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Chemistry of electron-deficient ynamines and ynamides

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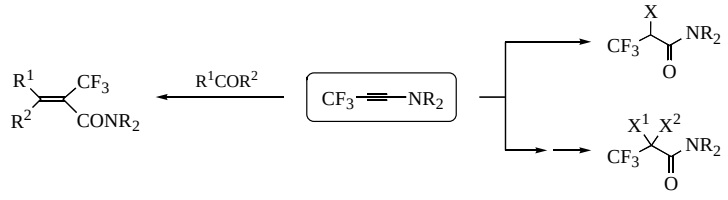
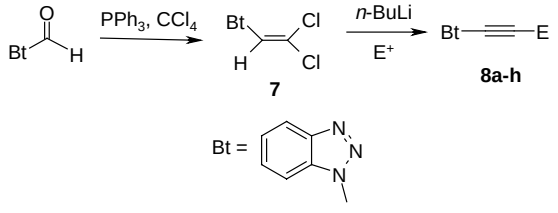
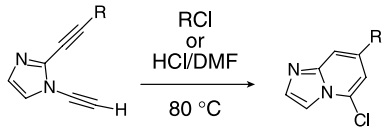
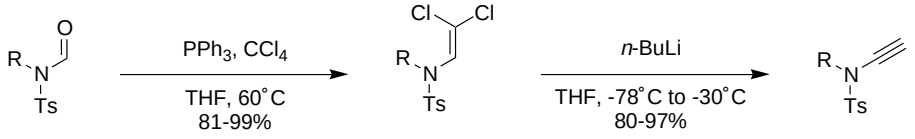
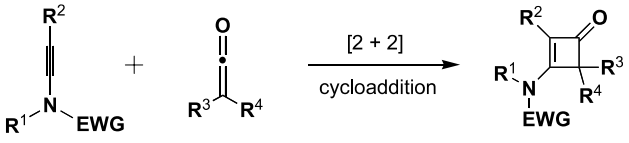


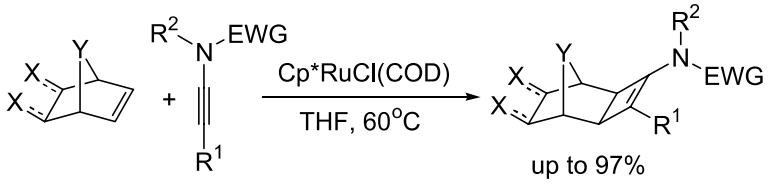






R: alkyl, allyl, benzyl, aryl





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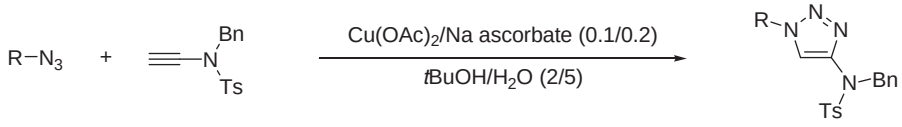

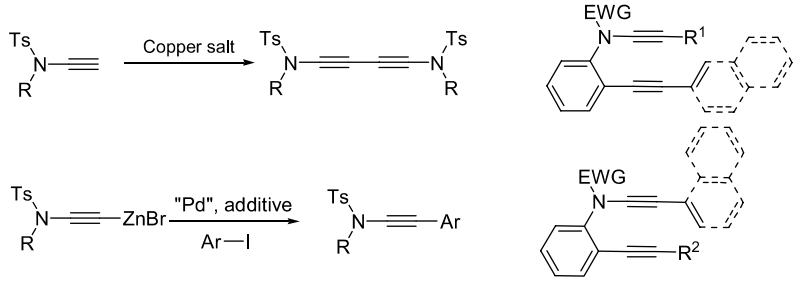

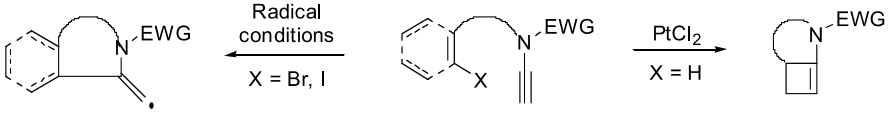

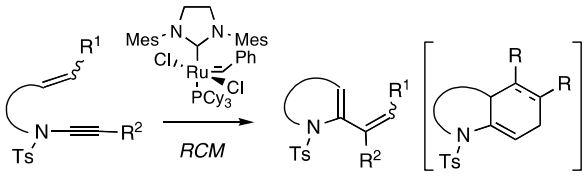

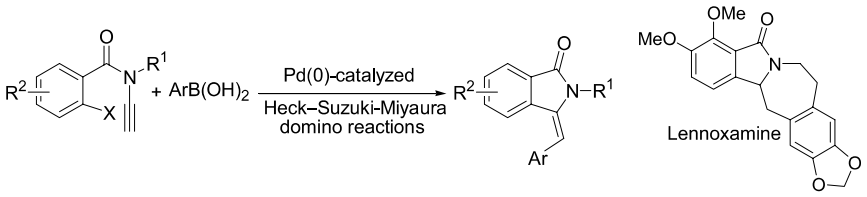

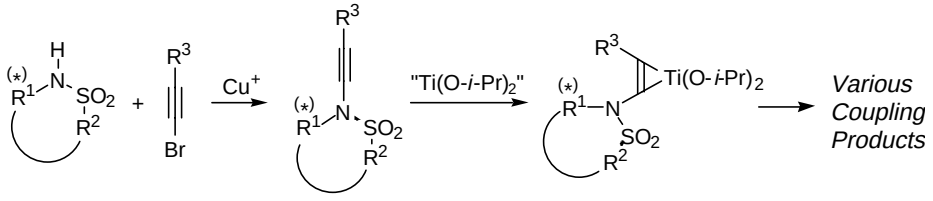

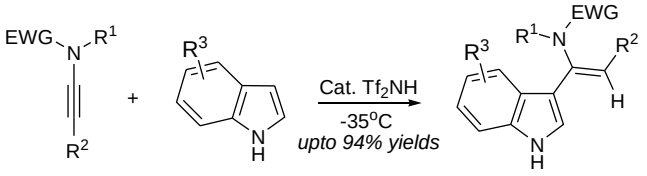

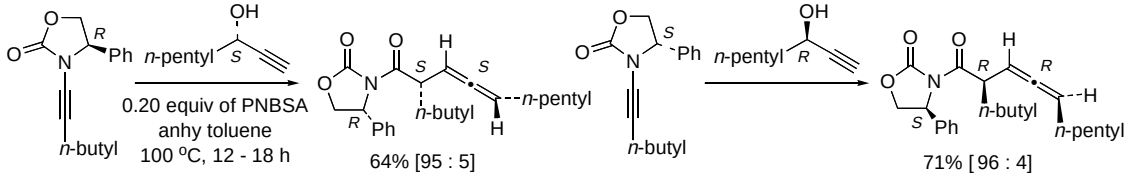

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COVER

The cover highlights all 14 outstanding contributions in this issue of Tetrahedron Symposium-in-Print on Chemistry of Electron-Deficient Ynamines and Ynamides that provides an excellent coverage of syntheses and an array of impressive methodologies employing different types of electron-deficient ynamines and ynamides, which can be seen either as starting materials in the box or embedded in various reaction products out side the box.

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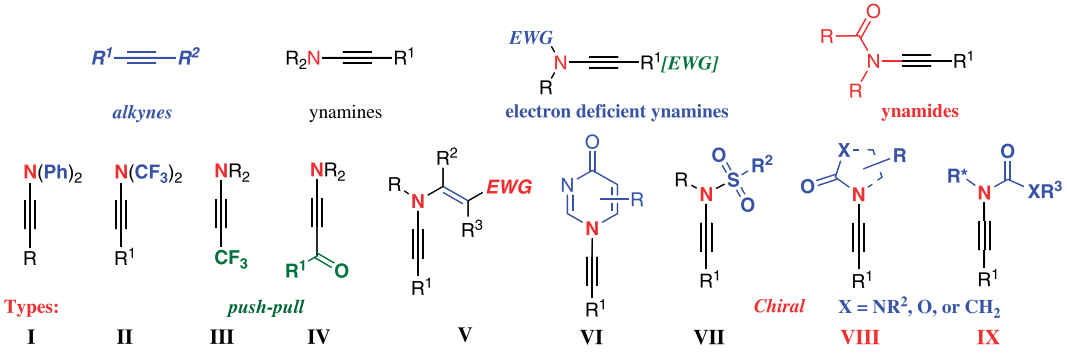
Preface

Chemistry of electron-deficient ynamines and ynamides

Ynamines [1-amino-alkynes or *N*-alkynyl amines] became synthetically one of the most useful subgroups of alkynes after the establishment of a practical synthesis in 1963. In the ensuing 20 years, reactivities of 1-amino-alkynes were thoroughly explored. However, unlike its close relative enamines, this synthetic prominence did not persist. The extent of synthetic applications of ynamines has suffered a dramatic decline during the last 20 years. The limited application of ynamines is largely due to the difficulties in their preparation and handling. Their unusual sensitivity toward hydrolysis and their high reactivity toward electrophiles have rendered traditional ynamines synthetically inaccessible in diversity. Diminishing ynamines' electron-density by substituting the nitrogen atom with an electron-withdrawing group, or through substitutions in the alkyne, represents a unique strategy for improving ynamines' stability, thereby regaining their usefulness in organic synthesis. These new generations of ynamines may be classified as electron-deficient ynamines [Type I–VI] and/or simply ynamides [Type VII–IX]. The concept of improving ynamine's thermal stability and stability toward hydrolytic conditions should be credited to Viehe who in 1972 reported the synthesis of the first ynamides [Type IX].



Despite the precedent of electron-deficient ynamines and ynamides, and their improved stability, it is not until recently have these functionally rich organic building blocks, especially ynamides, recaptured the attention of organic chemists. These recent developments and efforts have begun to revitalize interest within the synthetic community in utilizing nitrogen-substituted alkynes in organic synthesis, thereby providing an ideal timing for this special issue of Tetrahedron Symposium-in-Print focusing on the chemistry of electron-deficient ynamines and ynamides. Although regrettably this Symposium is missing some earlier chemistry from Professors Peter Stang [push–pull Type IV] and Ken Feldman [chiral ynamides Types VII and IX], pioneering work from Professors Bernhard Witulski and Jon Rainier on transition metal-mediated cycloadditions using ynamides of Type VII, and some enyne metathesis form Professor Javier Pérez-Castells, this issue is comprised of 14 outstanding contributions that provide an excellent coverage of different types of electron deficient ynamines and ynamides, and their syntheses as well as an array of impressive methodologies including the ultimate goal of applying their chemistry to the natural products synthesis.

This symposium contains: (1) Ishihara's excellent fluorine chemistry on both the synthesis and reactivities of *N*,*N*-dialkyl(3,3,3-trifluoro-1-propynyl)amines [push–pull Type III]: the reactivities included additions of halogens and formally a hetero metathesis process with aldehydes. (2) Katritzky's concise synthesis of 1-(2,2-dichlorovinyl)benzotriazole [Type VI] and its subsequent lithiation–substitution with a range of electrophiles, thereby precisely demonstrating the principle of attaining highly functionalized electron-deficient ynamines or ynamides from the terminally unsubstituted system [or the parent system]. (3) Kerwin's nifty thermolysis of 1,2-dialkynylimidazoles [Type VI] in an aza-Bergman-like cyclization that led to some very interesting mechanistic observations as well as useful heterocycles such as imidazolyl–pyridines. (4) Brückner's clever solution to the synthesis of *N*-ethynyl-tosyl-amides [a parent system for Type VII], which had been a challenge.

A range of cycloadditions, cyclizations, and annulations are described here. These contributions include: (1) Danhesier's elegant [2+2] ketene-cycloadditions that gave an array of substituted 3-amino-cyclobut-2-en-1-ones: this work also reiterates details and the elegance of the copper-promoted

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N-alkynylation of carbamates and sulfonamides in the preparations of ynamides [Type VII–IX]. (2) Tam's clever ruthenium-catalyzed diastereoselective [2+2] cycloadditions between bicyclic alkenes and chiral ynamide: this work further demonstrates that the ynamide moiety with an improved stability could readily survive conditions involving transition metals. (3) Cintrat's fine work on the first examples of highly regioselective 'click reaction' employing *N*-benzyl-*N*-tosyl-ynamide and various highly functionalized azides in a [3+2] cycloaddition manner. (4) Saá's copper-catalyzed dimerization of *N*-aryl- or *N*-alkyl-tosyl-ynamides in the preparations of *N*,*N*′-aryl- and *N*,*N*′-alkyl-buta-1,3-diyne-1,4-di-tosyl-amides. In this paper, Negishi couplings of *N*-ethynyl(zinc)-tosyl-amides with heteroaryl iodides were shown to afford *N*-aryl- and *N*-alkyl-*N*-aryl-ynamides. In addition, an intramolecular dehydro-[4+2] cycloaddition reaction of ynamides was shown to be feasible to provide novel benzannulated and heteroannulated carbazoles. Three separate topics on reactions of ynamides for the price of one. (5) Malacria's beautiful radical cascade that entailed a *5-exo-dig* cyclization followed by a *6-endo-trig* radical trapping to transform ynamides into an array of nitrogen heterocycles. In addition, a formally [2+2] cycloaddition of ene-tosylynamides could be promoted with Pt(II). Two very interesting synthetic methods employing ynamides are presented in one paper. (6) Mori's pioneering ring-closing metathesis of ene-ynamide employing a second-generation Ru–carbene complex that led to nitrogen-containing heterocycles with a dienamide motif that can undergo various Diels–Alder cycloadditions to give highly functionalized indoles or quinolines. (7) Cossy's elegant synthesis of 3-(arylmethylene)-isoindolin-1-ones from various ynamides and boronic acids via a Heck–Suzuki–Miyaura domino sequence: this methodology was applied to the total synthesis of lennoxamine, which constitutes as the first example of ynamides as a key intermediate in the natural product synthesis. It is highly noteworthy that many of these studies demonstrate a key principle or significance advantage of 1-amino-alkynes over simple alkynes: the nitrogen atom remains a key component of various reaction products.

Last but not the least, this Symposium also includes: (1) Urabe's elegant usage of acetylene–titanium complexes generated from *N*-(1-alkynyl)sulfonamides and Ti(O-*i*-Pr)$_4$/*i*-PrMgCl in highly regio- and diastereoselective additions to aldehydes that afforded allylic alcohols. In addition, inter- or intramolecular coupling reaction with acetylenes or olefins using also Ti(O-*i*-Pr)$_4$/*i*-PrMgCl led to stereoselective syntheses of various (sulfonylamino)dienes. This work further supports copper(I)-catalyzed amidations of 1-bromo-1-alkynes as an efficient protocol in the synthesis of *N*-(1-alkynyl)sulfonamides. This represents another paper that contains two elegant bodies of work. (2) Zhang's highly regio- and stereoselective Brønsted acid-catalyzed coupling of ynamides with pyrroles, furans, and indoles, which represents an equivalent of hydro-arylation of ynamides. Finally, (3) Hsung's work on a Brønsted acid-catalyzed highly diastereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols, leading to interesting mechanistic understanding this pericyclic rearrangement as well as a highly diastereoselective synthesis of chiral allenes.

These 14 contributions literally have provided 20 or more syntheses, methods, and applications! I thank all the contributing authors for making this Symposium possible and bailing me out, and Professor Harry Wasserman for providing this invaluable opportunity to organize this Symposium and for his guidance and patience throughout this entire process for which I was completely clueless.

We hope that this Symposium can firmly illustrate that the chemistry of ynamines is actually alive and well but in the forms of electron-deficient ynamines and ynamides. They have achieved the right balance between reactivity and stability, allowing them to be handled easily, thereby leading to highly stereoselective and intramolecular reactions that otherwise would be very difficult to accomplish using traditional ynamines. With such a compelling evidence for the reemergence of the ynamine chemistry, we hope that an even greater interest will come forth in the near future, leading to new methodologies employing electron-deficient ynamines and ynamides.

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Preparation of trifluoromethylated ynamines and their reactions with some electrophilic reagents

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Abstract—*N*,*N*-Dialkyl(3,3,3-trifluoro-1-propynyl)amines were prepared by a three-step procedure starting from commercially available 2,2,3,3,3-pentafluoropropanol. The reactions of these trifluoromethylated ynamines with some electrophiles, such as aldehydes, halogens or *N*-halosuccinimides (NXS), were investigated. The fluorinated ynamines reacted with aldehydes in the presence of a catalytic amount of Lewis acid to provide the corresponding α-(trifluoromethyl)-α,β-unsaturated amides in good to excellent yields with high *Z*-stereoselectivity. These ynamines reacted with molecular bomine to give, after treatment with sodium hydrogen carbonate, *N*,*N*-dialkyl-2-bromo-3,3,3-trifluoropropanamides in good yields. The reaction with an equimolecular amount of NXS in aqueous acetonitrile also gave the corresponding 2-halo-3,3,3-trifluoropropanamides in good to excellent yields. On the other hand, the reaction of the ynamine with NXS in anhydrous acetonitrile led to the formation of the addition products in high yields. Upon treating the addition products with an equimolecular amount of NX′S in aqueous acetonitrile, the corresponding 2,2-dihalo(X,X′)-3,3,3-trifluoropropanamides were produced in nearly quantitative yields.

1. Introduction

N,*N*-Disubstituted-1-alkynylamines, the common name 'ynamines,' are regarded as the alkynes activated through the interaction of the amino group linked directly to a triple bond, and thereby liable to undergoing the reactions with a variety of electrophiles. Many kinds of ynamines have hitherto been prepared and utilized in organic synthesis.[1–5] Although fluorine-containing counterparts are expected to be useful building blocks for preparing various organofluorine compounds, there are found few or no reports on their preparations and synthetic applications[6,7] in the literature. On the other hand, the theoretical data obtained from the MO calculations for *N*,*N*-dimethyl-3,3,3-trifluoro-1-propynylamine as well as *N*,*N*-dimethyl-1-propynylamine inform us with the differences in electronic states between these ynamines, as shown in Figure 1. These situations prompted us to develop the method for the preparation of trifluoromethylated ynamines, *N*,*N*-dialkyl(3,3,3-trifluoro-1-propynyl)amines (**2**), by use of commercially available 2,2,3,3,3-pentafluoropropanol, and to examine their reactivities toward several electrophilic reagents.[8–12]

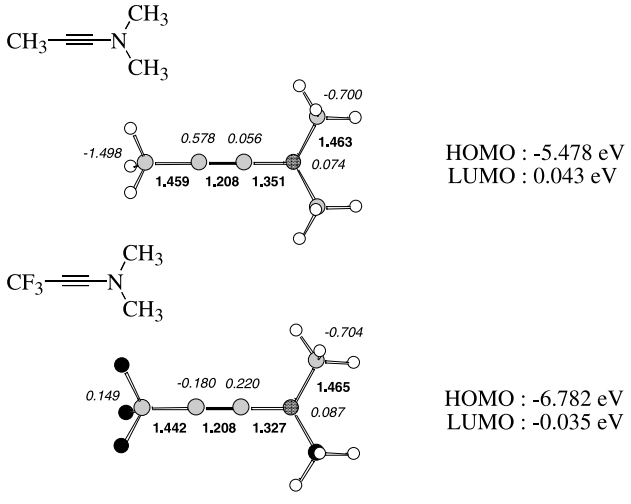

Fig. 1. MO calculations for nonfluorinated and fluorinated ynamines.

