. They received the Nobel Prize in Chemistry in 1950 for their work on the eponymous reaction.

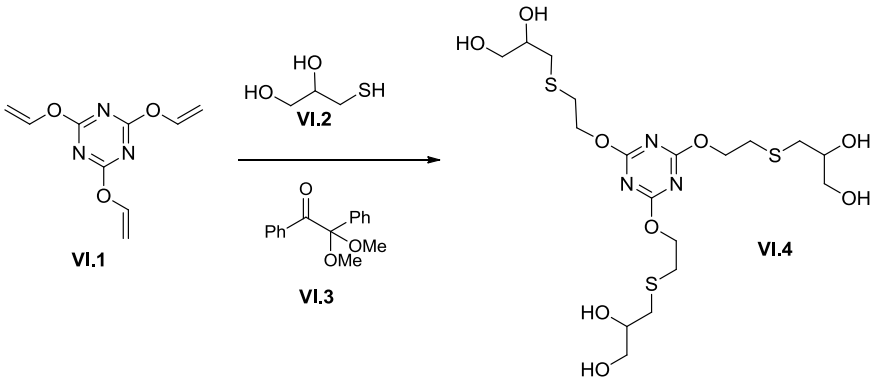
[216] a) Holmes, H. L.; Husband, R. M.; Lee, C. C.; Kawulka, P. *J. Am. Chem. Soc.* **1948**, *70*, 141. b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem.* **2002**, *114*, 1742; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.

[217] Gacal, B.; Akat, H.; Balta, D. K.; Arsu, N.; Yagci, Y. *Macromolecules* **2008**, *41*, 2401.



Scheme VI.2. *Side-chain functionalization of PS-N3 with anthracene-thioxanthone (TX-A) in the presence of N-propargyl-7-oxynorbornene (PON) as Click linker via double Click chemistry.*[217]

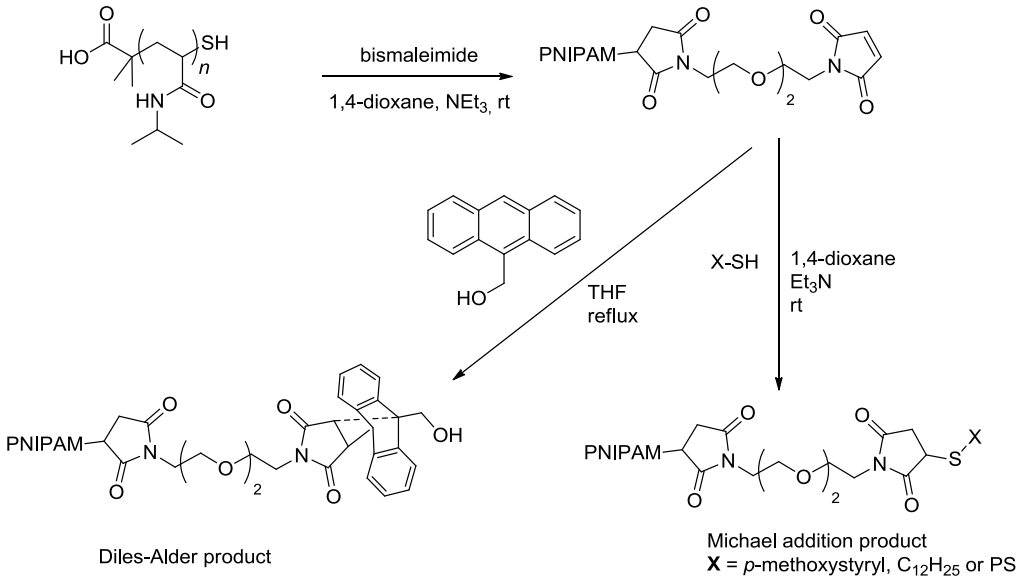
Hawker and co-workers reported a robust, efficient, and orthogonal synthesis of fourth generation dendrimers by using thiol-ene click reactions.[218] The solvent-free reaction between alkene **VI.1** and thiol **VI.2** was performed under ambient conditions by irradiation for 30 minutes with a hand-held UV lamp (λ=365 nm). Trace amounts of photoinitiator **VI.3** were added to increase the radical concentration and, thus, increase the reaction rate. The first generation of dendrimer **VI.4** is shown in Scheme VI.3. Higher generations were synthesized in the same manner, with purification by simple precipitation in diethyl ether.



Scheme VI.3. *Thiol-ene click chemistry for the synthesis of a G1 dendrimer.*[218]

[218] Killops, K. L.; Campos, L. M.; Hawker, C. J. *J. Am. Chem. Soc.* **2008**, *130*, 5062.

Sumerlin and co-workers demonstrated the successful synthesis of block copolymers by Michael additions or Diels–Alder reactions on polymers prepared by the reversible addition/fragmentation chain transfer (RAFT) technique.[219] As illustrated in Scheme VI.4, the polymerization and following click reactions were all performed in the absence of any metal catalyst. The Michael addition of maleimide-terminated poly(*N*-isopropylacrylamide) with sulfhydryl-terminated poly(styrene) (PSSH) occurred under an inert atmosphere within 24 h at room temperature. The excess of PS-SH was removed from the reaction mixture by immobilization onto an insoluble iodoacetate-functionalized support, which represents an elegant method that avoids chromatographic purification steps. These model reactions confirm the potential of this methodology to combine RAFT-synthesized thiol-terminated polymers with a variety of other macromolecular thiols.



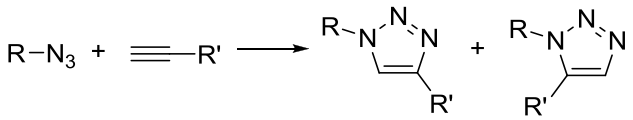
Scheme VI.4. *End-group modification of poly(N-isopropyl acrylamide) (PNIPAM) with bismaleimide and subsequent Michael addition or Diels Alder-reaction.*[219]

6.1.1 Huisgen 1,3-dipolar cycloaddition

Among all the reactions which achieve 'click status', the Huisgen 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles is undoubtedly the premier example of a click reaction. The ease of synthesis of the alkyne and azide functionalities, coupled with their kinetic stability and tolerance to a wide variety of functional groups and reaction conditions, make these complementary coupling partners particularly attractive.

[219] Li, M.; P. De, Gondi, S. R. ; Sumerlin, B. S. *J. Polym. Sci. Part A* **2008**, *46*, 5093.

Several types of reactions have been identified that fulfill these criteria. For example, an examination of the azide-alkyne cycloaddition shows that it fulfils many of the prerequisites. Many of the starting monosubstituted alkynes and organic azides are available commercially, many others can easily be synthesized with a wide range of functional groups, and their cycloaddition reaction selectively gives 1,2,3-triazoles. (Scheme VI.5) Unfortunately, the thermal Huisgen-1,3-dipolar-cycloaddition[220,221] of alkynes to azides requires high temperatures and produces mixtures of the two regioisomers. The classic 1,3-dipolar cycloaddition fails as a true click reaction.



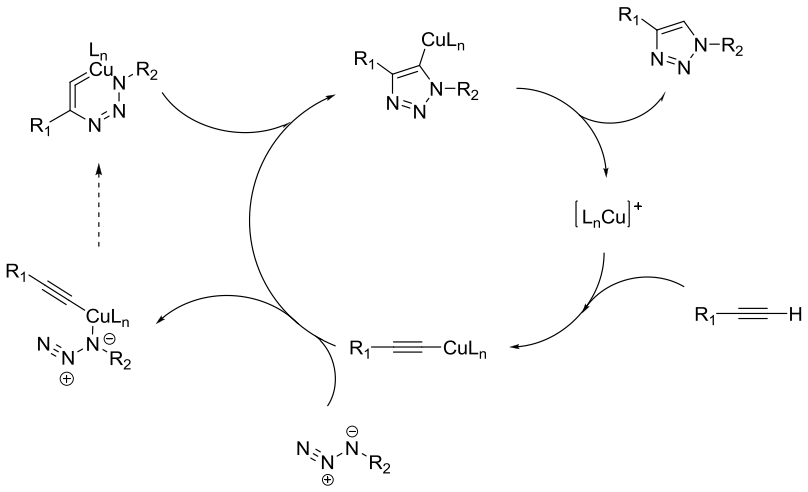
Scheme VI.5. *Classical thermal 1,3-dipolar cycloaddition.*

6.1.2 Copper-catalyzed azide-alkyne cycloaddition (CuAAC)

The discovery of copper (I) catalyst for regioselective [3+2]-cycloaddition of azides with alkynes opened its broad exploitation in medicinal and material sciences. Herein, the catalytic activities of copper systems on Click chemistry are reviewed.[222]

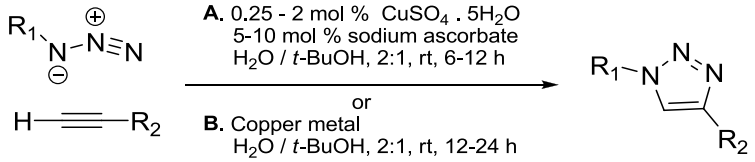
As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) features an enormous rate acceleration of 10^7 to 10^8 compared to the uncatalyzed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or crystallization. The active Cu(I) catalyst can be generated from Cu(I) salts or Cu(II) salts

[220] Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 633.
[221] Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*,565.
[222] Diez-Gonzalez, S. *Catal. Sci. Technol.* **2011**, ***1***, 166.



Scheme VI.6. *Mechanism of copper-catalyzed synthesis of 1,2,3-triazoles.*

by sodium ascorbate as the reducing agent. (Scheme 6.7) Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. Disproportionation of a Cu(II) salt in presence of a Cu wire can also be used to form active Cu(I).[223] The CuAAC process works only with terminal alkynes.



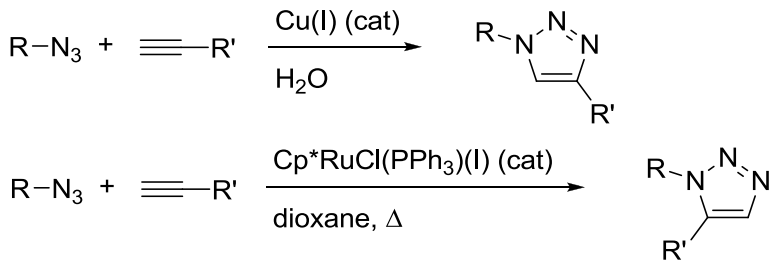
Scheme VI.7. *Example of copper-catalyzed preparation of 1,4-disubstituted 1,2,3-triazoles.*[224]

A copper-catalyzed variant that follows a different mechanism can be conducted under aqueous conditions at room temperature. Additionally, the copper-catalyzed reaction allows the synthesis of 1,4-disubstituted regioisomers specifically. A later developed ruthenium-catalyzed reaction gives the opposite regioselectivity with the formation of 1,5-disubstituted triazoles.[225] (Scheme VI.8)

[223] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.*, **2005**, *127*, 210.

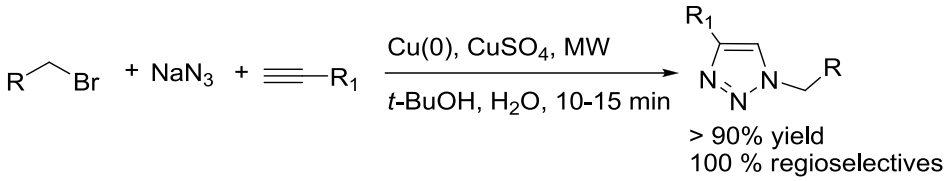
[224] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

[225] http://www.organic-chemistry.org/namedreactions/click-chemistry.shtm (visited 20.5.2013)



Scheme VI.8. *Copper and ruthenium-catalyzed 1,3-dipolar cycloaddition.*

In 2004 a microwave assisted three-component click chemistry reaction was reported by Eycken[226] and co-workers in order to prepare a series of 1,4-disubstituted-1,2,3-triazoles from corresponding alkyl halides, sodium azide, and alkynes. This procedure eliminates the need to handle organic azides, as they are generated *in situ*, making this already powerful click process even more user-friendly and safe. (Scheme VI.9)



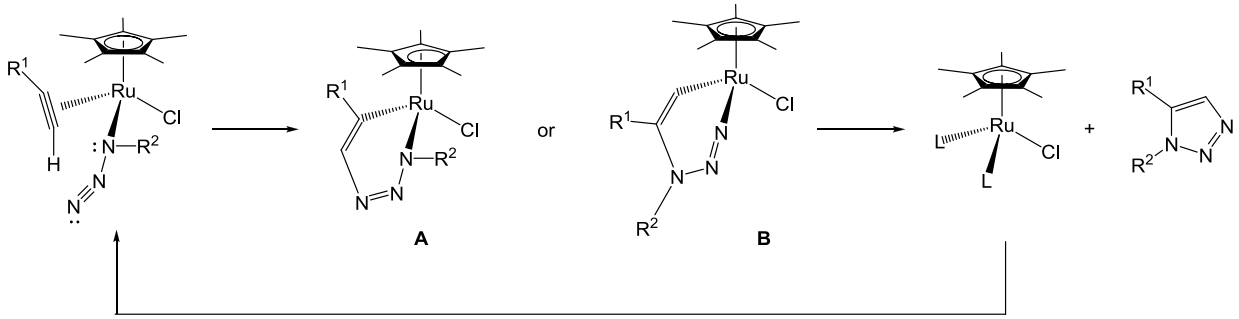
Scheme VI.9. *A microwave assisted three-component copper-catalyzed click reaction.*[226]

6.1.3 Ruthenium-catalyzed azide alkyne cycloaddition (RuAAC)

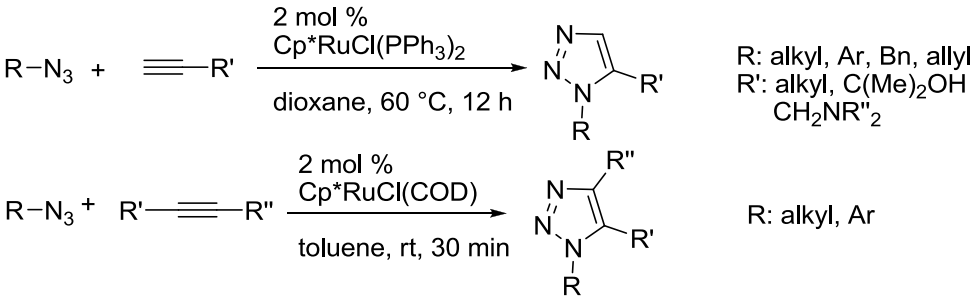
The ruthenium-catalyzed process (RuAAC)[227,228] provides access to the complementary 1,5-regioisomers of 1,2,3- triazole. Furthermore, internal alkynes also participate in the RuAAC. The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and the alkyne to give a six-membered ruthenacycle, in which the first new carbon-nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal selectively

[226] Appakkuttan, P.; Dehaen, W.; Fokin, V. V.; Eycken, E. V. *Org. Lett.* 2004, *6*, 4223.
[227] Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
[228] Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680.

nitrogen of the azide. This step is followed by reductive elimination, which forms the 1,5-regioisomeric triazole product.[229] (Scheme VI.10)



Scheme VI.10. *Mechanism of ruthenium-catalyzed synthesis of 1,2,3-triazoles.*[229]

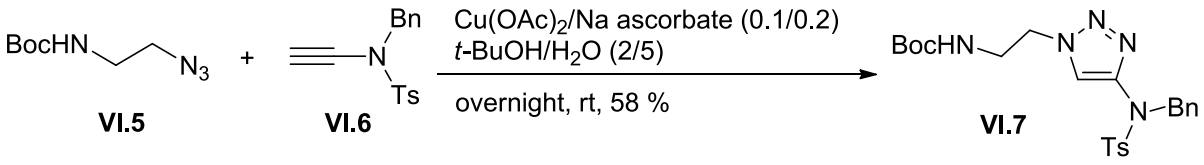


Scheme VI.11. *Examples of ruthenium-catalyzed preparation of 1,5-disubstituted 1,2,3-triazoles.*[229]

6.1.4 Click chemistry with ynamides

In 2006, Cintrat and IJsselstijn published a work,[230] where they described a preparation of a serie of 1-substituted 4-amino 1,2,3-triazoles, which were synthesized by [3+2] cycloaddition between azides and ynamides. (Scheme VI.12) This copper catalyzed process represents the first examples of a Click reaction employing ynamides and should expand the scope of the ynamide chemistry both synthetically and industrially. Various azides (even highly functionalized) were allowed to react with *N*-benzyl, *N*-tosyl ynamide to give the corresponding triazole adducts in high yields and with very high levels of regioselectivity.

[229] Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.
[230] Cintrat, J.C.; IJsselstijn, M. *Tetrahedron* **2006**, *62*, 3837.

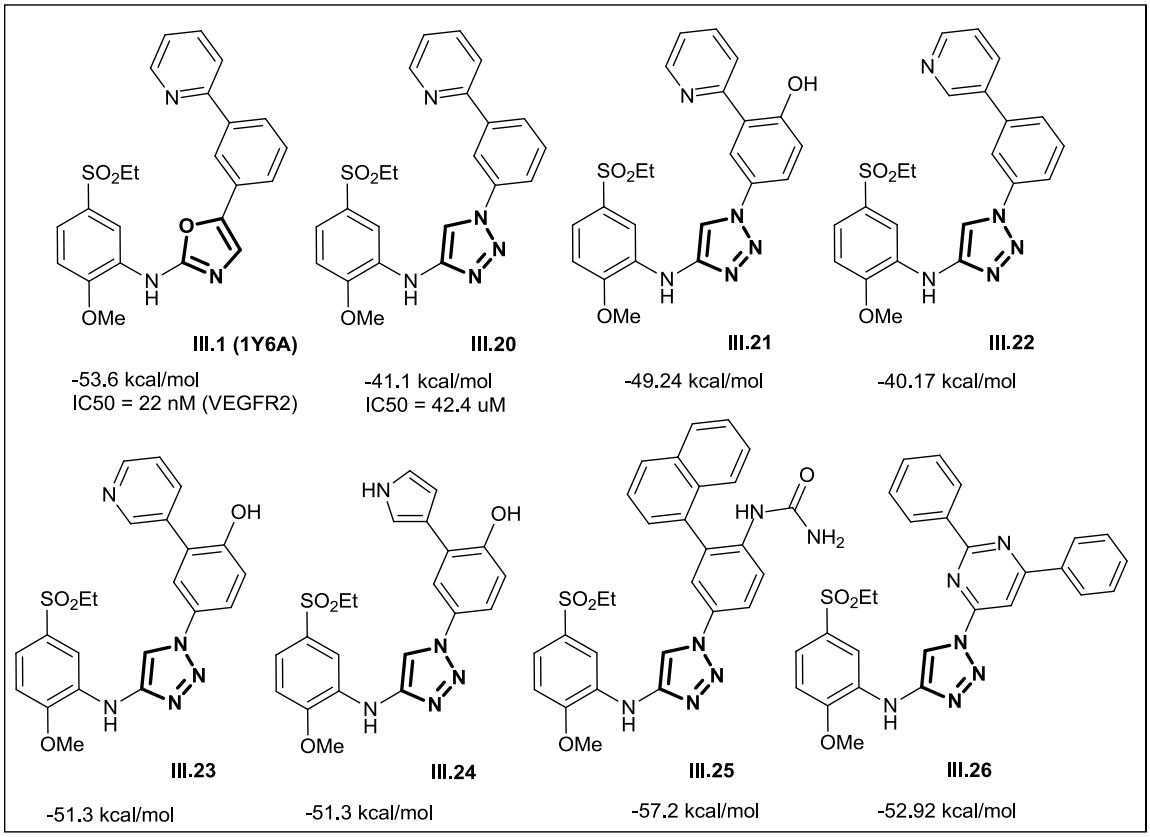


VI.5 **VI.6** **VI.7**

Scheme VI.12. *Preparation of 1,4-disubstituted 1,2,3-triazole by copper catalyzed click chemistry with ynamide.*[230]

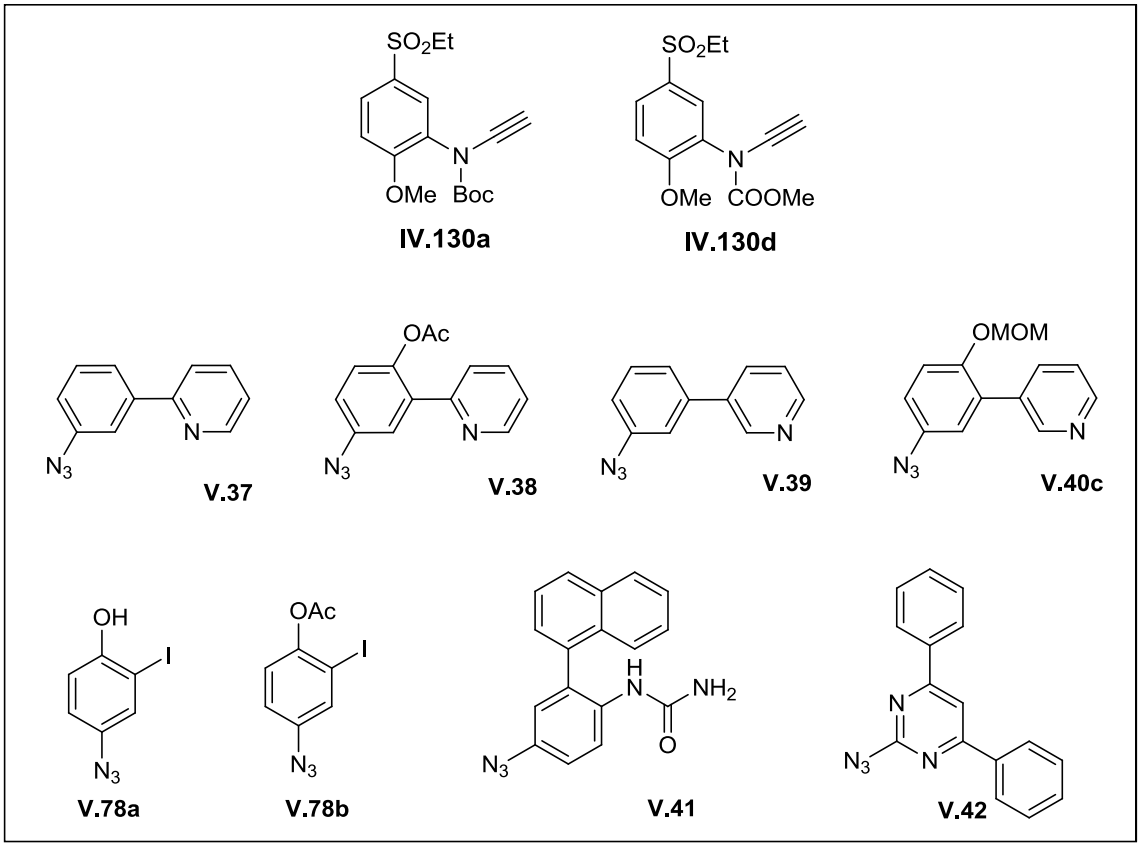
6.2 Preparation of *In Silico* predicted triazoles

Predicted 1,2,3-triazolic analogues **III.20-26** derived from oxazolic **III.1** (AAZ ligand, PDB complex 1Y6A) were proposed to prepare by Click reaction. In order to get selectively the 1,4-regioisomeric triazoles, the copper mediated cycloaddition was considered. (Scheme VI.13)



Scheme VI.13. *Predicted triazolic analogues **III.20** – **III.26** of oxazole **III.1** (PDB:1Y6A).*

For the Click chemistry based synthesis of the mentioned triazoles **III.20** – **III.26** we synthesized two types of building blocks: ynamides **IV.130a,d** (Chapter 4) and arylazides **V.37**-**V.42** and **V.78a**,**b** (Chapter 5). (Scheme VI.14)

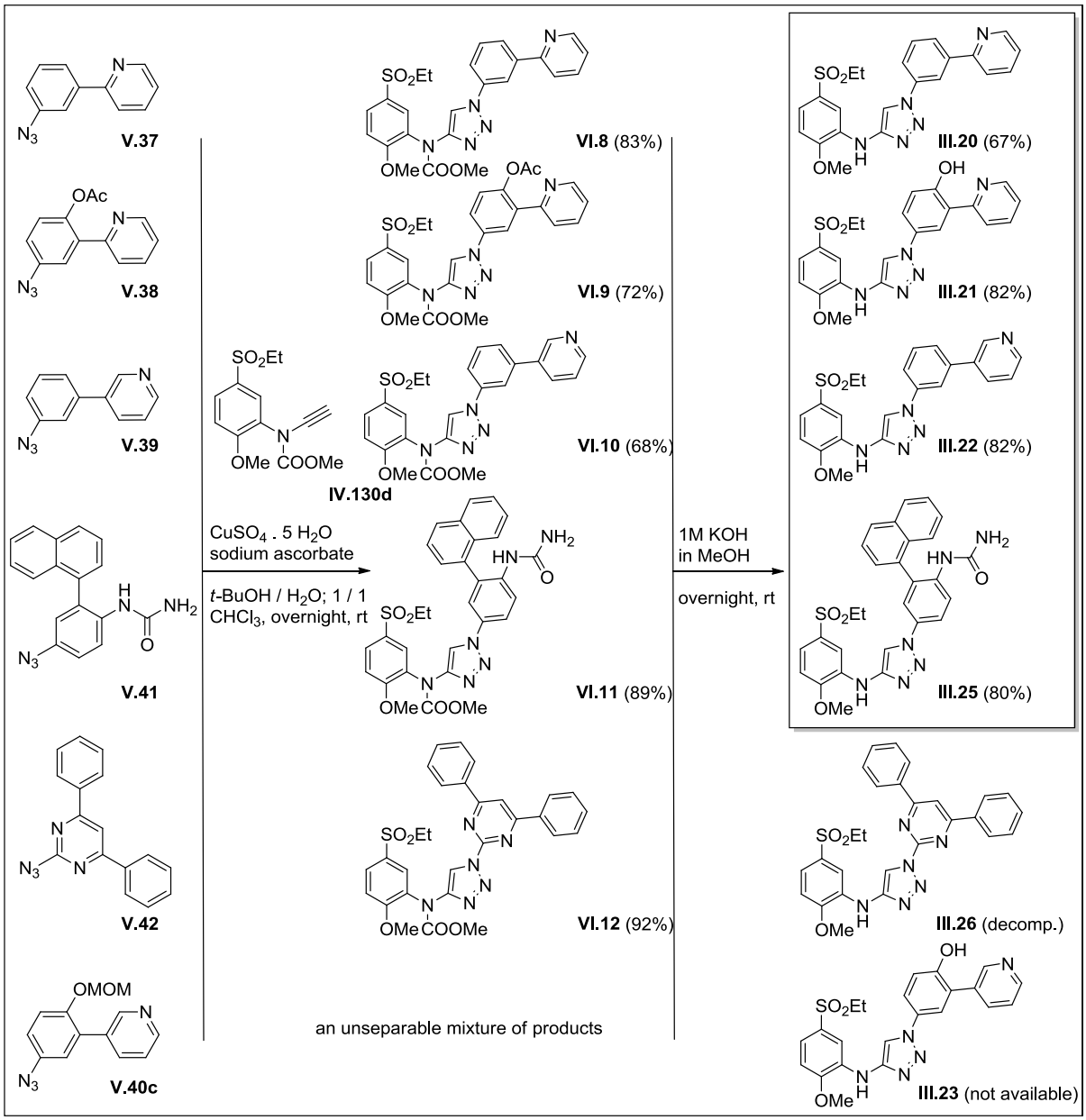


Scheme VI.14. *Already prepared ynamides **IV.130a**, **d** and azides **V.37**-**V.42** and **V.78a**,**b**.*

6.2.1 Preparation of triazole III.20-23, III.25-26

Synthesis of predicted 1,4-triazoles **III.20-III.23** and **III.25-26** was performed via [3+2] cycloaddition carried out under mild conditions with copper based catalytic system: 5 mol % of $CuSO_4$. $5H_2O$ / 10 mol % of sodium ascorbate, in the solvent mixture: tert-butanol / water / chloroform at room temperature.

All triazoles **VI.8**-**VI.12** were obtained with a total regioselectivity and rather good isolated yields - 68-92 %. (Scheme VI.15) The crude reaction mixtures were filtered through short pad of silica gel in order to remove metallic species. Cleavage of electron-withdrawing group (-COOMe) was quantitatively performed in basic conditions (1 M solution of potassium hydroxide), except for triazole VI.12 which underwent to degradation in these conditions. Part of product was lost during the purification (short pad of silica gel) and the corresponding triazoles **III.20-22** and **III.25** were isolated as pure compounds in a range of 67-80 % yields.



Scheme VI.15. *Preparation of proposed target molecules **III.20, III.21, III.22, III.25** and **III.26** via Click chemistry approach.*

A typical brought singlet for triazolic proton was observed in ^{1}H NMR spectrum of compounds **III.20, III.21, III.22** and **III.25.**

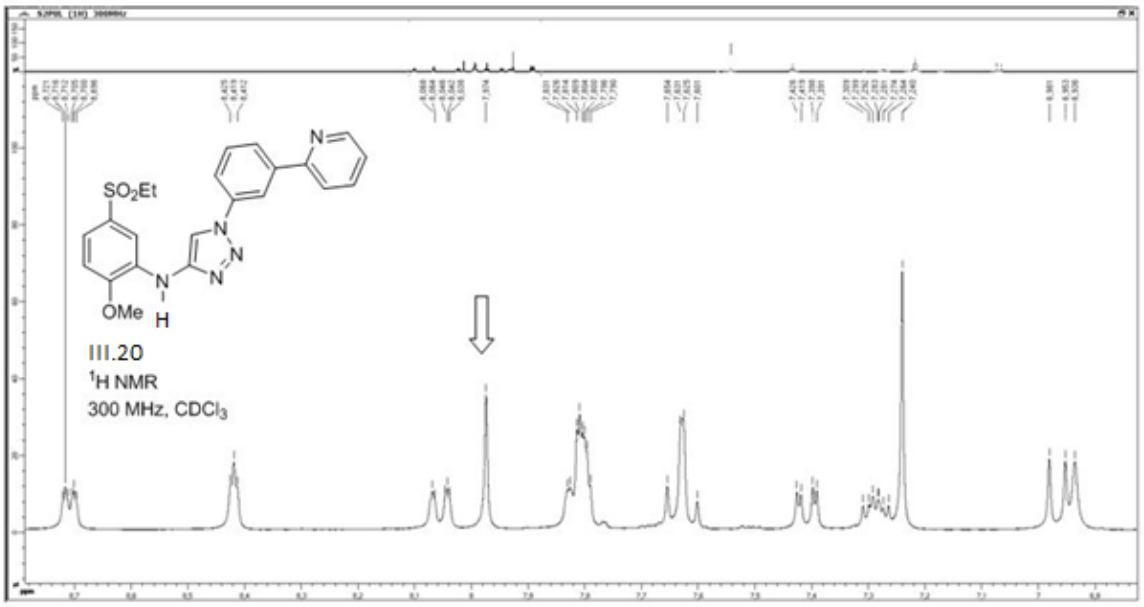


Figure VI.1. *^{1}H NMR spectrum of aromatic part of triazole **III.20**.*

You will find below the ^{1}H NMR spectrums of the aromatic part of each final compound.

