Faculty of Science

Department of Chemistry

Molecular Design & Synthesis

University of Leuven (KU Leuven)

Transition metal-catalyzed cycloisomerizations of propargylic ureas and guanidines derived *in situ* from secondary propargylamines

Promoter

Prof. Dr. Erik Van der Eycken

Doctoral Thesis

Olga P. Pereshivko

April 2013

ISBN 978-90-8649-634-1
D/2013/10.705/49

Members of the jury

Prof. Dr. Wim Dehaen

Prof. Dr. Wim De Borggraeve

Prof. Dr. Dirk De Vos

Prof. Dr. Johan Van der Eycken

Prof. Dr. Wouter Maes

Prof. Dr. Tatjana Parac-Vogt

Prof. Dr. Erik Van der Eycken (Promoter)

Acknowledgment

First of all, I would like to express my deep appreciation to my supervisor, Prof. Dr. Erik V. Van der Eycken, who gave me the great opportunity to join his group even though I had little synthetic experience.

I am grateful to the members of my examination committee Prof. Dr. Wim De Borggraeve, Prof. Dr. Wim Dehaen, Prof. Dr. Dirk De Vos, Prof. Dr. Johan Van der Eycken, Prof. Dr. Tatjana Parac-Vogt, Prof. Dr. Wouter Maes for important comments and suggestions while evaluating my thesis.

I would like to thank Mr. Karel Duerinckx and Ing. Bert Demarsin for their friendly cooperation in the preparation of NMR spectra and High Resolution Mass Spectra (HRMS). Thanks are also given to Prof. Dr. Kristof Van Hecke, Jeroen Jacobs and Prof. Dr. Luc Van Meervelt for carrying out the X-ray crystallographic analysis.

I owe particular thanks to my husband, Vsevolod Peshkov, for his kind assistance and permanent collaboration all over these years.

I would like to acknowledge Dr. Denis Ermolat'ev who provided to me the possibility to work on the 2-aminoimidazole project.

Also I want to thank Anatoly Peshkov and Sofie Van Hove who helped me with experimental work.

During my time at KU Leuven I have had the privilege of working closely with many people. Thank you all for making a great working environment and readily lending a hand if needed.

And at last but not least I would like to thank my family and friends for their love, support, and encouragement.

Summary

This thesis is devoted to the exploration of synthetic strategies for the generation of secondary *N*-alkylpropargylamines, as well as to the study of their synthetic utility for the construction of small heterocycles. A substantial part of this work deals with additions of secondary propargylamines to various heteroallennes, followed by transition metal-catalyzed cycloisomerizations. Also special attention is given to the regio- and chemoselectivity of these processes in the context of existing methodologies. The elaborated protocols rely on modern transition metal catalysis and utilize readily available starting materials.

Chapter 1 serves as an introduction to the chemistry of propargylamines in general, and secondary *N*-alkylpropargylamines in particular, highlighting the A^3-coupling reaction as a modern method for their synthesis. Several processes which are relevant to the present study and which utilize secondary *N*-alkylpropargylamines as starting materials, are also briefly outlined. The objectives of the current research are summarized in this chapter.

Chapter 2 is dedicated to the elaboration of microwave-assisted Cu(I)-catalyzed coupling of a ketone, an alkyne and a primary amine (KA^2-coupling), providing a general access to quaternary carbon-containing secondary *N*-alkylpropargylamines.

Chapter 3 describes the application of the above propargylamines in the Ag(I)-mediated tandem guanylation/cycloisomerization reaction previously developed in our group, in order to access a structurally interesting class of heterocycles featuring a spiro-cyclic guanidine unit.

Chapter 4 deals with a comparative study on transition metal-catalyzed cycloisomerizations of propargylic ureas derived *in situ* from secondary propargylamines and tosyl isocyanate. The influence of the catalytic system on the reaction outcome was thoroughly studied with two model examples, resulting in the establishment of two selective protocols for both *O*- and *N*-cyclizations, leading to oxazolidin-2-imines and imidazolidin-2-ones, respectively. An attempt to rationalize the observed chemoselectivity is given.

Chapter 5 is dedicated to the unexpected regio- and chemoselectivity of cationic gold-catalyzed cycloisomerizations of propargylic ureas derived *in situ* from secondary propargylamines and aryl or alkyl isocyanates, providing an efficient access to the 3,4-dihydropyrimidin-2(1*H*)-one core.

Finally, **General conclusions and perspectives** are highlighted.

Samenvatting

In deze doctoraatsthesis worden strategieën ontwikkeld voor de synthese van secundaire *N*-alkylpropargylamines. Hun toepassing voor de synthese van kleine heterocyclische verbindingen wordt geëvalueerd. Een groot deel van dit werk omvat de studie van de additie van secundaire propargylamines aan verschillende types van heteroallenen, en de daaropvolgende cycloisomerisaties. Speciale aandacht gaat naar de regio- en chemoselectiviteit van deze processen, dit in het licht van bestaande methodologieën. De op punt gestelde procedures maken gebruik van moderne transitiemetaalkatalyse, uitgaande van gemakkelijk toegankelijke startverbindingen.

Hoofdstuk 1 geeft een inleiding in de chemie van propargylamines in het algemeen, en van secundaire *N*-alkylpropargylamines in het bijzonder. De A^3-koppelingsreactie, als voorbeeld van een moderne synthesemethode voor dergelijke verbindingen, wordt beschreven. Er wordt tevens aandacht besteed aan verschillende processen die relevant zijn voor deze studie en die gebruik maken van secundaire *N*-alkylpropargylamines als uitgangsproducten. De objectieven van dit doctoraatsonderzoek worden in dit hoofdstuk opgelijst.

Hoofdstuk 2 beschrijft de ontwikkeling van een microgolf-geassisteerde Cu(I)-gekatalyseerde koppeling van een keton, een alkyn en een primair amine (KA^2-koppeling). Deze geeft toegang tot secundaire N-alkylpropargylamines welke een quaternair koolstofatoom bevatten.

Hoofdstuk 3 beschrijft de toepassing van de gesynthetiseerde propargylamines in de Ag(I)-gekatalyseerde tandem guanilering /

cycloïsomerisatiereactie, welke in onze groep ontwikkeld werd. Een structureel interessante klasse van heterocyclische verbindingen welke een spiro-cyclisch guanidine bevatten, kan op deze manier gesynthetiseerd worden.

Hoofdstuk 4 beschrijft een vergelijkende studie van transitiemetaalgekatalyseerde cycloïsomerisaties van propargyl urea, welke *in situ* afgeleid zijn van secundaire propargylamines en tosylisocyanaat. In twee modelvoorbeelden wordt de invloed van het katalytisch systeem op de reactie onderzocht. Dit leverde twee selectieve procedures op voor de synthese van oxazolidin-2-imines en imidazolidin-2-onen via respectievelijk O- en N- cyclisaties. Er wordt een voorstel gedaan om de waargenomen chemoselectiviteit te verklaren.

Hoofdstuk 5 is gew ijd aan de onverwachte regio- en chemoselectiviteit van kationisch goud-gekatalyseerde cycloïsomerisaties van propargyl urea, welke *in situ* gevormd werden uit secundaire propargylamines en aryl- of alkylisocyanaten. Een efficiënte toegang tot 3,4-dihydropyrimidin-2(1*H*)-onen wordt bekomen.

Algemene conclusies en perspectieven.

List of abbreviations

Boc	*tert*-butyloxycarbonyl
Cbz	carboxybenzyl
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMBA	1,3-dimethylbarbituric acid
DMF	*N*,*N*-dimethylformamide
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
HRMS	high-resolution mass spectra
MSDS	material safety data sheet
MW	microwave or microwave irradiation
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
rt	room temperature
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl

Table of Contents

Reproduced in part with permission from

[A walk around the A^3-coupling, Vsevolod A. Peshkov, Olga P. Pereshivko, and Erik V. Van der Eycken, *Chemical Society Reviews*, **2012**, *41*, 3790–3807] Copyright © 2012, The Royal Society of Chemistry.

[Tetrasubstituted 2-Imidazolones *via* Ag(I)-Catalyzed Cycloisomerization of Propargylic Ureas, Vsevolod A. Peshkov, Olga P. Pereshivko, Sweta Sharma, Thirumal Meganathan, Virinder S. Parmar, Denis S. Ermolat'ev, and Erik V. Van der Eycken, *Journal of Organic Chemistry*, **2011**, *76*, 5867–5872] Copyright © 2011, American Chemical Society.

[Unprecedented Cu(I)-Catalyzed Microwave-Assisted Three-Component Coupling of a Ketone, an Alkyne, and a Primary Amine, Olga P. Pereshivko, Vsevolod A. Peshkov, and Erik V. Van der Eycken, *Organic Letters*, **2010**, *12*, 2638–2641] Copyright © 2010, American Chemical Society.

[Diversity-Oriented Silver(I)-Mediated Synthesis of Spiro-2-aminoimidazoles, Olga P. Pereshivko, Vsevolod A. Peshkov, Denis S. Ermolat'ev, Sofie Van Hove, Kristof Van Hecke, Luc Van Meervelt, and Erik V. Van der Eycken, *Synthesis*, **2011**, 1587–1594] Copyright © 2011, Georg Thieme Verlag Stuttgart · New York

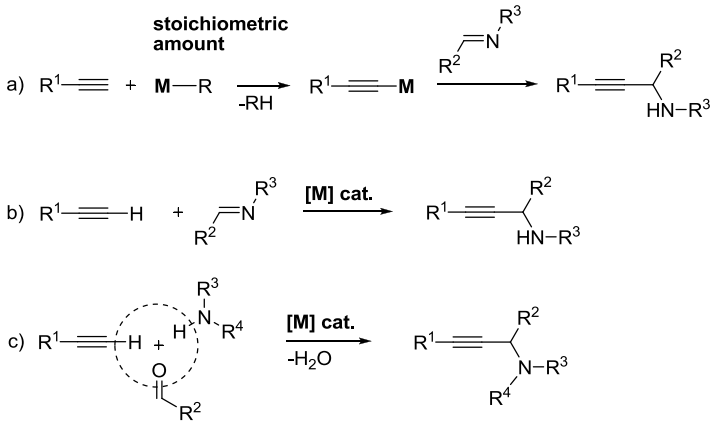
[Cationic Gold- and Silver-Catalyzed Cycloisomerizations of Propargylic Ureas: a Selective Entry to Oxazolidin-2-imines and Imidazolidin-2-ones, Olga P. Pereshivko, Vsevolod A. Peshkov, Jeroen Jacobs, Luc Van Meervelt, and Erik V. Van der Eycken, *Advanced Synthesis & Catalysis*, **2013**, *355*, 781–789] Copyright © 2013, John Wiley and Sons.

Chapter 1

1. Introduction and objectives of the work

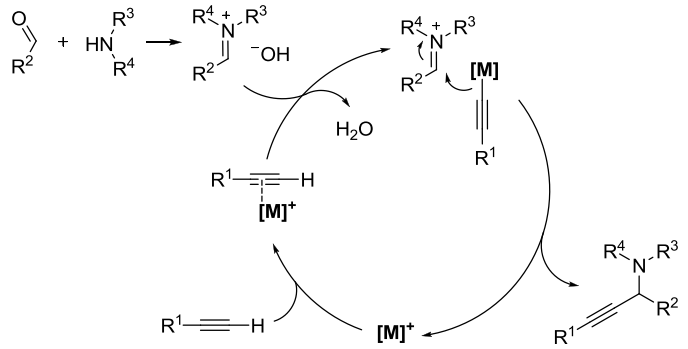
1.1. From A^3-coupling to KA^2-coupling

Recently, propargylamines have received considerable attention as convenient starting materials and widely found intermediates for the construction of various heterocyclic frameworks, biologically active compounds and natural products. The classical method for the synthesis of propargylamines is the addition of a metal acetylide to an imine exploiting the relatively high acidity of a terminal alkyne applying strong bases such as butyllithium to form metal acetylides (Scheme 1, eq a).[1] The stoichiometric quantities of the organometallic reagent as well as its high moisture sensitivity designate such processes as fairly unattractive. Therefore a more convenient and atom economic transition-metal catalyzed addition of a terminal alkyne to an imine or enamine has been developed (Scheme 1, eq b).[2] The idea to form the imine or iminium ion *in situ* from an aldehyde and an amine led to the discovery of straightforward transition-metal catalyzed three-component coupling of an aldehyde, an alkyne and an amine commonly referred to as A^3-coupling (Scheme 1, eq c).[3]



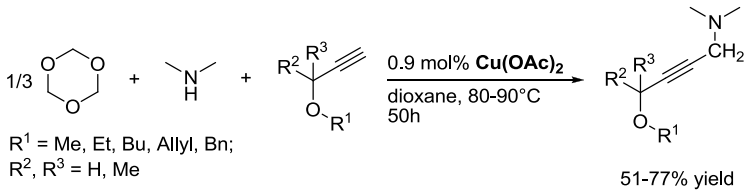
Scheme 1 Various procedures for the synthesis of propargylamines

A tentative mechanism for the A^3-coupling involves C-H activation of the alkyne by the metal catalyst. The metal acetylide formation, a common step for Sonogashira and A^3-coupling, is still poorly understood. Weak bases present in the reaction media (starting amine, final propargylamine *etc.*) are not able to deprotonate the terminal alkyne directly. Therefore, an intermediate π-metal-alkyne complex might be formed first making the alkyne proton more acidic for further abstraction. The *in situ* generated metal acetylide reacts with the imine or iminium ion, resulting in the formation of a propargylamine with concomitant regeneration of the metal catalyst (Scheme 2).



Scheme 2 Tentative mechanism of the A^3-coupling

The simplest example of such a process, the copper-catalyzed Mannich reaction of a terminal alkyne, a secondary amine and formaldehyde (trioxane) has been established as early as in the middle of the 20th century.[4] Particularly, one of the first described examples deals with the preparation of propargylic amino ethers (Scheme 3).[4a]

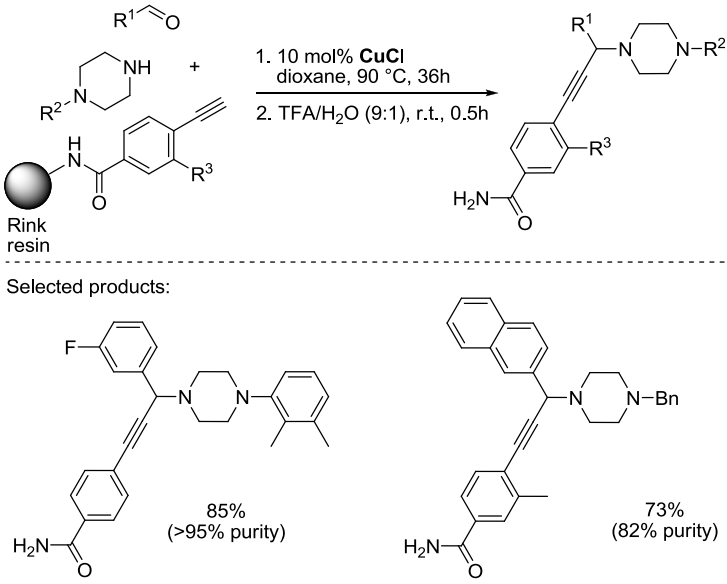


Scheme 3 $Cu(OAc)_2$-catalyzed Mannich reaction leading to propargylic amino ethers

Despite the considerable interest to this process the first true A^3-coupling protocols also allowing the variation of an aldehyde component have appeared only recently. During the last two decades, substantial progress has been made and the A^3-coupling promptly became one of the most widely used tools for the synthesis of various propargylamines. Furthermore, several

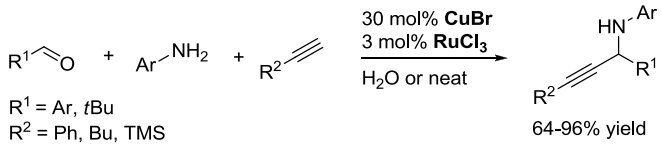
impressive A^3-coupling-based tandem and one-pot approaches were developed for the fast assembly of a wide range of small heterocycles with no need for the isolation of intermediate propargylamines.[5]

In 1998 Dax and co-workers reported the solid-phase synthesis of propargylamines via a three-component coupling of an aldehyde, an alkyne, and a secondary amine promoted by 2 equiv of CuCl where either amine or aldehyde component could be attached to the resin.[6] While this is an interesting example of solid-phase methodology it does not completely meet the criteria of the A^3-coupling process as it utilizes a stoichiometric amount of CuCl. Nevertheless, later, in the same year Dyadkin and Rivero described a complementary protocol employing polymer-supported aryl alkynes and variously substituted aldehydes and secondary amines to form propargylamines in the presence of a catalytic amount (10 mol %) of CuCl (Scheme 4).[7] To the best of our knowledge, this protocol represents the first example of an A^3-coupling in general and its solid-phase modification in particular.



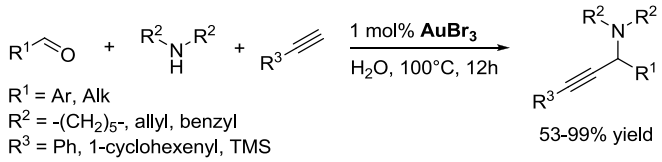
Scheme 4 A^3-coupling with polymer-supported aryl alkynes

A great number of further pioneering contributions has been made by the group of Li that also introduced the term "A^3-coupling". In 2002, Li and Wei reported the application of a CuBr-$RuCl_3$ catalytic system in water and under solvent-free conditions for the synthesis of N-arylpropargylamines *via* A^3-coupling.[8] Interestingly, the authors reported that several copper salts such as CuCl, $CuCl_2$, CuBr, CuI *etc.* all showed catalytic activity even in the absence of a co-catalyst, but the addition of $RuCl_3$ (3 mol%) dramatically increased the yield of the desired propargylamine from 30% to 90% (Scheme 5). While both aromatic and aliphatic alkynes were effective for the reaction, the scope of this procedure was limited to the use of anilines and aromatic or aliphatic aldehydes without α-hydrogen.



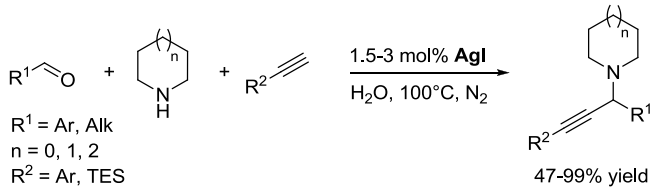
Scheme 5 CuBr-$RuCl_3$-co-catalyzed A^3-coupling for the synthesis of N-arylpropargylamines

Subsequently, in 2003, the same authors described a gold-catalyzed A^3-coupling procedure for the synthesis of tertiary propargylamines from aldehydes, secondary amines and alkynes.[9] Both Au(I) and Au(III) salts were demonstrated to be efficient catalysts in this process with a generally low loading (1 mol%). Surprisingly, the use of water as a solvent afforded the best results, while employment of common organic solvents, such as toluene, THF or DMF, resulted in lower conversion and byproduct formation. A number of substrates, including both aromatic and aliphatic alkynes and aldehydes, were successfully applied under optimal conditions (1 mol% of $AuBr_3$) delivering the corresponding propargylamines with yields ranging from 53 to 99% (Scheme 6). Aromatic aldehydes usually react better than aliphatic ones; the authors ascribed this to the competitive trimerization of aliphatic aldehydes. The methodology was also limited to the use of secondary dialkylamines.



Scheme 6 $AuBr_3$-catalyzed A^3-coupling for the synthesis of tertiary propargylamines

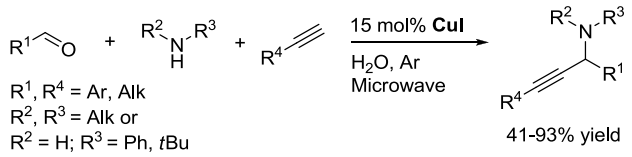
In an effort to achieve better yields for the reaction with aliphatic aldehydes, Li and co-workers found that the above described A^3-coupling process could be efficiently performed employing several Ag(I) salts as the catalyst.[10] Remarkably, a reversal of the reactivity of aliphatic and aromatic aldehydes was observed compared to the earlier Au(III)-catalyzed procedure. Typically the reactions were performed in water with 1.5 mol% of AgI (3 mol% for aromatic aldehydes) but organic solvents such as toluene and DMF were also found suitable. The success of this procedure was largely restricted to the use of cyclic secondary amines (Scheme 7).



Scheme 7 AgI-catalyzed A^3-coupling

Although the protocols reported by Li collectively provide a direct and environmentally friendly access to a wide range of propargylamines, all of them possess several substrate scope limitations and generally require considerably long reaction times. This problem was identified by Tu and co-workers. In 2004, they reported a fast and universal microwave-assisted CuI-catalyzed A^3-coupling procedure.[11] The reactions were carried out in water with 15 mol% of CuI; both aromatic and aliphatic aldehydes and alkynes as well as secondary amines, aniline and *tert*-butyl amine were successfully employed (Scheme 8). The beneficial role of microwave irradiation was discussed. Subsequently, Varma and co-workers described a microwave-assisted CuBr-catalyzed solvent-free A^3-coupling procedure limited however, to the use of

secondary amines.[12] It is worth noting that these protocols operate with unmodified domestic microwave ovens.



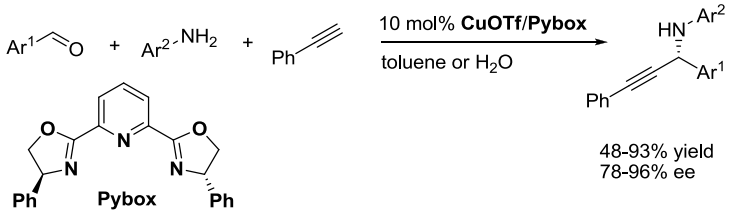
Scheme 8 Universal microwave-assisted CuI-catalyzed A^3-coupling protocol

A profound and systematic study of the A^3-coupling under microwave irradiation using a dedicated microwave apparatus (CEM Discover) was performed by Leadbeater and co-workers.[13] The reactions were carried out with 10 mol% of CuCl in dioxane doped with an ionic liquid. Several useful practical recommendations concerning the use of different substrates under microwave irradiation were pointed out.

The application of microwave-assisted continuous-flow organic synthesis (MACOS) in the A^3-coupling process catalyzed by gold and copper thin films provides a possibility to attain large quantities of propargylamines as was described by Organ, Li and co-workers.[14]

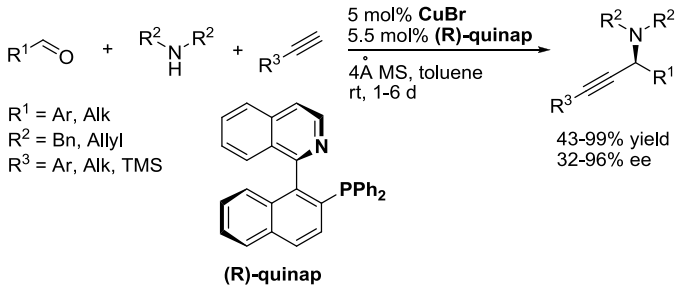
The first enantioselective version of an A^3-coupling was described in 2002 by Wei and Li.[15] Several chiral bis(oxazolinyl) ligands in combination with CuOTf were examined and the highest enantiomeric excess was obtained with the tridentate bis(oxazolinyl)pyridine (pybox) ligand. Under optimal conditions, a variety of aromatic imines (preformed *in situ* from the appropriate aromatic aldehydes and anilines) were coupled with phenyl acetylene furnishing the corresponding propargylamines in up to 93% yield and 96% ee (Scheme 9). Both toluene and water were successfully used as solvents although reactions in toluene provided slightly higher yields and enantioselectivities. Later the scope of this protocol was extended to the use

of various aliphatic alkynes. However the enantiomeric excesses of the corresponding propargylamines did not exceed 85%.[16]



Scheme 9 CuOTf/pybox-catalyzed AA^3-coupling

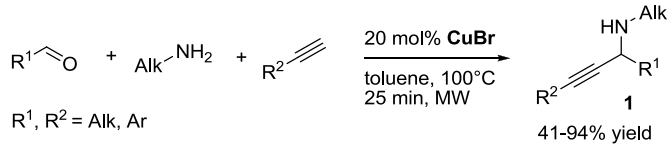
In 2002, Knochel and co-workers described the application of the chiral bidentate P,N-ligand Quinap in an enantioselective synthesis of propargylamines via CuBr-catalyzed addition of alkynes to enamines (derived from secondary amines and aliphatic aldehydes or ketones).[17] Subsequently the use of this ligand was extended to the related three-component CuBr/Quinap-catalyzed assymetric A^3-coupling protocol.[18] Secondary amines (generally dibenzyl or diallylamine), aromatic and aliphatic aldehydes and alkynes were successfully utilized providing enantiomerically enriched tertiary propargylamines in good to high yields and enantioselectivities (Scheme 10). The highest enantioselectivities were typically obtained with trimethylsilylacetylene.



Scheme 10 CuBr/Quinap-catalyzed AA^3-coupling

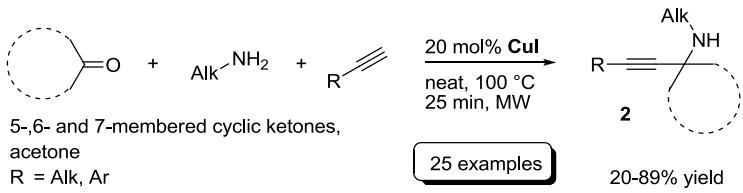
In total, a great number of transition-metal catalysts were exploited that activate the C-H bond of the terminal alkyne in the A^3-coupling process. The Cu(I)/Cu(II), Ag(I), Au(I)/Au(III) salts remain the most extensively applied and studied. Furthermore the ability to catalyze the A^3-coupling was also demonstrated for Fe(III),[19] In(III),[20] Zn(II),[21] Ni(II)[22] and Hg(I).[23]

It is important to stress that despite great advancements, the A^3-coupling process was mainly optimized with anilines and secondary amines, for the synthesis of secondary N-arylpropargylamines and tertiary propargylamines respectively. Primary amines were considered to be difficult substrates thus limiting the access to synthetically useful[24] secondary N-alkylpropargylamines **1**. Very recently, a microwave-assisted Cu(I)-catalyzed A^3-coupling procedure optimized specifically for the use of primary aliphatic amines has been developed in our laboratory (Scheme 11).[25] This method now represents a general approach towards secondary N-alkylpropargylamines **1**.



Scheme 11 Microwave-assisted CuBr-catalyzed A^3-coupling for the synthesis of secondary N-alkylpropargylamines

The first attempt to incorporate a ketone in the A^3-coupling process was performed by Ramon and co-workers using impregnated copper on magnetite as the catalyst.[26] While this catalyst showed excellent results with aldehydes delivering propargylamines in up to 99% isolated yield, the application of 3-pentanone and acetophenone was somewhat problematic. The yields for the ketone-derived propargylamines were significantly lower (38% and 29%, respectively) with the reaction times being longer. ***Therefore our goal was to find suitable conditions which should allow the A^3-coupling-type reaction to be efficiently performed with ketones instead of aldehydes.***[27] A resulting microwave-assisted Cu(I)-catalyzed coupling of a ketone, an alkyne and a primary amine (KA^2-coupling) providing a general access to quaternary carbon-containing secondary propargylamines **2** in up to 89% yield is disclosed in ***Chapter 2***. The reactions worked notably well when 6-membered (hetero)cyclic ketones were used (Scheme 12).



Scheme 12 CuI-catalyzed coupling of a ketone, an alkyne, and a primary amine (KA^2-coupling)

Subsequently the scope of the KA^2-coupling was expanded by Ji and co-workers to the use of secondary amines under mild gold(III)-catalysis.[28] Furthermore Larsen and co-workers have described a Cu(II)/Ti(IV) catalytic system which was specifically developed for the application of inactive acyclic ketones.[29]

1.2. Reactions of secondary propargylamines with heteroallenes and subsequent cycloisomerizations

As it was already mentioned, propargylamines in general and secondary propargylamines in particular possess an exceptional synthetic utility due to the presence of several reactive centers (Figure 1).

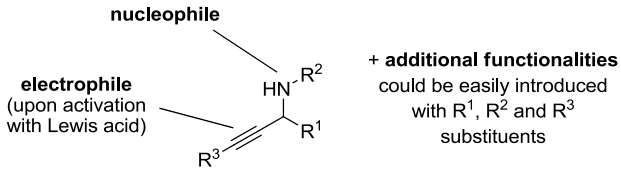
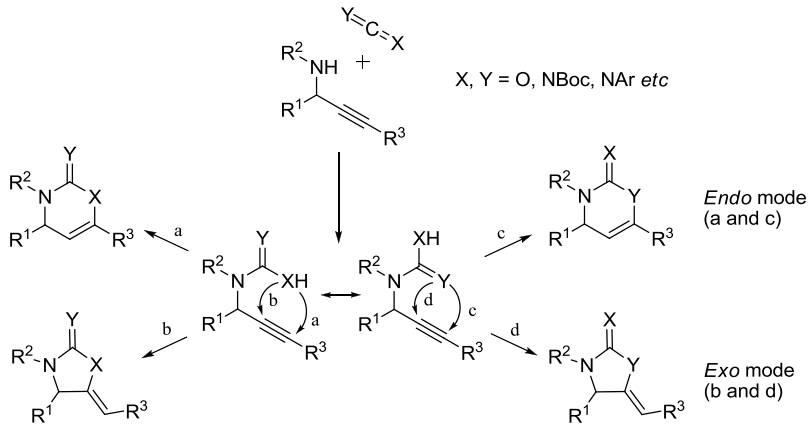


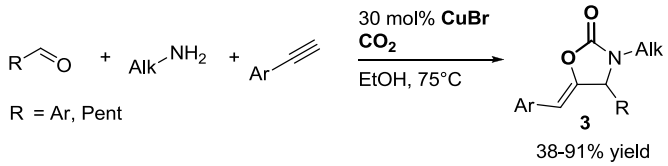
Figure 1 Reactive centers in the secondary (A^3-coupling derived) propargylamines

Additions of secondary propargylamines to various heteroallenes and subsequent transition metal-catalyzed cycloisomerizations are of particular interest. Depending on the nature of the heteroallene reactant and employed transition metal catalyst different chemo- and regioselectivities could be achieved allowing the directed synthesis of a number of important small heterocycles.



Scheme 13 Application of secondary propargylamines in the construction of small heterocycles *via* reactions with heteroallenes and subsequent cycloisomerizations

In 2008, Li and co-workers reported an efficient Cu(I)-catalyzed four-component, tandem A^3-coupling/carboxylative cyclization process in which CO_2 serves as both promoter and reagent for the facile synthesis of oxazolidinones **3**.[30] The couplings were successfully accomplished with 30 mol% of the Cu(I)-catalyst in ethanol at 75°C under atmospheric pressure of CO_2 (Scheme 14). In 2012 our group reported a modification of this process in which 3-substituted propiolic acids were used to generate acetylides through the Cu(I)-catalysed decarboxylation process and also served as a source of CO_2 for the reaction.[31]



Scheme 14 Synthesis of oxazolidinones *via* CuBr-catalyzed four-component, tandem A^3-coupling/carboxylative cyclization reaction

2-Aminoimidazoles and (cyclic) guanidines are found as structural elements in a great number of complex natural products.[32] Marine sponges proved to be an important source of 2-aminoimidazole alkaloids with diverse biological activities.[33] For example, chemical investigation of the genus *Leucetta* sponges resulted in the isolation of several families of imidazole alkaloids, such as naamines,[34,35,36] isonaamines,[38,39,37] naamidines[39,38] and calcaridines (Figure 2).[39]

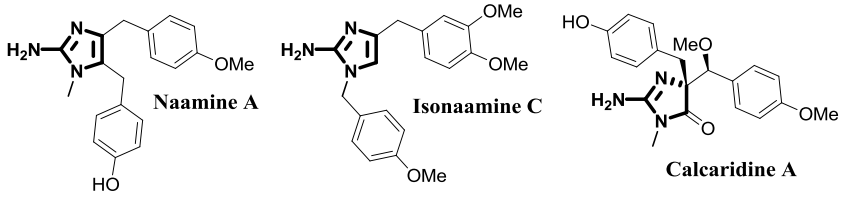
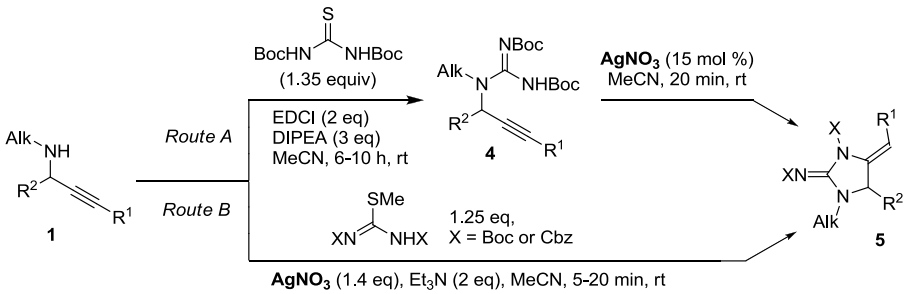


Figure 2 Alkaloids of the 2-aminoimidazole family

As we mention already 2-aminoimidazole derivatives possess a number of biological applications. For instance they have been reported as potent modulators of bacterial biofilms formation and dispersion,[40] human b-secretase (BACE1) inhibitors,[41] and tubulin-binding agents.[42]

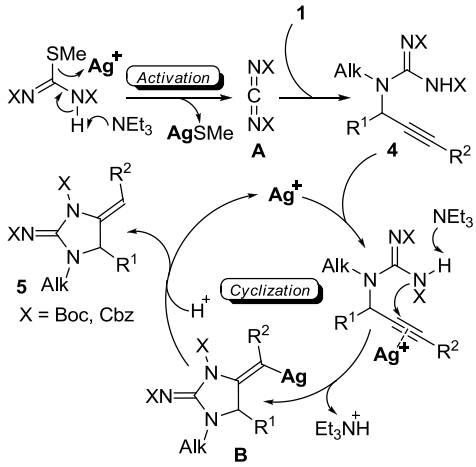
In the course of a long-term program devoted to the synthesis of variously substituted 2-aminoimidazoles,[43] our group has recently described a rapid and diversity-oriented synthesis of *bis*-protected 2-iminoimidazolines **5** *via*

guanylation of secondary propargylamines followed by 5-exo-dig cycloisomerization (Scheme 15).[44] Two complementary routes have been developed. The first sequential ***route A*** relays on EDCI-promoted propargylamine guanylation with N,N'-*bis*-*Boc*-protected thiourea followed by Ag(I)-catalyzed cyclization. The second ***route B*** is based on Ag(I)-mediated tandem guanylation/cycloisomerization reaction of secondary propargylamine with *bis*-protected S-methylisothioureas.



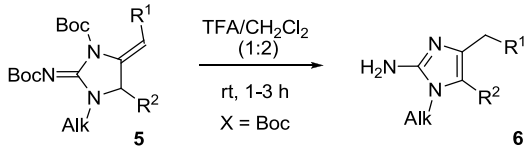
Scheme 15 Synthesis of bis-protected 2-iminoimidazolines **5** via a guanylation/5-exo-dig cycloisomerization sequence

A tentative mechanism for the Ag(I)-mediated tandem guanylation/cycloisomerization reaction is depicted in Scheme 16. In the first step the *bis*-protected *S*-methylisothiourea undergoes a Ag(I)-promoted methylsulfide elimination in the presence of base to form the reactive carbodiimide intermediate **A**. Addition of propargylamine **1** to this *in situ* generated carbodiimide **A** gives *bis*-protected propargylguanidine **4**. Ag(I)-catalyzed 5-*exo*-dig cycloisomerization and subsequent protonolysis of intermediate **B** finally results in the formation of the *bis*-protected 2-iminoimidazoline **5**.



Scheme 16 Proposed mechanism of the Ag(I)-mediated tandem guanylation/cycloisomerization reaction

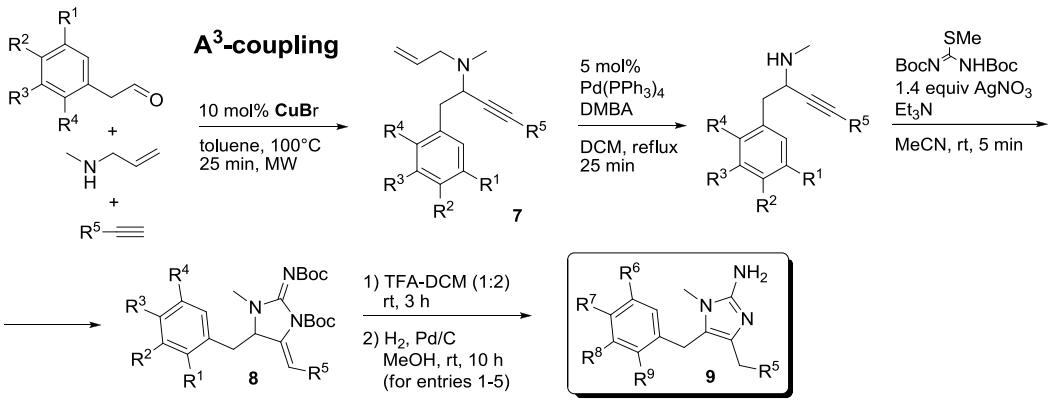
The Boc-protecting groups could be further removed with TFA/DCM (1:2) at room temperature providing 2-aminoimidazoles **6** as free bases (Scheme 17) which were found to effectively inhibit biofilm formation by pathogenic *Salmonella Typhimurium* and *Pseudomonas aeruginosa* bacteria without a significant influence on planktonic growth.