In this paper, we wish to describe the practical methods for the preparation of the trifluoromethylated ynamines **2** and the results of their reactions with several electrophiles, such as aldehydes, halogens, and *N*-halosuccinimides (NXS), leading to α-(trifluoromethyl)-α,β-unsaturated amides, 2-halo- and 2,2-dihalo-3,3,3-trifluoropropanamides, which are

Keywords: Ynamine; Carbonyl compound; Halogen; *N*-Halosuccinimide; α-Trifluoromethyl-α,β-unsaturated amide; 2-Halo-3,3,3-trifluoropropanamide; 2,2-Dihalo-3,3,3-trifluoropropanamide; Trifluoromethylated cyclobutene cyanine.
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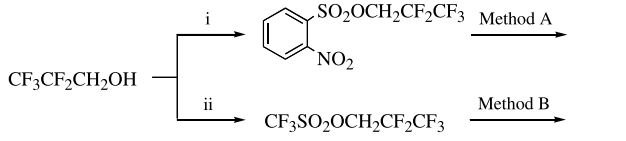
exceedingly valuable and fundamental synthons for the construction of trifluoromethylated carbon frameworks.[13–17]

2. Results and discussion

2.1. Preparation of the trifluoromethylated ynamines 2

N,*N*-Dialkyl(2,2,3,3,3-pentafluoropropyl)amines (**1**) were chosen as the precursors of the trifluoromethylated ynamines **2**. The amines **1** were prepared by the two different procedures starting from commercially available 2,2,3,3,3-pentafluoropropanol, as shown in Scheme 1. The polyfluoro alcohol was converted into the sulfonate esters by the reaction with *o*-nitrobenzenesulfonyl chloride and NaOH in H_2O at 60 °C for 2 h (98%)[18] or by the reaction with trifluoromethanesulfonic anhydride at reflux temperature for 3 h (84%).[19] *o*-Nitrobenzenesulfonate and trifluoromethanesulfonate were subjected to the Hofmann-like degradation reaction with *N*,*N*-dimethylbenzylamine[20] (Method A) or polyfluoroalkylation of a secondary amine (Method B).



$CF_3CF_2CH_2NR_2$

1a-d

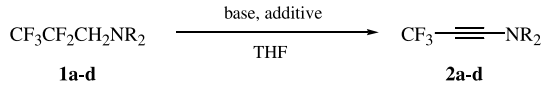
R = Bu (**a**), Me (**b**), -$(CH_2)_5$- (**c**), *i*-Pr (**d**)

i: *o*-nitrobenzenesulfonyl chloride, NaOH/H_2O, 60 °C, 2 h.
ii: $(CF_3SO_2)_2O$, neat, reflux, 3 h.
Method A: R_2NH or $BnNMe_2$, neat, 140-160 °C.
Method B: R_2NH, neat.

Scheme 1.

The degradation between *o*-nitrobenzenesulfonate and dibutylamine (Method A) provided *N*,*N*-dibutyl(2,2,3,3,3-pentafluoropropyl)amine (**1a**) in a lower yield (48%), compared with the reaction using trifluoromethanesulfonate (Method B, 93%). This trend was observed for preparing *N*-(2,2,3,3,3-pentafluoropropyl)piperidine (**1c**) by the reactions of *o*-nitrobenzenesulfonate and trifluoromethanesulfonate. Such trends in the yields of **1** are attributable to the difference in reactivity between the two sulfonate esters. Worth remarking is that the degradation reaction between *o*-nitrobenzenesulfonate and excess *N*,*N*-dimethylbenzylamine (3 equiv) (Method A) is recommended for obtaining *N*,*N*-dimethyl-(2,2,3,3,3-pentafluoropropyl)amine (**1b**) in good yield.[20] *N*,*N*-Diisopropyl-(2,2,3,3,3-pentafluoropropyl)amine (**1d**) was obtained in 45% yield according to Method B.

These fluorinated amines **1** could be converted into the desired ynamines **2** by dehydrofluorination with a base (Scheme 2). The results are summarized in Table 1. The reaction of **1a** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C for 2 h gave the ynamine **2a** in 14% yield, together with 75% of the starting amine **1a** recovered (entry 1). The reaction conducted at room



1a-d **2a-d**

Scheme 2.

Table 1. Preparation of **2** from the tertiary amines **1**

Entry	**1**	Base (2.2 equiv)	Additive (2.2 equiv)	Temperature (°C)	Time (h)	Yield of **2** (%)[a]
1	**1a**	LDA	None	0	2	14
2	**1a**	LDA	None	Room temperature	2	47
3	**1a**	LDA	None	Room temperature	24	66
4	**1a**	LDA	DMPU	0	2	84
5	**1a**	LDA	DMPU	Room temperature	2	94 (75)
6	**1a**	BuLi	None	Room temperature	2	5
7	**1a**	*t*-BuOK	None	Room temperature	24	23[b]
8	**1b**	LDA	DMPU	0	2	92
9	**1c**	LDA	DMPU	Room temperature	2	97
10	**1d**	LDA	DMPU	Room temperature	24	66

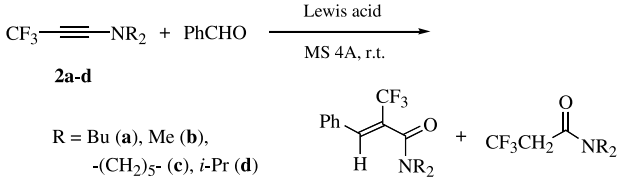
[a] Measured by ^{19}F NMR. Value in parentheses is of isolated yield.
[b] *N*,*N*-Dibuty(2,3,3,3-tetrafluoro-1-propenyl)amine was given in 33% yield.

temperature and/or for a long reaction period resulted in increasing the yields of **2a** (entries 2 and 3). The use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as an additive permitted the reaction to proceed very efficiently (entries 4 and 5). Other bases, such as butyllithium and potassium *t*-butoxide, were not so useful for the reaction (entries 6 and 7). *N*,*N*-Dialkyl(3,3,3-trifluoropropynyl)amines **2b–d** were also prepared by the reactions of **1b–d** with LDA in THF–DMPU at 0 °C or room temperature, as shown in entries 8–10.

It should be mentioned that all of these ynamines **2** are highly susceptible to hydrolysis under acidic conditions.[12] Thus, on simple treatment of **2** with a 5% HCl aqueous solution at ambient temperature for 15 min, the corresponding *N*,*N*-dialkyl-3,3,3-trifluoropropanamides **4** were produced in 65–90% yields.

2.2. Reaction of the ynamines 2 with carbonyl compounds

The reaction of **2a** with benzaldehyde was initially investigated under various conditions, as shown in Scheme 3, and the results are summarized in Table 2.



2a-d

R = Bu (**a**), Me (**b**), -$(CH_2)_5$- (**c**), *i*-Pr (**d**)

3aa-3da **4a-d**

Scheme 3.

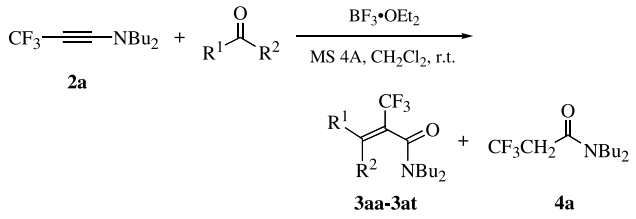
Table 2. Reaction of the ynamines **2** with benzaldehyde

Entry	2	Lewis acid[a]	Solvent	Time (h)	Yield of **3a** (%)[b]
1	**2a**	None	CH_2CL_2	24	3
2	**2a**	$BF_3\cdot OEt_2$	CH_2CL_2	1	92
3[c]	**2a**	$BF_3\cdot OEt_2$	CH_2CL_2	1	28
4	**2a**	$ZnBr_2$	CH_2CL_2	1	90
5	**2a**	$TiCl_4$	CH_2CL_2	1	80
6	**2a**	$SnCl_4$	CH_2CL_2	1	81
7	**2a**	$BF_3\cdot OEt_2$	Toluene	1	84
8	**2a**	$BF_3\cdot OEt_2$	Et_2O	1	82
9	**2a**	$BF_3\cdot OEt_2$	THF	1	82
10[c]	**2a**	$La(OTf)_3$[d]	CH_2CL_2	24	71
11[c]	**2b**	$La(OTf)_3$[d]	CH_2CL_2	24	65
12[c]	**2c**	$La(OTf)_3$[d]	CH_2CL_2	24	73
13	**2d**	$BF_3\cdot OEt_2$	CH_2CL_2	1	40

[a] Lewis acid (0.1 equiv) used, unless otherwise noted.
[b] Isolated yields.
[c] Without MS 4 Å.
[d] $La(OTf)_3$ (0.3 equiv) used.

The treatment of **2a** with benzaldehyde in dichloromethane (CH_2Cl_2) in the presence of molecular sieves 4 Å (MS 4 Å) revealed little or no evidence of reaction. Workup of this reaction mixture with a 5% HCl aqueous solution afforded *N*,*N*-dibutyl-3,3,3-trifluoropropanamide (**4a**) and the corresponding α-(trifluoromethyl)-α,β-unsaturated amide **3aa** in 79 and 3% yield, respectively (entry 1). The addition of boron trifluoride etherate ($BF_3\cdot OEt_2$) (0.1 equiv) as a Lewis acid promoted the reaction effectively, leading to a high yield of the amide **3aa** as an isomeric mixture of *Z*/*E*=>97:<3 (entry 2). MS 4 Å was requisite to suppress the formation of **4a**, which may be based upon the acidic hydration with a small quantity of water contaminating **2a**. ^{19}F NMR analysis of the reaction in the absence of MS 4 Å revealed the in situ formation of **4a** (66%) as well as **3aa** (28%) (entry 3). Zinc bromide, titanium(IV) chloride, and tin(IV) chloride were applicable to the reaction, giving good yields of **3aa** (entries 4–6). Toluene, diethyl ether, and THF could be used as the solvents (entries 7–9). In addition, lanthanum(III) triflate, known to be hard to hydrolysis,[21] was effective for the reaction of **2a** without MS 4 Å, affording an acceptable result (entry 10). The similar reaction of **2b** or **2c** with benzaldehyde in the presence of $La(OTf)_3$ offered the corresponding α,β-unsaturated amides **3ba** and **3ca** in fairly good yields with high *Z*-stereoselectivity (entries 11 and 12). The ynamine **2d** reacted reluctantly in the presence of $BF_3\cdot OEt_2$ to give the amide **3da** in 40% yield (entry 13). It is likely that the bulky isopropyl groups on the nitrogen of **2d** are responsible for low efficiency of the reaction.

Next, the reactions of **2a** with other aldehydes or ketones were carried out by using $BF_3\cdot OEt_2$ as a Lewis acid and CH_2Cl_2 as a solvent (Scheme 4). Various sorts of aldehydes, such as aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes, were made to react with **2a** in the presence of 0.1 equiv of $BF_3\cdot OEt_2$ and MS 4 Å in CH_2Cl_2 at room temperature for 1 h, and the usual workup provided the corresponding α-(trifluoromethyl)-α,β-unsaturated amides **3ab–at** in 75–97% yields. Of synthetic value is that the reactions of **2a** with aldehydes, except 2,2-dimethylpropanal, occurred in a highly stereoselective fashion to give the (*Z*)-isomers of **3a** predominantly

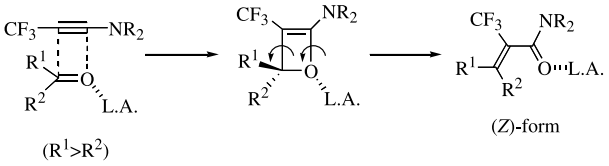


R^1, R^2 = Ph, H (**a**), *p*-MeC_6H_4, H (**b**), *p*-$MeOC_6H_4$, H (**c**), *p*-ClC_6H_4, H (**d**), 1-naphthyl, H (**e**), 2-thienyl, H (**f**), 2-furyl, H (**g**), (*E*)-PhCH=CH, H (**h**), (*Z*)-PhCH=CF, H (**i**), (*E*)-MeCH=CH, H (**j**), CH_2=C(Me), H (**k**), Pr, H (**l**), Hex, H (**m**), *i*-Pr, H (**n**), *c*-Hex, H (**o**), *t*-Bu, H (**p**), Me, Me (**q**), Et, Et (**r**), -$(CH_2)_5$- (**s**), Ph, Me (**t**)

Scheme 4.

(>96% *Z*). Although the reaction with 2,2-dimethylpropanal required 0.2 equiv of $BF_3\cdot OEt_2$ and a longer reaction time (2 h), the corresponding amide **3ap** was given in 68% yield as a mixture of *Z*/*E*=56:44. A variety of ketones, such as acetone, 3-pentanone, cyclohexanone, and acetophenone, were also found to participate in the reaction with **2a** to give the corresponding α,β-unsaturated amides **3aq–at** in 72–85% yields. All the reactions with ketones necessitated a prolonged reaction time (2 h) for obtaining satisfactory results. The reaction with acetophenone took place with an appreciably low stereoselectivity to form **3at** as a mixture of *Z*/*E*=71:29.

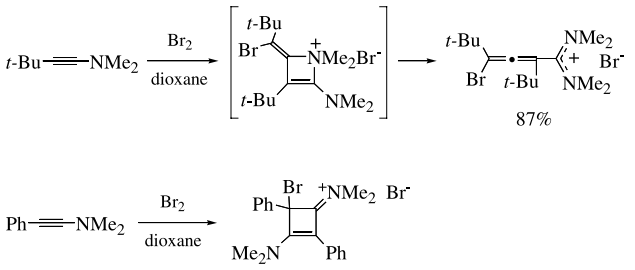
The above-cited reactions of **2** with carbonyl compounds are presumed to occur via the mechanism shown in Scheme 5, which is essentially analogous to that proposed recently for the reaction between alkynolates and carbonyl compounds.[22] Thus, the ynamine **2** may attack a carbonyl compound activated by a Lewis acid[23] to form an intermediary oxetene. This intermediate would be subject to a metathesis process in such a way that both the Lewis acid part and the substituent R^1 or R^2 ($R^1>R^2$) exert their repulsive interaction minimally, leading to the preferential formation of the (*Z*)-isomers of **3**.



Scheme 5.

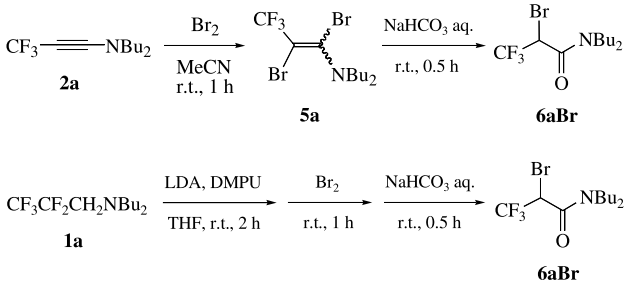
2.3. Reaction of the ynamines 2 with bromine or iodine

The nonfluorinated ynamines are known to undergo the unique reactions with bromine to give a different type of product depending on an alkynyl substituent, as depicted in Scheme 6. Thus, *t*-butylethynyl(dimethyl)amine reacts with bromine in dioxane to afford the corresponding allene amidinium salt,[24] and the reaction of phenylethynyl(dimethyl)amine gives rise to the cyclobutene cyanine salt.[25] Such unique behaviors of the ynamines strongly stimulated us to examine the reaction of the fluorinated ynamines **2** with bromine.



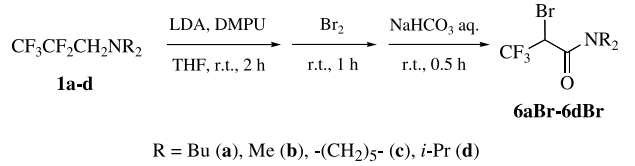
Scheme 6.

As shown in Scheme 7, when the ynamine **2a** was allowed to react with bromine (1.1 equiv) in acetonitrile (MeCN) in the presence of MS 4 Å at ambient temperature for 1 h, *N*,*N*-dibutyl(1,2-dibromo-3,3,3-trifluoro-1-propenyl)amine (**5a**) was formed quantitatively. Although the enamine **5a** was not so stable for isolation, its structural determination was made by IR and ^{13}C NMR analyses of the crude product after filtration and concentration of the reaction mixture. ^{19}F NMR analysis indicated that **5a** consisted of two geometrical isomers in a ratio of 78:22. Other solvents, such as CH_2Cl_2, THF, diethyl ether, and dioxane, could also be employed similarly. The resultant enamine **5a** was readily hydrolyzed to *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) by simple treatment with a saturated $NaHCO_3$ aqueous solution at room temperature for 0.5 h. In order to simplify the access to 2-bromo propanamide **6aBr**, we examined the one-pot reaction starting from **1a**, the precursor of **2a**. Thus, the amine **1a** was treated with LDA (2.2 equiv) and DMPU (2.2 equiv) in THF at room temperature for 2 h, and bromine (2.0 equiv) was successively added to the reaction mixture at 0 °C. After stirring at room temperature for 1 h, addition of a saturated $NaHCO_3$ aqueous solution, followed by a usual workup, led to the amide **6aBr** in 75% overall yield.



Scheme 7.

This one-pot reaction procedure was applicable for other amines **1b–d**, as shown in Scheme 8. The results are summarized in Table 3. The alkyl substituents at the nitrogen atom of **1** were observed to influence the yields of the amides **6Br**. The amines **1a–c** carrying a butyl, methyl and pentamethylene group provided the corresponding



Scheme 8.

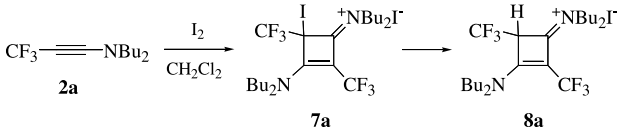
Table 3. The one-pot preparation of **6Br** from **1**

Entry	R	Temperature (°C)	Yield of **6Br** (%)[a]	
1	Bu	Room temperature	**6aBr**	75
2	Me	0	**6bBr**	64
3	$-(CH_2)_5-$	Room temperature	**6cBr**	78
4	*i*-Pr	Room temperature	**6dBr**	37 (41)

[a] Isolated yields. Value in parentheses stands for the recovery of **1** determined by ^{19}F NMR.

bromo amides **6aBr–cBr** in satisfactory yields, as shown in entries 1–3, but the amine **1d** having a bulky group, such as isopropyl, gave **6dBr** in a lower yield, along with the recovery of unchanged **1d** (entry 4).

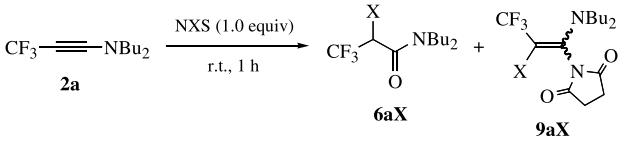
The reaction of the ynamine **2a** with iodine was also performed under the similar conditions to that with bromine. As depicted in Scheme 9, the corresponding cyclobutene cyanine **7a** was obtained in 51% yield, no addition product like **5a** being detected in the reaction mixture. The product **7a** could be isolated as a white solid and be kept for several days at ambient temperature under argon without any detectable changes. Interestingly, on standing for several days in contact with air, **7a** was deiodinated gradually to form **8a**. The mechanistic details of this transformation remain obscure at the present time. Successive treatment of the in situ formed **7a** with water gave rise to **8a** in 49% overall yield.



Scheme 9.