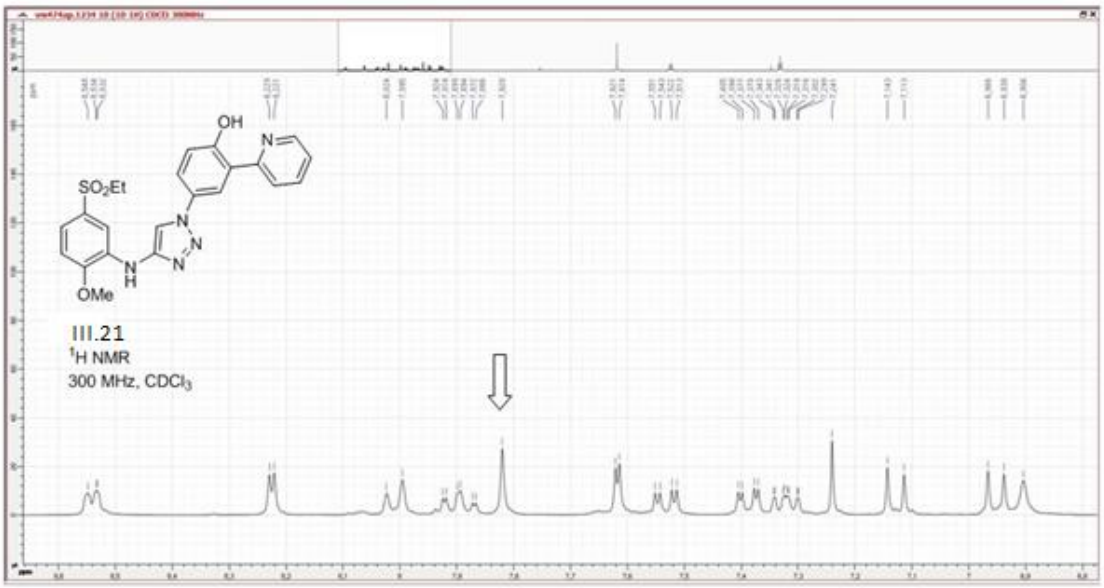


Figure VI.2. *^{1}H NMR spectrum of aromatic part of triazole **III.21**.*

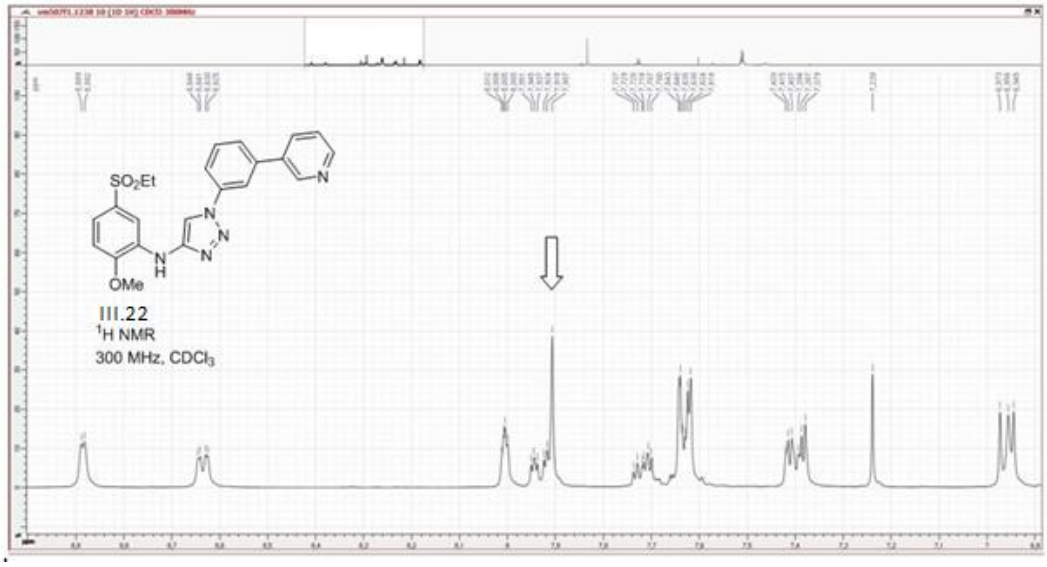


Figure VI.3. *^{1}H NMR spectrum of aromatic part of triazole **III.22**.*

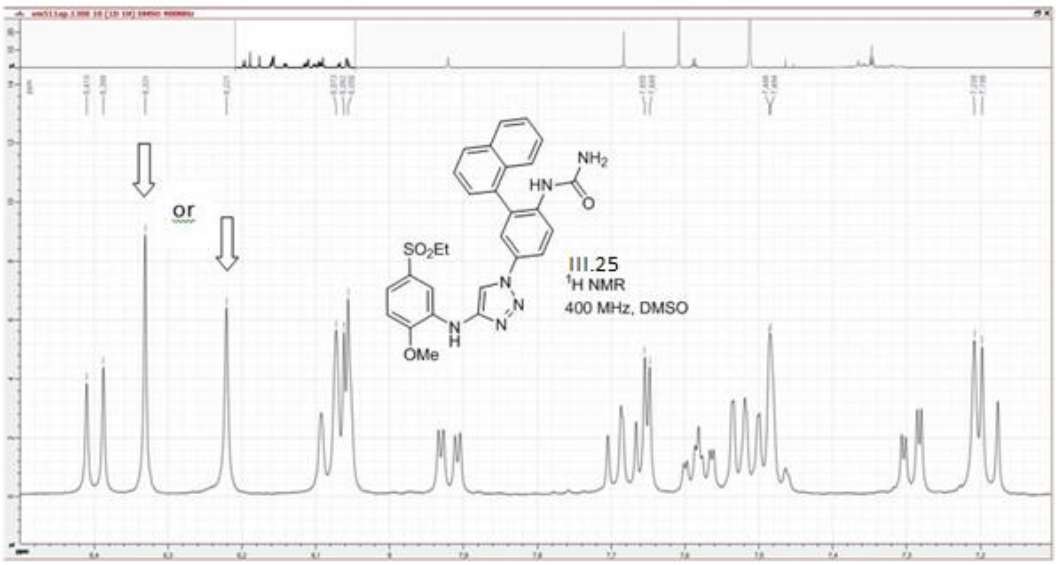
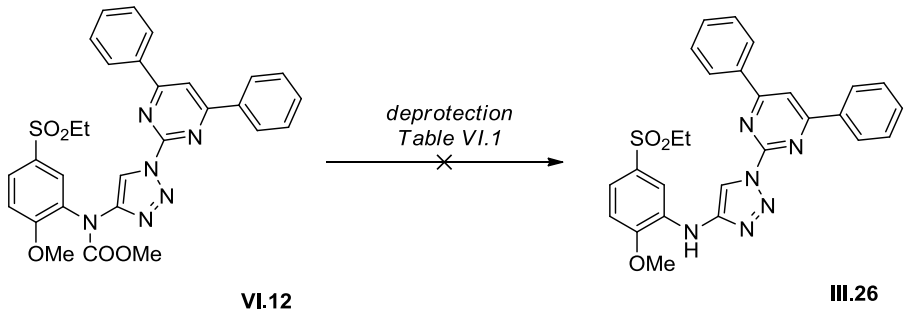


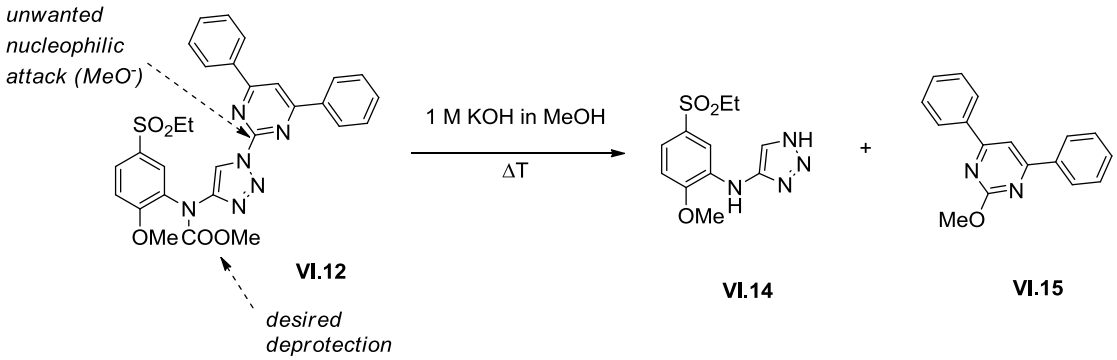
Figure VI.4. *^{1}H NMR spectrum of aromatic part of triazole **III.25**.*

Unfortunately, pyrimidine triazole **VI.12** was unstable in these previous standard conditions (1 M solution of KOH in MeOH, rt, Scheme VI.16). Different attempts were performed and the results are collected in Table VI.1. When the deprotection was run at room temperature, the reaction rate was very low and starting material was mainly recovered (Table VI.1, Entries 1,2, and 4).



Scheme VI.16. *Unsuccessful deprotection of MeCOO- group from pyrimidine triazole **VI.12**.*

Higher reaction temperature lead to decomposition products (Table VI.1, Entries 3 and 5). We suggest, that methanolate (MeO^-) is a strong nucleophile able to attack the activated position on pyrimidine core in α-position to the nitrogen (Scheme VI.17). Two products of decomposition **VI.14** and **VI.15** were isolated by HPLC. (Scheme VI.17)



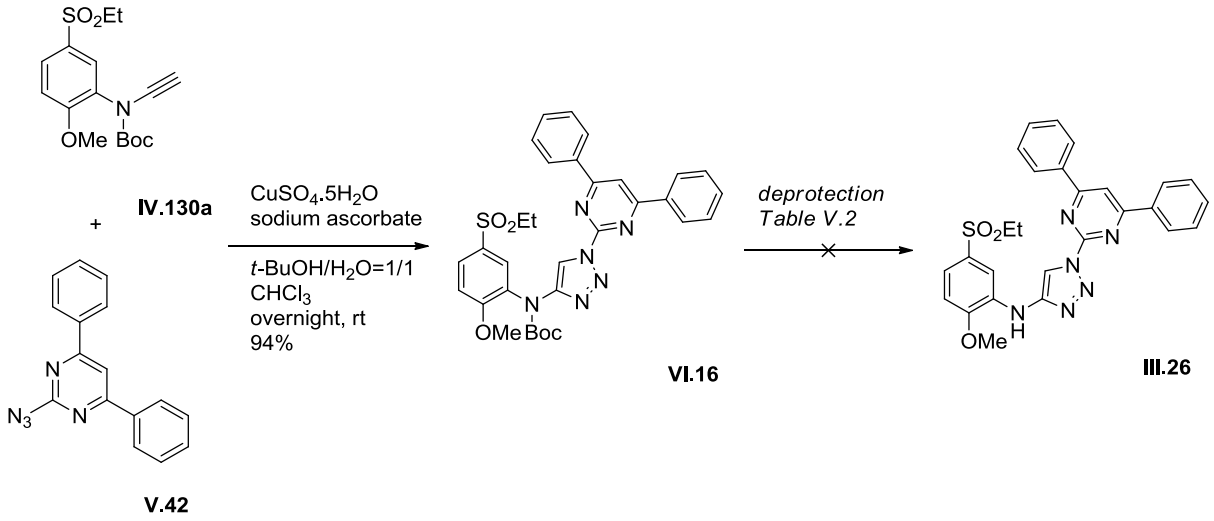
Scheme VI.17. *Products of decomposition **VI.14** and **VI.15** during the deprotection of COOMe- from triazole **VI.12** under reflux in basic conditions.*

Table VI.1. *The conditions and results used for deprotection of –COOMe from triazole **VI.12**.*

Entry	Conditions	Results
1	1 M KOH in MeOH, rt, overnight	Starting material **VI.12** + products of decomposition **VI.14** + **VI.15**
2	1 M KOH in MeOH, rt, 20 min	Starting material **VI.12**
3	1 M KOH in MeOH, reflux, 20 min	Products of decomposition **VI.14** + **VI.15**
4	0.5 M KOH in ethylene glycol + water, rt, 20 min	Starting material **VI.12**
5	0.5 M KOH in ethylene glycol + water, reflux, 20 min	Starting material **VI.12** + products of decomposition **VI.14** + **VI.15**

Due to the unsuccessful deprotection of –COOMe protecting group, we decided to prepare the *N*-Boc- protected pyrimidine triazole **VI.16**. First of all, *N*-Boc ynamide **IV.130a** was prepared according to previously described conditions (Chapter 4) and submitted to Click reaction with azide **V.42** to afford the protected pyrimidine **VI.16** in 94 % yield after purification. (Scheme VI.18)

Different conditions of deprotection of **VI.16** have been tested and results are collected in Table VI.2.



Scheme VI.18. *Preparation of Boc-protected triazole **VI.16** and its deprotection.*

Table VI.2. *Deprotection assays of N–Boc triazole **VI.16**.*

Entry	Conditions	Results
1	5 equiv TBAF, THF, rt, overnight	Starting material **VI.16**
2	5 equiv TBAF, THF, reflux, 30 min	Products of decomposition
3	12 M HCl / EtOAc = 1 / 2.3, rt, 1 hour[231]	Expected product **III.26** + Starting material **VI.16** + Products of decomposition
4	TFA, rt, 1 h[232]	Expected product **III.26** + products of decomposition

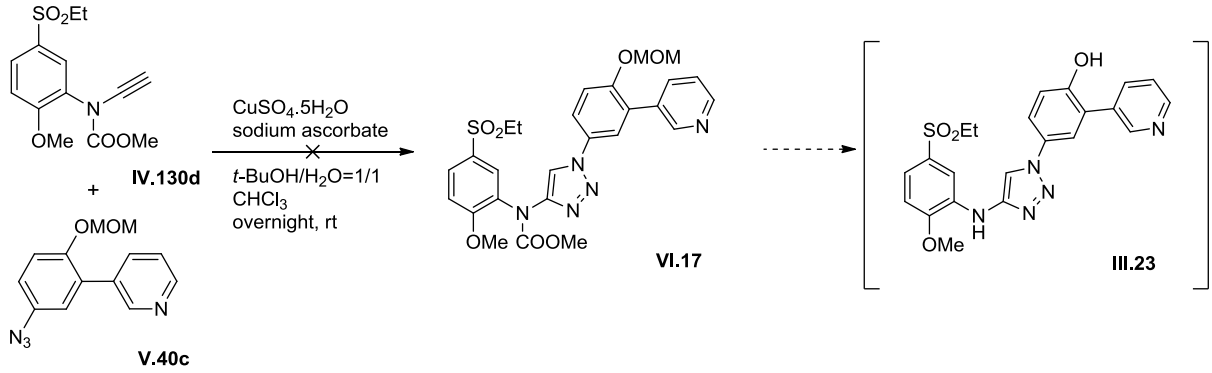
We were interested in the protocol of Routier *et al.*[233], which described mild and selective *N*-Boc deprotection using TBAF. Unfortunately, the reaction performed at room temperature

[231] Coleman, C. M.; O'Shea; D. F. *J. Am. Chem. Soc.* **2003**, 4054.
[232] Englund, E. A.; Gopi, H. N.; Appella; D. H. *Org. Lett.* **2004**, 213.
[233] Routier, S. ; Sauge, L.; Ayerbe, N. ; Coudert, C. ; Merour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589.

afforded only starting substrate **VI.16** and during the short-time reflux we have observed the products of decomposition. (Table VI.2, Entry 1,2)

The use of 12 M HCl in ethyl acetate or TFA in THF lead to expected triazole **III.26** (Table VI.2, Entry 3,4) with 80 and 90 % conversions respectively. Unfortunately, we were not able to isolate **III.26** as some decomposition on SiO_2 and Al_2O_3 was observed.

Cycloaddition of ynamide **IV.130d** with azide **V.40c** did not bring positive results. We observed a mixture of products including the desired triazole **VI.17**. Isolation of triazole **VI.17** was unsuccessful. According to these facts, we have planned the synthesis of triazole **III.23** using an alternative way. (Chapter 6.2.2)

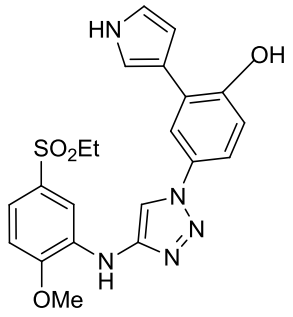


Scheme VI.19. *The Click reaction in order to get precursor **VI.17** of desired triazole **III.23**.*

6.2.2 Synthesis of triazoles III.24 and III.23 using alternative way

In order to circumvent the difficulties met with the preparation of azide **V.43** and **V.40d** , we decided to perform the click reaction prior to the Suzuki-Miyaura cross-coupling. (Scheme VI.20) This new strategy should open new horizons for optimization of the upper arylic part.

6.2.2.1 Preparation of triazole III.24



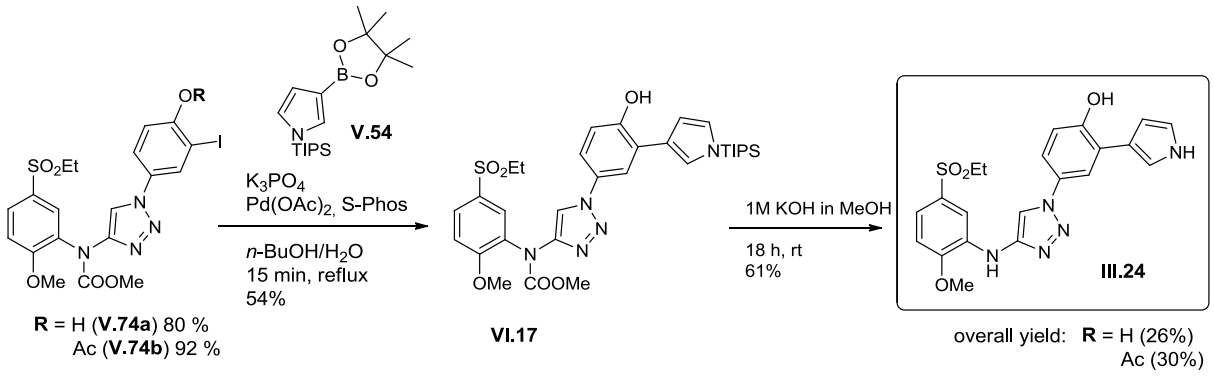
III.24

-51.3 kcal/mol

Figure VI.5. *Structure of predicted triazole **III.24**.*

In order to decrease the number of steps with the pyrrole core which appeared to be unstable, we performed the Suzuki-Miyaura as late as possible in the synthetic sequence. Finally, pyrrole triazole **III.24** has been prepared as depicted in Scheme VI.20 by performing the click reaction prior to the biaryl formation.

The synthesis started with the preparation of the functionalized azides **V.178a** and **V.178b**. Cycloaddition between ynamide **IV.130d** and azides **V.178a** and **V.178b** using standard conditions furnished triazole derivatives **V.174a** and **V.174b** in 80 and 92 % yield respectively. The latters were submitted to Suzuki-Miyaura coupling with pinacolboronic ester **V.54** to afford *N*-protected triazole **VI.18** which was finally deprotected in basic conditions to give triazole **III.24** in 5 % yield over 6 steps (with azide **V.178a**) or 8 % yield over 7 steps (with azide **V.178a)** from 2-iodophenol.



Scheme VI.20. *Performed synthesis of triazole **III.24**.*

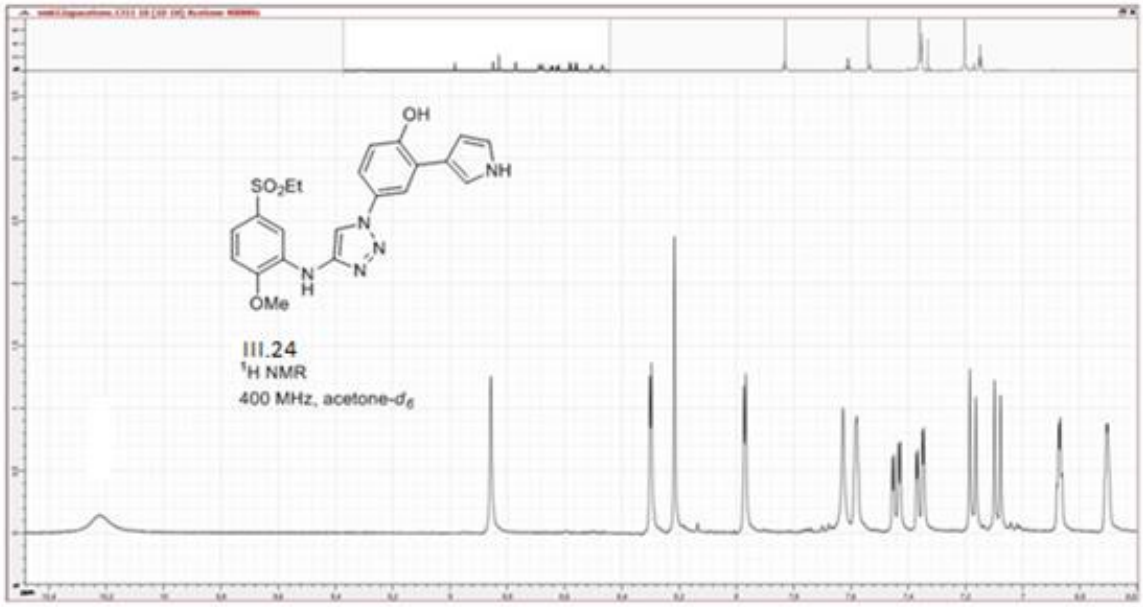
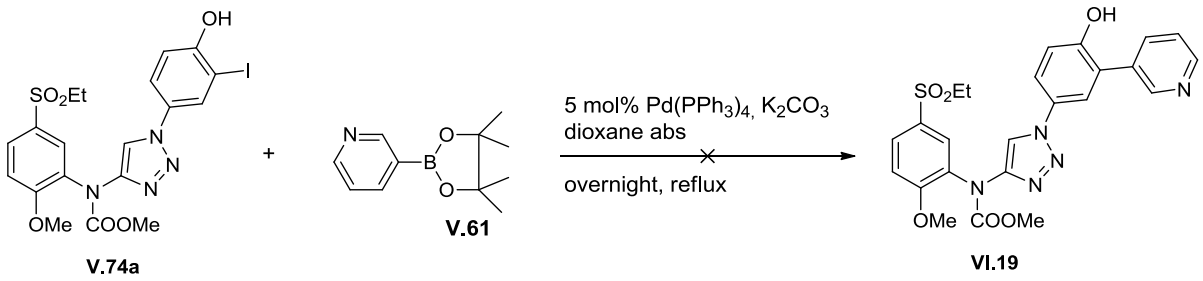


Figure VI.6. *^{1}H NMR spectrum of aromatic part of triazole **III.24**.*

6.2.2.2 Preparation of triazole III.23

Required triazole **VI.19** was prepared using a Suzuki-Miyaura cross-coupling between the triazole building block **V.74a** and pinacol boronic ester **V.61**.[234] Unfortunately, the resulting compound was almost unsoluble in all solvent tested and we were even unable to record a ^{1}H NMR spectra of the crude product.

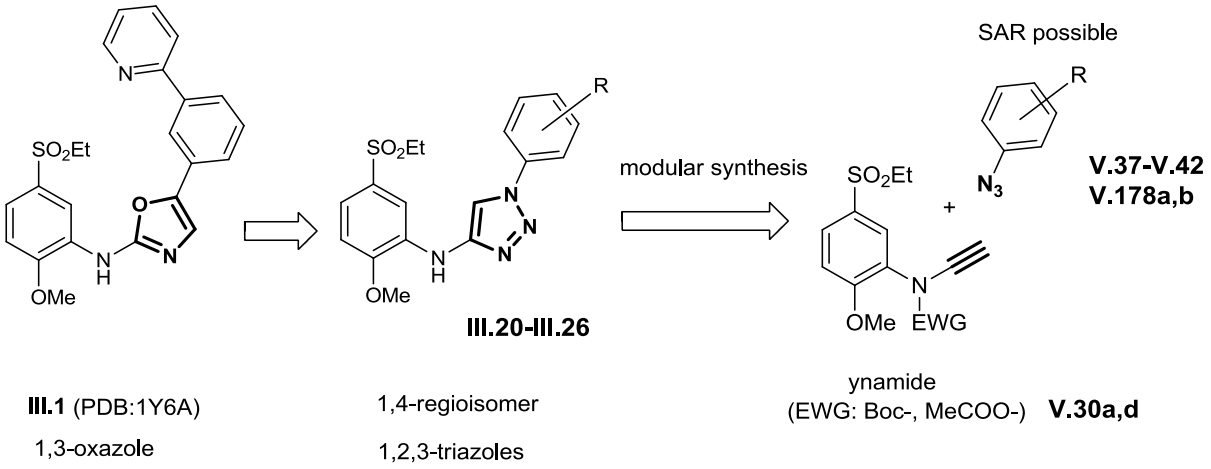


Scheme VI.21. *Unsuccessful preparation of triazole **VI.19** via alternative procedure.*

[234] Trokowski, R.; Akine, S.; Nabeshima, T. Dalton Trans. **2009**, *46*, 10359.

6.3 Conclusion to applied Click chemistry

In the presented Chapter we described the preparation of *in Silico* predicted triazolic analogues of **III.1** (AAZ from PDB:1Y6A). In order to prepare the 1,2,3-triazoles **III.20-26**, we have used the concept of Click chemistry introduced by Barry Sharpless in 2001. The copper catalyzed cycloaddition (CuAAc) between ynamides **IV.130a** and **IV.130d** (Chapter 4) and azides **V.37** – **V.42** and **V.178a,b** (Chapter 5) was selected to prepare desired 1,4-regioisomers of 1,2,3-triazoles **III.20 – III.26**. (Scheme VI.22)



Scheme VI.22. *Synthetic strategy leading to the triazole derivates of PDB:1Y6A.*

Successful deprotection of cycloadducts **VI.8** – **VI.11** lead to triazoles **III.20, III.21, III.22** and **III.25** in very good yields. (Figure VI.7)

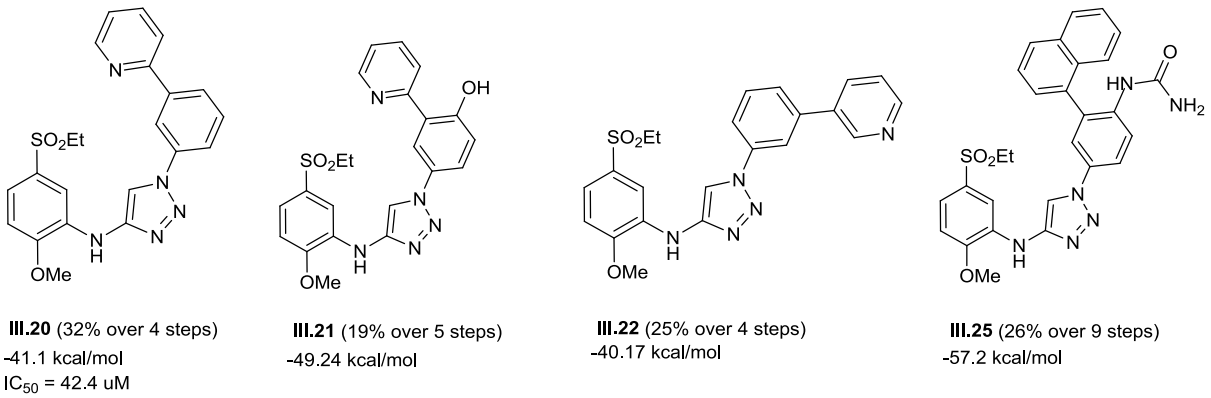
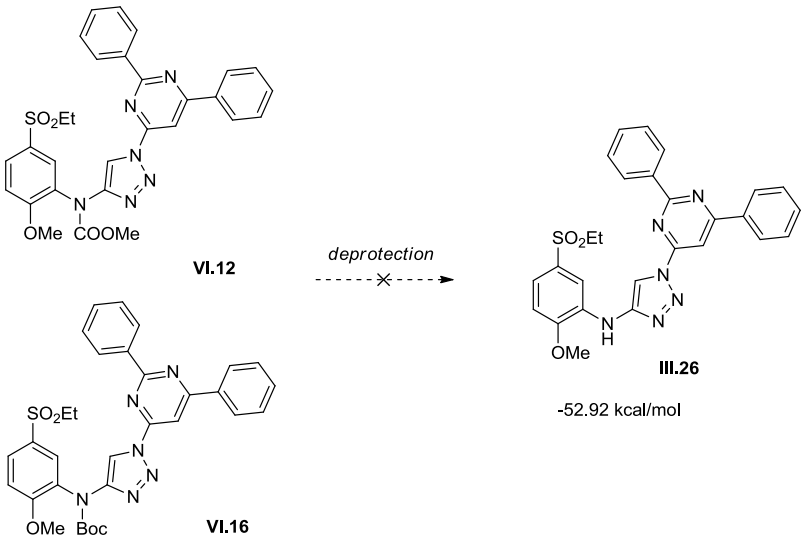


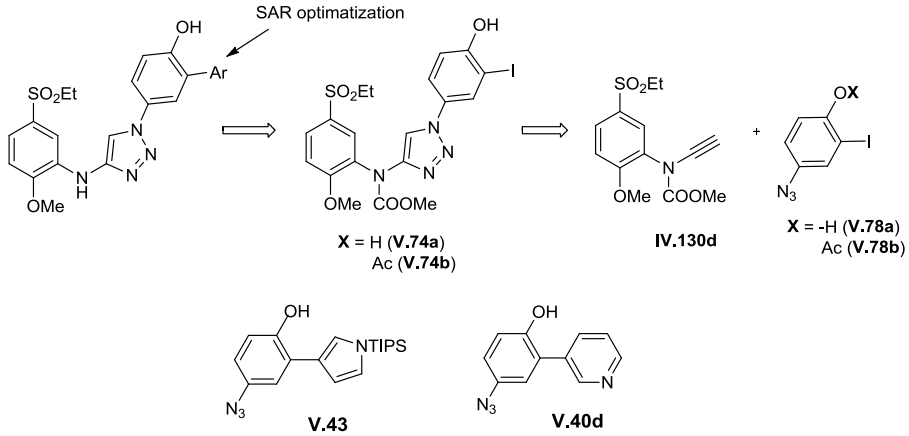
Figure VI.7. *The structures of successfully prepared triazoles **III.20, III.21, III.22** and **III.25**.*

Pyrimidine triazole **VI.12** was unfortunately not deprotected. We have prepared triazoles with 2 different electron-withdrawing group (Boc-, MeCOO-) with unsuccessful results. (Scheme VI.23) Consequently, triazole **III.26** was not prepared in pure form and was not sent for biological assays.



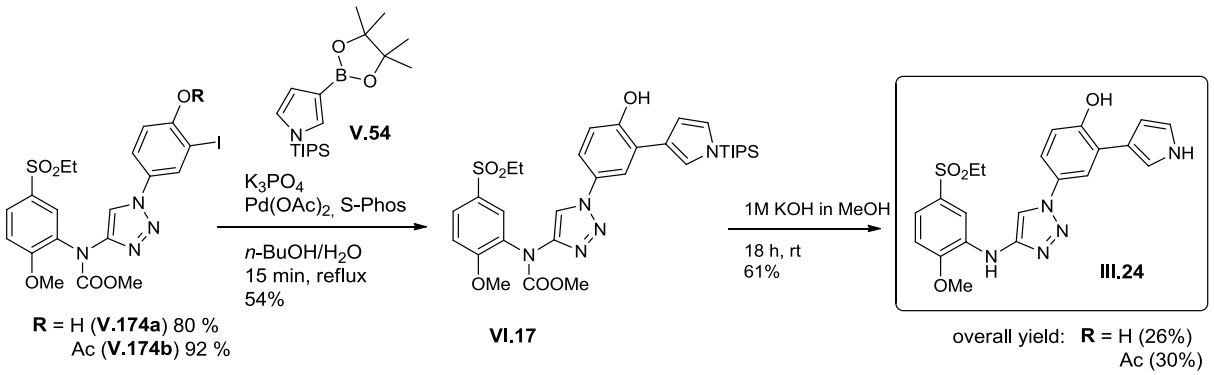
Scheme VI.23. *Prepared triazoles **VI.12** and **VI.16** and unsuccessful deprotection leading to target molecule **III.26**.*

Synthesis of pyrrole triazole has been successfully realized by forming the triazole heterocycles **V.174a, b** prior to the Suzuki-Miyaura coupling. (Scheme VI.24) This approach has been designed to circumvent the difficulties met with the preparation of azide building blocks **V.43** and **V.40d**. (Scheme VI.24)



Scheme VI.24. *New retrosynthetic strategy for preparation of triazole **III.24** and structures of two azide building blocks **V.43** and **V.40d** that we were not able to obtain.*

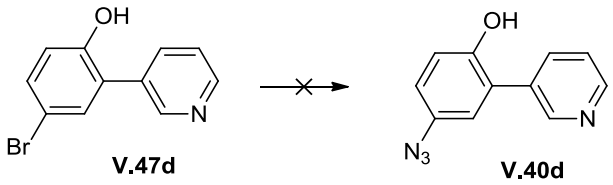
According to the sequence depicted in Scheme VI.25, pyrrole triazole **III.24** was successfully prepared.



Scheme VI.25. *Preparation of triazole **III.24**.*

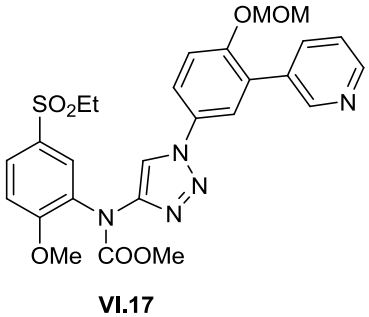
Finally, preparation of predicted triazole **III.23** failed in our hands, even we tested different ways:

- preparation of azide **V.40d** – we met very low solubility of bromo-biaryl **V.47d**



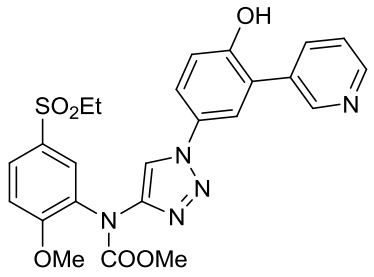
Scheme VI.26. *Unsuccessful preparation of azide **V.40d**.*

- Click reaction with MOM- protected biaryl – we met difficulties with isolation of the desired product **VI.17** (Scheme VI.27)



Scheme VI.27. *The Click reaction in order to get triazole **VI.17**.*

- alternative way to triazole presented in this chapter – the insolubility of final product **VI.19** (Figure VI.8)



VI.19

Figure VI.8. *Structure of insoluble triazole **VI.19**.*

Chapter 7. **Biological assays**

IC_{50} (VEGFR-2) biological activity values of oxazolic compounds **III.24** (40 100 nM), **III.25** (not active), **III.21** (6 960 nM), **III.22** (not active), **III.20** (42 000 nM) were obtained by radiometric protein kinase assay (33PanQinase® Activity Assay). Prepared compounds exhibited very different inhibitory properties from the inactive ones (**III.22** and **III.25**), to weakly (**III.20**, **III.24**; IC_{50} = 42, 40 uM, resp.) or moderately active triazoles (**III.21**: IC_{50} = 6.96 uM). Despite the compounds **III.20-22.** and **III.24-25** possess the same pharmacophoric *N*-(5-(ethylsulfonyl)-2-methoxyphenyl) fragment their activity seems to be highly dependent on the nature of the remaining aryltriazolic residue. Compounds **III.20**, **III.21** and **III.24** specifically bind to VEGFR-2 enzyme, since the enzymatic activity of VEGFR-2 kinase depends on the concentration of the inhibitor, and is represented by a current sigmoid curve. (Figure VII.1)

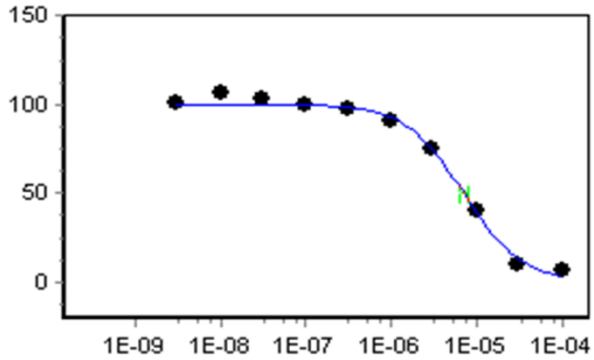


Figure VII.1. *Sigmoid curve showing a dependence of VEGFR2 kinase activity on the concentration of the inhibitor* ***III.21*** *(x: compound concentration, y: enzyme activity).*

Structures of **III.1** and triazoles **III.20-26** are shown together with their values of docking score and determined biological activity (IC_{50}, VEGFR2). (Figure VII.2)