Scheme 17 Deprotection of *bis*-*Boc*-protected 2-iminoimidazolines **5** into 2-aminoimidazoles **6**

Finally the overall strategy was efficiently applied for the synthesis of a number of 2-aminoimidazole alkaloids of the naamine family **9**.[44a] Palladium(0)-catalyzed deallylation of A^3-coupling derived tertiary

propargylamines **7** in the presence of DMBA, followed by silver(I)-promoted cycloguanylation and subsequent removal of the Boc- and Bn-protecting groups provided the target naamines A, C, E, F, G and leucettamine A in high overall yields (Scheme 18).



Entry	R^1	R^2	R^3	R^4	R^5	Yield of **8**	R^6	R^7	R^8	R^9	Overall yield for **9**
1	H	OBn	H	H	PMP	67	H	OH	H	H	**Naamine A** (40 %)
2	H	OMe	OMe	OBn	PMP	63	H	OMe	OMe	OH	**Naamine C** (37 %)
3	OBn	OMe	OH	H	PMP	79	OH	OMe	OH	H	**Naamine E** (50 %)
4	H	OBn	OMe	H	PMP	87	H	OH	OMe	H	**Naamine F** (57 %)
5	OMe	OBn	OMe	H	PMP	83	OMe	OH	OMe	H	**Naamine G** (55 %)
6	OCH_2O		H	H	3',4'-(OCH_2O)Ph	95	OCH_2O		H	H	**Leucettamine A** (55 %)

Scheme 18 CuI-catalyzed A^3-coupling as a key step in the total synthesis of the naamine family alkaloids

Another important class of marine sponge natural products consists of compounds containing a spiro-cyclic guanidine unit (Figure 3). Palau'amine,[45] a complex alkaloid belonging to the oroidin family,[46] possesses a spiro-cyclopentyl-2-aminoimidazole system. Lovely and coworkers have made several efforts to elaborate a general method for the construction of 5-imidazolones spiro-fused with a five-membered ring applying oxidative reactions of tetrahydrobenzimidazoles.[47] Tubastrindoles A–C (Figure 3) isolated from a stony coral, *Tubastraea* sp., are dimeric bisindole alkaloids containing a 2-imino-imidazolidin-4-one spiro-fused with a six-membered ring.[48] Dragmacidin E (Figure 3), originally isolated from the marine sponges *Dragmacidon* sp. and *Spongosorites* sp., is another structurally complex bisindole alkaloid containing a 2-aminoimidazole unit spiro-fused with a seven-membered ring.[49] These complex molecules still possess a great challenge to the synthetic community.[50]

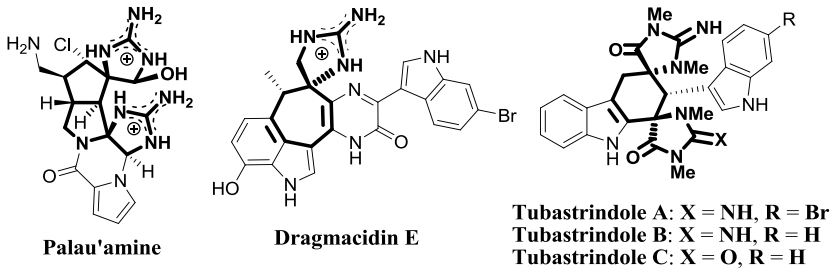
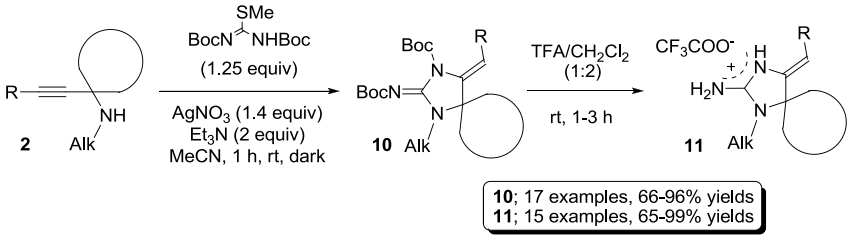


Figure 3 Marine sponge alkaloids containing a spirocyclic guanidine unit

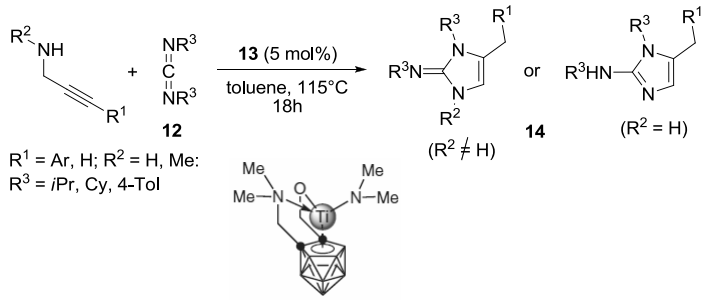
Therefore we aimed to employ our quaternary carbon-containing secondary propargylamines* 2 *in the Ag(I)-mediated tandem guanylation/cycloisomerization reaction developed in our group to access the structurally interesting class of heterocycles featuring a spiro-cyclic guanidine unit.[51] The resulting synthesis of *bis-Boc*-protected-2-

iminoimidazolines spiro-fused with a five- to seven-membered (heterocyclic)ring **10** which could, in most cases, be further deprotected into spiro-2-aminoimidazoles **11** (Scheme 19) is discussed in ***Chapter 3***.



Scheme 19 Ag(I)-mediated synthesis of spiro-2-aminoimidazole derivatives

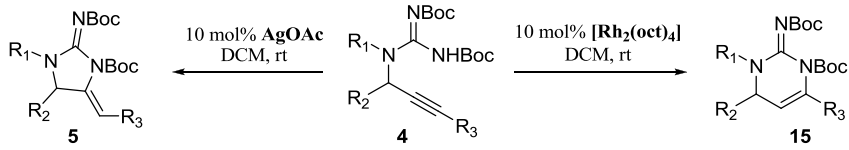
Apart from the *in situ* generated highly reactive bis-Boc- or bis-Cbz-protected carbodiimide intermediates **A** (Scheme 16) less reactive dialkyl and diaryl carbodiimides **12** could also be employed in a propargylamine guanylation/cycloisomerization sequence as was demonstrated by Xie and co-workers (Scheme 20).[52] The overall process was catalyzed by 5 mol% of titanacarborane monoamide **13** although the cycloisomerization step was proved to be possible just upon heating.



$[\sigma{:}\eta^1{:}\eta^5\text{-}(OCH_2)(Me_2NCH_2)C_2B_9H_9]Ti(NMe_2)$ = **13**

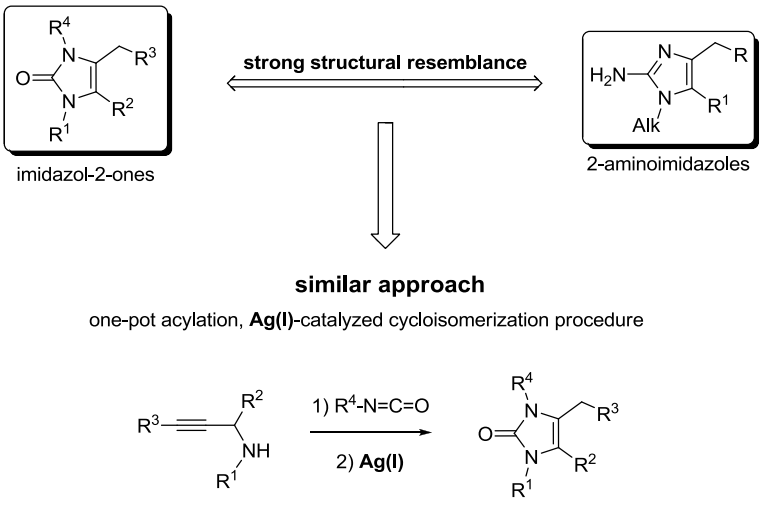
Scheme 20 Titanacarborane monoamide-catalyzed synthesis of 2-aminoimidazoles **14**

The regioselectivity aspect of the *bis*-*Boc*-protected propargylguanidine **4** cycloisomerization process was efficiently addressed by Looper and co-workers. While Ag(I) salts were confirmed to be efficient promoters for 5-*exo*-dig cycloisomerization resulting in the formation of *bis*-*Boc*-protected 2-iminoimidazolines **5**, rhodium(II)-catalyzed reactions showed an unusual selectivity for the formation of 6-membered cyclic guanidines **15** through 6-*endo*-dig cyclization (Scheme 21).[53]



Scheme 21 Regioselectivity of the *bis*-*Boc*-protected propargylguanidine **4** cycloisomerization process

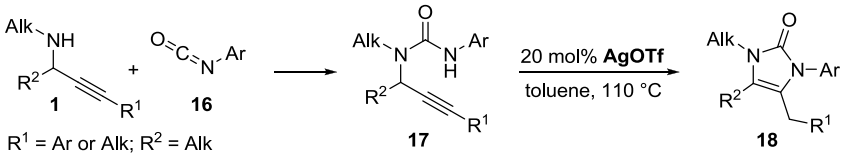
2-Iminoimidazolines possess a strong structural resemblance with 2-imidazolones which are widespread among pharmaceutically interesting compounds such as human dopamine D_4 receptor antagonists,[54] MurB enzyme inhibitors,[55] potential antitumor agents[56] and antioxidants.[57] Therefore our group became interested in the possibility to access 2-imidazolones from propargylamines and isocyanates *via* a one-pot acylation, Ag(I)-catalyzed cycloisomerization procedure (Scheme 22).



Scheme 22

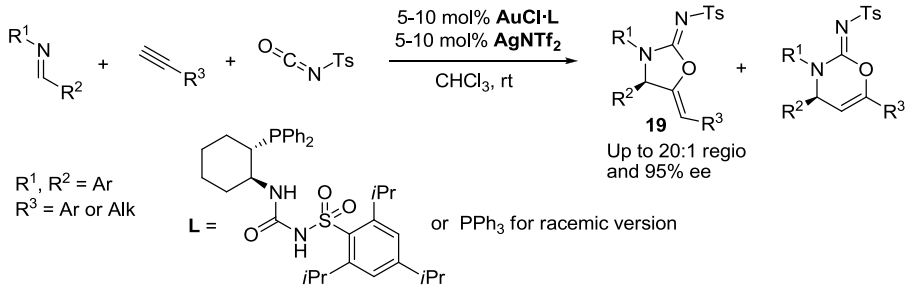
Previously, there was only one documented example regarding the transition metal-catalyzed ring-closure of propargylic urea.[58] In that process the 2-imidazolone core resulted from a primary propargylamine and a tosyl isocyanate via sequential acylation, Au(I)-catalyzed 5-exo-dig cyclization followed by *p*TsOH promoted double-bond migration.

Consequently our group has successfully established an efficient protocol for the synthesis of tetrasubstituted imidazol-2-ones **18** (Scheme 23).[59] The key step of this process is a Ag(I)-catalyzed cycloisomerization (*N*-cyclization) of propargylic urea **17**, derived *in situ* from a secondary N-alkylpropargylamine **1** and an aryl isocyanate **16**.



Scheme 23 Ag(I)-catalyzed synthesis of tetrasubstituted imidazol-2-ones

Simultaneously Campbell and Toste reported a profound study of a three-component reaction of an imine, an alkyne, and a tosyl isocyanate for the enantioselective synthesis of oxazolidin-2-imines **19** (Scheme 24).[60] In their process cationic Au(I)-species were first used to generate a propargylamine from an imine and terminal alkyne and secondly, to activate the generated internal triple bond toward intramolecular *O*-cyclization.

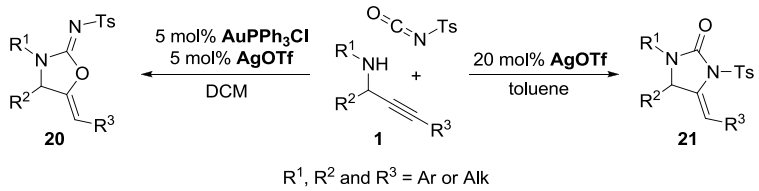


Scheme 24 Asymmetric Au(I)-catalyzed synthesis of oxazolidin-2-imines

Remarkably, both of these protocols rely on transition metal-catalyzed cycloisomerizations of the *in situ* generated propargylic ureas and although there are substantial differences in reaction conditions, catalysts and substrates, it is still not directly clear and very intriguing why they provide such different outcome. ***Therefore we intended to find a convenient common platform that should allow us to investigate and compare both processes and their scope with respect to already established procedures.***

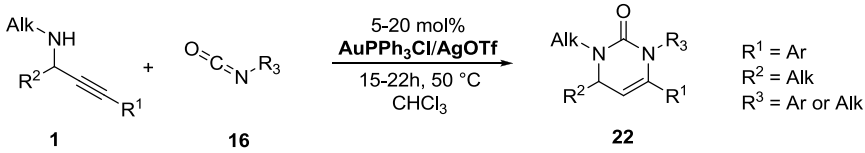
It is worth noting that the first attempt to elaborate selective protocols for *N*- and *O*-cyclizations of propargylic ureas without the use of transition metal catalysis was described already in 1964 by Easton *et al*.[61] Under influence of heat or a strong Brønsted acid various terminal propargylic ureas cyclized into oxazolidin-2-imines, while Brønsted base in most cases promoted cycloisomerization into imidazolidin-2-ones.

A comparative study on transition metal-catalyzed cycloisomerizations of propargylic ureas derived *in situ* from secondary propargylamines **1** and tosyl isocyanate is disclosed in ***Chapter 4***. The application of cationic gold(I) catalysis generally resulted in a formation of oxazolidin-2-imines **20** as a major products while the application of silver(I) triflate selectively provided corresponding imidazolidin-2-ones **21** (Scheme 25).[62]



Scheme 25 Cationic Au(I)- and Ag(I)-catalyzed cycloisomerizations of propargylic ureas

Interestingly cationic gold(I)-catalyzed cycloisomerization of propargylureas derived from aryl or alkyl isocyanates did not follow the above trend. Both chemo- and regioselectivity were altered compared to what was observed for the tosyl isocyanate derived ureas, resulting in the formation of tetrasubstituted 3,4-dihydropyrimidin-2(1*H*)-ones **22** (Scheme 26). A detailed investigation on the scope of this process is given in ***Chapter 5***.

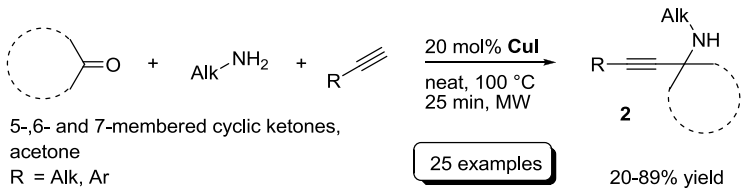


Scheme 26 Unexpected regio- and chemoselectivity of cationic Au(I)-catalyzed cycloisomerizations of aryl or alkyl isocyanate-derived propargylureas

It is important to stress that the dihydropyrimidone scaffold is an important pharmacophore[63] and therefore novel methodologies to access this core are highly desirable.[64] Therefore our procedure might be regarded as a welcome addition to the generally applied Biginelli reaction.[65,66]

Chapter 2

2. Cu(I)-Catalyzed Microwave-Assisted Three-Component Coupling of a Ketone, an Alkyne, and a Primary Amine for the Synthesis of Secondary Propargylamines



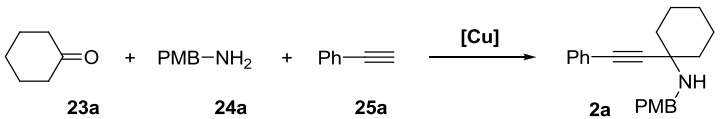
The results discussed in the current chapter may be regarded as a modification and extension of the aforementioned approach towards secondary propargylamines **1** *via* a microwave-assisted A^3-coupling reaction developed in our laboratory (see ***Chapter 1***). We were rather surprised to find out that the aldehyde component could be efficiently replaced by a ketone in this process. As to the best of our knowledge, previously there was no general protocol allowing the application of ketones in the A^3-coupling process. Herein, we report the Cu(I)-catalyzed coupling of a ketone, an alkyne, and a primary amine, called KA^2-coupling, for the synthesis of quaternary carbon-containing secondary propargylamines **2**.

2.1. Results and discussion

The reaction conditions for the KA^2-coupling were optimized using cyclohexanone (**23a)**, 4-methoxybenzylamine (**24a)**, and phenylacetylene (**25a)** (Table 1). When a (1:1.2:1.2) mixture of the respective compounds together with 20 mol % of CuI catalyst was irradiated under solventless con-

ditions at a set ceiling temperature of 100 °C and a maximum power of 80 W for 25 min, the desired propargylamine **2a** could be isolated in 51% yield (Table 1, entry 1). Changing the relative amounts of the three components it was found that the optimal ratio was (1.2:1:1.2) providing the desired compound in 76% yield (Table 1, entries 1-3). A lower reaction temperature of 80 °C reduced the yield of the propargylamine **2a** to 43% (Table 1, entry 4), while increasing the temperature to 120 °C also resulted in a decreased yield of 62% due to the formation of several unidentified byproducts (Table 1, entry 5). Solventless conditions proved to be most suitable for the reaction as the use of toluene resulted in a substantially decreased yield of 54% (Table 1, entry 6). When the reaction in toluene was conducted under conventional heating at the same temperature, the desired propargylamine **2a** was obtained in a comparable moderate yield of 59% after an extended reaction time of 20 h (Table 1, entry 7). A shorter irradiation time of 15 min (Table 1, entry 8) or a diminished concentration of the CuI catalyst to 10 mol % (Table 1, entry 9) all resulted in lower yields. The application of CuBr instead of CuI delivered compound **2a** in a comparable yield (Table 1, entries 3 and 10).

Table 1 Optimization of the KA^2-coupling conditions[a]



Entry	**23a**:**24a**:**25a** (mmol)	Catalyst (mol%)	Time (min)	Conditions	Yield[b]
1	1:1.2:1.2	CuI (20)	25	Neat, MW, 100°C	51[c]
2	1:1:1.2	CuI (20)	25	Neat, MW, 100°C	61
3	**1.2:1:1.2**	**CuI (20)**	**25**	**Neat, MW, 100°C**	**76**
4	1.2:1:1.2	CuI (20)	25	Neat, MW, 80°C	43
5	1.2:1:1.2	CuI (20)	25	Neat, MW, 120°C	62
6	1.2:1:1.2	CuI (20)	25	Toluene, MW, 100°C	54
7	1.2:1:1.2	CuI (20)	20h	Toluene, conv., 100°C	59
8	1.2:1:1.2	CuI (20)	15	Neat, MW, 100°C	54
9	1.2:1:1.2	CuI (10)	25	Neat, MW, 100°C	63
10	1.2:1:1.2	CuBr (20)	25	Neat, MW, 100°C	72

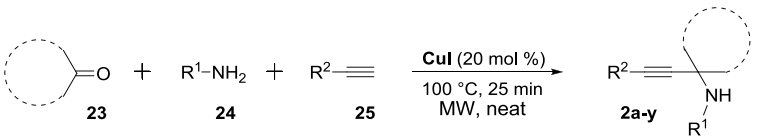
[a] When the reaction was run under microwave irradiation a maximum power of 80 W was used.

[b] Isolated yields based on 4-methoxybenzylamine.

[c] Isolated yield based on cyclohexanone.

The scope of the reaction was evaluated for various ketones, primary amines, and alkynes applying the optimal conditions (Table 1, entry 3). Both aromatic and aliphatic alkynes were explored as reaction partners, but the last afforded the target compounds **2g**,**h** only in low to moderate yields (Table 2, entries 7 and 8), even when 2 equiv of alkyne was used. To expand the scope of the protocol, a variety of primary amines was evaluated. All reactions seemed to be working well when 6-membered (hetero)cyclic ketones were used. When cyclohexanone (**23a**) was used, the desired compounds **2a-f**,**i-o** were obtained in 46-89% yield (Table 2, entries 1-6 and 9-15). When N-protected piperidinones **23b-f** were used, yields between 38% and 82% were obtained (Table 2, entries 16-20). 2-Methylcyclohexanone (**23g**) delivered the adducts **2u** (mixture of diastereomers (10:1)) in only 33% yield (Table 2, entry 21), clearly showing that sterical hindrance might play an important role for the outcome of the reaction. The fact that 3-methylcyclohexanone (**23h**) gives a better yield but lower diastereoselectivity (Table 2, entry 22) confirms this conclusion. It seemed that also conformational factors are playing a crucial role in this process, as when cycloheptanone (**23i**) was used the yield dropped to 21% (Table 2, entry 23). Analogously, a low yield of 20% was observed for reaction with cyclopentanone (**23j**) (Table 2, entry 24). It is probable that ketimines from 6-membered (hetero)cyclic ketones (see the mechanism below) are more accessible for copper acetylide attack than imines from other ketones.[67] Remarkably, the reaction with acetone (**23k**) also resulted in a low yield of 30% (Table 2, entry 25).

Table 2 Scope and limitations of the KA^2-coupling[a]



Entry	Ketone	R^1	R^2	Product	Yield (%)[b]
1	Cyclohexanone **(23a)**	PMB **(24a)**	Ph **(25a)**	**(2a)**	76
2	Cyclohexanone **(23a)**	PMB **(24a)**	4-methoxyphenyl **(25b)**	**(2b)**	75
3	Cyclohexanone **(23a)**	PMB **(24a)**	3-fluorophenyl **(25c)**	**(2c)**	64
4	Cyclohexanone **(23a)**	PMB **(24a)**	thiophene-3-yl **(25d)**	**(2d)**	75
5	Cyclohexanone **(23a)**	PMB **(24a)**	4-heptylphenyl **(25e)**	**(2e)**	74
6	Cyclohexanone **(23a)**	PMB **(24a)**	4-pentyloxyphenyl **(25f)**	**(2f)**	89
7	Cyclohexanone **(23a)**	PMB **(24a)**	Hexyl **(25g)**	**(2g)**	31[c]
8	Cyclohexanone **(23a)**	PMB **(24a)**	Cyclopropyl **(25h)**	**(2h)**	48[c]
9	Cyclohexanone **(23a)**	Hexyl **(24b)**	Ph **(25a)**	**(2i)**	61
10	Cyclohexanone **(23a)**	Octyl **(24c)**	Ph **(25a)**	**(2j)**	77
11	Cyclohexanone **(23a)**	Cycloheptyl **(24d)**	Ph **(25a)**	**(2k)**	46

Table 2 (continued)

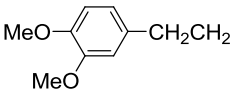
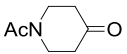
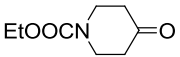
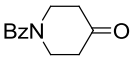
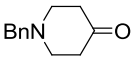
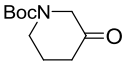
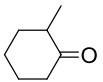
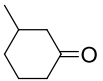
Entry	Ketone	R^1	R^2	Product	Yield (%)[b]
12	Cyclohexanone **(23a)**	$MeOCH_2CH_2$ **(24e)**	Ph **(25a)**	**(2l)**	62
13	Cyclohexanone **(23a)**	 **(24f)**	Ph **(25a)**	**(2m)**	68
14	Cyclohexanone **(23a)**	3-chlorobenzyl **(24g)**	*p*-tolyl **(25i)**	**(2n)**	82
15	Cyclohexanone **(23a)**	Bn **(24h)**	Ph **(25a)**	**(2o)**	74
16	 **(23b)**	PMB **(24a)**	Ph **(25a)**	**(2p)**	64
17	 **(23c)**	PMB **(24a)**	Ph **(25a)**	**(2q)**	82
18	 **(23d)**	PMB **(24a)**	Ph **(25a)**	**(2r)**	61
19	 **(23e)**	PMB **(24a)**	Ph **(25a)**	**(2s)**	38
20	 **(23f)**	PMB **(24a)**	Ph **(25a)**	**(2t)**	61
21	 **(23g)**	PMB **(24a)**	Ph **(25a)**	**(2u)**	33 10:1 dr
22	 **(23h)**	PMB **(24a)**	Ph **(25a)**	**(2v)**	75 3:1 dr

Table 2 (continued)

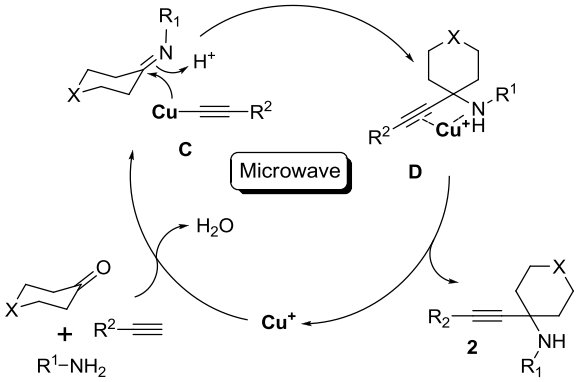
Entry	Ketone	R^1	R^2	Product	Yield (%)[b]
23	Cycloheptanone **(23i)**	PMB **(24a)**	Ph **(25a)**	**(2w)**	21
24	Cyclopentanone **(23j)**	PMB **(24a)**	Ph **(25a)**	**(2x)**	20
25	Acetone **(23k)**	PMB **(24a)**	Ph **(25a)**	**(2y)**	30

[a] A mixture of amine **23** (1.0 mmol), alkyne **24** (1.2 mmol), ketone **25** (1.2 mmol) and CuI (20 mol %) was irradiated at a set ceiling temperature of 100°C and a maximum power of 80 W for 25 min.

[b] Isolated yields are reported.

[c] 2 mmol of alkyne was used.

The tentative mechanism proposed for the KA^2-coupling is typical for A^3-coupling processes (Scheme 27). The copper catalyst reacts with the alkyne to form the copper acetylide. The *in situ* formed imine is attacked by the copper acetylide (transition state **C**) resulting in the copper-complexed intermediate **D**. Decomplexation produces the free propargylamine **2** and regenerates the Cu(I) catalyst.



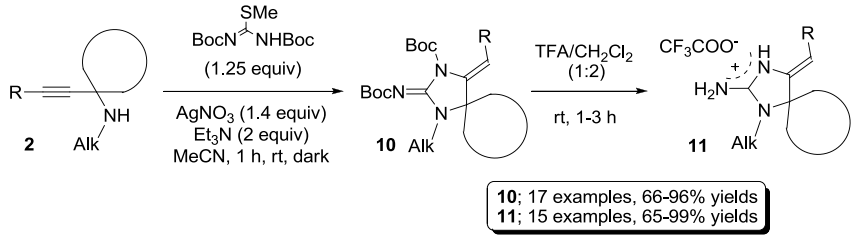
Scheme 27 Proposed mechanism for the KA^2-coupling

2.2. Conclusions

In conclusion, we have developed a novel Cu(I)-catalyzed microwave-assisted three-component coupling of a ketone, an alkyne and a primary amine, called KA^2-coupling reaction, which represents the first general protocol allowing an efficient replacement of an aldehyde for a ketone in the A^3-coupling-type process. Moreover, the application of primary amines, known to be difficult reaction partners for A^3-coupling reactions compared to secondary amines, results in the formation of synthetically useful secondary alkylpropargylamines. Therefore, this KA^2-coupling can be regarded as a welcome additional method for the generally applied A^3-coupling reaction.

Chapter 3

3. Diversity-Oriented Silver(I)-Mediated Synthesis of Spiro-2-aminoimidazoles



The current chapter describes the application of quaternary carbon-containing secondary propargylamines **2** prepared in ***Chapter 2*** in the Ag(I)-mediated tandem guanylation/cycloisomerization reaction developed in our group for the synthesis of a structurally interesting class of heterocycles containing a spiro-cyclic guanidine unit.

3.1. Results and discussion

When the reactions with propargylamines **2a-g,i-m,p,q,t,w,x** were run for 1h at rt with 1.25 equiv of protected *S*-methylisothiourea in the presence of 1.4 equiv of $AgNO_3$ and 2 equiv of Et_3N in MeCN, the corresponding protected spiro-2-iminoimidazolines **10a-g,i-m,p,q,t,w,x** were obtained in high yields ranging from 66 to 96% (Table 3). In most cases, the reaction proceeded regio- and stereoselectively as a 5-*exo*-dig heterocyclization process, providing exclusively the 5-membered imidazoline with *Z*-configuration of the exocyclic double bond. However, for the propargylamines **2b,f,g** bearing electron-donating R^2-group a competitive 6-*endo*-dig cyclization could also be partially realized (Figure 4). As a result the 6-membered spiro-guanidines

10b',f',g' are also formed as minor side compounds (Table 3, entries 2,6,7).[68]

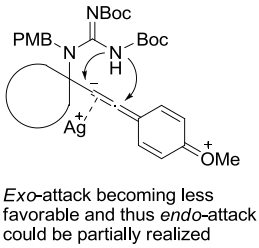
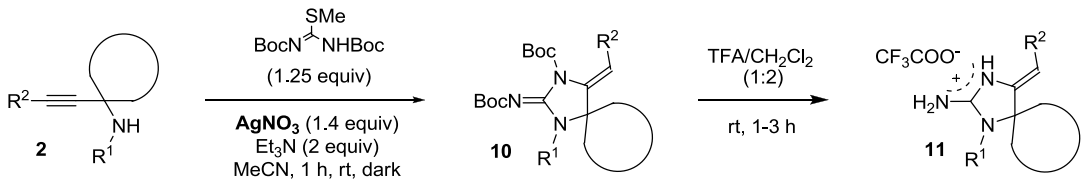


Figure 4 Rationale for the *endo*-cyclization of propargyl guanidines derived from **2b,f,g**

The Boc-deprotection of **10a-g,i-m,p,q,w** was achieved using TFA/DCM (1:2) at rt in 1-3 h, delivering the spiro-2-aminoimidazoles **11a-g,i-m,p,q,w** as trifluofoacetic acid salts in high yields (Table 3, entries 1-14, 16). However, in the case of **10t** containing an additional Boc-protective group, full decomposition was observed (Table 3, entry 15). The deprotected 2-aminoimidazole **11x** spiro-fused with a five-membered ring also undergoes intensive decomposition during workup, thus making isolation and characterization impossible (Table 2, entry 17). It is worth mentioning that other spiro-2-aminoimidazole trifluofoacetic acid salts **11a-g,i-m,p,q,w** were found considerably more stable than **11x**, although for some of them traces of decomposition were also observed during long term storage under air atmosphere.

Table 3 Ag(I)-mediated synthesis of *bis-Boc*-spiro-2-iminoimidazolines **10** followed by deprotection into spiro-2-aminoimidazoles **11**



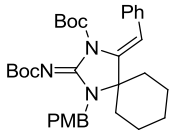
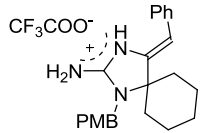
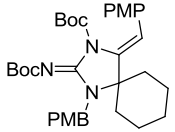
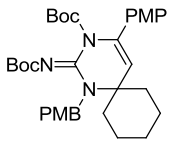
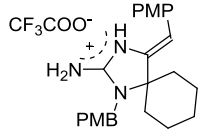
Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]	Spiro-2-aminoimidazole **11** (yield)[a]
1	**2a**	 **10a** (85%)	 **11a** (99%)
2	**2b**	 **10b** (87%)  **10b'** (9%)	 **11b** (97%)

Table 3 (continued)

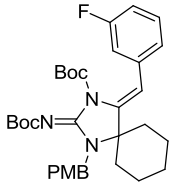
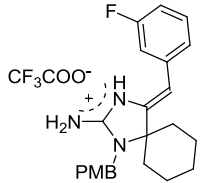
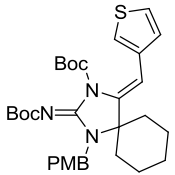
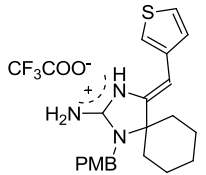
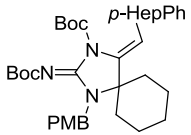
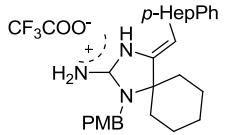
Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]	Spiro-2-aminoimidazole **11** (yield)[a]
3	**2c**	 **10c** (95%)	 **11c** (99%)
4	**2d**	 **10d** (91%)	 **11d** (92%)
5	**2e**	 **10e** (87%)	 **11e** (99%)

Table 3 (continued)

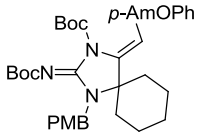
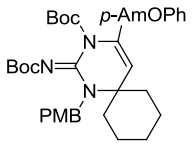
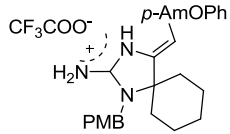
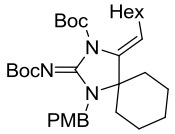
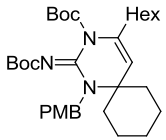
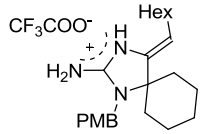
Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]	Spiro-2-aminoimidazole **11** (yield)[a]
6	**2f**	 **10f** (75%)  **10f'** (20%)	 **11f** (99%)
7	**2g**	 **10g** (77%)  **10g'** (19%)	 **11g** (65%)

Table 3 (continued)

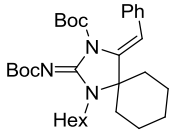
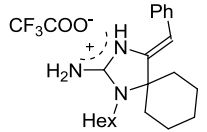
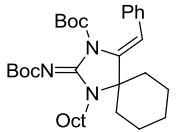
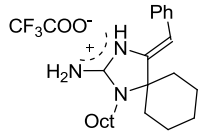
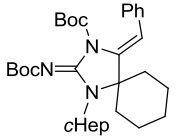
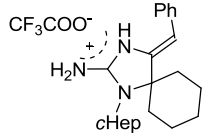
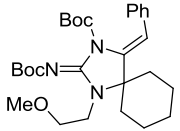
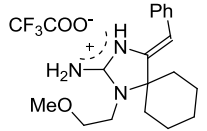
Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]		Spiro-2-aminoimidazole **11** (yield)[a]	
8	**2i**		**10i** (95%)		**11i** (92%)
9	**2j**		**10j** (96%)		**11j** (90%)
10	**2k**		**10k** (90%)		**11k** (95%)
11	**2l**		**10l** (77%)		**11l** (83%)

Table 3 (continued)

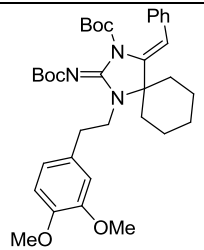
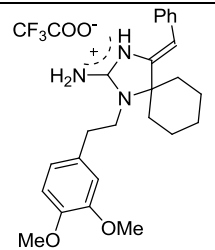
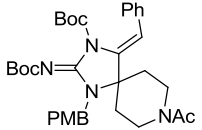
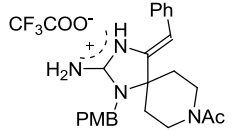
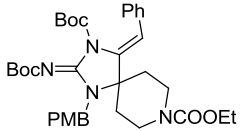
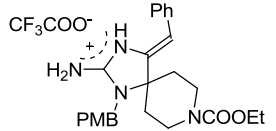
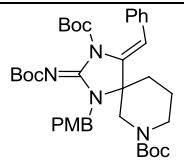
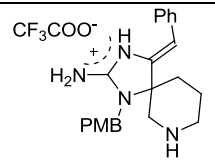
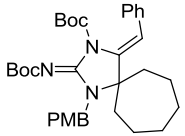
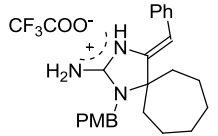
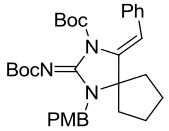
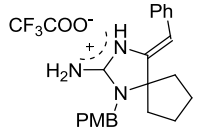
Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]	Spiro-2-aminoimidazole **11** (yield)[a]
12	**2m**	 **10m** (87%)	 **11m** (85%)
13	**2p**	 **10p** (67%)	 **11p** (92%)
14	**2q**	 **10q** (66%)	 **11q** (95%)

Table 3 (continued)

Entry	Propargylamine **2**	bis-Boc-spiro-2-iminoimidazoline **10** (yield)[a]	Spiro-2-aminoimidazole **11** (yield)[a]
15	**2t**	 **10t** (82%)	 **11t** (0%)[b]
16	**2w**	 **10w** (76%)	 **11w** (75%)
17	**2x**	 **10x** (77%)	 **11x** (-)[c]

[a] Isolated yields.

[b] Complete decomposition was observed.

[c] Intensive decomposition of **11x** during workup prevented isolation and complete characterization.

All the final spiro-2-aminoimidazole trifluoroacetic acid salts **11a-g,i-m,p,q,w** could be purified by column chromatography over silica gel, and their structures were confirmed by ^{1}H and ^{13}C NMR-spectroscopy and HRMS. In addition, the structure of **11d** was determined by X-ray crystallography (Figure 4).[69] This compound crystallized in the space group P-1, with the asymmetric unit containing two spiro-2-aminoimidazole molecules. A hydrogen bond network is formed, around crystallographic inversion centers, between the oxygen atoms of the trifluoroacetates and the hydrogen atoms of the 2-aminoimidazoles, for both molecules in the asymmetric unit (Figure 5).