2.4. Reaction of the ynamine 2a with NXS in a water-containing solvent

We next examined the reaction of the ynamine **2a** with *N*-bromosuccinimide (NBS), which is one of the easy-handling brominating agents,[26] as shown in Scheme 10 and Table 4. When the ynamine **2a** was allowed an exposure to NBS (1.0 equiv) in water at room temperature for 1 h, the amide **6aBr** was given in 57% yield, together with 27% yield of the addition product **9aBr**, which was a mixture of two geometrical isomers in a ratio of 76:24 (entry 1). A THF–H_2O (3/2 v/v) mixed solvent afforded a comparable yield of **6aBr** and an increased yield of **9aBr** (entry 2). With the reaction in acetone–H_2O (3/2 v/v), the yields were appreciably decreased (entry 3). Interestingly, the use of a carbon tetrachloride–H_2O (3/2 v/v) mixed solvent, a two phase solvent system, resulted in the formation of **9aBr** in preference to **6aBr** (entry 4). Eventually, the most satisfactory result was obtained for the reaction using a



Scheme 10.

Table 4. Reactions of **2a** with NXS in mixed solvents

Entry	NXS	Solvent	Yield of **6aX** (%)[a]	Yield of **9aX** (%)[a]
1	NBS	H_2O	57	27
2	NBS	THF–H_2O	54	44
3	NBS	Acetone–H_2O	31	20
4	NBS	CCl_4–H_2O	42	51
5	NBS	MeCN–H_2O	85	12
6	NBS[b]	MeCN–H_2O	27, 46[c]	10
7	NCS	MeCN–H_2O	85	3
8	NIS	MeCN–H_2O	80	tr

[a] Isolated yields.
[b] NBS (2.0 equiv) used.
[c] Isolated yields of 2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**).

MeCN–H_2O mixed solvent, where **6aBr** was provided in 85% yield and **9aBr** in 12% yield (entry 5).

With optimum conditions (entry 5) in hand, we conducted the halogenation reaction of **2a** with other *N*-halosuccinimides (NXS), such as NCS and NIS. As shown in entries 7 and 8, the reaction of **2a** with NCS or NIS proceeded efficiently to give the corresponding 2-halo amides **6aCl** and **6aI** in 85 and 80% yield, respectively. In both cases, the addition product **9aCl** or **9aI** was formed in less than 3% yield. The 2-chloro amide **6aCl** could also be obtained in 75% yield through the reaction of **2a** with aqueous sodium hypochloride (5 equiv) in MeCN at ambient temperature for 1 h. It is very interesting that the use of 2.0 equiv of NBS brought about the formation of *N*,*N*-dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**) as a major product, along with the products **6aBr** and **9aBr** (entry 6).

2.5. Reaction of the ynamine 2a with NXS in anhydrous MeCN

Next, the reaction between **2a** and NXS was investigated under anhydrous reaction conditions. The results of the reactions are summarized in Table 5.

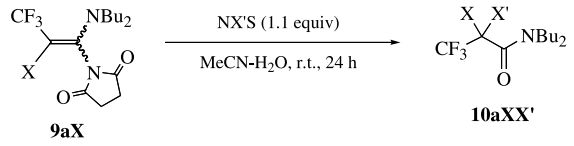
Table 5. Reaction of **2a** with NXS in anhydrous MeCN

Entry	NXS	Yield of **6aX** (%)[a]	Yield of **9aX** (%)[a]	Isomer ratio **9aX** (%)[b]
1	NBS	tr	99	74:26
2	NCS	tr	83	53:47
3	NIS	0	66 (87)	73:27

[a] Isolated yields. Value in parentheses is of yield measured by ^{19}F NMR.
[b] Determined by ^{19}F NMR.

When **2a** was allowed to react with NXS (1.0 equiv) in anhydrous MeCN in the presence of MS 4 Å at room temperature for 1 h, the corresponding addition product **9aX** was exclusively obtained in good yield as a mixture of the geometrical isomers. Little or no 2-halo propanamide **6aX** was produced in the reaction. The addition product **9aI** was susceptible to decomposition during isolation by silica gel column chromatography, resulting in a remarkable decrease in an isolated yield (entry 3). To be noted is that neither **9aBr** nor **9aCl** was changed even when treated with a HCl aqueous solution in MeCN–H_2O (3/2 v/v) at room temperature for 24 h, the corresponding 2-halo propanamides **6aBr** and **6aCl** being not obtained at all. These findings strongly suggest that the 2-halo propanamides **6aX**, formed in the reaction of **2a** under aqueous conditions (Scheme 10), are not derived from the hydrolysis of in situ formed **9aX** but from the addition of a halonium ion to the acetylenic β-carbon of **2a** followed by attack with water.

It was further found that these addition products **9aX** reacted readily with *N*-halosuccinimides (NX′S) in a MeCN–H_2O mixed solvent at room temperature, leading to high yields of the corresponding 2,2-dihalo propanamides **10aXX′**, which are extremely difficult to prepare, as shown in Scheme 11 and Table 6.



Scheme 11.

Table 6. Reaction of the addition products **9aX** with NX′S

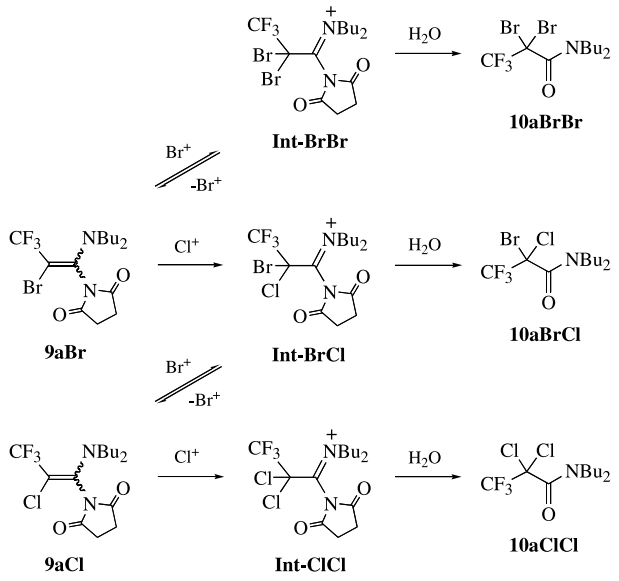
Entry	**9aX**	X′	Yield of **10aXX′** (%)[a]			
			ClCl	**ClBr**	**BrBr**	**ClI**
1	**9aCl**	Cl	99	0	0	0
2	**9aBr**	Br	0	0	99	0
3	**9aCl**	Br	0	99	0	0
4	**9aBr**	Cl	35	42	21	0
5[b]	**9aI**	Cl	27	0	0	0

[a] Isolated yields.
[b] The addition product **9aCl** was obtained in 5% yield.

Thus, on treating **9aCl** or **9aBr** with NCS or NBS (1.1 equiv) in MeCN–H_2O (3/2 v/v) at room temperature for 24 h, the corresponding 2,2-dihalo propanamides **10aClCl** and **10aBrBr** were obtained, respectively, in quantitative yields (entries 1 and 2). The treatment of **9aCl** with NBS likewise gave high yield of the amide **10aClBr** carrying two different halogens at the α carbon (entry 3). However, the reaction of **9aBr** with NCS under the same conditions led to **10aClCl**, **10aClBr**, and **10aBrBr** in 35, 42, and 21% yields, respectively (entry 4). The reaction of **9aI** with NCS gave rise to **10aClCl** and **9aCl** in 27 and 55% yields, respectively, no expected product **10aClI** being formed at all (entry 5).

2.6. Mechanistic aspects for the reaction of 9aX with NX′S

A possible mechanism for the reaction of **9aX** with NX′S is as follows. As shown in Scheme 12, the addition product **9aBr** reacts with chloronium ion, generated from NCS, to form the intermediate **Int-BrCl**, which undergoes hydrolysis with water to give the product 2-bromo-2-chloro propanamide **10aBrCl**. This intermediate **Int-BrCl** may also be subject to the elimination of bromonium ion to generate **9aCl**. No elimination of chloronium ion occurs on **Int-BrCl** in any extent, in view of the fact that the reaction of **9aCl** with NBS led to the exclusive formation of **10aClBr** (corresponding to **10aBrCl** in Scheme 12), as shown in entry 3 of Table 6. The in situ generated **9aCl** may react with chloronium ion to give the intermediate **Int-ClCl**, which is hydrolyzed with water to afford the product



Scheme 12.

10aClCl. On the other hand, **9aBr** may also react with bromonium ion, generated in situ via elimination from **Int-BrCl**, to form **Int-BrBr**, which is hydrolyzed to give the product **10aBrBr**.

It is also possible to explain the formation of **10aClCl** and **9aCl** in the reaction of **9aI** with NCS according to this mechanism.

3. Experimental

3.1. Measurements and materials

Infrared spectra (IR) were measured in a liquid film or KBr disk method with a Shimadzu FTIR-8200PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with GE QE-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and Bruker DRX-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometers in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane as an internal reference. A JEOL JNM EX90A (84.1 MHz) spectrometer was used to measure ^{19}F NMR spectra in $CDCl_3$ using trichlorofluoromethane as an internal standard. Mass (MS) and high resolution mass spectra (HRMS) were taken on a Hitachi M-80B and JEOL JMS-700 mass spectrometer by electron impact (EI) or chemical ionization (CI) method. Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. The elemental analyses of products were carried out with a Yanaco CHN CORDER MT-5 instrument.

THF and diethyl ether were freshly distilled from sodium benzophenone ketyl under argon. MeCN was distilled from calcium hydride and stored under argon. Other solvents were dried according to the conventional methods prior to use. Butyllithium (a 1.6 M hexane solution) was commercially available from Aldrich or Kanto Chemical Co. Aldehydes and ketones were distilled (or vacuum distilled) over calcium hydride or recrystallized from appropriate solvents, and were stored under argon. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. 2,2,3,3,3-Pentafluoropropyl *o*-nitrobenzenesulfonate and trifluoromethanesulfonate were prepared according to the literature method[18] or slightly modified procedure.[19] All reactions were carried out under an atmosphere of argon.

3.2. Typical procedure for the preparation of the tertiary amines 1

Method A. A mixture of *o*-nitrobenzenesulfonate (50.27 g, 150 mmol) and *N*,*N*-dimethylbenzylamine (60.84 g, 450 mmol) was heated with stirring at such temperatures (140–160 °C) that in situ formed tertiary amine **1b** was constantly distilled. The collected distillate was subjected to fractional distillation giving the amine **1b** (86% yield).

Method B. A mixture of trifluoromethanesulfonate (42.32 g, 150 mmol) and dibutylamine (58.16 g, 450 mmol) was stirred without solvent at 60 °C for 1 h. After cooling to room temperature, the mixture was filtered to remove dibutylammonium salt, which was washed with diethyl ether (ca. 50 mL). The filtrate was washed successively with 5% HCl (100 mL×2) and with water (50 mL), followed by drying over anhydrous Na_2SO_4, filtration, and concentration. The residual oil was distilled to afford **1a** (93% yield).

3.2.1. *N*,*N*-Dibutyl(2,2,3,3,3-pentafluoropropyl)amine (1a). Bp 75.0–76.0 °C/20 mmHg; IR (neat) 2960, 1190, 1110 (cm^{-1}); ^{1}H NMR δ 0.91 (t, J=7.1 Hz, 6H), 1.22–1.49 (m, 8H), 2.57 (t, J=7.1 Hz, 4H), 3.03 (tq, J=15.8, 1.1 Hz, 2H); ^{13}C NMR δ 13.9, 20.2, 29.4, 53.6 (t, J=21.8 Hz), 55.2, 115.0 (tq, J=253.9, 35.6 Hz), 119.2 (tq, J=35.6, 286.7 Hz); ^{19}F NMR δ −117.8 (t, J=15.8 Hz, 2F), −82.2 (t, J=1.1 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 261 (M^+, 6), 218 (100); HRMS (EI) calcd for $C_{11}H_{20}F_5N$ (M^+): 261.1516, found 261.1515. Anal. Calcd for $C_{11}H_{20}F_5N$: C 50.57, H 7.72, N 5.36. Found: C 49.94, H 7.62, N 5.41.

3.2.2. *N*,*N*-Dimethyl(2,2,3,3,3-pentafluoropropyl)amine (1b). Bp 58.0 °C; IR (neat) 2960, 1200, 1105 (cm^{-1}); ^{1}H NMR δ 2.41 (s, 6H), 2.93 (tq, J=15.6, 1.1 Hz, 2H); ^{13}C NMR δ 46.5, 57.8 (t, J=22.3 Hz), 115.0 (tq, J=254.1, 35.8 Hz), 119.1 (tq, J=35.8, 285.6 Hz); ^{19}F NMR δ −117.3 (t, J=15.6 Hz, 2F), −82.2 (t, J=1.1 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 177 (M^+, 100); HRMS (EI) calcd for $C_5H_8F_5N$ (M^+): 177.0577, found 177.0573.

3.2.3. *N*-(2,2,3,3,3-Pentafluoropropyl)piperidine (1c). Bp 122.0–123.0 °C; IR (neat) 2941, 1198, 1134 (cm^{-1}); ^{1}H NMR δ 1.38–1.46 (m, 2H), 1.55–1.463 (m, 4H), 2.58 (t, J=5.3 Hz, 4H), 2.91 (tq, J=15.6, 1.2 Hz, 2H); ^{13}C NMR δ 23.7, 26.0, 55.7, 57.4 (t, J=22.0 Hz), 114.9 (tq, J=290.1, 35.6 Hz), 119.1 (tq, J=35.6, 286.2 Hz); ^{19}F NMR δ −119.5 (t, J=15.6 Hz, 2F), −84.5 (t, J=1.2 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 217 (M^+, 19), 98 (100); HRMS (EI) calcd for $C_8H_{12}F_5N$ (M^+): 217.0870, found 217.0894.

3.2.4. *N*,*N*-Diisopropyl(2,2,3,3,3-pentafluoropropyl)-amine (1d). Bp 136.0–136.5 °C; IR (neat) 2972, 1194, 1153 (cm^{-1}); ^{1}H NMR δ 1.02 (d, J=6.5 Hz, 12H), 2.99–3.11 (m, 4H); ^{13}C NMR δ 20.8, 45.4 (t, J=22.3 Hz), 49.5, 114.7 (tq, J=252.1, 35.5 Hz), 119.6 (tq, J=35.5,

286.5 Hz); ^{19}F NMR δ −120.4 (t, J=15.6 Hz, 2F), −84.4 (s, 3F); MS (EI) *m/z* (rel intensity) 233 (M^+, 2), 176 (100); HRMS (EI) calcd for $C_9H_{16}F_5N$ (M^+): 233.2102, found 233.1207.

3.3. Typical procedure for the preparation of the ynamines 2

To a solution of LDA (2.2 mmol) in THF (3.0 mL) was gradually added a solution of **1a** (0.262 g, 1.0 mmol) in THF (1.0 mL) and DMPU (0.282 g, 2.2 mmol) at 0 °C under argon. The mixture was stirred at room temperature for 2 h. After being quenched with water, the resulting mixture was extracted with diethyl ether (20 mL×3) and the combined ethereal extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to leave crude **2a**, of which the yield was determined by ^{19}F NMR using α,α,α-trifluorotoluene as the reference. The ynamine **2a** was subjected to the following reactions without any purifications.

3.3.1. *N*,*N*-Dibutyl(3,3,3-trifluoro-1-propynyl)amine (2a). Bp 36 °C/15 mmHg; IR (neat) 2361 (cm^{-1}); ^{1}H NMR δ 0.94 (t, J=7.2 Hz, 6H), 1.31–1.43 (m, 4H), 1.55–1.65 (m, 4H), 2.98 (t, J=7.2 Hz, 4H); ^{13}C NMR δ 13.5, 19.7, 29.7, 52.6, 55.8 (q, J=52.08 Hz), 100.5 (q, J=7.12 Hz), 118.3 (q, J=255.01 Hz); ^{19}F NMR δ −46.2 (s, 3F); MS (EI) *m/z* (rel intensity) 221 (M^+, 19), 128 (100); HRMS (EI) calcd for $C_{11}H_{18}F_3N$ (M^+): 221.1391, found 221.1378.

3.3.2. *N*,*N*-Dimethyl(3,3,3-trifluoro-1-propynyl)amine (2b). IR (THF soln) 2218 (cm^{-1}); ^{19}F NMR (THF) δ −46.2 (s, 3F). Other spectral data could not be obtained due to contamination with the solvent.

3.3.3. *N*-(3,3,3-Trifluoro-1-propynyl)piperidine (2c). IR (neat) 2203 (cm^{-1}); ^{1}H NMR δ 1.22 (d, J=6.5 Hz, 12H), 3.19 (sept, J=6.5 Hz, 4H); ^{13}C NMR δ 21.2, 52.3, 60.7 (q, J=51.7 Hz), 98.7 (q, J=5.5 Hz), 118.7 (q, J=255.1 Hz); ^{19}F NMR δ −44.8 (s, 3F).

3.3.4. *N*,*N*-Diisopropyl(3,3,3-trifluoro-1-propynyl)amine (2d). IR (neat) 2203 (cm^{-1}); ^{1}H NMR δ 1.22 (d, J=6.5 Hz, 12H), 3.19 (sept, J=6.5 Hz, 4H); ^{13}C NMR δ 21.2, 52.3, 60.7 (q, J=51.7 Hz), 98.7 (q, J=5.5 Hz), 118.7 (q, J=255.1 Hz); ^{19}F NMR δ −44.8 (s, 3F).

3.4. Typical procedure for the reaction of the ynamines 2 with carbonyl compounds

To a solution of **2a** (1.0 mmol) in CH_2Cl_2 (3.0 mL) containing MS 4 Å (1.0 g) were dropwise added successively benzaldehyde (1.1 mmol) and $BF_3\cdot OEt_2$ (0.1 mmol) at 0 °C under an argon atmosphere. After stirring at room temperature for 1 h, the mixture was filtered to remove MS 4 Å. The filtrate was poured into 3% HCl (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a residual oil, which was submitted to ^{19}F NMR analysis. The residual oil was chromatographed on a silica gel column with benzene to provide analytically pure product **3aa** (92% yield), together with a small amount of **4a**.

3.4.1. *N*,*N*-Dibutyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3aa). IR (neat) 1640 (cm^{-1}); ^{1}H NMR δ 0.94 (t, J=7.1 Hz, 3H), 0.96 (t, J=7.1 Hz, 3H), 1.23–1.46 (m, 4H), 1.53–1.68 (m, 4H), 3.39 (t, J=7.9 Hz, 2H), 3.44 (t, J=7.6 Hz, 2H), 6.94 (s, 1H), 7.35–7.44 (m, 5H); ^{13}C NMR δ 13.7, 13.8, 19.9, 20.1, 29.2, 30.5, 44.4, 48.5, 121.8 (q, J=274.7 Hz), 127.5 (q, J=32.6 Hz), 128.4, 128.9 (q, J=2.0 Hz), 129.4, 132.5, 137.9 (q, J=4.1 Hz), 165.5 (q, J=2.1 Hz); ^{19}F NMR δ −54.7 (s, 3F); MS (EI) *m/z* (rel intensity) 327 (M^+, 7), 199 (100); HRMS (EI) calcd for $C_{18}H_{24}F_3NO$ (M^+): 327.1810, found 327.1807. Anal. Calcd for $C_{18}H_{24}F_3NO$: C 66.04, H 7.39, N 4.28. Found: C 66.48, H 7.45, N 4.07.