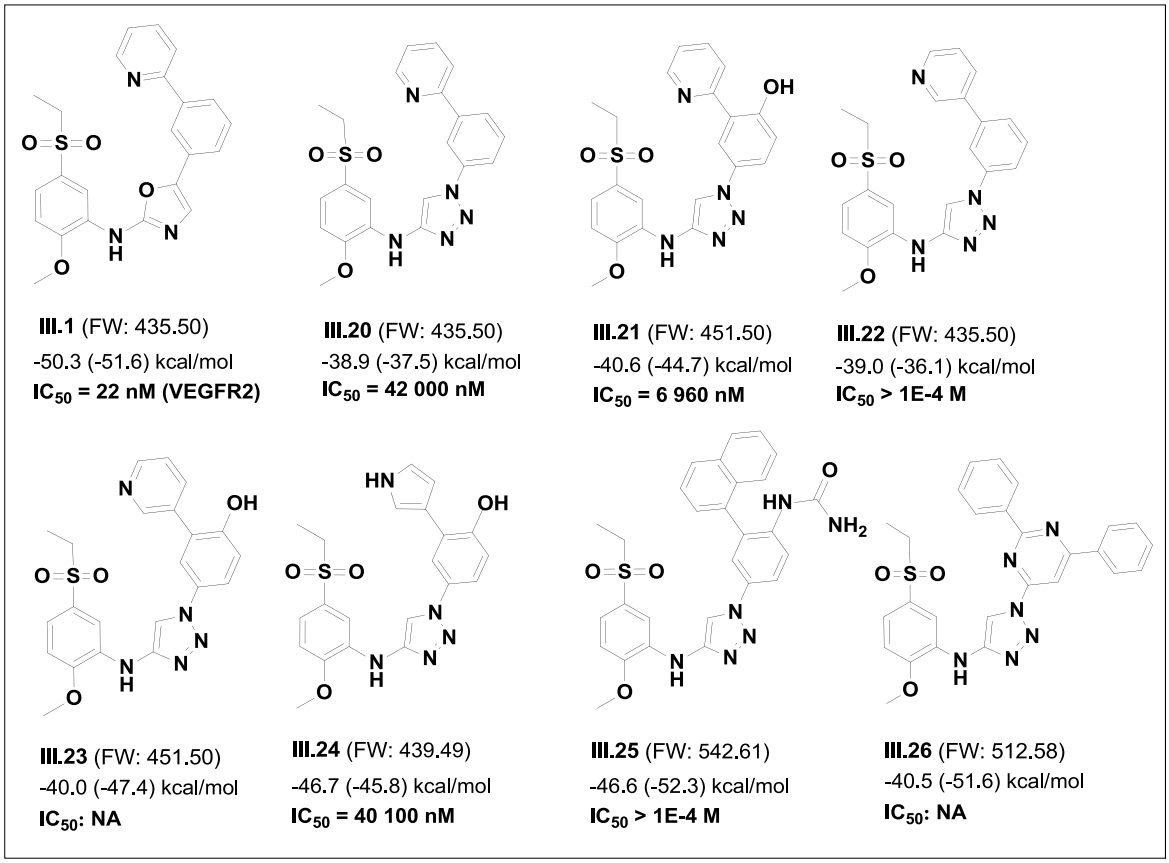


Figure VII.2. *The structures of oxazolic inhibitor **III.1** and its 1,2,3-triazolic analogues **III.20-26** with their score (software DOCK 3.6, protein from PDB: 1Y6B (1Y6A), resp.) and determined IC_{50} (VEGFR2) activity, if stated. NA: a compound that was not available.*

7.1 Redocking

Previously determined docking scores (DOCK 3.0) for triazoles **III.20** – **III.22**, **III.24** and **III.25** did not correlate well with the results of their biological activities. Triazoles **III.21** – **III.23** and **III.25** were assigned with better or similar affinities as their oxazolic precursor **AAZ** (*vide supra*). Therefore an additional docking experiment was performed with newer version of the docking program DOCK 3.6 with a more calibration reliable VEGFR2 protein from PDB: 1Y6B.[235] (Figure VII.3) Within our docking experiments we observed that all 1,2,3-triazolic compounds showed worse relative binding

[235] http://dock.compbio.ucsf.edu/DOCK3.6/ (visited 8th August 2013).

energies compare to their oxazolic analogues which evokes the conclusion that the these analogues are less suitable to inhibit VEGFR2 kinase compare with their isosteric oxazolic ligands. (Figure VII.3)

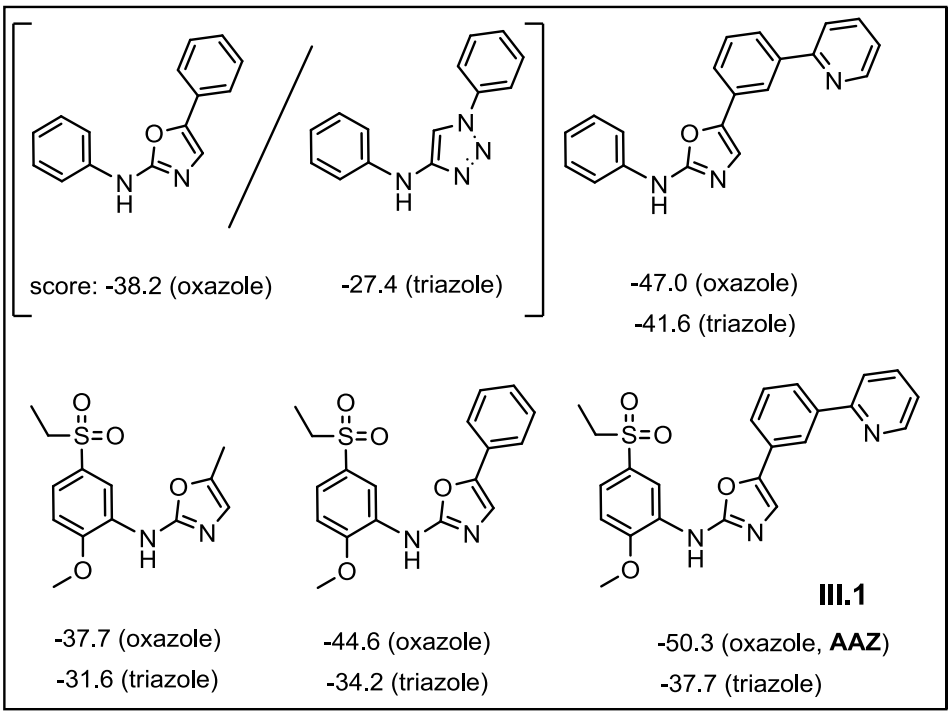


Figure VII.3. *The relative binding energies [kcal/mol] (score values) of isosteric oxazol / triazol pairs obtained after docking into VEGFR2 protein (from PDB: 1Y6B) by DOCK 3.6 software.*

The predicted binding energies of triazoles are on average about 21 % less favorable compare with their oxazolic isosters. (Figure VII.3) A similar result (22 %) we obtained for the triazolic / oxazolic isosteric pairs derived from the structures of compounds **III.20 - III.26**, **III.1** (PDB: 1Y6A) and **III.1b** (PDB: 1Y6B). (values not shown)

The structure of known inhibitor **AAZ** (PDB: 1Y6A) containing oxazolic core was optimized by authors for the best affinity with VEGFR2 receptor.[23] (Figure VII.4)

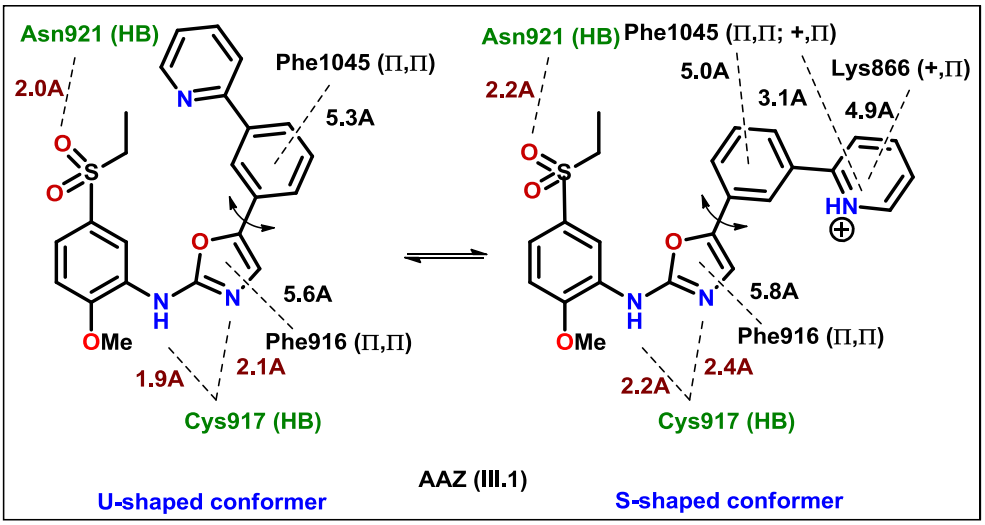


Figure VII.4. *Intermolecular interactions of oxazolic inhibitor **III.1** (PDB: 1Y6A, the complex contains two conformers U-and S-shaped).*

We wanted to exploit an important pharmacophoric fragment from **III.1** ligand (amino(ethylsulfonyl))methoxyphenyl group). Therefore it was important to maintain **III.1** (PDB: 1Y6A) binding pose in VEGFR2 receptor also for proposed 1,2,3-triazolic derivatives. Predicted poses and intermolecular interactions of triazoles **III.20** – **III.26** were similar to those know for **III.I** ligand conformers (Figure VII.4). Predicted intermolecular interactions of triazolic **III.21** (IC_{50} = 6 960 nM) and its oxazolic bioisostere **III.21-ox** are depicted. (Figure VII.5) VEGFR2 activity of **III.21-ox** (IC_{50} = 12.8 nM) was published recently.[236]

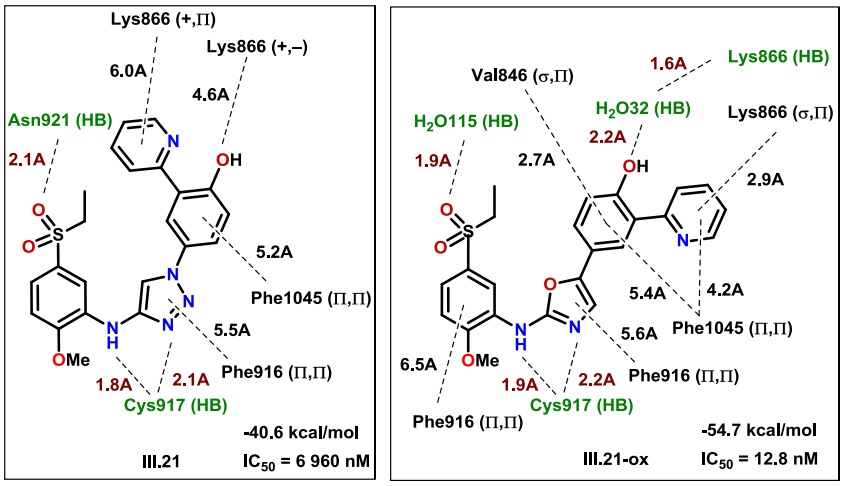


Figure VII.5. *The comparison of predicted binding interactions for triazolic **III.21** and its oxazolic bioisostere **III.21-ox** performed in DOCK 3.6 software with VEGFR2 protein from PDB complex 1Y6B.*

[236] Remko, M; Boháč, A.; Kováčiková, L. *Structural Chemistry* **2011**, 1.

7.2 Influence of isosteric oxazole / triazole replacement

1,2,3-Triazolic compounds **III.20** – **III.26** achieved predicted score lower than their oxazolic isosteres. Compounds **III.20** and **III.21** exhibit much less inhibitory activity against VEGFR-2 receptor compare to their oxazolic bioisosteres **III.21-ox** and **III.1:** (**III.21** / **III.21-ox**, IC_{50}: 6 950 nM / 12.8 nM = 543 and **III.20** / **AAZ**, IC_{50}: 42 400 / 22 = 1 927 times). Oxazolic core from **III.1** is in VEGFR-2 active place surrounded by lipophilic amino acid residues (Phe916, Val914, Val897, Ala864, Leu838, Leu1033, Cys917) that are less favourable to bind more polar triazolic nucleus. Different electronic properties (*e.g.* size and orientation of the dipole moment) are responsible for the observed differences in predicted affinities and obtained biological activities. (Figure VII.6)

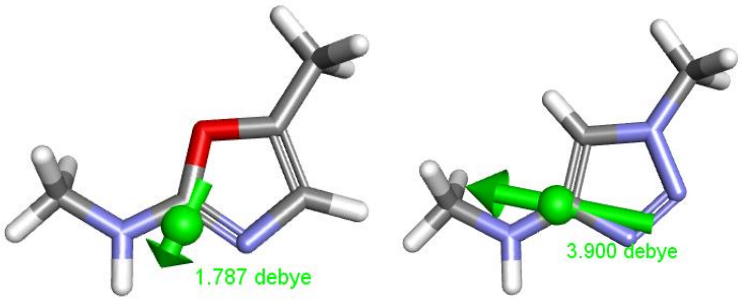


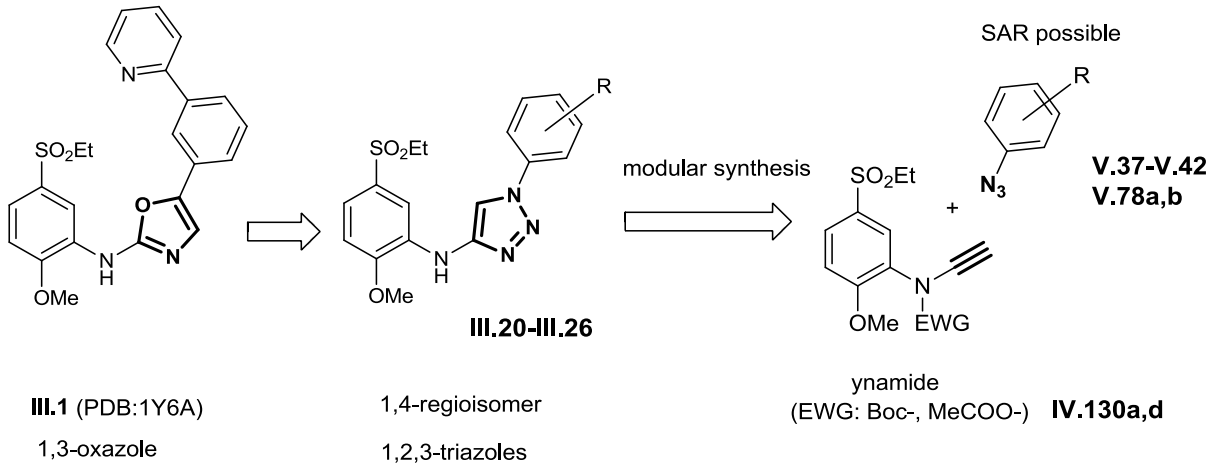
Figure VII.6. *Calculated dipole moment (value and orientation) for N,5-dimethyloxazol-2-amine (left) and its triazolic isostere (the right structure). The differences in the nature of two heterocycles can explain influence of the heterocyclic ring replacement on observed results from biological assay. The structures and their dipole moment were performed by Discovery Studio 3.5 software.*[237]

[237] Discovery Studio http://accelrys.com/products/discovery-studio/visualization-download.php (visited 2nd August 2013)

Chapter 8. **General conclusion**

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13 % of all deaths) in 2008. There are continuously developing active compounds for cancer treatment. We have decided to prepare new antiangiogenic compounds based on clinically tested III.1 oxazolic VEGFR2 inhibitor (ligand taken from PDB complex 1Y6A). Some of the *in Silico* designed triazolic isosteres **III.20**-**III.26** derived from oxazolic **III.1** were prepared *via* Click chemistry approach by reaction of differently protected key ynamide **IV.130a,d** and selected azides **V.37-42** and **V.78a,b**. The proposed disconnection approach is depicted in the Scheme VII.1.

Construction of the predicted triazoles was envisioned to proceed *via* Click cycloaddition of ynamide with different azides. This disconnection is depicted in Scheme VIII.1.

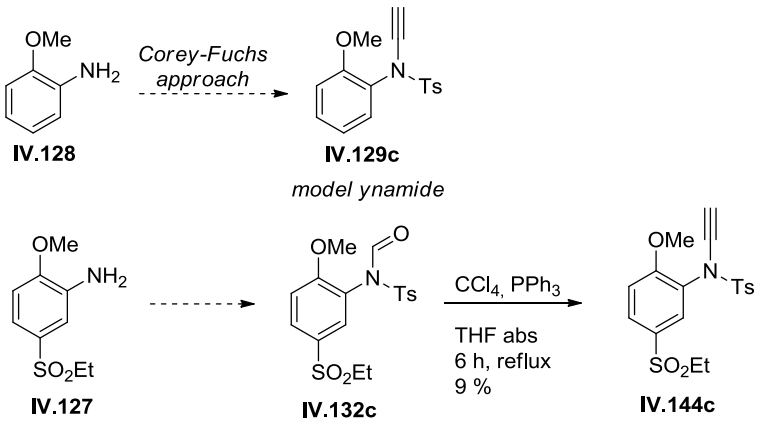


Scheme VIII.1. *General retrosynthetic plan proposed for preparation of designed triazoles **III.20-26** as isosteric analogues of oxazolic VEGFR2 inhibitor **III.1**.*

In Chapter IV is presented literature background of ynamides and subsequently the synthesis of desired ynamides **IV.130a** and **IV.130d**. We have proposed 4 synthetical pathways in order to prepare target ynamide: Corey-Fuchs approach (A), Bestmann-Ohira reaction (B), transformation of *N*-trichloroacetales to ynamides (C) and *N*-direct alkynylation using trifluoro alkynyl iodonium salts **IV.10** or bromoacetylenes **IV.160** (D).

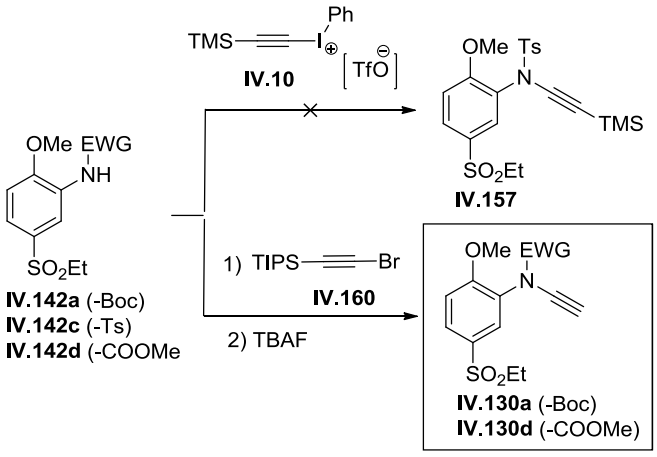
The selection of suitable electron-withdrawing group was crucial. Primary, *N*-tosylated model ynamide **IV.129c** was prepared *via* Corey-Fuchs homologation following the Brückner's protocol. (Scheme VIII.2) Bestmann-Ohira pathway (B) failed. Consequently, we applied this methodology to target aniline **IV.127**. We met with more difficulties in order to prepare *N*-tosylformamide **IV.132c** as

Corey-Fuchs precursor. *N*-Tosylformamide **IV.132c** in hands, we performed its conversion into the corresponding 1,1-dichlorovinyl **IV.144c** (Scheme VIII.2) using the conditions selected from model *o*-anisidine **IV.128** study. The poor yield of reaction (9 %) has turned our attention to proposed synthetical pathway C and D as alternatives.



Scheme VIII.2. *Preparation of model **IV.129c** and target ynamide **IV.144c** via Corey-Fuchs approach.*

Transformation of *N*-trichloroacetamides to ynamides (C) failed. Alternatively, *N*-direct alkynylation of arylamines (D) was studied. The iodonium triflate mediated *N*-alkynylation using hypervalent compound **IV.10** failed. (Scheme VIII.3) We turned our attention to transition metal mediated *N*-direct alkynylation of *N*-COOMe protected **IV.142d** using bromoacetylenes **IV.160**. Following the Skydrup's protocol ynamides **IV.130a** and **IV.130d** were prepared in excellent yields.



Scheme VIII.3. *Preparation of N-protected ynamides **IV.130a, d** via N-direct alkynylation.*

In Chapter V is described the preparation of azides suitable for Click reaction with already prepared ynamides **IV.130a**, **d**. The key reactions for preparation of azides **V.37**, **V.38**, **V.39** and **V.43** were Suzuki Miyuara coupling and copper-catalyzed transformation of bromobiaryl to desired

azidobiaryls. (Figure VIII.1) For the preparation of azide **V.38** we have also used a palladium-catalyzed C-H activation. The preparation of bromide **V.47d** was problematic and its subsequent transformation to azide due its low solubility as well. Alternatively, MOM- protected azide **V.40c** was prepared as precursor for triazole **III.23**. The preparation of pyrrole precursor **V.48** did not afford positive results and alternative way for preparation triazole **III.24** was selected. Desired urea azide **V.41** was prepared from *p*-nitroaniline with 37 % overall yield in 7 steps. One of the crucial step was Suzuki-Miyaura cross-coupling and the final transformation of amino group into urea using trichloroacetoisocyanate. Pyrimidine azide was prepared *via* pyrimidinone and its subsequent transformation to chloropyrimidine and to desired azide **V.42**. In addition, azides **V.78a**,**b** were synthetized as suitable synthons of an alternative way for preparation the desired triazoles. (Figure VIII.1)

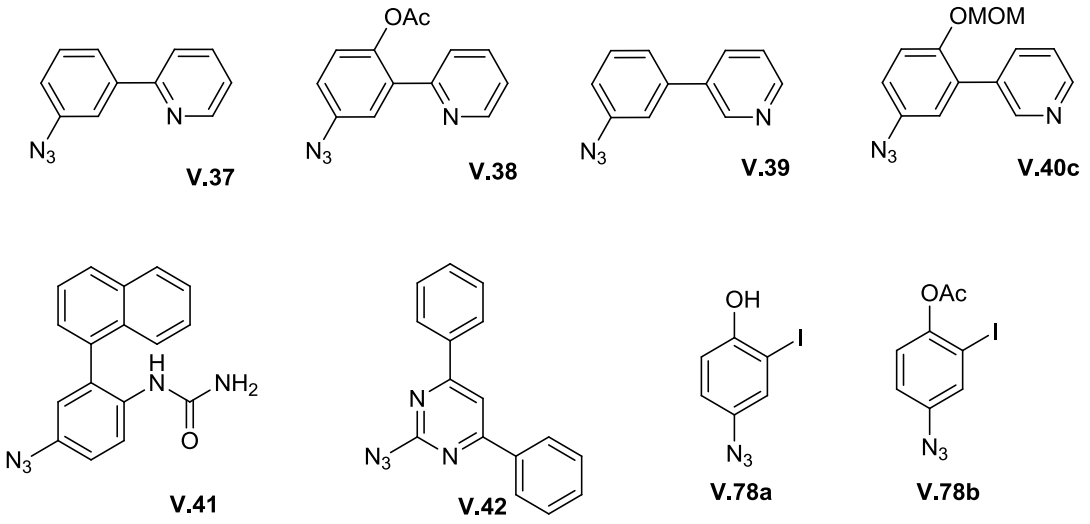


Figure VIII.1. *Prepared azides **V.37**-**V.42** and **V.78a**,**b** suitable for Click chemistry reaction.*

In Chapter VI is presented preparation predicted 1,4-regioisomers of 1,2,3-triazoles analogues of PDB: 1Y6A by copper catalyzed Click reaction. Synthetized ynamides **IV.130a**,**d** and azides **V.37-V.42** and **V.178a**, **b** were used as key synthons. (Figure VIII.2) Triazoles **VI.8** – **VI.12** were prepared in satisfied yield (68 – 92 %) in very mild conditions with 100 % regioselectivity. Subsequently, COOMe- electron-withdrawing group was removed in basic condition in order to prepare desired triazoles **III.20** – **III.25**. Deprotection of COOMe- protected pyrimidine triazole **VI.12** was not accomplished in these conditions. Alternatively, Boc protected triazole **VI.16** was prepared, but deprotection also failed. Triazole **VI.13** was not prepared due to the difficulties met with its isolation from the reaction mixture.

Five new triazolic compounds (**III.20** – **III.22, III.24** and **III.25**) were prepared and sent for biological assays. (Figure VIII.2) **III.20, III.21, III.24** modulate VEGFR-2 tyrosine kinase activity and two of them **III.25, III.22** are inactive: **III.24** (40.1 uM), **III.25** (not active), **III.21** (6.96 uM), **III.22** (not active), **III.20** (42.0 uM). The activities of new compounds are significantly lower than the activities of their oxazolic isosteres (*e.g.* **III.21** / **III.21-ox** 543 and **III.20** / **III.1** 1 927 times worse). The activity of triazoles **III.20** – **III.22, III.24** and **III.25** highly depends on the decoration of their aryl triazolic part. Despite the lower activity of triazoles **III.20**, **III.21** and **III.24,** they specifically bind to VEGFR-2 kinase because the activity of VEGFR-2 kinase depends on the concentration of **III.20**, **III.21** and **III.24** and has a typical sigmoid character.

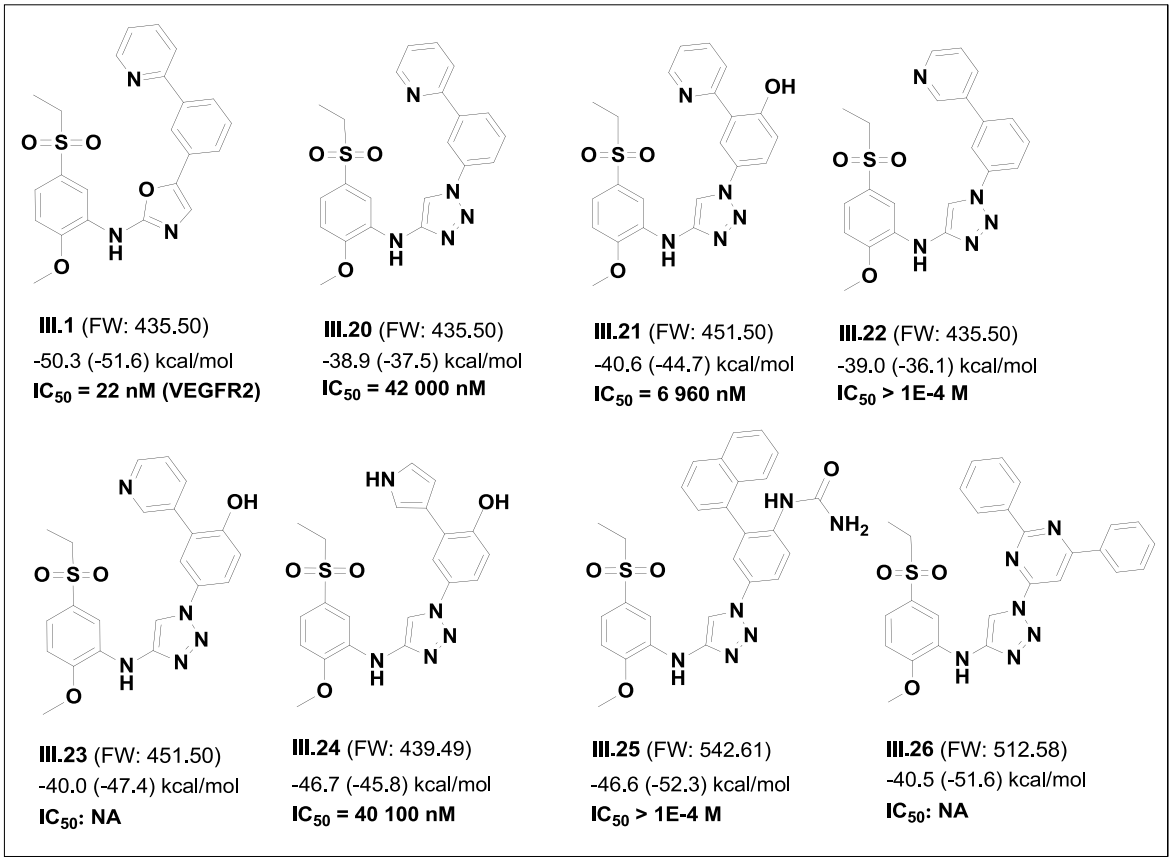


Figure VIII.2. *The s*tructures of oxazolic inhibitor III.1 and its 1,2,3-triazolic analogues III.20 – III.26 with their score (software DOCK 3.6, protein from PDB: 1Y6B (1Y6A), resp.) and determined IC_{50} (VEGFR2) activity, if stated. NA: the compound was not available.

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Experimental section

General

Commercially available compounds were purchased from Sigma-Aldrich, TCI, Alfa Aesar, and Apollo Scientific and were used without further purification. Solvents were obtained from Sigma-Aldrich and Carlos Erba; unless noticed reagent grade was used for reactions and column of chromatography and analytical grade was used for recrystallizations. When specified, anhydrous solvents were required; dichloromethane (DCM) was distilled over CaH_2 under argon. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. 1,4-Dioxane and dimethylformamide (DMF) were purchased anhydrous over molecular sieves from Sigma-Aldrich. Triethylamine (Et_3N), diisopropylethyl amine (DIPEA), pyrrolidine, piperidine were distilled over KOH under argon and stored over KOH. Toluene, THF, DCM, diethylether were also dried under argon by passage through an activated alumina column under argon.

Thin Layer Chromatography (TLC) was used to monitor reactions (*vide infra*).

Crude mixtures were purified either by recrystallization or by flash column of chromatography. The latter were performed using silica gel 60 (230-400 mesh, 0.040-0.063 mm) or alumiunium oxide purchased from E. Merck. Monitoring and primary characterization of products were achieved by Thin Layer Chromatography on aluminum sheets coated with silica gel 60 F254 purchased from E. Merck. Eluted TLC's were revealed under UV (325 nm and 254 nm) and with chemicals (*vide infra*).

High Pressure Liquid Chromatography (HPLC) experiments were performed on a Hewlett Packard HPLC with dual UV-Vis detection (254 nm and 325 nm) or on a Hitachi HPLC (detection at 254 nm).

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AC 300, Bruker AC 400 or Varian 300 with solvent peaks as reference. Carbon multiplicities were assigned by Distortionless Enhancement by Polarization Transfer (DEPT) experiments. ^{1}H and ^{13}C signals were assigned by correlation spectroscopy (COSY), Heteronuclear Single Quantum Correlation (HSQC), and Heteronuclear Multiple-Bond Correlation spectroscopy (HMBC). In the following NMR assignments, coupling constants (*J*) will be expressed in Hertz (Hz), multiplicity are described with (s) as singlet, (d) as doublet, (t) as triplet and (q) as quadruplet, broad singlet (br s).

Infrared (IR) spectra (cm^{-1}) were recorded neat on a Perkin-Elmer Spectrum One Spectrophotometer. UV-Vis spectra were recorded on a Varian Cary 50 spectrophotometer.

ESI-HRMS mass spectra were carried out on a Bruker MicroTOF spectrometer. LC-MS were performed on a ThermoFisher apparatus with ESI ionization. Elemental analysis were obtained from "Service commun d'analyses" from the University of Strasbourg and Comenius University. Melting

points were measured on Büchi® Schmeltzpunktbestimmungsapparat apparatus and are given uncorrected.

General procedures

A: Copper-catalyzed Click chemistry reaction :

To a stirred solution of ynamide (3 mmol, 1.0 mol equiv) and corresponding azide (3 mmol, 1.0 mol equiv) in 6 mL of *tert*-butanol and 6 mL of $CHCl_3$ was added a premixed solution of $CuSO_4.5H_2O$ (0.15 mmol, 5 mol%) and sodium ascorbate (0.3 mmol, 10 mol%) in 6 mL of H_2O (*tert*-butanol / H_2O = 1 / 1). After vigorous stirring overnight the mixture was diluted with 10 mL of H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 10 mL 3 % solution of NH_4OH in brine, dried over $MgSO_4$, filtered, evaporated and dried *in vacuo*. Purification using flash chromatography afforded expected protected triazole.

B: Deprotection of methoxycarbonyl protecting group from triazole:

Triazole (2 mmol, 1.0 mol equiv) was stirred in 1 M solution of KOH in MeOH (5 mL) at room temperature overnight. The progress of reaction was checked by LCMS or ^{1}H NMR. When the reaction was accomplished, the reaction mixture was neutralized with saturated solution of sodium carbonate, extracted in EtOAc (3 x 8 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, evaporated and dried *in vacuo*. Purification using flash chromatography afforded expected deprotected triazole.

C: Substitution of aromatic halide to azide:

Caution! Organic azides should be considered explosive, and all manipulations should take place behind a blast shield! Aryl azides are light sensitive, and all reactions and flash chromatography procedures should be conducted under diminished light.

Aryl bromide (2 mmol, 1.0 mol equiv), NaN_3 (4 mmol, 2 mol equiv), sodium ascorbate (0.1 mmol), CuI (0.2 mmol), *N,N*'-DMED (0.3 mmol), and 4 mL of EtOH–H_2O (7:3) were introduced into a two-necked round-bottom flask equipped with a stirring bar and a reflux condenser. After it was degassed, and then introduced under an argon atmosphere, the reaction mixture was stirred under reflux and the progress of the reaction was followed by TLC. When the aryl bromide was completely consumed, or when the progress of the reaction had stopped, the reaction mixture was allowed to cool down to room temperature, and the crude mixture was purified either by extraction and/or flash chromatography, giving the desired aryl azide.

D: Direct *N*-alkynylation with bromoalkyne using the Skydrup`s protocol:

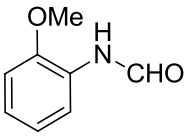
To a mixture of an amide (7.7 mmol, 1.0 mol equiv), K_3PO_4 (23.2 mmol, 3.0 mol equiv), $CuSO_4.5H_2O$ (1.5 mmol, 0.2 mol mol equiv) and 1,10-phenantroline (3.01 mmol, 0.4 mol mol equiv) in reaction vial was added a solution of 1-bromoalkyne (8.50 mmol, 1.1 mol mol equiv, 1 M solution in toluene) in toluene. The reaction mixture was capped and heated in oil bath at 65 – 75 °C for 20 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc and filtered through Celite®, and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography.

E: TIPS- deprotection:

To a solution of TIPS- protected ynamide (1.67 mmol, 1.0 mol mol equiv) in dry THF (8 mL) was added by dropwise 1M solution of TBAF in THF (1.67 mmol, 1.0 mol mol equiv). The reaction mixture was stirred 5 minutes at room temperature, solvent was evaporated in vaccuo, the concentrated raction mixture was dissolved in ethylacetate (15 mL), quenched with brine (20 mL), collected organic layers were on anhydrous $MgSO_4$, filtrated and concentrated *in vacuo* to yield desired compound.

Preparation of model ynamide IV.129c

<u>*N*-(2-methoxyphenyl)formamide</u> IV.133



$C_8H_9NO_2$
MW: 151,16

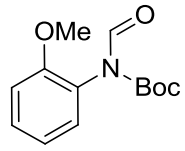
o-Anisidine **IV.128** (1.00 g, 0.92 mL, 8.12 mmol) was dissolved in DCM (10 mL) and treated successively with formic acid (0.61 mL, 1 2 mmol) and DCC (516 mg, 2.5 mmol). The temperature increased itself to 40 °C. The mixture was stirred for 18 h, diluted with DCM (10 mL) and filtered over a short pad of Celite®. After removal of the solvent the residue was purified by flash chromatography on silica gel (eluent: 1 Cy / 2 EtOAc) to give formamide **IV.133** (1.09 g, 89 %, 7.2 mmol). The analytical data corresponded to literature.[238]

White crystals; **mp** 83 - 85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM13f2.920(10)): δ 7.79 (1H, br s), 7.14-7.04 (1H, m), 7.00-6.87 (3H, m, arom.), 6.95-6.88 (1H, m, arom.), 3.89 (3H, s, -OMe).

^{13}C-NMR (75 MHz, $CDCl_3$, vm13f2.920(20)): δ 161.4 (s), 158.7, 147.8 (s), 124.3, 121.1, 120.5,110.0, 55.7 (-OMe).