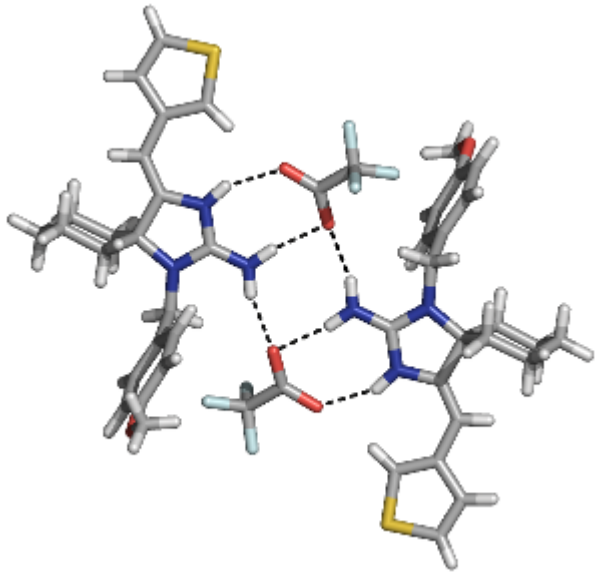
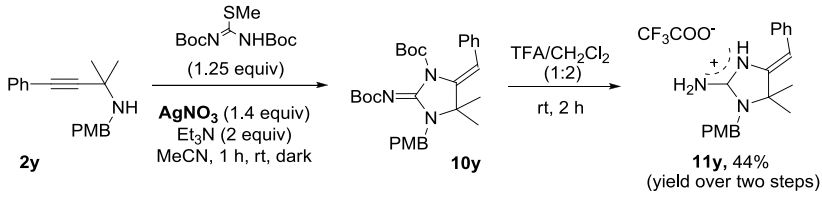


Figure 5 X-ray crystallographic structure of compound **11d**, showing the hydrogen bond network around a crystallographic inversion center

To expand the applicability of our protocol, we have investigated the Ag(I)-mediated tandem guanylation/cycloisomerization of propargylamine **2y**. Af-

ter cyclization the crude *bis-Boc*-protected 2-iminoimidazoline **10y** was directly subjected to the next Boc-deprotection step delivering compound **11y** in a good overall yield of 44% (Scheme 28).



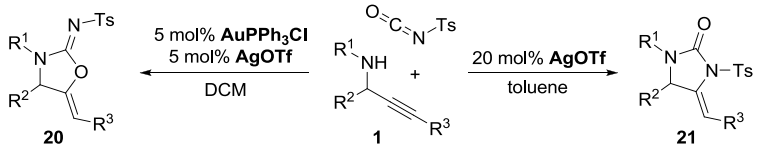
Scheme 28 Synthesis of 2-aminoimidazole **11y**

3.2. Conclusions

In conclusion, we have prepared a small library of variously substituted spiro-2-aminoimidazoles, starting from readily available quaternary carbon-containing secondary propargylamines. The key step of our protocol, a Ag(I)-mediated tandem guanylation/intramolecular cycloisomerization proved to be a powerful synthetic tool for the construction of spiro-cyclic guanidine systems.

Chapter 4

4. Cationic Gold- and Silver-Catalyzed Cycloisomerizations of Propargylic Ureas: a Selective Entry to Oxazolidin-2-imines and Imidazolidin-2-ones



This chapter is devoted to a comparative study of transition metal-catalyzed cycloisomerizations of propargylic ureas derived *in situ* from secondary propargylamines and tosyl isocyanate. The influence of the catalytic system on the reaction outcome was thoroughly studied on two model examples resulting in the establishment of two selective protocols for both *O*- and *N*-cyclizations. An attempt to rationalize the observed chemoselectivity is described. The scope of both processes was demonstrated through the use of variously substituted secondary propargylamines.

4.1. Results and discussion

As a first model case for our investigation we chose the cycloisomerization of terminal propargylic urea **27a** generated *in situ* from *N*-methylpropargylamine (**1a**) and tosyl isocyanate (**26**) (Table 4). Taking into account Toste's results[60] we reasoned that cationic Au-catalysis should promote *O*-cyclization. Therefore we set up a number of small-scale experiments using various combinations of monophosphine Au(I)-chlorides with different Ag(I)-salts which are known to produce *in situ* cationic Au(I)-species. Carrying out the reactions in deuterated solvents allowed direct re-

cording of ^{1}H NMR spectra and easy determination of the final mixture composition. As expected the application of 5 mol% of $AuPPh_3Cl/AgOTf$ in $CDCl_3$ resulted in almost exclusive formation of oxazolidin-2-imine **20a** through *O*-cyclization (Table 4, entry 1). Switching to CD_2Cl_2 as solvent resulted in even better selectivity (Table 4, entry 2). The use of $Au(XPhos)Cl/AgOTf$ or $AuPPh_3Cl/AgNTf_2$ in $CDCl_3$ allowed to maintain ultimate chemoselectivity and excellent yield of **20a** (Table 4, entries 3 and 4). However, when the reaction was performed in the presence of 5 mol% of $AuPPh_3Cl/AgBF_4$ a small drop of selectivity was observed (Table 4, entry 5). Further change of the counter ion through the application of $AuPPh_3Cl/AgSbF_6$ as catalyst resulted in reversed chemoselectivity. *N*-cyclized imidazolidin-2-one **21a** was obtained as a major product in 70% yield next to the only 30% of oxazolidin-2-imine **20a** (Table 4, entry 6). Nevertheless, when we employed 5 mol% of preformed cationic $[Au(JohnPhos)(MeCN)]SbF_6$ complex bearing the same counter ion but a bulkier phosphine ligand[70] the selectivity turned back providing an excellent yield of **20a** (Table 4, entry 7). The reaction catalyzed by 5 mol% of $AuPPh_3Cl/AgO_2CCF_3$ proceeded unselectively delivering a mixture of **20a**, **21a** and imidazole-2-one **28** with migrated double bond in 39%, 17% and 34% yield, respectively (Table 4, entry 8). Interestingly, $AuPPh_3Cl/AgNO_3$ appeared to be a much less reactive catalyst than all other above-described systems. At the same time the selectivity of the process turned to the *N*-cyclization mode delivering **20a** and **21a** in 4% and 23% yield next to 68% of uncyclized urea **27a** (Table 4, entry 9). Application of $AuPPh_3Cl$ as the sole catalyst continued these tendencies. Carrying out the reaction at rt for 1h provided almost quantitative yield of urea **27a** with only traces of imidazolidin-2-one **21a** (Table 4, entry 10). The cycloisomerization rate could be improved by applying a higher reaction temperature of 50°C and a

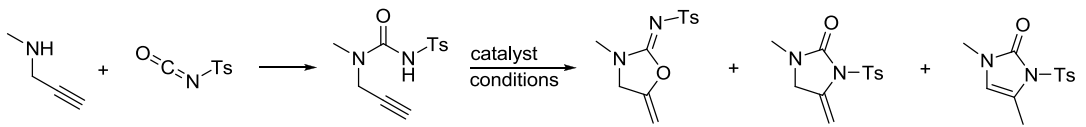
longer reaction time, but uncyclized urea **27a** was not completely consumed even after 22 h (Table 4, entries 11 and 12). Application of the (IPr)AuCl/AgOTf (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) catalytic system with N-heterocyclic carbene as ligand resulted in a slight decrease of selectivity compared to the analogous reaction with triphenylphosphine ligand (Table 4, entry 13 *versus* entry 1). With $AuCl_3$, a representative Au(III)-catalyst, a high rate and selectivity for *O*-cyclization were obtained (Table 4, entry 14). To drive the reaction through the N-cyclization mode, we have chosen AgOTf which was already proven by our group to be an appropriate catalyst for this process.[59] Nonetheless, additional investigation was required as in previous optimization studies other substrates were used. Running the reaction with 10 mol% of AgOTf in $CDCl_3$ at 80°C for 1h predictably resulted in predominate formation of *N*-cyclized products **21a** and **28** over *O*-cyclized oxazolidin-2-imine **20a** (Table 4, entry 15). A prolonged reaction time of 2h resulted in an increased yield of double-bond migrated imidazole-2-one **28** compare to imidazolidin-2-one **21a** but did not affect the general *N*-/*O*-selectivity (Table 4, entry 16). If the reaction was catalyzed with 20 mol% of AgOTf, imidazole-2-one **28** was found as the only *N*-cyclized product already after 1h.[71] However, this was accompanied by a slight drop of the selectivity (Table 4, entry 17). Similar observations were obtained for AgOTf-catalyzed reactions in toluene (Table 4, entries 18 and 19). The reaction catalyzed by 10 mol% of $AgSbF_6$ in toluene appeared to be slightly more N-selective then the analogous one with AgOTf, however, the combined yield of cycloisomerized products and the rate of double-bond migration in this case were lower (Table 4, entry 20 *versus* entry 18). Next we decided to examine whether addition of triphenylphosphine ligand affects the outcome of AgOTf-catalyzed cycloisomerization. We expected that the ligand might increase the cationic

character of the Ag catalyst which would disturb the chemoselectivity by making the process more prone towards *O*-cyclization. We were rather surprised to find that for this particular reaction the application of AgOTf/PPh_3 catalytic system in $CDCl_3$ induced the highest observed *N*-cyclization rate (Table 4, entry 21). Also interesting that double bond-migrated imidazole-2-one **28** was produced only in trace amounts, while imidazolidin-2-one **21a** was obtained in a high yield of 87%. These two observations suggest that PPh_3 most likely acts here as a poison to the Ag catalyst making it less reactive and more selective. We have also noticed that addition of PPh_3 prevents decomposition of the catalyst and precipitation as a silver mirror. A similar observation was made for AgOTf-catalyzed reactions in acetonitrile which itself can behave as a suitable ligand for the Ag catalyst providing an analogous poisoning effect. The rate of *N*-cyclization for these reactions was notably higher than for those in $CDCl_3$ or in toluene (Table 4, entries 22-24). Similarly to the AgOTf/PPh_3-catalyzed reaction imidazolidin-2-one **21a** was found to be the major product of AgOTf-catalyzed reactions in acetonitrile as well. This could be registered by ^{1}H NMR if after completion of reaction the resulting mixture was evaporated in vacuum at 20°C (Table 4, entry 22). If the final mixture was evaporated at a higher temperature of 50°C double-bond migration occurred and no **21a** could be detected (Table 4, entry 23). In wet acetonitrile the AgOTf-catalyst is decomposing in the course of reaction thus double bond migration during evaporation is almost suppressed (Table 4, entry 24). On applying catalytic amounts of a strong Brønsted acid no cycloisomerization products were obtained (Table 4, entry 25).

Finally we performed two control experiments in order to check the influence of temperature on the outcome of both cationic Au- and AgOTf-catalyzed reactions. Carrying out cycloisomerization in the presence of 5 mol% of AgOTf in $CDCl_3$ at rt resulted in incomplete conversion of **27a** and

decreased *N*-selectivity compared to the reaction at 80°C (Table 4, entry 26 *versus* entry 15). Nonetheless, the process still remains *N*-selective providing imidazolidin-2-one **21a** as a predominant product (Table 4, entry 26). At the same time the reaction catalyzed by 5 mol% of $AuPPh_3Cl/AgOTf$ being conducted at 80°C remained completely *O*-selective (Table 4, entry 27). These results indicate that the reaction temperature indeed affects the cycloisomerization outcome though its influence on the chemoselectivity is not crucial.

Table 4 Influence of the catalytic system on the cycloisomerization of propargylic urea **27a** derived from *N*-methylpropargylamine (**1a**) and tosyl isocyanate (**26**)[a]



1a **26** **27a** **20a** **21a** **28**

Entry	Catalyst	Conditions	Yield[b]			
			20a	**21a**	**28**	uncyclized **27a**
1	5 mol% $AuPPh_3Cl/AgOTf$	$CDCl_3$, rt, 1h	99 (92)[c]	1	nd	nd
2	5 mol% $AuPPh_3Cl/AgOTf$	CD_2Cl_2, rt, 1h	100	nd	nd	nd
3	5 mol% Au(XPhos)Cl/AgOTf	$CDCl_3$, rt, 1h	100	nd	nd	nd
4	5 mol% $AuPPh_3Cl/AgNTf_2$	$CDCl_3$, rt, 1h	100	nd	nd	nd
5	5 mol% $AuPPh_3Cl/AgBF_4$	$CDCl_3$, rt, 1h	94	6	nd	nd
6	5 mol% $AuPPh_3Cl/AgSbF_6$	$CDCl_3$, rt, 1h	30	70	nd	nd
7	5 mol% [Au(JohnPhos)(MeCN)]SbF_6	$CDCl_3$, rt, 1h	100	nd	nd	nd
8	5 mol% $AuPPh_3Cl/AgO_2CCF_3$	$CDCl_3$, rt, 1h	39	17	34	nd

Table 4 (continued)

Entry	Catalyst	Conditions	Yield[b]			
			20a	**21a**	**28**	uncyclized **27a**
9	5 mol% $AuPPh_3Cl/AgNO_3$	$CDCl_3$, rt, 1h	4	23	nd	68
10	5 mol% $AuPPh_3Cl$	$CDCl_3$, rt, 1h	nd	1	nd	99
11	5 mol% $AuPPh_3Cl$	$CDCl_3$, 50°C, 3h	2	11	nd	84
12	5 mol% $AuPPh_3Cl$	$CDCl_3$, 50°C, 22h	7	44	6	39
13	5 mol% (IPr)AuCl/AgOTf	$CDCl_3$, rt, 1h	97	3	nd	nd
14	5 mol% $AuCl_3$	$CDCl_3$, rt, 1h	92	nd	3	nd
15	10 mol% AgOTf	$CDCl_3$, 80°C, 1h	22	10	62	nd
16	10 mol% AgOTf	$CDCl_3$, 80°C, 2h	22	2	68	nd
17	20 mol% AgOTf	$CDCl_3$, 80°C, 1h	30	nd	64	nd
18[d]	10 mol% AgOTf	toluene, 80°C, 2h	15	10	66	nd
19[d]	20 mol% AgOTf	toluene, 80°C, 1h	20	nd	72	nd
20[d]	10 mol% $AgSbF_6$	toluene, 80°C, 2h	9	32	37	nd
21	10 mol% AgOTf/20 mol% PPh_3	$CDCl_3$, 80°C, 2h	5	87	3	nd
22[e]	10 mol% AgOTf	MeCN, 80°C, 2h	12	61	23	nd
23[d,f]	10 mol% AgOTf	MeCN, 80°C, 2h	11	nd	76	nd

Table 4 (continued)

Entry	Catalyst	Conditions	Yield[b]			
			20a	**21a**	**28**	uncyclized **27a**
24[d,f]	10 mol% AgOTf	MeCN (wet), 80°C, 2h	6-8[g]	52-75[g]	0-20[g]	nd
25	5 mol% TfOH	$CDCl_3$, rt, 1h	nd	nd	nd	100
26	5 mol% AgOTf	$CDCl_3$, rt, 1h	10	24	-	58
27	5 mol% $AuPPh_3Cl$/AgOTf	$CDCl_3$, 80°C, 1h	96	-	1	-

[a] Reactions were carried out on a 0.2 mmol scale in 0.8 mL of solvent. After completion of the indicated time an internal standard (3,4,5-trimethoxybenzaldehyde) was added and the resulting mixture was analyzed by ^{1}H NMR.

[b] Yields are determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. nd = not detected.

[c] Isolated yield is given in parenthesis.

[d] After completion of the indicated time the resulting mixture was evaporated at 50°C, diluted with $CDCl_3$, charged with 3,4,5-trimethoxybenzaldehyde and analyzed by ^{1}H NMR.

[e] Evaporated at 20°C.

[f] Repeated from ref.[59].

[g] Yields can vary depending on the wetness of the applied MeCN.

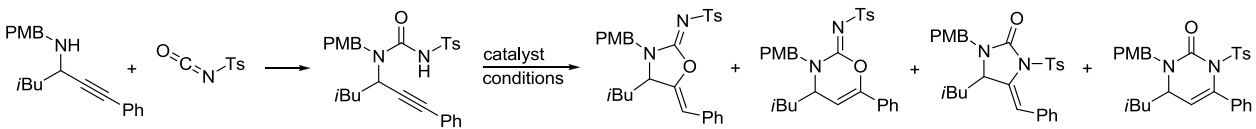
Next we investigated the transition metal-catalyzed cycloisomerization of propargylic urea **27b** in order to adjust our preliminary findings to the case of polysubstituted propargylamine-derived ureas (Table 5). It is important to stress that for these reactions, in addition to the chemoselectivity, the regioselectivity aspect (5-*exo-dig versus* 6-*endo-dig* cyclization) had to be considered.[72] On the other hand, in contrast to the first model case (Table 4) and our earlier study[59] (Scheme 23, ***Chapter 1***) no double bond migration occurred.

We were pleased to find that the $AuPPh_3Cl/AgOTf$-catalyzed reaction showed high regio- and chemoselectivity in both $CDCl_3$ and CH_2Cl_2 delivering oxazolidin-2-imine **20b** as the major product in a good yield of 75% and 73%, respectively (Table 5, entries 1 and 2). Interestingly, the $AuPPh_3Cl/AgNTf_2$ catalytic system which was proved to be efficient for Toste's substrates[60] gave rather poor results. Being applied in $CDCl_3$ it gave a lower rate of cycloisomerization while the reaction in CH_2Cl_2 was unselective (Table 5, entries 3 and 4). Therefore we decided to test a few more representative catalytic systems which gave promising selectivity of *O*-cyclization during the first model study. The reaction catalyzed by preformed cationic $[Au(JohnPhos)(MeCN)]SbF_6$ complex appeared to be moderately selective but extremely slow (Table 5, entry 5). The $AuCl_3$-catalyzed reaction proceeded faster but rather unselectively with predominant formation of *N*-cyclized products (Table 5, entry 6). These results demonstrate that the *O*-cycloisomerization reaction with polysubstituted propargylic urea **27b** is much more sensitive to the choice of the catalytic system compared to the reaction with terminal propargylic urea **27a**.

The AgOTf-catalyzed *N*-cycloisomerization of **27b** proceeded almost equally well in $CDCl_3$, toluene and acetonitrile as solvents though the reaction in toluene provided a slightly higher yield of the desired imidazolidin-2-one

21b (Table 5, entries 7-9). The application of $AgSbF_6$ in toluene delivered a similar result (Table 5, entry 10). In contrast to the first model case the addition of triphenylphosphine ligand did not improve the rate of *N*-cyclization. Instead the chemoselectivity of the process was disturbed in accordance with our initial expectations. On the other hand, this was accompanied by a drop of the general cycloisomerization rate (Table 5, entries 11 and 12).[73]

Table 5 Influence of the catalytic system on the cycloisomerization of propargylic urea **27b** derived from propargylamine **1b** and tosyl isocyanate (**26**)[a]



Entry	Catalyst	Conditions	Yield[b]				
			20b	**29b**	**21b**	**30b**	uncyclized **27b**
1	5 mol% $AuPPh_3Cl/AgOTf$	$CDCl_3$, 50°C, 2 h	75	6	2	2	nd
2[c]	5 mol% $AuPPh_3Cl/AgOTf$	CH_2Cl_2, 50°C, 2 h	73	4	6	5	nd
3	5 mol% $AuPPh_3Cl/AgNTf_2$	$CDCl_3$, 50°C, 2 h	24	3	5	3	49
4[c]	5 mol% $AuPPh_3Cl/AgNTf_2$	CH_2Cl_2, 50°C, 2 h	49	3	17	19	nd
5	5 mol% [Au(JohnPhos)(MeCN)]SbF_6	$CDCl_3$, 50°C, 2 h	8	nd	2	2	75
6	5 mol% $AuCl_3$	$CDCl_3$, 50°C, 2 h	15	nd	19	4	32
7[d]	20 mol% AgOTf	$CDCl_3$, 80°C, 1h	3	nd	74	1	nd

Table 5 (continued)

Entry	Catalyst	Conditions	Yield[b]				
			20b	**29b**	**21b**	**30b**	uncyclized **27b**
8[c,d]	20 mol% AgOTf	toluene, 80°C, 1h	5	nd	79	nd	nd
9[c, d]	20 mol% AgOTf	MeCN, 80°C, 1h	11	nd	74	nd	nd
10[c,d]	20 mol% $AgSbF_6$	toluene, 80°C, 1h	4	nd	79	1	nd
11[d]	20 mol% AgOTf/40 mol% PPh_3	$CDCl_3$, 80°C, 1h	24	nd	43	nd	15
12[c,d]	20 mol% AgOTf/40 mol% PPh_3	toluene, 80°C, 1h	15	nd	22	nd	48

[a] Reactions were carried out on a 0.1 mmol scale in 0.4 mL of solvent, unless otherwise specified. After completion of the indicated time the internal standard (3,4,5-trimethoxybenzaldehyde) was added and the resulting mixture was analyzed by ^{1}H NMR.

[b] Yields are determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. nd = not detected.

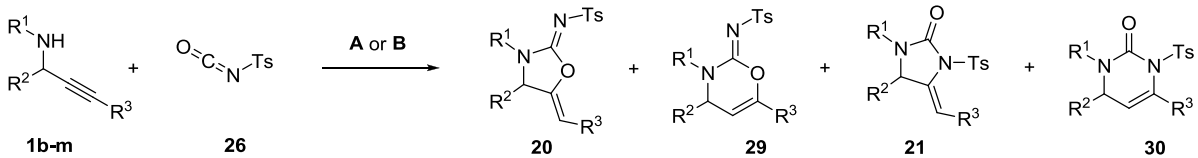
[c] After completion of the indicated time the resulting mixture was evaporated at 50°C, diluted with $CDCl_3$, charged with 3,4,5-trimethoxybenzaldehyde and analyzed by ^{1}H NMR.

[d] Reaction was carried out in 0.5 mL of solvent.

Having two selective protocols for *O*- and *N*-cycloisomerizations successfully established we decided to evaluate their scope employing various polysubstituted secondary N-alkylpropargylamines **1b-m** in combination with tosyl isocyanate **26** (Table 6). In most cases $AuPPh_3Cl$/AgOTf-catalyzed reactions (protocol A) proceeded selectively through the *O*-cyclization mode delivering oxazolidin-2-imines **20** as major products in good to high yields (Table 6, entries 1, 3, 5, 7, 9, 11, 13, 15 and 17). Analogously, AgOTf-catalyzed reactions (protocol B) generally gave rise to the corresponding imidazolidin-2-ones **21** *via* *N*-cyclization (Table 6, entries 2, 4, 6, 8, 10, 12, 14, 16 and 18). However, two exceptions for which we were unable to find any reasonable explanation were observed. Propargylic ureas derived from propargylamines **1k** and **1l** being subjected to protocols A and B in both cases provided imidazolidin-2-ones **21k** and **21l** as major products (Table 6, entries 19-22).

Finally, we decided to check the behavior of N-arylpropargylamine **1m** which might be regarded as a Toste-type substrate. The cationic gold(I) catalyzed *O*-cycloisomerization of **1m**-derived urea confirmed to be extremely chemoselective providing oxazolidin-2-imine **20m** in an excellent yield of 90% as the sole reaction product (Table 6, entry 23). At the same time, the selectivity of the AgOTf-catalyzed *N*-cycloisomerization of this substrate was not that impressive. Nevertheless, imidazolidin-2-one **21m** was isolated as the major product in 46% yield next to oxazolidin-2-imine **20m** which was also obtained in a significant amount of 33% (Table 6, entry 24).

Table 6 Investigation of the substrate scope of the cationic gold- and silver-catalyzed cycloisomerizations of propargylic ureas[a]



A = 5 mol% **$AuPPh_3Cl$**, 5 mol% **AgOTf**, DCM, 2-20h, rt or 50 °C
B = 20 mol% **AgOTf**, toluene, 1-2h, 80 °C

Entry	**1**	R^1	R^2	R^3	Protocol	Yield[b]			
						20	**29**	**21**	**30**
1	**1b**	PMB	*i*Bu	Ph	**A**	**74**[c]	5[c]	6[c]	5[c]
2					**B**	5[c]	nd	**80**	nd
3	**1c**	Bn	Pr	Ph	**A**	**72**[c]	3[c]	8[c]	6[c]
4					**B**	5[c]	traces	**91**	nd
5	**1d**	Bn	*p*-Tol	Ph	**A**	**71**[c]	2[c]	nd	nd
6					**B**	30[c]	1[c]	**67**	nd

Table 6 (continued)

Entry	**1**	R^1	R^2	R^3	Protocol	Yield[b]			
						20	**29**	**21**	**30**
7	**1e**	Cyclooctyl	Pent	Ph	**A**	**71**	nd	28	nd
8					**B**	15	nd	**83**	nd
9	**1f**	PMB	*p*-FC_6H_4	*p*-(*t*Bu)C_6H_4	**A**	**63**[c]	12[c]	nd	nd
10					**B**	24[c]	3[c]	**72**	nd
11	**1g**	$MeOCH_2CH_2$	Pr	*p*-PrC_6H_4	**A**	**90**	nd	nd	nd
12					**B**	5[c]	nd	**46**	nd
13	**1h**	PMB	Pr	Bn	**A**	**73**[c]	nd	6[c]	nd
14					**B**	5[c]	nd	**77**[c]	nd
15	**1i**	PMB	$PhCH_2CH_2$	Bn	**A**	**63**	nd	2[c]	nd
16					**B**	6[c]	nd	**57**	nd
17	**1j**	PMB	Et	Thiophen-3-yl	**A**	**82**	nd	nd	nd
18					**B**	34	nd	**47**	nd
19	**1k**	*t*Bu	*i*Bu	*p*-FC_6H_4	**A**	20[c]	nd	**60**	nd
20					**B**	23[c]	nd	**51**	nd

Table 6 (continued)

Entry	**1**	R^1	R^2	R^3	Protocol	Yield[b]			
						20	**29**	**21**	**30**
21	**1l**	Bn	Ph	Cyclopentyl	**A**	6[c]	1[c]	**42**	nd
22					**B**	23[c]	11[c]	**55**	nd
23	**1m**	Ph	Ph	Ph	**A**	**90**	nd	nd	nd
24					**B**	33[c]	nd	**46**	nd

[a] Reactions were carried out on a 0.2-0.5 mmol scale. For details see experimental section and supporting information.

[b] Isolated yields.

[c] Yield calculated from ^{1}H NMR spectra. nd = not detected or not possible to determine clearly.

The structures of the representative oxazolidin-2-imine **20d** and the corresponding imidazolidin-2-one **21d** were determined by X-ray crystallographic analysis (Figure 6).[74] The connectivity pattern of other obtained oxazolidin-2-imines **20b-j,l,m** and imidazolidin-2-ones **21b-k,m** was verified applying of NMR and IR spectroscopy. The comparison of some characteristic signal values is given in Figure 7. The minor 6-membered products of *O*- and *N*-cycloisomerizations were not isolated in a pure form. Their assignment was performed relying on ^{1}H NMR and IR spectra of mixtures with other reaction products (see experimental section for details).

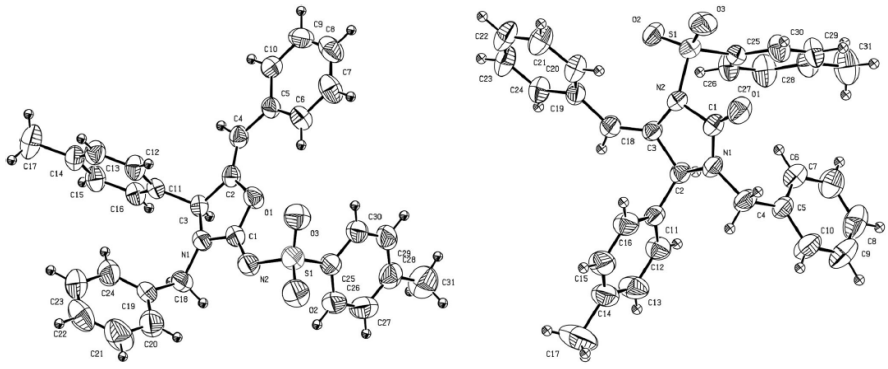


Figure 6 X-ray crystallographic structures of oxazolidin-2-imine **20d** (left) and imidazolidin-2-one **21d** (right), showing thermal ellipsoids at the 50% probability level and atom labeling scheme

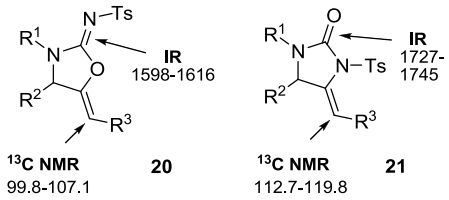
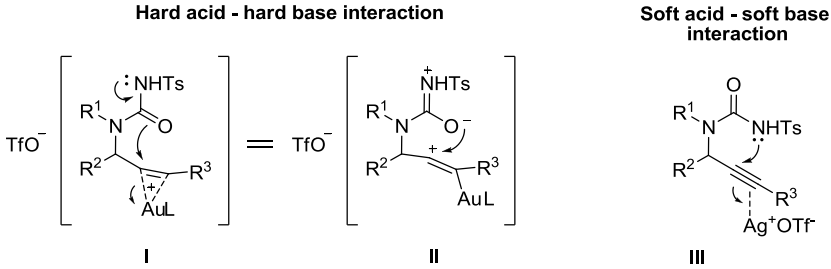


Figure 7 Comparison of C=N/C=O stretching IR absorption peaks and ^{13}C NMR characteristic signal values for oxazolidin-2-imines **20** and imidazolidin-2-ones **21**

Ag[75,76a]- and Au[76]-catalyzed cycloisomerizations involving attack of a heteroatom nucleophile on a C-C multiple bond became an attractive and rapidly growing field of organic synthesis. In our previous study we have demonstrated a remarkable chemoselectivity for the cyclization of 5-chloro-3-(2-alkynylphenylamino)-pyrazin-2(1*H*)-ones using Ag- or Au-catalyzed protocols resulting in the formation of pyrazino[2,1-*b*]quinazolines or 3-indolyl-2(1*H*)-pyrazinones, respectively.[77] It should be noted that it is not always easy to give a precise mechanistic explanation for such observations. To rationalize the outcome of the current propargyl urea cyclization process we decided to apply the Pearson's concept of hard and soft acids and bases (HSAB).[78] Although the HSAB treatment of ambident reactivity of organic compounds[79] has recently gained considerable criticism[80] we are still convinced that it would be appropriate to examine our process for compatibility with the HSAB principle.

We presume that in the $AuPPh_3Cl/AgOTf$-catalyzed process propargylic urea **27** coordinates into cationic Au complex **I** where the triflate counter ion is pushed outside of the ligand sphere. The triple bond in this case might be viewed as completely aurated. The resulting carbocation is a hard Lewis acid which would preferably react with the small and highly electronegative

carbamide oxygen *via* a hard-hard interaction **II**. In the Ag(I)-catalyzed process AgOTf supposedly does not dissociate in the reaction mixture. It exists as a contact ion-pair which could readily form a π-complex with the triple bond of propargylic urea **27**. This π-complex is a highly polarized soft Lewis acid which would preferably react with less electronegative amide nitrogen bearing two acceptors (carbamoyl and tosyl groups) *via* a soft-soft interaction **III**.



Scheme 29 Rationalization of the chemoselectivity of $AuPPh_3Cl$/AgOTf- and AgOTf-catalyzed cycloisomerization processes applying the HSAB principle.

4.2. Conclusions

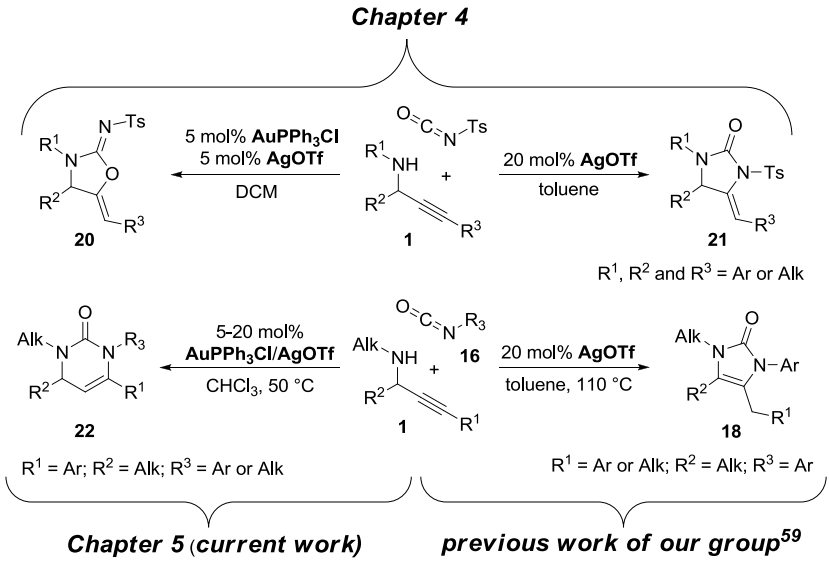
In this chapter we have studied the transition metal-catalyzed O- and N-cycloisomerizations of propargylic ureas to identify their optimal parameters. Two extensive optimization surveys were performed to provide a deeper insight into the mode of action of different catalytic systems. It was shown that the application of cationic Au(I) catalysis generally results in the formation of O-cyclized oxazolidin-2-imines as the major products while the application of AgOTf selectively provides the corresponding N-cyclized imidazolidin-2-ones.

From a synthetic point of view the developed procedures offer straightforward access to a large variety of polysubstituted oxazolidin-2-imines and imidazolidin-2-ones and thus could be regarded as a welcome expansion of previous methodologies (see ***Chapter 1***).

Chapter 5

5. Unexpected Regio- and Chemoselectivity of Cationic Gold-Catalyzed Cycloisomerization of Propargylic Ureas: An Access towards Tetrasubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones

This chapter describes the cationic gold-catalyzed 6-*endo*-dig cycloisomerization of propargylic ureas derived from alkyl or aryl isocyanates leading to 3,4-dihydropyrimidin-2(1*H*)-ones **22**. This work is continuing our efforts on the comparison of cationic Au(I) and Ag(I) catalysis described in ***Chapter 4***. In that sense the results presented herein are complementary to our previously described Ag(I)-catalyzed 5-*exo*-dig cycloisomerization of aryl isocyanate-derived ureas resulting in imidazol-2-ones **18** (***Chapter 1***, Scheme 23).[59]



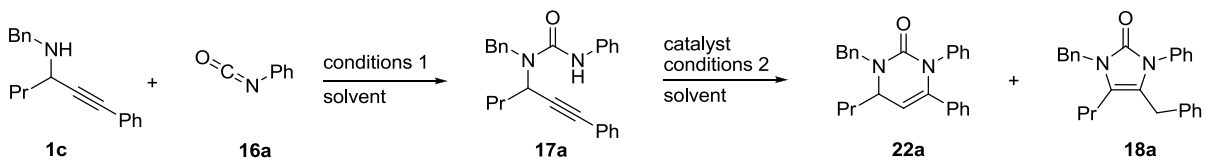
Interestingly the obtained data are very different from what was observed for tosyl isocyanate-derived ureas in ***Chapter 4*** in term of both chemo- and regioselectivity.

5.1. Results and discussion

We selected cycloisomerization of urea **17a**, derived *in situ* from propargylamine **1c** and phenyl isocyanate (**16a)**, as a model reaction for the optimization survey (Table 7). Initially we have found that the reaction catalyzed by 5 mol% of $AuPPh_3Cl/AgOTf$, being conducted for 23 hours at room temperature in $CDCl_3$, produces 3,4-dihydropyrimidin-2(1*H*)-one **22a** in a low yield of 18% next to 76% of uncyclized urea **17a** (Table 7, entry 1). To our great satisfaction the cycloisomerization rate could be dramatically improved by elevating the reaction temperature up to 50 °C, delivering **22a** in a good yield of 84% next to some minor amounts of imidazol-2-one **18a** (Table 7, entry 2). Further we found out that the reaction time could be shorted to 15 hours without any losses in the reaction rate providing even slightly improved yield of **22a** (Table 7, entry 3). However, further reduction to 5 hours reaction gave incomplete conversion of **17a** (Table 7, entry 4). Switching to CD_2Cl_2 as a solvent gave somewhat poorer result in terms of regioselectivity and general cycloisomerization rate (Table 7, entry 5). Changing the counter ion through the use of other silver(I) salts or the use of preformed $[Au(JohnPhos)(MeCN)]SbF_6$ complex as well as the application of persistent N-heterocyclic carbene instead of phosphine ligands, all resulted in either diminished or comparable yield of the desired product (Table 7, entries 6-10). The gold(III) chloride-catalyzed reaction gave very poor cycloisomerization rate while remaining 6-*endo*-dig selective (Table 7, entry 11). Catalytic amounts of a strong Brønsted acid did not facilitate cycloisomerization at all (Table 7, entry 12). The silver(I) triflate catalyzed

reaction selectively producing imidazol-2-one **18a**, which was documented by us previously[59], is also added here for comparison (Table 7, entry 13).