3.4.2. *N*,*N*-Dimethyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3ba). Mp 71–72 °C; IR (KBr) 1628 (cm^{-1}); ^{1}H NMR δ 3.05 (s, 3H), 3.12 (s, 3H), 6.98 (s, 1H), 7.36–7.45 (m, 5H); ^{13}C NMR δ 34.9, 38.6, 121.7 (q, J=274.7 Hz), 126.8 (q, J=32.7 Hz), 128.4, 129.0, 129.6, 132.3, 138.8 (q, J=4.0 Hz), 165.6 (q, J=2.3 Hz); ^{19}F NMR δ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 243 (M^+, 31), 199 (100); HRMS (EI) calcd for $C_{12}H_{12}F_3NO$ (M^+): 243.0871, found 243.0871. Anal. Calcd for $C_{12}H_{12}F_3NO$: C 59.26, H 4.97, N 5.76. Found: C 59.54, H 5.03, N 5.34.

3.4.3. *N*,*N*-Pentamethylene-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3ca). IR (neat) 1639 (cm^{-1}); ^{1}H NMR δ 1.57–1.66 (m, 6H), 3.53–3.63 (m, 4H), 6.94 (s, 1H), 7.31–7.44 (m, 5H); ^{13}C NMR δ 24.2, 25.2, 26.0, 42.8, 48.2, 121.7 (q, J=274.9 Hz), 126.7 (q, J=32.6 Hz), 128.3, 128.9, 128.9, 129.4, 132.3, 138.0 (q, J=3.2 Hz), 163.8 (q, J=2.4 Hz); ^{19}F NMR δ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 283 (M^+, 24), 199 (100); HRMS (EI) calcd for $C_{15}H_{16}F_3NO$ (M^+): 283.1184, found 283.1176.

3.4.4. *N*,*N*-Diisopropyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3da). IR (neat) 1639 (cm^{-1}); ^{1}H NMR δ 1.24 (d, J=6.4 Hz, 6H), 1.50 (d, J=6.2 Hz, 6H), 3.41–3.60 (m, 1H), 4.11–4.30 (m, 1H), 6.86 (s, 1H), 7.35–7.46 (m, 5H); ^{13}C NMR δ 20.0, 20.2, 45.9, 51.1, 121.9 (q, J=274.8 Hz), 128.3, 128.6 (q, J=31.8 Hz), 128.9 (q, J=1.9 Hz), 129.2, 132.5, 136.2 (q, J=3.4 Hz), 164.4 (q, J=2.2 Hz); ^{19}F NMR δ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 299 (M^+, 11), 199 (100); HRMS (EI) calcd for $C_{16}H_{20}F_3NO$ (M^+): 299.1498, found 299.1500.

3.5. Reaction of the ynamine 2a with bromine

To a mixture of the ynamine **2a** (1.0 mmol) and MS 4 Å (1.0 g) in anhydrous MeCN was gradually added bromine (0.320 g, 2.0 mmol) at 0 °C. After stirring at room temperature for 1 h, a saturated $NaHCO_3$ aqueous solution (20 mL) was added to the mixture at room temperature and then the resultant mixture was stirred for 0.5 h. Water (10 mL) and diethyl ether (30 mL) were added to the mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL×4). The combined ethereal layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvents, the residue was chromatographed on silica gel

with hexane–benzene (1/1) to give *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) (87% yield).

On the other hand, after treating **2a** with bromine at 0 °C for 1 h as described above, the reaction mixture was concentrated under reduced pressure. Hexane was added to the resulting residue to precipitate a crude solid, which was too labile to be purified. However, spectral analyses of this crude solid made it possible to determine successfully the structure of the product **5a**.

3.5.1. *N*,*N*-Dibutyl-2-bromo-3,3,3-trifluoropropanamide (6aBr). Yield 87%; IR (neat) 2963, 2936, 2874, 1663, 1458, 1346, 1277, 1161, 1119, 876, 698, 671 (cm^{-1}); ^1H NMR δ 0.93 (t, J=7.5 Hz, 3H), 0.98 (t, J=7.5 Hz, 3H) 1.26–1.73 (m, 8H), 3.19–3.54 (m, 4H), 4.77 (q, J=6.0 Hz, 1H); ^{13}C NMR δ 13.4, 13.5, 19.7, 19.7, 28.9, 31.1, 37.1 (q, J=33.1 Hz), 46.3, 48.2, 122.2 (q, J=278.1 Hz), 161.6; ^{19}F NMR δ −69.0 (d, J=6.0 Hz, 3F); MS (CI) *m*/*z* (rel intensity) 320 (M+H+2, 100), 318 (M+H, 100), 274 (38), 238 (100), 231 (52), 196 (50), 156 (55); HRMS (CI) calcd for $C_{11}H_{20}BrF_3NO$: 318.0680, found 318.0643. Anal. Calcd for $C_{11}H_{19}BrF_3NO$: C 41.52, H 6.02, N 4.40. Found: C 41.72, H 5.82, N 4.21.

3.5.2. *N*,*N*-Dibutyl(1,2-dibromo-3,3,3-trifluoropropenyl)-amine (5a). Yield 99%; IR (neat) 3506, 2963, 2936, 2874, 1651, 1601, 1578, 1466, 1346, 1250, 1192, 1119, 876 (cm^{-1}); ^1H NMR δ 0.90 (t, J=7.0 Hz, 6H), 1.25–1.35 (m, 4H), 1.41–1.51 (m, 4H), 2.68 (t, J=7.8 Hz, 4H) for the major isomer, 2.91 (t, J=7.3 Hz, 4H) for the minor isomer; ^{13}C NMR δ 13.6, 20.2, 29.0, 55.4, 111.1 (q, J=35.0 Hz), 120.6 (q, J=273.9 Hz), 151.1 for the major isomer; 13.6, 20.2, 29.4, 53.7, 97.0 (q, J=37.6 Hz), 121.0 (q, J=272.1 Hz), 139.3 (q, J=3.8 Hz) for the minor isomer; ^{19}F NMR δ −57.5 (s, 3F) for the major isomer, −55.3 (s, 3F) for the minor isomer.

3.6. Typical procedure for the one-pot synthesis of *N*,*N*-dialkyl-2-bromo-3,3,3-trifluoropropanamides (6aBr–dBr) from the tertiary amines 1

To a solution of LDA (2.2 mmol) in anhydrous THF (2.0 mL) was dropwise added a solution of **1a** (0.261 g, 1.0 mmol) in THF (1.0 mL) and DMPU (0.282 g, 2.2 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. After addition of bromine (0.320 g, 2.0 mmol) at 0 °C, the mixture was stirred at room temperature for 1 h. A saturated $NaHCO_3$ aqueous solution (30 mL) was then added to the reaction mixture at room temperature and the mixture was stirred for 0.5 h. This mixture was treated in the same manner as described above to give **6aBr** (75% yield).

The similar reactions of other amines **1b–d** provided the corresponding 2-bromo propanamides **6bBr–dBr**.

3.6.1. *N*,*N*-Dimethyl-2-bromo-3,3,3-trifluoropropanamide (6bBr). Yield 64%; IR (neat) 2993, 1659, 1501, 1458, 1420, 1358, 1281, 1258, 1204, 1165, 1115, 1065, 876, 841, 691, 656 (cm^{-1}); ^1H NMR δ 2.97 (s, 3H), 3.08 (s, 3H), 4.82 (q, J=6.0 Hz, 1H); ^{13}C NMR δ 36.2, 37.2 (q, J=32.9 Hz), 37.7, 122.2 (q, J=277.7 Hz), 162.1; ^{19}F NMR δ −69.0 (d, J=6.0 Hz, 3F).

3.6.2. *N*,*N*-Pentamethylene-2-bromo-3,3,3-trifluoropropanamide (6cBr). Yield 78%; IR (neat) 3001, 2986, 2947, 2858, 1643, 1462, 1369, 1323, 1373, 1157, 1123, 1015, 964, 872, 853, 806, 783, 691, 656 (cm^{-1}); ^1H NMR δ 1.53–1.68 (m, 6H), 3.34–3.67 (m, 4H), 4.84 (q, J=6.2 Hz, 1H); ^{13}C NMR δ 24.0, 25.1, 25.9, 37.2 (q, J=32.6 Hz), 43.4, 47.6, 122.3 (q, J=277.7 Hz), 160.3; ^{19}F NMR δ −70.7 (d, J=6.2 Hz, 3F).

3.6.3. *N*,*N*-Diisopropyl-2-bromo-3,3,3-trifluoropropanamide (6dBr). Yield 37%; IR (neat) 2974, 2939, 2882, 1655, 1477, 1450, 1377, 1362, 1335, 1273, 1200, 1150, 1126, 1045, 876, 799, 691, 640 (cm^{-1}); ^1H NMR δ 1.29 (d, J=6.5 Hz, 3H), 1.27 (d, J=7.0 Hz, 3H), 1.38 (d, J=6.5 Hz, 3H), 1.39 (d, J=6.5 Hz, 3H), 3.54 (br s, 1H), 3.86 (sept, J=6.5 Hz, 1H), 4.68 (q, J=6.0 Hz, 1H); ^{13}C NMR δ 19.6, 20.2, 20.4, 21.1, 38.8 (q, J=31.8 Hz), 46.9, 49.9, 122.4 (q, J=277.8 Hz), 160.7; ^{19}F NMR δ −68.6 (d, J=6.0 Hz, 3F).

3.7. Reaction of the ynamine 2a with iodine

To a mixture of the ynamine **2a** (1.0 mmol) and MS 4 Å (1.0 g) in anhydrous MeCN (3.0 mL) was gradually added iodine (0.254 g, 1.0 mmol) at room temperature under argon and the mixture was stirred for 1 h. A saturated $NaHCO_3$ aqueous solution (20 mL) was added to the mixture at room temperature, and the whole mixture was stirred for 0.5 h. The solvent was removed in vacuo to leave the crude product, which was recrystallized from diethyl ether to give pure *N*,*N*,*N*′,*N*′-tetrabutyl-4-iodo-2,4-bis(trifluoromethyl)-1-cyclobutene cyanine iodide (**7a**) (51% yield). On standing in contact with the atmosphere or treating with water, this salt was readily converted into *N*,*N*,*N*′*N*′-tetrabutyl-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (**8a**).

3.7.1. *N*,*N*,*N*′,*N*′-Tetrabutyl-4-iodo-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (7a). Yield 51%; mp 133–1350 °C; IR (KBr) 2963, 2905, 2878, 1589, 1462, 1315, 1250, 1153, 1126, 1080, 1061, 941, 737 (cm^{-1}); ^1H NMR δ 0.96 (t, J=7.5 Hz, 6H), 0.99 (t, J=7.5 Hz, 6H), 1.33–1.45 (m, 8H), 1.49–1.89 (m, 8H), 3.43–3.58 (m, 4H), 3.63–3.69 (m, 2H), 3.77–3.83 (m, 2H); ^{13}C NMR δ 13.3, 13.6, 19.4, 19.5, 28.6, 29.5, 43.1 (q, J=31.2 Hz), 52.0 (q, J=4.1 Hz), 53.3 (q, J=2.0 Hz), 95.7 (q, J=41.8 Hz), 117.9 (q, J=268.6 Hz), 121.8 (q, J=279.2 Hz), 160.4; ^{19}F NMR δ −52.2 (s, 3F), −63.5 (s, 3F); MS (FAB) *m*/*z* (rel intensity) 1265 (2M−I, 100); HRMS (FAB) calcd for $C_{44}H_{72}F_{12}I_3N_4$ (2M−I): 1265.2699, found 1265.2708.

3.7.2. *N*,*N*,*N*′,*N*′-Tetrabutyl-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (8a). Yield 49%; mp 136.5–137.0 °C; IR (KBr) 2963, 2936, 2874, 1728, 1620, 1466, 1373, 1331, 1258, 1234, 1215, 1173, 1119, 1080, 1053, 983, 937, 864, 733, 652 (cm^{-1}); ^1H NMR δ 0.93 (t, J=7.0 Hz, 6H), 0.94 (t, J=6.5 Hz, 6H), 1.31–1.43 (m, 8H), 1.49–1.58 (m, 2H), 1.68–1.84 (m, 4H), 1.88–1.97 (m, 2H), 3.44–3.66 (m, 8H), 6.72–6.74 (m, 1H); ^{13}C NMR δ 13.3, 13.5, 19.7, 19.7, 28.9, 29.7, 51.5 (q, J=3.9 Hz), 54.7, 58.0 (q, J=30.2 Hz), 100.3 (q, J=42.0 Hz), 117.8 (q, J=267.7 Hz), 122.4 (q, J=282.0 Hz), 155.8; ^{19}F NMR δ −54.5 (s, 3F), −65.4 (d, J=4.4 Hz, 3F); MS (FAB) *m*/*z* (rel intensity) 1013 (2M−I, 100); HRMS (FAB) calcd for $C_{44}H_{74}F_{12}IN_4$

(2M−I): 1013.4766, found 1013.4760. Anal. Calcd for $C_{22}H_{37}F_6IN_2$: C 46.32, H 6.54, N 4.91. Found: C 45.97, H 6.23, N 4.55.

3.8. Typical procedure for the reaction of the ynamine 2a with NXS in a water-containing solvent

To a solution of **2a** (1.0 mmol) in MeCN–water (3/2 v/v, 5 mL) was added NBS (0.180 g, 1.0 mmol) at room temperature. After stirring at room temperature for 1 h, the mixture was extracted with diethyl ether (20 mL×4). The combined extracts were washed with brine (20 mL), followed by drying over anhydrous Na_2SO_4, filtration and concentration in vacuo. The crude residue was purified by column chromatography on silica gel with hexane–benzene (1/2) to afford *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) (85% yield) and *N*-[2-bromo-1-(*N*,*N*-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (**9aBr**) (12% yield).

Other 2-bromo propanamides **6aX** were synthesized in a similar manner.

3.8.1. *N*,*N*-Dibutyl-2-chloro-3,3,3-trifluoropropanamide (6aCl). Yield 85%; IR (neat) 2963, 2936, 2874, 1670, 1458, 1350, 1281, 1165, 1119, 934, 887, 733, 687, 644 (cm^{-1}); ^1H NMR δ 0.93 (t, J=7.2 Hz, 3H), 0.97 (t, J=7.2 Hz, 3H), 1.26–1.43 (m, 4H), 1.50–1.61 (m, 4H), 3.25–3.47 (m, 4H), 4.85 (q, J=6.6 Hz, 1H); ^{13}C NMR δ 13.6, 13.6, 19.8, 19.9, 29.2, 31.3, 46.5, 48.1, 49.9 (q, J=33.4 Hz), 122.2 (q, J=279.6 Hz), 161.3; ^{19}F NMR δ −71.4 (d, J=6.6 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 275 (M+2, 1), 273 (M^+, 3), 238 (47), 232 (9), 230 (26), 190 (33), 188 (100), 174 (14), 156 (14); HRMS (EI) calcd for $C_{11}H_{19}ClF_3NO$: 273.1107, found 273.1082. Anal. Calcd for $C_{11}H_{19}ClF_3NO$: C 48.27, H 7.00, N 5.12. Found: C 48.12, H 6.67, N, 5.12.

3.8.2. *N*,*N*-Dibutyl-2-iodo-3,3,3-trifluoropropanamide (6aI). Yield 80%; IR (neat) 2963, 2936, 2874, 1659, 1458, 1342, 1265, 1157, 1145, 1092, 664, 617 (cm^{-1}); ^1H NMR δ 0.93 (t, J=7.2 Hz, 3H), 0.98 (t, J=7.2 Hz, 3H), 1.26–1.43 (m, 4H), 1.48–1.77 (m, 4H), 3.10–3.59 (m, 4H), 4.84 (q, J=6.6 Hz, 1H); ^{19}F NMR δ −66.0 (d, J=6.6 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 365 (M^+, 1), 322 (51), 280 (66), 238 (100), 209 (12), 196 (47), 156 (16), 86 (84); HRMS (EI) calcd for $C_{11}H_{19}F_3INO$: 365.0465, found 365.0463.

3.9. Typical procedure for the reaction of the ynamine 2a with NXS in anhydrous MeCN

To a mixture of **2a** (1.0 mmol) and MS 4 Å (1.0 g) in MeCN (3.0 mL) was gradually added NBS (0.180 g, 1.0 mmol) at ambient temperature under an argon atmosphere. After stirring for 1 h, the mixture was filtered to remove the resulting solids and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using benzene as an eluent to provide a mixture of the *E* and *Z* isomers of *N*-[2-bromo-1-(*N*,*N*-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (**9aBr**) (99% yield).

Other addition products **9aX** were prepared in a similar manner.

3.9.1. *N*-[2-Bromo-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aBr). Yield 99%; mp 55–57 °C; IR (KBr) 2962, 2936, 2874, 1732, 1605, 1462, 1381, 1346, 1273, 1169, 1115, 1053, 1003, 941, 679 (cm^{-1}); ^1H NMR δ 0.91 (t, J=7.2 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H), 1.23–1.58 (m, 8H), 2.81 (s, 4H) for the major isomer, 2.82 (s, 4H) for the minor isomer, 3.03 (t, J=7.5 Hz, 2H), 3.07 (t, J=7.5 Hz, 2H); ^{19}F NMR δ −59.4 (s, 3F) for the major isomer, −59.9 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 400 (M+2, 11), 398 (M^+, 11), 319 (100), 299 (9), 221 (12), 220 (11), 164 (61); HRMS (EI) calcd for $C_{15}H_{22}BrF_3N_2O_2$: 398.0817, found 398.0822. Anal. Calcd for $C_{15}H_{22}BrF_3N_2O_2$: C 45.13, H 5.55, N 7.02. Found: C 44.66, H 5.38, N, 6.74.

3.9.2. *N*-[2-Chloro-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aCl). Yield 83%; mp 44.0–45.5 °C; IR (KBr) 2963, 2936 (s), 2878, 1732, 1670, 1620, 1462, 1427, 1350, 1281, 1234, 1119, 1057, 968, 945, 683 (cm^{-1}); ^1H NMR δ 0.92 (t, J=7.5 Hz, 6H) for the major isomer, 1.25–1.34 (m, 4H), 1.49–1.56 (m, 4H), 2.81 (br s, 4H), 3.06 (t, J=7.5 Hz, 4H), 0.90 (t, J=7.5 Hz, 6H) for the minor isomer, 1.25–1.34 (m, 4H), 1.49–1.56 (m, 4H), 2.83 (br s, 4H), 3.02 (t, J=7.5 Hz, 4H); ^{13}C NMR δ 13.8, 19.9, 28.2, 30.2, 50.1, 97.3 (q, J=36.7 Hz), 121.9 (q, J=269.9 Hz), 137.2, 174.7 for the major isomer, 13.7, 19.9, 28.3, 29.9, 51.1, 97.4 (q, J=36.7 Hz), 121.9 (q, J=269.9 Hz), 140.0 (q, J=2.4 Hz), 174.2 for the minor isomer; ^{19}F NMR δ −62.7 (s, 3F) for the major isomer, −63.3 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 356 (M+2, 7), 354 (M^+, 22), 319 (100), 313 (19), 311 (55), 277 (46), 263 (22), 229 (12), 164 (34), 162 (12), 151 (11), 57 (13); HRMS (EI) calcd for $C_{15}H_{22}ClF_3N_2O_2$: 354.1321, found 354.1316. Anal. Calcd for $C_{15}H_{22}ClF_3N_2O_2$: C 50.78, H 6.25, N 7.90. Found: C 51.00, H 6.12, N 7.71.