<u>*tert*-Butyl formyl(2-methoxyphenyl)carbamate</u> IV.131a



$C_{13}H_{17}NO_4$
MW: 251,28

To a solution of formamide **IV.133** (1.233 g, 8.16 mmol, 1.0 mol mol equiv) in 10 mL of THF was added dropwise Et_3N (1.1 mL, 8.16 mmol, 1.0 mol equiv). After 30 minutes of stirring at room temperature $(Boc)_2O$ (2.70 g, 12.24 mmol, 1.5 mol equiv) was added. The mixture was stirred overnight at room temperature and evaporated to dryness. The residue was partitioned between

[238] Di Nunno, L. *Tetrahedron* **1986**, *42*, 3913.

EtOAc (15 mL) and a saturated solution of NH_4Cl (10 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (eluent: 3 Cy / 1 EtOAc). The desired product **IV.131a** was obtained in 85 % yield (1.743 g, 6.94 mmol).

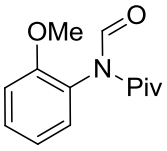
White solid; **mp** 121 - 123°C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM13f2.920(10)): δ 9.31 (1H, br s, -C*H*O), 7.31-7.26 (1H, m, arom.), 7.04-6.88 (2H, m, arom.), 3.73 (3H, s, -OMe), 1.40 (9H, s, 3 x CH_3, -Boc).

^{13}C-NMR (75 MHz, VM13.920(10)): δ 178.2, 161.8, 153.6 (Cq), 151.3 (Cq), 129.0, 128.5, 119.6, 110.7, 82.8 (Cq, -Boc), 54.6, 26.9 (3 x C, -Boc).

LC/MS (ESI): $[M+H]^+$ m/z 252.

***N*-formyl-*N*-(2-methoxyphenyl)pivalamide IV.131b**



$C_{13}H_{17}NO_3$
MW: 235,28

To a solution of formamide **IV.133** (845 mg, 5.6 mmol, 1.0 mol equiv) in 8 mL DCM was added dropwise Et_3N (0.91 mL, 6.7 mmol, 1.2 mol equiv). After stirring during 30 min, pivaloyl chloride (0.83 mL, 6.71 mmol, 1.2 mol equiv) was added dropwise at 0 °C. The mixture was stirred 24 hours at room temperature and evaporated to dryness. The residue was partitioned between EtOAc (10 mL) and saturated solution of $NaHCO_3$ (10 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel. The desired product **IV.131b** was obtained in 68 % yield (849 mg, 3.80 mmol).

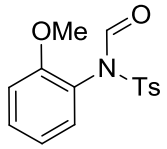
Colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM41clean.930(10)): δ 9.37 (1H, br s, -C*H*O), 7.37-7.31 (1H, m, arom.), 7.09-6.89 (3H, m, arom.), 3.74 (3H, s, -OMe), 1.06 (9H, s, 3 x CH_3, -Piv).

^{13}C-NMR (75 MHz, VM41clean.930(20)): δ 179.7 (Cq), 162.7, 154.2 (Cq), 122.3 (Cq), 116.1, 115.4, 128.2, 124.6, 55.8 (-OMe), 36.6 (Cq, -C::O from -Boc), 28.0 (3xCH_3 from -Boc).

LC/MS (ESI): $[M+H]^+$ m/z 236.

***N*-(2-methoxyphenyl)-*N*-tosylformamide IV.131c**



$C_{15}H_{15}NO_4S$
MW: 305,35

To a solution of formamide **IV.133** (1.57 g, 10.4 mmol, 1.0 mol equiv) in 10 mL DCM was added Et_3N (1.70 mL, 12.5 mmol, 1.2 mol equiv). The mixture was stirring for 30 minutes. *p*-toluensulfonyl chloride (2.38 g, 12.5 mmol, 1.2 mol equiv) was subsequently added. The mixture was stirred overnight at room temperature and evaporated to dryness. The residue was partitioned between EtOAc (15 mL) and a saturated solution of NH_4Cl (10 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (eluent: 2 Cy / 1 EtOAc). The desired product **IV.131c** was obtained in 96 % yield (3.04 g, 10 mmol).

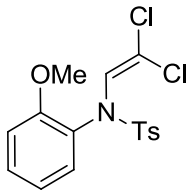
Pale yellow solid; **mp** 115 - 117 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM78ac.947(10)): δ 9.26 (1H, br s, -C*H*O), 7.61-7.59 (2H, m, Ts-), 7.42-7.36 (1H, m, arom.), 7.30-7.28 (2H, m, Ts-), 7.20-7.17 (1H, m, arom.), 7.03-6.97 (1H, m, arom.), 6.83-6.80 (1H, m, arom.), 3.36 (3H, s, -OMe), 2.45 (3H, s, Me- from Ts-).

^{13}C-NMR (75 MHz, $CDCl_3$, VM78ac.947(20)): δ 160.5 (Cq, -*C*HO), 155.4 (Cq), 145.1 (q), 134.9 (Cq), 131.8, 131.6, 129.4, 128.3, 127.3, 120.9, 120.4, 111.8, 55.2 (-OMe), 21.6 (Me- from Ts-). 1 chyba

LC/MS (ESI): $[M+H]^+$ m/z 306.

***N*-(2,2-dichlorovinyl)-*N*-(2-methoxyphenyl)-4-methylbenzenesulfonamide IV.135c**



$C_{16}H_{15}Cl_2NO_3S$
MW: 372,27

Formamide **IV.131c** (1.54 g, 5.0 mmol, 1.0 mol equiv) and PPh_3 (3.97 g, 15.132 mmol, 3.0 mol equiv) were dissolved in THF (25 mL). CCl_4 (4.89 mL, 50.4 mmol, 10.0 mol equiv) was added *via* syringe over a period of 6 h at 60 °C. After stirring for an additional hour, the mixture was diluted with TBME (30 mL). Aqueous workup with saturated $NaHCO_3$ (30 mL) afforded after flash chromatography on silica gel (eluent: 2 Cy / 1 EtOAc) dichlorovinylamide **IV.135c** (1.82 g, 4.89 mmol) 96 %).

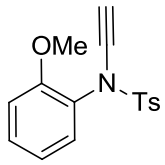
Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM82ac.948(10)): δ 7.46-7.43 (2H, m, Ts-), 7.34-7.30 (1H, m, arom.), 7.25-7.16 (3H, m, arom.), 6.98 (1H, s, -C*H*::CCl_2), 6.91-6.85 (1H, m, arom.), 6.68-6.65 (1H, m, arom.), 3.29 (3H, s, -OMe), 2.35 (3H, s, Me- from Ts-).

^{13}C-NMR (75 MHz, VM82ac.947(20)): δ 154.6 (Cq), 142.9 (Cq), 134.7 (Cq), 131.8, 129.2, 128.2, 126.8, 125.1, 124.3 (Cq), 119.5, 115.0 (Cq), 110.4, 54.1 (-OMe), 20.5 (Me- from Ts-). 1 chyba

LC/MS (ESI): $[M+H]^+$ m/z 373.

***N*-ethynyl-*N*-(2-methoxyphenyl)-4-methylbenzenesulfonamide IV.129c**



$C_{16}H_{15}NO_3S$
MW: 301,36

A solution of dichlorovinylamide **IV.135c** (542 mg, 1.5 mmol, 1.0 mol equiv) in THF (7 mL) was cooled to 78 °C and treated with *n*-BuLi (1.0 mL, 1.56 M in hexane, 1.6 mmol). The mixture was warmed to -30 °C within 2 hours and then MeOH (15 mL) was added. Dilution with TBME (20 mL) and workup using satd $NaHCO_3$ (10 mL) gave a yellow crude product, which was purified by flash chromatography on basic aluminia (eluent: pentane / TBME = 6 / 1) to yield the desired ynamide **IV.129c** (439 mg, 1.5 mmol, 69 %).

Yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM85c.949(10)): δ 7.68-7.65 (2H, m, Ts), 7.26-7.14 (4H, m, arom.), 6.88-6.79 (2H, m, arom.), 3.51 (3H, s, -OMe) 2.68 (1H, s, -C:::C*H*), 2.38 (3H, s, -OMe).

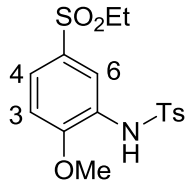
^{13}C-NMR (75 MHz, VM85ac.947(20)): δ 147.4 (Cq), 137.6 (Cq), 136.7 (Cq), 132.3 (Cq), 129.3 (2xC), 128.3 (2xC), 122.6, 121.8, 117.3, 113.4, 87.8 (Cq, -*C*:::CH), 74.1 (-C:::*C*H), 55.8 (-OMe), 21.3 (Me- from Ts-).

LC/MS (ESI): $[M+H]^+$ m/z 302.

Preparation of target ynamide

Preparation of target ynamide *via* Corey-Fuchs pathway

<u>*N*-(5-(ethylsulfonyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide</u> IV.142c



$C_{16}H_{19}NO_5S_2$
MW: 369,46

To a solution of 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** (2.78 g, 12.9 mmol, 1.0 mol equiv) in 15 mL of dry DCM was added dropwise dry pyridine (1.14 mL, 1.12 g, 14.1 mmol, 1.1 mol equiv). The mixture was well premixed. Afterwards, the *p*-toluensulfonyl chloride (2.70 g, 14.1 mmol, 1.1 mol equiv) was added portionwise. The reaction mixture was stirred 2 hours at room temperature under argon atmosphere. The reaction was monitored by TLC. After completion, the reaction mixture was neutralized with NH_4Cl. The aqueous layer was extracted with DCM (2 x 30 mL). The collected organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The resulted product was filtered through a short pad of silica gel in order to get 4.65 g (12.6 mmol, 98 %) of desired tosylated product **IV.142c**.

Pale crystals; **mp** 140 - 142 °C.

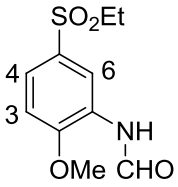
^{1}H-NMR (300 MHz, $CDCl_3$, VM93ac2.1004(10)): δ 7.99 (1H, d, *J*(4,6) = 2.2 Hz, H-C(6)), 7.75-7.71 (2H, m, Ts), 7.57 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.2 Hz, H-C(4)), 7.28-7.22 (3H, m), 6.89 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.82 (3H, s, -OMe), 3.08 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 2.37 (3H, s, Me- from Ts), 1.23 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, VM93ac2.1004(20)): δ 167.7 (Cq), 152.6 (Cq), 144.4 (Cq), 135.7 (Cq), 130.9, 129.7, 128.8, 127.4, 127.1 (Cq), 125.4, 119.1. 110.5, 56.3 (-OMe), 50.7 (-$SO_2CH_2CH_3$), 21.5 (Me- from Ts-), 7.5 (-$SO_2CH_2CH_3$).

IR υ (neat): 3235, 2942, 1597, 1498, 1395, 1340, 1307, 1163, 1124, 1088, 666, 543 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}NO_5S_2$ (369.46): C 52.01; H 5.18; N 3.79. Found: C 52.17, H 5.16, N 3.78.

***N*-(5-(ethylsulfonyl)-2-methoxyphenyl)formamide IV.141**



$C_{10}H_{13}NO_4S$
MW: 243,28

5-(Ethylsulfonyl)-2-methoxyaniline **IV.127** (1.00 g, 4.6 mmol, 1.0 mol equiv) was dissolved in DCM (20 mL) and treated successively with formic acid (0.66 mL, 17.4 mmol, 2.0 mol equiv) and CDI (1.88 g, 11.6 mmol, 2.5 mol equiv). The temperature rose to 40°C. The mixture was stirred for 1 h, diluted with DCM (20 mL) and filtered over a short pad of Celite®. After removal of the solvent the residue was purified by flash chromatography on silica gel (eluent: 1 Cy / 2 EtOAc) to give formamide **IV.141** (1.09 g, 4.1 mmol, 89 %).

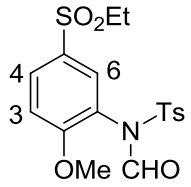
White crystals; **mp** 127 - 130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM135ap-10): δ 8.90 (1H, d, *J*(4,6) = 2.2 Hz, H-C(6)), 8.51 (1H, d, *J*=1.4 Hz, -C*H*O), 7.86 (1H, br s, -N*H*), 7.68 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.2 Hz, H-C(4)), 7.02 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 4.00 (3H, s, -OMe), 3.14 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, $SO_2CH_2CH_3$), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, VM135ap2-10): δ 160.4 (-*C*HO), 154.6 (Cq), 131.4 (Cq), 127.6, 125.2 (Cq), 121.8, 115.5, 55.8 (-OMe), 51.7 (-$SO_2CH_2CH_3$), 7.1 (-$SO_2CH_2CH_3$).

LC/MS (ESI): $[M+H]^+$ m/z 244.

***N*-(5-(ethylsulfonyl)-2-methoxyphenyl)-*N*-tosylformamide IV.132c**



$C_{17}H_{19}NO_6S_2$
MW: 397,47

To a suspension of stabilized sodium hydride (60 % in mineral oil) (265 mg, 6.6 mmol, 1.2 mol equiv) in dry DCM (10 mL) was canulated a solution of *N*-tosylated aniline **IV.142c** (2.04 g, 5.5 mmol, 1.0 mol equiv) in dry DCM (15 mL) under inert atmosphere. The mixture was stirred 45 min at room temperature. Subsequently, the acetic formic anhydride **IV.143** (0.53 mL, 8.3 mmol, 1.50 mol equiv) was added dropwise. The reaction was stirred 45 min and monitored by TLC. The reaction was quenched with saturated solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 20 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified through short pad of silica gel. The desired product **IV.132c** was obtained in 94 % yield (5.2 mmol, 2.05 g).

White solid; **mp** 162 - 165 °C.

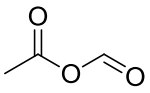
^{1}H-NMR (300 MHz, $CDCl_3$, VM173ap1.1041(12)): δ 9.22 (1H, br s, -C*H*O), 8.03-8.00 (2H, m, Ts-), 7.92 (1H, dd, *J*(3,4) = 8.8 Hz, *J*(4,6) = 2.3 Hz, H-C(4)), 7.57 (1H, d, *J*(4,6) = 2.3 Hz, H-C(6)), 7.34-7.30 (2H, m, Ts-), 6.97 (1H, d, *J*(3,4) = 8.8 Hz, H-C(3)), 3.53 (3H, s, -OMe), 3.06 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 2.45 (3H, s, Me- from Ts-), 1.26 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, VM173ap1.1041(10)): δ 160.1 (Cq,-*C*HO), 160.0, 159.8 (Cq), 145.8 (Cq), 134.5 (Cq), 132.2 (2xC), 130.7 (Cq), 129.8 (2xC), 128.2, 121.4 (Cq), 112.2, 56.1 (-OMe), 50.9 (-$SO_2CH_2CH_3$), 21.7 (Me- from Ts-), 7.6 (-$SO_2CH_2CH_3$).

IR υ (neat): 1712, 1596, 1498, 1363, 1317, 1292, 1145, 1172, 1078, 1019, 863, 671, 583, 546 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}NO_6S_2$ (397.47): C 51.37, H 4.82, N 3.52. Found: C 51.40, H 4.90, N 3.42.

Acetic fromic anhydride IV.143



$C_3H_4O_3$
MW: 88,06

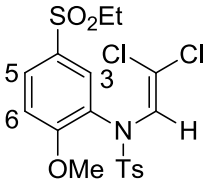
A dry, three-necked, round-bottomed flask equipped with a stirrer, a thermometer, a reflux condenser fitted with a calcium chloride tube, and a dropping funnel was charged with sodium formate (10.00 g, 147 mmol, 1.2 mol equiv) and 10 mL of anhydrous diethyl ether. To this stirred mixture was added of acetyl chloride (9.80 g, 8.9 mL, 125 mmol, 1.0 mol equiv) as quick as possible, while the temperature was maintained at 23 – 27 °C. After the addition was complete, the mixture was stirred for 5.5 hours at 23–27 °C to ensure complete reaction. The mixture was then filtered with suction, the solid residue was rinsed with 10 mL of ether, and the washings were added to the original filtrate. The ether was removed by distillation at reduced pressure, and the residue was distilled, yielding 6.63 g (75 mmol, 60 %) of acetic-formic anhydride **IV.143**. The analytical data corresponded to literature.[239]

Colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$, VM177c.1041(21)): δ 9.00 (1H, s), 2.20 (3H, s).

LC/MS (ESI): $[M+H]^+$ m/z 89.

***N*-(2,2-dichlorovinyl)-N-(5-(ethylsulfonyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide IV.144c**



$C_{18}H_{19}Cl_2NO_5S_2$
MW: 464,38

Formamide **IV.132c** (1.88 g, 4.7 mmol, 1.0 mol equiv) and PPh_3 (3.72 g, 14.2 mmol, 3.0 mol equiv) were dissolved in THF (30 mL). CCl_4 (4.6 mL, 47.3 mmol, 10.0 mol equiv) was added *via* syringe over a period of 6 h at 60 °C. After stirring for an additional hour, the mixture was diluted with TBME

[239] Krimen, L. I. *Org. Synth.* **1970**, *50*, 1.

(30 mL). Aqueous workup with saturated $NaHCO_3$ (30 mL) afforded after flash chromatography on silica gel (eluent: 1 Cy / 2 EtOAc) dichlorovinylamide **IV.144c** (199.4 mg, 0.4 mmol, 9 %).

White solid; **mp** 143 - 146 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM175p2.1041(12)): δ 7.86 (1H, dd, *J*(3,4) = 8.5 Hz, *J*(4,6) = 2.3 Hz, H-C(4)), 7.84 (1H, d, *J*(4,6) = 2.3 Hz, H-C(6)), 7.57-7.55 (2H, m, Ts-), 7.32-7.29 (2H, m, Ts-), 7. 04 (1H, s, vinyl), 6.95 (1H, d, *J*(3,4) = 8.5 Hz, H-C(3)), 3.57 (3H, s, -OMe), 3.10 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 2.45 (3H, s, Me- from Ts-), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

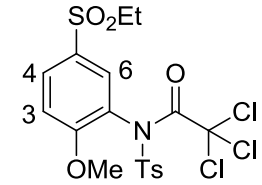
^{13}C-NMR (75 MHz, VM175ap2.1041(10)): δ 159.8 (Cq), 144.7 (Cq), 135.3 (Cq), 132.8, 130.7, 130.2 (Cq), 129.7 (2xC), 127.7 (2xC), 126.3 (Cq), 125.4, 117.3 (Cq), 112.0, 56.0 (-OMe), 50.9 (-$SO_2CH_2CH_3$), 21.7 (Me- from Ts-), 7.7 (-$SO_2CH_2CH_3$).

IR υ (neat): 2944, 1738, 1595, 1496, 1363, 1317, 1284, 1171, 1143, 1087, 1113, 733, 555, 544 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}Cl_2NO_5S_2$ (464.38): C 46.55, H 4.12, N 3.02. Found: C 46.31, H 3.90, N 3.32.

Preparation of target ynamide *via* transformation of trichloroacetamides

2,2,2-trichloro-*N*-(5-(ethylsulfonyl)-2-methoxyphenyl)-*N*-tosylacetamide IV.149



$C_{18}H_{18}Cl_3NO_6S_2$
MW: 514,83

To a solution of **IV.142c** (206 mg, 0.5 mmol, 1.0 mol equiv) in 4 mL of THF was added NaH (15 mg, 0.06 mmol, 1.1 mol equiv) at room temperature. The reaction mixture was stirred under inert atmosphere 5 minutes. Subsequently, trichloroacetyl chloride (124 µL, 0.01 mmol, 2.0 mol equiv) was added. The reaction mixture was stirred 1 hour at room temperature and monitored by TLC. The accomplished reaction was partitioned between ethyl acetate (5 mL) and a saturated solution of NH_4OH (6 mL). The water layer was extracted with ethyl acetate (3 x 5 mL), collected organic layers

were dried over $MgSO_4$, filtered, evaporated and dried *in vacuo*. The crude product was purified by column chromatography on silica gel pad (eluent: 1 Cy / 2 EtOAc) to give 248 mg (0.4 mmol, 86 %).

Pale yellow solid; **mp** 110 - 114°C

^{1}H-NMR (300 MHz, $CDCl_3$, VM148ap-10): δ 8.04-8.00 (2H, m, arom.), 7.97-7.94 (2H, m, Ts-), 7.40-7.37 (2H, m, Ts-), 7.10-7.07 (1H, m, arom.), 3.87 (3H, s, -OMe), 3.14 (2H, q, $J(CH_2CH_3)$ = 7.4 Hz, -$SO_2CH_2CH_3$), 2.49 (3H, s, Me- from Ts-), 1.30 (3H, t, $J(CH_2CH_3)$ = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.7 (Cq), 158.9 (Cq), 146.1 (Cq), 134.5, 132.9, 130.1, 129.6, 129.5, 129.5, 124.2 (Cq), 112.6, 111.8, 92.1 (Cq), 64.4 (Cq), 56.2 (-OMe), 51.0 (-$SO_2CH_2CH_3$), 21.8 (Me- from Ts-), 7.7 (-$SO_2CH_2CH_3$).

LC/MS (ESI): $[M+H]^+$ m/z 515.

Preparation of target ynamides IV.130a and IV.130d *via N*-direct alkynylation

Preparation of reagents IV.10 and IV.160

(Bromoethynyl)triisopropylsilane IV.160

$C_{11}H_{21}BrSi$
MW: 261,27

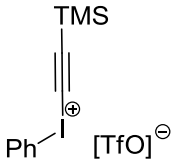
To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added a solution of triisopropylsilylacetylene **IV.161** (1 mL, 821 mg, 4.5 mmol, 1.0 mol equiv) in anhydrous THF (5 mL). The solution was cooled to -78 °C, and *n*- BuLi (1.6 M solution in hexane, 2.9 mL, 4.73 mmol, 1.05 mol equiv) was added by syringe through the septum. The reaction was stirred for 30 min at -78 °C, and Br_2 (0.25 mL, 5.0 mmol, 1.10 mol equiv) was added slowly through the septum using a syringe. The reddish brown color from Br_2 disappeared as it was consumed upon addition. The solution remained reddish brown when the addition was complete. The mixture was stirred for 15 min at -78 °C and then quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL) after removal of the septum. The reaction mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was further extracted with methyl *tert*-butyl ether (TBME) (3 x 5 mL), and the combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered and concentrated on a rotary evaporator to yield the crude alkynyl bromide **IV.160** (1.11 g, 4.3 mmol, 95 %). Alkynyl bromide **IV.160** was used without further purification. The analytical data corresponded to the literature.[240]

Pale oil.

^{1}H-NMR (300 MHz, $CDCl_3$, vmTIPSacetylene.1040(10)): δ 1.09-1.04 (21 H, m); **LC/MS (ESI):** $[M+H]^+$ m/z 262.

[240] Sagamova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359.

Phenyl(trimethylsilylethynyl)iodonium triflate IV.10



MW: 450.29

(Diacetoxyiodo)benzene (500 mg, 1.6 mmol, 1.0 mol equiv) was dissolved in dry DCM (8 mL) and the solution was cooled to 0 °C. Trifluoroethanesulfonic anhydride (127 μL, 0.8 mmol, 0.5 mol equiv) was added to this solution by using a glass pipette. After stirring at 0 °C for 30 min, bis(trimethylsilyl)acetylene **IV.156** (325 μL,1.6 mmol, 1.0 mol equiv) was added to this solution by using a glass pipette. After stirring at 0 °C for 2 h, the resulting solution was concentrated in vacuo at rt to give an oily residue. This oil was poured dropwise into stirred *n*hexane (100 mL) at rt. The resulting solid materials were collected by filtration, washed with Et_2O, and dried *in vacuo* to give phenyl(trimethylsilylethynyl)iodonium triflate **IV.10** (1.04 g, 1.3 mmol, 79 %) as a colorless solid. The analytical data corresponded to the literature.[241]

*Note: Although workup and crystallization procedures can be carried out in air, compound **IV.10** should be stored under a dry inert atmosphere to avoid its decomposition.*

Colorless solid.

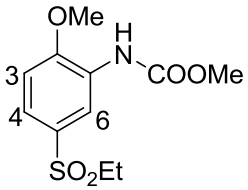
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.07 (2H, d, *J* = 8.3 Hz, arom.), 7.66 (1H, s, arom.), 7.55 (2H, m, arom.), 0.24 (9H, s, TMS).

^{13}C-NMR (300 MHz, $CDCl_3$): δ 133.9, 132.4, 119.7 (Cq, *J* = 319 Hz), 119.1, 116.2, 43.3, -1.1.

LC/MS (ESI): $[M+H]^+$ m/z 451.

[241] Tanaka, K.; Takeishi, K. *Synthesis* **2007**, *18*, 2920.

Methyl 5-(ethylsulfonyl)-2-methoxyphenylcarbamate IV.142d



$C_{11}H_{15}NO_5S$
MW: 273,31

To a solution of aniline **IV.127** (4.15 g, 19.3 mmol, 1.0 mol equiv) in 35 mL of dry CH_2Cl_2 was added pyridine (1.7 mL, 21.2 mmol, 1.1 mol equiv). To a well stirred mixture was added dropwise methyl chloroformate ClCOOMe (1.6 mL, 21.2 mmol, 1.1 mol equiv) at 0°C. The reaction mixture was stirred at rt for 2.5 hour and progress of reaction was checking by TLC. After accomplishing of reaction, the mixture was quenched with brine (2 x 30 mL), the organic layers were collected, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by recrystallization from Et_2O with charcoal to yield 3.15 g (13.9 mmol, 72 %) of white crystalic compound **IV.142d**.

White crystals; **mp** 121 - 123 °C

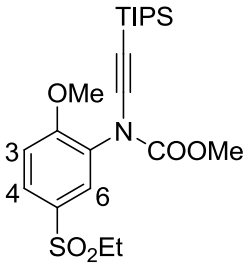
^{1}H-NMR (300 MHz, $CDCl_3$, VM218ap.1101 (10)): δ 8.61 (1H, br s, -N*H*), 7.59 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.2 Hz, H-C(4)), 7.29 (1H, br s, H-C(6)), 6.97 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.96 (3H, s, -OC*H*$_3$), 3.81 (3H, br s, -COOC*H*$_3$), 3.12 (2H, q, *J*(-CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.27 (3H, t, *J*(-CH_2CH_3) = 7.4 Hz, $SO_2CH_2CH_3$).

^{13}C-NMR (300 MHz, $CDCl_3$, vm218ap.1101 (20)): δ 153.6 (CH_3CO-), 151.2 (C2), 130.9 (C1), 128.5 (C5), 123.7 (C4), 117.6 (C6), 109.7 (C3), 56.2 (CH_3O-), 52.6 (CH_3CO-), 50.6 (CH_3CH_2-), 7.6 (CH_3CH_2-).

IR υ (neat): 3416, 1721, 1595, 1535, 1304, 1275, 1264, 1239, 1127, 1064, 766 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_5S$ (273.31): C 48.34, H 5.53, N 5.12. Found: 48.30, H 5.47, N 5.02.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl((triisopropylsilyl)ethynyl)carbamate IV.164d



$C_{22}H_{35}NO_5SSi$
MW: 453,67

Compound **IV.164d** was prepared according to the general procedure **D**. Yield: 97 %. Purification: Filtration through silica gel (eluent: 1 Cy / 1 EtOAc).

Pale yellow solid; **mp** 42 - 45°C.

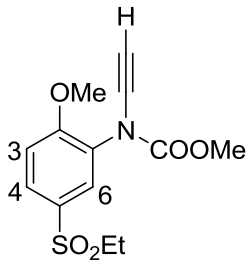
^{1}H-NMR (300 MHz, $CDCl_3$, VM222ap1.1102(10)): δ 7.82 (1H, br s, H-C(6)), 7.81 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.3 Hz, H-C(4)), 7.10 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.88 (3H, s, -OC*H*$_3$), 3.77 (3H, br s -COOC*H*$_3$), 3.02 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.45 (3H, septet, *J*(CH,CH_3) = 7.5 Hz, 3xCH), 1.20 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 0.98 (18H, d, *J*(CH,CH_3) = 7.5 Hz, 6xCH_3).

^{13}C-NMR (300 MHz, $CDCl_3$, vm222ap1.1102 (10)): δ 158.6 (Cq), 154.6 (Cq), 130.3 (Cq), 130.3, 128.8, 128.7 (Cq), 112.4, 96.2 (Cq, C:::C), 67.7 (Cq, C:::C), 56.3 (*C*H_3O-), 54.5 (*C*H_3CO-), 50.9 (*C*H_3CH_2-), 18.6 (6xCH_3, TIPS), 11.3 (3xCH, TIPS), 7.6 (CH_3CH_2-). 7 chyba

IR υ (neat): 2941, 2864, 2180, 1744, 1440, 1290, 1132, 730 cm^{-1}.

Anal. Calcd for $C_{22}H_{35}NO_5SSi$ (453.67): C 58.24, H 7.78, N 3.09. Found: C 58.04, H 7.78, N 2.91.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl(ethynyl)carbamate IV.130d



$C_{13}H_{15}NO_5S$
MW: 297,33

Compound **IV.130d** was prepared according to the general procedure **E**. Yield: 97 %. Purification: Filtration through silica gel (eluent: 1 Cy / 2 EtOAc).

Pale yellow solid; **mp** 158 - 163°C.

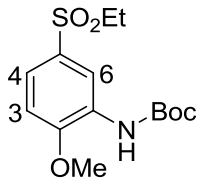
^{1}H-NMR (300 MHz, $CDCl_3$, vm227ap1.1102(11)): δ 7.91-7.88 (2H, m, H-C(6), H-C(3)), 7.13-7.10 (1H, m, H-C(4)), 3.90 (3H, s, -OCH_3), 3.79 (3H, br s -COOC*H*$_3$), 3.04 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -SO_2C*H*$_2CH_3$), 2.74 (1H, s, -C:::C-*H*), 1.23 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -SO_2CH_2C*H*$_3$).

^{13}C-NMR (300 MHz, $CDCl_3$, vm222ap1.1102 (10)): δ 158.8 (CH_3*C*O-), 154.6 (C2), 130.7 (C1), 130.6 (C5), 129.0 (C4), 128.2 (C6), 112.5 (C3), 75.8 (-C:::*C*-*C*), 57.5 (-*C*:::C-H), 56.5 (*C*H_3O-), 54.7 (*C*H_3CO-), 50.9 (*C*H_3CH_2-), 7.5 (CH_3*C*H_2-).

IR υ (neat): 3267, 2152, 1726, 1500, 1443, 1315, 1293, 1130, 1089, 827, 730 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_5S$ (297.33): C 52.51, H 5.09, N 4.71. Found: C 52.62, H 5.16, N 4.39.

***tert*-Butyl 5-(ethylsulfonyl)-2-methoxyphenylcarbamate IV.142a**



$C_{14}H_{21}NO_5S$
MW: 315,39

To a solution of 5-(ethylsulfonyl)-2-methoxyaniline **IV.127** (190 mg, 8.8 x 10^{-4} mol, 1.0 mol equiv) in dry tetrahydrofurane (7 mL) was added under argon atmosphere DMAP (11 mg, 8.8 x 10^{-5} mol, 0.1 mol equiv) and subsequently di-*tert*-butyl dicarbonate (212 mg, 9.7 x 10^{-4}mol, 1.1 mol equiv). The reaction was refluxed overnight and monitored by TLC. The accomplished reaction was cooled down, THF was evaporated and the reaction was partitioned between ethyl acetate (10 mL) and water (10 mL). The water layer was extracted with ethyl acetate (3 x 10 mL), collected organic layers were dried over $MgSO_4$, filtered, evaporated and dried *in vacuo*. The crude product was purified by column chromatography on silica gel pad (eluent: 1 Cy / 1 EtOAc) to give 249 mg (8.8 x 10^{-4} mol, 89 %) of **IV.142a**.

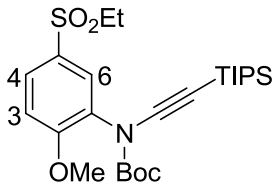
White crystals; **mp** 80 - 82 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, VM582ap.1307(10)): δ 8.58 (1H, br s, -N*H*), 7.52 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 1.8 Hz, H-C(4)), 7.11 (1H, br s, H-C(6)), 6.93 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.93 (3H, s, -OMe), 3.08 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -SO_2C*H*$_2CH_3$), 1.53 (9H, s, -Boc) 1.24 (t, 3H, *J*(CH_2CH_3) = 7.4 Hz, -SO_2CH_2C*H*$_3$).

^{13}C-NMR (100 MHz, VM582ap.1307(11)): δ 158.8 (Cq, -*C*O from -Boc), 151.2 (Cq, C(2)), 130.7 (Cq, C(5)), 129.0 (C(4)), 123.1 (Cq, C(1)), 117.2 (C(6)), 109.5 (C(3)), 82.9 (Cq, -Boc), 56.2 (-OMe), 50.5 (-$SO_2CH_2CH_3$), 28.3 (3xCH_3, -Boc), 7.5 (-$SO_2CH_2CH_3$).

IR υ (neat): 2979, 1726, 1594, 1524, 1262, 1308, 1146, 1129, 1087, 736, 723 cm^{-1}.

***tert*-Butyl 5-(ethylsulfonyl)-2-methoxyphenyl((triisopropylsilyl)ethynyl)carbamate IV.164a**



$C_{25}H_{41}NO_5SSi$
MW: 495,75

Compound **IV.164a** was prepared according to the general procedure **D**. Yield: 62 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 1 EtOAc).

Yellow oil.

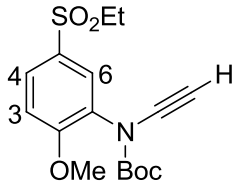
^{1}H-NMR (400 MHz, $CDCl_3$, VM578f1.1307(10)): δ 7.89 (1H, d, *J*(4,6) = 1.8 Hz, H-C(6)), 7.83 (1H, dd, *J*(3,4) = 8.7 Hz, *J*(4,6) = 1.8 Hz, H-C(4)), 7.07 (1H, d, *J*(3,4) = 8.7 Hz, H-C(3)), 3.94 (3H, s, -OMe), 3.08 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.50 (9H, s, -Boc), 1.45 (3H, septet, *J*(CH,CH_3) = 7.5 Hz, 3xCH) 1.26 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.04 (18H, d, *J*(CH,CH_3) = 7.5 Hz, 6xCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, VM580ap.1307(10)): δ 158.5 (Cq, -*C*O from -Boc), 152.6 (Cq, C(2)), 130.1 (Cq, C(5)), 129.8 (C(4)), 129.3 (Cq, C(1)), 128.6 (C(6)), 112.2 (C(3)), 97.0 (Cq, -C:::*C*-TIPS), 83.4 (Cq, -Boc), 66.9 (Cq, -*C*:::C-TIPS), 56.2 (-OMe), 50.9 (-$SO_2CH_2CH_3$), 28.0 (3xCH_3, -Boc), 18.6 (6xCH_3, TIPS), 11.4 (3xCH, TIPS), 7.6 (-$SO_2CH_2CH_3$).

IR υ (neat): 2942, 2864, 2176, 1736, 1304, 1157, 1134, 730, 672 cm^{-1}.