Table 7 Optimization of the reaction parameters of cationic gold-catalyzed cycloisomerization of phenyl isocyanate-derived propargylic urea **17a**[a]



Entry	Solvent	Conditions 1	Catalyst	Conditions 2	Yields[b]		
					22a	**18a**	Uncyclized **17a**
1	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	23h, 25 °C	18	-	76
2	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	23h, 50 °C	84	5	-
3	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	15h, 50 °C	89[c]	6	-
4	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	5h, 50 °C	46	-	51
5	CD_2Cl_2	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	15h, 50 °C	82	10	4
6	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgNTf_2$	15h, 50 °C	87	6	2
7	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgSbF_6$	15h, 50 °C	61	2	35
8	$CDCl_3$	5 min, rt	5 mol% [Au(JohnPhos)(MeCN)]SbF_6	15h, 50 °C	87	3	-

Table 7 (continued)

Entry	Solvent	Conditions 1	Catalyst	Conditions 2	Yields[b]		
					22a	**18a**	Uncyclized **17a**
9	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgBF_4$	15h, 50 °C	58	3	30
10	$CDCl_3$	5 min, rt	5 mol% (IPr)AuCl/AgOTf	15h, 50 °C	88	5	-
11	$CDCl_3$	5 min, rt	5 mol% $AuCl_3$	15h, 50 °C	29	2	57
12	$CDCl_3$	5 min, rt	10 mol% TfOH	15h, 50 °C	-	-	84
13[d]	toluene	1 h, 110°C	20 mol% AgOTf	2h, 110 °C	-	72[e]	-

[a] Reactions were carried out on a 0.1 mmol scale in 0.4 mL of dry solvent. After completion of the indicated time an internal standard (3,4,5-trimethoxybenzaldehyde) was added and the resulting mixture was analyzed by ^1H NMR.

[b] Yields are determined by ^1H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard.

[c] This value corresponds to both NMR and isolated yields from 0.1 mmol and 0.2 mmol scale reactions in $CDCl_3$ and in $CHCl_3$, respectively.

[d] Reproduced from ref.[59].

[g] Isolated yield from a 0.33 mmol scale reaction conducted in 2.5 mL of toluene.

We decided to perform an X-ray crystallographic analysis of both cycloisomerization products to ensure our structural assignments before coming to a detailed substrate scope investigation. The resulting ORTEP representations of 3,4-dihydropyrimidin-2(1*H*)-one **22a** and imidazol-2-one **18a** are shown in Figure 8.

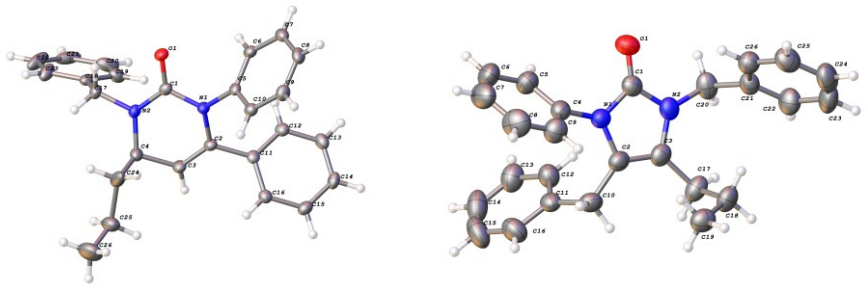
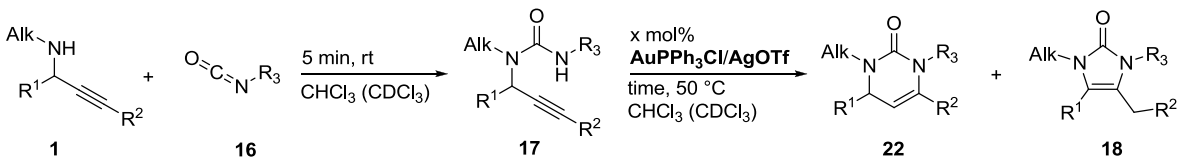


Figure 8 X-ray crystallographic structures of 3,4-dihydropyrimidin-2(1*H*)-one **22a** (left) and imidazol-2-one **18a** (right), showing thermal ellipsoids at the 50% probability level and atom labeling scheme

Having completed the optimization study and structural assignment of the representative products we decided to evaluate the scope and limitations of our process (Table 8). First we reacted propargylamine **1c** with various aromatic isocyanates **16a,b,c**. In all cases the *in situ* formed ureas **17a,b,c** could be successfully cyclized into the expected 3,4-dihydropyrimidin-2(1*H*)-ones **22a,b,c** in high yields ranging from 89% to 93% (Table 8, entries 1-3). The formation of minor imidazol-2-one products **18a,b,c** was also detected but their yields did not exceed 6%. The reaction of **1c** with aliphatic benzyl isocyanate **22d** under the standard conditions gave only 43% yield of desired product **18d** next to 49% of uncyclized urea **17d** (Table 8, entry 4). To our

delight the cycloisomerization could be driven to completion through the increasing of the reaction time and the catalyst loading allowing the isolation of 3,4-dihydropyrimidin-2(1*H*)-one **22d** in an excellent yield of 95% as a single reaction product (Table 8, entry 5). Further we have successfully applied these modified conditions to the reactions of **1c** with a few other aliphatic isocyanates **16e,f,g**. In all cases 3,4-dihydropyrimidin-2(1*H*)-ones **22e,f,g** were produced in very high yields as the only reaction products (Table 8, entries 6-8). Remarkably, an attempt to cyclize the propargyl urea **17h** derived form secondary cyclopentyl isocyanate **16h** almost failed and thus should be regarded rather as a limitation considering that the reaction catalyzed by 20 mol% of $AuPPh_3Cl/AgOTf$ at 50 °C for 22 hours provided only 19% of desired 3,4-dihydropyrimidin-2(1*H*)-one **22e** (Table 8, entry 9). Finally we have evaluated several propargylamines **1b,j,n,o** in combination with various aromatic and aliphatic isocyanates **16a,c,d,i**. In all cases the *in situ* formed propargylic ureas **17i-p** could be efficiently cyclized into corresponding 3,4-dihydropyrimidin-2(1*H*)-ones **22i-p** following the above described trends established for the **1c**-derived ureas **17a-g** (Table 8, entries 10-18).

Table 8 Scope and limitations of cationic gold-catalyzed cycloisomerization of aryl or alkyl isocyanate-derived propargylic ureas **17**[a]



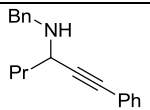
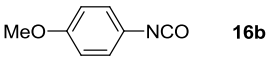
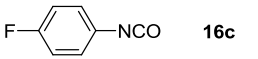
Entry	x	Time	Propargylamine **1**	Isocyanate **16**	Yields[b]		
					22	**18**	Uncyclized **17**
1	5	15	 **1c**	Ph–NCO **16a**	89	6[c]	-
2	5	15	**1c**	 **16b**	92	5[c]	-
3	5	15	**1c**	 **16c**	93	6[c]	-
4	5	15	**1c**	Bn–NCO **16d**	43	-	49
5	15	16.5	**1c**	**16d**	95	-	-

Table 8 (continued)

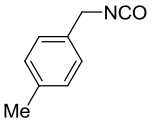
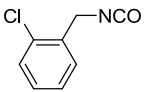
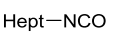
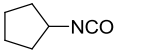
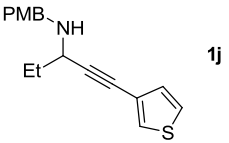
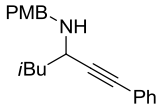
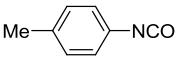
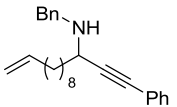
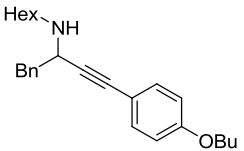
Entry	x	Time	Propargylamine **1**	Isocyanate **16**	Yields[b]		
					22	**18**	Uncyclized **17**
6	15	16.5	**1c**	 **16e**	95	-	-
7	15	16.5	**1c**	 **16f**	93	-	-
8	15	16.5	**1c**	 **16g**	88	-	-
9	20	22	**1c**	 **16h**	19	-	61
10	5	15	 **1j**	**16a**	80	-	-
11	5	15	**1j**	**16c**	91	2[c]	-
12	5	15	**1j**	**16d**	37	-	56
13	15	18.5	**1j**	**16d**	92	-	-

Table 8 (continued)

Entry	x	Time	Propargylamine **1**	Isocyanate **16**	Yields[b]		
					22	**18**	Uncyclized **17**
14	5	15	 **1b**	**16a**	89	7	-
15	5	15	**1b**	 **16i**	88	6	-
16	15	16	**1b**	**16d**	94	-	-
17	5	15	 **1n**	**16a**	90	6[c]	-
18	15	16.5	 **1o**	**16d**	84	-	-

[a] Reactions were carried out on a 0.15-0.45 mmol scale in 0.6-1.8 mL of dry $CHCl_3$ respectively.

[b] Isolated yields.

[c] Yields determined by ^1H NMR from the corresponding 0.1 mmol scale reaction in $CDCl_3$ using 3,4,5-trimethoxybenzaldehyde as internal standard.

5.2. Conclusions

In conclusion, we have discovered an unusual propargyl urea cycloisomerization pathway resulting in the formation of the 3,4-dihydropyrimidin-2(1*H*)-one core through the application of cationic gold catalysis. The overall process relies on the application of easily accessible secondary propargylamines and commercial aryl and alkyl isocyanates allowing straightforward introduction of four diversity points and could be potentially useful for the generation of libraries of biologically active compounds.

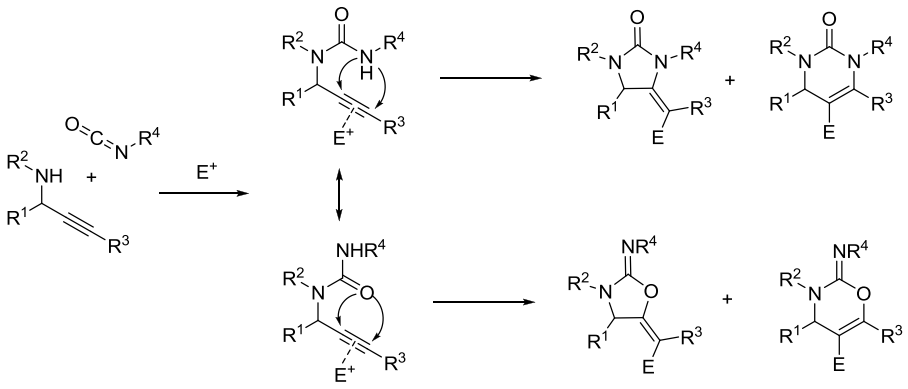
General conclusions and perspectives

The work presented in this thesis lies in the framework of a broad research program devoted to the preparation and utilization of secondary propargylamines which was recently initiated in our group. In that sense our current findings not only complement the existing array of synthetic approaches but also offer some key points interesting for the mechanistic consideration.

In the ***Chapter 2*** we have demonstrated that the substitution of an aldehyde component on a closely related ketone in the A^3-coupling-type process for the purpose of general protocol establishment is not a trivial task which, nevertheless, was successfully solved for the first time.[27] Simultaneously, another synthetic problem such as difficult application of primary amines in the A^3-coupling reactions was also efficiently ameliorated for the second time shortly after the first precedent[25] also originated from our group. In overall, this provided a straightforward and general access towards synthetically useful class of secondary alkylpropargylamines bearing quaternary carbon center. Subsequently, in the ***Chapter 3*** we were first who have shown their synthetic utility through the Ag(I)-mediated tandem guanylation/cycloisomerization reaction leading to structurally interesting class of heterocycles featuring spiro-cyclic guanidine unit.[51,81]

In the ***Chapter 4*** we performed a comparative study on the transition metal-catalyzed cycloisomerizations of propargylic ureas derived *in situ* from secondary propargylamines and tosyl isocyanate highlighting the dependence of

the chemoselectivity of this process on the employed catalytic system.[62] While already in the ***Chapter 5*** devoted to the cationic gold-catalyzed cycloisomerization of aryl and alkyl isocyanate-derived propargylic ureas we came to know that the regio- and chemoselectivity of such processes, apparently, to some extent, are substrate-driven. It is also worth to emphasize that ***Chapter 4*** and ***Chapter 5*** collectively provide a universal entry to a wide range of important small heterocycles such as oxazolidin-2-imines, imidazolidin-2-ones and 3,4-dihydropyrimidin-2(1*H*)-ones starting from the common propargylamine precursors. In this regard, further mechanistic studies involving quantum-chemical calculations might be drawn aiming better understanding of already established processes and, maybe, to help in the development of novel procedures with yet unexplored selectivities. The current work might also be expanded if the cyclization of described propargyl guanidines and ureas would be attempted through the use of different electrophiles (I_2, ICl, PhSeCl *etc.*) instead of transition metal catalysis (Scheme 30).[82]



Scheme 30 An outlook towards an electrophile-mediated cyclizations of propargyl ureas.

Finally, we are also anticipating that some of our methodologies could be useful for the targeted synthesis of compound libraries for the biological screening.

Experimental part

General information

^{1}H and ^{13}C NMR spectra were recorded with 300 and 75 MHz respectively (unless otherwise specified) using Bruker Avance instruments. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference.

Low resolution mass spectra were recorded using a Thermo Finnigan LCQ Advantage apparatus (ESI) or a Hewlett-Packard 5989A mass spectrometer (EI and CI mode).

High-resolution EI mass spectra were recorded on a Kratos MS50TC system with a resolution of 10000. The ion source temperature was 150-250 °C, as required. High-resolution ESI mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL/min and spectra were obtained in positive ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

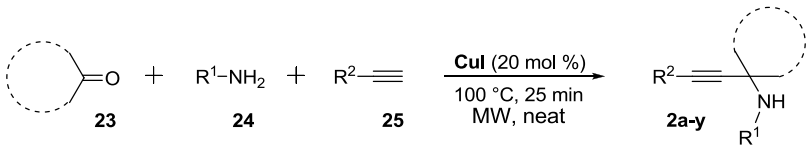
Infrared (IR) spectra were recorded neat on a Bruker ALPHA FT-IR Spectrometer, and wavelengths are reported in cm^{-1}.

The microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W and utilization of the standard absorbance level of 300 W. The reactions were carried out in 10 mL glass tubes, sealed with a Teflon septum and placed in the microwave

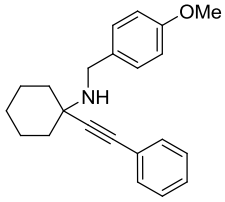
cavity. The reactions were irradiated at the required set temperature for the stipulated time and then cooled to ambient temperature with air jet cooling.

Chapter 2

General procedure for the synthesis of secondary propargylamines 2



To a microwave vial equipped with a magnetic stirring bar ketone (1.2 mmol), primary amine (1 mmol), acetylene (1.2 mmol) and CuI (38 mg, 20 mol %) were added. The mixture was degassed and flushed with argon. The reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor at a set temperature of 100 °C and a maximum power of 80 W for 25 min. Upon completion of the reaction the vial was cooled with a stream of air. The resulting reaction mixture was directly purified by column chromatography over silica gel (eluent 10–30% EtOAc in heptane) to afford the corresponding propargylamine.



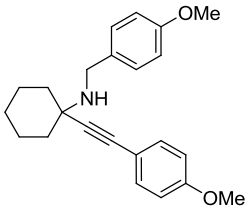
2a: 76%

***N*-(4-methoxybenzyl)-1-(phenylethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.41 (m, 2H), 7.40-7.25 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 3.91 (s, 2H), 3.78 (s, 3H), 2.10-1.90 (m, 2H), 1.82-1.16 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 133.2, 131.6, 129.6, 128.2, 127.7, 123.7, 113.8, 93.6, 84.7, 55.25, 55.22, 47.4, 38.2, 25.9, 23.0.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{22}H_{25}ON$: 319.1936; found: 319.1936.



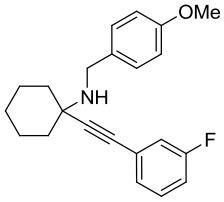
2b: 75%

***N*-(4-methoxybenzyl)-1-(2-(4-methoxyphenyl)ethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J=8.6 Hz, 2H), 7.30 (d, J=8.6 Hz, 2H), 6.89-6.80 (m, 4H), 3.90 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.01-1.87 (m, 2H), 1.77-1.16 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 158.5, 133.3, 133.0, 129.6, 115.8, 113.84, 113.80, 92.0, 84.4, 55.27, 55.25, 47.4, 38.3, 26.0, 23.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}O_2N$: 349.2042; found: 349.2052.



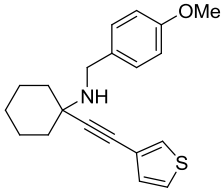
2c: 64%

***N*-(4-methoxybenzyl)-1-(2-(3-fluorophenyl)ethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.20 (m, 4H), 7.18-7.10 (m, 1H), 7.04-6.96 (m, 1H), 6.86 (d, J=8.60 Hz, 2H), 3.89 (s, 2H), 3.79 (s, 3H), 2.01-1.89 (m, 2H), 1.79-1.19 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 160.8, 158.6, 133.1, 129.8, 129.7, 129.6, 127.6, 127.6, 125.6, 125.5, 118.6, 118.3, 115.2, 115.0, 113.8, 94.8, 83.6, 83.5, 55.3, 55.2, 47.4, 38.1, 25.9, 23.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{22}H_{24}ONF$: 337.1842; found: 337.1844.



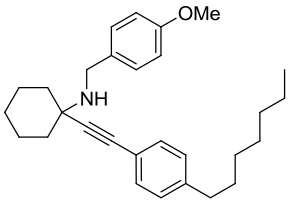
2d: 75%

***N*-(4-methoxybenzyl)-1-(2-(thiophen-3-yl)ethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.38 (m, 1 H), 7.33-7.23 (m, 3H), 7.14-7.09 (m, 1H), 6.86 (d, J=8.6 Hz, 2H), 3.89 (s, 2H), 3.79 (s, 3H), 2.01-1.88 (m, 2H), 1.78-1.17 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 133.2, 130.1, 129.6, 127.8, 125.1, 122.6, 113.8, 93.2, 79.5, 55.3, 47.4, 38.2, 25.9, 23.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{20}H_{23}ONS$: 325.1500; found: 325.1501.



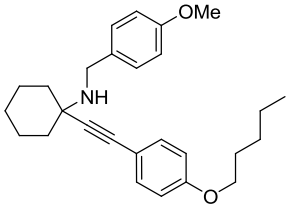
2e: 74%

***N*-(4-methoxybenzyl)-1-(2-(4-heptylphenyl)ethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): 7.37 (d, J=8.0 Hz, 2H), 7.3 (d, J=8.6 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 3.91 (s, 2H), 3.78 (s, 3H), 2.63-2.53 (t, J=7.7, Hz, 2H), 2.01-1.89 (m, 2H); 1.77-1.16 (m, 18H); 0.93-0.82 (t, J=6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 158.6, 142.9, 133.3, 131.6, 129.7, 128.4, 120.8, 113.8, 92.9, 84.8, 55.33, 55.28, 47.5, 38.3, 35.9, 31.8, 31.4, 29.22, 29.20, 26.0, 23.1, 22.7, 14.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{29}H_{39}ON$: 417.3032; found: 417.3032.



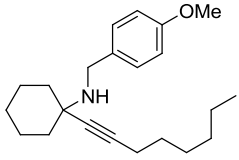
2f: 89%

***N*-(4-methoxybenzyl)-1-(2-(4-(pentyloxy)phenyl)ethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): 7.38 (d, J=8.6 Hz, 2H), 7.30 (d, J=8.5 Hz, 2H), 6.88-6.80 (m 4H), 3.99-3.87 (m, 4H), 3.78 (s, 3H), 2.00-1.78 (m, 2H), 1.84-1.18 (m, 14 H), 0.97-0.89 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 158.8, 158.6, 133.3, 133.0, 129.7, 115.6, 114.4, 113.8, 91.9, 84.5, 68.1, 55.31, 55.29, 47.4, 38.3, 28.9, 28.2, 26.0, 23.1, 22.5, 14.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{27}H_{35}O_2N$: 405.2668; found: 405.2661.



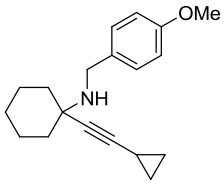
2g: 31%

***N*-(4-methoxybenzyl)-1-(oct-1-ynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J=8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 3.82 (s, 2H), 3.79 (s, 3H), 2.30-2.20 (t, J=6.8 Hz, 2H), 1.90-1.75 (m, 2H), 1.70-1.08 (m, 16H), 0.94-0.84 (t, J=6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 133.4, 129.6, 113.8, 84.5, 83.9, 55.3, 54.8, 47.3, 38.4, 31.4, 29.2, 28.6, 26.0, 23.0, 22.6, 18.7, 14.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{22}H_{33}ON$: 327.2562; found: 327.2563.



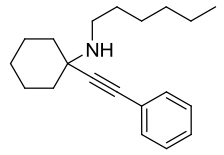
2h: 48%

***N*-(4-methoxybenzyl)-1-(2-cyclopropylethynyl)cyclohexanamine**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, J=8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 3.79 (s, 5H), 1.85-1.74 (m, 2H), 1.7-1.11 (m, 9H), 0.82-0.61 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.49, 133.39, 129.59, 113.76, 87.72, 79.06, 55.26, 54.69, 47.23, 38.38, 25.95, 22.98, 8.57, -0.43.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{19}H_{25}ON$: 283.1936; found 283.1932.



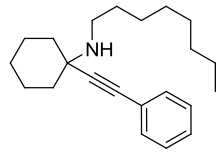
2i: 61%

***N*-hexyl-1-(2-phenylethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.36 (m, 2H), 7.34-7.20 (m, 3H), 2.85-2.72 (t, J=7.1 Hz, 2H), 2.00-1.86 (m, 2H), 1.77-1.13 (m, 16H), 0.94-0.80 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 131.6, 128.2, 127.7, 123.8, 93.7, 84.4, 55.0, 43.3, 38.3, 31.8, 30.7, 27.2, 26.0, 23.1, 22.7, 14.1.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{20}H_{29}N$: 283.2300; found: 283.2289.



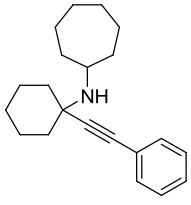
2j: 77%

***N*-octyl-1-(2-phenylethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): 7.47-7.36 (m, 2H), 7.32-7.24 (m, 3H), 2.84-2.73 (t, J=7.15 Hz, 2H), 2.00-1.87 (m, 2H), 1.75-1.14 (m, 20 H), 0.92-0.80 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 131.6, 128.2, 127.7, 123.8, 93.7, 84.4, 55.0, 43.3, 38.3, 31.9, 30.7, 29.6, 29.3, 27.5, 26.0, 23.1, 22.7, 14.1.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{22}H_{33}N$: 311.2613; found: 311.2605.



***N*-(1-(2-phenylethynyl)cyclohexyl)cycloheptanamine**

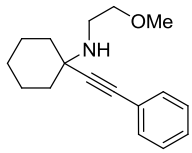
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.35 (m, 2H), 7.35-7.17 (m, 3H), 3.14-2.99 (m, 1H), 2.02-1.81 (m, 4H), 1.74-1.33 (m, 16H), 1.29-1.00 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5, 128.2, 127.6, 123.9, 94.3, 83.9, 55.6, 54.7, 39.2, 38.2, 28.2, 25.8,

24.7, 23.2.

2k: 46%

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{21}H_{29}N$: 295.2300; found: 295.2315.



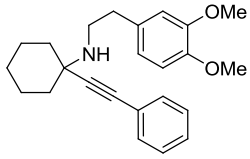
2l: 62%

***N*-(2-methoxyethyl)-1-(2-phenylethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.37 (m, 2H), 7.31-7.23 (m, 3H), 3.60-3.51 (t, J=5.2 Hz, 2H), 3.37 (s, 3H), 3.04-2.95 (t, J=5.2 Hz, 2H), 2.01-1.87 (m, 2H), 1.77-1.13 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 131.6, 128.2, 127.7, 123.7, 93.2, 84.7, 72.5, 58.6, 54.8, 42.5, 38.2, 25.9, 23.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{17}H_{23}ON$: 257.1780; found: 257.1770.



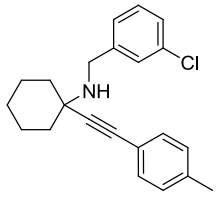
2m: 68%

***N*-(3,4-dimethoxyphenethyl)-1-(2-phenylethynyl)cyclohexanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.34 (m, 2H), 7.32-7.22 (m, 3H), 6.83-6.72 (m, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.16-2.99 (m, 2H), 2.86-2.73 (t, J=7.0 Hz, 2H), 1.98-1.83 (m, 2H), 1.74-1.12 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 147.4, 132.5, 131.6, 128.2, 127.7, 123.6, 120.6, 111.8, 111.2, 93.4, 84.5, 55.9, 55.7, 55.0, 44.3, 38.2, 36.2, 25.9, 23.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{24}H_{29}O_2N$: 363.2198; found: 363.2181.



2n: 82%

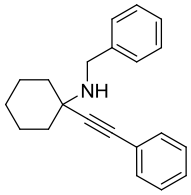
***N*-(3-chlorobenzyl)-1-(2-*p*-tolylethynyl)cyclohexanamine**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 (s, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.29-7.17 (m, 3H), 7.12 (d, J=8.0 Hz, 2H), 3.94 (s, 2H), 2.35 (s, 3H), 2.01-1.87 (m, 2H), 1.78-1.17 (m, 8H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.38, 137.90, 134.19, 131.56, 129.63, 129.04, 128.55, 126.98, 126.56, 120.47, 92.51, 84.91, 55.31, 47.55, 38.30, 25.94, 23.02, 21.47.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{22}H_{24}NCl$:

337.1597; found: 337.1597.



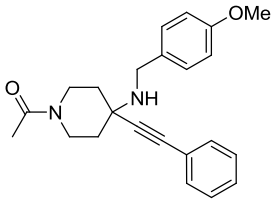
2o: 74%

***N*-benzyl-1-(2-phenylethynyl)cyclohexanamine**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51-7.16 (m, 10H), 3.97 (s, 2H), 2.03-1.90 (m, 2H), 1.80-1.18 (m, 8H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.07, 131.64, 128.46, 128.41, 128.24, 127.76, 126.84, 123.65, 93.57, 84.69, 55.29, 48.06, 38.20, 25.92, 23.00.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{21}H_{23}N$: 289.1830; found: 289.1811.



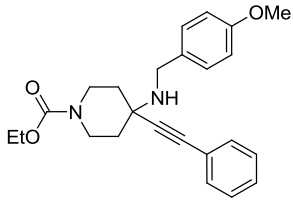
2p: 64%

1-(4-(4-methoxybenzylamino)-4-(2-phenylethynyl)piperidin-1-yl)ethanone

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.40 (m, 2H), 7.37-7.25 (m, 5H), 6.87 (d, J=8.6 Hz, 2H), 4.38-4.25 (m, 1H), 3.92 (s, 2H), 3.83-3.68 (m, 4H), 3.54-3.41 (m, 1H), 3.32-3.19 (m, 1H), 2.11 (s, 3H), 2.04-1.91 (m, 2H), 1.78-1.63 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 158.8, 132.5, 131.7, 129.6, 128.4, 128.3, 122.8, 113.9, 91.2, 85.8, 55.3, 53.8, 47.4, 43.4, 38.4, 38.0, 37.1, 21.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{26}O_2N_2$: 362.1994; found: 362.1968.



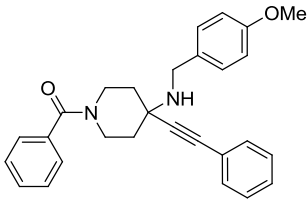
2q: 82%

Ethyl 4-(4-methoxybenzylamino)-4-(2-phenylethynyl)piperidine-1-carboxylate

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.40 (m, 2H), 7.36-7.27 (m, 5H), 6.87 (d, J=8.6 Hz, 2H), 4.19-4.09 (q, J=7.1 Hz, 2H), 4.09-3.93 (m, 2H), 3.91 (s, 2H), 3.80 (s, 3H), 3.39-3.22 (m, 2H), 2.01-1.85 (m, 2H), 1.76-1.59 (m, 2H), 1.30-1.23 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 155.5, 132.7, 131.7, 129.6, 128.4, 128.2, 123.0, 113.9, 91.4, 85.8, 61.3, 55.3, 53.8, 47.4, 40.8, 37.3, 14.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{24}H_{28}O_3N_2$: 392.2100; found: 392.2096.



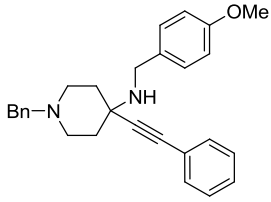
2r: 61%

(4-(4-methoxybenzylamino)-4-(2-phenylethynyl)piperidin-1-yl)(phenyl)methanone

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.44 (m, 2H), 7.40 (s, 5H), 7.36-7.27 (m, 5H), 6.87 (d, J=8.6 Hz, 2H), 4.58-4.34 (m, 1H), 3.91 (s, 2H), 3.83-3.59 (m, 4H), 3.55-3.36 (m, 2H), 2.14-1.59 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.32, 158.77, 136.19, 132.52, 131.75, 129.63, 129.59, 128.52, 128.43, 128.36, 126.89, 122.84, 113.93, 91.29, 85.87, 55.31, 53.96, 47.48, 44.71, 39.14, 38.19, 37.27.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{28}H_{28}O_2N_2$: 424.2151; found: 424.2076.



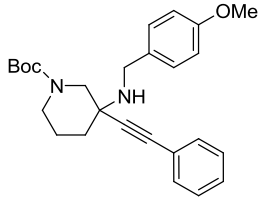
2s: 38%

***N*-(4-methoxybenzyl)-1-benzyl-4-(2-phenylethynyl)piperidin-4-amine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.39 (m, 2H), 7.37-7.19 (m, 10H), 6.85 (d, J=8.6 Hz, 2H), 3.90 (s, 2H), 3.77 (s, 3H), 3.56 (s, 2H), 2.86-2.71 (m, 2H), 2.53-2.37 (m, 2H), 2.01-1.89 (m, 2H), 1.87-1.71 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.66, 138.67, 133.09, 131.70, 129.64, 129.17, 128.34, 128.24, 127.99, 126.99, 123.49, 113.86, 92.77, 85.54, 62.93, 55.31, 53.74, 50.30, 47.44, 37.69.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{28}H_{30}ON_2$: 410.2358; found: 410.2357.



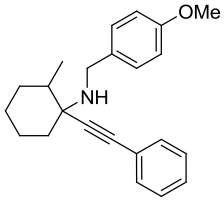
2t: 61%

***tert*-butyl 3-(4-methoxybenzylamino)-3-(2-phenylethynyl)piperidine-1-carboxylate**

^{1}H NMR (300 MHz, $CDCl_3$): 7.48-7.38 (m, 2H), 7.35-7.23 (m, 5H), 6.85 (d, J=8.3 Hz, 2H), 397-3.55 (m, 7H), 3.38-3.13 (m, 2H), 2.07-1.30 (m, 13H).

^{13}C NMR (75 MHz, $CDCl_3$): 158.7, 154.8, 132.8, 131.8, 129.6, 128.2, 128.0, 123.2, 113.8, 91.3, 84.9, 79.5, 55.3, 53.9, 53.3, 52.1, 47.6, 44.7, 43.5, 36.8, 28.4, 21.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{26}H_{32}O_3N_2$: 420.2413; found: 420.2421.



2u: 33% 10:1 dr

***N*-(4-methoxybenzyl)-2-methyl-1-(2-phenylethynyl)cyclohexanamine**

Major diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49-7.39 (m, 2H), 7.36-7.26 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 3.87-3.72 (m, 5H), 2.10-1.92 (m, 2H), 1.73-1.48 (m, 6H), 1.46-1.30 (m, 1H), 1.06 (d, J=7.0, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.52, 133.46, 131.63, 129.57, 128.22, 127.63, 123.83, 113.73, 95.00, 83.46, 56.70, 55.28, 47.01, 39.34, 34.65, 29.20, 23.92, 21.46, 15.14.

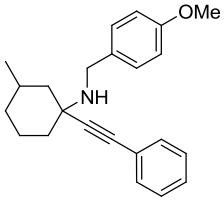
HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}ON$: 333.2093; found: 333.2098.

Minor diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51-7.42 (m, 2H), 7.36-7.24 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 3.96 (d, J=11.6 Hz, 1H), 3.85-3.72 (m, 4H), 2.26-2.14 (m, 1H), 1.77-1.38 (m, 8H); 1.03 (d, J=6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.60, 133.23, 131.70, 129.65, 128.27, 127.77, 123.77, 113.88, 91.25, 86.33, 59.85, 55.30, 47.43, 41.36, 36.87, 32.12, 25.81, 23.52, 16.63.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}ON$: 333.2093; found: 333.2106.



2v: 75% 3:1 dr

***N*-(4-methoxybenzyl)-3-methyl-1-(2-phenylethynyl)cyclohexanamine**

Major diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51-7.36 (m, 2H), 7.36-7.21 (m, 5H), 6.85 (d, J=8.6 Hz, 2H), 3.87-3.65 (m, 5H), 2.07-1.31 (m, 8H), 0.98-0.72 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): 158.51, 133,43, 131.63, 129.54, 128.20, 127.65, 123.68, 113.70, 95.71, 81.91, 55.25, 53.16, 47.49, 45.46, 36.34, 34.50, 26.50, 22.36, 20.70.

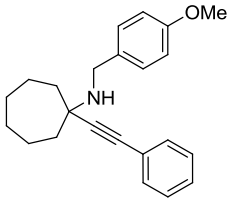
HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}ON$: 333.2093; found: 333.2088.

Minor diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50-7.40 (m, 2H), 7.35-7.26 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 3.93 (s, 2H), 3.78 (s, 3H), 2.05-1.66 (m, 6H), 1.44-1,30 (m, 1H), 1.19-1.06 (t, J=12, 1H), 0.98-0.80 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.57, 133.12, 131.64, 129.64, 128.25, 127.77, 123.64, 113.83, 93.56, 84.91, 55.92, 55.26, 47.46, 46.74, 38.06, 34.75, 29.58, 23.23, 22.39.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}ON$: 333.2093; found: 333.2088.



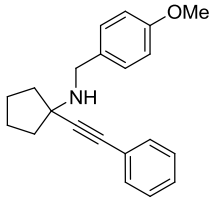
2w: 21%

***N*-(4-methoxybenzyl)-1-(2-phenylethynyl)cycloheptanamine**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.40 (m, 2H), 7.37-7.25 (m, 5H), 6.85 (d, J=8.6 Hz, 2H), 3.88 (s, 2H), 3.78 (s, 3H), 2.08-1.91 (m, 2H); 1.85-1.50 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 133.1, 131.6, 129.6, 128.2, 127.7, 123.7, 113.8, 94.7, 83.8, 58.3, 55.2, 48.0, 40.7, 28.2, 22.7.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}ON$: 333.2093; found: 333.2093.



2x: 20%

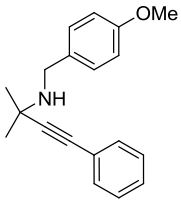
***N*-(4-methoxybenzyl)-1-(2-phenylethynyl)cyclopentanamine**

The reaction was run under conventional heating at 100°C for 20 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.42 (m, 2H), 7.38-7.30 (m, 5H), 6.89 (d, J=8.6 Hz, 2H), 3.92 (s, 2H), 3.82 (s, 3H), 2.13-2.02 (m, 2H), 1.93-1.81 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 133.1, 131.6, 129.6, 128.2, 127.7, 123.7, 113.8, 94.5, 82.9, 61.2, 55.3, 49.2, 40.7, 23.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{21}H_{23}ON$: 305.1780; found: 305.1782.



2y: 30%

***N*-(4-methoxybenzyl)-2-methyl-4-phenylbut-3-yn-2-amine**

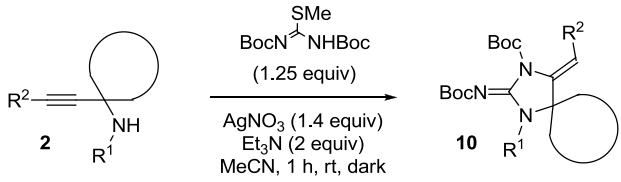
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.39 (m, 2H), 7.35-7.25 (m, 5H), 6.86 (d, J=8.6 Hz, 2H), 3.90 (s, 2H), 3.79 (s, 3H), 1.50 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 132.7, 131.6, 129.7, 128.3, 127.9, 123.4, 113.9, 94.5, 82.4, 55.3, 50.7, 48.5, 29.6.

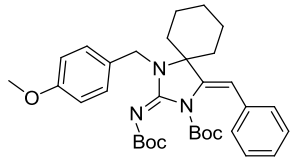
HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{19}H_{21}ON$: 279.1623; found: 279.1626.