3.9.3. *N*-[2-Iodo-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aI). Yield 66%; mp 66–69 °C; IR (KBr) 2963, 2939, 2874, 1728, 1639, 1585, 1462, 1339, 1250, 1165, 1096, 930, 706 (cm^{-1}); ^1H NMR δ 0.90 (t, J=7.3 Hz, 6H), 1.21–1.34 (m, 4H), 1.47–1.55 (m, 4H), 2.76–2.86 (m, 4H), 3.07 (t, J=7.8 Hz, 4H); ^{13}C NMR δ 13.7, 19.9, 28.5, 29.9, 51.3, 59.9 (q, J=37.3 Hz), 122.3 (q, J=268.9 Hz), 144.7 (q, J=2.8 Hz), 174.2 for the major isomer, 13.8, 20.0, 28.2, 30.0, 51.1, 59.9 (q, J=37.3 Hz), 122.3 (q, J=268.9 Hz), 144.7 (q, J=2.8 Hz), 174.2 for the minor isomer; ^{19}F NMR δ −54.0 (s, 3F) for the major isomer, −56.0 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 446 (M^+, 28), 403 (37), 347 (11), 319 (100), 278 (16), 277 (99), 238 (42), 236 (20), 235 (22), 221 (22), 196 (25), 165 (40), 164 (81), 86 (60), 84 (13), 57 (38); HRMS (EI) calcd for $C_{15}H_{22}F_3IN_2O_2$: 446.0678, found 446.0687.

3.10. Typical procedure for the reaction of 9aX with NXS or NX′S in a MeCN–water mixed solvent

To a solution of **9aBr** (0.399 g, 1.0 mmol) in MeCN–water (3/2 v/v, 5 mL) was gradually added NBS (0.196 g, 1.1 mmol) and then the mixture was stirred at ambient temperature for 24 h. After addition of water (20 mL), the mixture was extracted with diethyl ether (10 mL×5). The combined ethereal extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvents, the resulting residue was chromatographed on silica gel with hexane–benzene

(1/1) to give *N*,*N*-dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**) (99% yield).

The reactions between **9aX** and various NXS or NX′S were carried out in the same manner.

3.10.1. *N*,*N*-Dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (10aBrBr). Yield 99%; IR (neat) 2963, 2936, 2874, 1663, 1466, 1427, 1292, 1238, 1200, 1173, 895, 814, 710, 664 (cm^{-1}); ^1H NMR δ 0.87 (t, $J=7.2$ Hz, 3H), 0.92 (t, $J=7.2$ Hz, 3H), 1.19–1.71 (m, 8H), 3.28 (t, $J=7.5$ Hz, 2H), 3.63 (t, $J=8.0$ Hz, 2H); ^{13}C NMR δ 13.6, 13.7, 19.9, 20.0, 28.5, 29.4, 46.5, 49.7, 50.9 (q, $J=29.2$ Hz), 121.2 (q, $J=279.9$ Hz), 159.7; ^{19}F NMR δ −70.5 (s, 3F); MS (EI) *m*/*z* (rel intensity) 399 (M+4, 1), 397 (M+2, 2), 395 (M^+, 1), 356 (52), 354 (100), 352 (55), 310 (81), 300 (17), 298 (35), 296 (17), 276 (13), 274 (14), 256 (11), 214 (15), 212 (16); HRMS (EI) calcd for $C_{11}H_{18}Br_2F_3N$: 394.9707, found 394.9718. Anal. Calcd for $C_{11}H_{18}Br_2F_3N$: C 33.27, H 4.57, N 3.53. Found: C 33.01, H 4.40, N 3.30.

3.10.2. *N*,*N*-Dibutyl-2-bromo-2-chloro-3,3,3-trifluoropropanamide (10aClBr). Yield 99%; IR (neat) 2963, 2936, 2874, 1670, 1466, 1377, 1292, 1242, 1207, 1177, 910, 833, 679 (cm^{-1}); ^1H NMR δ 0.94 (t, $J=7.5$ Hz, 3H), 0.99 (t, $J=7.5$ Hz, 3H), 1.31–1.43 (m, 2H), 1.54–1.60 (m, 2H), 1.68–1.76 (m, 2H), 3.26–3.42 (m, 4H), 3.54–3.60 (m, 2H), 3.75–3.81 (m, 2H); ^{13}C NMR δ 13.8, 19.0, 20.0, 28.6, 29.7, 46.7, 49.2, 64.6 (q, $J=30.1$ Hz), 121.3 (q, $J=281.2$ Hz), 159.7; ^{19}F NMR δ −72.6 (s, 3F); MS (CI) *m*/*z* (rel intensity) 356 (M+H+4, 79), 355 (M+4, 22), 354 (M+H+2, 35), 353 (M+2, 19), 352 (M+H, 55), 310 (20), 308 (15), 274 (20), 272 (49), 238 (16), 156 (39); HRMS (CI) calcd for $C_{11}H_{19}BrClF_3NO$ (M+H): 352.0291, found 352.0254. Anal. Calcd for $C_{11}H_{18}BrClF_3NO$: C 37.47, H 5.15, N 3.97. Found: C 37.51, H 5.10, N 3.91.

3.10.3. *N*,*N*-Dibutyl-2,2-dichloro-3,3,3-trifluoropropanamide (10aClCl). Yield 99%; IR (neat) 2963, 2878, 1674, 1466, 1431, 1381, 1250, 1215, 1180, 922, 860, 718, 691 (cm^{-1}); ^1H NMR δ 0.93 (t, $J=7.5$ Hz, 3H), 0.97 (t, $J=7.5$ Hz, 3H), 1.32 (tq, $J=7.5$, 7.5 Hz, 2H), 1.37 (tq, $J=7.5$, 7.5 Hz, 2H), 1.56 (tt, $J=7.5$, 7.5 Hz, 2H), 1.68 (tt, $J=7.5$, 7.5 Hz, 2H), 3.32 (t, $J=7.5$ Hz, 2H), 3.62 (t, $J=7.5$ Hz, 2H); ^{13}C NMR δ 13.7, 19.9, 20.1, 28.7, 29.9, 46.8, 48.8, 76.9 (q, $J=30.7$ Hz), 121.3 (q, $J=282.2$ Hz), 159.5; ^{19}F NMR δ −75.5 (s, 3F); MS (EI) *m*/*z* (rel intensity) 311 (M+4, 1), 309 (M+2, 2), 307 (M^+, 2), 274 (31), 272 (77), 268 (18), 266 (80), 264 (90), 230 (21), 226 (45), 224 (94), 222 (100), 210 (55), 208 (70), 156 (68), 84 (18), 57 (81); HRMS (EI) calcd for $C_{11}H_{18}Cl_2F_3NO$: 307.0717, found 307.0719. Anal. Calcd for $C_{11}H_{18}Cl_2F_3NO$: C 42.87, H, 5.89, N 4.55. Found: C 42.00, H 5.65, N 4.01.

3.11. Reaction of the ynamine 2a with sodium hypochloride

To a solution of the ynamine **2a** (1.0 mmol) in MeCN (2.0 mL) was gradually added aqueous sodium hypochloride (5.0 mmol) at 0 °C. After stirring at room temperature for 1 h, water (10 mL) and diethyl ether (30 mL) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL × 4). The combined extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvents, the resultant residue was chromatographed on silica gel with hexane–benzene (1/1) to give **6aCl** (75% yield).

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A convenient synthesis of functionalized *N*-(ethynyl)benzotriazoles

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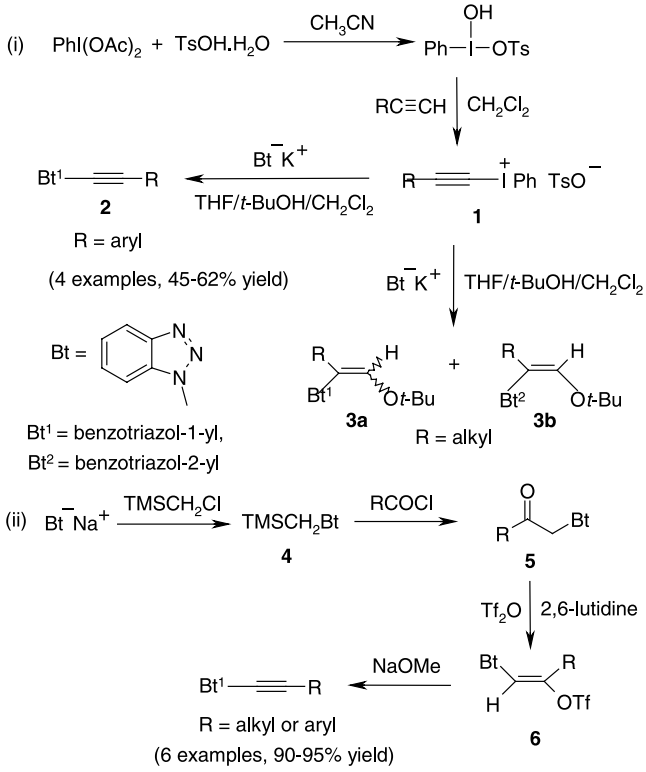
Abstract—1-(2,2-Dichlorovinyl)benzotriazole (**7**) was prepared by the reaction of 1-formylbenzotriazole with PPh_3/CCl_4. Lithiation–substitution of **7** with electrophiles gave a variety of functionalized *N*-(ethynyl)benzotriazoles **8a**–**h** in 32–84% yields.

1. Introduction

The carbon–carbon triple bond plays an important part in the preparation of compounds ranging from enediyne antitumor antibiotics to molecular electronics.[1] Acetylenes have been regarded as one of the key synthetic, structural, and functional tools of future chemistry[2] and *N*-(ethynyl)-benzotriazoles are versatile reagents for the synthesis of disubstituted acetylenes,[3a] esters,[3b] and carboxylic acids.[3c]

Previously reported methods for the direct introduction of a CC-triple bond on the nitrogen atom of 1*H*-benzotriazole involve (i) use of hypervalent iodine chemistry[4] in reactions of alkynylphenyliodonium tosylates with potassium benzotriazolate[5] or (ii) base treatment of benzotriazolyl enol triflates.[3b,c] The first method requires preparation of hypervalent iodonium salts **1**[4b] and is limited to the preparation of *N*-(arylethynyl)benzotriazoles **2**; attempted preparations of *N*-(alkylethynyl)benzotriazoles are reported to give mixtures of (*E*)- and (*Z*)-1-vinyl-1*H*-benzotriazoles **3a** and (*Z*)-2-vinyl-2*H*-benzotriazole **3b** as the main products.[5a] The second method proceeds through 1-(trimethylsilylmethyl)benzotriazole (**4**), *N*-acylbenzotriazoles **5** and benzotriazolyl enol triflates **6**, which on further treatment with base give *N*-(arylethynyl)- or *N*-(alkylethynyl)benzotriazoles (Scheme 1).[3c]



Scheme 1.

Corey and Fuchs introduced the well-known conversion of aldehydes to alkynes in 1972, and this method has been widely used in many synthetic protocols.[6] In a similar approach, we have devised a direct preparation of *N*-(ethynyl)benzotriazoles **8a**–**h** starting from commercially available 1-formylbenzotriazole. Treatment of 1-formylbenzotriazole with PPh_3/CCl_4 gave 1-(2,2-dichlorovinyl)-benzotriazole (**7**), which on subsequent lithiation–

Keywords: Benzotriazole; Lithiation; Electrophiles; Acetylenes; Substitution.
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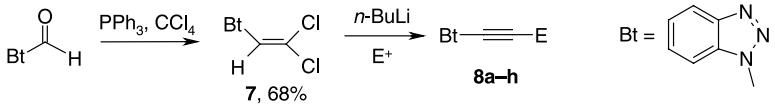
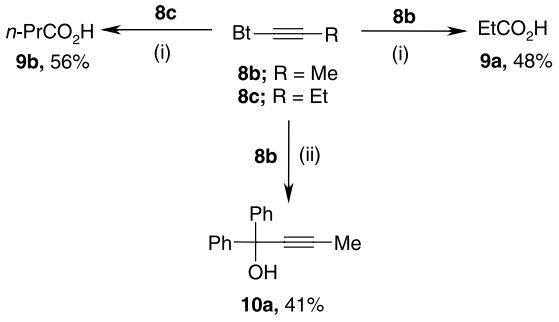
Table 1. Preparation of *N*-(ethynyl)benzotriazoles **8a–h**



Entry	Electrophile (E^+)	E	Product (% yield)[a]
1	MeOH	H	**8a** (73)
2	MeI	Me	**8b** (84)
3	EtI	Et	**8c** (58)
4	Me_3SiCl	Me_3Si	**8d** (82)
5	Ph_2CO	$Ph_2C(OH)$	**8e** (84)
6	Me_2CO	$Me_2C(OH)$	**8f** (71)
7	PhCHO	PhCH(OH)	**8g** (32)
8	*trans*-Chalcone	PhCH=CHC(OH)Ph	**8h** (43)

[a] Isolated yield.



(i) (a) *p*-TSA in CH_3CN, reflux, (b) TBAF in THF, reflux; (ii) Lithium naphthalenide in THF, Ph_2CO, -78 °C.

Scheme 2.

substitution with a range of electrophiles gave *N*-(ethynyl)benzotriazoles **8a–h**.

2. Results and discussion

Reaction of 1-formylbenzotriazole with PPh_3 and CCl_4 under Corey–Fuchs conditions[6] gave 1-(2,2-dichlorovinyl)-benzotriazole (**7**) in 68% yield as a crystalline solid. The ^1H NMR spectrum of **7** showed the vinylic proton at 7.69 ppm as a singlet, and the ^{13}C NMR spectrum showed the disappearance of the carbonyl signal at 159.7 ppm and the appearance of additional signals at 125.1 and 121.5 ppm due to the vinylic moiety. Subsequent treatment of **7** with 2 equiv of *n*-BuLi at −78 °C in THF for 1 h and reaction with a variety of electrophiles gave the corresponding *N*-(ethynyl)benzotriazoles **8a–h** in good yields (Table 1).

1-(2,2-Dichlorovinyl)benzotriazole (**7**) and *N*-(ethynyl)-benzotriazoles **8a–h**, except **8b**, are novel compounds and were characterized by their ^1H and ^{13}C NMR spectra and elemental analysis. As expected, the ^1H NMR spectra of *N*-(ethynyl)benzotriazoles **8a–h** revealed the disappearance of the vinylic proton at 7.69 ppm and appearance of additional signals from the newly attached substituent. In the ^{13}C NMR spectra, the signals from vinylic carbons at 121.5 and 125.1 ppm were replaced by new signals corresponding to the acetylenic carbons. The signals from benzotriazolyl moiety in all of the benzotriazolylacetylenes **8a–h** experienced a negligible change in the chemical shift values from those in the ^1H and ^{13}C NMR spectra of the precursor 1-(2,2-dichlorovinyl)benzotriazole (**7**).

Treatment of **8b**,**c** with *p*-toluenesulfonic acid followed by hydrolysis using TBAF gave carboxylic acids **9a**,**b** in 48 and 56% yields, respectively. Also, reaction of **8b** with benzophenone in presence of lithium naphthalenide furnished propargyl alcohol **10a** in 41% yield (Scheme 2).

In summary, a general method has been introduced for a short synthesis of functionalized *N*-(ethynyl)benzotriazoles starting from commercially available 1-formylbenzotriazole in overall two steps. It has also been shown that functionalized *N*-(ethynyl)benzotriazoles can be used to prepare carboxylic acids and propargyl alcohols.

3. Experimental

3.1. General

Melting points are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^1H and chloroform-*d* for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. THF was distilled from sodium/benzophenone prior to use. All of the reactions were carried out under N_2. Column chromatography was performed on silica gel 200–425 mesh.

1-Formylbenzotriazole was prepared according to the published procedure.[7]

3.1.1. Procedure for the preparation of 1-(2,2-dichlorovinyl)-1*H*-1,2,3-benzotriazole (7). 1-Formylbenzotriazole (1.0 g, 6.80 mmol) and PPh_3 (5.35 g, 20.4 mmol) were dissolved in THF (70 mL). Carbon tetrachloride (7 mL, 68 mmol) was added slowly at 60 °C and the mixture was heated under reflux for 6 h. After stirring for an additional hour, the mixture was diluted with ethyl acetate. Aqueous work-up with satd $NaHCO_3$ and purification by flash column chromatography on silica gel using hexanes–EtOAc (9.5/0.5) as eluent afforded **7** (1.0 g, 68%).

3.1.1.1. 1-(2,2-Dichlorovinyl)-1*H*-1,2,3-benzotriazole (7). Yellow microcrystals (from hexanes); mp 88–90 °C; yield, 68%; ^{1}H NMR δ 7.43–7.48 (m, 1H), 7.53–7.62 (m, 2H), 7.69 (s, 1H), 8.12 (d, J=8.4 Hz, 1H); ^{13}C NMR δ 110.1, 120.4, 121.5, 124.7, 125.1, 128.6, 132.2, 145.2. Anal. Calcd for $C_8H_5Cl_2N_3$: C, 44.89; H, 2.35; N, 19.63. Found: C, 45.09; H, 2.25; N, 19.28.

3.1.2. General procedure for the preparation of benzotriazolylacetylenes 8a–h by lithiation–electrophilic substitution of 7. To a solution of **7** (0.22 g, 1 mmol) in dry THF (20 mL) at −78 °C, was added *n*-BuLi (1.33 mL, 2.1 mmol, 1.6 M). The mixture was stirred at −78 °C for 1 h and an appropriate electrophile (1.0 mmol) was added. The reaction mixture was allowed to warm to 25 °C and quenched by adding water. Aqueous work-up and purification by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent afforded **8a**–**h**.

3.1.2.1. 1-Ethynyl-1*H*-1,2,3-benzotriazole (8a). Yellow prisms (from hexanes); mp 71–72 °C; yield, 73%; ^{1}H NMR δ 3.86 (s, 1H), 7.44–7.49 (m, 1H), 7.61–7.69 (m, 2H), 8.11 (d, J=8.4 Hz, 1H); ^{13}C NMR δ 68.6, 69.4, 109.9, 120.5, 125.4, 129.6, 134.2, 143.6. Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 66.76; H, 3.39; N, 29.67.

3.1.2.2. 1-(1-Propynyl)-1*H*-1,2,3-benzotriazole (8b).[3b] Colorless oil; yield, 84%; ^{1}H NMR δ 2.22 (s, 3H), 7.38–7.43 (m, 1H), 7.54–7.64 (m, 2H), 8.06 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 3.4, 66.7, 76.2, 109.8, 120.0, 124.8, 128.8, 134.1, 143.5.

3.1.2.3. 1-(1-Butynyl)-1*H*-1,2,3-benzotriazole (8c). White microcrystals (from hexanes); mp 44 °C; yield, 58%; ^{1}H NMR δ 1.35 (t, J=7.5 Hz, 3H), 2.61 (q, J=7.5 Hz, 2H), 7.41–7.46 (m, 1H), 7.57–7.68 (m, 2H), 8.09 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 12.4, 13.5, 67.3, 81.7, 110.0, 120.3, 125.0, 129.0, 134.3, 143.7. Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30. Found: C, 70.48; H, 5.65.

3.1.2.4. 1-[2-(Trimethylsilyl)ethynyl]-1*H*-1,2,3-benzotriazole (8d). Yellow oil; yield 82%; ^{1}H NMR δ 0.48 (s, 9H), 7.50–7.62 (m, 1H), 7.68–7.86 (m, 2H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (major peaks) δ −0.4, 83.6, 87.3, 110.0, 120.3, 125.2, 129.3, 134.0, 143.5. HRMS calcd for $C_{11}H_{14}N_3Si$ $[M+H]^+$216.0952, found: 216.0956.