Anal. Calcd for $C_{25}H_{41}NO_5SSi$ (495.75): C 60.57, H 8.34, N 2.83. Found: C 60.50, H 8.24, N 2.75.

***tert*-Butyl 5-(ethylsulfonyl)-2-methoxyphenyl(ethynyl)carbamate IV.130a**



$C_{16}H_{21}NO_5S$
MW: 339,41

Compound **IV.130a** was prepared according to the general procedure **E**. Yield: 95 %. Purification: filtration through short pad of silica gel (eluent: 1 Cy / 1 EtOAc).

Pale oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM580ap.1307(10)): δ 7.86-7.83 (2H, m, H-C(4) and H-C(6)), 7.08 (1H, d, *J*(3,4) = 9.3 Hz, H-C(3)), 3.95 (3H, s, -OMe), 3.09 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2C\mathit{H}_2CH_3$), 2.75 (1H, s, -C:::C-*H*), 1.46 (9H, s, -Boc), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2C\mathit{H}_3$).

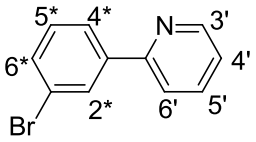
^{13}C-NMR (100 MHz, $CDCl_3$, VM580ap.1307(10)): δ 158.7 (Cq, -*C*O from -Boc), 152.7 (Cq, C(2)), 130.4 (Cq, C(5)), 130.3 (C(4)), 128.8 (C(6)), 112.2 (C(3)), 83.8 (Cq, -Boc), 76.5 (Cq, -*C*:::C-H), 57.2 (-C:::*C*-H), 56.4 (-OMe), 51.0 (-$SO_2\mathit{C}H_2CH_3$), 27.9 (3x$\mathit{C}H_3$, -Boc), 7.5 (-$SO_2CH_2\mathit{C}H_3$). 1 chyba

IR υ (neat): 3274, 2943, 2146, 1732, 1499, 1307, 1149, 1131, 1047, 729, 531, 489 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_5S$ (339.41): C 56.62, H 6.24, N 4.13. Found: C 56.40, H 6.01, N 4.02.

Preparation of triazole III.20

2-(3-Bromophenyl)pyridine V.44



$C_{11}H_8BrN$
MW: 234,09

A degassed mixture of 2-bromopyridine **V.50** (2.4 mL, 24.9 mmol, 1.0 mol equiv), Na_2CO_3 (5.75 g, 54.8 mmol, 2.2 mol equiv), water (27.5 mL), EtOH (20 mL), dimethoxyethane (62.5 mL), 3-bromophenylboronic acid (5.00 g, 24.9 mmol, 1.0 mol equiv), and $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) was heated at reflux for 18 h. The reaction mixture was filtered through a Celite® pad. Water layer was separated and extracted with EtOAc (2 x 35 mL), collected oranganic layers were washed with water (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (eluent: 9 Cy / 1 EtOAc) to afford 3.96 g (16.9 mmol, 68 %) of **V.44** as colorless oil. The analytical data corresponded to the literature.[242]

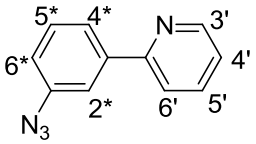
Colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, vm226ap2f1.1103 (10)): δ 8.62 (1H, m, H-C(3')), 8.13 (1H, t, *J* = 1.8 Hz), 7.86-7.84 (1H, m), 7.69 (1H, dt, *J* = 7.5 Hz, 1.5 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 7.50-7.47 (1H, m), 7.28 (1H, t, *J* = 7.9 Hz), 7.22-7.17 (1H, m).

^{13}C-NMR (300 MHz, $CDCl_3$, vm226ap.1102 (2)): δ 155.8 (Cq), 149.8, 141.4 (Cq), 136.5, 131.9, 130.3, 130.0, 125.4, 123.1 (Cq), 122.7, 120.6.

Anal. Calcd for $C_{11}H_8BrN$ (234.09): C 56.44, H 3.44, N 5.98. Found: C 56.28, H 3.48, N 5.98.

2-(3-Azidophenyl)pyridine V.37



$C_{11}H_8N_4$
MW: 196,21

[242] van der Sluis, M.; Beverwijk, V.; Termaten, A.; Bickelhaupt, F.; Kooijman, H.; Spek, A. L. *Organ-OMetallics* **1999**, *18*, 1402.

Compound **V.37** was prepared according to the general procedure **C**. Yield: 84 %. Purification: Filtration through silica gel (eluent: 1 Cy / 1 EtOAc).

Colorless liquid.

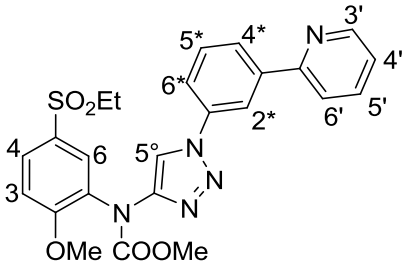
^{1}H-NMR (300 MHz, $CDCl_3$, vm236ap.1105 (12)): δ 8.66 – 8.64 (1H, m, H-C(3')), 7.62 – 7.61 (4H, m, H-C(2*), H-C(4*), H-C(5'), H-C(6')), 7.36 (1H, dd, *J*(5*,6*) = 7.9 Hz, *J*(4*,5*) = 7.7 Hz, H-C(5*)), 7.17 (1H, ddd, *J*(4',5') = 7.3 Hz, *J*(3',4') = 4.9 Hz, *J*(4',6') = 1.7 Hz, H-C(4')), 6.98 (1H, ddd, *J*(5*,6*) = 7.9 Hz, *J*(2*,6*) = 2.0 Hz, *J*(4*,6*) = 1.0 Hz, H-C(6*)).

^{13}C-NMR (300 MHz, $CDCl_3$, vm236ap.1105 (10)): δ 156.1 (Cq), 149.7, 141.1 (Cq), 140.6 (Cq), 136.8, 130.0, 123.3, 122.6, 120.5, 119.5, 117.5.

IR υ (neat): 3053, 2095, 1578, 1564, 1463, 1449, 1414, 1295, 1270, 1260, 991, 879, 765, 736, 666 cm^{-1}.

Anal. Calcd for $C_{11}H_8N_4$ (196.21): C 67.34, H 4.11. Found: C 67.41, H 4.17.

Methyl 2-(ethylsulfonyl)-5-methoxyphenyl(1-(3-(pyridin-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)carbamate VI.8



$C_{24}H_{23}N_5O_5S$
MW: 493,53

Compound **VI.8** was prepared according to the general procedure **A**. Yield: 83 %. Purification: column chromatography on silica gel (eluent: 1 Cy / 1 EtOAc).

Pale yellow foam; **mp** 204 - 205 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.73 (1H, ddd, *J*(3',4') = 4.9 Hz, *J*(3',5') = 1.3 Hz, *J*(3',6') = 1.2 Hz, H-C(3')), 8.56 (1H, br s, H-C(5°)), 8.41 (1H, dd, *J*(2*,4*) = 2.0 Hz, *J*(2*,6*) = 1.8 Hz, H-C(2*)), 8.06 (1H, ddd, *J*(5*,6*) = 7.9 Hz, *J*(2*,6*) = 1.8 Hz, *J*(4*,6*) = 1.1 Hz, H-C(6*)), 7.97 (dd, 1H, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.3 Hz, H-C(4)), 7.91 (1H, d, *J*(4,6) = 2.3 Hz, H-C(6)), 7.86 (1H, ddd, *J*(4*,5*) = 8.1 Hz, *J*(2*,4*) = 2.0 Hz, *J*(4*,6*) = 1.1 Hz, H-C(4*)), 7.83-7.79 (2H, m, H-C(5'), H-C(6')), 7.63 (1H, dd, *J*(4*,5*) = 8.1 Hz, *J*(5*,6*) = 7.9 Hz, H-C(5*)), 7.31 (1H, ddd, (1H, ddd, *J*(4',5') = 8.6 Hz, *J*(3',4') = 4.9 Hz, *J*(4',6') = 1.4 Hz, H-C(4')),

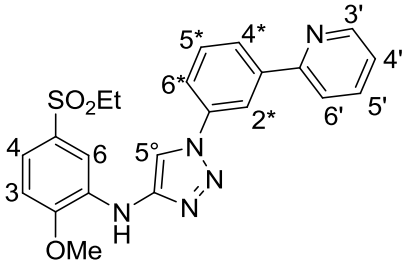
7.17 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.90 (3H, s, -OC*H*$_3$), 3.79 (3H, br s, -COOC*H*$_3$), 3.15 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.33 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (300 MHz, $CDCl_3$, vm237ap1-11-13C): δ 159.8, 155.7 (2xC), 149.9, 141.1, 137.7, 137.0 (2xC), 131.1, 130.6, 130.3, 130.1, 126.9 (2xC), 122.9, 120.7, 120.6, 118.7, 112.3, 56.4 (CH_3O-), 53.9 (-$COCH_3$), 51.1 (CH_3CH_2-), 7.6 (CH_3CH_2-). (1 missing)

IR υ (neat): 3096, 2911, 1725, 1564, 1498, 1475, 1445, 1433, 1370, 1310, 1280, 1237, 1127, 1095, 1020, 780, 742, 688 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}N_5O_5S$ (493.53): C 58.41, H 4.70, N 14.19. Found: C 58.20, H 4.51, N 14.09.

***N*-(2-(ethylsulfonyl)-5-methoxyphenyl)-1-(3-(pyridin-2-yl)phenyl)-1*H*-1,2,3-triazol-4-amine III.20**



$C_{22}H_{21}N_5O_3S$
MW: 435,50

Compound **III.20** was prepared according to the general procedure **B**. Yield: 67 %. Purification: Column chromatography on silica gel (1 Cy / 5 EtOAc).

Pale yellow foam; **mp** 152 - 155 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, vmT1Y6A-11): δ 8.73 (1H, dt, *J*(3',4') = 4.8 Hz, *J*(3',5') = 1.3 Hz, H-C(3')), 8.41 (1H, t, *J*(2*,4*) or *J*(2*,6*) = 1.8 Hz, H-C(2*)), 8.06 (1H, dt, *J*(5*,6*) = 7.8 Hz, *J*(4*,6*) = 1.8 Hz, H-C(6*)), 8.00 (1H, s, H-C(5°)), 7.86-7.31 (3H, m), 7.68-7.63 (2H, m), 7.43 (1H, dd, *J*(3,4) = 8.4 Hz, *J*(4,6) = 2.1 Hz, H-C(4)), 7.33-7.29 (1H, m), 6.99 (1H, d, *J*(3,4) = 8.4 Hz, H-C(3)), 6.96 (1H, br s, -N*H*), 4.02 (3H, s, -OC*H*$_3$), 3.11 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.28 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

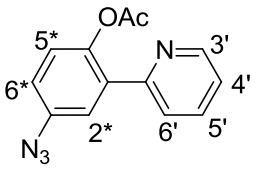
^{13}C-NMR (300 MHz, $CDCl_3$, vm249ap2-11-13c): δ 155.7, 150.7, 149.9, 147.1, 141.2, 137.6, 141.2, 137.6, 137.1, 130.2, 127.0, 123.0, 120.7, 120.7, 120.5, 118.8, 111.0, 109.6, 109.1, 56.2 (-OCH_3), 50.8 (CH_3CH_2-), 7.6 (CH_3CH_2-).

IR υ (neat): 3355, 2966, 1601, 1575, 1460, 1431, 1300, 1258, 1141, 1121, 1084, 1020, 802, 772, 734 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}N_5O_3S$ (435.30): C 60.67, H 4.86, N 16.08. Found: C 60.40, H 4.56, N 15.87.

Preparation of triazole III.21

4-Azido-2-(pyridin-2-yl)phenyl acetate V.38



$C_{13}H_{10}N_4O_2$
MW: 254,24

Substrate **V.37** (675 mg, 3.4 mmol, 1.0 mol equiv), $PhI(OAc)_2$ (1.22 g, 3.8 mmol, 1.1 mol equiv), and $Pd(OAc)_2$ (38.6 mg, 0.17 mmol, 0.05 mol equiv) were combined in benzene (8 mL) and Ac_2O (8 mL) in a 50 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 1.5 h. The solvent was removed under vacuum, and the resulting oil was purified by chromatography on silica gel (eluent: 3 Cy / 1 EtOAc). The product **V.38** was in 57 % yield (1.9 mmol, 466 mg).

Pale yellow oil.

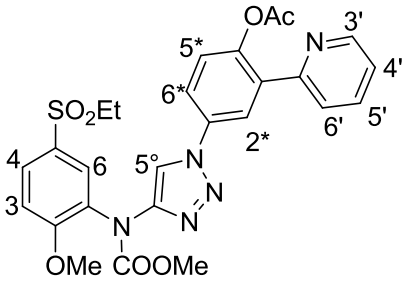
^{1}H-NMR (300 MHz, $CDCl_3$, VM293F3.1142(10)): δ 8.70 (1H, ddd, *J*(3',4') = 5.0 Hz, *J*(3',5') = 1.8 Hz, *J*(3',6') = 1.0 Hz H-C(3')), 7.74 (1H, ddd, *J*(4',5') = 7.8 Hz, *J*(5',6') = 7.8 Hz, *J*(3',5') = 1.8 Hz H-C(5')), 7.57-7.52 (1H, m, H-C(6')), 7.41 (1H, d, *J*(2*,6*) = 2.7 Hz, H-C(2*)), 7.26 (1H, ddd, (1H, ddd, *J*(4',5') = 7.5 Hz, *J*(3',4') = 4.9 Hz, *J*(4',6') = 1.0 Hz, H-C(4')), 7.15 (1H, d, *J*(5*,6*) = 8.6 Hz, H-C(5*)), 7.06 (1H, dd, *J*(5*,6*) = 8.6 Hz, *J*(2*,6*) = 2.7 Hz, H-C(6*)), 2.17 (3H, s, -COC*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$, VM378ap.1310(11)): δ 169.3 (Cq, -*C*OCH$_3$), 154.6 (Cq), 149.7, 145.0 (Cq), 138.0 (Cq), 136.4, 134.5 (Cq), 124.8, 123.6, 122.7, 121.0, 120.1, 20.9 (-CO*C*H$_3$).

IR υ (neat): 2958, 2928, 2107, 1724, 1595, 1486, 1463, 1287, 1269, 1240, 1128, 1072, 887, 781, 738, 719, 663 cm^{-1}.

Anal. calcd for $C_{13}H_{10}N_4O_2$ (254.24): C 61.41, H 3.96. Found: C 61.09, H 4.07.

4-(4-((5-(Ethylsulfonyl)-2-methoxyphenyl)(methoxycarbonyl)amino)-1H-1,2,3-triazol-1-yl)-2-(pyridin-2-yl)phenyl acetate VI.9



$C_{26}H_{25}N_5O_7S$
MW: 551,57

Compound **VI.9** was prepared according to the general procedure **B**. Yield: 72 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 3 EtOAc).

Pale yellow foam; **mp** 115 - 157 °C.

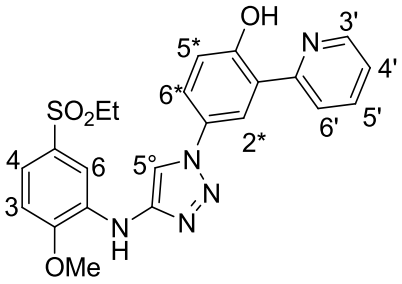
^{1}H-NMR (300 MHz, $CDCl_3$, VM480ma.1235(12)): δ 8.70 (1H, ddd or m, *J*(3',4') = 4.9 Hz, *J*(3',5') = 1.8 Hz, *J*(3',6') = 1.0 Hz H-C(3')), 8.48 (1H, br s, H-C(5°)), 8.12 (1H, d, *J*(4,6) = 2.6 Hz, H-C(6)), 7.94 (1H, dd, *J*(3*,4*) = 8.7 Hz, *J*(6*,4*) = 2.2 Hz, H-C(4*)), 7.89 (1H, d, *J*(6*,4*) = 2.2 Hz, H-C(6*)), 7.86 (1H, dd, *J*(3,4) = 8.7 Hz, *J*(4,6) = 2.6 Hz, H-(C4)), 7.79 (1H, ddd, *J*(4',5') = 7.8 Hz, *J*(5',6') = 7.8 Hz, *J*(3',5') = 1.8 Hz, H-C(5')), 7.60-7.65 (1H, m, H-C(6')), 7.33 (1H, d, *J*(3*,4*) = 8.7 Hz, H-C(3*)), 7.31 (1H, ddd, *J*(4',5') = 7.8 Hz, *J*(3',4') = 4.9 Hz, *J*(4',6') = 1.0 Hz, H-C(4')), 7.15 (1H, d, *J*(3,4) = 8.7 Hz, H-C(3), 3.88 (3H, s, -OC*H*$_3$), 3.77 (3H, br s, -COOC*H*$_3$), 3.13 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 2.22 (3H, s, -OAc), 1.34 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, $SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM480ma.1235(10)): δ 154.8 (Cq), 153.6 (Cq), 149.8, 148.0 (Cq), 147.2 (Cq), 136.6 (2xC), 135.1 (Cq), 134.5 (Cq), 131.1 (2xC), 130.5, 130.4 (Cq), 124.9, 123.7, 122.9 (Cq), 122.9, 122.6, 121.4, 112.3, 56.4 (-O*C*H_3), 53.9 (CH_3*C*H_2-), 51.1 (-COO*C*H_3), 21.0 (-CO*C*H_3), 7.6 (*C*H_3CH_2-).

IR υ (neat): 2955, 1764, 1725, 1565, 1500, 1443, 1371, 1313, 1182, 1132, 1091, 1039, 735, 532 cm^{-1}.

Anal. calcd for $C_{26}H_{25}N_5O_7S$ (551.57): C 56.62, H 4.7, N 12.70. Found: C 56.72, H 4.97, N 15.40.

4-(4-(5-(ethylsulfonyl)-2-methoxyphenylamino)-1*H*-1,2,3-triazol-1-yl)-2-(pyridin-2-yl)phenol III.21



$C_{22}H_{21}N_5O_4S$
MW: 451,50

Compound **III.21** was prepared according to the general procedure **B**. Yield: 82 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 4 EtOAc).

Pale yellow foam; **mp** 148 - 149 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM474ap.1234(10)): δ 8.56 (1H, ddd, *J*(3',4') = 5.1 Hz, *J*(3',5') = 1.7 Hz, *J*(3',6') = 1.0 Hz H-C(3')), 8.25 (1H, d, *J*(4,6) = 2.6 Hz, H-C(6)), 8.03 (1H, d, *J*(3*,4*) = 8.4 Hz, H-C(3*)), 7.92 (1H, ddd, *J*(4',5') = 7.8 Hz, *J*(5',6') = 7.8 Hz, *J*(3',5') = 1.7 Hz H-C(5')), 7.84 (1H, br s, H-C(5°)), 7.64 (1H, d, *J*(6*,4*) = 2.1 Hz, H-C(6*)), 7.55 (1H, dd, *J*(3,4) = 8.8 Hz, *J*(4,6) = 2.6 Hz, H-(C4)), 7.41 (1H, dd, *J*(3*,4*) = 8.4 Hz, *J*(6*,4*) = 2.1 Hz, H-C(4*)), 7.34 (1H, ddd, *J*(4',5') = 7.3 Hz, *J*(3',4') = 5.1 Hz, *J*(4',6') = 0.8 Hz, H-C(4')), 7.15 (1H, d, *J*(3,4) = 8.8 Hz, H-C(3)), 7.15 (1H, d, H-C(6')), 6.92 (1H, br s, -N*H*), 4.01 (3H, s, -OMe), 3.10 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2C\mathit{H}_2CH_3$), 1.68 (1H, br s, -O*H*), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2C\mathit{H}_3$).

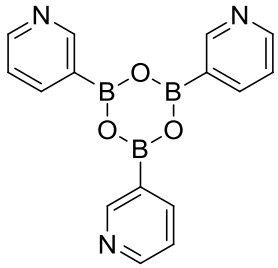
^{13}C-NMR (75 MHz, $CDCl_3$, VM474ap.1234(20)): δ 160.6 (Cq), 156.5 (Cq), 150.7 (Cq), 146.9 (Cq), 145.9, 138.3, 133.4 (Cq), 130.7 (Cq), 124.0 (Cq), 123.7, 122.5, 120.4, 119.5, 119.3 (Cq),119.0, 111.0, 109.6, 109.5, 56.2 (-O*C*H_3), 51.1 ($CH_3\mathit{C}H_2$-), 21.0 (-CO*C*H_3), 7.6 (*C*H_3CH_2-).

IR υ (neat): 3354, 2939, 1597, 1566, 1509, 1428, 1302, 1260, 1142, 1123, 792, 735 cm^{-1}.

Anal. calcd for $C_{22}H_{21}N_5O_4S$ (451.50): C 58.52, H 4.69, N 15.51. Found: C 58.62, H 4.62, N 15.40.

Preparation of triazole III.22

3-Pyridylboronic acid [tris(3-pyridyl)boroxin] V.63



$C_{15}H_{12}B_3N_3O_3$
MW: 314,71

A flask equipped with a thermometer was charged with 43 mL of toluene, 11 mL of THF, triisopropyl borate (7.43 mL, 32.0 mmol, 1.2 mol equiv), and 3-bromopyridine **V.62** (2.6 mL, 26.7 mmol, 1.0 mol equiv) . The mixture was cooled to -40 °C and 96 mL of *n*-BuLi solution (1.6 M in hexane, 20 mL, 32.0 mmol, 1.2 mol equiv) was added dropwise with a syringe pump over 1 h. The reaction mixture was stirred for an additional 30 min maintaining the temperature at -40 °C. The ice bath was then removed, and the reaction mixture was allowed to warm to -20 °C whereupon a solution of 27 mL of 2 M HCl solution was added. When the mixture reached room temperature, it was transferred to separatory funnel and the aqueous layer (pH ~ 1) was drained into a Erlenmeyer flask equipped with a magnetic stir bar. The pH of the aqueous layer was adjusted to 7.6 - 7.7 using 5 M aqueous NaOH. A white solid precipitates out as the pH approaches 7. The aqueous mixture was then saturated with solid NaCl, and extracted with THF (3 x 20 mL). The combined organic phases were concentrated on a rotary evaporator to leave a solid residue which was suspended in 15 mL of acetonitrile for crystallization. The mixture was heated to 70 °C, stirred for 30 min, and then allowed to cool slowly to room temperature and then to 0 °C in an ice bath. After being stirred at 0 °C for 30 min, the mixture was filtered through a fritted-glass funnel. The solid was washed with 5 mL of cold acetonitrile, and then dried *in vaccuo* to afford 2.77 g (27.8 mmol, 87 %) of tris(3-pyridyl)boroxin . H_2O **V.63** as a white solid. The analytical data corresponded to literature.[243]

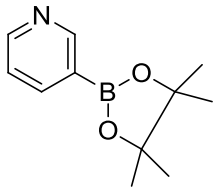
White solid.

^{1}H-NMR (300 MHz, MeOD): δ 8.61 (1H, br s), 8.51 (1H, dd, *J* = 1.2, 4.4 Hz), 8.38 (1H, d, *J* = 6.6 Hz), 7.66 (1H, br s).

[243] Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D; Larsen, R. D. *Org. Synth.* **2005**, *11*, 393.

LC/MS (ESI): $[M+H]^+$ m/z 315.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine V.61



$C_{11}H_{16}BNO_2$
MW: 205,06

Flask equipped with a magnetic stirbar and a Dean-Stark trap fitted with a condenser was charged with tris(3-pyridyl)boroxin·0.85 H_2O **V.63** (1.96 g, 5.9 mmol, 1.0 mol equiv), pinacol (2.65 g, 22.4 mmol, 3.8 mol equiv) and 80 mL of toluene. The solution was heated at reflux for 2.5 h in a 120 °C oil bath. The reaction was complete when the mixture changed from cloudy-white to clear. The solution was then concentrated under reduced pressure on a rotary evaporator to afford a solid residue. This solid was suspended in 5 mL of cyclohexane and the slurry is heated to 85 °C, stirred at this temperature for 30 min, and then allowed to cool slowly to room temperature. The slurry was filtered, rinsed twice using the mother liquors, washed with 3 mL of cyclohexane, and dried *in vaccuo* to afford 2.81 g (13.7 mmol, 77 %) of 3-pyridylboronic acid pinacol ester **V.61**. The analytical data corresponded to the literature.[244]

White solid.

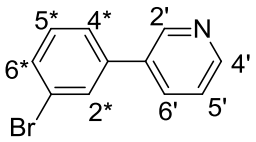
^{1}H-NMR (300 MHz, $CDCl_3$, vm269c2.1138(10)): δ 8.93 (1H, d, *J* = 1.1 Hz), 8.64 (1H, dd, *J* = 1.9, 4.9 Hz), 8.03 (1H, dt, *J* = 1.8, 7.5 Hz), 7.25 (1H, ddd, *J* = 1.1, 4.9, 7.5 Hz), 1.33 (12H, s).

^{13}C-NMR (75 MHz, $CDCl_3$, vm269c2.1138(20)): δ 155.5, 152.0, 142.2, 123.0, 84.1, 24.8.

LC/MS (ESI): $[M+H]^+$ m/z 206.

[244] Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D; Larsen, R. D. *Org. Synth.* **2005**, *11*, 393.

3-(3-bromophenyl)pyridine V.46



$C_{11}H_8BrN$
MW: 234,09

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **V.61** (2.39 g, 11.6 mmol, 1.0 mol equiv), 1,3-dibromobenzene (2.8 mL, 5.49 g, 23.3 mmol, 2.0 mol equiv.) and tetrakis(triphenylphosphine) palladium (672 mg, 0.6 mmol, 0.05 mol equiv) were placed in a flask. Dioxane (65 ml) degassed *via* three freeze-pump-thaw cycles and potassium carbonate (4.0196 g, 29.084 mmol, 2.5 mol equiv) were added, and the resulting mixture was then stirred at 80 °C for 22 hours. The mixture was poured into water (70 mL) and extracted with chloroform (4 x 40 ml). The combined organic layers were dried with anhydrous $MgSO_4$. Solvents were removed and the residue was purified by column chromatography (eluent: 9 Cy / 1 EtOAc) on silica gel to afford **V.46** as a colorless oil (1.46 g, 5.8 mmol, 50 %). The analytical data corresponded to the literature.[245]

Colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM278ap2.1138(10)): δ 8.79 (1H, d, *J*(2' 6') = 2.4 Hz, H-(C2')), 8.60 (1H, dd, *J*(4',5') = 5.1 Hz, *J*(4',6') = 1.8 Hz, H-(C4')), 7.80 (1H, dt, *J*(5',6') = 8.1 Hz, *J*(2',6') = 2.1 Hz, H-(C6')), 7.68 (1H, t, *J*(2*,4*) = 1.8 Hz, *J*(2*,6*) = 1.8 Hz, H-(C2*)), 7.46–7.52 (2H, m), 7.29–7.36 (2H, m).

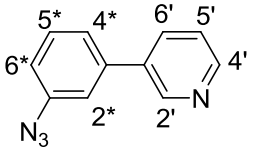
^{13}C-NMR (100 MHz, CDCl3): δ 123.2, 123.6, 125.7, 130.1, 130.5, 131.0, 134.3, 135.1, 139.9, 148.1, 149.0.

IR υ (neat): 3032, 1577, 1467, 1327, 1270, 1100, 778, 690 cm^{-1}.

Anal. calcd for $C_{11}H_8BrN$ (234.09): C 56.44, H 3.44, N 5.98. Found: C 56.62, H 3.62, N 6.06.

[245] Trokowski, R.; Akine, S.; Nabeshima, T. *Dalton Trans.* **2009**, *46,* 10359.

3-(3-Azidophenyl)pyridine V.39



$C_{11}H_8N_4$
MW: 196,21

Following the general procedure **C**, azide **V.39** was prepared in 89 % yield after purification on silica gel column chromatography (eluent: 3 Cy / 1 EtOAc).

Brown oil.

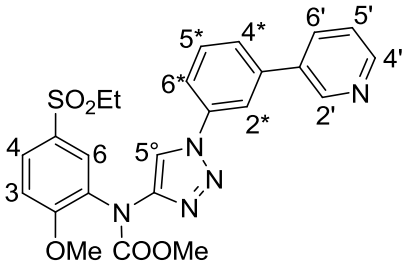
^{1}H-NMR (300 MHz, $CDCl_3$, VM282ap.1139(12)): δ 8.72 (1H, br s, H-(C2')), 8.51 (1H, br s, H-(C4')), 7.35-7.28 (1H, m, H-(C6')), 7.25-7.15 (2H, m), 7.07-7.04 (2H, m), 6.95 – 6.91 (1H, m).

^{13}C-NMR (75 MHz, $CDCl_3$, VM282ap.1139(10)): δ 148.9 (C4'), 148.1 (C2'), 140.8 (Cq), 139.5 (Cq), 134.1 (C6'), 130.3 (2xC), 123.5 (2xC), 118.4, 118.0.

IR υ (neat): 3032, 2098, 1586, 1468, 1403, 1304, 1254, 1019, 778, 753, 709, 692, 677 cm^{-1}.

HRMS (ESI+): $[M+H]^+$ Calcd. m/z 197.08; Found m/z 197.08.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl(1-(3-(pyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)carbamate VI.10



$C_{24}H_{23}N_5O_5S$
MW: 493,53

Following the general procedure **B,** it was obtained in 68 % after purification on column chromatography using silica gel (eluent: 95% DCM / 5% MeOH).

Pale yellow foam; **mp** 118 - 120 °C.

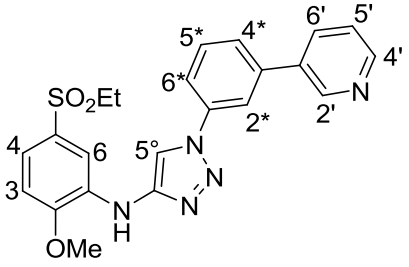
^{1}H-NMR (300 MHz, $CDCl_3$, VM496ap.1237(10)): δ 8.90 (1H, br s, H-(C2')), 8.65 (1H, br s, H-(C4')), 8.50 (1H, br s, H-C(5°)), 7.98 (1H, t, *J*(2*,4*) = 1.4 Hz, *J*(2*,6*) = 1.4 Hz, H-(C2*)), 7.94 (1H, dd, *J*(3,4) = 8.6 Hz, *J*(4,6) = 2.3 Hz, H-C(4)), 7.92-7.90 (1H, m), 7.89 (1H, d, *J*(4,6) = 1.8 Hz, H-C(6)), 7.79-7.75 (1H, m), 7.66-7.62 (2H, m), 7.41 (1H, dd, *J*(4',5') = 4.7 Hz, *J*(5',6') = 7.2 Hz, H-C(5')), 7.16 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.89 (3H, s, -OC*H*$_3$), 3.77 (3H, br s, -COOC*H*$_3$), 3.13 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.31 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM496ap.1237(30)): δ 159.8 (Cq), 153.6 (Cq), 149.3 (C2'), 148.2 (C4'), 147.3 (Cq), 147.3 (2xC), 139.7 (Cq), 137.8 (Cq), 134.5 (C6), 131.0, 130.6 (2xC), 130.5, 130.4 (Cq), 127.4, 119.7, 119.0 (C2*), 112.3 (C3), 56.4 (CH_3O-), 53.9 (-$COCH_3$), 51.1 (CH_3CH_2-), 7.6 (CH_3CH_2-).

IR υ (KBr): 1727, 1565, 1444, 1372, 1314, 1134, 1092, 1037, 738 cm^{-1}.

Anal. calcd for $C_{24}H_{23}N_5O_5S$ (493.14): C 58.41, H 4.70, N 14.19. Found: C 58.31, H 4.57, N 14.02.

***N*-(5-(Ethylsulfonyl)-2-methoxyphenyl)-1-(3-(pyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-4-amine III.22**



$C_{22}H_{21}N_5O_3S$
MW: 435,50

Compound **III.22** was prepared according to the general procedure **B**. Yield: 82 %. Purification: Column chromatography on silica gel (eluent: 95% DCM / 5% MeOH).

Pale yellow foam; **mp** 116 – 118°C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM507f1.1238(10)): δ 8.84 (1H, d, *J*(2' 6') = 1.9 Hz, H-(C2')), 8.59 (1H, dd, *J*(4',5') = 4.8 Hz, *J*(4',6') = 1.4 Hz, H-(C4')), 7.97-7.94 (2H, m), 7.91-7.86 (3H, m), 7.69-7.66 (2H, m), 7.62-7.57 (3H, m), 6.92 (1H, d, *J*(3,4) = 8.5 Hz, H-C(3)), 6.93 (1H, br s, -N*H*), 4.01 (3H, s, -OC*H*$_3$), 3.10 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

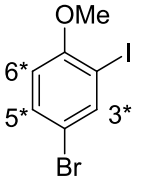
^{13}C-NMR (75 MHz, $CDCl_3$, VM507ap.1309(10)): δ 150.8 (Cq), 149.3, 148.3, 147.3 (Cq), 139.9 (Cq), 137.8 (Cq), 135.2 (Cq), 134.6, 133.2 (Cq), 130.7 (Cq), 130.5, 127.4, 123.7, 120.6. 119.8, 119.2, 111.2, 109.7, 108.9, 56.2 (CH_3O-), 50.8 (CH_3CH_2-), 7.6 (CH_3CH_2-).

IR υ (neat): 3353, 2926, 1603, 1576, 1510, 1302, 1260, 1123, 1021, 786, 733 cm^{-1}.

Anal. calcd for $C_{22}H_{21}N_5O_3S$ (435.50): C 60.67, H 4.86, N 16.08. Found: C 60.90, H 4.80., N 15.98.

Preparation of triazole III.23

4-bromo-2-iodo-1-methoxybenzene V.65



C_7H_6BrIO
MW: 312,93

To a solution of *p*-bromoanisole **V.64** (0.5 mL, 747 mg, 4.0 mmol, 1.0 mol equiv) in DCM (8 mL) was added silver trifluoroacetate (882 mg, 4.0 mmol, 1.0 mol equiv). The mixture was cooled down to -15°C. Afterwards, iodine (1.03 g, 4.1 mmol, 1.02 mol equiv) was added portionwise. The mixture was stirred 5 minutes at -15°C. The reaction was monitored by TLC. The crude reaction mixture was filtered through a Celite® pad. The filtrate was washed with 15 mL of a saturated solution of sodium thiosulfate, dried over $MgSO_4$, filtered and evapored under reduced pressure. The crude product was filtered through short pad of silica gel. The desired product **V.65** was obtained in 98 % yield (3.9 mmol, 1.23 g). The analytical data corresponded to the data in literature.[246]

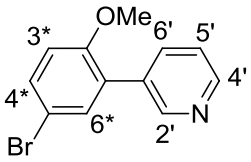
White solid, **mp** 64 - 65 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, vm368c.1213(10)): δ 7.88 (1H, d, *J*(3*,5*) = 2.4 Hz, H-C(3*)), 6.89 (1H, dd, *J*(5*,6*) = 8.7 Hz, *J*(3*,5*) = 2.4 Hz, H-C(5*)), 6.87 (1H, d, *J*(5*,6*) = 8.7 Hz, H-C(6*)), 3.85 (3H, s, OCH_3).