Chapter 3

General procedure for the Ag(I)-mediated tandem guanylation/intramolecular cyclization



To a solution of the respective propargylamine **2** (0.5 mmol) and *N,N'*-di-Boc-S-methylisothiourea (181 mg, 0.625 mmol) in MeCN (2.5 mL) triethylamine (101 mg, 1 mmol) was added under an argon atmosphere. After dissolution, silver nitrate (119 mg, 0.7 mmol) was added and the heterogeneous reaction mixture was vigorously stirred for 1h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to afford an oily substance. The crude product was loaded onto a silica gel column for chromatography (eluent 20-100% EtOAc in heptane) providing the target *bis-Boc*-protected-2-iminoimidazoline **10** as an amorphous white foam.

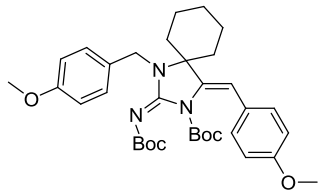


10a: 85%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.54 (m, 2H), 7.34-7.30 (m, 2H), 7.28-7.18 (m, 3H), 6.82 (d, J=8.6 Hz, 2H), 6.33 (s, 1H), 4.6 (s, 2H), 3.77 (s, 3H), 1.80-1.43 (m, 19H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 158.7, 152.0, 148.5, 138.7, 136.2, 130.2, 129.0, 128.6, 128.2, 127.3, 116.7, 113.8, 82.7, 79.1, 64.8, 55.2, 43.1, 31.9, 28.2, 27.3, 24.9, 23.0.

MS (ESI): m/z = 562.3 $[M+H]^+$.

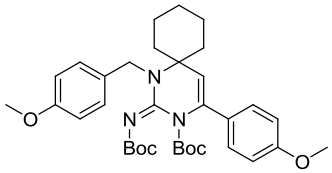


10b: 87% (major product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J=8.6 Hz, 2H), 7.24 (d, J=8.6 Hz, 2H), 6.89 (d, J=8.6 Hz, 2H), 6.8 (d, J=8.6 Hz, 2H), 6.27 (s, 1H), 4.59 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 1.80-1.42 (m, 19H), 1.07 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 158.8, 158.7, 152.3, 148.7, 137.1, 130.4, 130.2, 128.8, 128.6, 116.4, 113.8, 113.6, 82.5, 79.1, 64.9, 55.3, 55.2, 43.1, 31.9, 28.2, 27.4, 24.9, 23.0.

MS (ESI): m/z = 593.2 $[M+H]^+$.

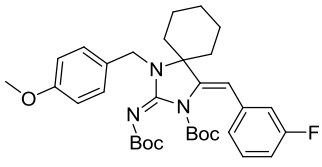


10b': 9% (minor product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J=8.6 Hz, 2H), 7.20 (d, J=8.6 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 5.76 (s, 1H), 4.88 (bs, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 1.83-1.40 (m, 19H), 1.15 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 159.6, 158.4, 151.9, 149.5, 139.1, 131.1, 130.6, 128.1, 127.4, 119.2, 113.8, 113.6, 82.5, 78.6, 60.1, 55.4, 55.2, 46.8, 34.7, 28.3, 27.6, 25.0, 23.3.

MS (ESI): m/z = 593.2 $[M+H]^+$.

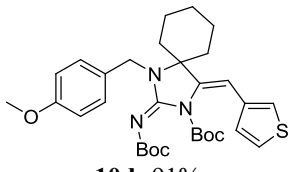


10c: 95%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.19 (m, 5H), 6.99-6.89 (m, 1H), 6.82 (d, J=8.6 Hz, 2H), 6.30 (s, 1H), 4.60 (s, 2H), 3.77 (s, 3H), 1.82-1.45 (m, 19H), 1.07 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4, 161.1, 160.2, 158.7, 151.9, 148.3, 140.0, 138.3, 138.2, 130.0, 129.7, 129.6, 128.6, 124.8, 124.7, 115.8, 115.68, 115.64, 115.55, 114.3, 114.1, 113.8, 82.9, 79.3, 64.9, 55.2, 43.1, 31.9, 28.2, 27.4, 24.8, 23.0.

MS (ESI): m/z = 580.8 $[M+H]^+$.



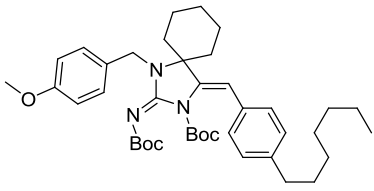
10d: 91%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.47 (m, 1H), 7.45-7.37 (m, 1H), 7.32-7.17 (m, 3H), 6.80 (d, J=8.6 Hz, 2H), 6.40 (s, 1H), 4.59 (s, 2H), 3.76 (s, 3H), 1.78-1.44 (m, 19 H), 1.12 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 158.7, 152.3, 148.8, 138.1, 137.0, 130.1, 128.6, 128.4,

124.9, 124.4, 113.8, 112.0, 82.6, 79.1, 64.9, 55.2, 43.1, 31.9, 28.2, 27.4, 24.8, 24.0.

MS (ESI): m/z = 568.8 $[M+H]^+$.

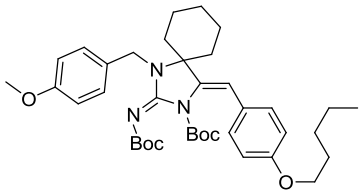


10e: 87%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=7.9 Hz, 2H), 7.24 (d, J=8.6 Hz, 2H), 7.16 (d, J=7.9 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.31 (s, 1H), 4.60 (s, 2H), 3.77 (s, 3H), 2.64-2.54 (t, J=7.4 Hz, 2H), 1.81-1.09 (m, 29H), 1.03 (s, 9H), 0.91-0.84 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 158.7, 152.1, 148.6, 142.2, 137.9, 133.5, 130.2, 128.9, 128.6, 128.3, 116.7, 113.8, 82.5, 79.1, 64.8, 55.2, 43.1, 35.7, 31.94, 31.87, 31.6, 29.2, 29.1, 28.3, 27.3, 24.9, 23.0, 22.7, 14.1.

MS (ESI): m/z = 661.1 $[M+H]^+$.

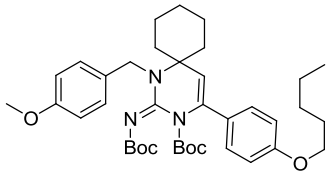


10f: 75% (major product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J=8.6 Hz, 2H), 7.24 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.27 (s, 1H), 4.59 (s, 2H), 4.02-3.90 (t, J=6.60 Hz, 2H), 3.77 (s, 3H), 1.87-1.33 (m, 25H), 1.07 (s, 9H), 0.97-0.90 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 158.7, 158.3, 152.2, 148.7, 136.9, 130.3, 130.2, 128.60, 128.57, 116.5, 114.2, 113.8, 82.4, 79.0, 68.1, 64.9, 55.2, 43.1, 31.9, 28.9, 28.25, 28.15, 27.4, 24.9, 23.0, 22.5, 14.0.

MS (ESI): m/z = 648.6 $[M+H]^+$.



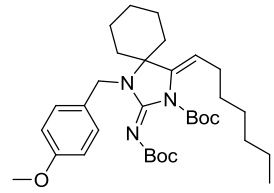
10f': 20% (minor product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=8.6 Hz, 2H), 7.18 (d, J=8.6 Hz, 2H), 6.91 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 6.73 (s, 1H), 4.97-4.73 (m, 2H), 4.02-3.94 (t, J=6.60 Hz, 2H), 3.75 (s, 3H), 1.87-1.31 (m, 25H), 1.13 (s, 9H), 0.98-0.90 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 159.1, 158.4, 151.9, 149.5, 139.1, 131.0, 130.3, 128.1, 127.3, 119.0, 114.2, 113.8, 82.4, 78.6, 68.1, 60.0, 55.2, 46.7, 34.7, 28.9, 28.3, 28.0, 27.6,

25.0, 23.3, 22.5, 14.0.

MS (ESI): m/z = 648.6 $[M+H]^+$.

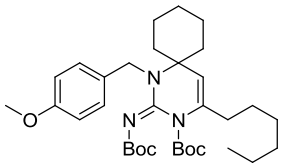


10g: 77% (major product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J=8.6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 5.43-5.33 (t, J=6.7 Hz, 1H), 4.54 (s, 2H), 3.78 (s, 3H), 2.22-2.11 (m, 2H), 1.70-1.19 (m, 36H); 0.94-0.84 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 158.6, 152.7, 149.8, 138.1, 130.4, 128.5, 119.8, 113.7, 82.6, 78.7, 64.3, 55.2, 43.0, 32.0, 31.8, 29.2, 29.0, 28.5, 28.2, 28.1, 24.9, 23.1, 22.6, 14.1.

MS (ESI): m/z = 571.0 $[M+H]^+$.

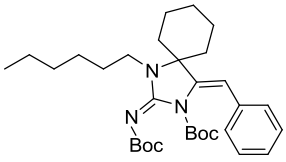


10g': 19% (minor product)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J=8.6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 5.50 (s, 1H), 4.81 (bs, 2H), 3.78 (s, 3H), 2.58-2.48 (t, J=7.7 Hz, 2H), 1.69-1.27 (m, 36H); 0.94-0.84 (t, J=6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 158.4, 152.4, 149.9, 140.5, 131.2, 128.1, 121.6, 113.7, 82.7, 78.3, 59.8, 55.2, 46.5, 34.7, 33.1, 31.6, 29.0, 28.3, 28.2, 28.0, 25.0, 23.2, 22.6, 14.1.

MS (ESI): m/z = 571.2 $[M+H]^+$.

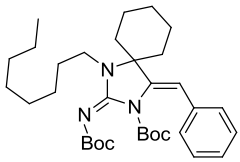


10i: 95%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.51 (m, 2H), 7.36-7.28 (m, 2H), 7.24-7.16 (m, 1H), 6.33 (s, 1H), 3.32-3.18 (m, 2H), 1.88-1.44 (m, 19H), 1.36-1.14 (m, 8H), 1.00 (s, 9H), 0.90-0.84 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 150.9, 148.5, 138.9, 136.3, 128.9, 128.2, 127.2, 116.5, 82.4, 78.9, 64.6, 40.5, 31.9, 31.6, 29.7, 28.3, 27.3, 26.7, 24.9, 23.0, 22.6, 14.1.

MS (ESI): m/z = 526.6 $[M+H]^+$.

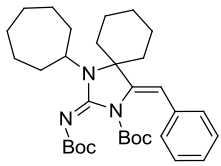


10j: 96%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.50 (m, 2H), 7.38-7.28 (m, 2H), 7.24-7.15 (m, 1H), 6.34 (s, 1H), 3.33-3.19 (t, J=7.90 Hz, 2H), 1.88-1.46 (m, 19H), 1.37-1.15 (m, 12H), 1.01 (s, 9H), 0.92-0.82 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 150.9, 148.5, 138.9, 136.3, 128.9, 128.2, 127.2, 116.5, 82.4, 78.9, 64.6, 40.5, 31.9, 31.8, 29.7, 29.3, 29.2, 28.3, 27.3, 27.0, 24.9, 23.0, 22.6, 14.1.

MS (ESI): m/z = 554.8 $[M+H]^+$.

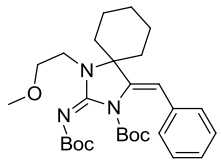


10k: 90%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.52 (m, 2H), 7.37-7.28 (m, 2H), 7.25-7.15 (m, 1H), 6.34 (s, 1H), 3.48-2.98 (m, 1H), 2.79-2.39 (m, 2H), 1.90-1.23 (m, 29H), 0.99 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 148.5, 139.1, 136.6, 128.8, 128.2, 127.0, 116.0, 82.3, 78.5, 65.4, 54.9, 32.9, 32.0, 28.3, 27.7, 27.3, 26.3, 24.8, 23.0.

MS (ESI): m/z = 538.8 $[M+H]^+$.

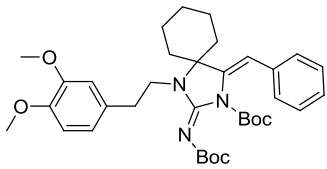


10l: 77%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.52 (m, 2H), 7.37-7.28 (m, 2H), 7.25-7.17 (m, 1H), 6.36 (s, 1H), 3.55-3.49 (m, 4H), 3.33 (s, 3H), 1.87-1.62 (m, 10H), 1.57 (s, 9H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 151.3, 148.5, 138.8, 136.2, 128.9, 128.2, 127.2, 116.8, 82.6, 79.2, 70.6, 64.5, 58.7, 40.3, 31.7, 28.2, 27.3, 24.8, 23.1.

MS (ESI): m/z = 500.8 $[M+H]^+$.



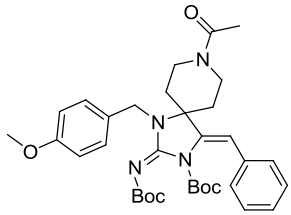
10m: 87%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.51 (m, 2H), 7.38-7.29 (m, 2H), 7.25-7.18 (m, 1H), 6.85-6.73 (m, 3H), 6.30 (s, 1H), 3.89-3.79 (m, 6H), 3.55-3.43 (m, 2H), 2.95-2.83 (m, 2H), 1.83-1.48 (m, 19H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 150.6, 148.8, 148.5, 147.5, 138.8, 136.2, 131.9, 128.9, 128.2, 127.3, 120.7, 116.6, 112.5, 111.1, 82.6, 78.9, 64.6, 55.9, 42.2, 34.7, 31.7, 28.3, 27.3,

24.9, 23.0.

MS (ESI): m/z = 606.7 $[M+H]^+$.

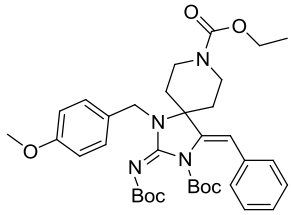


10p: 67%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.53 (m, 2H), 7.45-7.18 (m, 5H), 6.82 (d, J=8.6 Hz, 2H), 6.27 (s, 1H), 4.74-4.39 (m, 3H), 3.84-3.65 (m, 4H), 3.48-3.29 (m, 1H), 3.14-2.95 (m, 1H), 2.09 (s, 3H), 1.98-1.53 (m, 13H), 1.03 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 159.8, 158.9, 151.3, 148.2, 137.3, 135.4, 129.4, 129.0, 128.5, 128.4, 127.8, 117.1, 114.0, 83.3, 79.5, 62.7, 55.2, 43.3, 43.0, 38.4, 31.9, 30.7, 28.2, 27.3, 21.4.

MS (ESI): m/z = 605.9 $[M+H]^+$.

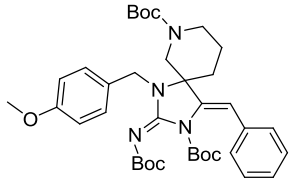


10q: 66%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.52 (m, 2H), 7.42-7.31 (m, 2H), 7.29-7.18 (m, 3H), 6.86-6.75 (m, 2H), 6.27 (s, 1H), 4.6 (s, 2H), 4.24-3.92 (m, 4H), 3.77 (s, 3H), 3.24-3.06 (t, J=12.6 Hz, 2H), 1.96-1.45 (m, 13H), 1.30-1.22 (t, J= 6.8 Hz, 3H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 158.9, 155.4, 151.5, 148.2, 137.4, 135.5, 129.6, 129.0, 128.44, 128.39, 127.7, 117.2, 114.0, 83.2, 79.4, 62.8, 61.7, 55.2, 43.2, 40.6, 31.1, 28.2, 27.3, 14.7.

MS (ESI): m/z = 635.7 $[M+H]^+$.

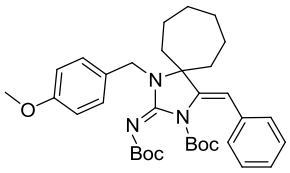


10t: 82%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.45 (m, 2H), 7.37-7.17 (m, 5H), 6.83 (d, J=8.5 Hz, 2H), 6.21 (s, 1H), 4.72-4.55 (m, 2H), 4.18-3.96, (m, 2H), 3.78 (s, 3H), 3.22-2.86 (m, 1H), 2.68-2.50 (m, 1H), 1.82-1.29 (m, 22H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 159.0, 154.3, 151.8, 148.4, 136.4, 136.0, 129.6, 129.0, 128.8, 128.2, 127.4, 116.7, 114.0, 83.2, 79.5, 61.6, 55.2, 43.8, 28.3, 28.2, 27.3.

MS (ESI): m/z = 663.9 $[M+H]^+$.

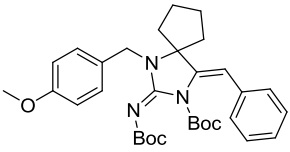


10w: 76%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.50 (m, 2H), 7.39-7.16 (m, 5H), 6.82 (d, J=8.6 Hz, 2H), 6.09 (s, 1H), 4.63 (s, 2H), 3.78 (s, 3H), 1.85-1.44 (m, 21H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 158.7, 151.7, 148.6, 138.8, 136.4, 130.1, 128.8, 128.7, 128.2, 127.2, 115.2, 113.8, 82.9, 79.1, 68.7, 55.2, 43.9, 35.6, 31.0, 28.2, 27.3, 23.4.

MS (ESI): m/z = 576.7 $[M+H]^+$.

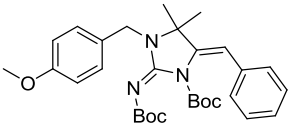


10x: 77%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.41 (m, 2H), 7.38-7.28 (m, 2H), 7.26-7.12 (m, 3H), 6.82 (d, J=8.5 Hz, 2H), 5.89 (s, 1H), 4.60 (s, 2H), 3.77 (s, 3H), 1.89-1.66 (m, 8H), 1.58 (s, 9H), 1.03 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 158.8, 151.8, 148.4, 140.4, 136.3, 129.7, 128.8, 128.4, 128.2, 127.1, 113.9, 113.6, 83.0, 79.1, 72.2, 55.2, 43.6, 34.3, 28.2, 27.3, 24.1.

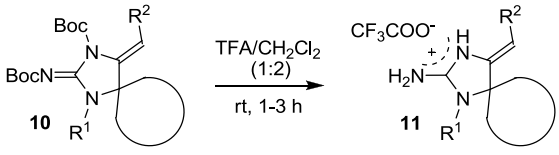
MS (ESI): m/z = 548.9 $[M+H]^+$.



10y

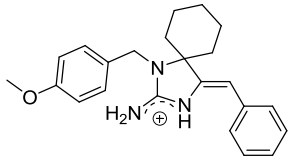
MS (ESI): m/z = 522.6 $[M+H]^+$.

General procedure for the Boc-deprotection of bis-Boc-2-iminoimidazolines 10 into spiro-2-aminoimidazoles 11



The respective *Bis-Boc*-protected-2-iminoimidazoline **10** (0.3 mmol) was dissolved in CH_2Cl_2 (4 mL) and TFA (2 mL) was added. The reaction mix-

ture was stirred at rt for 1-3 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography over silica gel (eluent 5-10% MeOH in CH_2Cl_2) to give the spiro-2-aminoimidazoles **11** as trifluoroacetic acid salts.

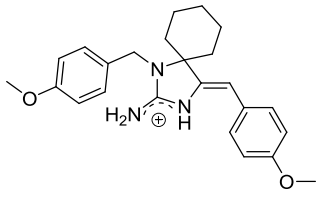


11a: 99%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.30 (m, 4H), 7.25-7.17 (m, 1H), 7.13 (d, J=8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 5.94 (s, 1H), 4.60 (s, 2H), 3.76 (s, 3H), 1.92-1.66 (m, 9H), 1.34-1.17 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 156.3, 140.5, 134.1, 128.9, 127.9, 127.6, 126.9, 126.5, 114.5, 104.4, 68.5, 55.3, 43.1, 33.8, 23.9, 20.8.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{23}H_{27}ON_3$: 361.2154; found: 361.2171.

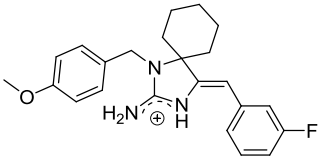


11b: 97%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J=8.6 Hz, 2H), 7.14 (d, J=8.6 Hz, 2H), 6.92-6.84 (m, 4H), 5.90 (s, 1H), 4.57 (s, 2H), 3.82-3.75 (m, 6H), 1.94-1.67 (m, 9H), 1.33-1.14 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 158.4, 156.3, 138.9, 129.2, 127.6, 126.7, 126.3, 114.6, 114.3, 104.3, 68.4, 55.32, 55.26, 43.2, 33.9, 24.0, 20.8.

HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{24}H_{29}O_2N_3$: 391.2260; found: 391.2255.

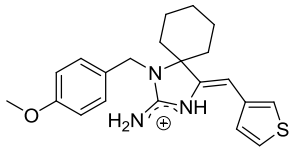


11c: 99%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 1H), 7.19-7.07 (m, 3H), 7.05-6.96 (m, 1H), 6.94-6.79 (m, 3H), 5.87 (s, 1H), 4.59 (s, 2H), 3.76 (s, 3H), 1.93-1.64 (m, 9H), 1.34-1.18 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 161.4, 159.4, 156.3, 141.9, 136.4, 136.3, 130.4, 130.3, 127.6, 126.4, 123.54, 123.50, 115.1, 114.8, 114.5, 113.9, 113.6, 103.14, 103.11, 68.6, 55.3, 43.1, 33.8, 23.8, 20.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{26}ON_3F$: 379.2060; found: 379.2069.

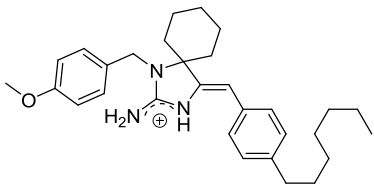


11d: 92%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.39 (m, 1H), 7.33-7.27 (m, 1H), 7.17-7.07 (m, 3H), 6.84 (d, J=8.6 Hz, 2H), 5.93 (s, 1H), 4.61 (s, 2H), 3.75 (s, 3H), 1.91-1.64 (m, 9H), 1.34-1.14 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 156.1, 139.5, 134.6, 127.9, 127.5, 126.6, 125.8, 122.1, 114.5, 99.1, 68.5, 55.3, 43.0, 33.8, 23.9, 20.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{21}H_{25}ON_3S$: 367.1718; found: 367.1719.

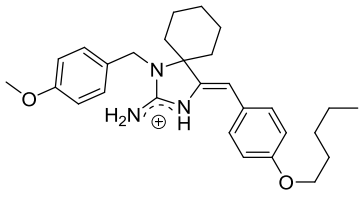


11e: 99%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.08 (m, 6H), 6.86 (d, 8.6 Hz, 2H), 5.94 (s, 1H), 4.56 (s, 2H), 3.76 (s, 3H), 2.63-2.51 (t, J=7.7 Hz, 2H), 1.96-1.15 (m, 20H), 0.96-0.78 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 156.1, 141.9, 139.5, 131.4, 129.0, 127.7, 127.5, 126.2, 114.6, 104.7, 68.6, 55.3, 43.2, 35.7, 33.8, 31.8, 31.4, 29.3, 29.2, 23.9, 22.7, 20.8, 14.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{30}H_{41}ON_3$: 459.3250; found: 459.3250.

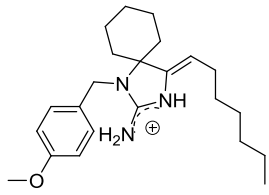


11f: 99%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, J=8.6 Hz, 2H), 7.11 (d, J=8.6 Hz, 2H), 6.92-6.80 (m, 4H), 5.92 (s, 1H), 4.53 (s, 2H), 3.99-3.87 (t, J=6.60 Hz, 2H), 3.75 (s, 3H), 1.95-1.61 (m, 11H), 1.19-1.15 (m, 5H), 0.97-0.87 (t, J=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 158.1, 155.9, 138.6, 129.0, 127.5, 126.4, 126.2, 115.0, 114.6, 104.5, 68.6, 68.0, 55.3, 43.1, 33.8, 28.9, 28.2, 23.9, 22.5, 20.8, 14.0.

MS (ESI): *m*/*z* = 448.8 $[M+H]^+$.

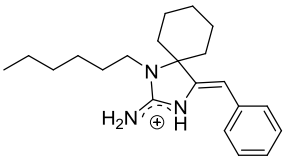


11g: 65%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.95-4.84 (t, J=7.4 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 2.19-2.09 (m, 2H), 1.87-1.56 (m, 9H), 1.47-1.05 (m, 9H), 0.94-0.81 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 155.9, 139.6, 127.6, 126.3, 114.7, 105.5, 67.5, 55.3, 43.0, 33.8, 31.6, 29.6, 28.7, 26.6, 24.0, 22.6, 20.6, 14.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{35}ON_3$: 369.2780; found: 369.2768.

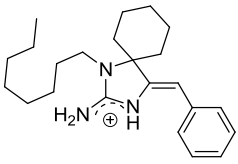


11i: 92%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.28 (m, 4H), 7.24-7.16 (m, 1H), 5.87 (s, 1H), 3.40-3.30 (m, 2H), 1.98-1.47 (m, 9H), 1.42-1.17 (m, 8H), 0.92-0.82 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 140.6, 134.4, 128.9, 127.7, 126.7, 103.5, 68.3, 40.4, 33.8, 31.5, 29.3, 26.1, 24.0, 22.5, 20.8, 14.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{21}H_{31}N_3$: 325.2518; found: 325.2516.

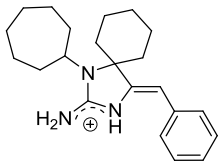


11j: 90%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.13 (m, 5H), 5.92 (s, 1H), 3.36-3.22 (t, J=8.1 Hz, 2H), 1.99-1.49 (m, 10H), 1.41-1.16 (m, 12H), 0.93-0.78 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 140.3, 134.2, 129.0, 127.6, 127.0, 104.1, 68.5, 40.4, 33.7, 31.7, 29.2, 29.1, 26.9, 26.6, 23.9, 22.6, 20.7, 14.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{23}H_{35}N_3$: 353.2831; found: 353.2819.

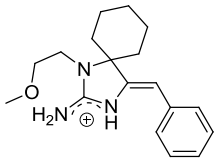


11k: 95%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 4H), 7.23-7.15 (m, 1H), 5.87 (s, 1H), 3.43-3.27 (m, 1H), 2.32-2.11 (m, 2H), 2.01-1.20 (m, 20H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 140.4, 134.4, 128.8, 127.7, 126.7, 103.3, 69.3, 54.5, 33.4, 32.4, 26.9, 26.1, 23.8, 20.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{22}H_{31}N_3$: 337.2518; found: 337.2529.

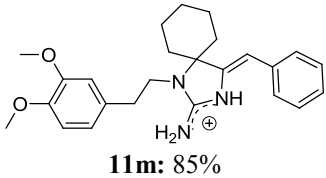


11l: 83%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.31 (m, 4H), 7.26-7.18 (m, 1H), 5.93 (s, 1H), 3.59-3.47 (m, 4H), 3.38 (s, 3H), 1.95-1.57 (m, 9H), 1.37-1.18 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 140.4, 134.0, 128.8, 128.0, 127.0, 104.6, 72.9, 68.5, 59.2, 41.3, 33.5, 23.9, 20.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{18}H_{25}ON_3$: 299.1998; found: 299.2002.

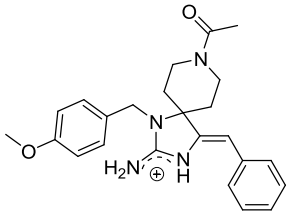


11m: 85%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.16 (m, 5H), 6.90-6.73 (m, 3H), 5.88 (s, 1H), 3.85-3.81 (m, 6H), 3.66-3.54 (t, J=7.7 Hz, 2H), 2.95-2.85 (t, J=7.7 Hz, 2H), 1.95-1.57 (m, 9H), 1.34-1.20 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 149.1, 148.0, 140.3, 134.3, 130.1, 129.0, 127.7, 126.8, 121.0, 112.3, 111.3, 103.8, 68.6, 55.9, 42.0, 34.4, 33.6, 24.0, 20.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{25}H_{31}O_2N_3$: 405.2416; found: 405.2421.

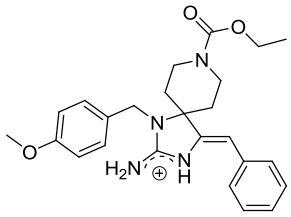


11p: 92%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 4H), 7.26-7.17 (m, 1H), 7.01 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.85 (s, 1H), 4.58 (s, 2H), 4.43-4.28 (m, 1H), 3.82-3.56 (m, 5H), 3.37-3.19 (m, 1H), 2.09 (s, 3H), 2.03-1.81 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 159.5, 156.6, 139.8, 133.4, 129.0, 128.0, 127.5, 127.4, 126.2, 114.6, 104.5, 66.3, 55.3, 43.3, 41.2, 36.6, 33.8, 32.8, 21.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{24}H_{28}O_2N_4$: 404.2212; found: 404.2227.

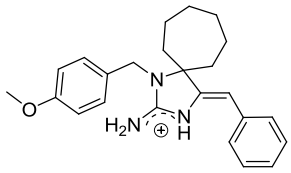


11q: 95%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.15 (m, 5H), 7.14-7.02 (m, 2H), 6.90-6.79 (m, 2H), 5.89 (s, 1H), 4.59 (s, 2H), 4.22-3.85 (m, 4H), 3.76 (s, 3H), 3.50-3.29 (t, J=11.5 Hz, 2H), 2.08-1.74 (m, 4H), 1.32-1.19 (t, J=7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 156.5, 155.4, 139.5, 133.5, 129.0, 127.9, 127.5, 127.3, 126.1, 114.6, 104.7, 66.5, 61.9, 55.3, 43.2, 38.7, 33.1, 14.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{25}H_{30}O_3N_4$: 434.2318; found: 434.2298.

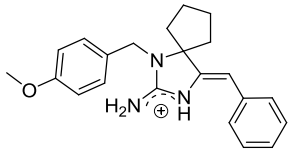


11w: 75%

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.30 (m, 4H), 7.25-7.11 (m, 3H), 6.88 (d, J=8.6 Hz, 2H), 5.70 (s, 1H), 4.65 (s, 2H), 3.79 (s, 3H), 2.15-2.01 (m, 2H), 2.00-1.85 (m, 2H), 1.76-1.51 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 155.9, 141.5, 133.9, 128.8, 127.84, 127.82, 126.9, 126.2, 114.6, 103.1, 72.8, 55.3, 44.3, 39.2, 31.6, 23.4.

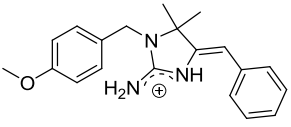
HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{24}H_{29}ON_3$: 375.2311; found: 375.2307.



11x

Intensive decomposition of **11x** during workup prevents its isolation and careful characterisation.

MS (ESI): *m*/*z* = 348.9 $[M+H]^+$.



11y: 44% (2 steps)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.29 (m, 4H), 7.23-7.13 (m, 3H), 6.88 (d, J=8.6 Hz, 2H), 5.48 (s, 1H), 4.57 (s, 2H), 3.78 (s, 3H), 1.45 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 156.2, 140.7, 133.9, 128.9, 128.3, 127.6, 126.8, 126.4, 114.6, 101.4, 67.2, 55.3, 43.7, 27.6.

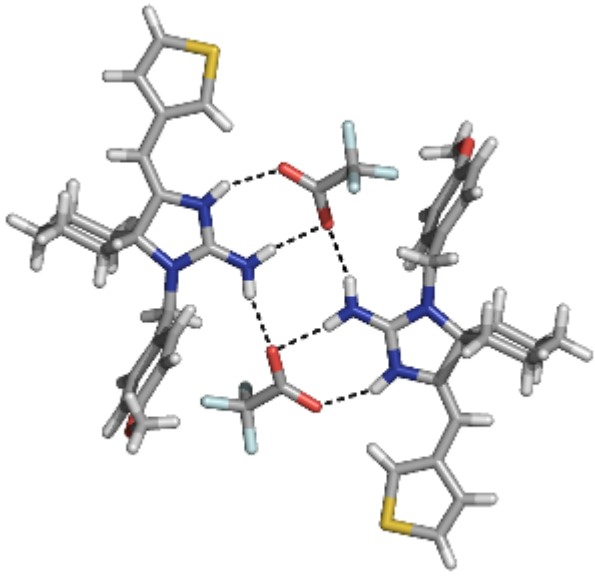
HRMS (EI): *m*/*z* $[M]^+$ calcd. for $C_{20}H_{23}ON_3$:

321.1841; found: 321.1853.

X-ray Crystallography

For the structure of compound **11d**, X-ray intensity data were collected on a SMART 6000 diffractometer equipped with CCD detector using CuKα radiation (λ = 1.54178 Å), using ϕ and ω scans. The images were interpreted and integrated with the program SAINT from Bruker.[83] The structures was solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL program package.[84] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups). CCDC-801762 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

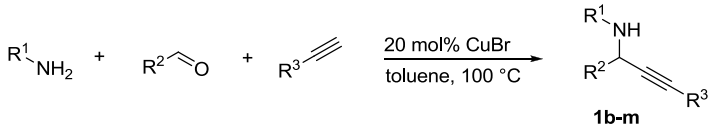
*Crystal data for compound **11d***. $C_{47}H_{54}Cl_2F_6N_6O_6S_2$, M = 1048.00, triclinic, P-1 (No. 2), a = 9.8074(2), b = 15.0025(3), c = 18.1506(3) Å, α = 67.6600(10), β = 82.5560(10), γ = 89.0140(10)°, V = 2447.84(8) Å^3, T = 100(2) K, Z = 2, ρ_{calc} = 1.422 g cm^{-3}, μ(Cu-Kα) = 2.658 mm^{-1}, F(000) = 1092, crystal size 0.5 × 0.3 × 0.2 mm, 8488 independent reflections (R_{int} = 0.0457). Final R = 0.0382 for 7742 reflections with $I > 2\sigma(I)$ and $wR2$ = 0.0988 for all data.



The asymmetric unit contains two molecules. The thiophene ring of one of these molecules was found disordered in two positions. Nitrogen atoms N1 and N4 of the imidazole rings are clearly protonated (established from a difference Fourier map). Two trifluoroacetate and one dichloromethane solvent molecules were observed in the structure. Hydrogen bond networks are formed, around crystallographic inversion centers, between the carboxyl oxygen atoms of the trifluoroacetate molecules and the 2-aminoimidazole and 1-imidazole hydrogen atoms, for both molecules in the asymmetric unit.

Chapter 4

Synthesis of starting propargylamines



Propargylamines **1b-f,l**[25] and propargylamine **1j**[59] were synthesized as described previously.

General procedure for the synthesis of propargylamines 1g-i,k,m

Copper bromide (43 mg, 0.3 mmol), toluene (1.5 mL), amine (2.25 mmol), aldehyde (1.5 mmol) and acetylene (4.5 mmol) were consecutively loaded to a microwave vial equipped with a magnetic stirring bar. The mixture was degassed and flushed with argon. The reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor for 25 min at the set temperature of 100 °C. The resulting reaction mixture was cooled to ambient temperature and subjected to column chromatography to afford desired propargylamine.

***N*-(2-methoxyethyl)-1-(4-propylphenyl)hex-1-yn-3-amine** (**1g**): Isolated by column chromatography with 20% of EtOAc in heptane as eluent. Yield = 316 mg (77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.66-3.47 (m, 3H), 3.37 (s, 3H), 3.15 (ddd, J = 4.2, 4.4, 12.2 Hz, 1H), 2.80 (ddd, J = 4.2, 4.4, 12.2 Hz, 1H), 2.56 (t, J = 7.6 Hz, 2H), 1.77-1.45 (m, 6H), 0.96 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.7, 131.5, 128.4, 120.6, 90.1, 83.9, 72.1, 58.7, 50.7, 46.9, 38.3, 37.9, 24.4, 19.4, 13.9, 13.7.

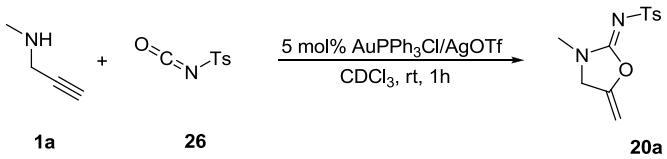
***N*-(4-methoxybenzyl)-1-phenylhept-2-yn-4-amine** (**1h**): Isolated as a 4:1 mixture with **1i**[85] by column chromatography with 10% to 20% of EtOAc in heptane as eluent with the yield of 41% (calculated from the ^{1}H NMR spectra). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.10 (m, 7H), 6.84 (d, J = 8.1 Hz, 2H), 3.97 (d, J = 12.6 Hz, 1H), 3.78 (s, 3H), 3.76 (d, J = 12.6 Hz, 1H), 3.66 (s, 2H), 3.41 (t, J = 6.1 Hz, 1H), 1.70-1.42 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 137.3, 132.3, 129.6, 128.5, 127.8, 126.5, 113.7, 84.0, 81.2, 55.2, 50.9, 49.3, 38.5, 25.2, 19.4, 13.9; MS (ESI) (m/z, relative intensity): 309.3 ($[M+H]^+$, 100).