3.1.2.5. 3-(1*H*-1,2,3-Benzotriazol-1-yl)-1,1-diphenyl-2-propyn-1-ol (8e). White needles (from EtOAc/hexanes); mp 125–126 °C; yield, 84%; ^{1}H NMR δ 3.72 (s, 1H), 7.30–7.39 (m, 7H), 7.42–7.58 (m, 2H), 7.69–7.71 (m, 4H), 8.02 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 74.0, 74.8, 82.9, 109.9, 120.3, 125.3, 126.0, 128.0, 128.4, 129.4, 134.2, 143.5, 144.0. Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.29; H, 4.69; N, 12.82.

3.1.2.6. 4-(1*H*-1,2,3-Benzotriazol-1-yl)-2-methyl-3-butyn-2-ol (8f). Light yellow oil; yield, 71%; ^{1}H NMR δ 1.75 (s, 3H), 1.76 (s, 3H), 2.90 (s, 1H), 7.42–7.46 (m, 1H), 7.47–7.65 (m, 2H), 8.09 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 31.3, 65.6, 69.7, 84.4, 110.0, 120.5, 125.3, 129.4, 134.2, 143.8. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.38; H, 5.53; N, 20.63.

3.1.2.7. 3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenyl-2-propyn-1-ol (8g). Light yellow oil; yield, 32%; ^{1}H NMR δ 3.61 (s, 1H), 5.91 (s, 1H), 7.35–7.44 (m, 4H), 7.53–7.66 (m, 4H), 8.05 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 64.6, 73.2, 80.2, 110.0, 120.4, 125.4, 126.6, 128.7, 128.8, 129.5, 134.1, 139.5, 143.6. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45. Found: C, 72.21; H, 5.03.

3.1.2.8. (*E*)-5-(1*H*-1,2,3-Benzotriazol-1-yl)-1,3-diphenyl-1-penten-4-yn-3-ol (8h). White microcrystals (from hexanes); mp 138–140 °C; yield, 43%; ^{1}H NMR δ 3.34 (br s, 1H), 6.52 (d, J=15.8 Hz, 1H), 7.07 (d, J=15.8 Hz, 1H), 7.23–7.45 (m, 9H), 7.50–7.62 (m, 2H), 7.77–7.80 (m, 2H), 8.10 (d, J=8.2 Hz, 1H); ^{13}C NMR δ 73.3, 74.3, 81.3, 110.0, 120.5, 125.4, 125.7, 127.0, 128.2, 128.4, 128.6, 128.6, 129.6, 130.0, 131.8, 134.3, 135.7, 142.5, 143.8. HRMS calcd for $C_{23}H_{17}N_3ONa$ $[M+Na]^+$372.1264, found: 374.1272.

3.1.3. General procedure for the preparation of carboxylic acids 9a,b. To a solution of **8b**,**c** (1 mmol) in acetonitrile (10 mL) was added *p*-toluenesulfonic acid monohydrate (0.20 g, 1 mmol) at room temperature. The reaction mixture was stirred under reflux for 8 h. The resulting mixture was concentrated in vacuo to dryness and the residue was treated with TBAF (1.2 mL, 1.2 mmol, 1 M) in THF (10 mL) under reflux for 10 h. The reaction mixture was diluted with diethyl ether and washed with 1 N HCl. Evaporation of the solvent gave a residue, which was purified by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent to give **9a**,**b**.

3.1.3.1. Propionic acid (9a).[8] Colorless oil; yield, 48%; ^{1}H NMR δ 1.16 (t, J=7.6 Hz, 3H), 2.39 (q, J=7.6 Hz, 2H), 10.9 (br s, 1H); ^{13}C NMR δ 8.8, 27.4, 181.0.

3.1.3.2. *n*-Butyric acid (9b)[9] Colorless oil; yield, 56%; ^{1}H NMR δ 0.98 (t, J=7.4 Hz, 3H), 1.61–1.73 (m, 2H), 2.34 (t, J=7.3 Hz, 2H), 11.0 (br s, 1H); ^{13}C NMR δ 13.6, 18.1, 35.9, 180.2.

3.1.4. Procedure for the preparation of propargyl alcohol 10a. A mixture of lithium powder (0.070 g, 10 mmol) and naphthalene (1.28 g, 10 mmol) in THF (20 mL) was stirred at 25 °C until a dark green color appeared. The suspension of lithium naphthalenide thus formed was cooled to −78 °C and **8b** (0.35 g, 2.1 mmol) was added. The reaction mixture was stirred at −78 °C for

2 h before adding benzophenone (0.36 g, 2.1 mmol). The mixture was allowed to warm to 25 °C and stirred overnight. Aqueous work up followed by flash column chromatography on silica gel using hexanes–EtOAc (9/1) as eluent gave **10a**.

3.1.4.1. 1,1-Diphenyl-2-butyn-1-ol (10a)[10] Colorless oil; yield, 41%; ^{1}H NMR δ 1.93 (s, 3H), 2.81 (s, 1H), 7.19–7.32 (m, 6H), 7.57–7.60 (m, 4H); ^{13}C NMR δ 3.8, 74.4, 82.1, 83.6, 126.0, 126.8, 127.4, 128.1, 128.2, 128.3, 128.5, 129.3, 129.5, 145.4.

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Thermal cyclization of 1,2-dialkynylimidazoles to imidazo[1,2-*a*]pyridines

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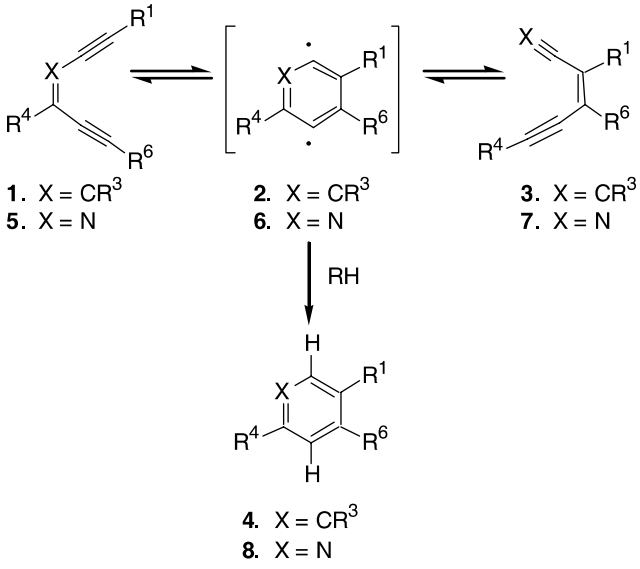
Abstract—Thermolysis of 1,2-dialkynylimidazoles in chlorinated solvents leads to 5-chloroimidazo[1,2-*a*]-pyridine products, which are also formed in DMF containing 1 equiv of HCl. Deuterium labeling of the starting dialkynylimidazoles indicates that reaction may proceed by multiple pathways, depending upon conditions and substituents. Dialkynylimidazoles can also give rise to 5-diethylamino-substituted imidazopyridines when the thermolysis is carried out in the presence of diethylamine.

1. Introduction

The enediyne structural moiety (**1**, Scheme 1) is present in several naturally occurring anticancer antibiotics like calicheamicin,[1] dynemicin A[2] and C-1027.[3] A Bergman cyclization[4] of these enediynes generates 1,4-benzenoid diradicals (**2**, Scheme 1) that abstract hydrogen atoms from the sugar-phosphate backbone of DNA (**2**→**4**, Scheme 1) thus inducing DNA cleavage and cell death.[5] The isolation of the enediyne antitumor antibiotics has led to a search for alternative diradical-generating cyclizations that might be incorporated in the design of improved DNA-cleavage agents.[6] This search has led to the examination of aza-enediynes, or *C*,*N*-dialkynyl imines (**5**, Scheme 1) as potential precursors of 2,5-didehydropyridine diradicals (**6**, Scheme 1).[7]

The incorporation of an *N*-alkynylimine (ynimine) moiety in the aza-enediynes **5** has a profound effect on their cyclization chemistry. First, the cyclization barrier for aza-enediynes is substantially lower than for comparable enediynes, such that sterically unencumbered aza-enediynes undergo cyclization at room temperature and below.[7] Second, whereas the Bergman cyclization of hex-3-ene-1,5-diyne in the absence of hydrogen atom donors is thermoneutral (i.e., **1**→**3**, R^1–R^6=H), the aza-Bergman rearrangement of aza-enediynes to β-alkynylacrylonitriles (**5**→**7**) is exothermic by ca. 40 kcal/mol.[7] This



Scheme 1. Bergman cyclization of enediynes and aza-Bergman cyclization of aza-enediynes.

thermochemical driving force is accompanied by a very low kinetic barrier for the collapse of 2,5-didehydropyridine **6** to nitrile **7**.[7,8] As a result, the elusive 2,5-didehydropyridine intermediate **6** derived from aza-Bergman cyclization of aza-enediynes **5** does not enter into hydrogen atom abstraction or radical cyclization reactions; despite some effort,[7,8,9,10] there has been no success in trapping **6** to give pyridine-containing products **8** from the thermolysis of aza-enediynes under neutral conditions. Based on computational studies, it has been proposed that the didehydropyridine

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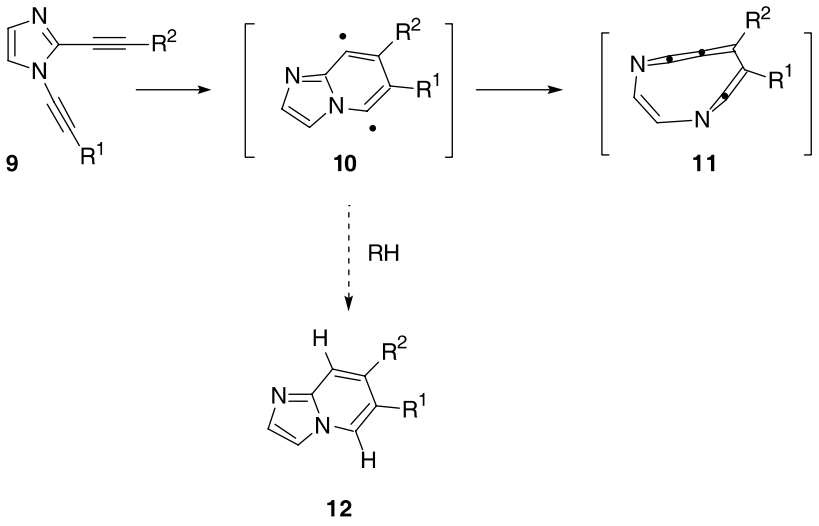


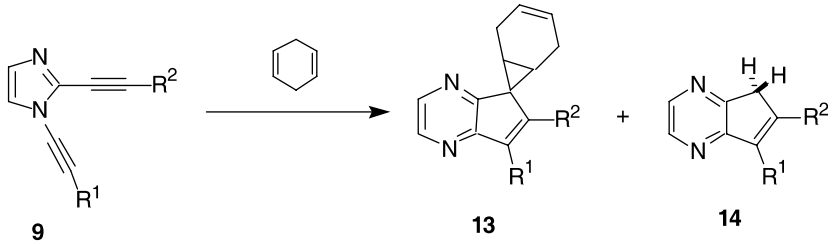
Scheme 2. Proposed aza-Bergman cyclization of 1,2-dialkynylimidazoles.

intermediate **6** derived from these aza-enediynes is selectively reactive only under acidic conditions,[8] such as occur in tumor tissue. This increased reactivity is due to an increase in the barrier for collapse of the protonated didehydropyridine, along with a more favorable singlet–triplet gap for this diradical.[10,11] However, the reactivity of the ynimine functionality of aza-enediynes can preclude this approach to trap **6**. Under aqueous acidic conditions, aza-enediyne **5** ($R^1=R^4=$Ph, $R^6=$H) undergoes addition of water across the ynimine triple bond. The resulting *N*-acyl-*C*-alkynylimine cyclizes to an oxazolyl carbene.[9]

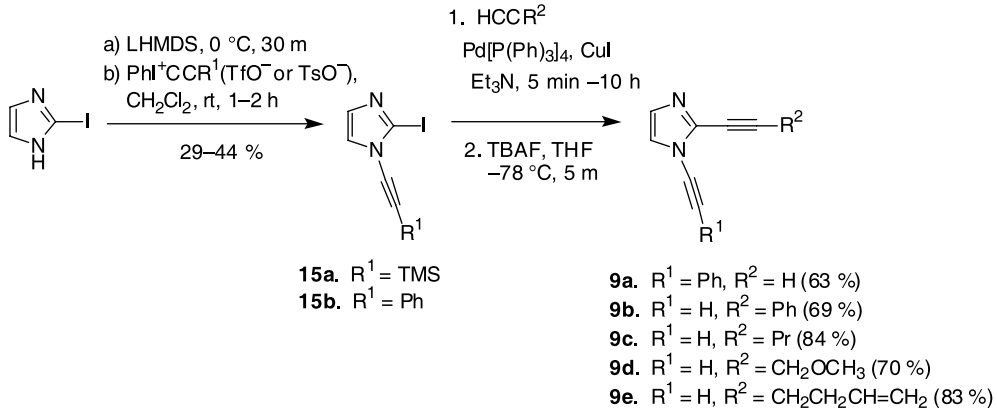
In our continuing studies of aza-Bergman cyclizations, we considered the previously unknown 1,2-dialkynyl imidazoles (**9**, Scheme 2) as heterocyclic aza-enediyne analogs.[12] It was presumed that aza-Bergman cyclization of these aza-enediyne analogs would give rise to 5,8-didehydroimidazo[1,2-*a*]pyridine intermediates **10**, collapse of which to **11** (Scheme 2) would be disfavored relative to the facile collapse of didehydropyridines **6** to nitriles **7** (Scheme 1). Trapping of **10** by hydrogen atom abstraction, perhaps facilitated by protonation as in the case of aza-enediynes, would lead to the imidazopyridines **12** (Scheme 2). In addition to these considerations, the dialkynylimidazoles might have other advantages over simple acyclic aza-enediynes, such as increased hydrolytic stability and enforcement of the desired stereochemical arrangement of the alkyne groups, resulting from formal replacement of the imine functionality with the imidazole ring.

Despite these predictions, initial studies of the thermolysis of these dialkynylimidazoles did not lead to imidazopyridine products. Instead, mild thermolysis (75–100 °C) of **9** (R^1 or $R^2=$H) in 1,4-cyclohexadiene led to the isolation of cyclopentapyrazines **13** and **14** (Scheme 3),[12,13] both presumably arising from the corresponding cyclopentapyrazine carbene. The cyclization of disubstituted dialkynylimidazoles (e.g., **9**, $R^1=R^2=$Ph) required more forcing conditions, and did not afford isolable products.[12]

In this report, we present the results of studies that began as an effort to optimize reaction conditions for this fascinating rearrangement of dialknylimidazoles to cyclopentapyrazine carbenes, particularly in an effort to trap these carbenes in an intramolecular sense to afford polycyclic pyrazines.[14] Examining the effect of varying the solvent on this rearrangement led to the isolation of 5-chloroimidazo[1,2-*a*]-pyridine products from reactions carried out in a variety of chlorinated solvents. This cyclization of dialkynylimidazoles to 5-chloroimidazopyridines can also be accomplished in DMF containing HCl. While the transformation is general, there is a very pronounced substituent effect on both the rate of the reaction and the regiochemical outcome. We have employed deuterium labeling of the starting dialkynylimidazoles to provide insight into the mechanism of the transformation and these substituent effects. These studies indicate that reaction may proceed by multiple pathways, depending upon conditions and substituents. Finally, we note that dialkynylimidazoles can also give rise



Scheme 3. Formation of cyclopentapyrazines from 1,2-dialkynylimidazoles.



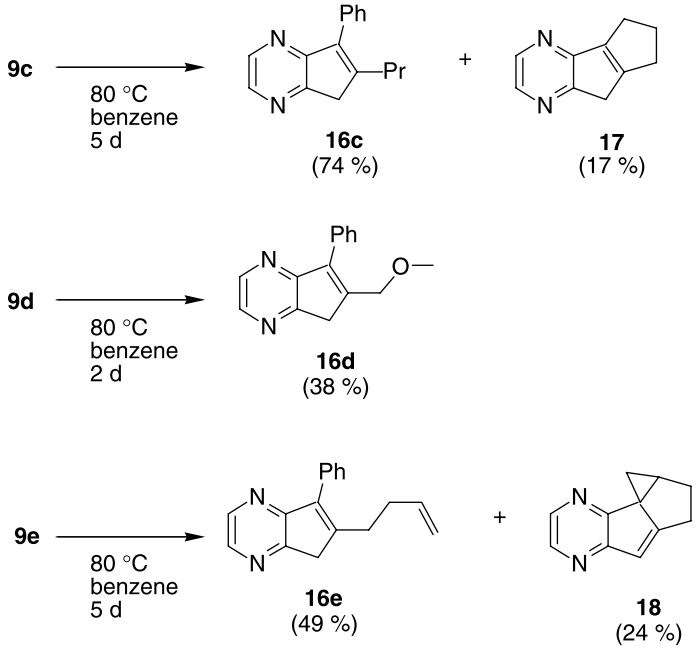
Scheme 4. Synthesis of 1,2-dialknylimidazoles.

to 5-(diethylamino)-substituted imidazopyridines when the thermolysis is carried out in the presence of diethylamine.

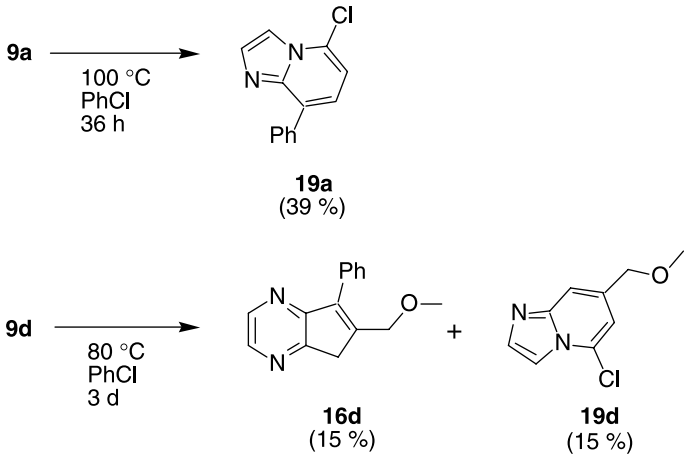
2. Results and discussion

Prior to embarking upon this exploration of thermal chemistry of dialkynylimines, we required the synthesis of these *N*-alkynyl heterocycles. A recent review on the synthesis of *N*-alkynyl heterocycles has appeared.[15] As there were no previous examples of *N*-alkynylimidazoles, we explored various routes to these *N*-alkynyl heterocycles.[12] We found that a variety of dialkynylimidazoles can be prepared by a two-step sequence (Scheme 4). In the first step, the lithium anion of the imidazole is allowed to react with an alkynyl iodonium tosylate or triflate to afford the *N*-alkynyl-2-iodoimidazoles **15a**,**b** in moderate yield. Subsequent Sonogashira[16] coupling of these 2-iodoimidazoles with a variety of terminal acetylenes proceeds in good yield. The desired mono-substituted dialkynylimidazoles are obtained after protodesilylation with TBAF during work-up (Scheme 4).