LC/MS (ESI): $[M+H]^+$ m/z 313.

[246] Muraki, T.; Togo, H.; Yokoyama, M. *J. Org. Chem.* **1999**, *64*, 2883.

3-(5-bromo-2-methoxyphenyl)pyridine V.47b



$C_{12}H_{10}BrNO$
MW: 264,12

3-(4,4,5,5-Tetramethyl- 1,3,2-dioxaborolan-2-yl)pyridine **V.61** (320 mg, 1.6 mmol, 1.5 mol equiv), 4-bromo-2-iodo-1-methoxybenzene (325 mg, 1.0 mmol, 1.0 mol equiv.) and tetrakis(triphenylphosphine) palladium (60 mg, 5.2 x 10^{-5} mol, 0.05 mol equiv) were placed in a flask. Dioxane (8 ml) degassed *via* three freeze-pump-thaw cycles and potassium carbonate (359 mg, 2.6 mmol, 2.5 mol equiv) were added, and the resulting mixture was then stirred at 80 °C for 16 hours. The cold mixture was poured into water (10 mL) and extracted with chloroform (3 x 10 ml). The combined organic layers were dried with anhydrous $MgSO_4$. Solvents were removed and the residue was purified by column chromatography (eluent: 3 Cy / 1 EtOAc) on silica gel to afford **V.47b** (250 mg, 0.8 mmol, 75 %).

Pale yellow oil.

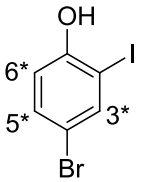
^{1}H-NMR (300 MHz, $CDCl_3$, vm396ap.1219(10)): δ 8.58 (1H, d, *J*(2',6') = 1.9 Hz, H-(C2')), 8.41 (1H, dd, *J*(4',5') = 4.8 Hz, *J*(4',6') = 1.5 Hz, H-(C4')), 7.64 (1H, dt, *J*(5',6') = 7.9 Hz, *J*(2',6') = 1.9 Hz H-(C6')), 7.30–7.25 (2H, m), 7.16 (1H, dd, *J*(4',5') = 4.8 Hz, *J*(5',6') = 7.8 Hz, H-C(5')), 6.70 (1H, *J*(3*,4*) = 1.9 Hz, H-(C6*)), 3.62 (3H, s, OC*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$,vm396ap.1219(11)): δ 155.7 (Cq), 150.1, 148.5, 136.7, 133.1, 132.9 (Cq), 132.0, 129.1 (Cq), 123.0, 113.2 (Cq), 113.0, 55.8 (-O*C*H_3).

IR υ (neat): 3393, 3029, 2039, 1492, 1470, 1386, 1265, 1237, 1181, 1141, 1025, 1009, 810, 712 cm^{-1}.

Anal. calcd for $C_{12}H_{10}BrNO$ (264.12): C 54.57, H 3.82, N 5.30. Found: C 54.60, H 3.80, N 5.28.

4-bromo-2-iodophenol V.69



C_6H_4BrIO
MW: 298,90

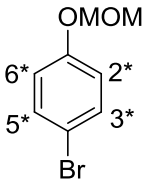
To a solution of **V.65** (10.45 g, 33.4 mmol, 1.0 mol equiv) in dry DCM (60 mL) was added dropwise 1M solution in BBr_3 (66.8 mL, 66.8 mmol, 2.0 mol equiv) at 0 °C. An inert atmosphere was established and maintained. The mixture was stirred 1 hour at 0 °C. The reaction mixture was warmed up to room temperature and stirred over 30 min with saturated solution of $NaHCO_3$ (70 mL). The organic layer was separated, the aqueous layer washed with DCM (3x40 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtred and concentrated under reduced pressure. The crude product was filtered through silica gel (eluent : 3 Cy /1 EtOAc) to afford **V.69** in 98 % yield (32.7 mmol, 9.75 g). The analytical data corresponded to the literature.[247]

White solid; **mp** 70 – 71 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, vm486c.1235(10)): δ 7.76 (1H, d, *J*(3*,5*) = 2.3 Hz, H-C(3*)), 7.34 (1H, dd, *J*(5*,6*) = 8.7 Hz, *J*(3*,5*) = 2.3 Hz, H-C(5*)), 6.87 (1H, d, *J*(5*,6*) = 8.7 Hz, H-C(6*)), 5.31 (1H, br s, -O*H*).

LC/MS (ESI): $[M+H]^+$ m/z 299.

<u>1-bromo-4-(methoxymethoxy)benzene</u> V.67



$C_8H_9BrO_2$
MW: 217,06

4-Bromophenol **V.66** (1.0 g, 5.8 mmol, 1.0 mol equiv) in dry DCM (5 mL) was added dropwise to a stirred slurry of sodium hydride (146 mg, 6.1 mmol, 1.05 mol equiv) in DCM (10 mL) at room temperature. The reaction mixture was stirred until the evolution of hydrogen ceased (30 min). The cholоromethyl methyl ether (0.46 mL, 6.1 mmol, 1.05 mol equiv) was added during 30 min. The reaction was stirred for an additional 45 min after which excess sodium hydride was destroyed by cautious addition of methanol (3 mL). The reaction mixture was diluted with ether, washed with water and brine, and dried over $MgSO_4$. The crude product was purified *via* SiO_2 flash

[247] Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A. ; Bennani, Y. L. ; Black, L. A.; Pan, L.; Marsh, K. C.; Sullivan, J. P.; Esbenshade, T. A.; Fox, G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38.

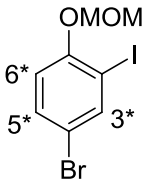
chromatography (eluent: 5 Cy / 1 EtOAc)to give the pure product **V.67** (1.10 g, 5.1 mmol, 88 % yield). The analytical data corresponded to the data in literature.[248]

Pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, VM429c.1224(10)): δ 7.38 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 5.14 (2H, s, -CH_2- from MOM), 3.47 (3H, s, -CH_3 from MOM).

LC/MS (ESI): $[M+H]^+$ m/z 218.

4-bromo-2-iodo-1-(methoxymethoxy)benzene V.70



$C_8H_8BrIO_2$
MW: 342,96

An oven-dried round bottom flask was charged with 4-bromo-2-iodo-phenol **V.69** (247 mg, 0.9 mmol, 1.0 mol equiv) and capped with an inlet adapter with a three-way stopcock and then evacuated and back-filled with argon. Anhydrous DCM (5 mL) was added. Then the mixture was cooled to 0 ºC. Triethylamine (248 μL, 1.8 mmol, 2.0 mol equiv) was added, followed by addition of chloromethyl methyl ether (135 μL, 1.8 mmol, 2.0 mol equiv). Reaction was checked by TLC. After completion, water was added to the reaction mixture. The reaction mixture was extracted with DCM (10 mL). Aqueous layers were extracted twice with DCM (2x10 mL). The combined organic layers were washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The crude product was filtered through short pad of silica gel to afford protected phenol **V.70** (260 mg, 0.8 mmol, 85 %).

Pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, vm501f1.1237(10)): δ 7.88 (1H, d, *J*(3*,5*) = 2.4 Hz, H-C(3*)), 7.37 (1H, dd, *J*(5*,6*) = 8.8 Hz, *J*(3*,5*) = 2.4 Hz, H-C(5*)), 6.94 (1H, d, *J*(5*,6*) = 8.8 Hz, H-C(6*)), 5.20 (2H, s, -CH_2- from MOM), 3.49 (3H, s, -CH_3 from MOM).

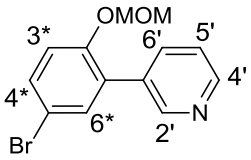
[248] Miyakawa, M.; Scanlan, T. S. *Synth. Commun.* **2006**, *36*, 891.

^{13}C-NMR (75 MHz, $CDCl_3$, vm501f1.1237(21)): 155.4 (Cq), 141.2, 132.2, 116.0, 114.8 (Cq), 95.1 (CH_3OCH_2), 87.9 (Cq), 56.5 (CH_3OCH_2).

IR υ (neat): 2928, 2902, 1464, 1264, 1235, 1199, 1158, 1143, 1081 1028, 971, 921, 870, 801, 661 cm^{-1}.

Anal. calcd for $C_8H_8BrIO_2$ (342.96): C 28.02, H 2.35. Found: C 27.97, H 2.24.

3-(5-bromo-2-(methoxymethoxy)phenyl)pyridine V.47c



$C_{13}H_{12}BrNO_2$
MW: 294,14

3-(4,4,5,5-Tetramethyl- 1,3,2-dioxaborolan-2-yl)pyridine **V.61** (144 mg, 0.7 mmol, 1.2 mol equiv), 4-bromo-2-iodo-1-(methoxymethoxy)benzene **V.70** (200 mg, 0.6 mmol, 1.0 mol equiv) and tetrakis(triphenylphosphine) palladium (34 mg, 2.9 . 10^{-5} mol, 0.05 mol equiv) were placed in a flask. Dioxane (5 ml) degassed *via* three freeze-pump-thaw cycles and potassium carbonate (202 mg, 1.5 mmol, 2.5 mol equiv) were added, and the resulting mixture was then stirred at 80 °C for 16 hours. The cold mixture was poured into water (8 mL) and extracted with chloroform (3 x 8 ml). The combined organic layers were dried with anhydrous $MgSO_4$. Solvents were removed and the residue was purified by column chromatography (eluent: 1 Cy / 1 EtOAc) on silica gel to afford **V.47c** as a pale yellow oil (93 mg, 0.3 mmol, 54 %).

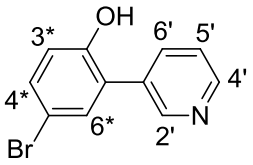
Pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, vm500ap.1237(10)): δ 8.74 (1H, d, *J*(2',6') = 1.5 Hz, H-(C2')), 8.57 (1H, dd, *J*(4',5') = 4.7 Hz, *J*(4',6') = 1.2 Hz, H-(C4')), 7.80 (1H, dt, *J*(5',6') = 7.9 Hz, *J*(2',6') = 1.9 Hz H-(C6')), 7.42–7.40 (2H, m), 7.34 (1H, dd, *J*(4',5') = 4.7 Hz, *J*(5',6') = 7.8 Hz, H-C(5')), 7.13-7.11 (1H, m), 5.11 (2H, s, -CH_2- from MOM), 3.37 (3H, s, -CH_3 from MOM).

^{13}C-NMR (75 MHz, $CDCl_3$,vm502f2.1238(11)): δ 153.4 (Cq), 150.1, 148.5, 136.6, 133.2, 132.9 (Cq), 132.2, 130.0 (Cq), 123.0, 117.0, 114.6 (Cq), 95.0 (CH_3OCH_2-), 56.3 (CH_3OCH_2-).

Anal. calcd for $C_{13}H_{12}BrNO_2$ (294.14): C 53.08, H 4.11, N 4.76. Found: C 53.00, H 4.16, N 4.8.

4-bromo-2-(pyridin-3-yl)phenol V.47d



$C_{11}H_8BrNO$
MW: 250,09

Prepared from V.65 (methoxy protected form): To a solution of **V.47b** (1.06 g, 4.0 mmol, 1.0 mol equiv) in dry DCM (15 mL) was added dropwise a 1M solution of BBr_3 in DCM (8.1 mL, 8.1 mmol, 2.0 mol equiv) at -78 °C. An inert atmosphere was established and maintained. The mixture was stirred 1 hour at -78 °C. The reaction mixture was warmed up to room temperature and stirred over 30 min with saturated solution of $NaHCO_3$ (15 mL). The organic layer was separated, the water layer washed with DCM (2x30 mL). The collected organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent : 1 Cy / 2 EtOAc) on silica gel to afford **V.47d** as a white solid (302 mg, 1.2 mol equiv, 30 %).

Prepared from V.70 (MOM protected form): To a solution of 3-(5-bromo-2-(methoxymethoxy)phenyl)pyridine **V.47c** (21 mg, 7.2 x 10^{-5} mol, 1.0 mol equiv) in MeOH (2 mL) were added 2 drops of concentrated hydrochloric acid. The solution was stirred under reflux over 40 min. The reaction was checked by TLC. After completion, reaction mixture was cool down to room temperature and neutralized with saturated solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were collected, dried over anhydrous $MgSO_4$ and concentred under reduced pressure. The desired compound **V.47d** was obtained almost in quantitative yield (17 mg, 6.9 x 10^{-5} mol, 96 %).

White solid; **mp** 154 - 157 °C.

^{1}H-NMR (300 MHz, DMSO, vm482ap.1320(12)): δ 10.13 (1H, br s), 8.73 (1H, d, *J*(2',6') = 1.6 Hz, H-(C2')), 8.52 (1H, dd, *J*(4',5') = 4.7 Hz, *J*(4',6') = 1.2 Hz, H-(C4')), 7.96 (1H, dt, *J*(5',6') = 7.9 Hz, *J*(2',6') = 1.8 Hz H-(C6')), 7.47–7.42 (2H, m), 7.38 (1H, dd, *J*(3*,4*) = 8.6 Hz, *J*(4*,6*) = 2.6 Hz, H-C(4*)), 6.95 (1H, d, *J*(3*,4*) = 8.6 Hz, H-C(3*)).

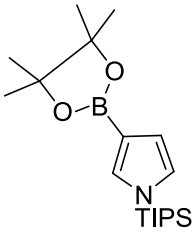
^{13}C-NMR (75 MHz, DMSO,vm482ap.1320(11)): 154.0 (Cq), 146.0, 144.5, 140.5, 132.5, 132.4, 125.0 (Cq), 124.4, 118.3, 110.7 (Cq).

Anal. calcd for $C_{11}H_8BrNO$ (250.09): C 52.83, H 3.22, N 5.60. Found: C 52.60, H 3.20, N 5.58.

Preparation of triazole III.24

Preparation of pyrrole azide V.43

3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-*1*H-pyrrole V.54



$C_{19}H_{36}BNO_2Si$
MW: 349,39

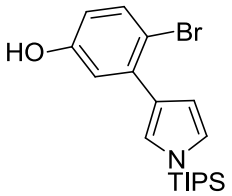
An oven-dried Schlenk tube was charged with $PdCl_2(CH_3CN)_2$ (51.5 mg, 0.2 mmol, 3.0 mol%) and *S*-Phos (244 mg, 0.6 mmol, 9.0 mol%). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon. Toluene (10 mL) was added *via* syringe, through the septum, followed by the addition of 3-bromo-1-(triisopropyl-silanyl)-1*H*-pyrrole **V.71** (1.74 mL, 2.00 g, 6.6 mmol, 1.0 mol equiv), pinacol borane **V.72** (1.15 mL, 1.02 g, 7.9 mmol, 1.2 mol equiv) and triethylamine (2.3 mL, 16.5 mmol, 2.5 mol equiv). The reaction mixture was heated to 90 °C and stirred for 18 h. At this point the reaction mixture was allowed to cool to room temperature. The solution was then filtered though a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (eluent: 20 Cy /1 EtOAc) to provide the title compound **V.54** in a 81 % yield (5.3 mmol, 2.31 g). The analytical data corresponded to the literature.[249]

Yellow solid; **mp** 69 – 72 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM428ap2.1315(12)): δ 7.17-7.16 (1H, m, pyrrole), 6.74-6.72 (1H, m, pyrrole), 6.55-6.54 (1H, m, pyrrole), 1.46 (3H, sept, *J* = 7.0 Hz, TIPS), 1.33 (12H, s, pinacol), 1.09 (18H, d, *J* = 7.0 Hz, TIPS).

[249] Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.

4-bromo-3-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)phenol V.48



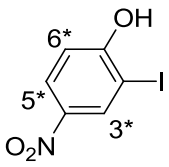
$C_{19}H_{28}BrNOSi$
MW: 394,42

A mixture of $Pd(OAc)_2$ (6 mg, 8.6 . 10^{-6} mol, 0.4 mol equiv), *S*-Phos (7 mg, 1.7 . 10^{-6} mol, 8 mol %), K_3PO_4 (91 mg, 0.4 mmol), pyrrole-borane **V.54** (70 mg, 0.2 mmol, 1.0 mol equiv), and 4-bromo-2-iodophenol (64 mg, 0.2 mmol, 1.0 mol equiv) in *n*-BuOH (5 ml) and H_2O (2 ml) was stirred at 80 °C for 3 h. After cooling to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. Purification of the crude material was performed by column chromatography on alumina. The product degraded and it was isolated only in analytical quantity in order to make LCMS analysis.

LC/MS (ESI): $[M+H]^+$ m/z 395.

Alternative approach to triazole III.24

2-iodo-4-nitrophenol V.76



$C_6H_4INO_3$
MW: 265,01

2-Iodophenol **V.75** (1.88 g, 8.5 mmol, 1.0 mol equiv) was dissolved in DCM (20 mL) and 70 % nitric acid (652 µL, 10.6 mmol, 1.24 mol equiv) was added. The reaction stirred at room temperature for 3.75 hours, then DCM and water were added and the layers separated. The organic layer was concentrated and purification by column chromatography (eluent: 3 Cy / 1 EtOAc) afforded 0.95 g of 2-iodo-4-nitrophenol **V.76** (3.5 mmol, 41 %) The analytical data corresponded to the literature.[250]

Pale yellow solid; **mp** 87 - 89 °C.

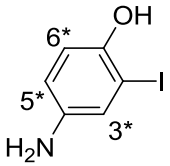
[250] Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N. ; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445.

^{1}H-NMR (300 MHz, $CDCl_3$, VM314ap3.1147(10)): δ 8.59 (1H, d, *J*(3*,5*) = 2.6 Hz, H-C(3*)), 8.16 (1H, dd, *J*(5*,6*) = 9.0 Hz, *J*(3*,5*) = 2.6 Hz, C(5*)), 7.06 (1H, *J*(5*,6*) = 9.0 Hz, C(6*)), 6.41 (1H, br s, -O*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 136.4, 134.4, 126.1, 115.7, 114.6, 84.4.

Anal. Calcd for $C_6H_4INO_3$ (265.01): C 27.19, H 1.52, N 5.29. Found: C 27.01, H 1.41, N 5.11.

4-amino-2-iodophenol V.77



C_6H_6INO
MW: 235,02

A mixture of **V.76** (357 mg, 1.3 mmol, 1.0 mol equiv) and $SnCl_2$ (1.28 g, 6.7 mmol, 5.0 mol equiv) in 10 mL of absolute ethanol was refluxed at 70 °C under argon atmosphere. After 30 min the starting material disappeared and the solution was allowed to cool down and then poured into ice. The pH was made slightly basic (pH=7-8) by addition of 5 % aqueous solution of sodium bicarbonate before being extracted with EtOAc (3 x 10 mL). The organic phase was washed with 20 mL of brine and dried over $MgSO_4$. Evaporation of solvent left 307 mg (1.3 mmol, 97 %) of desired aniline **V.77**. The analytical data corresponded to the literature.[251]

Brown solid; mp 112 - 114 °C.

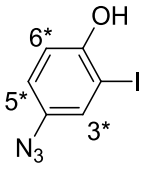
^{1}H-NMR (300 MHz, $CDCl_3$, VM478ap.1307): δ 8.57 (1H, d, *J*(3*,5*) = 2.7 Hz, H-C(3*)), 8.15 (1H, dd, *J*(5*,6*) = 8.8 Hz, *J*(3*,5*) = 2.7 Hz, H-C(5*)), 7.05 (1H, *J*(5*,6*) = 8.8 Hz, 1 H, H-C(6*)), 6.00 (1H, br s, O*H*), 5.25 (2H, br s, -NH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.4, 134.4, 126.1, 115.7, 114.6, 84.4 (*C*-I).

LC/MS (ESI): $[M+H]^+$ m/z 236.

[251] Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782.

4-Azido-2-iodophenol V.78a



$C_6H_4IN_3O$
MW: 261,02

$NaNO_2$ (108 mg, 1.6 mmol, 1.2 mol equiv) in H_2O (3 mL) was added dropwise to a slurry of aniline **V.77** (307 mg, 1.3 mmol, 1.0 mol equiv) in H_2O / HCl (1 / 1, 15 mL) at 0 °C and stirred for 1 h. A solution of NaN_3 (102 mg, 1.6 mmol, 1.2 mol equiv) in H_2O (3 mL) was then added dropwise and the resulting suspension was allowed to warm to rt over 2 h. The mixture was diluted with EtOAc (15 mL) and the aqueous layer was extracted further with EtOAc (2 x 15 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to get 118 mg (0.4 mmol, 34 %) of desired azide **V.78a**.

Brown oil.

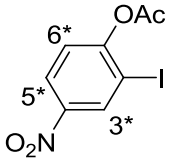
^{1}H-NMR (400 MHz, $CDCl_3$, VM611c.1311(11)): δ 7.25 (1H, d, *J*(3*,5*) = 2.5 Hz, H-C(3*)), 6.89 (1H, dd, *J*(5*,6*) = 8.6 Hz, *J*(3*,5*) = 2.5 Hz, H-C(5*)), 6.87 (1H, *J*(5*,6*) = 8.6 Hz, H-C(6*)), 5.17 (1H, br s, -O*H*).

^{13}C-NMR (75 MHz, $CDCl_3$**,** VM611ap.1312(10)): 152.4 (Cq), 133.5 (Cq), 128.2, 120.9, 115.7, 85.8 (Cq, C(2*)).

IR υ (neat): 3468, 2113, 1577, 1478, 1408, 1278, 1183, 787 cm^{-1}.

Anal. Calcd for $C_6H_4IN_3O$ (261.02): C 27.61, H 1.54. Found: C 27.50, H 1.40.

2-iodo-4-nitrophenyl acetate V.79



$C_8H_6INO_4$
MW: 307,04

In a round bottom flask, 2-iodo-4-nitrophenyl **V.76** dichloromethane, pyridine (728 mg, 740 µL, 9.2 mmol, 1.1 mol equiv) and acetic anhydride (1.02 g, 950 µL, 10.0 mmol, 1.2 mol equiv)

were added and allowed to react for 30 min under argon atmosphere. The reaction was washed with water (30 mL) once and with saturated $NaHCO_3$ (20 mL) once. The solvent was removed by rotary evaporation and flash chromatography was performed (eluent: 2 Cy/1 EtOAc) affording a yellow solid at 76 % yield (6.4 mmol, 1.96 g). The compound **V.79** is known[252], but not fully described.

Yellow solid; **mp** 33 - 36 °C.

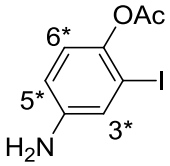
^{1}H-NMR (300 MHz, $CDCl_3$, VM324ap.1150(12)): δ 8.59 (1H, d, *J*(3*,5*) = 2.6 Hz, H-C(3*)), 8.16 (1H, dd, *J*(5*,6*) = 8.9 Hz, *J*(3*,5*) = 2.6 Hz, H-C(5*)), 7.19 (1H, d, *J*(5*,6*) = 8.9 Hz, H-C(6*)), 2.32 (3H, s, C*H*$_3$CO-).

^{13}C-NMR (75 MHz, $CDCl_3$, VM324ap.1150(10)): δ 167.6 (Cq, CH_3*C*O-), 156.2 (Cq, C(1*)), 145.7 (Cq, C(4*)), 134.7 (C(3*)), 124.8 (C(6*), 123.3 (C(5*)), 90.5 (Cq, C(2*)), 21.2 (*C*H_3CO-).

IR υ (neat): 2928, 1769, 1581, 1524, 1346, 1174, 909, 746 cm^{-1}.

Anal. Calcd for $C_8H_6INO_4$ (307.04): C 31.29, H 1.97, N 4.56. Found: C 31.20, H 1.65, N 4.54.

4-amino-2-iodophenyl acetate V.80



$C_8H_8INO_2$
MW: 277,06

A mixture of **V.79** (1.24 g, 4.0 mmol, 1.0 mol equiv) and $SnCl_2$ (3.82 g, 20.2 mmol, 5.0 mol equiv) in 30 mL of absolute ethanol was refluxed at 70 °C under argon atmosphere. After 30 min the starting material disappeared and the solution was allowed to cool down and then poured into ice. The pH was made slightly basic (pH = 7 - 8) by addition of 5 % aqueous solution sodium bicarbonate before being extracted with EtOAc (3 x 40 mL). The organic phase was washed with 50 mL of brine and dried over $MgSO_4$. Evaporation of solvent left 1.04 g (3.7 mmol, 93 %) of desired aniline **V.80**.

Pale yellow solid; **mp** 92 - 95 °C.

[252] Atta, A. K. ; Kim, S.-B.; Cho, D.-G. *Org. Lett.* **2013**, *15*, 1072.

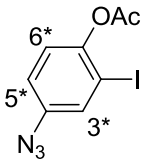
^{1}H-NMR (300 MHz, $CDCl_3$, VM620c.1313(10)): δ 7.04 (1H, d, *J*(3*,5*) = 2.6 Hz, H-C(3*)), 6.80 (1H, d, *J*(5*,6*) = 8.6 Hz, H-C(6*)), 6.56 (1H, dd, *J*(5*,6*) = 8.6 Hz, *J*(3*,5*) = 2.6 Hz, H-C(5*)), 3.72 (2H, br s, -N*H*$_2$) 2.31 (3H, s, C*H*$_3$CO-).

^{13}C-NMR (75 MHz, $CDCl_3$, VM620c.1313(11)): δ 169.7 (Cq, CH_3*C*O-), 145.8 (Cq), 143.0 (Cq), 124.7, 122.9, 115.9, 90.8 (Cq, *C*-I), 21.3 (*C*H_3CO-).

IR υ (neat): 3372, 1756, 1597, 1486, 1369, 1220, 1193, 1028, 909, 640 cm^{-1}.

Anal. Calcd for $C_8H_6INO_4$ (277.06): C 34.68, H 2.91, N 5.06. Found: C 34.60, H 2.83, N 4.94.

4-azido-2-iodophenyl acetate V.78b



$C_8H_6IN_3O_2$
MW: 303,06

$NaNO_2$ (312 mg, 4.5 mmol, 1.2 mol equiv) in H_2O (10 mL) was added dropwise to a slurry of aniline **V.80** (1.04 g, 3.8 mmol, 1.0 mol equiv) in H_2O/HCl (1:1, 40 mL) at 0 °C then stirred for 1 h. A solution of NaN_3 (294 mg, 4.5 mmol, 1.2 mol equiv) in H_2O (10 mL) was then added dropwise and the resulting suspension was allowed to warm to room temperature over 2 h. The mixture was diluted with EtOAc (30 mL) and the aqueous layer was extracted further with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to deliver a compound **V.78b** (745 mg, 2.5 mol equiv, 65 %).
Brown oil.

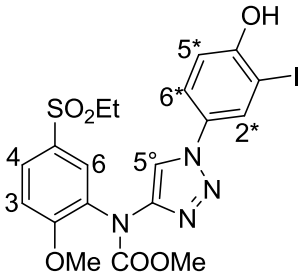
^{1}H-NMR (400 MHz, $CDCl_3$, VM566f1.1306(10)): δ 7.47 (1H, d, *J*(3*,5*) = 2.2 Hz, H-C(3*)), 7.06 (1H, d, *J*(5*,6*) = 8.6 Hz, H-C(6*)), 7.01 (1H, dd, *J*(5*,6*) = 8.6 Hz, *J*(3*,5*) = 2.2 Hz H-C(5*)), 2.36 (3H, s, C*H*$_3$CO-).

^{13}C-NMR (75 MHz, $CDCl_3$, VM566f1.1306(11)): δ 168.7 (Cq, C*H*$_3$CO-), 148.3 (Cq), 138.8 (Cq), 129.4, 123.6, 120.0, 91.2 (Cq, C-I), 22.7.

IR υ (neat): 2106, 1764, 1586, 1764, 1474, 1300, 1128, 1178, 1128, 904, 465 cm^{-1}.

Anal. Calcd for $C_8H_6IN_3O_2$ (303.06): C 31.71, H 2.00. Found: C 31.79, H 2.03.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl(1-(4-hydroxy-3-iodophenyl)-1*H*-1,2,3-triazol-4-yl)carbamate V.74a



$C_{19}H_{19}IN_4O_6S$
MW: 558,35

Compound **V.74a** was prepared according to the general procedure **A**. Yield: 80 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 4 EtOAc).

Pale yellow foam; **mp** 135 - 136 °C.

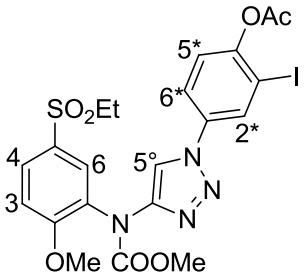
^{1}H-NMR (300 MHz, $CDCl_3$, VM567ap.1306(10)): δ 8.35 (1H, br s, H-C(5°)), 8.04 (1H, d, *J* = 2.4 Hz), 7.94 (1H, dd, *J* = 8.7 Hz, 2.2 Hz), 7.86 (1H, d, *J* = 2.2 Hz), 7.59 (1H, dd, *J* = 8.6 Hz, 2.4 Hz), 7.15 (1H, d, *J* = 8.6 Hz), 7.06 (1H, d, *J* = 8.7 Hz), 6.39 (1H, br s,-O*H*), 3.89 (3H, s, -OC*H*$_3$), 3.78 (3H, br s, -COOC*H*$_3$), 3.13 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.31 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM567AP.1310(11)): δ 159.9 (Cq), 156.4 (Cq), 153.6 (Cq), 130.9 (Cq), 130.8, 130.8 (2xC), 130.7, 130.4 (Cq), 122.3 (2xC), 115.4, 112.6, 84.7 (Cq, C(3*)), 56.5 (-O*C*H$_3$), 54.0 (-CO*C*H$_3$), 51.1 (-$SO_2CH_2CH_3$), 7.6 (-$SO_2CH_2CH_3$). (1 missing)

IR υ (neat): 2954, 1724, 1501, 1442, 1312, 1288, 1132, 1094, 758, 727, 532, 496 cm^{-1}.

Anal. Calcd for $C_{19}H_{19}IN_4O_6S$ (558.35): C 40.87, H 3.43, N 10.03. Found: C 40.90, H 3.43, N 10.10.

4-(4-((5-(Ethylsulfonyl)-2-methoxyphenyl)(methoxycarbonyl)amino)-*1H*-1,2,3-triazol-1-yl)-2-iodophenyl acetate V.74b



$C_{21}H_{21}IN_4O_7S$
MW: 600,38

Compound **V.74b** was prepared according to the general procedure **A**. Yield: 92 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 4 EtOAc).

Pale yellow foam; **mp** 125 - 126 °C.

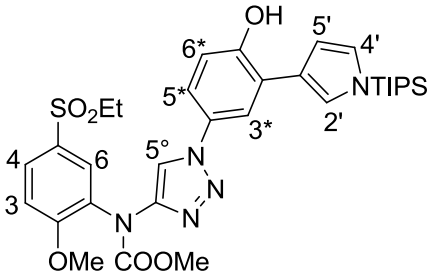
^{1}H-NMR (300 MHz, $CDCl_3$, VM574ap.1306(12)): δ 8.39 (1H, br s, H-C(5°)), 8.21 (1H, d, *J* = 2.4 Hz), 7.93 (1H, dd, *J*= 8.7 Hz, 2.1 Hz), 7.87(1H, d, *J* = 2.1 Hz), 7.76 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz), 7.25 (1H, d, *J* = 2.4 Hz), 7.15 (1H, d, *J* = 8.7 Hz) , 3.87 (3H, s, OC*H*$_3$), 3.76 (3H, br s, -COOC*H*$_3$), 3.12 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -SO_2C*H*$_2CH_3$), 2.38 (3H, s, C*H*$_3$CO-), 1.30 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -SO_2CH_2C*H*$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM574ap.1306(10)): δ 168.3 (Cq), 159.8(Cq), 153.5(Cq), 151.4(Cq), 135.4(Cq), 131.0, 130.9, 130.6, 130.4 (Cq), 129.4, 123.8, 123.6, 121.2, 120.0 (Cq), 112.3, 91.2 (Cq, C(3*)), 56.4 (-OCH_3), 53.9 (-COOCH_3), 51.0 (-SO_2C*H*$_2CH_3$), 31.2 (-OCCH_3), 7.6 (-SO_2CH_2C*H*$_3$).

IR υ (neat): 2958, 1768, 1727, 1497, 1444, 1371, 1314, 1183, 1134, 1093, 1039, 907, 735, 533 cm^{-1}.

HRMS (ESI+): $[M+H]^+$ Calcd. m/z 601.025; Found m/z 601.027.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl(1-(4-hydroxy-3-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)phenyl)-1H-1,2,3-triazol-4-yl)carbamate VI.17



$C_{32}H_{43}N_5O_6SSi$
MW: 653,86

A mixture of $Pd(OAc)_2$ (0.7 mg, 8.2 x 10^{-6} mol, 4 mol %), S-Phos (3 mg, 6.5 x 10^{-6} mol, 8 mol %), K_3PO_4 (35 mg, 0.16 mmol, 2.0 mol equiv), pyrrole-borane **V.54** (34 mg, 1 x 10^{-4} mol, 1.2 mol equiv), and triazole **V.74b** (49 mg, 8 x 10^{-5} mol, 1.0 mol equiv) in *n*-BuOH (5 mL) and H_2O (2 mL) was stirred at 80°C for 15 min. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 10mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of crude material by column chromatography on silica gel (eluent: 1 Cy /1 EtOAc to 1 Cy/4 EtOAc) afforded the title compound **VI.17** in 54 % (8 x 10^{-5} mol, 30 mg).

Grey solid, **mp** 128 – 130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM608ap.1311(10)): δ 8.36 (1H, br s, H-C(5°)), 7.92 (1H, dd, *J* = 8.7, 2.1 Hz), 7.88 (1H, d, *J* = 2.1 Hz), 7.68 (1H, d, *J* = 2.6 Hz), 7.44 (1H, dd, *J* = 8.6 Hz, 2.6 Hz), 7.13 (1H, d, *J*= 8.7 Hz), 7.09-7.08 (1H, m, pyrrole), 7.02 (1H, d, *J* = 8.6 Hz), 6.91 (1H, t, *J* = 2.3 Hz, pyrrole), 6.55 (1H, dd, *J* = 1.4 Hz, 2.5 Hz, pyrrole), 6.22 (1H, br s, -O*H*), 3.88 (3H, s, -OC*H$_3$*), 3.76 (3H, br s, -COOC*H$_3$*), 3.11 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.49 (3H, septet, *J*(CH,CH_3) = 7.5 Hz, 3x CH), 1.30 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.13 (18H, d, *J*(CH,CH_3) = 7.5 Hz, 6xCH_3).