***N*-(4-methoxybenzyl)-1,6-diphenylhex-4-yn-3-amine** (**1i**): Isolated by column chromatography with 10% to 20% of EtOAc in heptane as eluent. Yield = 325 mg (59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.10 (m, 12H), 6.83 (d, J = 8.0 Hz, 2H), 3.96 (d, J = 12.6 Hz, 1H), 3.76 (s, 3H), 3.74 (d, J = 12.6 Hz, 1H), 3.68 (s, 2H), 3.41 (t, J = 6.4 Hz, 1H), 2.91-2.69 (m, 2H), 2.07-1.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 141.8, 137.2, 132.2, 129.6, 128.5, 128.3, 127.9, 126.5, 125.8, 113.7, 83.7, 81.7, 55.2, 50.9, 49.1, 37.9, 32.4, 25.2; HRMS (EI) for $C_{26}H_{27}NO$ calcd. 369.2093, found 369.2075.

***N*-*tert*-butyl-1-(4-fluorophenyl)-5-methylhex-1-yn-3-amine** (**1k**): Isolated by column chromatography with 7% to 15% of EtOAc in heptane as eluent. Yield = 263 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.29 (m, 2H), 7.03-6.89 (m, 2H), 3.62 (t, J = 7.5 Hz, 1H), 2.01-1.82 (m, 1H), 1.66-1.51 (m,1H), 1.51-1.37 (m, 1H), 1.20 (s, 9H), 0.95 (d, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.8, 160.5, 133.2, 133.1, 120.0, 119.9, 115.5, 115.2, 94.12, 94.11, 81.4, 51.3, 47.9, 42.8, 29.9, 25.1, 22.9, 22.2; MS (ESI) (m/z, relative intensity): 262.6 ($[M+H]^+$, 100).

***N*-(1,3-diphenylprop-2-ynyl)aniline** (**1m**)[86]: Isolated by column chromatography with 5% of EtOAc in heptane as eluent. Yield = 157 mg (37%).

Synthesis of (Z)-4-methyl-N-(3-methyl-5-methyleneoxazolidin-2-ylidene)benzenesulfonamide (20a)

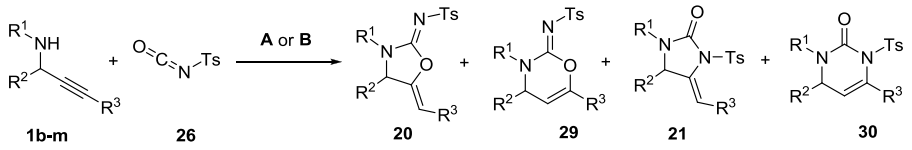


1a **26** **20a**

N-Methylpropargylamine **(1a)** (14 mg, 0.2 mmol) was dissolved in $CDCl_3$ (0.8 mL) followed by addition of tosyl isocyanate **(26)** (43 mg, 0.22 mmol). After stirring at rt for about 5 min AgOTf (2.6 mg, 0.01 mmol) and $AuPPh_3Cl$ (5.0 mg, 0.01 mmol) were added. The reaction mixture was kept stirring at rt for 1h in a sealed screw cap vial under air atmosphere. The resulting mixture was directly subjected to column chromatography with EtOAc as eluent delivering **20a** (49 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 4.97-4.86 (m, 1H), 4.51-4.39 (m, 1H), 4.26-4.12 (m, 2H), 2.96 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 149.8, 142.6, 139.7, 129.1, 127.1, 89.3, 50.0, 31.5, 21.5; HRMS (EI) for $C_{12}H_{12}N_2O_3S$ calcd. 266.0725, found 266.0739.

Scope and comparison of $AuPPh_3Cl$/AgOTf- and AgOTf-catalyzed protocols

CAUTION! All starting polysubstituted propargylamines **1b-m** were used freshly prepared. The use of propargylamines stored for a considerable time under ambient conditions gives reduced combined yields of cycloizomerized products. In addition the selectivity of the AgOTf-catalyzed process might be strongly affected.



A = 5 mol% **AuPPh$_3$Cl**, 5 mol% **AgOTf**, DCM, 2-20h, rt or 50 °C
B = 20 mol% **AgOTf**, toluene, 1-2h, 80 °C

General procedure for the AuPPh$_3$Cl/AgOTf-catalyzed cycloisomerization of propargylic ureas (Protocol A)

Propargylamine **1** (0.5 mmol) was dissolved in dry CH_2Cl_2 (2 mL) followed by addition of tosyl isocyanate **26** (108.5 mg, 0.55 mmol). After stirring at rt for about 5 min AgOTf (6.4 mg, 0.025 mmol) and AuPPh$_3$Cl (12.4 mg, 0.025 mmol) were added. The reaction mixture was kept with a stirring at rt or 50°C for 2-20h in a sealed screw cap vial under air atmosphere. The resulting mixture was directly subjected to the column chromatography to give desired cycloisomerization products.

Table 6, ***Entry 1.*** The reaction was carried out at 50°C for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→3:7) as eluent delivering first mixture of **21b** with **30b** and then **20b** (major product), slightly contaminated with **29b**.

Table 6, ***Entry 3.*** Reaction was carried out at rt for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→3:7) as eluent delivering first mixture of **21c** with **30c** and then **20c** (major product), slightly contaminated with **29c**.

Table 6, ***Entry 5.*** Reaction was carried out at rt for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering **20d** (major product), slightly contaminated with **29d**.

Table 6, *Entry 7.* The reaction was carried out at 50°C for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering first **21e** and then **20e** (major product).

Table 6, *Entry 9.* The reaction was carried out at 50°C for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:7) as eluent delivering **20f** (major product), contaminated with **29f**.

Table 6, *Entry 11.* The reaction was carried out at rt for 2h on a 0.4 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:1) as eluent delivering **20g** (major product).

Table 6, *Entry 13.* The reaction was carried out at 50°C for 20h on a 0.4 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:17→3:7) as eluent delivering first **21h** and then **20h** (major product), contaminated[87] with **21i** and **20i** respectively.

Table 6, *Entry 15.* The reaction was carried out at 50°C for 20h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→2:3) as eluent delivering first **21i** contaminated with other reaction byproducts and then **20i** (major product) contaminated with Ts-NH_2. Pure **20i** was obtained by recrystallization from diethyl ether.

Table 6, *Entry 17.* The reaction was carried out at rt for 2h on a 0.2 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:7) as eluent delivering **20j** (major product).

Table 6, *Entry 19.* The reaction was carried out at 50°C for 4h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering first **21k** (major product) and then **20k**, contaminated with other reaction byproducts.

Table 6, *Entry 21.* The reaction was carried out at 50°C for 4h on a 0.25 mmol scale. Column chromatography was performed with ethyl ace-

tate/heptane (1:9→3:7) as eluent delivering first **21l** (major product) and then **20l**, contaminated with **29l** and other reaction byproducts.

Table 6, *Entry 23.* The reaction was carried out at rt for 2h on a 0.3 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→3:7) as eluent delivering **20m** (major product).

General procedure for the AgOTf-catalyzed cycloisomerization of propargylic ureas (Protocol B)

Propargylamine **1** (0.5 mmol) was dissolved in dry toluene (2.5 mL) followed by addition of tosyl isocyanate **(26)** (108.5 mg, 0.55 mmol). After stirring at rt for about 5 min AgOTf (26 mg, 0.1 mmol) was added. The reaction mixture was heated with stirring at 80°C for 1-2h in a sealed screw cap vial under air atmosphere. The resulting mixture was directly subjected to column chromatography to give the desired cycloisomerization products.

Table 6, *Entry 2.* The reaction was carried out for 1h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering **21b** (major product).

Table 6, *Entry 4.* The reaction was carried out for 1h on a 0.3 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→3:7) as eluent delivering first **21c** (major product) and then **20c**, slightly contaminated with **29c**.

Table 6, *Entry 6.* The reaction was carried out for 1h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering first **21d** (major product) and then **20d**, slightly contaminated with **29d**.

Table 6, *Entry 8.* The reaction was carried out for 1h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:17→1:4) as eluent delivering first **21e** (major product) and then **20e**.

Table 6, *Entry 10.* The reaction was carried out for 1h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→3:7) as eluent delivering first **21f** (major product) and then **20f**, contaminated with **29f**.

Table 6, *Entry 12.* The reaction was carried out for 2h on a 0.22 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:3) as eluent delivering first **21g** (major product) and then **20g**, contaminated with other reaction byproducts.

Table 6, *Entry 14.* The reaction was carried out for 1h on a 0.4 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:17→3:7) as eluent delivering first **21h** (major product) and then **20h**, contaminated[5] with **21i** and **20i** respectively.

Table 6, *Entry 16.* The reaction was carried out for 2h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4→2:3) as eluent delivering first 2**1i** (major product) and then **20i**, contaminated with Ts-NH_2 and other reaction byproducts.

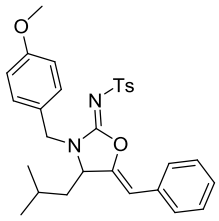
Table 6, *Entry 18.* The reaction was carried out for 1h on a 0.3 mmol scale. Column chromatography was performed with ethyl acetate/heptane (3:17→3:7) as eluent delivering first **21j** (major product) and then **20j**.

Table 6, *Entry 20.* The reaction was carried out for 1h on a 0.5 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→1:4) as eluent delivering first **21k** (major product) and then **20k**, contaminated with unknown impurity.

Table 6, *Entry 22.* The reaction was carried out for 1h on a 0.25 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:9→3:7) as eluent delivering first **21l** (major product) and then mixture of **20l** with **29l**.

Table 6, *Entry 24.* The reaction was carried out for 1h on a 0.3 mmol scale. Column chromatography was performed with ethyl acetate/heptane (1:4) as eluent delivering first 2**1m** (major product) and then **20m**, contaminated with Ts-NH_2.

Spectral data for oxazolidin-2-imines 20b-j,l,m



20b

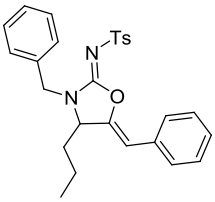
(*Z*)-*N*-((*Z*)-5-benzylidene-4-isobutyl-3-(4-methoxybenzyl)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.61-7.52 (m, 2H), 7.42-7.33 (m, 2H), 7.30-7.23 (m, 1H), 7.21-7.13 (m, 4H), 6.84 (d, J = 8.5 Hz, 2H), 5.49 (s, 1H), 5.05 (d, J = 15.0 Hz, 1H), 4.30-4.22 (m, 1H), 4.02 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 2.34 (s, 3H), 1.83-1.53 (m, 3H), 0.89 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7, 155.0, 147.3, 142.4, 140.0, 132.4, 129.7, 129.1, 128.7, 128.6, 127.6, 126.8, 125.7, 114.4, 105.4 (O-C=*C*), 56.9, 55.3, 45.8, 41.1, 23.8, 23.3, 22.4, 21.5.

IR (ATR): *v* = 2925, 1609 (C=N), 1514, 1441, 1301, 1252, 1157, 1077, 1029, 938, 818, 759, 688, 650, 581, 548 cm^{-1}.

HRMS (EI) for $C_{29}H_{32}N_2O_4S$ calcd. 504.2083, found 504.2098.



20c

(*Z*)-*N*-((*Z*)-3-benzyl-5-benzylidene-4-propyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20c)

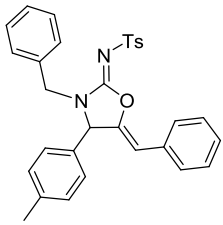
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.61-7.52 (m, 2H), 7.41-7.22 (m, 8H), 7.18 (d, J = 8.1 Hz, 2H), 5.50 (d, J = 1.4 Hz, 1H), 5.01 (d, J = 15.1 Hz, 1H), 4.38-4.29 (m, 1H), 4.10 (d, J = 15.1 Hz, 1H), 2.34 (s, 3H), 1.89-1.73 (m, 1H), 1.68-1.52 (m, 1H), 1.35-1.01 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.2, 146.8, 142.5,

139.9, 133.9, 132.3, 129.1, 129.0, 128.7, 128.55, 128.51, 128.3, 127.5, 126.7, 104.9 (O-C=*C*), 58.5, 46.2, 33.8, 21.4, 15.7, 13.6.

IR (ATR): *v* = 2924, 1614 (C=N), 1443, 1307, 1273, 1160, 1143, 1126, 909, 843, 816, 687, 584, 546 cm^{-1}.

HRMS (EI) for $C_{27}H_{28}N_2O_3S$ calcd. 460.1821, found 460.1815.



20d

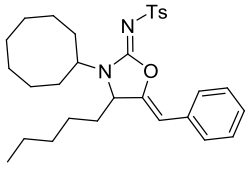
(*Z*)-*N*-((*Z*)-3-benzyl-5-benzylidene-4-p-tolyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 8.1 Hz, 2H), 7.55-7.47 (m, 2H), 7.39-7.18 (m, 10H), 7.16-7.03 (m, 4H), 5.27 (s, 1H), 5.12 (s, 1H), 5.05 (d, J = 14.8 Hz, 1H), 3.67 (d, J = 14.8 Hz, 1H), 2.38 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.8, 148.0, 142.6, 139.98, 139.95, 133.6, 132.4, 132.3, 130.2, 129.2, 128.9, 128.74, 128.69, 128.53, 128.50, 128.2, 127.7, 126.8, 106.9 (O-C=*C*), 62.9, 46.0, 21.5, 21.3.

IR (ATR): *v* = 1608 (C=N), 1436, 1313, 1154, 1072, 920, 805, 701, 681, 586, 551 cm^{-1}.

HRMS (EI) for $C_{31}H_{28}N_2O_3S$ calcd. 508.1821, found 508.1823.



20e

(*Z*)-*N*-((*Z*)-5-benzylidene-3-cyclooctyl-4-pentyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20e)

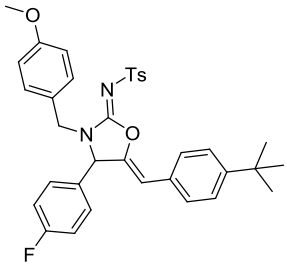
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.1 Hz, 2H), 7.62-7.51 (m, 2H), 7.43-7.32 (m, 2H), 7.29-7.21 (m, 1H), 7.16 (d, J = 8.1 Hz, 2H), 5.50 (s, 1H), 4.61-4.51 (m, 1H), 3.81 (t, J = 9.9 Hz, 1H), 2.32 (s, 3H), 2.08-1.13 (m, 22H), 0.91-0.78 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1, 147.2, 142.1, 140.4, 132.6, 129.0, 128.6, 128.5, 127.4, 126.6, 104.4 (O-C=*C*), 59.7, 56.2, 34.2, 31.9, 31.4, 30.9, 26.23, 26.21, 25.8, 25.0, 24.7, 22.4, 22.0, 21.4, 13.9.

IR (ATR): *v* = 2923, 1598 (C=N), 1433, 1284,

1155, 1076, 812, 695, 662, 585, 553 cm^{-1}.

HRMS (EI) for $C_{30}H_{40}N_2O_3S$ calcd. 508.2760, found 508.2773.



20f

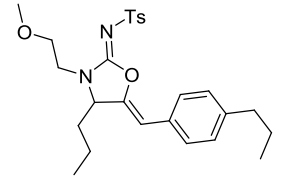
(*Z*)-*N*-((*Z*)-5-(4-tert-butylbenzylidene)-4-(4-fluorophenyl)-3-(4-methoxybenzyl)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.22-7.06 (m, 4H), 7.02 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.24 (d, J = 1.7 Hz, 1H), 5.15 (d, J = 1.7 Hz, 1H), 4.97 (d, J = 14.8 Hz, 1H), 3.80 (s, 3H), 3.63 (d, J = 14.8 Hz, 1H), 2.39 (s, 3H), 1.32 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0, 161.7, 159.8, 154.8, 151.0, 147.2, 142.6, 140.0, 131.62, 131.58, 130.3, 130.1, 129.28, 129.26, 128.5, 126.8, 125.5, 125.4, 116.7, 116.4, 114.3, 107.1 (O-C=*C*), 62.3, 55.3, 45.7, 34.7, 31.2, 21.5.

IR (ATR): *v* = 2964, 1609 (C=N), 1511, 1445, 1284, 1230, 1160, 1080, 913, 807, 698, 655, 596, 568, 547 cm^{-1}.

HRMS (EI) for $C_{35}H_{35}N_2O_4SF$ calcd. 598.2302, found 598.2327.



20g

(*Z*)-*N*-((*Z*)-3-(2-methoxyethyl)-4-propyl-5-(4-propylbenzylidene)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20g)

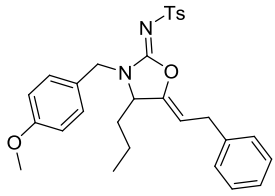
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.24-7.12 (m, 4H), 5.52 (s, 1H), 4.71 (bs, 1H), 3.93-3.80 (2H), 3.65-3.46 (m, 2H), 3.34-3.17 (m, 4H), 2.61 (t, J = 7.5 Hz, 2H), 2.34 (s, 3H), 2.00-1.83 (m, 1H), 1.74-1.56 (m, 3H), 1.35-1.07 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.1, 146.7, 142.3, 142.2, 140.0, 129.9, 129.1, 128.7, 128.5, 126.8, 104.6 (O-C=*C*), 70.3, 60.6, 58.9, 42.1, 37.8, 34.0, 24.5, 21.5, 15.7, 13.8, 13.7.

IR (ATR): *v* = 2930, 1616 (C=N), 1445, 1285,

1152, 813, 664, 551 cm^{-1}.

HRMS (EI) for $C_{26}H_{24}N_2O_4S$ calcd. 470.2239, found 470.2191.



20h

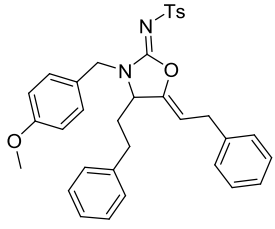
(*Z*)-*N*-((*Z*)-3-(4-methoxybenzyl)-5-(2-phenylethylidene)-4-propyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 8.1 Hz, 2H), 7.32-7.12 (m, 7H), 7.08-6.99 (m, 2H), 6.85 (d, J = 8.3 Hz, 2H), 4.97 (d, J = 14.9 Hz, 1H), 4.75 (t, J = 7.6 Hz, 1H), 4.13 (bs, 1H), 3.99 (d, J = 14.9 Hz, 1H), 3.79 (s, 3H), 3.55-3.28 (m, 2H), 2.35 (s, 3H), 1.79-1.60 (m, 1H), 1.57-1.40 (m, 1H), 1.23-1.02 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7, 155.1, 147.5, 142.4, 140.1, 139.4, 129.8, 129.1, 128.6, 128.3, 127.1, 126.4, 125.9, 114.3, 104.1 (O-C=*C*), 57.0, 55.3, 45.7, 33.6, 31.2, 21.5, 15.8, 13.7.

IR (ATR): *v* = 2931, 1611 (C=N), 1511, 1457, 1309, 1242, 1158, 1076, 1028, 913, 839, 688, 598, 548 cm^{-1}.

MS (CI) (m/z, relative intensity): 505 ($[M+H]^+$, 100), 349 (31).



20i

(*Z*)-*N*-((*Z*)-3-(4-methoxybenzyl)-4-phenethyl-5-(2-phenylethylidene)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20i)

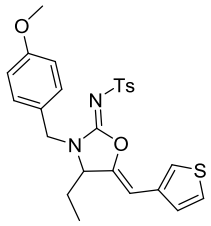
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 8.2 Hz, 2H), 7.32-7.12 (m, 10H), 7.11-7.04 (m, 2H), 6.94-6.87 (m, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.88-4.75 (m, 2H), 4.27-4.17 (m, 1H), 3.96 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 3.50 (dd, J = 8.0, 15.4 Hz, 1H), 3.41 (dd, J = 7.8, 15.4 Hz, 1H), 2.51-2.24 (m, 5H), 2.15-1.97 (m, 1H), 1.87-1.68 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 155.1, 147.1, 142.5, 140.0, 139.9, 139.3, 129.9, 129.2, 128.64, 128.63, 128.3, 128.2, 127.1, 126.44, 126.39, 125.8, 114.4, 104.5 (O-C=*C*), 57.0, 55.3, 45.9, 33.3, 31.3, 28.7, 21.5.

IR (ATR): *v* = 1608 (C=N), 1512, 1452, 1246,

1156, 1080, 814, 698, 593, 550 cm^{-1}.

HRMS (EI) for $C_{34}H_{34}N_2O_4S$ calcd. 566.2239, found 566.2234.



20j

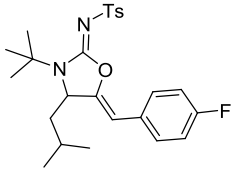
(*Z*)-*N*-((*Z*)-4-ethyl-3-(4-methoxybenzyl)-5-(thiophen-3-ylmethylene)oxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20j)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 7.9 Hz, 2H), 7.61-7.52 (m, 1H), 7.41-7.35 (m, 1H), 7.35-7.28 (m, 1H), 7.24 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 5.62 (s, 1H), 5.00 (d, J = 15.0 Hz, 1H), 4.37-4.27 (m, 1H), 3.98 (d, J = 15.0 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 2.00-1.55 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7, 155.1, 145.7, 142.5, 140.2, 132.9, 129.8, 129.3, 128.2, 126.6, 125.8, 125.6, 124.3, 114.4, 99.8 (O-C=*C*), 58.5, 55.3, 45.7, 24.5, 21.5, 6.5.

IR (ATR): *ν* = 2925, 1610 (C=N), 1513, 1442, 1299, 1245, 1156, 1072, 1031, 919, 813, 661, 579, 550.

HRMS (EI) for $C_{25}H_{26}N_2O_4S_2$ calcd. 482.1334, found 482.1330.



20k

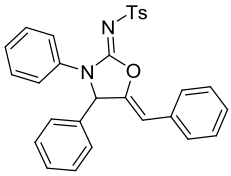
(*E*)-*N*-((*Z*)-3-tert-butyl-5-(4-fluorobenzylidene)-4-isobutyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20k)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 7.9 Hz, 2H), 7.66-7.53 (m, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.14-7.00 (m, 2H), 5.45 (s, 1H), 4.51 (d, J = 9.4 Hz, 1H), 2.36 (s, 3H), 1.91-1.54 (m, 3H), 1.51 (s, 9H), 0.99-0.90 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.6, 160.3, 153.3, 146.0, 145.9, 142.2, 140.4, 130.6, 130.5, 129.1, 128.7, 128.6, 126.4, 115.7, 115.4, 104.0 (O-C=*C*), 59.2, 56.4, 44.6, 28.1, 23.9, 23.4, 21.5, 21.0.

IR (ATR): *ν* = 2958, 1601 (C=N), 1509, 1412, 1286, 1228, 1160, 1090, 1061, 907, 813, 660, 577, 548.

HRMS (EI) for $C_{25}H_{31}N_2O_3SF$ calcd. 458.2039, found 458.2049.



20m

(*Z*)-*N*-((*Z*)-5-benzylidene-3,4-diphenyloxazolidin-2-ylidene)-4-methylbenzenesulfonamide (20m)

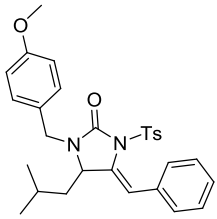
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.2 Hz, 2H), 7.67-7.55 (m, 2H), 7.42-7.08 (m, 15H), 5.90 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 2.0 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.3, 147.0, 142.8, 139.7, 136.4, 134.6, 132.2, 129.6, 129.4, 129.3, 129.2, 128.9, 128.7, 127.9, 127.7, 127.1, 126.9, 124.2, 107.0 (O-C=*C*), 66.3, 21.5.

IR (ATR): *v* = 1611 (C=N), 1412, 1311, 1161, 1080, 772, 659, 543.

HRMS (EI) for $C_{29}H_{24}N_2O_3S$ calcd. 480.1508, found 480.1512.

Spectral data for imidazolidin-2-ones 21b-k,m



21b

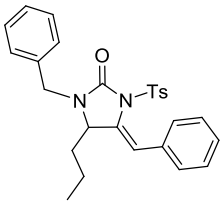
(*Z*)-4-benzylidene-5-isobutyl-1-(4-methoxybenzyl)-3-tosylimidazolidin-2-one (21b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.1 Hz, 2H), 7.41-7.32 (m, 2H), 7.29-7.15 (m, 5H), 7.05 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.95 (s, 1H), 4.81 (d, J = 15.1 Hz, 1H), 3.96 (d, J = 15.1 Hz, 1H), 3.92-3.83 (m, 2H), 3.76 (s, 3H), 2.43 (s, 3H), 1.96-1.79 (m, 1H), 1.50-1.27 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 154.6, 144.7, 135.7, 135.5, 131.4, 129.3, 129.1, 128.8, 128.6, 128.2, 127.5, 127.2, 117.7 (N-C=*C*), 114.2, 58.3, 55.2, 44.6, 41.1, 23.9, 23.5, 21.9, 21.7.

IR (ATR): *v* = 2923, 1729 (C=O), 1675, 1512, 1416, 1365, 1236, 1168, 1024, 816, 753, 697, 662, 573, 531.

HRMS (EI) for $C_{29}H_{32}N_2O_4S$ calcd. 504.2083, found 504.2070.



21c

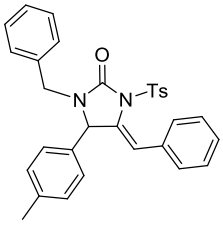
(*Z*)-1-benzyl-4-benzylidene-5-propyl-3-tosylimidazolidin-2-one (21c)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 2H), 7.40-7.32 (m, 2H), 7.29-7.17 (m, 8H), 7.08-7.00 (m, 2H), 5.97 (s, 1H), 4.86 (d, J = 15.3 Hz, 1H), 4.05-3.91 (m, 2H), 2.43 (s, 3H), 1.73-1.30 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 144.7, 135.8, 135.4, 130.9, 129.1, 128.7, 128.5, 128.2, 127.9, 127.1, 116.9 (N-C=*C*), 59.5, 45.0, 33.7, 21.7, 16.6, 13.9.

IR (ATR): *v* = 2928, 1733 (C=O), 1358, 1170, 1087, 814, 745, 699, 663, 570.

HRMS (EI) for $C_{27}H_{28}N_2O_3S$ calcd. 460.1821, found 460.1812.



21d

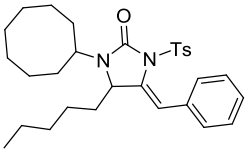
(*Z*)-1-benzyl-4-benzylidene-5-p-tolyl-3-tosylimidazolidin-2-one (21d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.41-7.33 (m, 2H), 7.31-7.11 (m, 10H), 7.04 (d, J = 7.9 Hz, 2H), 6.77-6.67 (m, 2H), 5.69 (d, J = 1.4 Hz, 1H), 4.96-4.79 (m, 2H), 3.44 (d, J = 14.8 Hz, 1H), 2.48 (s, 3H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 144.8, 139.2, 135.8, 134.7, 133.3, 129.9, 129.4, 128.8, 128.5, 128.44, 128.40, 128.2, 128.1, 127.8, 127.3, 119.3 (N-C=*C*), 63.8, 44.7, 21.8, 21.2.

IR (ATR): *v* = 2920, 1745 (C=O), 1383, 1175, 1085, 814, 761, 721, 692, 665, 572, 518.

HRMS (EI) for $C_{31}H_{28}N_2O_3S$ calcd. 508.1821, found 508.1827.



(*Z*)-4-benzylidene-1-cyclooctyl-5-pentyl-3-tosylimidazolidin-2-one (21e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.35-7.27 (m, 2H), 7.25-7.15 (m, 5H),

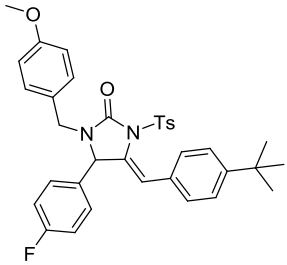
21e

5.97 (s, 1H), 4.14-3.97 (m, 1H), 3.68-3.50 (m, 1H), 2.41 (s, 3H), 2.08-1.27 (m, 22H), 0.93 (t, J = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.9, 144.3, 136.2, 135.7, 131.6, 128.9, 128.6, 128.5, 128.2, 127.0, 116.9 (N-C=*C*), 61.2, 55.2, 34.0, 32.8, 31.9, 31.7, 26.2, 26.0, 25.1, 24.9, 23.7, 22.5, 21.6, 14.1.

IR (ATR): *v* = 2923, 1734 (C=O), 1360, 1168, 1088, 813, 699, 664, 571, 541.

HRMS (EI) for $C_{30}H_{40}N_2O_3S$ calcd. 508.2760, found 508.2765.



21f

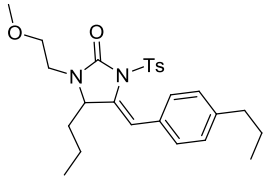
(*Z*)-4-(4-tert-butylbenzylidene)-5-(4-fluorophenyl)-1-(4-methoxybenzyl)-3-tosylimidazolidin-2-one (21f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.34-7.20 (m, 6H), 7.19-7.11 (m, 2H), 7.11-7.01 (m, 2H), 6.69 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.63 (d, J = 1.9 Hz, 1H), 4.89 (d, J = 1.9 Hz, 1H), 4.85 (d, J = 14.7 Hz, 1H), 3.78 (s, 3H), 3.39 (d, J = 14.7 Hz, 1H), 2.49 (s, 3H), 1.30 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 161.4, 159.2, 155.1, 150.4, 144.8, 135.9, 132.45, 132.35, 132.33, 132.32, 130.2, 130.1, 129.7, 129.4, 128.8, 128.3, 126.5, 125.1, 119.8 (N-C=*C*), 116.4, 116.1, 113.9, 63.4, 55.2, 44.3, 34.6, 31.3, 21.8.

IR (ATR): *v* = 1744 (C=O), 1511, 1408, 1352, 1249, 1163, 1073, 842, 742, 662, 581, 545.

HRMS (EI) for $C_{35}H_{35}N_2O_4SF$ calcd. 598.2302, found 598.2323.



21g

(*Z*)-1-(2-methoxyethyl)-5-propyl-4-(4-propylbenzylidene)-3-tosylimidazolidin-2-one (21g)

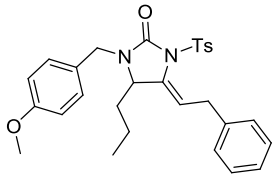
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.31-7.18 (m, 4H), 7.04 (d, J = 7.9 Hz, 2H), 6.00 (s, 1H), 4.30-4.19 (m, 1H), 3.73 (dt, J = 14.8, 4.2 Hz, 1H), 3.53-3.32 (m, 2H), 3.27 (s,

3H), 3.13 (ddd, J = 4.2, 7.8, 14.8 Hz, 1H), 2.57 (t, J = 7.6 Hz, 2H), 2.42 (s, 3H), 1.78-1.32 (m, 6H), 0.96 (t, J = 7.2 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 144.4, 141.7, 136.1, 133.0, 130.7, 129.0, 128.7, 128.4, 128.3, 117.1 (N-C=*C*), 70.9, 61.5, 58.8, 41.1, 37.9, 33.9, 24.4, 21.7, 16.9, 14.0, 13.9.

IR (ATR): *v* = 2929, 1740 (C=O), 1361, 1164, 1088, 813, 661, 573, 539.

HRMS (EI) for $C_{26}H_{34}N_2O_4S$ calcd. 470.2239, found 470.2218.



21h

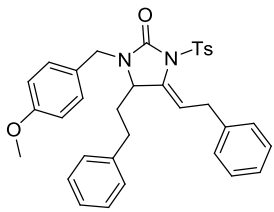
(*Z*)-1-(4-methoxybenzyl)-4-(2-phenylethylidene)-5-propyl-3-tosylimidazolidin-2-one (**21h**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.0 Hz, 2H), 7.38-7.12 (m, 7H), 7.03-6.95 (m, 2H), 6.78 (d, J = 8.1 Hz, 2H), 5.12 (t, J = 6.6 Hz, 1H), 4.77 (d, J = 15.1 Hz, 1H), 3.90 (d, J = 15.1 Hz, 1H), 3.83-3.52 (m, 5H), 2.46 (s, 3H), 1.60-1.18 (m, 4H), 0.85 (t, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 154.6, 144.8, 140.5, 136.4, 130.9, 129.5, 129.3, 128.53, 128.52, 128.46, 127.5, 126.3, 118.1 (N-C=*C*), 114.1, 59.0, 55.2, 44.5, 35.6, 33.7, 21.7, 16.8, 13.9.

IR (ATR): *v* = 2930, 1741 (C=O), 1512, 1413, 1360, 1244, 1167, 1087, 1030, 813, 733, 700, 662, 589, 539.

HRMS (EI) for $C_{29}H_{32}N_2O_4S$ calcd. 504.2083, found 504.2075.



21i

(*Z*)-1-(4-methoxybenzyl)-5-phenethyl-4-(2-phenylethylidene)-3-tosylimidazolidin-2-one (**21i**)

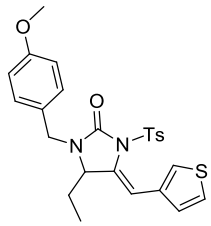
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.3 Hz, 2H), 7.35-7.13 (m, 10H), 7.02-6.94 (m, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 5.22 (t, J = 6.8 Hz, 1H), 4.74 (d, J = 15.1 Hz, 1H), 3.92 (d, J = 15.1 Hz, 1H), 3.87-3.54 (m, 6H), 2.55

(t, J = 8.2 Hz, 2H), 2.44 (s, 3H), 1.92-1.61 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 154.7, 144.9, 140.7, 140.4, 136.3, 130.6, 129.6, 129.5, 128.7, 128.62, 128.58, 128.5, 128.3, 127.4, 126.4, 126.2, 118.5 (N-C=*C*), 114.2, 58.7, 55.3, 44.7, 35.8, 33.1, 29.5, 21.8.

IR (ATR): *v* = 1727 (C=O), 1686, 1510, 1432, 1366, 1242, 1165, 1088, 1039, 844, 812, 748, 702, 662, 590, 563, 537, 495.

MS (CI) (m/z, relative intensity): 567 ($[M+H]^+$, 100), 413 (71).



21j

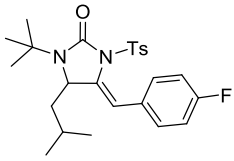
(*Z*)-4-ethyl-3-(4-methoxybenzyl)-5-(thiophen-3-ylmethylene)-1-tosylimidazolidin-2-one (21j)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 8.1 Hz, 2H), 7.40-7.33 (m, 1H), 7.33-7.18 (m, 4H), 6.86 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 8.3 Hz, 2H), 6.01 (s, 1H), 4.79 (d, J = 15.1 Hz, 1H), 3.94-3.81 (m, 2H), 3.78 (s, 3H), 2.47 (s, 3H), 1.80-1.60 (m, 1H), 1.60-1.41 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 155.0, 144.8, 136.2, 135.7, 129.8, 129.34, 129.27, 128.9, 127.9, 127.2, 124.9, 124.3, 114.1, 112.7 (N-C=*C*), 59.9, 55.3, 44.4, 24.0, 21.8, 7.6.

IR (ATR): *v* = 2925, 1740 (C=O), 1512, 1404, 1360, 1237, 1165, 1026, 811, 777, 657, 637, 569.

HRMS (EI) for $C_{25}H_{26}N_2O_4S_2$ calcd. 482.1334, found 482.1337.



21k

(*Z*)-1-tert-butyl-4-(4-fluorobenzylidene)-5-isobutyl-3-tosylimidazolidin-2-one (21k)

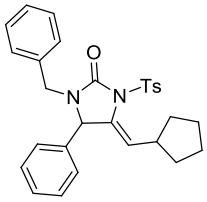
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H), 7.40-7.27 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.95-6.81 (m, 2H), 5.92 (s, 1H), 4.16 (d, J = 10.5 Hz, 1H), 2.42 (s, 3H), 2.05-1.82 (m, 1H), 1.51-1.26 (m, 11H), 1.03 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.4, 160.1, 153.4, 144.5, 136.1, 131.56, 131.55, 131.4, 131.3,

130.5, 130.4, 129.0, 128.6, 116.3 (N-C=*C*), 115.3, 115.0, 60.5, 54.8, 43.4, 28.4, 24.1, 23.9, 21.6, 21.1.

IR (ATR): ν = 2957, 1733 (C=O), 1508, 1351, 1225, 1165, 1046, 814, 657, 594, 566, 538.

HRMS (EI) for $C_{25}H_{31}N_2O_3SF$ calcd. 458.2039, found 458.2040.



21l

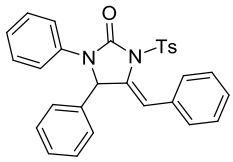
(*Z*)-1-benzyl-4-(cyclopentylmethylene)-5-phenyl-3-tosylimidazolidin-2-one (21l)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.41-7.27 (m, 5H), 7.25-7.17 (m, 1H), 7.17-7.08 (m, 2H), 7.08-6.99 (m, 2H), 6.71-6.58 (m, 2H), 4.82 (d, J = 14.8 Hz, 1H), 4.71–4.57 (m, 2H), 3.36 (d, J = 14.8 Hz, 1H), 3.13-2.94 (m, 1H), 2.49 (s, 3H), 2.06-1.90 (m, 1H), 1.88-1.73 (m, 1H), 1.62-1.44 (m, 4H), 1.23-1.06 (m, 1H), 1.05-0.89 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9, 144.6, 136.7, 136.1, 134.8, 131.4, 129.6, 129.01, 128.99, 128.48, 128.44, 128.38, 128.3, 128.2, 127.7, 63.5, 44.7, 39.6, 33.2, 32.9, 25.4, 25.3, 21.8.