The dialkynylimidazoles **9c**–**e** contain substitutents that can participate in intramolecular carbene C–H insertion or olefin addition reactions. Thermolysis of these dialkynylimidazoles in benzene was expected to lead to polycyclic pyrazine products. In the event, modest yields of tricycle **17** and tetracycle **18** were obtained, along with the products of formal benzene C–H insertion by the carbene (**16c**–**e**), which were the major products in all cases (Scheme 5).[14] The propensity of the carbene derived from these dialkynylimidazoles to undergo addition to benzene led us to explore alternative solvents for these intramolecular trapping reactions. While we eventually found that **17** and **18** can be obtained as the major products in high yield from thermolyses carried out in hexafluorobenzene,[14] products apparently derived from an alternative cyclization mode were observed from thermolyses carried out in chlorinated solvents.



Scheme 5. Thermolysis of 1,2-dialkynylimidazoles in benzene leads to inter- and intramolecular carbene trapping products.



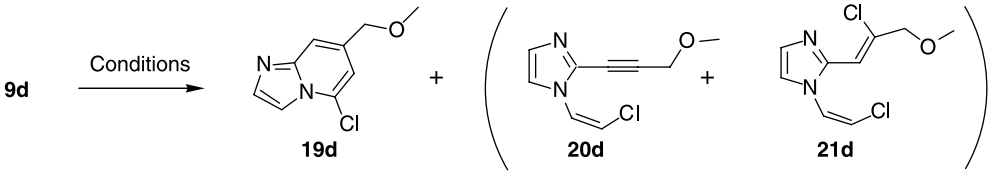
Scheme 6. Thermolysis of 1,2-dialkynylimidazoles in chlorobenzene.

In a previous communication, we reported that thermolysis of **9a** in chlorobenzene afforded the 5-chloroimidazopyridine **19a** (Scheme 6).[12] Examination of the structure of chloroimidazopyridine **19a** reveals that it is not related to the potential intermediate 5,8-didehydroimidazopyridine **10** (Scheme 2) through any straight-forward process, such as hydrogen- and chlorine-atom abstraction from chlorobenzene solvent. The 5-chloroimidazopyridine **19d**, which could be formed from intermediate **10** through chlorine- and hydrogen-atom abstraction, was obtained from thermolysis of **9d** in chlorobenzene, along with the phenyl substituted cyclopentapyrazine **16d** (Scheme 6), the same product obtained in benzene as solvent (Scheme 5). No products of intramolecular C–H insertion were observed. The structures of both **19a** and **19d** were assigned based upon 2D NMR (COSY, NOESY, and HMBC) experiments.

Due to the wide-spread interest in imidazo[1,2-*a*] pyridines[17,18] and the interesting mechanistic implications of the formation of **19a**,**d** from dialkynylimidazoles **9a**,**d**, we set out to optimize the conditions for this cyclization starting with dialkynylimidazole **9d** (Table 1). Thermolysis of **9d** in a variety of chlorinated solvents (chlorobenzene, dichloromethane, 1,2-dichloroethane) affords chloroimidazopyridine **19d** in moderate yield (entries 1–3), with the best yields obtained in 1,2-dichloroethane. With the exception of chlorobenzene, in which the cyclopentapyrazine **16d** is also produced, no other products were observed in ^{1}H NMR spectra of the reaction mixtures prior to chromatographic purification. The remainder of the reaction mixture was a polar, tarry material, presumably polymeric.

In order to address the potential role of HCl generated from these chlorinated solvents in the cyclization, reactions were performed in the presence of added excess tetramethylammonium chloride and trifluoroacetic acid in dichloromethane (entry 4). Although this reaction proceeded to completion more quickly than those performed in the absence of added proton and chloride ion sources, no imidazopyridine product was obtained; instead, the *N*-(2-chlorovinyl)imidazoles **20d** and **21d** were isolated. The (*Z*)-stereochemistry of the *N*-(2-chlorovinyl)groups of **20d** and **21d** was assigned based on the observed ^{1}H NMR coupling constants for the vinylic protons, and, in the case of **21d**, NOESY data, which also confirmed the (*Z*)-stereochemical arrangement of the 2-(2-chloro-3-methoxypropenyl)substituent. Although contrary to the normal regiochemistry of ynamine additions, the addition of nucleophiles to the 2-position of *N*-ethynylpyrrole[19] and *N*-alkynylbenzotriazoles[20] is known. In the latter case, the stereochemistry of the addition is also the same that we observe here, leading to exclusively the (*Z*)-isomers.

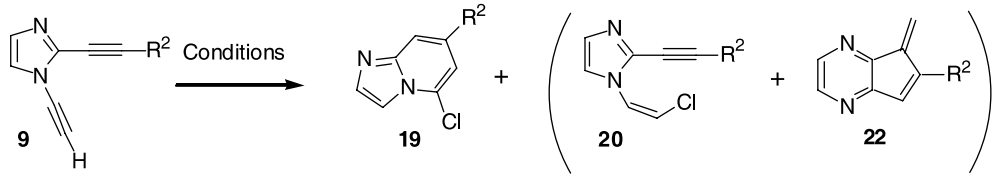
Table 1. Optimization of the cyclization of dialkynylimidazole **9d**



Entry	Reaction conditions	Yield of **19d** [a]	Other products (yield)[a]
1	PhCl, 80 °C, 3 days	15%	**16d** (15%)
2	CH_2Cl_2, 80 °C, 4 days	19%	nd[b]
3	$Cl(CH_2)_2Cl$, 80 °C, 4 days	31%	nd[b]
4	Me_4NCl (3 equiv), TFA (3 equiv), CH_2Cl_2, 80 °C, 12 h	nd[b]	**20d** (10%), **21d** (36%)
5	HCl_{aq} (1.2 equiv) DMF, 80 °C, 14 h	64%	**20d** (9%)
6	HCl_{aq} (4 equiv), DMF, 80 °C,12 h	nd[b]	**21d** (84%)
7	Me_4NCl (1 equiv), TFA (1 equiv), DMF, 80 °C, 4 h	71%	**20d** (8%)

[a] Isolated yield.
[b] Not detected.

Table 2. Cyclization of dialkynylimidazoles under various reaction conditions



Entry	Series	R^2	Reaction conditions		
			CH_2Cl_2, 80 °C	HCl_{aq} (1 equiv), DMF, 80 °C	Me_4NCl (1 equiv), TFA (1 equiv), DMF, 80 °C
			Product (yield)		
1	**b**	Ph	**19b** (18%)[a], **22b** (7%)[a]	**20b** (69%)[b]	nd
2	**c**	Pr	**19c** (12%)[c], **22c** (14%)[c]	**19c** (14%)[d], **20c** (56%)[d]	**19c** (35%)[e], **20c** (40%)[e]
3	**d**	CH_2OCH_3	**19d** (19%)[f]	**19d** (64%)[g], **20d** (9%)[g]	**19d** (71%)[h], **20d** (8%)[h]

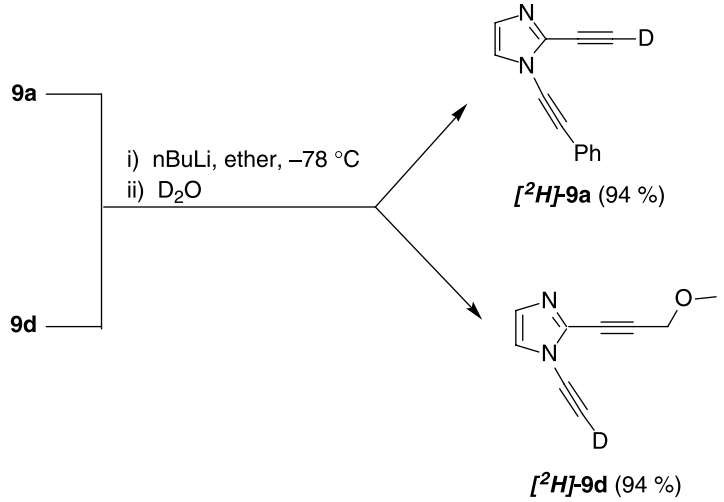
[a] Reaction time=31 days.
[b] Reaction time=68 h.
[c] Reaction time=31 days.
[d] Reaction time=56 h.
[e] Reaction time=56 h.
[f] Reaction time=4 days.
[g] Reaction time=14 h.
[h] Reaction time=4 h.

Good yields of **19d** are obtained from reactions carried out with 1 equiv of HCl (entry 5) or 1 equiv each of tetramethylammonium chloride and trifluoroacetic acid (entry 7) in DMF; however, excess HCl in DMF leads again to the formation of the *N*-chlorovinylimidazole **21d** (entry 6), which is obtained in high yield under these conditions.

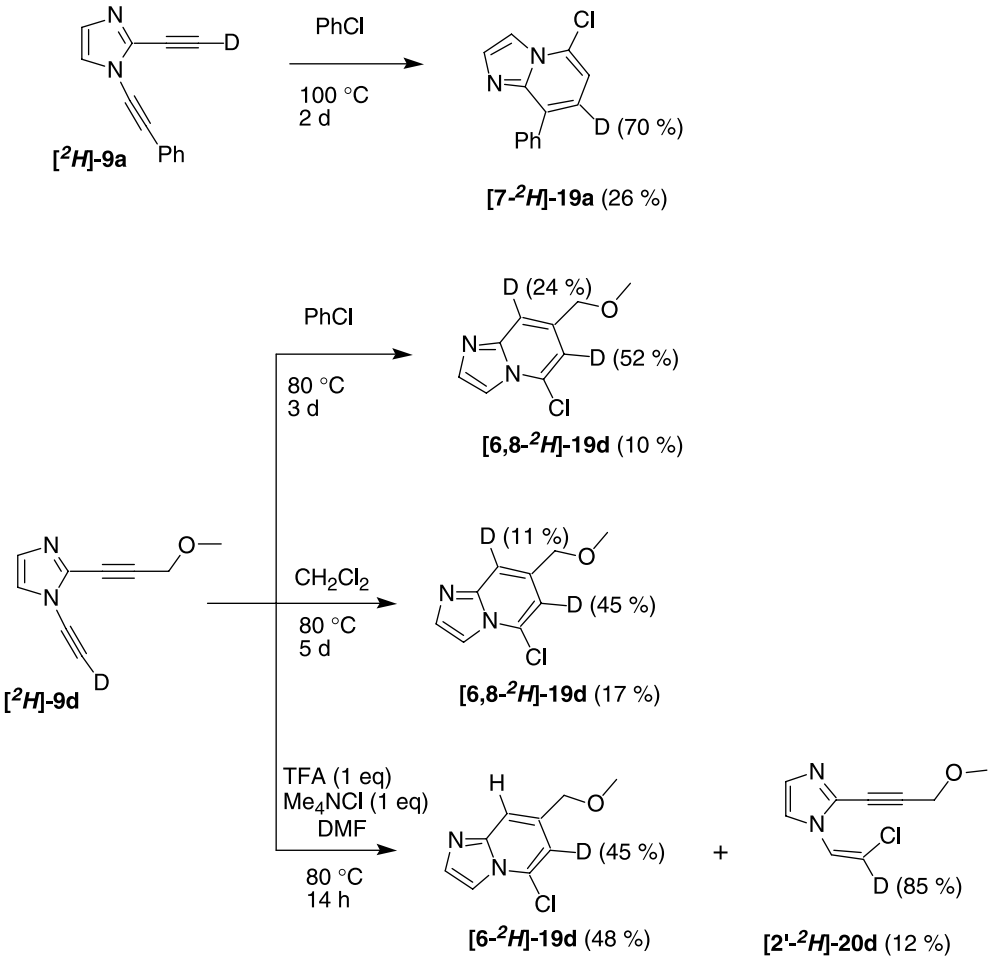
In order to examine the generality of the cyclization of dialkynylimidazoles to chloroimidazopyridines, two additional dialkynylimidazoles were subjected to the optimized cyclization reactions conditions in DMF and thermolysis in dichloromethane (Table 2). The phenyl-substituted analog **9b** affords only the *N*-chlorovinylimidazole **20b** in DMF containing 1 equiv of HCl, and a mixture of chloroimidazopyridine **19b** and the methylenylcyclopentapyrazine **22b** in dichloromethane (entry 1). In both cases, the reaction times were excessive, up to 31 days for the case of thermolysis in dichloromethane. Similarly, the reaction times required for consumption of the propyldialkynylimidazole **9c** were also very long (entry 2), but moderate yields of chloroimidazopyridine **19c** were obtained in DMF, accompanied by the *N*-chlorovinylimidazole **20c**, which was the major product. Thermolysis of **9c** in dichloromethane eventually afforded low yields of the **19c** and the methylenylcyclopentapyrazine **22c** (entry 2).

From the above results, it is apparent that the dialkynylimidazole substituents affect both the facility and efficiency of the cyclization to chloroimidazopyridines. In order to probe this effect in more detail, and to provide some insight into the mechanism of this transformation, the deuterated dialkynylimidazoles [^2H]-**9a** and [^2H]-**9d** were prepared (Scheme 7). Deprotonation of the dialkynylimidazoles with *n*-BuLi in ether followed by D_2O quench afforded these deuterated dialkynylimidazoles in good yield and isotopic purity of >95%, as determined by ^1H NMR.

Thermolysis of [^2H]-**9a** in chlorobenzene afforded the deuterated chloroimidazopyridine **19a** with 70% isotopic

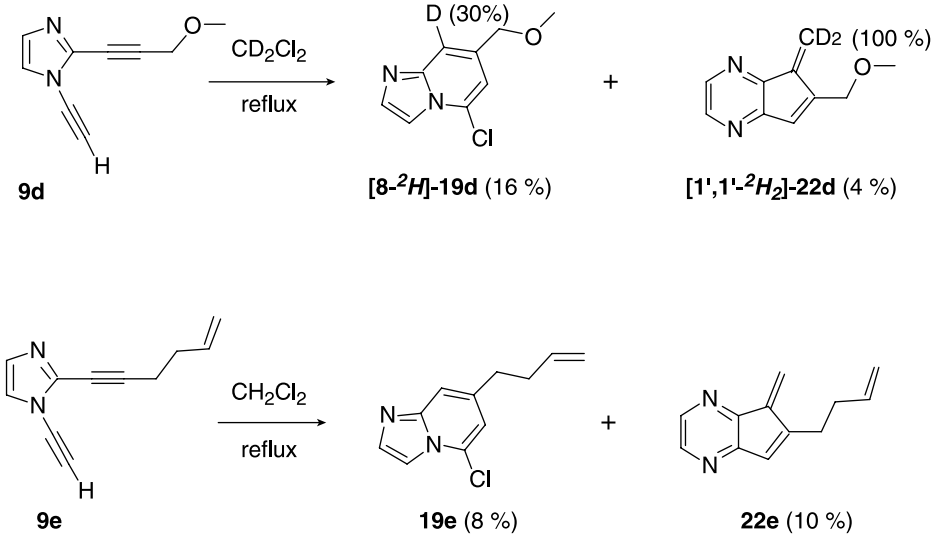


Scheme 7. Preparation of deuterated 1,2-dialkynylimidazoles.

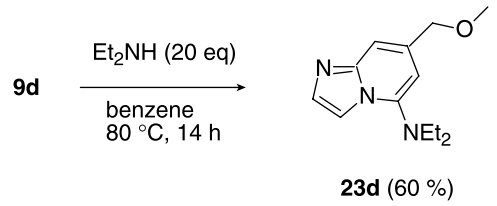


Scheme 8. Thermolysis of deuterated 1,2-dialkynylimidazoles.

label at the 7-position (Scheme 8). In contrast, thermolysis of [^2H]-**9d** in chlorobenzene leads to the isolation of chloroimidazopyridine **19d** in which the deuterium label is both at the 6- (major) and 8- (minor) positions (Scheme 8). A similar result is obtained when [^2H]-**9d** is subjected to thermolysis in dichloromethane. This is not the case for cyclization of [^2H]-**9d** in DMF in the presence of tetramethylammonium chloride and TFA, which leads to chloroimidazopyridine with deuterium label only at the 6-position, along with the deuterated-*N*-(2-chlorovinyl)imidazole. There is significant loss of deuterium label in all these cases, particularly in the case of chloroimidazopyridine **19d** from cyclization in DMF.



Scheme 9.

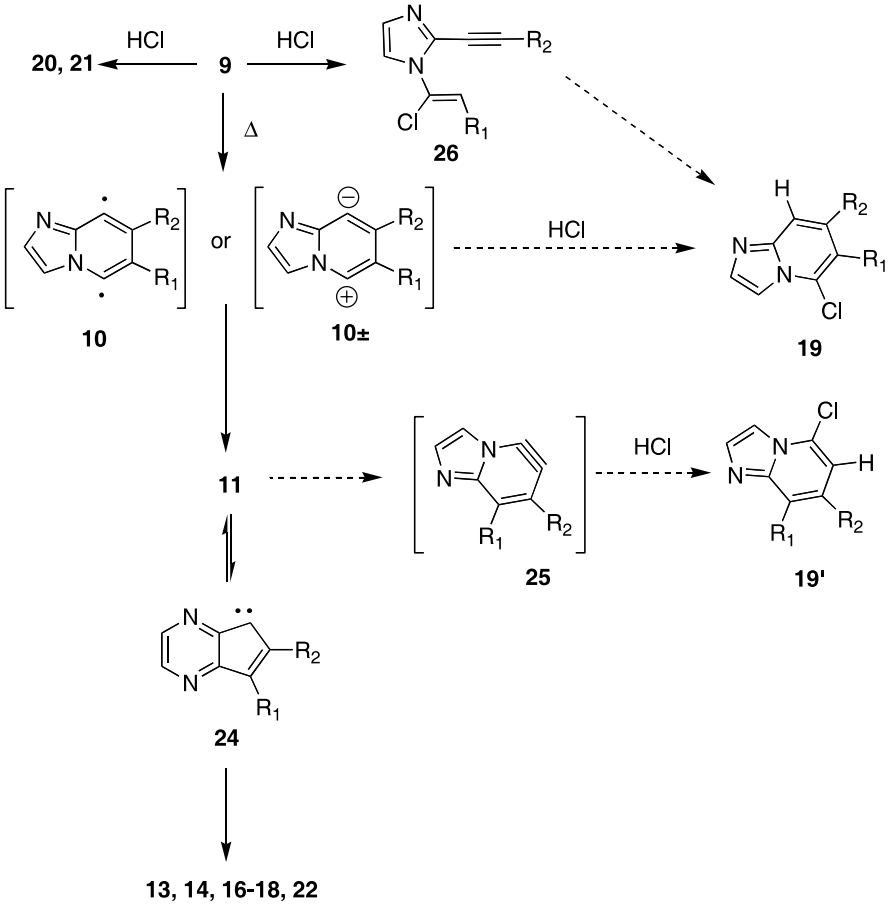


Scheme 10.

These deuterium labeling results reflect a difference in the cyclization of **9b** when compared to **9d** in chlorinated solvents, as well as a difference in the cyclization carried out in chlorinated solvents versus that in DMF in the presence of acid and chloride ion. The deuterium label originating from the 2-ethynyl substituent of [^2H]-**9a** is found exclusively at the 7-position in the product imidazopyridine; however, in no case did we observe products derived from dialkynylimidazoles in which an alkyl or aryl substituent from the 2-alkynyl moiety of the imidazole was found at the imidazopyridine 7-position. This indicates that either there is a regiospecific migration of the deuterium in [^2H]-**9a** to the 7-position of the product that does not occur for non-hydrogen substituents, or there are two different pathways involved in this cyclization—the pathway leading to [7-^2H]-**19a** from [^2H]-**19a**, which also accounts for the minor 8-deuterated products derived from [^2H]-**9d**, and a separate pathway leading to [6-^2H]-**19d** from [^2H]-**9d**. If this is the case, it is the later pathway that predominates in the cyclization of [^2H]-**9d** carried out in DMF. It is interesting to note that this pathway can be rationalized by the trapping of aza-Bergman cyclization product **10**, as the closed-shell, zwitterionic form, by HCl, although there are other mechanistic schemes that also account for these results (see below).