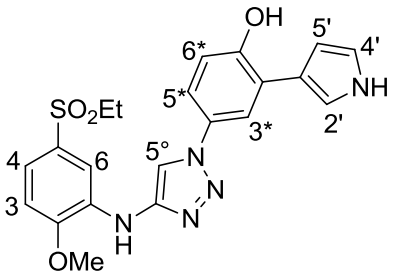
^{13}C-NMR (75 MHz, $CDCl_3$, VM577ap.1306(20)): δ 159.9 (Cq), 153.6 (Cq), 153.1 (Cq), 131.0, 130.5, 130.4 (Cq), 126.3, 124.2 (Cq), 122.9, 122.1, 121.5, 120.3 (Cq), 119.8, 116.3, 116.1, 112.3, 110.0, 56.4 (-O*C*H_3), 53.8 (-COO*C*H_3), 51.1 (-$SO_2CH_2CH_3$), 17.8 (6xC),11.7 (3xC), 7.6 (-$SO_2CH_2CH_3$).

IR υ (neat): 2948, 2873, 1728, 1503, 1443, 1315, 1286, 1134, 1093, 737 cm^{-1}.

HRMS (ESI+): $[M+H]^+$ Calcd. m/z 654.278; Found m/z 654.277.

4-(4-((5-(ethylsulfonyl)-2-methoxyphenyl)amino)-1H-1,2,3-triazol-1-yl)-2-(1*H*-pyrrol-3-yl)phenol

III.24



$C_{21}H_{21}N_5O_4S$
MW: 439,49

Compound **III.24** was prepared according to the general procedure **B**. Yield: 61 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 4 EtOAc).

Pale yellow foam; **mp** 90 – 93 °C.

^{1}H-NMR (400 MHz, acetone-d_6, VM612apacetone.1311(10)): δ 10.23 (1H, br s), 8.86 (1H, br s, -N*H*), 8.30 (1H, d, *J* = 2.2 Hz), 8.22 (1H, br s, -N*H*), 7.98 (1H, d, *J* = 2.7 Hz), 7.63 (1H, br s), 7.59 (1H, dd, *J* = 4.2 Hz, 1.8 Hz, pyrrole), 7.45 (1H, dd, *J* = 8.6 Hz, 2.7 Hz), 7.36 (1H, dd, *J* = 8.4 Hz, 2.2 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.09 (1H, d, *J* = 8.6 Hz), 6.88 (1H, dd *J* = 4.8 Hz, 2.6 Hz), 6.71 (1H, dd, *J* = 4.2 Hz, 2.6 Hz), 4.05 (3H, s, -OCH_3), 3.13 (2H, q, $J(CH_2CH_3)$ = 7.4 Hz, -$SO_2CH_2CH_3$), 1.21 (3H, t, $J(CH_2CH_3)$ = 7.4 Hz, -$SO_2CH_2CH_3$).

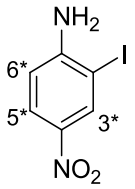
^{13}C-NMR (100 MHz, VM612apacetone.1311(11)): δ 153.8 (Cq), 150.6 (Cq), 147.7 (Cq), 134.0 (Cq), 131.4 (Cq), 130.4 (Cq), 124.8 (Cq), 119.6, 119.3, 119.0 (Cq), 118.9, 117.9, 116.4, 112.0, 110.4, 109.7, 106.9, 55.7 (-OCH$_3$), 50.1 (-$SO_2CH_2CH_3$), 7.0 (-$SO_2CH_2CH_3$).

IR υ (neat): 3373, 2925, 2854, 1600, 1730, 1577, 1511, 1439, 1262, 1123, 736 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}N_5O_4S$ (439.49): C 57.39, H 4.82, N 15.94. Found: C 57.43, H 4.80, N 15.90.

Preparation of triazole III.25

2-Iodo-4-nitrophenylamine V.82



$C_6H_5IN_2O_2$
MW: 264,02

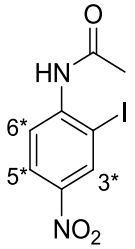
p-Nitroaniline **V.81** (24.00 g, 174 mmol, 1.0 mol equiv), iodine (22.07 g, 87.0 mmol, 0.5 mol equiv, 0.5 mol equiv) dissolved in ethanol (175 ml) by warming, iodic acid (9.18 g, 52. 2 mmol, 0.3 mol equiv) dissolved in water (10 ml) were added with shaking and refluxed on boiling water bath for 5 min. On cooling, solid separated out. Obtained solid product was filtered off and crystallized from ethanol to get **V.82** (44.53 g, 169 mmol, 97 %). The analytical data corresponded to the literature.[253]

Orange powder; **mp** 113 - 115 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM301c.1144(10)): δ 8.52 (1H, d, *J*(3*,5*) = 2.5 Hz, H-C(3*)), 8.02 (1H, dd, *J*(5*,6*) = 9.0 Hz, *J*(3*,5*) = 2.5 Hz, C(5*)), 6.70 (1H, *J*(5*,6*) = 9.0 Hz, C(6*)), 4.95 (2H, br s,-NH_2).

LC/MS (ESI): $[M+H]^+$ m/z 265.

***N*-(2-Iodo-4-nitro-phenyl)acetamide V.83**



$C_8H_7IN_2O_3$
MW: 306,06

To a solution of 2-iodo-4-nitrophenylamine **V.82** (19.14 g, 72.2 mmol, 1.0 mol equiv) in dichloromethane (120 mL) was added pyridine (6.40 mL, 6.29 g, 80 mmol, 1.0 mol equiv). Acetylchloride (6.7 mL, 7.37 g, 93.9 mmol, 1.3 mol equiv) was added dropwise at 0 °C. The reaction

[253] Jensen, A. E.; Knochel, P. *J. Organ-OMet. Chem.* **2002**, *653,* 122.

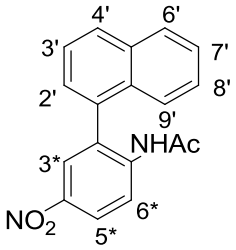
mixture was stirred at 20 °C for 20 min. and was checked by TLC (1 Cy / 1 EtOAc). The reaction was neutralized with 1 M water solution of HCl, water layer was extracted 3 x 100 mL with dichloromethane, the organic layers combined were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification was carried out by flash column chromatography (eluent: 1 Cy/1 EtOAc) to yield *N*-(2-iodo-4-nitro-phenyl)-acetamide **V.83** (19.04 g, 62.1 mmol, 86 %). The analytical data corresponded to the data reported in the literature.[254]

Pale yellow solid; **mp** 138 – 140 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, VM349ap.1210(10)): δ 8.66 (1H, d, *J*(3*,5*) = 2.5 Hz, H-(C3*)), 8.56 (1H, d, *J*(5*,6*) = 9.2 Hz, H-(C6*)), 8.23 (1H, dd, *J*(5*,6*) = 9.2 Hz, *J*(3*,5*) = 2.5 Hz, H-(C5*)), 7.73 (1H, br s, -N*H*), 2.32 (3H, s, -COC*H*$_3$).

LC/MS (ESI): $[M+H]^+$ m/z 307.

<u>*N*-(2-Naphthalen-2-yl-4-nitro-phenyl)-acetamide</u> V.84



$C_{18}H_{14}N_2O_3$
MW: 306,32

To three-necked flask under nitrogen atmosphere was added *N*-(2-iodo-4-nitro-phenyl)-acetamide **V.83** (2.43 g, 7.9 mmol, 1.0 mol equiv), 1-phenylboronic acid (2.05 g, 11.9 mmol, 1.5 mol equiv), $Pd(PPh_3)_4$ (1.38 g, 1.2 mmol, 0.15 mol equiv), K_2CO_3 (3.29 g, 23.8 mmol, 3.0 mol equiv), dimethoxyethane (30 mL), EtOH (20 mL) and water (10 mL). The reaction mixture was stirred at 80 °C for 10 min. After completion of the reaction, the reaction mixture was poured in cold water (40 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtred and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: 3 Cy / 1 EtOAc) on silica gel to afford *N*-(2-Naphthalen-2-yl-4-nitro-phenyl)acetamide **V.84** (2.39 g, 7.7 mmol, 98 %).

[254] Kotha, S.; Shah, V. R. *Eur. J. Org. Chem.* **2008**, 1054.

Pale solid; **mp** 120 - 123 °C.

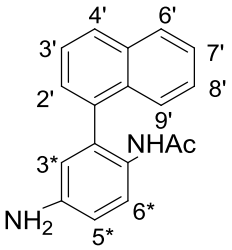
^{1}H-NMR (300 MHz, $CDCl_3$, VM354ap2.1212(10)): δ 8.71 (1H, d, *J*(5*,6*) = 9.2 Hz, H-(C6*)), 8.31 (1H, dd, *J*(5*,6*) = 9.2 Hz, *J*(3*,5*) = 2.7 Hz, H-(C5*)), 8.17 (1H, d, *J*(3*,5*) = 2.7 Hz, H-(C3*)), 8.05-7.98 (2H, m, naphtyl), 7.65-7.41 (5H, m, naphtyl), 7.07 (1H, br s,- N*H*), 1.81 (3H, s, -COC*H*$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM354ap2.1212(20)): δ 168.5 (Cq, -*C*OCH_3), 143.2 (Cq), 141.8 (Cq), 133.9 (Cq), 132.5 (Cq), 131.0 (Cq), 130.0, 129.9 (Cq), 128.9, 128.2, 127.5, 126.9, 126.4, 125.8, 124.7, 124.6, 120.1, 24.8 (-CO*C*H_3).

IR υ (neat): 3346, 1695, 1532, 1497, 1337, 1310, 1285, 1268, 1221, 738 cm^{-1}.

HRMS (ESI+): $[M+Na]^+$ Calcd. *m/z* 329.089; Found *m/z* 329.090.

***N*-(4-Amino-2-naphthalen-2-yl-phenyl)-acetamide V.85**



$C_{18}H_{16}N_2O$
Molecular Weight: 276,33

To a suspension of *N*-(2-naphthalen-2-yl-4-nitro-phenyl)-acetamide **V.84** (2.40 g, 7.8 mmol, 1.0 mol equiv) in a mixture of EtOH (60 mL) and H_2O (3 mL), iron powder (1.30 g, 23.4 mmol, 3.0 mol equiv), and $CaCl_2$ (866 mg, 7.8 mmol, 1.0 mol equiv) were added. The resulting suspension was stirred at 60 °C for 16 h. Progress of the reaction was monitored by TLC (1 Cy / 2 EtOAc). After completion, the reaction mixture was filtered to remove the iron residues, which were washed with EtOAc (2 × 40 mL). The organic extracts were washed with H_2O (3 × 20 mL), brine (2 × 20 mL), and dried over anhydrous $MgSO_4$, the organic phase was evaporated, and the residue directly loaded onto a silica column (eluent: 1 Cy / 2 EtOAc) to yield 1.75 g (6.6 mmol) of compound **V.85** in 85 % yield.

Pale solid; **mp** 135 - 137 °C.

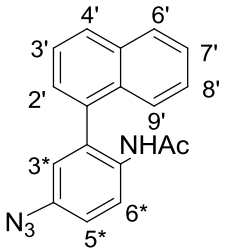
^{1}H-NMR (300 MHz, $CDCl_3$, VM319AP.1149(10)): δ 7.96 (1H, d, *J*(5*,6*) = 8.6 Hz, H-(C6*)), 7.92-7.88 (2H, m, arom.), 7.60-7.37 (5H, m, naphtyl), 6.78 (1H, dd, *J*(5*,6*) = 8.6 Hz, *J*(3*,5*) = 2.6 Hz, H-(C5*)), 6.61 (1H, d, *J*(3*,5*) = 2.6 Hz, H-(C3*)), 6.53 (1H, br s, -N*H*$COCH_3$), 3.61 (2H, br s, -NH_2), 1.67 (3H, s, -CO*CH*$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$, VM319AP.1149(20)): δ 168.2 (Cq, -*C*OCH_3), 143.0 (Cq), 135.8 (Cq), 133.7 (Cq), 132.5 (Cq), 131.5 (Cq), 128.5, 128.4, 127.5, 127.4 (Cq), 126.7, 126.3, 125.8, 125.6, 123.9, 117.4, 115.4, 24.1 (-CO*C*H_3).

IR υ (neat): 3420, 3229, 1659, 1517, 1464, 1438, 1368, 1288,1251, 806, 668 cm $^{-1}$.

HRMS (ESI+): $[M+Na]^+$ Calcd. *m/z* 299.115; Found *m/z* 299.113.

***N*-(4-Azido-2-naphthalen-1-yl-phenyl)acetamide V.86**



$C_{18}H_{14}N_4O$
MW: 302,33

Compound **V.85** (1.7 mg**,** 6.3 mmol, 1.0 mol equiv) was added to 50 mL of cooled glacial acetic acid containing 5 mL of concentrated sulfuric acid. Keeping the reaction mixture below 10 °C, a solution of sodium nitrite (433 mg, 6.3 mmol, 1.0 mol equiv) in a minimum amount of cold water was then added dropwise. After 10 min., a solution of sodium azide (429 mg**,** 6.6 mmol, 1.05 mol equiv) in a minimum amount of cold water was added dropwise. The reaction was allowed to warm to room temperature and diluted with 40 mL of water to deprotect aldehyde. The reaction was extracted with ether and the combined ether layers washed with saturated solution $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 1 Cy / 1 EtOAc) on silica gel to yield **V.86** (1.52 g, 5.0 mmol, 80 %).

Orange solid; **mp** 134 - 137 °C.

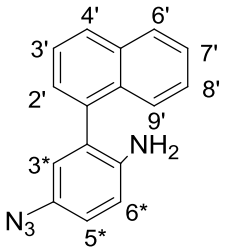
^{1}H-NMR (300 MHz, $CDCl_3$, VM472apma2.1230(12)): δ 8.32 (d, 1H, *J*(5*,6*) = 8.8 Hz, H-(C6*)), 7.95 – 7.90 (2H, m, naphtyl), 7.60-7.40 (5H, m, naphtyl), 7.11 (1H, dd, *J*(5*,6*) = 8.8 Hz, *J*(3*,5*) = 2.6 Hz, H-(C5*)), 6.96 (1H, d, *J*(3*,5*) = 2.6 Hz, H-(C3*)), 6.81 (1H, s, -N*H*), 1.70 (3H, s, -COC*H$_3$*).

^{13}C-NMR (75 MHz, $CDCl_3$, VM472apma2.1230(10)): δ 168.2 (Cq, -*C*OCH_3), 135.7 (Cq), 134.3 (Cq), 133.8 (Cq), 133.0 (Cq), 131.9 (Cq), 131.3 (Cq), 129.3, 128.6, 127.8, 127.1, 125.6, 125.7, 125.3, 122.9, 121.2, 119.2, 24.4 (-CO*C*H_3).

IR υ (neat): 3287, 2098, 1677, 1509, 1417, 1300, 1275, 1249, 804, 778 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}N_4O$ (302.33): C 71.51, H 4.67. Found: C 71.40, H 4.80.

4-Azido-2-naphthalen-1-yl-phenylamine V.87



$C_{16}H_{12}N_4$
MW: 260,29

N-(4-Azido-2-naphthalen-1-yl-phenyl)acetamide **V.86** (3.18 g, 10.4 mmol, 1.0 mol equiv) was treated with 0.5 M water solution of KOH (4.21 g, 10.4 mmol, 7.5 mol equiv) in MeOH (150 mL) at room temperature for 20 min. The reaction was monitored by TLC and purified by quick filtration (eluent: 1 Cy / 1 EtOAc) on short pad of aluminia to yield 2.61 g (9.9 mmol, 95 %) 4-Azido-2-naphthalen-1-yl-phenylamine **V.87**.

Brown oil.

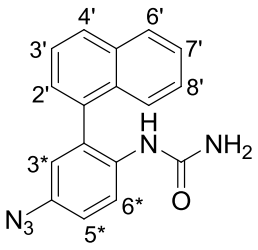
^{1}H-NMR (400 MHz, $CDCl_3$, VM478MA.1310(12)): δ 7.95-7.91 (2H, m), 7.63-7.42 (5H, m, arom.), 6.95 (1H, dd *J*(5*,6*) = 8.5 Hz, *J*(3*,5*) = 2.6 Hz, H-(C5*)), 6.88 (1H, d, *J*(3*,5*) = 2.6 Hz, H-(C3*)), 6.82 (1H, d, *J*(5*,6*) = 8.5 Hz, H-(C6*)), 3.45 (2H, br s, N*H$_2$*).

^{13}C-NMR (100 MHz, $CDCl_3$, VM478MA.1310(10)): δ 141.9 (Cq), 135.9 (Cq), 133.9 (Cq), 131.4 (Cq), 130.0 (Cq), 128.5 (C2' and C9'), 127.6, 127.3 (Cq), 126.6, 126.2, 125.8, 125.7, 121.7 (C3*), 119.6 (C5*), 116.5 (C6*).

IR υ (neat): 3464, 3375, 2102, 1497, 1283, 804, 776 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_4$ (260.29): C 73.83, H 4.65, N 21.52. Found: C 73.60, H 4.60, N 21.51.

(4-Azido-2-naphthalen-1-yl-phenyl)-urea V.41



$C_{17}H_{13}N_5O$
MW: 303,32

To a solution of **V.87** (103 mg, 0.4 mmol, 1.0 mol equiv) in anhydrous DCM (8 mL) was slowly added a solution of trichloroacetyl isocyanate (2.53 g, 13.4 mmol, 1.0 mol equiv) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at room temperature, and then the solvent was removed under reduced pressure. To the residue was added MeOH (8 mL) and K_2CO_3 (5.5 mg, 4 x 10^{-5} mmol, 0.1 mol equiv). The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel (eluent : 1 Cy / 2 EtOAc) to give the desired product **V.41** (84 mg, 0.3 mmol, 70 %).

Yellow solid; **mp** 135 – 136 °C.

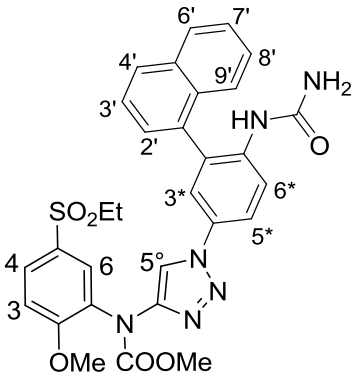
^{1}H-NMR (300 MHz, DMSO-d_6, VM398ap2.1220(10)): δ 8.20 (1H, d, *J*(5*,6*) = 8.9 Hz, H-(C6*)), 8.09-8.06 (2H, m), 7.71-7.65 (1H, m), 7.62-7.57 (1H, m), 7.53 - 7.42 (3H, m, naphtyl), 7.21 (1H, dd, *J*(5*,6*) = 8.9 Hz, *J*(3*,5*) =2.7 Hz, H-(C5*)), 7.08 (1H, br s, -N*H*CONH$_2$), 6.88 (1H, d, *J*(3*,5*) = 2.7 Hz, H-(C3*)), 5.93 (2H, br s, - NHCON*H$_2$*);

^{13}C-NMR (75 MHz, DMSO-d_6, VM398ap2.1220(20)): δ 155.9 (Cq, NH$_2$*C*ONH-), 135.4 (Cq), 134.9 (Cq), 133.4 (Cq), 132.5 (Cq), 131.2 (Cq), 131.1 (Cq), 128.5, 128.4, 127.8, 126.5, 126.0, 125.8, 125.0, 122.7 (C3*), 121.1 (C5*), 118.7 (C6*).

IR υ (neat): 3489, 3343, 3195, 2103, 1667, 1518, 1418, 1342, 779 cm^{-1}.

Anal. Calcd for $C_{17}H_{13}N_5O$ (303.32): C 67.32, H 4.32. Found: C 67.43, H 4.56.

Methyl 5-(ethylsulfonyl)-2-methoxyphenyl(1-(3-(naphthalen-1-yl)-4-ureidophenyl)-1*H*-1,2,3-triazol-4-yl)carbamate VI.11



$C_{30}H_{28}N_6O_6S$
MW: 600,64

Compound **VI.11** was prepared according to the general procedure **A**. Yield: 89 %. Purification: Column chromatography on silica gel (eluent: 95 % DCM/ 5 % MeOH).

Pale foam; **mp** 173 - 175 °C.

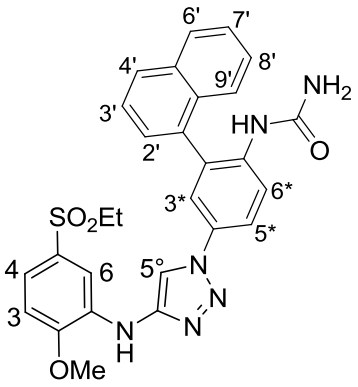
^{1}H-NMR (400 MHz, $CDCl_3$, VM485ap.1308(10)): δ 8.35 (1H, br s, H-C(5°)), 8.31 (1H, d, *J*(5*,6*) = 9.0 Hz, H-(C6*)), 7.89-7.86 (3H, m), 7.81 (1H, d, *J*(4,6) = 1.8 Hz, H-C(6)), 7.75 (1H, dd, *J*(5*,6*) = 9.0 Hz, *J*(3*,5*) =2.5 Hz, H-(C5*)), 7.58 (1H, d, *J*(3*,5*) = 2.5 Hz, H-(C3*)), 7.53-7.40 (5H, m), 7.11 (1H, d, *J*(3,4) = 8.8 Hz, H-C(3)), 6.32 (1H, br s, -N*H*CONH$_2$), 4.52 (2H, br s, -NHCON*H$_2$*), 3.85 (3H, s, -OC*H$_3$*), 3.72 (3H, br s, -COOC*H$_3$*), 3.06 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -SO_2C*H$_2$*CH_3), 1.27 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -SO_2CH_2C*H$_3$*).

^{13}C-NMR (100 MHz, $CDCl_3$, VM485ap.1308(11)): δ 159.8 (Cq), 155.4 (Cq), 153.5 (Cq), 146.9 (Cq), 137.5 (Cq), 134.1 (Cq), 133.8 (Cq), 131.9 (Cq), 131.4 (Cq), 131.0, 130.8 (Cq), 130.5, 130.3 (Cq), 129.2, 128.5, 128.0, 127.2, 126.6, 125.7, 125.2, 122.8, 121.5, 120.5, 112.3, 56.4 (*C*H_3O-), 53.9 (-CO*C*H_3), 51.0 (CH_3*C*H_2), 30.9 (*C*H_3CH_2-). (2 missing)

IR υ (neat): 3463, 3363, 2977, 1698, 1522, 1313, 1132, 1094, 1037, 1132, 1094, 751, 733, 530, 492 cm^{-1}.

Anal. Calcd for $C_{30}H_{28}N_6O_6S$ (600.64): C 59.99, H 4.70, N 13.99. Found: C 59.92, H 4.56, N 13.80.

1-(4-(4-(5-(Ethylsulfonyl)-2-methoxyphenylamino)-1*H*-1,2,3-triazol-1-yl)-2-(naphthalen-1-yl)phenyl)urea III.25



$C_{28}H_{26}N_6O_4S$
MW: 542,61

Compound **III.25** was prepared according to the general procedure **B**. Yield: 80 %. Purification: Column chromatography on silica gel (eluent: 95 % DCM / 5 % MeOH).

Pale foam; **mp** 161 - 163 °C.

^{1}H-NMR (400 MHz, DMSO-d_6, VM511ap.1308(10)): δ 8.36 (1H, d, *J*(5*,6*) = 8.9 Hz, H-(C6*)), 8.30 (1H, br s, H-C(5°) or -N*H*CONH$_2$), 8.19 (1H, br s, H-C(5°) or -N*H*CONH$_2$), 8.06 – 8.02 (3H, m), 7.88 (1H, dd, *J*(5*,6*) = 8.9 Hz, *J*(3*,5*) =2.7 Hz, H-(C5*)), 7.67 – 7.63 (1H, m), 7.62 (1H, d, *J*(3*,5*) = 2.7 Hz, H-(C3*)), 7.56 – 7.53 (1H, m), 7.50 – 7.42 (3H, m), 7.26 (1H, dd, *J*(3,4) = 8.4 Hz, *J*(4,6) = 2.2 Hz, H-C(4)), 7.17 – 7.14 (2H, m), 5.99 (2H, br s, -NHCON*H$_2$*), 3.94 (3H, s, -OC*H$_3$*), 3.12 (2H, q., *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.05 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

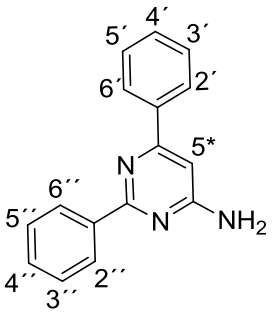
^{13}C-NMR (100 MHz, $CDCl_3$, VM511ap.1308(11)): δ 156.2 (Cq), 150.9 (Cq), 148.2 (Cq), 139.0 (Cq), 135.1 (Cq), 134.1 (Cq), 134.0 (Cq), 131.8 (Cq), 131.1 (Cq), 130.8 (Cq), 130.5 (Cq), 129.2, 128.9, 128.5, 127.2, 126.6, 126.4, 125.5, 122.6, 121.9, 120.2, 119.7, 112.0, 111.9, 110.8, 56.6 (CH_3O-), 50.1 (CH_3CH_2-), 7.8 (CH_3CH_2-).

IR υ (neat): 3368, 2953, 2930, 2854, 1685; 1600, 1576, 1299, 1256, 1114, 1143, 785 cm^{-1}.

Anal. Calcd for $C_{28}H_{26}N_6O_4S$ (542.61): C 61.98, H 4.83, N 15.49. Found: C 61.78, H 4.66, N 15.34.

Preparation of triazole III.26

2,6-diphenylpyrimidin-4-amine V.90



$C_{16}H_{13}N_3$
MW: 247,29

A mixture of the amine **V.89** (5.00 g, 30.5 mmol, 1.0 mol equiv), phenylboronic acid (11.16 g, 91.5 mmol, 3.0 mol equiv), $Pd(PPh_3)_4$ (3.52 g, 3.0 mmol, 0.1 mol equiv), and Na_2CO_3 (16.16 g, 152.4 mmol, 3.0 mol equiv) in 355 mL of a mixture of DME/H20 (3:1) was stirred at 110 °C for 12 h. The resulting mixture was concentrated *in vacuo* and then EtOAc (100 mL) was added. This solution was washed with water and 1M NaOH to remove the boronic acid excess. The organic layer was collected, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent : 2 Cy / 1 EtOAc) to give 7.54 g (28.1 mmol 92 %) of the desired product **V.90**. The analytical data corresponded to the literature.[255]

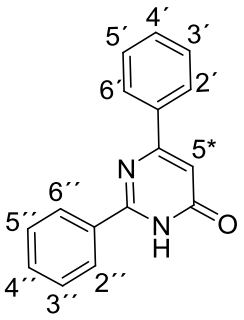
White solid; **mp** 125 - 127 °C.

^{1}H-NMR (300 MHz, DMSO, VM331apf1.1206 (21)): δ 8.07-8.04 (4H, m, arom.), 7.53-7.48 (6H, m, arom.), 7.47 (1H, s, H-C(5*)), 5.25 (2H, s, -NH_2).

LC/MS (ESI): $[M+H]^+$ m/z 248.

[255] Yaziji, V,; Rodriguez, D.; Guierrez-de-Terran, H.; Coehlo, A. ; Caamano, O. ; Garcia-Mera, X. ; Brea, J. ; Loza, M. I. ; Cadavid, M. I. ; Sotelo, E. *J. Med. Chem.* **2011**, *54*, 457.

2,6-diphenylpyrimidin-4(3*H*)-one V.93



$C_{16}H_{12}N_2O$
MW: 248,28

Benzamidine hydrochloride **V.92** (1.25 g, 8.0 mmol, 1.0 mol equiv) was dissolved in a minimal amount of water (5 mL), to this was added sodium hydroxide pellets (320 mg, 8.0 mmol, 1.0 mol equiv) dissolved in water (1mL), followed by ethylbenzoylacetate **V.91** (1.5 mL, 1.61 g, 8.4 mmol, 1.05 mol equiv). Ethanol was then added until a clear solution was obtained. The reaction mixture was then allowed to stir at room temperature overnight yielding a thick suspension, which was then filtered to give a white solid. After washing with diethyl ether to remove unreacted β–ketoester the solid was dried under *vacuo* to give 1.98 g (4.5 mmol, 56 %) of desired product **V.93**. The analytical data corresponded to literature.[256]

White solid; **mp** 290 – 292 °C.

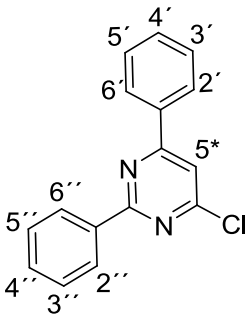
^{1}H-NMR (300 MHz, DMSO-d_6, VM393ap.1217 (12)): δ 8.31-8.18 (5H, m, arom.), 7.60-7.54 (5H, m, arom.), 6.92(1H, s, H-C(5*)), 3.34 (1H, br s, -N*H*).

^{13}C-NMR (75 MHz, DMSO-d_6, VM393ap.1217(10)): δ 165.3 (Cq), 160.7 (Cq), 157.9 (Cq), 136.5 (Cq), 133.5 (Cq), 131.4, 130.4, 128.7 (2xC), 128.6 (2xC), 127.8 (2xC), 126.9 (2xC), 106.4 (C5*).

IR υ (neat): 3064, 2946, 1650, 1539, 1491, 1308, 985, 739, 690, 670 cm^{-1}.**LC/MS (ESI):** $[M+H]^+$ m/z 249.

[256] Chang, L. C. W.; Spanjersberg, R. F.; von Frijtag Drabbe Kunzel, J. K.; van den Hout, T. M. K. G.; Beukers, M. W.; Brussee, J.; IJzerman, A. P. *J. Med. Chem.* **2004**, *47*, 6529.

4-Chloro-2,6-diphenylpyrimidine V.94



$C_{16}H_{11}ClN_2$
MW: 266,72

Phosphorous oxychloride (1.5 mL, 2.50 g, 16.3 mmol, 7.5 mol equiv) was added dropwise to 2,6-diphenylpyrimidin-4(3*H*)-one **V.93** (539 mg, 2.2 mmol, 1.0 mol equiv) in a vigorous reaction. To this mixture was added slowly phosphorous pentachloride (453 mg, 2.2 mmol, 1.0 mol equiv) and the reaction mixture was stirred at reflux for 3 hours. The reaction mixture was then quenched by pouring into ice-water, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and then concentred *in vacuo* to give a yellow solid. The crude product was recrystallised from hot ethanol to give 512 mg (1.9 mmol) **V.94** in 88 % yield. The analytical data corresponded to literature.[256]

White needles; **mp** 103 - 105 °C.

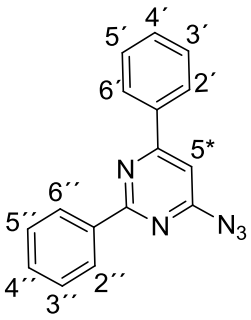
^{1}H-NMR (300 MHz, $CDCl_3$, VM397c.1308(10)): δ 8.59-8.56 (2H, m, H-C(2´´) and H-C(6´´)), 8.21-8.19 (2H, m, H-C(2´) and H-C(6´)), 7.63(1H, s, H-C(5*)), 7.57-7.49 (6H, m).

^{13}C-NMR (75 MHz, $CDCl_3$, VM397c.1218(10)): δ 165.7 (Cq), 165.3 (Cq), 152.3 (Cq), 136.5 (Cq), 135.9 (Cq), 131.5, 131.4, 129.1 (2xC), 128.7 (2xC), 128.6 (2xC), 127.4 (2xC), 114.5 (C(5*)).

IR υ (neat): 3055, 1657, 1556, 1530, 1495, 1376, 1326, 822, 770, 684, 662 cm^{-1}.

LC/MS (ESI): $[M+H]^+$ m/z 267.

4-Azido-2,6-diphenylpyrimidine V.42



$C_{16}H_{11}N_5$
MW: 273,29

To a solution of chloropyrimidine **V.94** (3.48 g, 13.1 mmol, 1.0 mol equiv) in 30 mL dry acetone was added NaN_3 (2.55 g, 39.2 mmol, 3.0 mol equiv), *n*-tetrabutyl ammonium bromide (4.21 g, 13.1 mmol, 1.0 mol equiv) and the mixture was stirred under reflux for 12 hours. After cooling down the reaction mixture, the acetone was evaporated, and to the residue was added water (30 mL) and the mixture extracted with ethyl acetate (3 x 20mL), dried over $MgSO_4$, concentrated *in vacuo.* The crude product was filtered through short silica gel pad (eluent: 9 Cy / 1 EtOAc). The product contained 87 % (11.4 mmol, 3.11 g) of desired azide compound and 13 % of starting material. The separation by column chromatography or crystallisation was not possible in our hands. The azide **V.42** was used in this form in the next step of synthesis.

Grey solid; **mp** 68 – 70 °C.

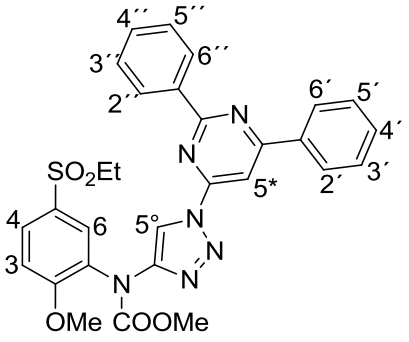
^{1}H-NMR (300 MHz, $CDCl_3$, VM518c.1307(20)): δ 8.62-8.60 (2H, m, H-C(2´´) and H-C(6´´)), 8.20-8.17 (2H, m, H-C(2´) and H-C(6´)), 7.54-7.52 (6H, m, arom.), 7.08 (1H, s, H-C(5*)).

^{13}C-NMR (75 MHz, $CDCl_3$, VM518c.1307(10)): δ 165.8 (Cq), 164.4 (Cq), 163.2 (Cq), 137.1 (Cq), 136.6 (Cq), 131.1, 131.1, 128.9 (2xC), 128.5 (2xC), 128.5 (2xC), 127.3 (2xC), 103.8 (C-5*).

IR υ (neat): 2960, 2926, 2130, 1594, 1569, 1537, 1360, 1234, 747, 690 cm^{-1}.

HRMS (ESI+): $[M+Na]^+$ Calcd. m/z 296.091; Found m/z 296.093.

[1-(2,6-Diphenyl-pyrimidin-4-yl)-*1*H-[1,2,3]triazol-4-yl]-(5-ethanesulfonyl-2-methoxy-phenyl)-carbamic acid methyl ester VI.12



$C_{29}H_{26}N_6O_5S$
MW: 570,62

Compound **VI.12** was prepared according to the general procedure **A**. Yield: 92 %. Purification: Column chromatography on silica gel (eluent: 1 Cy / 1 EtOAc).