IR (ATR): ν = 2925, 1741 (C=O), 1367, 1170, 1085, 733, 698, 667, 573, 541, 510.

HRMS (EI) for $C_{29}H_{30}N_2O_3S$ calcd. 486.1977, found 486.1970.



21m

(*Z*)-4-benzylidene-1,5-diphenyl-3-tosylimidazolidin-2-one (21m)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.3 Hz, 2H), 7.40 – 7.15 (m, 16H), 7.09–7.01 (m, 1H), 6.07 (s, 1H), 5.67 (d, J = 1.0 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.4, 145.0, 137.1, 136.5, 135.5, 135.4, 131.5, 129.3, 129.14, 129.10, 128.94, 128.88, 128.5, 128.2, 127.4, 126.6, 125.3, 121.5, 117.8 (N-C=*C*), 66.4, 21.7.

IR (ATR): ν = 1735 (C=O), 1596, 1493, 1375, 1171, 1127, 1085, 756, 693, 666, 572, 532.

HRMS (EI) for $C_{29}H_{24}N_2O_3S$ calcd. 480.1508,

found 480.1519.

Crystallography

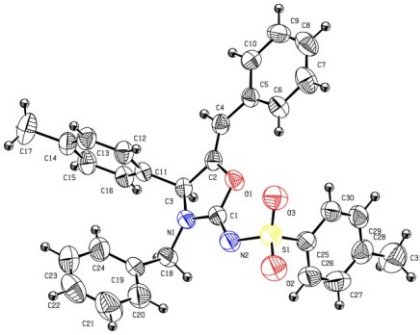
X-ray intensity data were collected at room temperature on an Agilent Supernova diffractometer, equipped with an Atlas CCD detector, using Mo Kα radiation (λ = 0.7107 Å). The images were interpreted and integrated with the CrysAlisPro software from Agilent Technologies.[88] Using Olex2,[89] the structures were solved with the ShelxS[90] structure solution program using Direct Methods and refined with the ShelxL[90] refinement package using full-matrix least squares minimization on F^2. Non hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times U_{eq} of the parent atoms (1.5 for methyl groups). CCDC 904954 and 904955 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystallographic data for 20d

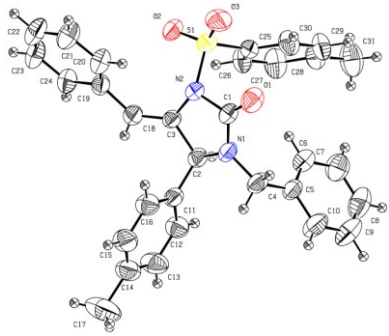
$C_{31}H_{28}N_2O_3S$, M = 508.61 g mol^{-1}, monoclinic, $P2_1/c$ (no. 14), a = 10.6680(6) Å, b = 10.7440(5) Å, c = 23.2151(13) Å, β = 92.519(5), V = 2658.3(2) $Å^3$, T = 293(2) K, Z = 4, ρ_{calcd} = 1.271 g cm^{-3}, μ(Mo Kα) = 0.157 mm^{-1}, F(000) = 1072.0, crystal size 0.5 x 0.3 x 0.1 mm^3, 20843 reflections measured, 5427 unique (R_{int} = 0.0370) which were used in all calculations. The final wR_2 was 0.1414 (all data) and R_1 was 0.0587 (>2sigma(I)).

Crystallographic data for 21d

$C_{31}H_{28}N_2O_3S$, M = 508.61 g mol^{-1}, triclinic, P-1 (no. 2), a = 11.2858(8) Å, b = 11.5920(14) Å, c = 12.0847(12) Å, α = 66.078(10), β = 71.250(7), γ = 72.449(8), V = 1341.4(2) Å^3, T = 293(2) K, Z = 4, ρ_{calcd} = 1.259 g cm^{-3}, μ(Mo Kα) = 0.155 mm^{-1}, F(000) = 536.0, crystal size 0.3 x 0.2 x 0.1 mm^3, 10020 reflections measured, 5452 unique (R_{int} = 0.0284) which were used in all calculations. The final wR_2 was 0.1336 (all data) and R_1 was 0.0529 (>2sigma(I)).



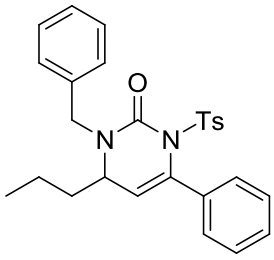
20d



21d

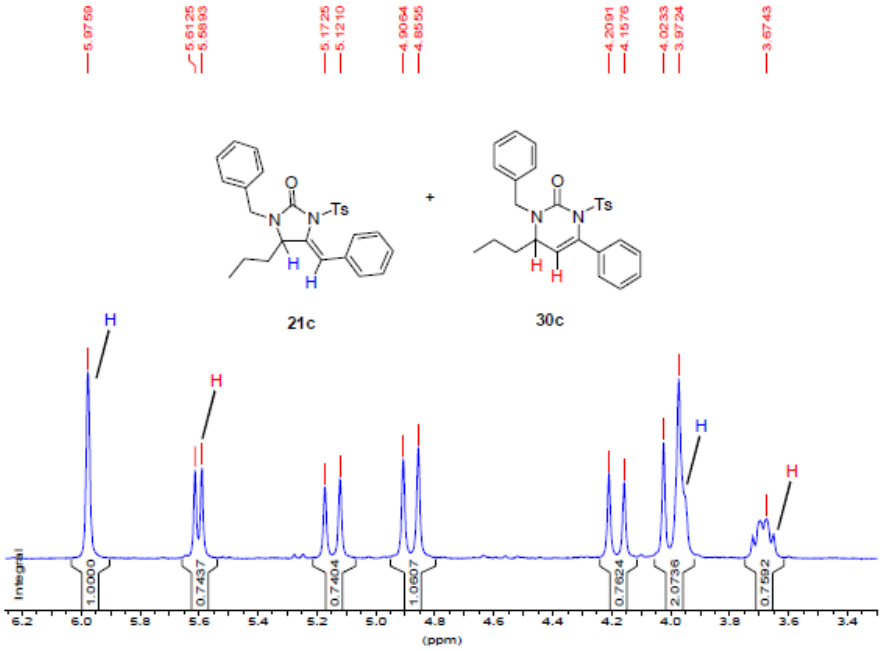
Assignment of some minor 6-membered *O*- and *N*-cyclized products

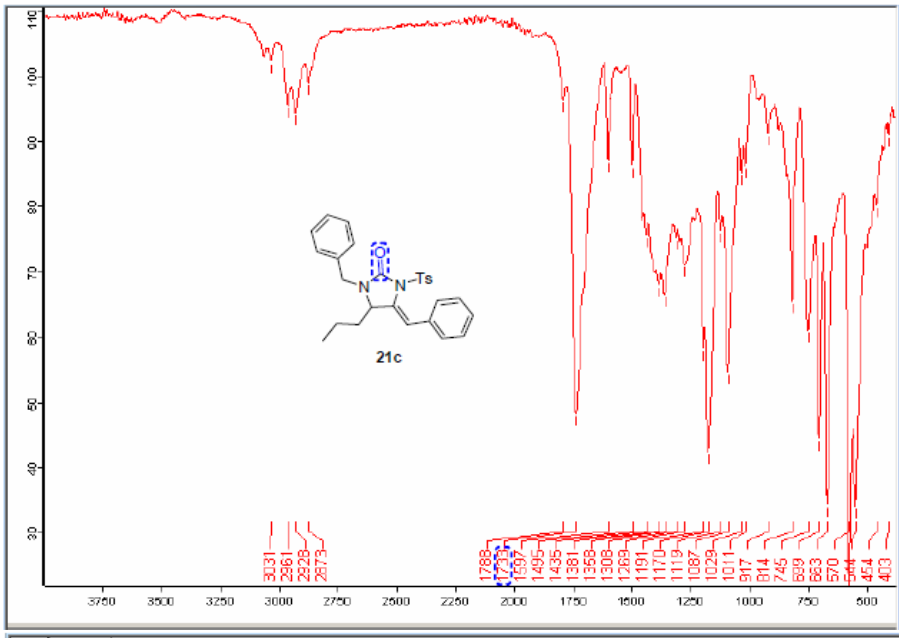
Assignment of 30c

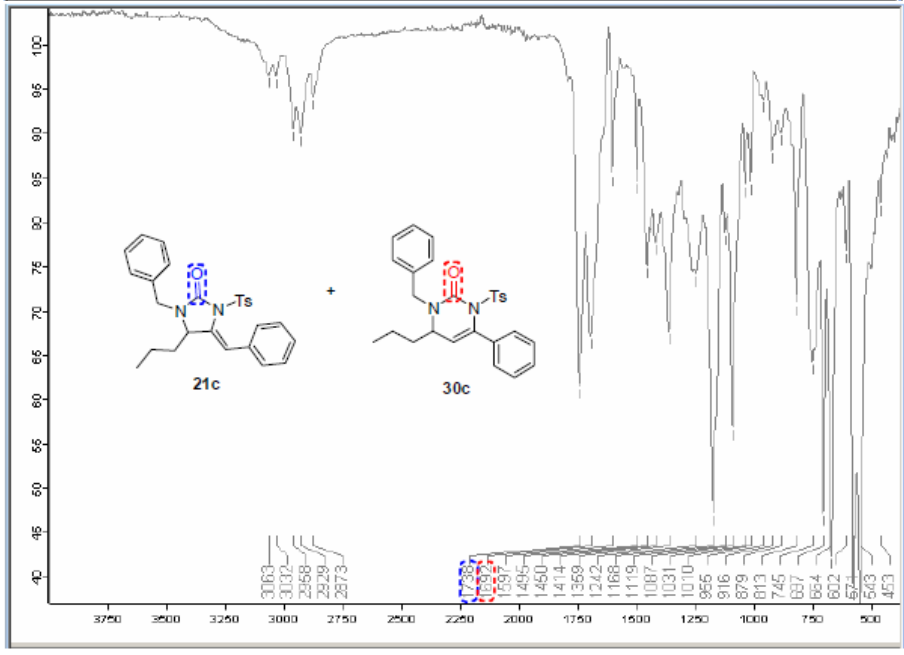


30c

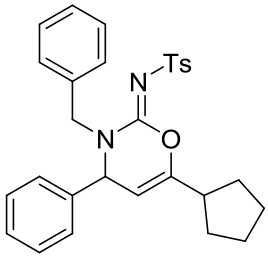
1. Endo-pattern is assigned from the ^{1}H NMR spectra of **30c**/**21c** (~3:4) mixture.
2. *N*-cyclization pattern is determined by comparing IR spectra of pure **21c** with IR spectra of **30c**/**21c** (~3:4) mixture. The assignment is based on C=O stretching IR adsorption peak value of **30c**.
3. In addition, **30c** has R_f value similar to **21c**.


5.9759
5.6125
5.5893
5.1725
5.1210
4.9064
4.8555
4.2091
4.1576
4.0233
3.9724
3.6743
O
N
N
Ts
H
H
+
21c
30c
H
H
H
H
Integral
1.0000
0.7437
0.7404
1.0607
0.7624
2.0736
0.7692
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
(ppm)


21c
3031
2961
2928
2873
1788
1735
1597
1495
1435
1381
1358
1308
1269
1191
1170
1119
1087
1029
1011
917
814
745
689
663
570
544
454
403

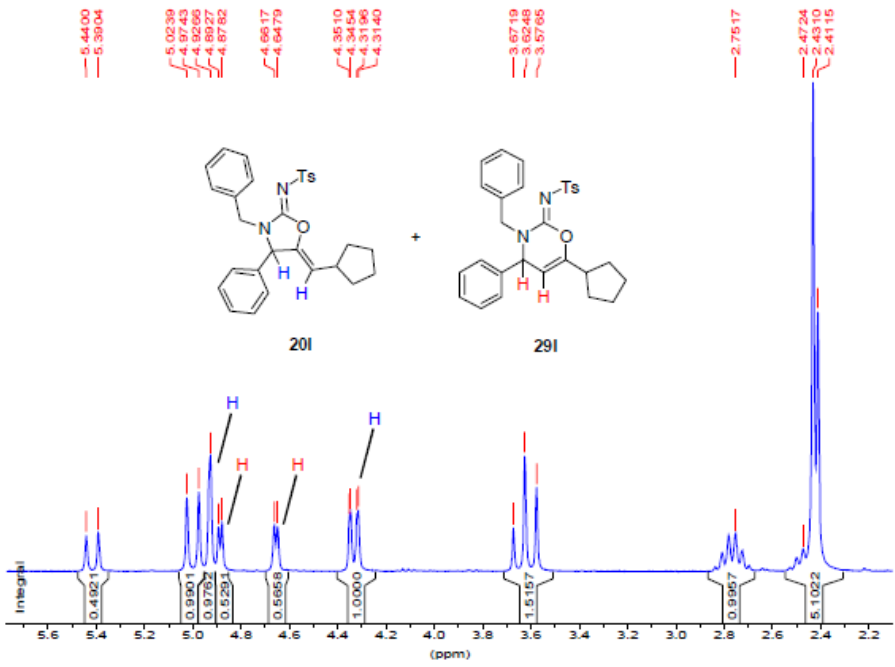

21c
+
30c
3063
3032
2958
2929
2873
1738
1597
1495
1450
1414
1359
1242
1168
1119
1087
1031
1010
965
916
879
813
745
697
664
602
543
453

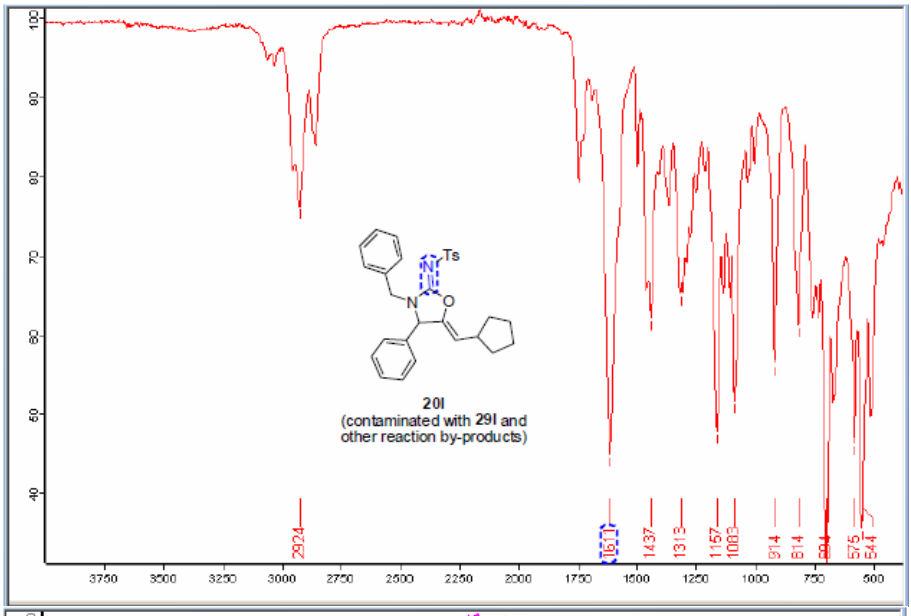
Assignment of 29l[91]

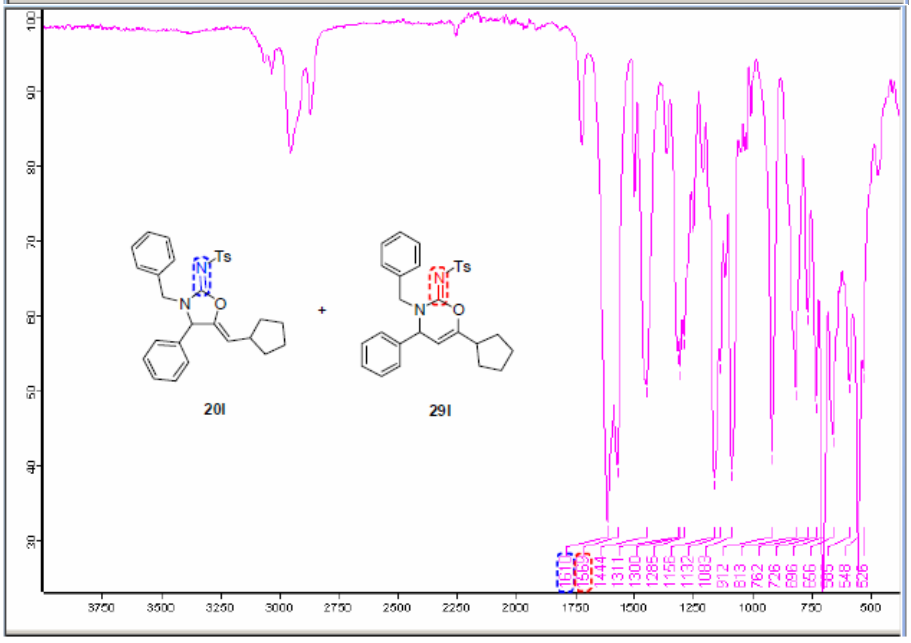


29l

1. Endo-pattern is assigned from the ^{1}H NMR spectra of **29l**/**20l** (~1:2) mixture.
2. *O*-cyclization pattern is determined by comparing IR spectra of **20l** contaminated with **29l** and other reaction byproducts with IR spectra of **29l**/**20l** (~1:2) mixture. The assignment is based on C=N stretching IR adsorption peak value of **29l**.
3. In addition, **29l** has R_f value similar to **20l**.


5.4400
5.3904
5.0239
4.9743
4.9266
4.8927
4.8782
4.6617
4.6479
4.3510
4.3454
4.3196
4.3140
3.6719
3.6248
3.5765
2.7517
2.4724
2.4310
2.4115
Ts
N
O
H
20l
+
29l
Integral
0.4921
0.9901
0.9762
0.5291
0.5658
1.0000
1.5157
0.9957
5.1022
(ppm)

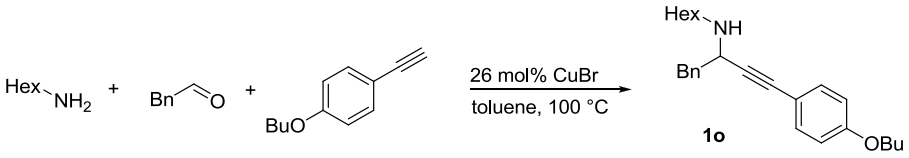

Ts
N
O
20l
(contaminated with 29l and
other reaction by-products)
2924
1611
1437
1313
1157
1083
914
814
575
544
100
90
80
70
60
50
40
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500


Ts
N
O
+
20l
29l
1611
1583
1444
1311
1300
1286
1156
1132
1083
912
813
762
726
696
656
605
548
526
100
90
80
70
60
50
40
30
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500

Chapter 5

Synthesis of starting propargylamines

Propargylamines **1b**[25] and propargylamine **1c,j,n**[59] were synthesized as described previously.



***N*-(4-(4-butoxyphenyl)-1-phenylbut-3-yn-2-yl)hexan-1-amine** (**1o**). Copper bromide (56 mg, 0.39 mmol), toluene (2 mL), amine (2.25 mmol), aldehyde (1.5 mmol) and acetylene (3 mmol) were consecutively loaded to a screw cap vial equipped with a magnetic stirring bar. The mixture was degassed and flushed with argon. The reaction vessel was heated with stirring for 4 h at 100 °C. The resulting reaction mixture was cooled to ambient temperature and subjected to column chromatography with (EtOAc-heptane, 1:9) to afford 300 mg (68%).

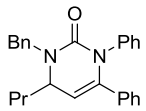
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.15 (m, 7H), 6.80 (d, J = 8.6 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 3.87-3.79 (m, 1H), 3.11-2.83 (m, 3H), 2.71-2.59 (m, 1H), 1.82-1.69 (m, 2H), 1.56-1.40 (m, 4H), 1.36-1.19 (m, 6H), 0.97 (t, J = 7.3 Hz, 3H), 0.91-0.81 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 138.0, 132.9, 129.8, 128.3, 126.6, 115.3, 114.4, 88.9, 84.4, 67.7, 52.1, 47.6, 42.4, 31.8, 31.3, 30.0, 27.1, 22.7, 19.3, 14.1, 13.9. HRMS (ESI) for $C_{26}H_{35}NO$ calcd. $(M+H)^+$ 378.2791, found 378.2787.

Representative procedure for the $AuPPh_3Cl$/AgOTf-catalyzed cycloisomerization of propargylic ureas derived from aryl or alkyl isocyanate

Propargylamine **1** (0.4 mmol) was dissolved in dry $CHCl_3$ (1.6 mL) followed by addition of isocyanate **16** (0.48 mmol). After stirring at rt for about 5 min AgOTf (5.1 mg, 0.02 mmol) and $AuPPh_3Cl$ (9.9 mg, 0.02 mmol) were added. The reaction mixture was kept with stirring at 50°C for 15h in a sealed screw cap vial under air atmosphere. The resulting mixture was directly subjected to column chromatography to give desired cycloisomerization products. Elution was performed using 8–30% EtOAc in heptane first delivering 3,4-dihydropyrimidin-2(1H)-ones **22** followed by propargylic ureas **17d,k,h** or imidazol-2-ones **18l,m**.

Spectral data for 3,4-dihydropyrimidin-2(1H)-ones 22



22a

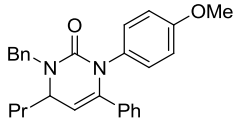
3-benzyl-1,6-diphenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-6.99 (m, 15 H), 5.30-5.19 (m, 2H), 4.15 (d, J = 15.3 Hz, 1H), 3.97-3.88 (m, 1H), 1.80-1.44 (m, 4H), 0.95 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9, 141.1, 139.8, 137.7, 135.9, 128.6, 128.5, 127.9, 127.84, 127.77, 127.3, 125.9, 102.9, 53.9, 49.2, 36.6, 17.6, 14.2.

IR (ATR); v = 3202, 1565 (C=O), 1386, 1259, 1104, 1070, 761, 697.

HRMS (EI) for $C_{26}H_{26}N_2O$ calcd. $(M+H)^+$ 383.2118, found 383.2112.



22b

3-benzyl-1-(4-methoxyphenyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

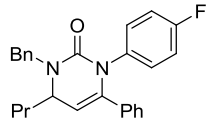
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.23 (m, 5H), 7.20-7.06 (m, 7H), 6.73-6.64 (m, 2H), 5.28-5.13 (m, 2H), 4.16 (d, J = 15.2 Hz, 1H), 3.98-3.87 (m, 1H), 3.69 (s, 3H), 1.80-

1.42 (m, 4H), 0.95 (t, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 155.2, 141.2, 137.8, 136.0, 132.7, 129.6, 128.6, 128.1, 128.0, 127.8, 127.7, 127.3, 113.3, 106.1, 55.3, 53.9, 49.2, 36.6, 17.5, 14.2.

IR (ATR); v = 2930, 1654 (C=O), 1509, 1444, 1358, 1240, 1170, 1030, 910, 829, 726, 696, 555.

HRMS (EI) for $C_{27}H_{28}N_2O_2$ calcd. $(M+H)^+$ 413.2224, found 413.2217.



22c

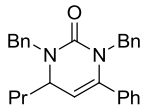
3-benzyl-1-(4-fluorophenyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.12 (m, 12H), 6.84 (t, J = 8.6 Hz, 2H), 5.30-5.18 (m, 2H), 4.15 (d, J = 15.3 Hz, 1H), 3.98-3.89 (m, 1H), 1.80-1.42 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 158.9, 154.9, 140.9, 137.6, 135.73, 135.69, 135.65, 130.1, 130.0, 128.6, 128.02, 127.96, 127.9, 127.4, 115.0, 114.7, 106.7, 53.9, 49.2. 36.6, 17.5, 14.2.

IR (ATR); v = 2960, 1661 (C=O), 1507, 1447, 1217, 1153, 831, 750, 697, 529.

HRMS (EI) for $C_{26}H_{25}FN_2O$ calcd. $(M+H)^+$ 401.2024, found 401.2022.



22d

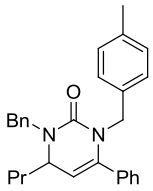
1,3-dibenzyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.11 (m, 13H), 7.04-6.95 (m, 2H), 5.29 (d, J = 15.3 Hz, 1H), 5.17 (d, J = 15.2 Hz, 1H), 4.86 (d, J = 6.0 Hz, 1H), 4.31 (d, J = 15.2 Hz, 1H), 4.01 (d, J = 15.3 Hz, 1H), 3.76 (q, J = 5.9 Hz, 1H), 1.44-1.09 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.8, 140.8, 138.7, 137.8, 135.6, 128.5, 128.4, 128.2, 128.04, 128.01, 127.7, 127.2, 126.9, 105.5, 53.9, 48.9, 47.6, 36.4, 17.5, 14.1.

IR (ATR); v = 2958, 1650 (C=O), 1447, 1228, 751, 696.

HRMS (EI) for $C_{27}H_{28}N_2O$ calcd. $(M+H)^+$ 397.2274, found 397.2269.



22e

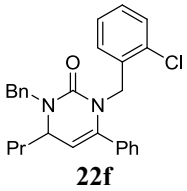
3-benzyl-1-(4-methylbenzyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.20 (m, 10H), 7.00 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 5.30 (d, J = 15.4 Hz, 1H), 5.14 (d, J = 15.1 Hz, 1H), 4.87 (d, J = 6.0 Hz, 1H), 4.26 (d, J = 15.1 Hz, 1H), 4.00 (d, J = 15.4 Hz, 1H), 3.81-3.69 (m, 1H), 2.28 (s, 3H), 1.45-1.09 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.9, 140.9, 137.9, 136.4, 135.8, 135.7, 128.7, 128.5, 128.42, 128.38, 128.3, 128.0, 127.7, 127.2, 105.5, 53.8, 48.9, 47.4, 36.4, 21.1, 17.5, 14.1.

IR (ATR); v = 2957, 1653 (C=O), 1447, 753, 698, 477.

HRMS (EI) for $C_{28}H_{30}N_2O$ calcd. 411.2431, found 411.2428.



22f

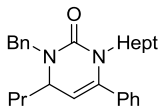
3-benzyl-1-(2-chlorobenzyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.07 (m, 14H), 5.29 (d, J = 15.4 Hz, 1H), 5.07 (d, J = 16.0 Hz, 4.86 (d, J = 5.8 Hz, 1H) 4.53 (d, J = 16.0 Hz, 1H), 4.05 (d, J = 15.4 Hz, 1H), 3.89-3.79 (m, 1H), 1.73-1.25 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.5, 141.3, 137.8, 136.4, 135.5, 132.9, 129.8, 129.2, 128.5, 128.44, 128.37, 128.2, 128.0, 127.7, 127.2, 126.4, 104.6, 54.0, 48.9, 45.9, 36.3, 17.8, 14.1.

IR (ATR); v = 2959, 1656 (C=O), 1443, 1039, 748, 697.

HRMS (EI) for $C_{27}H_{27}ClN_2O$ calcd. $(M+H)^+$ 431.1885, found 431.1880.



22g

3-benzyl-1-heptyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

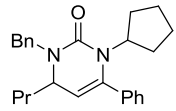
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.20 (m, 10H), 5.27 (d, J = 15.4 Hz, 1H), 4.84 (d, J = 6.1 Hz, 1H), 4.06 (d, J = 15.4 Hz, 1H), 4.02-3.90 (m, 1H), 3.83-3.73 (m, 1H), 3.15-3.03 (m, 1H), 1.71-1.02 (m,. 14H), 0.93 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.8, 141.1, 138.1, 135.9, 128.5, 128.3, 128.2, 127.7, 127.2, 104.8, 53.8, 48.9, 44.1, 36.3, 31.7, 29.3, 28.8, 26.6, 22.5, 17.7, 14.2, 14.1.

IR (ATR); v = 2927, 1660 (C=O), 1448, 698.

HRMS (EI) for $C_{27}H_{36}N_2O$ calcd. $(M+H)^+$ 405.2900, found

405.2892.



22h

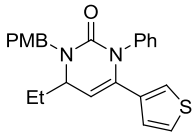
3-benzyl-1-cyclopentyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.20 (m, 10H), 5.25 (d, J = 15.5 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.03 (d, J = 15.5 Hz, 1H), 3.74-3.51 (m, 2H), 2.50-2.33 (m, 1H), 2.12-1.20 (m, 11H), 0.92 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.6, 143.2, 138.0, 137.0, 128.5, 128.3, 127.9, 127.7, 127.1, 105.3, 60.0, 53.2, 48.4, 36.1, 31.1, 29.8, 25.7, 25.1, 17.8, 14.2.

IR (ATR); v = 2925, 1703, 1650 (C=O), 1447, 1383, 1352, 1249, 730, 698.

HRMS (EI) for $C_{25}H_{30}N_2O$ calcd. $(M+H)^+$ 375.2431, found 375.2428.



22i

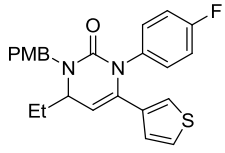
4-ethyl-3-(4-methoxybenzyl)-1-phenyl-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.06 (m, 7H), 7.04-6.83 (m, 4H), 6.76-6.69 (m, 1H), 5.26-5.12 (m, 2H), 4.07 (d, J = 15.1 Hz, 1H), 3.95-3.85 (m, 1H), 3.80 (s, 3H), 1.84-1.69 (m, 1H), 1.67-1.52 (m, 1H), 1.02 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 154.7, 139.8, 136.8, 136.4, 129.6, 129.4, 128.5, 128.1, 127.2, 126.2, 124.8, 123.7, 114.0, 105.0, 55.2, 54.5, 48.4, 26.8, 8.4.

IR (ATR); v = 2929, 1653 (C=O), 1511, 1441, 1242, 1173, 1031, 729, 696.

HRMS (EI) for $C_{24}H_{24}N_2O_2S$ calcd. $(M+H)^+$ 405.1631, found 405.1630.



22j

4-ethyl-1-(4-fluorophenyl)-3-(4-methoxybenzyl)-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one

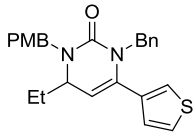
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.14 (m, 4H), 7.07-6.82 (m, 6H), 6.73-6.66 (m, 1H), 5.23-5.10 (m, 2H), 4.07 (d, J = 15.1 Hz, 1H), 3.96-3.86 (m, 1H), 3.81 (s, 3H), 1.86-1.68 (m, 1H), 1.66-1.50 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.4, 159.1, 159.0, 154.6, 136.6, 136.3, 135.73, 135.68, 130.1, 130.0, 129.45, 129.40, 127.2, 125.1, 123.8, 115.1, 114.8, 114.0, 104.9, 55.3, 54.5, 48.5, 26.8, 8.3.

IR (ATR); v = 2931, 1652 (C=O), 1506, 1450, 1240, 1174,

1032, 729.

HRMS (EI) for $C_{24}H_{23}FN_2O_2S$ calcd. $(M+H)^+$ 423.1537, found 423.1530.



22k

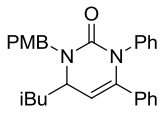
1-benzyl-4-ethyl-3-(4-methoxybenzyl)-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-6.83 (m, 12H), 5.23 (d, J = 15.1 Hz, 1H), 5.10 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 5.7 Hz, 1H), 4.39 (d, J = 15.5 Hz, 1H), 3.96 (d, J = 15.1 Hz, 1H), 3.85-3.71 (m, 4H), 1.61-1.38 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 155.4, 139.0, 136.5, 136.0, 129.7, 129.2, 128.1, 127.8, 127.5, 126.8, 125.6, 124.5, 113.9, 104.1, 55.3, 54.7, 48.1, 47.7, 26.8, 8.4.

IR (ATR); v = 2927, 1645 (C=O), 1511, 1450, 1243, 1174, 1030, 695, 510.

HRMS (EI) for $C_{25}H_{26}N_2O_2S$ calcd. $(M+H)^+$ 419.1788, found 419.1782.



22l

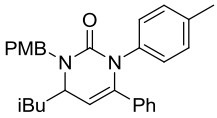
4-isobutyl-3-(4-methoxybenzyl)-1,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.23 (m, 4H), 7.21-7.07 (m, 7H), 7.07-6.97 (m, 1H), 6.92-6.82 (m, 2H), 5.36 (d, J = 6.5 Hz, 1H), 5.16 (d, J = 15.1 Hz, 1H), 4.06 (d, J = 15.1 Hz, 1H), 3.89-3.74 (m, 4H), 1.91-1.47 (m, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 155.0, 140.9, 139.8, 135.8, 129.6, 129.4, 128.2, 128.0, 127.91, 127.86, 127.8, 125.8, 114.0, 108.0, 55.3, 52.0, 48.8, 44.1, 24.6, 24.0, 22.1.

IR (ATR); v = 2955, 1664 (C=O), 1511, 1446, 1243, 1173, 1031, 909, 756, 729, 695, 570.

HRMS (EI) for $C_{28}H_{30}N_2O_2$ calcd. $(M+H)^+$ 427.2380, found 427.2375.



22m

4-isobutyl-3-(4-methoxybenzyl)-6-phenyl-1-p-tolyl-3,4-dihydropyrimidin-2(1*H*)-one

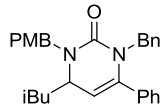
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 7.8 Hz, 2H), 7.21-7.05 (m, 7H), 6.95 (d, J = 7.6 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 5.32 (d, J = 6.0 Hz, 1H), 5.14 (d, J = 15.1 Hz, 1H), 4.06 (d, J = 15.1 Hz, 1H), 3.88-3.72 (m, 4H), 2.18 (s, 3H), 1.91-1.47 (m, 3H), 0.97 (d, J = 6.0 Hz, 3H), 0.90 (d, J

= 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 155.1, 140.9, 137.2, 135.9, 135.4, 129.7, 129.4, 128.6, 128.0, 127.9, 127.8, 127.7, 113.9, 107.6, 55.2, 52.0, 48.8, 44.1, 24.5, 24.0, 22.1, 20.9.

IR (ATR); v = 2955, 1663 (C=O), 1510, 1446, 1242, 1173, 1032, 909, 817, 754, 729, 697, 516.

HRMS (EI) for $C_{29}H_{32}N_2O_2$ calcd. $(M+H)^+$ 441.2537, found 441.2528.



22n

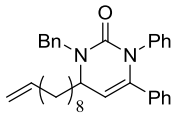
1-benzyl-4-isobutyl-3-(4-methoxybenzyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.30 (m, 3H), 7.29-7.15 (m, 7H), 7.03-6.97 (m, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.28-5.16 (m, 2H), 4.98 (d, J = 6.4 Hz, 1H) 4.25 (d, J = 15.1 Hz, 1H), 3.91 (d, J = 15.1 Hz, 1H), 3.77 (s, 3H), 3.73-3.63 (m, 1H), 1.67-1.52 (m, 1H), 1.38-1.15 (m, 2H), 0.84-0.71 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 156.1, 140.7, 138.8, 135.6, 129.8, 129.2, 128.43, 128.35, 128.3, 128.11, 128.06, 127.0, 113.9, 106.3, 55.2, 51.8, 48.4, 47.6, 43.6, 24.2, 23.8, 21.9.

IR (ATR); v = 2925, 1656 (C=O), 1511, 1447, 1244, 1174, 1030, 820, 752, 698, 584, 512.

HRMS (EI) for $C_{29}H_{32}N_2O_2$ calcd. $(M+H)^+$ 441.2537, found 441.2532.



22o

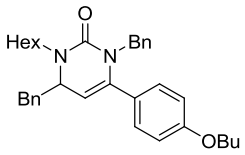
3-benzyl-4-(dec-9-enyl)-1,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-6.98 (m, 15H), 5.90-5.73 (m, 1H), 5.28-5.17 (m, 2H), 5.05-5.89 (m, 2H), 4.16 (d, J = 15.3 Hz, 1H), 3.97-3.87 (m, 1H), 2.05 (q, J = 6.8 Hz, 2H), 1.81-1.22 (m, 14H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 141.2, 139.8, 139.2, 137.8, 135.9, 128.6, 128.5, 128.0, 127.9, 127.8, 127.4, 125.9, 114.2, 107.0, 54.1, 49.3, 34.4, 33.8, 29.6, 29.5, 29.4, 29.1, 29.0, 24.3.

IR (ATR); v = 2925, 1662 (C=O), 1494, 1446, 756, 695.

HRMS (EI) for $C_{33}H_{38}N_2O$ calcd. $(M+H)^+$ 479.3057, found 479.3052.



22p

1,4-dibenzyl-6-(4-butoxyphenyl)-3-hexyl-3,4-dihydropyrimidin-2(1*H*)-one

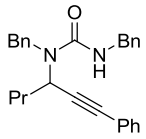
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.13 (m, 6H), 7.08 (d, J = 8.4 Hz, 2H), 7.04-6.97 (m, 3H), 6.82 (d, J = 8.4 Hz, 2H), 5.09 (d, J = 15.1 Hz, 1H), 4.73 (d, J = 6.2 Hz, 1H), 4.23 (d, J = 15.1 Hz, 1H), 4.00-3.83 (m, 4H), 2.78-2.65 (m, 2H), 2.51-2.40 (m, 1H), 1.83-1.71 (m, 2H), 1.65-1.42 (m, 4H), 1.35-1.23 (m, 7H), 0.98 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 6.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 155.5, 140.8, 139.1, 137.3, 129.6, 129.5, 128.3, 128.2, 128.0, 127.7, 126.9, 126.4, 114.2, 104.2, 67.7, 56.6, 47.5, 46.8, 41.9, 31.6, 31.3, 28.1, 26.5, 22.6, 19.2, 14.0, 13.9.

IR (ATR); v = 2928, 1660 (C=O), 1603, 1510, 1453, 1247, 1172, 698.

HRMS (EI) for $C_{34}H_{42}N_2O_2$ calcd. $(M+H)^+$ 511.3319, found 511.3314.

Spectral data for propargylic ureas 17d,k,h



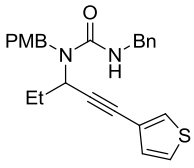
17d

1,3-dibenzyl-1-(1-phenylhex-1-yn-3-yl)urea

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.16 (m, 13H), 7.06-6.94 (m, 2H), 5.52 (t, J = 7.6 Hz, 1H), 4.7-4.67 (m, 2H), 4.48-4.26 (m, 3H), 1.78 (q, J = 7.6 Hz, 2H), 1.65-1.40 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.6, 139.2, 138.0, 131.5, 128.9, 128.4, 128.19, 128.15, 127.6, 127.1, 127.0, 126.8, 122.8, 88.3, 84.7, 48.6, 47.8, 44.8, 37.0, 19.6, 13.7.

HRMS (EI) for $C_{27}H_{28}N_2O$ calcd. 396.2202, found 396.2214.



17k

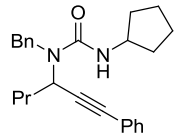
3-benzyl-1-(4-methoxybenzyl)-1-(1-(thiophen-3-yl)pent-1-yn-3-yl)urea

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.16 (m, 7H), 7.05-6.92 (m, 3H), 6.89-6.79 (m, 2H), 5.40 (t, J = 7.5 Hz, 1H), 4.80-4.70 (m, 1H), 4.84 (d, J = 8.4 Hz, 1H), 4.42-4.25 (m, 3H), 3.79 (s, 3H), 1.87-1.71 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 157.7, 139.2, 129.84, 129.79, 128.6, 128.4, 128.0, 127.1, 127.0, 125.2, 121.7,

114.3, 87.7, 79.8, 55.3, 50.2, 47.2, 44.8, 28.1, 10.9.

HRMS (EI) for $C_{25}H_{26}N_2O_2S$ calcd. 418.1715, found 418.1727.



17h

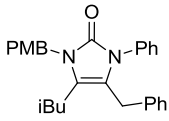
1-benzyl-3-cyclopentyl-1-(1-phenylhex-1-yn-3-yl)urea

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.14 (m, 10H), 5.51(t, J = 7.5 Hz, 1H), 4.68 (d, J = 8.5 Hz, 1H), 4.42-4.21 (m, 2H), 4.11-3.97 (m, 1H), 1.88-0.93 (m, 15H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 138.4, 131.5, 128.9, 128.2, 128.1, 127.6, 126.7, 122.9, 88.6, 84.5, 52.5, 48.3, 47.8, 37.0, 33.32, 33.28, 23.3, 23.2, 19.6, 13.7.

HRMS (EI) for $C_{25}H_{30}N_2O$ calcd. $(M+H)^+$ 375.2431, found 375.2429.

Spectral data for imidazol-2-ones 18l,m



18l

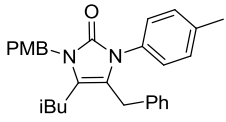
4-benzyl-5-isobutyl-1-(4-methoxybenzyl)-3-phenyl-1*H*-imidazol-2(3*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.04 (m, 10H), 6.91-6.77 (m, 4H), 4.90 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 2.26-2.18 (m, 2H), 1.81-1.63(m, 1H), 0.93-0.86 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.6, 138.2, 135.3, 130.1, 128.8, 128.3, 128.2, 128.0, 127.8, 127.5, 126.2, 119.8, 117.7, 114.0, 55.3, 44.4, 32.6, 29.7, 29.5, 28.6, 22.3.

IR (ATR); v = 2923, 1676 (C=O), 1513, 1406, 1245, 1175, 1030, 807, 758, 694, 506.

HRMS (EI) for $C_{28}H_{30}N_2O_2$ calcd. 426.2307, found 426.2323.



18m

4-benzyl-5-isobutyl-1-(4-methoxybenzyl)-3-*p*-tolyl-1*H*-imidazol-2(3*H*)-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.04 (m, 7H), 6.99-6.92 (m, 2H), 6.90-6.80 (m, 4H), .4.89 (s, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.30 (s, 3H), 2.23-2.16 (m, 2H), 1.79-1.64 (m, 1H), 0.88 (d, J = 3.2 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.7, 138.3, 137.4, 132.6, 130.1, 129.5, 128.23, 128.22, 127.8, 126.2, 119.6, 117.8, 114.0, 55.3, 44.4, 32.6, 29.7, 29.4, 28.6, 22.3, 21.1.

IR (ATR); v = 2924, 1688 (C=O), 1512, 1405, 1245, 1175,

1031, 815, 702, 545, 510.

HRMS (EI) for $C_{29}H_{32}N_2O_2$ calcd. 440.2464, found 440.2469.

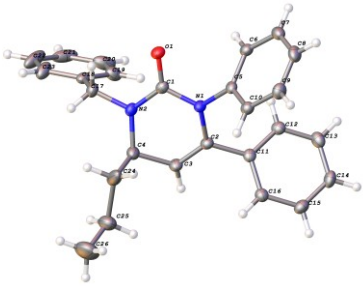
Crystallography

X-ray intensity data for **22a** and **18a** were collected at respectively 100K and room temperature on an Agilent Supernova diffractometer, equipped with an Atlas CCD detector, using Mo Kα radiation (λ = 0.7107 Å). The images were interpreted and integrated with the CrysAlisPro software from Agilent Technologies.[88] Using Olex2,[89] the structure was solved with the ShelxS[90] structure solution program using Direct Methods and refined with the ShelxL[90] refinement package using full-matrix least squares minimization on F^2. In structure **22a**, C25 and C26 are modeled in two positions with occupancies of 0.5. Non hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times U_{eq} of the parent atoms (1.5 for methyl groups).

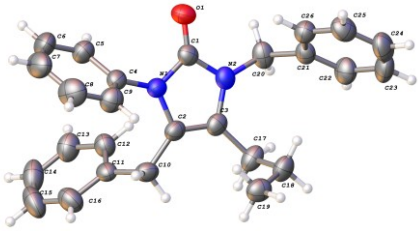
Crystallographic data

22a $C_{26}H_{26}N_2O$, M = 382.49 g mol^{-1}, monoclinic, $P2_1/n$ (no. 14), a = 9.9630(9) Å, b = 10.2126(5) Å, c = 21.0844(18) Å, β = 97.452(10), V = 2127.2(3) Å^3, T = 100.5(9) K, Z = 4, ρ_{calcd} = 1.194 g cm^{-3}, μ(Mo Kα) = 0.073 mm^{-1}, F(000) = 816.0, crystal size 0.2 x 0.2 x 0.2 mm^3, 9185 reflections measured, 4353 unique (R_{int} = 0.0253) which were used in all calculations. The final wR_2 was 0.1122 (all data) and R_1 was 0.0458 (>2sigma(I)).

18a $C_{26}H_{26}N_2O$, M = 382.49 g mol^{-1}, triclinic, P-1 (no. 2), a = 7.8694(12) Å, b = 10.0748(12) Å, c = 13.8855(9) Å, α = 101.946(8) Å, β = 92.094(8), γ = 105.143(12) Å, V = 1034.8(2) $Å^3$, T = 293(2) K, Z = 2, ρ_{calcd} = 1.228 g cm^{-3}, μ(Mo Kα) = 0.075 mm^{-1}, F(000) = 408.0, crystal size 0.6 x 0.4 x 0.2 mm^3, 21448 reflections measured, 4251 unique (R_{int} = 0.0164) which were used in all calculations. The final wR_2 was 0.1156 (all data) and R_1 was 0.0427 (>2sigma(I)).



22a



18a

Safety aspects

This section includes some guidelines for the safe handling of materials and chemicals, when repeating the procedures described in this thesis.

First of all, before setting any experiment, it is highly recommended to read the MSDS for all involved chemicals. For example, in the current work we have used a number of commercially available primary amines, aldehydes, ketones, terminal alkynes and isocyanates as starting materials. Most of these compounds are also included in the KU Leuven Database of Hazardous Products which is another main source of the information for the risk assessments.

Aromatic isocyanates are particularly toxic. For example phenyl isocyanate is extremely hazardous in case of inhalation. Severe over-exposure could be fatal. Therefore it should only be handled in a well functionating fumehood. Moreover, general ventilation, *e.g.* fresh air impute, is also required. All syringes and laboratory glass exposed to phenyl isocyanate should be washed in the fumehood and all generated wastes should be treated with water before they could be discarded.

We would also like to emphasize that in case of inappropriate handling some commonly used solvents and materials may also possess a certain danger for the health which is multiplied by their bulk quantities. For example chronic exposure to DCM is associated with a possible cancer hazard. Long-term exposure (10 years or more) even to relatively low concentrations of silica dust may result in developing chronic silicosis.[92]

Curriculum vitae

Personal Information

Name	Olga P. Pereshivko
Date of birth	April 7, 1985
Citizenship	Russia
Marital status	Married to Vsevolod A. Peshkov (Dipl. Chem.)
E-mail	olga.pereshivko@student.kuleuven.be, olgaperesh@gmail.com

Professional Career and Education

2009-2013	PhD at University of Leuven (KU Leuven), Belgium, Thesis title: "Transition metal-catalyzed cycloisomerizations of propargylic ureas and guanidines derived in situ from secondary propargylamines", Supervisor: Prof. Dr. Erik V. Van der Eycken.
2006-2008	M.S. in Chemistry, D. Mendeleyev University of Chemical Technology of Russia, Russia
2002-2006	B.S. in Chemistry, D. Mendeleyev University of Chemical Technology of Russia, Russia

List of publications

1. Cationic Gold- and Silver-Catalyzed Cycloisomerizations of Propargylic Ureas: a Selective Entry to Oxazolidin-2-imines and Imidazolidin-2-ones, **Olga P. Pereshivko**,[#] Vsevolod A. Peshkov,[#] Jeroen Jacobs, Luc Van Meervelt, and Erik V. Van der Eycken, *Advanced Synthesis & Catalysis*, **2013**, *355*, 781–789.
[#] = equal contribution.

2. Fast Assembly of 1*H*-Imidazo[1,2-*a*]imidazol-5-amines *via* Groebke–Blackburn–Bienaymé Reaction with 2-Aminoimidazoles, **Olga P. Pereshivko**,[#] Vsevolod A. Peshkov,[#] Denis S. Ermolat'ev and Erik V. Van der Eycken, *Synlett*, **2013**, *24*, 351-354.
[#] = equal contribution.

3. Synthesis of Azocino[5,4-*b*]indoles *via* Au-Catalyzed Intramolecular Alkyne Hydroarylation, Vsevolod A. Peshkov, **Olga P. Pereshivko**, and Erik V. Van der Eycken, *Advanced Synthesis & Catalysis*, **2012**, *354*, 2841–2848.

4. Alkylation of 3,5-Dichloro-2(1*H*)-pyrazinones Using Malonate Esters, Nigam M. Mishra, Vsevolod A. Peshkov, **Olga P. Pereshivko**, Sachin G. Modha, and Erik V. Van der Eycken, *Tetrahedron Letters*, **2012**, *53*, 4676–4678.

5. A walk around the A^3-coupling, Vsevolod A. Peshkov, **Olga P. Pereshivko**, and Erik V. Van der Eycken, *Chemical Society Reviews*, **2012**, *41*, 3790–3807.

6. Synthesis of Isoquinolinium-2-yl Amides *via* Silver(I)-catalyzed Ring Closure of N'-(2-Alkynylbenzylidene)hydrazides, Vsevolod A. Peshkov, **Olga P. Pereshivko**, Sofie Van Hove, Denis S. Ermolat'ev, and Erik V. Van der Eycken, *Synthesis*, **2011**, 3371–3374.

7. Tetrasubstituted 2-Imidazolones *via* Ag(I)-Catalyzed Cycloisomerization of Propargylic Ureas, Vsevolod A. Peshkov, **Olga P. Pereshivko**, Sweta Sharma, Thirumal Meganathan, Virinder S. Parmar, Denis S. Ermolat'ev, and Erik V. Van der Eycken, *Journal of Organic Chemistry*, **2011**, *76*, 5867–5872.

8. Diversity-Oriented Silver(I)-Mediated Synthesis of Spiro-2-aminoimidazoles, **Olga P. Pereshivko**, Vsevolod A. Peshkov, Denis S. Ermolat'ev, Sofie Van Hove, Kristof Van Hecke, Luc Van Meervelt, and Erik V. Van der Eycken, *Synthesis*, **2011**, 1587–1594.

9. Synthesis of the Azocino[*cd*]indole Framework through Pd-Catalyzed Intramolecular Acetylene Hydroarylation, Vsevolod A. Peshkov, Sofie Van Hove, Pavel A. Donets, **Olga P. Pereshivko**, Kristof Van Hecke, Luc Van Meervelt, and Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2011**, 1837–1840.

10. Diversity-Oriented Microwave-Assisted Synthesis of the 3-Benzazepine Framework, Vsevolod A. Peshkov, **Olga P. Pereshivko**, Pavel A. Donets, Vaibhav P. Mehta, and Erik V. Van der Eycken, *European Journal of Organic Chemistry*, **2010**, 4861–4867.

11. Unprecedented Cu(I)-Catalyzed Microwave-Assisted Three-Component Coupling of a Ketone, an Alkyne, and a Primary Amine, **Olga P. Pereshivko**, Vsevolod A. Peshkov, and Erik V. Van der Eycken, *Organic Letters*, **2010**, *12*, 2638–2641.

References

[1] a) G. Magueur, B. Crousse, D. Bonnet-Delpon *Tetrahedron Lett.* **2005**, *46*, 2219; b) K. B. Aubrecht, M. D. Winemiller, D. B. Callum *J. Am. Chem. Soc.* **2000**, *122*, 11084.

[2] a) K. C. Brannock, R. D. Burpitt, J. G. Thweatt *J. Org. Chem.* **1963**, *28*, 1462; b) C. Fischer, E. M. Carreira *Org. Lett.* **2001**, *3*, 4319; enantioselectively: c) M. Benaglia, D. Negri, G. Dell'Anna *Tetrahedron Lett.* **2004**, *45*, 8705; d) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, G. Celentano *J. Org. Chem.* **2006**, *71*, 2064.

[3] For focused reviews on A^3-coupling, see: a) C. Wei, L. Zhang, C.-J. Li *Synlett* **2004**, 1472; b) W.-J. Yoo, L. Zhao, C.-J. Li *Aldrichim. Acta* **2011**, *44*, 43; c) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken *Chem. Soc. Rev.* **2012**, *41*, 3790; for other related reviews providing some representative examples of A^3-coupling, see: d) L. Zani, C. Bolm *Chem. Commun.* **2006**, 4263; e) C.-J. Li *Acc. Chem. Res.* **2010**, *43*, 581; f) V. V. Kouznetsov, L. Y. Vargas Méndez *Synthesis* **2008**, *4*, 491.

[4] a) J. P. Guermont, *Bull. Soc. Chim. Fr.* **1953**, 386; b) R. Epsztein, M. Olomucki and I. Marszak *Bull. Soc. Chim. Fr.* **1953**, 952.

[5] For selected examples, see: a) B. Yan, Y. Liu *Org. Lett.* **2007**, *9*, 4323; b) N. Sakai, N. Uchida T. Konakahara, *Tetrahedron Lett.* **2008**, *4*9, 3437–3440; c) H. Li, J. Liu, B. Yan, Y. Li, *Tetrahedron Lett.* **2009**, *50*, 2353; d) Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno *J. Org. Chem.* **2009**, *74*, 7052; e) N. Chernyak, V. Gevorgyan *Angew. Chem., Int. Ed.* **2010**, *49*, 2743; f) D. Chernyak, N. Chernyak, V. Gevorgyan *Adv. Synth. Catal.* **2010**, *352*, 961; g) Q. Zhang, M. Chang, X. Y. Hu, B. G. Li, J. X. Ji *J. Am. Chem. Soc.* **2010**, *132*, 7256; h) E. R. Bonfield, C.-J. Li *Adv. Synth. Catal.* **2008**, *350*, 370.

[6] J. J. McNally, M. A. Youngman, S. L. Dax *Tetrahedron Lett.* **1998**, *39*, 967.

[7] A. B. Dyatkin, R. A. Rivero *Tetrahedron Lett.* **1998**, *39*, 3647.

[8] C.-J. Li, C. Wei *Chem. Commun.* **2002**, 268.

[9] C. We, C.-J. Li *J. Am. Chem. Soc.* **2003***, 125,* 9584.

[10] C. Wei, Z. Li, C.-J. Li *Org. Lett.* **2003**, *5*, 4473.

[11] L. Shi, Y. Q. Tu, M. Wang, F. M. Zhang, C. A. Fan *Org. Lett.* **2004**, *6*, 1001.

[12] Y. Ju, C.-J. Li, R. S. Varma *QSAR Comb. Sci*. **2004**, *23*, 891.

[13] N. E. Leadbeater, H. M. Torenius, H. Tye *Mol. Diversity* **2003**, *7*, 135.

[14] G. Shore, W.-J. Yoo, C.-J. Li, M. G. Organ *Chem. Eur. J.* **2010**, *16*, 126.

[15] C. M. Wei, C.-J. Li *J. Am. Chem. Soc.* **2002**, *124*, 5638.

[16] C. Wei, J. T. Mague, C.-J. Li *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5749.

[17] a) C. Koradin, K. Polborn, P. Knochel *Angew. Chem. Int. Ed.* **2002**, *41*, 2535; b) C. Koradin, N. Gommermann, K. Polborn, P. Knochel *Chem.–Eur. J.* **2003**, *9*, 2797.

[18] N. Gommermann, C. Koradin, K. Polborn, P. Knochel *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

[19] a) P. Li*,* Y. Zhang, L. Wang *Chem. Eur. J.* **2009***, 15,* 2045; b) W.-W. Chen, R. V. Nguyen, C.-J. Li *Tetrahedron Lett.* **2009**, *50*, 2895.

[20] Y. Zhang, P. Li, M. Wang, L. Wang *J. Org. Chem.* **2009**, *74*, 4364.

[21] E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa *Tetrahedron Lett.* **2007**, *48*, 7184.

[22] S. Samai, G. C. Nandi, M. S. Singh *Tetrahedron Lett.* **2010**, *51*, 5555.

[23] P. Li, L. Wang *Chin. J. Chem.* **2005**, *23*, 1076.

[24] For the application in the synthesis of polysubstituted pyrroles, see: W. S. Bremner, M. G. Organ *J. Comb. Chem.* **2008**, *10*, 142.

[25] J. B. Bariwal, D. S. Ermolat'ev, E. V. Van der Eycken *Chem. Eur. J.* **2010**, *16*, 3281.

[26] M. J. Aliaga, D. J. Ramón, M. Yus *Org. Biomol. Chem.* **2010**, *8*, 43.

[27] O. P. Pereshivko, V. A. Peshkov, E. V. Van der Eycken *Org. Lett.* **2010**, *12*, 2638.

[28] M. Cheng, Q. Zhang, X.-Y. Hu, B.-G. Li, J.-X. Ji, A. S. C. Chan *Adv. Synth. Catal.* **2011**, *353*, 1274.

[29] C. J. Pierce, M. Nguyen, C. H. Larsen *Angew. Chem. Int. Ed.* **2012**, *51*, 12289.

[30] W.-J. Yoo, C.-J. Li *Adv. Synth. Catal.* **2008**, *350*, 1503.

[31] H. Feng, D. S. Ermolat'ev, G. Song, E. V. Van der Eycken *Adv. Synth. Catal.* **2012**, *354*, 505.

[32] a) R. G. S. Berlinck, A. C. B. Burtoloso, A. E. Trindade-Silva, S. Romminger, R. P. Morais, K. Bandeira, C. M. Mizuno *Nat. Prod. Rep.* **2010**, *27*, 1871; b) R. G. S. Berlinck, A. C. B. Burtoloso, M. H. Kossuga *Nat. Prod. Rep.* **2008**, *25*, 919; c) R. G. S. Berlinck, M. H. Kossuga *Nat. Prod. Rep.* **2005**, *22*, 516; d) R. G. S. Berlinck *Nat. Prod. Rep.* **2002**, *19*, 617.

[33] a) Z. Jin *Nat. Prod. Rep.* **2003**, *20*, *584*. b) Z. Jin *Nat. Prod. Rep.* **2005***, 22,* 196. c) Z. Jin *Nat. Prod. Rep.* **2006**, *23*, 464. d) Z. Jin *Nat. Prod. Rep.* **2009***, 26,* 382. e) S. M. Weinreb *Nat. Prod. Rep.*, **2007**, *24*, 931. f) J. D. Sullivan, R. L. Giles, R. E. Looper *Curr. Bioact. Compd.* **2009**, *5*, 39. g) H. Hoffmann, T. Lindel *Synthesis*, **2003**, *12*, 175. h) P. B. Koswatta, C. J. Lovely *Nat. Prod. Rep.* **2010**, *28*, 511.

[34] a) D. C. Dunbar, J. M. Rimoldi, A. M. Clark, M. Kelly, M. T. Hamann *Tetrahedron* **2000**, *56,* 8795. b) P. Crews, D. P. Clark, K. Tenney *J. Nat. Prod.* **2003**, *66,* 177. c) W. Hassan, R. Edrada, R. Ebel, V. Wray, A. Berg, R. Van Soest, S. Wiryowidagdo, P. Proksch *J. Nat. Prod.* **2004**, *67*, 817.

[35] a) X. Fu, J. R. Barnes, T. Do, F. J. Schmitz *J. Nat. Prod.* **1997**, *60*, 497. b) H. Gross, S. Kehraus, G. M. König, G. Woerheide, A. D. Wright *J. Nat. Prod*. **2002**, *65*, 1190.

[36] a) S. Carmely, Y. Kashman *Tetrahedron Lett*. **1987**, *28*, 3003. b) S. Carmely, M. Ilan, Y. Kashman *Tetrahedron* **1989**, *45*, 2193.

[37] X. Fu, F.J. Schmitz, R. S. Tanner, M. Kelly-Borges *J. Nat. Prod.* **1998,** *61,* 384.

[38] a) R. K. Akee, T. R. Carroll, W. Y. Yoshida, P. J. Scheuer, T. J. Stout, J. Clardy *J. Org. Chem.* **1990**, *55*, 1944. b) A. R. Carroll, B. F. Bowden, J. C. Coll *Aust. J. Chem.* **1993**, *46*, 1229. c) I. Mancini, G. Guella, C. Debitus, F. Pietra *Helv. Chim. Acta* **1995**, *78*, 1178. d) A. Plubrukarn, D. Smith, R. Cramer, B. Davidson *J. Nat. Prod*. **1997**, *60*, 712.

[39] R. A. Edrada, C. C. Stessman, P. Crews *J. Nat. Prod*. **2003**, *66*, 939.

[40] For anti-biofilm activity of 2-aminoimidazoles, see: a) R. W. Huigens, J. J. Richards, G. Parise, T. E. Ballard, W. Zeng, R. Deora, C. Melander *J. Am. Chem. Soc.* **2007**, *129*, 6966. b) S. A. Rogers, C. Melander *Angew. Chem.* **2008**, *120*, 5307; *Angew. Chem. Int. Ed.* **2008**, *47*, 5229. c) T. E. Ballard, J. J. Richards, A. L. Wolf, C. Melander *Chem. Eur. J.* **2008**, *14*, 10745.

[41] (a) M. S. Malamas, J. Erdei, I. Gunawan,. J. Turner, Y. Hu, E. Wagner, K. Fan, R. Chopra, A. Olland, J. Bard, S. Jacobsen, R. L. Magolda, M. Pangalos, A. J. Robichaud *J. Med. Chem.* **2010**, *53*, 1146. b) M. S. Malamas, J. Erdei, I. Gunawan, K. Barnes, M. Johnson, Y. Hui, J. Turner, Y. Hu, E. Wagner, K. Fan, A. Olland, J. Bard, A. J. Robichaud *J. Med. Chem.* **2009**, *52*, 6314.

[42] a) R. S. Coleman, E. L. Campbell, D. J. Carper *Org. Lett.* **2009**, *11*, 2133. b) M. Nodwell, A. Pereira, J. L. Riffell, C. Zimmermann, B. O. Patrick, M. Roberge, R. J. Andersen *J. Org. Chem.* **2009**, *74*, 995.

[43] a) D. S. Ermolat'ev, E. V. Babaev, E. V. Van der Eycken *Org. Lett.* **2006**, *8*, 5781. b) D. S. Ermolat'ev, V. L. Alifanov, V. B. Rybakov, E. V. Babaev, E. V. Van der Eycken *Synthesis* **2008**, *13*, 2083. c) D. S. Ermolat'ev, E. V. Van der Eycken *J. Org. Chem.* **2008**, *73*, 6691. d) D. S. Ermolat'ev, E. P. Svidritzky, E. V. Babaev, E. Van der Eycken *Tetrahedron Lett.* **2009**, *50*, 5218. e) S. G. Modha, V. P. Mehta, D. S. Ermolat'ev, J. Balzarini, K. Van Hecke, L. Van Meervelt, E. Van der Eycken *Mol. Divers.* **2010**, 14, 767.

[44] a) D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker, E. V. Van der Eycken *Angew. Chem. Int. Ed.* **2010**, *49*, 9465. b) D. S. Ermolat'ev, PhD thesis, Katholieke Universiteit Leuven (Belgium), **2008**.

[45] Original isolation: a) R. B. Kinnel, H. P. Gehrken, P. J. Scheuer *J. Am. Chem. Soc.* **1993**, *115*, 3376. b) R. B. Kinnel, H. P. Gehrken, R. Swali, G. Skoropowski, P. J. Scheuer *J. Org. Chem.* **1998**, *63*, 3281. Structural reassignment: c) M. S. Buchanan, A. R. Carroll, R. J. Quinn *Tetrahedron Lett.* **2007**, *48*, 4573. Total Synthesis: d) I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi, P. S. Baran *Angew. Chem. Int. Ed.* **2010**, *49*, 1095 and references cited therein.

[46] For a review about the synthesis of alkaloids belonging to the Oroidin family, see: H. D. Arndt, M. Riedrich *Angew. Chem. Int. Ed.* **2008**, *47*, 4785.

[47] a) R. Sivappa, P. Koswatta, C. J. Lovely *Tetrahedron Lett.* **2007**, *48*, 5771. b) R. Sivappa, N. M. Hernandez, Y. He, C. J. Lovely *Org. Lett.* **2007**, *9*, 3861. c) C. J. Lovely, H. Du, Y. He, H. V. R. Dias *Org. Lett.* **2004**, *6*, 735.

[48] T. Iwagawa, M. Miyazaki, H. Okamura, M. Nakatani, M. Doe, K. Takemura *Tetrahedron Lett.* **2003**, *44,* 2533.

[49] R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler, A. R. Carroll *J. Nat. Prod.* **1998**, *61*, 660.

[50] For synthetic efforts towards Dragmacidin E, see: a) K. S. Feldman, P. Ngernmeesri *Org. Lett*. **2005**, *7*, 5449. b) R. J. Huntley, R. L. Funk *Org. Lett.* **2006**, *8*, 4775. c) K. S. Feldman, P. Ngernmeesri *Org. Lett*. **2010**, *12*, 4502.

[51] O. P. Pereshivko, V. A. Peshkov, D. S.Ermolat′ev, S. Van Hove, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken *Synthesis* **2011**, 1587.

[52] Y. Wang, H. Shen, Z. Xie *Synlett* **2011**, 969.

[53] M. J. Gainer, N. R. Bennett, Y. Takahashi, R. E. Looper *Angew. Chem. Int. Ed.* **2011**, *50*, 684.

[54] R. W. Carling, K. W. Moore, C. R. Moyes, E. A. Jones, K. Bonner, F. Emms, R. Marwood, S. Patel, S. Patel, A. E. Fletcher, M. Beer, B. Sohal, A. Pike, P. D. Leeson *J. Med. Chem.* **1999**, *42,* 2706.

[55] J. J. Bronson, K. L. DenBleyker, P. L. Falk, R. A. Mate, H.-T. Ho, M. J. Pucci, L. B. Snyder *Bioorg. Med. Chem. Lett.* **2003**, *13,* 873.

[56] a) C. Congiu, M. T. Cocco, V. Onnis *Bioorg. Med. Chem. Lett.* **2008**, *18,* 989. b) N. Xue, X. Yang, R. Wu, J. Chen, Q. He, B. Yang, X. Lu, Y. Hu *Bioorg. Med. Chem.* **2008**, *16*, 2550.

[57] K. Watanabe, Y. Morinaka, Y. Hayashi, M. Shinoda, H. Nishi, N. Fukushima, T. Watanabe, A. Ishibashi, S. Yuki, M. Tanaka *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1478.

[58] G. Verniest, A. Padwa *Org. Lett.* **2008**, *10*, 4379.

[59] V. A. Peshkov, O. P. Pereshivko, S. Sharma, T. Meganathan, V. S. Parmar, D. S. Ermolat'ev, E. V. Van der Eycken *J. Org. Chem.* **2011**, *76*, 5867.

[60] M. J. Campbell, F. D. Toste *Chem. Sci.* **2011**, *2*, 1369.

[61] N. R. Easton, D. R. Cassady, R. D. Dillard *J. Org. Chem.* **1964**, *29*, 1851.

[62] O. P. Pereshivko, V. A. Peshkov, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken *Adv. Synth. Cat.* **2013**, *355*, 781.

[63] For a review, see: C. O. Kappe *Eur. J. Med. Chem.* **2000**, *35*, 1043.

[64] K. M. Oberg, T. Rovis *J. Am. Chem. Soc.* **2011**, *133*, 4785.

[65] P. Biginelli *Gazz. Chim. Ital.* **1893**, *23*, 360.

[66] For reviews, see: a) C. O. Kappe *J. Org. Chem.* **1997**, *62*, 7201; b) C. O. Kappe *Acc. Chem. Res.* **2000**, *33*, 879; c) J.-P. Wan, Y. Liu *Synthesis* **2010**, *23*, 3943.

[67] For the addition of lithium acetylides and *n*-BuLi to six-membered ketimines, see: Y. Ma, E. Lobkovsky, D. B. Collum *J. Org. Chem.* **2005**, *70,* 2335.

[68] The difference in R_f-values allows to isolate both minor and major products through gradient-elution column chromatography.

[69] CCDC-801762 contains the supplementary crystallographic data for this compound and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

[70] For a focused review on ligand effects in homogeneous Au catalysis, see: D. J. Gorin, B. D. Sherry, F. D. Toste *Chem. Rev.* **2008**, *108*, 3351.

[71] A possible role of the Ag catalyst in accelerating the double bond migration (**20a→28**) has already been investigated by our group (see ref.[59]). For a study covering a similar migration aspect in the Au(III)-catalyzed synthesis of 2,5-disubstituted oxazoles, see: A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats *Org. Lett.* **2004**, *6*, 4391.

[72] This 5-*exo-dig versus* 6-*endo-dig* competition was previously documented by Campbell and Toste in their process involving cationic Au(I)-catalyzed cycloisomerization of propargylic ureas (see ref.[60]). Similar competition was described in cationic Au(I)-catalyzed cycloisomerization of nonterminal propargylic amides, see: a) A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger *Eur. J. Org. Chem.* **2011**, 4595; b) A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan *Organometallics*

2011, *30*, 6328. Another relevant example of such competition was observed in a Ag(I)-catalyzed cycloisomerization of propargylic guanidines (see ref.[51] and ref.[53]). In most cases as well as in the current study 5-*exo*-*dig* cyclized products are prevailing. Selective cationic gold-catalyzed 6-*endo*-*dig* *N*-cycloisomerization of aryl isocyanate-derived propargylureas is described in ***Chapter 5***.

[73] This correlates with the drop of the double bond migration rate for the $AgOTf/PPh_3$-catalyzed reaction in the first model case (Table 4, entry 21).

[74] CCDC-904954 and CCDC-904955 contain the supplementary crystallographic data for this chapter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[75] For selected reviews, see: a) J.-M. Weibel, A. Blanc, P. Pale *Chem. Rev.* **2008**, *108*, 3149; b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García *Chem. Rev.* **2008**, *108*, 3174; c) P. Belmont in *Silver in Organic Chemistry* (Ed.: M. Harmata), John Wiley & Sons, Inc., Hoboken, **2010**, pp. 143–165.

[76] For selected reviews, see: a) P. Belmont, E. Parker *Eur. J. Org. Chem.* **2009**, 6075; b) R. A. Widenhoefer, F. Song in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**, pp. 437–461; c) R. A. Widenhoefer, F. Song in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2010**, pp. 463–492; d) H. Huang, Y. Zhou, H. Liu *Beilstein J. Org. Chem.* **2011**, *7*, 897; e) H. C. Shen *Tetrahedron* **2008**, *64*, 3885; f) A. Arcadi *Chem. Rev.* **2008**, *108*, 3266; g) Z. Li, C. Brouwer, C. He *Chem. Rev.* **2008**, *108*, 3239; h) A. S. K. Hashmi *Chem. Rev.* **2007**, *107*, 3180; i) A. S. K. Hashmi, M. Rudolph *Chem.*

Commun. **2011**, *47*, 6536; j) A. S. K. Hashmi, M. Bührle *Aldrichimica Acta* **2010**, *43*, 27.

[77] D. D. Vachhani, V. P. Mehta, S. G. Modha, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken *Adv. Synth. Catal.* **2012**, *354*, 1593.

[78] a) R. G. Pearson *J. Am. Chem. Soc.* **1963**, *85*, 3533; b) R. G. Pearson *Science* **1966**, *151*, 172; c) R. G. Pearson, J. Songstad *J. Am. Chem. Soc.* **1967**, *89*, 1827; d) R. G. Pearson *J. Chem. Educ.* **1968**, *45*, 581; e) R. G. Pearson *J. Chem. Educ.* **1968**, *45*, 643; f) R. G. Pearson *Chemical Hardness*, Wiley-VCH, Weinheim, **1997**.

[79] a) G. Klopman *J. Am. Chem. Soc.* **1968**, *90*, 223; b) T.-L. Ho Chem. Rev. 1975, 75, 1. For the classical Kornblum's investigation on the alkylation of the ambident nitrite anion which was further generalized within Pearson's HSAB principle, see: c) N. Kornblum, B. Taub, H. E. Ungnade *J. Am. Chem. Soc.* **1954**, *76*, 3209; d) N. Kornblum, R. A. Smiley, H. E. Ungnade, A. M. White, B. Taub, S. A. Herbert, Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5528; e) N. Kornblum, L. Fishbein, R. A. Smiley *J. Am. Chem. Soc.* **1955**, *77*, 6261; f) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, G. E. Graham *J. Am. Chem. Soc.* **1956**, *78*, 1497.

[80] a) H. Mayr, M. Breugst, A. R. Ofial *Angew. Chem. Int. Ed.* **2011**, *50*, 6470; b) R. Gompper, H.-U. Wagner *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321; c) R. S. Drago *J. Chem. Educ.* **1974**, *51*, 300.

[81] For another recent application as intermediates in the synthesis of spirooxazolidinones, see: J. Zhao, H. Huang, C. Qi, H. Jiang *Eur. J. Org. Chem.* **2012**, 5665.

[82] For the recent progress in this direction, see: C. Madaan, S. Saraf, G. Priyadarshani, P. P. Reddy, S. K. Guchhait, A. C. Kunwar, B. Sridhar, *Synlett* **2012**, *23*, 1955.

[83] SAINT, Manual Version 5/6.0, Bruker Analytical X-ray Systems Inc.: Madison, Wisconsin, **1997**.

[84] SHELXTL-NT, Manual Version 5.1, Bruker Analytical X-ray Systems Inc.: Madison, Wisconsin, **1997**.

[85] In this case byproduct **1i** forms then 2 equivalents of prop-2-ynylbenzene react with 1 equivalent of 4-methoxybenzylamine *via* a Cu(I)-catalyzed tandem *anti*-Markovnikov hydroamination, alkyne addition reaction. For the leading reference, see: L. Zhou, D. S. Bohle, H. F. Jiang, C. J. Li *Synlett* **2009**, 937.

[86] Analytical data for **1m** are described in the supporting information of ref. [11]

[87] Contamination is a result of impurity of starting propargylamine **1h**.

[88] CrysAlis PRO. Agilent Technologies UK Ltd, Yarnton, Oxfordshire, England, **2012**.

[89] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339.

[90] G. M. Sheldrick *Acta Cryst.* **2008**, *A64*, 112.

[91] The full characterization of compound of this type is given in supporting information of ref.[60].

[92] D. N. Weisman, D. E. Banks In *Interstitial Lung Disease* 4th ed. London, BC Decker Inc. **2003**.