Pale yellow foam; **mp** 125 - 126 °C.

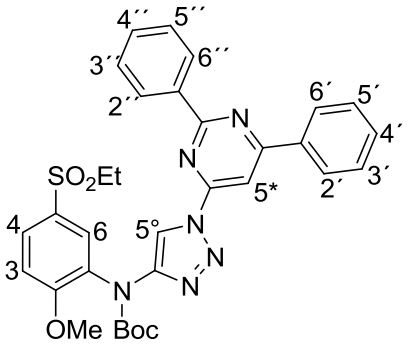
^{1}H-NMR (300 MHz, $CDCl_3$, VM469f2.1229(10)): δ 9.12 (1H, br s, H-(C5°)), 8.67-8.64 (2H, m, H-C(2´´) and H-C(6´´)), 8.36 (1H, s, H-(C5*)), 8.31-8.27 (2H, m, H-C(2´) and H-C(6´)), 7.99-7.94 (2H, m), 7.58-7.54 (6H, m), 7.18 (1H, d, *J*(3,4) = 8.7 Hz, H-C(3)), 3.91 (3H, s, -OC*H$_3$*), 3.15 (3H, br s, -COOC*H$_3$*), 3.15 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.34 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

^{13}C-NMR (100 MHz, $CDCl_3$, VM469f2.1230(10)): δ 167.0 (Cq), 164.9 (Cq), 159.8 (Cq), 156.5 (Cq), 153.6 (Cq), 147.1 (Cq), 136.6 (Cq), 136.3 (Cq), 131.6, 131.6, 131.1, 130.7, 130.5, 129.1 (2xC), 128.7 (2xC), 128.6 (2xC), 127.5 (2xC), 112.3, 102.5, 56.4, 54.0, 51.1, 7.6. (1 missing)

IR υ (neat): 2926, 1729, 1592, 1574, 1549, 1368, 1306, 1275, 1132, 1021, 749, 693 532 cm^{-1}.

Anal. Calcd for $C_{29}H_{26}N_6O_5S$ (570.62): C 61.04, H 4.59, N 14.73. Found: 59.92, H 4.76, N 14.68.

***tert*-Butyl 1-(2,6-diphenylpyrimidin-4-yl)-*1*H-1,2,3-triazol-4-yl(5-(ethylsulfonyl)-2-methoxyphenyl)carbamate VI.16**



$C_{32}H_{32}N_6O_5S$
MW: 612,70

Compound **VI.16** was prepared according to the general procedure **A**. Yield: 94 %. Purification: Column chromatography on silica gel (eluent: 1 Cy /1 EtOAc).

Pale foam; **mp** 114 - 116 °C.

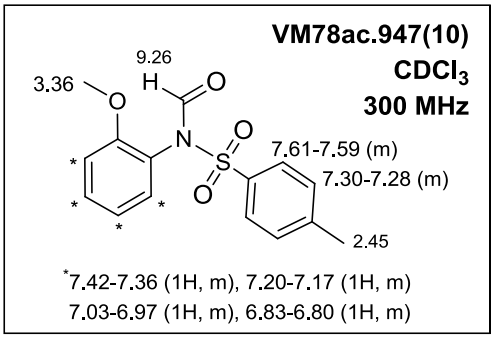
^{1}H-NMR (300 MHz, $CDCl_3$, VM586ap.1308(10)): δ 9.10 (1H, br s, H-C(5°)), 8.68 - 8.66 (2H, m, arom.), 8.37 (1H, s, H-C(5*)), 8.31-8.29 (2H, m, arom.), 7.97-7.92 (2H, m, H-C(4) and H-C(6)), 7.58-7.56 (6H, m), 7.16 (1H, d, *J*(3,4) = 8.6 Hz, H-C(3)), 3.92 (3H, s, -OC*H*$_3$), 3.15 (2H, q, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$), 1.48 (9H, s, -Boc), 1.33 (3H, t, *J*(CH_2CH_3) = 7.4 Hz, -$SO_2CH_2CH_3$).

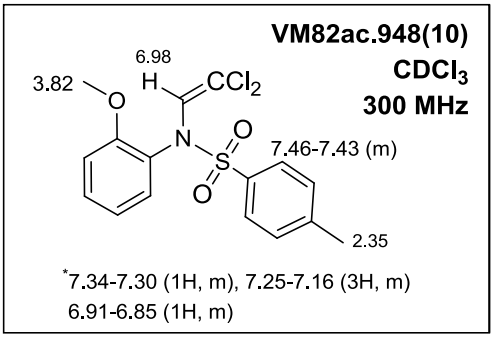
^{13}C-NMR (100 MHz, $CDCl_3$, VM586ap.1308(10)): δ 166.9 (Cq), 164.9 (Cq), 159.7 (Cq), 158.6 (Cq), 151.8 (Cq), 147.3 (Cq), 136.6 (Cq), 136.3 (Cq), 136.6, 136.3 (2xC), 131.6, 131.5 (2xC), 131.0, 130.2, 130.2, 129.1 (2xC), 128.7, 128.7, 127.5, 112.0, 102.6, 83.8 (Cq, -Boc), 56.2 (-O*C*H_3), 51.1 (-$SO_2CH_2CH_3$), 28.1 (3xCH_3, -Boc), 7.7 (-$SO_2CH_2CH_3$). (1 missing)

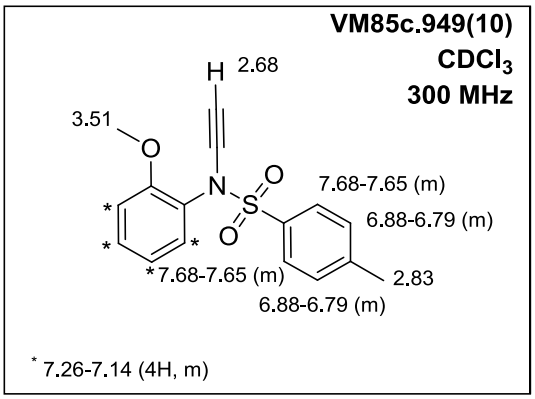
IR υ (neat): 2979, 1722, 1593, 1575, 1550, 1367, 1311, 1277, 1148, 1133, 1021, 750, 732, 693 cm^{-1}.

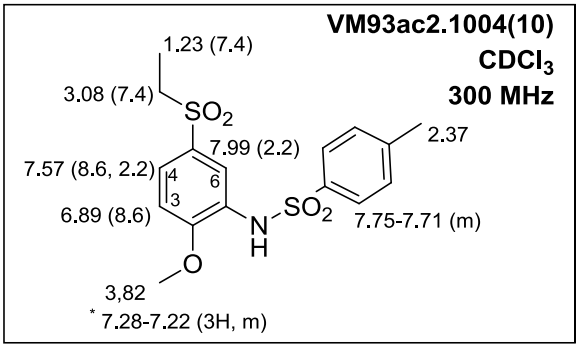
HRMS (ESI+): $[M+H]^+$ Calcd. *m/z* 613.223; Found *m/z* 613.225.

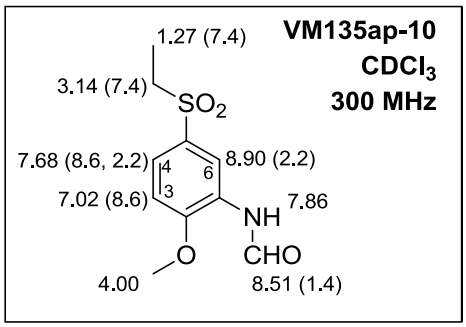
Graphical abstract of ^{1}H NMR

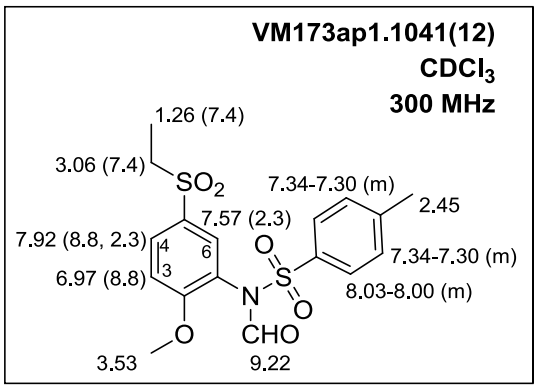

VM78ac.947(10)
CDCl3
300 MHz
9.26
3.36
7.61-7.59 (m)
7.30-7.28 (m)
2.45
*7.42-7.36 (1H, m), 7.20-7.17 (1H, m)
7.03-6.97 (1H, m), 6.83-6.80 (1H, m)

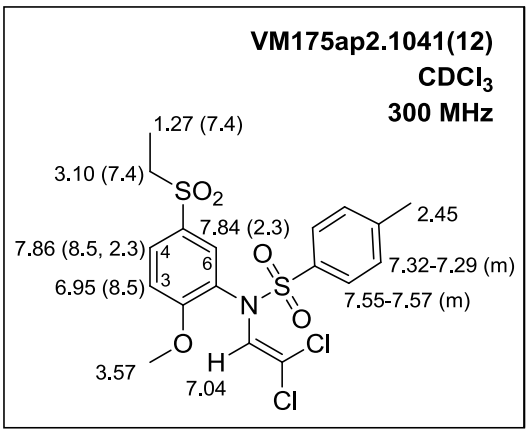

VM82ac.948(10)
CDCl3
300 MHz
6.98
3.82
7.46-7.43 (m)
2.35
*7.34-7.30 (1H, m), 7.25-7.16 (3H, m)
6.91-6.85 (1H, m)

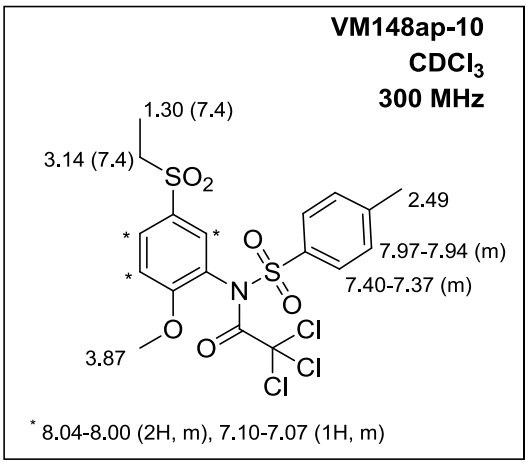

VM85c.949(10)
CDCl3
300 MHz
2.68
3.51
7.68-7.65 (m)
6.88-6.79 (m)
2.83
*7.68-7.65 (m)
6.88-6.79 (m)
* 7.26-7.14 (4H, m)


VM93ac2.1004(10)
CDCl3
300 MHz
1.23 (7.4)
3.08 (7.4)
7.99 (2.2)
2.37
7.57 (8.6, 2.2)
6.89 (8.6)
7.75-7.71 (m)
3,82
* 7.28-7.22 (3H, m)

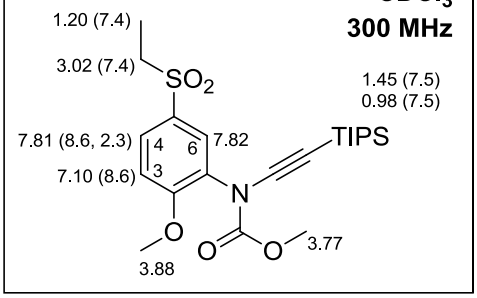

VM135ap-10
CDCl3
300 MHz
1.27 (7.4)
3.14 (7.4)
7.68 (8.6, 2.2)
8.90 (2.2)
7.02 (8.6)
7.86
4.00
8.51 (1.4)


VM173ap1.1041(12)
CDCl3
300 MHz
1.26 (7.4)
3.06 (7.4)
7.34-7.30 (m)
2.45
7.57 (2.3)
7.92 (8.8, 2.3)
7.34-7.30 (m)
6.97 (8.8)
8.03-8.00 (m)
3.53
9.22

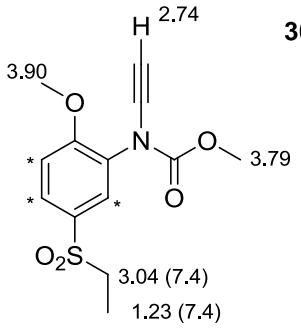

VM175ap2.1041(12)
CDCl3
300 MHz
1.27 (7.4)
3.10 (7.4)
7.84 (2.3)
2.45
7.86 (8.5, 2.3)
7.32-7.29 (m)
6.95 (8.5)
7.55-7.57 (m)
3.57
7.04


VM148ap-10
CDCl3
300 MHz
1.30 (7.4)
3.14 (7.4)
2.49
7.97-7.94 (m)
7.40-7.37 (m)
3.87
* 8.04-8.00 (2H, m), 7.10-7.07 (1H, m)

VM222ap1.1102(10)
$CDCl_3$
300 MHz

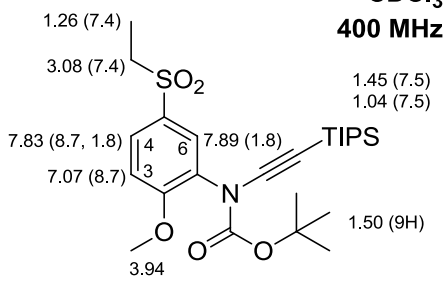


VM227ap1.1102(11)
$CDCl_3$
300 MHz

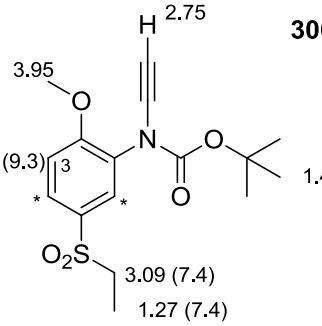


* 7.91-7.88 (2H, m), 7.13-7.10 (1H, m)

VM578f1.1307(10)
$CDCl_3$
400 MHz

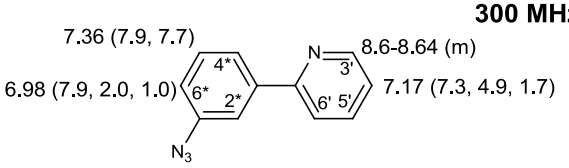


VM580ap.1307(10)
$CDCl_3$
300 MHz



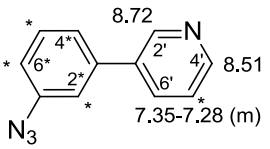
* 7.86-7.83 (2H, m)

VM236ap.1105(12)
$CDCl_3$
300 MHz



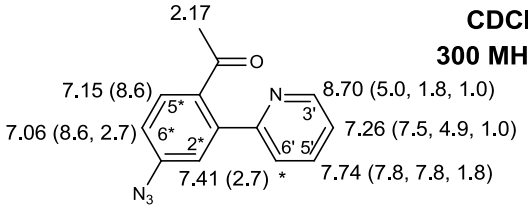
* 7.62-7.61 (4H, m) - C-H(2*), C-H(4*), C-H(5'), C-H(6')

VM282ap.1139(12)
$CDCl_3$
300 MHz



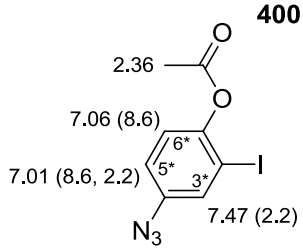
* 7.25-7.15 (2H, m), 7.07-7.04 (1H, m), 6.95-6.91 (1H, m)

VM293F3.1142(10)
$CDCl_3$
300 MHz

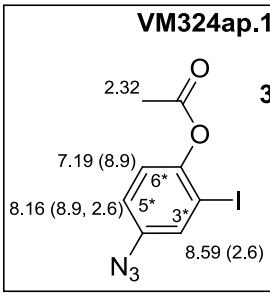


*7-57 - 7.52 (m, C-(H6')

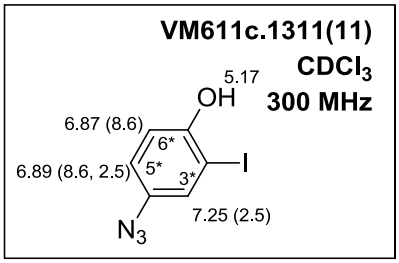
VM566f1.1306(10)
$CDCl_3$
400 MHz



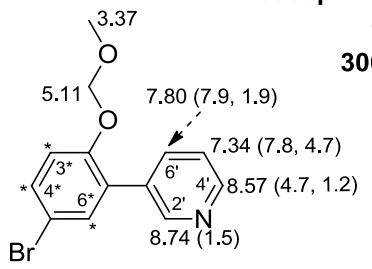
VM324ap.1150(12)
$CDCl_3$
300 MHz



VM611c.1311(11)
$CDCl_3$
300 MHz

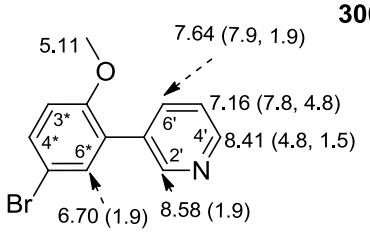


VM500ap.1237(10)
$CDCl_3$
300 MHz



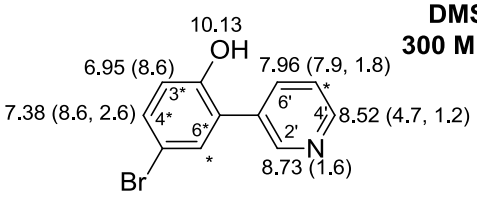
* 7.42-7.40 (2H, m), 7.13-7.11 (1H, m)

VM500ap.1237(10)
$CDCl_3$
300 MHz



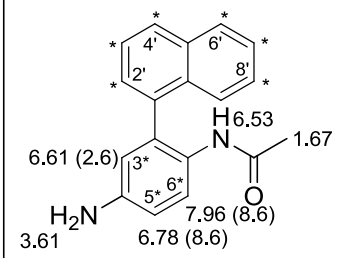
* 7.30-7.25 (2H, m) - C-(H3*), C-(H5*)

VM482ap.1320(12)
DMSO
300 MHz



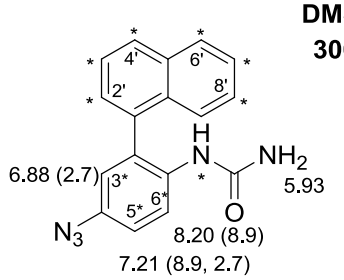
* 7.47-7.42 (2H, m) - C-(H6*) and C-(H5')

VM319AP.1149(10)
$CDCl_3$
300 MHz



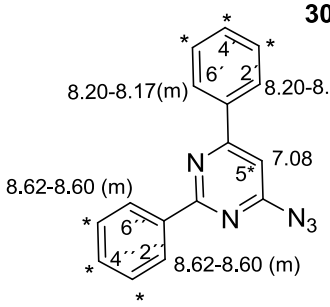
* 7.92-7.88 (2H, m), 7.60-7.37 (5H, m)

VM389ap2.1220(10)
DMSO-d_6
300 MHz



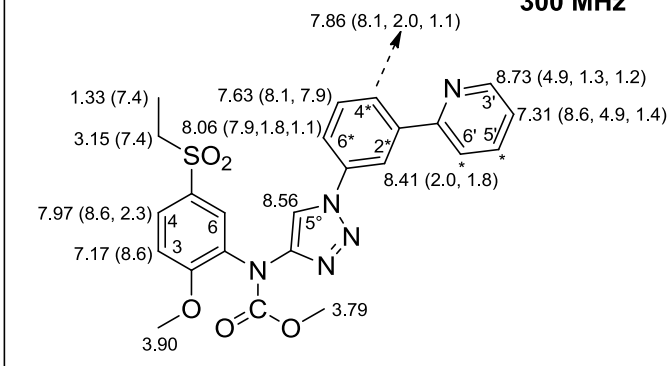
* 8.09-8.06 (2H, m), 7.71-7.65 (1H, m),
7.62-7.57 (1H, m),
7.53-7.42 (3H, m, naphtyl)

VM518c.1307(20)
$CDCl_3$
300 MHz



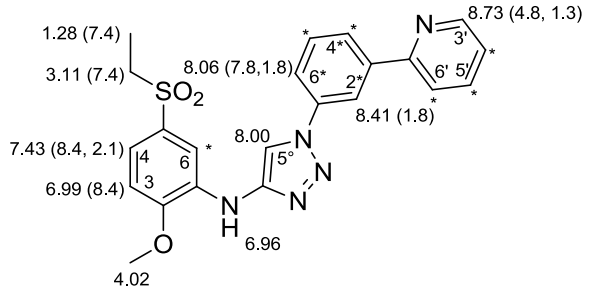
* 7.54-7.52 (6H, m, arom.)

VM-237ap-10
$CDCl_3$
300 MHz

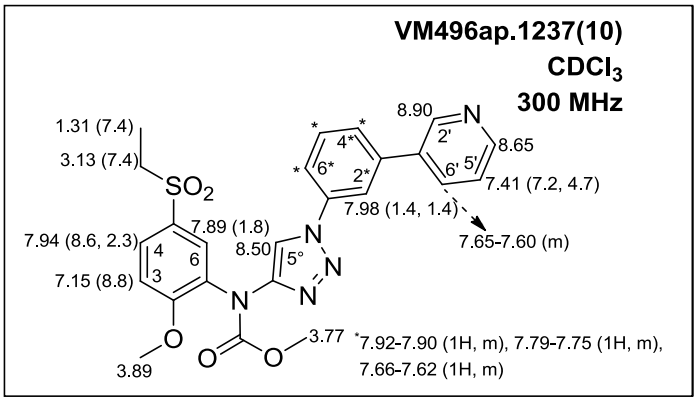


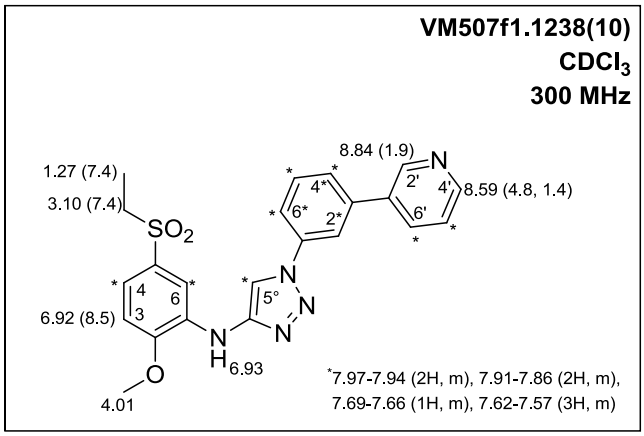
*7.83-7.79 (2H, m) C-H(5'), C-H(6')

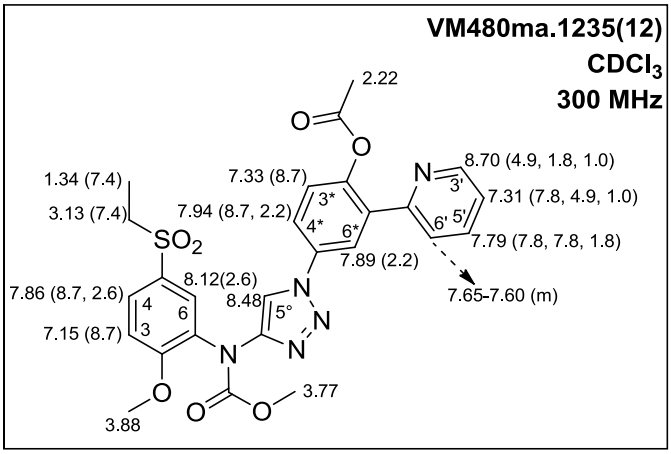
VMT1Y6A-11
$CDCl_3$
300 MHz

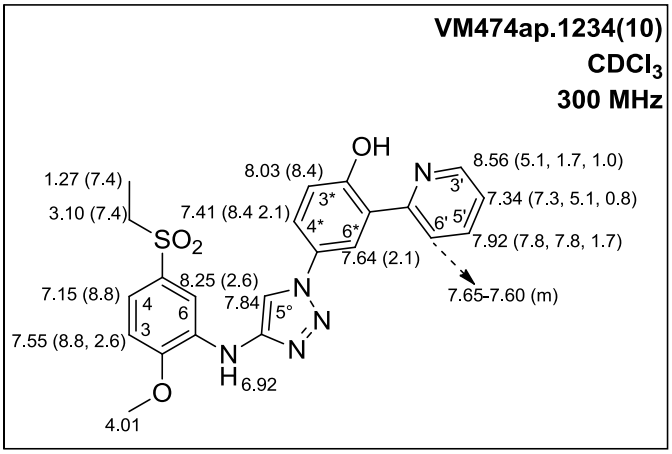


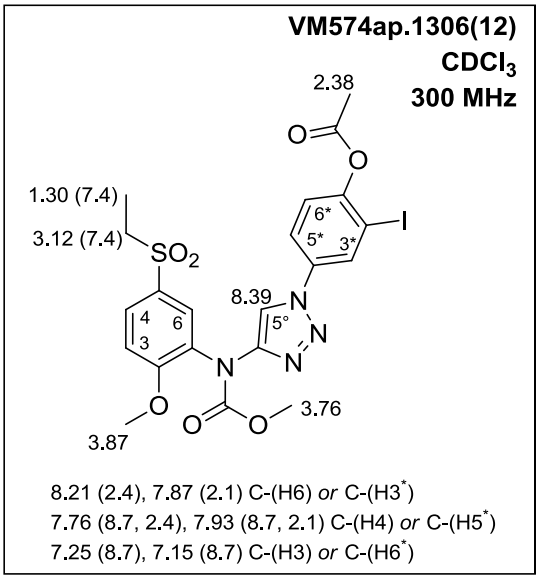
*7.86-7.31 (3H, m), 7.68-7.63 (2H, m), 7.33-7.29 (1H, m)

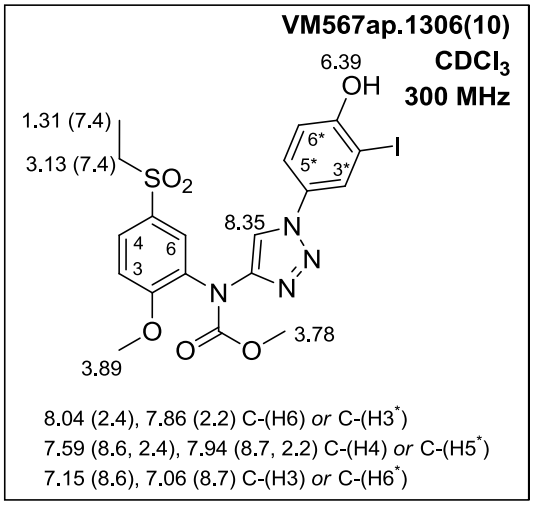

VM496ap.1237(10)
CDCl3
300 MHz
1.31 (7.4)
3.13 (7.4)
SO2
7.94 (8.6, 2.3)
7.89 (1.8)
8.50
7.15 (8.8)
3.89
3.77
8.90
8.65
7.41 (7.2, 4.7)
7.98 (1.4, 1.4)
7.65-7.60 (m)
*7.92-7.90 (1H, m), 7.79-7.75 (1H, m),
7.66-7.62 (1H, m)


VM507f1.1238(10)
CDCl3
300 MHz
1.27 (7.4)
3.10 (7.4)
SO2
6.92 (8.5)
6.93
4.01
8.84 (1.9)
8.59 (4.8, 1.4)
*7.97-7.94 (2H, m), 7.91-7.86 (2H, m),
7.69-7.66 (1H, m), 7.62-7.57 (3H, m)

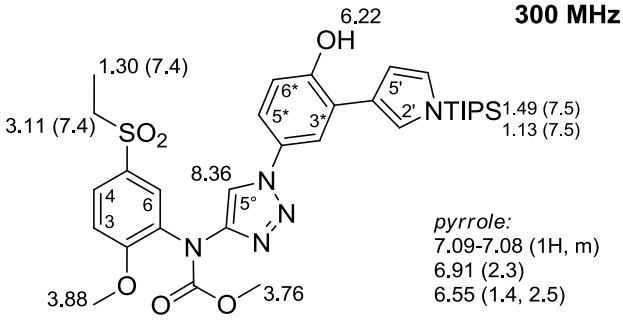

VM480ma.1235(12)
CDCl3
300 MHz
2.22
1.34 (7.4)
3.13 (7.4)
SO2
7.86 (8.7, 2.6)
7.15 (8.7)
3.88
3.77
7.33 (8.7)
7.94 (8.7, 2.2)
7.89 (2.2)
8.70 (4.9, 1.8, 1.0)
7.31 (7.8, 4.9, 1.0)
7.79 (7.8, 7.8, 1.8)
8.12(2.6)
8.48
7.65-7.60 (m)


VM474ap.1234(10)
CDCl3
300 MHz
1.27 (7.4)
3.10 (7.4)
SO2
7.15 (8.8)
7.55 (8.8, 2.6)
6.92
4.01
8.03 (8.4)
OH
7.41 (8.4 2.1)
7.64 (2.1)
8.56 (5.1, 1.7, 1.0)
7.34 (7.3, 5.1, 0.8)
7.92 (7.8, 7.8, 1.7)
8.25 (2.6)
7.84
7.65-7.60 (m)


VM574ap.1306(12)
CDCl3
300 MHz
2.38
1.30 (7.4)
3.12 (7.4)
SO2
3.87
3.76
8.39
8.21 (2.4), 7.87 (2.1) C-(H6) or C-(H3*)
7.76 (8.7, 2.4), 7.93 (8.7, 2.1) C-(H4) or C-(H5*)
7.25 (8.7), 7.15 (8.7) C-(H3) or C-(H6*)

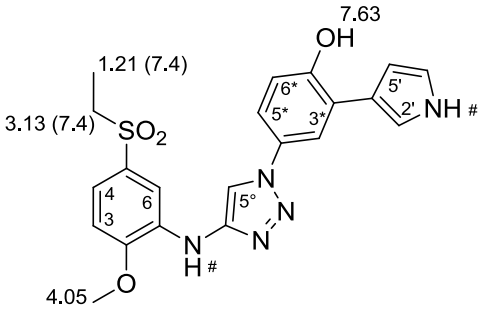

VM567ap.1306(10)
CDCl3
300 MHz
6.39
OH
1.31 (7.4)
3.13 (7.4)
SO2
3.89
3.78
8.35
8.04 (2.4), 7.86 (2.2) C-(H6) or C-(H3*)
7.59 (8.6, 2.4), 7.94 (8.7, 2.2) C-(H4) or C-(H5*)
7.15 (8.6), 7.06 (8.7) C-(H3) or C-(H6*)

VM608ap.1311(10)
$CDCl_3$
300 MHz



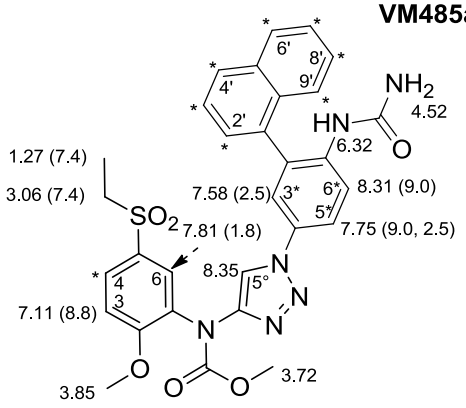
8.86 (NH), 8.22 (NH)
7.88 (2.1), 7.68 (2.6) C-(H6) *or* C-(H3*),
7.92 (8.7, 2.1), 7.44 (8.6, 2.6) C-(H4) *or* C-(H5*)
7.13 (8.7), 7.02 (8.6) C-(H3) *or* C-(H6*)

VM612apacetone.1311(10)
acetone-d_6
400 MHz



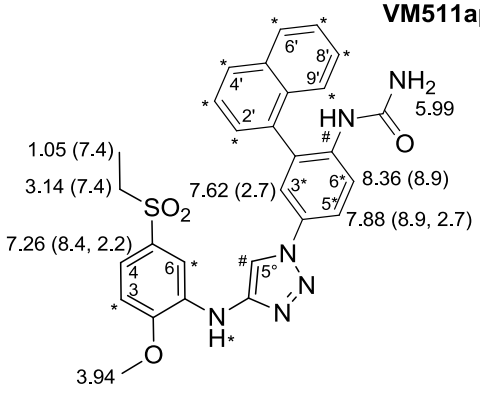
8.86 (NH), 8.22 (NH)
8.30 (2.2), 7.98 (2.7) C-(H6) *or* C-(H3*),
7.36 (8.4, 2.2), 7.45 (8.6, 2.7) C-(H4) *or* C-(H5*)
7.09 (8.6), 7.18 (8.4) C-(H3) *or* C-(H6*)

VM485ap.1308(10)
$CDCl_3$
400 MHz



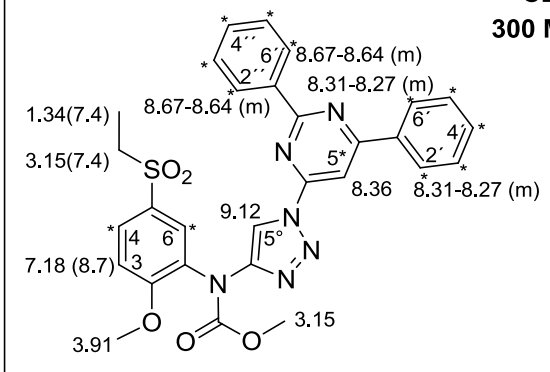
*7.89-7.86 (3H, m), 7.53-7.40 (5H, m)

VM511ap.1308(10)
DMSO-d_6
400 MHz



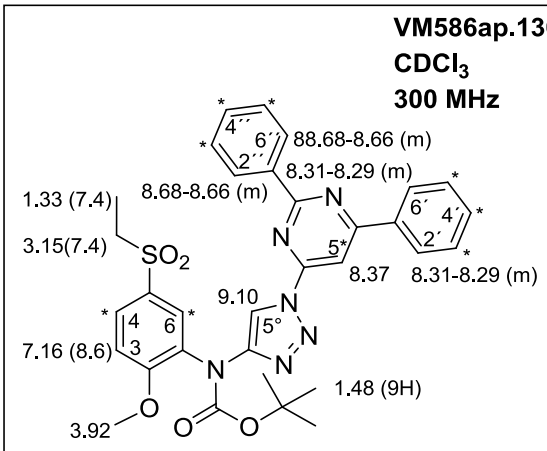
8.30 (1H, br s, H-C(5°) *or* -NHCONH$_2$)
8.19 (1H, br s, H-C(5°) *or* -NHCONH$_2$)
* 8.06-8.02 (3H, m), 7.67-7.63 (1H, m), 7.56-7.53 (1H, m)
7.50-7.42 (3H, m), 7.17-7.14 (2H, m)

VM469f2.1229(10)
$CDCl_3$
300 MHz



* 7.99-7.94 (2H, m); 7.58-7.54 (6H, m)

VM586ap.1308(10)
$CDCl_3$
300 MHz



* 7.97-7.92 (2H, m); 7.58-7.56 (6H, m)