We also carried out the thermolysis of **9d** in deuterated dichloromethane (Scheme 9). In this case, the product imidazopyridine contains deuterium only at the 8-position, although the efficiency of deuterium incorporation is low. We also isolated a small amount of the methylenylcyclopentapyrazine **22d** in which the exocyclic methylene group was deuterated. In order to address the potential role of diradical **10** (Scheme 2) in these cyclization reactions, the butenyl analog **9e** was also subjected to thermolysis in dichloromethane. No products corresponding to radical cyclization of diradical **10** onto the butenyl side chain were observed, instead, low yields of the chloroimidazopyridine **19e** and methylenylcyclopentapyrazine **22e** were isolated (Scheme 9).

Interestingly, this cyclization of dialkynylimidazoles to imidazopyridines is also observed when a benzene solution of **9d** is heated in the presence of excess diethylamine, which affords the 5-(diethylamino)imidazopyridine **23b** in good yield (Scheme 10). However, under the same reaction conditions, no imidazopyridines were obtained from **9a–c**. Analysis of the crude reaction products in these cases demonstrated that the exclusive products were those of diethylamine addition to the *N*-alkynyl substituents.



Scheme 11.

The resulting enamines were unstable to chromatographic purification and were not isolated.

We have previously proposed a mechanism for the formation of the cyclopentapyrazine carbene **24** via cyclization of the cyclic cumulene **11**, which is derived from the dialkynylimidazole **9** by collapse of the aza-Bergman cyclization intermediate **10** (Scheme 11).[12,13] Perhaps the most striking mechanistic observation about the cyclization of dialkynylimidazoles to imidazo[1,2-*a*]-pyridines is that while certain products (**19** in Scheme 11) can be formally derived from trapping of **10**, or its corresponding zwitterion **10**$\pm$ (e.g., **19b–e**), other products (e.g., **19a**) cannot. Instead, these products (**19′** in Scheme 11) appear to be derived from a 5,6-didehydroimidazo-pyridine intermediate[12,13] (**25**, Scheme 11). Deuterium labeling studies support this distinction, in that the 2-ethynyl substituent of [^2H]-**9a** (R_2=D) maps to the imidazopyridine 7-position. While **19b–e** might also be derived from the same 5,6-didehydroimiazolopyridine intermediate, the deuterium labeling studies with [^2H]-**9d** map the *N*-ethynyl substituent (R^1=D) predominantly to the imidazopyridine 6-position, which is commensurate with either trapping of intermediate **10**$\pm$, or addition of HCl to the *N*-alkynyl substituent in the 'normal' ynamine regiochemical sense to give **27**, followed by cyclization (Scheme 11). In the presence of excess HCl, addition to the *N*-ethynyl substituent occurs in the opposite regiochemical sense to afford the β-chloroenamines **20** and **21** (Scheme 11). Some of the deuterium label of [^2H]-**9d** is found in the product imidazopyridine at the 8-position. This scrambling may simply reflect a competition between pathways involving **10**$\pm$ (or **27**) and the 5,6-didehydro intermediate **25**.

3. Conclusions

Dialkynylimidazoles **9** have been investigated as aza-enediyne analogs which, upon aza-Bergman cyclization, might lead to 5,8-didehydroimidazo[1,2-*a*]pyridine diradical intermediates **10** (Scheme 1). Previous work had shown that thermolysis of dialkynylimidazoles in cyclohexadiene or benzene led instead to products apparently derived from a cyclopentapyrazine carbene intermediate, which has been proposed[12,13] to be derived from the ring-opened form of **10** (Scheme 11). In an attempt to optimize this carbene-generating reaction for intramolecular cascade cyclizations, we have found that thermolysis of **9** in chlorinated solvents affords 5-chloroimidazo[1,2-*a*]pyridines, which can also be obtained from reactions carried out in DMF with 1 equiv of either aqueous HCl or trifluoroacetic acid and tetramethyl-ammonium chloride. In addition to providing access to these synthetically important halogenated imidazo-pyridines, this cyclization is mechanistically interesting due to the potential involvement of the diradical **10**, or its closed-shell, zwitterionic form.

In summary, the results presented here demonstrate the many-faceted chemistry of aza-enediynes such as 1,2-dialkynyl-imidazoles. Unlike enediyne chemistry, which is dominated by reactive diradicals derived from Bergman cyclization, no such reactive diradicals have been observed from thermal cyclization of aza-enediynes. In the case of dialkynylimidazoles, cyclization to imidazopyridine products is observed; however, the mechanism for this transformation is apparently complex, and further investigation is required.

4. Experimental

4.1. General

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. THF, ether, and benzene were distilled from sodium/benzophenone immediately prior to use. Dichloromethane and chlorobenzene were distilled from CaH_2 immediately prior to use. Diethylamine was distilled from CaH_2 and stored over KOH, and 1,4-cyclohexadiene was distilled immediately prior to use. DMF was dried over $CaSO_4$ overnight before distillation under reduced pressure. Unless otherwise noted, organic extracts were dried with Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 mmHg). R_f values are reported for analytical thin-layer chromatography (TLC) performed on EM Reagent 0.25 mm silica gel 60-F plates with UV light visualization. Flash chromatography was performed with EM Reagent silica gel (230–400 mesh) using the mobile phase indicated. Melting points (open capillary) are uncorrected. Unless otherwise noted, ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ on a spectrometer operating at 300 and 75 MHz, respectively, and are reported in ppm using solvent as internal standard (7.26 ppm for ^1H and 77.0 ppm for ^{13}C). All mass spectra were obtained in the positive mode by chemical ionization using methane as the ionizing gas.

4.2. General procedure for N-alkynylation

4.2.1. 2-Iodo-1-(2-(trimethylsilyl)ethynyl)-1*H*-imidazole 15a. To a solution of 2-iodoimidazole[21] (900 mg, 4.64 mmol) in 36 ml of dry THF at 0 °C was added LiHMDS (1 M in hexanes, 4.74 ml). After stirring at 0 °C for 30 min, the solution was transferred via cannula to a solution of 2-(trimethylsilyl)ethynyl(phenyl)iodonium trifluoromethanesulfonate[22] (3.2 g, 7.11 mmol) in 36 ml CH_2Cl_2. After stirring at room temperature for about 2 h, the solvent was removed in vacuo and the residue washed with H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (0–20% EtOAc/hexanes) to afford **15a** (585 mg, 44% yield) as a cream-colored solid: mp 84–86 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=2 Hz, 1H), 6.98 (d, J=1.6 Hz, 1H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 125.2, 94.1, 90.3, 77.9, −0.3; HRMS *m/z* 290.9814 (calculated 290.9816, $C_8H_{12}N_2SiI$).

4.2.2. 2-Iodo-1-phenylethynylimidazole 2b. Following the general procedure above, and using phenyl(phenylethynyl)-iodinium tosylate,[23] 135 mg (29% yield) of **2b** was obtained as a light yellow oil: ^1H NMR δ 7.07 (d, J=1.5 Hz, 1H), 7.32 (d, J=1.5 Hz, 1H), 7.36–7.41 (m, 3H), 7.54–7.57 (m, 2H); ^{13}C NMR δ 74.4, 78.5, 94.1, 120.8, 125.4, 128.5,

129.2, 131.6, 132.4; HRMS *m/z* 294.9743 (calculated 294.9732, $C_{11}H_8N_2I$).

4.3. General procedure for the preparation of 1,2-dialkynylimidazoles 9

In a glove box, a reaction flask was charged with **15a** (150 mg, 0.52 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol), and CuI (10 mg, 0.05 mmol). Dry Et_3N (7 ml) was added, and the terminal alkyne (0.6 mmol) was slowly added to the reaction mixture, which was heated to 50 °C for 15 min. The reaction mixture was filtered and the solid washed with Et_2O. The filtrate was evaporated, and the residue was purified by flash chromatography (0–10% EtOAc/hexanes) to afford the silylated dialkynylimidazole. To this material in THF (16 ml) at −78 °C was added a solution of TBAF (112 mg, 0.43 mmol) in THF, and the mixture was stirred at −78 °C for 5 min. The solvent was removed in vacuo and the residue purified by flash chromatography (0:30% EtOAc/hexanes) to afford the dialkynylimidazole **9**.

4.3.1. 2-Ethynyl-1-phenylethynyl-1*H*-imidazole (9a). Following the general procedure above, 17 mg of **9a** (63% yield) was obtained as a white solid: mp 107–108 °C; ^{1}H NMR δ 7.51–7.54 (m, 2H), 7.36–7.39 (m, 3H), 7.19 (d, J=1.5 Hz, 1H), 7.15 (d, J=1.5 Hz, 1H), 3.40 (s, 1H); ^{13}C NMR δ 134.5, 132.0, 129.9, 129.4, 128.8, 122.8, 121.2, 82.5, 77.3, 73.7, 72.2; HRMS *m/z* 193.0762 (calculated 193.0766, $C_{13}H_9N_2$).

4.3.2. 1-Ethynyl-2-(2-phenylethynyl)-1*H*-imidazole (9b). Following the general procedure above, 70 mg of **9b** (69% yield) was obtained as a white solid: mp 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 7.40–7.34 (m, 3H), 7.16 (d, J=1.6 Hz, 1H), 7.06 (d, J=1.6 Hz, 1H), 3.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 132.0, 129.7, 129.5, 128.4, 122.4, 121.1, 93.9, 77.2, 70.9, 61.9; HRMS *m/z* 193.0764 (calculated 193.0766, $C_{13}H_9N_2$).

4.3.3. 1-Ethynyl-2-(pent-1-ynyl)-1*H*-imidazole (9c). Following the general procedure above, 93 mg of **9c** (84% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J=1.6 Hz, 1H), 6.95 (d, J=1.6 Hz, 1H), 3.12 (s, 1H), 2.44, (t, J=7.2 Hz, 2H), 1.65 (quintet, J=7.2 Hz, 2H), 1.04 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 129.0, 121.7, 96.0, 71.1, 69.2, 61.3, 21.5, 21.2, 13.4; HRMS *m/z* 159.0928 (calculated 159.0922, $C_{10}H_{11}N_2$).

4.3.4. 1-Ethynyl-2-(3-methoxyprop-1-ynyl)-1*H*-imidazole (9d). Following the general procedure above, 111 mg of **9d** (70% yield) was obtained as a white solid: mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J=1.2 Hz, 1H), 7.01 (d, J=1.6 Hz, 1H), 4.36 (s, 2H), 3.45 (s, 3H), 3.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 129.7, 122.8, 90.4, 74.7, 70.9, 62.3, 60.1, 58.0; HRMS *m/z* 161.0708 (calculated 161.0715, $C_9H_9N_2O$).

4.3.5. 1-Ethynyl-2-hex-5-en-1-ynyl-1*H*-imidazole (9e). Following the general procedure above using hex-1-en-5-yne,[24] 57 mg (83% yield) of **9e** was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J=1.5 Hz, 1H), 6.94 (d, J=1.5 Hz, 1H), 5.87 (ddt, J=17.2, 10.4, 6.4 Hz, 1H), 5.10 (dq, J=16.8, 1.6 Hz, 1H), 5.03 (dq, J=10.2, 1.2 Hz, 1H), 3.12 (s, 1H), 2.54 (t, J=7.2 Hz, 2H), 2.36 (q, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.7, 129.1, 121.8, 116.1, 95.2, 71.0, 69.4, 61.4, 32.0, 19.1; HRMS *m/z* 171.0925 (calculated 171.0922, $C_{11}H_{11}N_2$).

4.4. General procedure for thermolysis of dialkynylimidazoles in benzene and chlorinated solvents

4.4.1. 7-Phenyl-6-propyl-5*H*-cyclopentapyrazine (16c) and 5,6,7,8-tetrahydropentaleno[2,1-*b*]pyrazine (17). A solution of **9c** (36 mg, 0.228 mmol) in benzene (7 ml) in a sealed vial purged with argon was heated for 5 days at 80 °C. Periodically, the reaction vial was allowed to cool, carefully opened under a stream of argon, sampled for TLC analysis, resealed and returned to the heating bath. Upon the disappearance of **9c** by TLC, the solvent was evaporated and the residue purified by flash chromatography (0–15% EtOAc/hexanes) to afford 40 mg (74% yield) of **16c** as a yellow oil and 6 mg (17% yield) of **17** as a tan solid. Compound **16c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J=2.5 Hz, 1H), 8.19 (d, J=3 Hz, 1H), 7.48–7.45 (m, 4H), 7.38–7.34 (m, 1H), 3.53 (d, J=0.5 Hz, 2H), 2.64 (t, J=7.5 Hz, 2H), 1.65 (sextet, J=7 Hz, 2H), 0.95 (t, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.2, 151.4, 141.9, 138.5, 138.2, 132.8, 129.3, 128.5, 127.7, 39.2, 31.7, 22.8, 14.2; HRMS *m/z* 237.1389 (calculated 237.1392, $C_{16}H_{16}N_2$). Compound **17**: mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=3.2 Hz, 1H), 8.11 (d, J=3.2 Hz, 1H), 3.33–3.32 (m, 2H), 2.80–2.72 (m, 4H), 2.43 (quintet, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 158.9, 155.8, 146.7, 141.0, 137.3, 38.3, 35.3, 30.8, 27.1; HRMS *m/z* 159.0918 (calculated 159.0922, $C_{10}H_{11}N_2$).

4.4.2. 6-Methoxymethyl-7-phenyl-5*H*-cyclopentapyrazine (16d). Following the general procedure above with **9d** in benzene, 18 mg (38% yield) of **16d** was obtained as a white-pink solid: mp 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J=2.8 Hz, 1H), 8.29 (d, J=3.2 Hz, 1H), 7.54–7.48 (m, 4H), 7.44–7.40 (m, 1H), 4.50 (s, 2H), 3.73 (s, 2H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.2, 146.3, 142.0, 140.0, 139.4, 131.9, 129.2, 128.5, 128.3, 68.9, 58.7, 38.4; HRMS *m/z* 239.1182 (calculated 239.1184, $C_{15}H_{14}N_2O$).

4.4.3. 6-(But-3-enyl)-7-phenyl-5*H*-cyclopenta[*b*]pyrazine (16e) and cyclopropane 18. Following the general procedure above with **9e** in benzene, 18 mg (49% yield) of **16e** was obtained as a beige crystalline solid along with 6 mg (24% yield) of **18** as a yellow-brown oil. Compound **16e**: mp 77–79 °C; ^{1}H NMR δ 8.34 (d, J=3 Hz, 1H), 8.22 (d, J=3 Hz, 1H), 7.50–7.46 (m, 4H), 7.41–7.37 (m, 1H), 5.82 (ddt, J=17.1, 10.2, 6.6 Hz, 1H), 5.09–4.08 (m, 2H), 3.57 (s, 2H), 2.80 (t, J=7.8 Hz, 2H), 2.41 (q, J=7.8 Hz, 2H); ^{13}C NMR δ 158.5, 158.0, 150.4, 141.9, 138.6, 138.51 137.2, 132.6, 129.2, 128.5, 127.8, 115.7, 39.3, 33.3, 28.9; HRMS (CI) *m/z* 249.1390 (calculated 249.1392, $C_{17}H_{17}N_2$). Compound **18**: ^{1}H NMR δ 8.24 (d, J=2.7 Hz, 1H), 8.04 (d, J=2.7 Hz, 1H), 6.66 (br s, 1H), 2.66–2.57 (m, 2H), 2.55–2.45 (m, 2H), 2.42–2.31 (m, 1H), 2.22 (dd, J=8.1, 3.9 Hz, 1H), 1.68 (t, J=4.5 Hz, 1H); ^{13}C NMR δ 164.9, 160.8,

159.6, 140.8, 136.7, 118.1, 44.8, 33.4, 29.3, 21.9, 19.4; HRMS *m/z* 171.0924 (calculated 171.0922, $C_{11}H_{11}N_2$).

4.4.4. 5-Chloro-8-phenyl-imidazo[1,2-*a*]pyridine, (19a). Following the general procedure above with **9a** in chlorobenzene, 13 mg (39% yield) of **19a** was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 1H, J=7.6 Hz, H6), 7.30 (d, 1H, J=8 Hz, H7), 7.40–7.44 (m, 1H, *para*-H), 7.48–7.52 (m, 2H, *meta*-H), 7.78 (d, 1H, J=1.2 Hz, H2), 7.85 (d, 1H, J=1.2 Hz, H3), 7.93–7.96 (m, 2H, *ortho*-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.1 (C2), 112.4 (C6), 123.3 (C7), 125.1 (C8), 128.6 (*para*-C), 128.7 (*ortho*-C), 129.0 (*meta*-C), 129.2 (C5), 133.9 (C3), 135.9 (*ipso*-C), 144.8 (C9); HRMS (CI) *m/z* 229.0530 (calculated 229.0533, $C_{13}H_{10}N_2Cl$).

4.4.5. 5-Chloro-7-phenyl-imidazo[1,2-*a*]pyridine (19b). Following the general procedure above starting with **9b** in CH_2Cl_2, 6 mg (18% yield) of **19b** was obtained as a tan solid along with 2 mg (7% yield) of **22b**. Compound **19b**: mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, J=1 Hz, 1H), 7.77 (s, 1H), 7.74 (d, J=1 Hz, 1H), 7.65–7.63 (m, 2H), 7.51–7.47 (m, 2H), 7.44–7.34 (m, 1H), 7.21 (d, J=1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 138.2, 137.9, 134.4, 129.2, 128.6, 126.8, 126.4, 112.9, 111.9, 111.1; HRMS *m/z* 229.0532 (calculated 229.0533, $C_{13}H_{10}ClN_2$). Compound **22b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J=2.8 Hz, 1H), 8.35 (d, J=2.8 Hz, 1H), 7.87–7.84 (m, 2H), 7.52–7.47 (m, 3H), 7.33 (s, 1H), 4.51 (d, J=10.8 Hz, 1H), 4.18 (d, J=10.8 Hz, 1H); HRMS (CI) *m/z* 207.0920 (calculated 207.0922, $C_{14}H_{11}N_2$).

4.4.6. 5-Chloro-7-propyl-imidazo[1,2-*a*]pyridine (19c). Following the general procedure above starting with **9c** in CH_2Cl_2, 6 mg (12% yield) of **19c** was obtained as a yellow oil along with 6 mg (14% yield) of **22c**. Compound **19c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 6.76 (s, 1H), 2.63 (t, J=7.6 Hz, 2H), 1.69 (sextet, J=6 Hz, 2H), 0.97 (t, J=6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 140.5, 133.4, 125.7, 114.0, 113.8, 110.8, 37.3, 23.4, 13.6; HRMS *m/z* 195.0689 (calculated 195.0689, $C_{10}H_{12}ClN_2$). Compound **22c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=3 Hz, 1H), 8.26 (d, J=3 Hz, 1H), 6.78 (t, J=2 Hz, 1H), 4.37 (d, J=10.8 Hz, 1H), 3.96 (d, J=10.8 Hz, 1H), 2.55–2.27 (m, 2H), 1.88–1.77 (m, 2H), 1.104 (t, J=8 Hz, 3H); HRMS (CI) *m/z* 173.1083 (calculated 173.1078, $C_{11}H_{13}N_2$).

4.4.7. 5-Chloro-7-(methoxymethyl)-imidazo[1,2-*a*]-pyridine (19d). Following the general procedure above with **9d** in chlorobenzene, 7 mg (15% yield) of **19d** was obtained as yellow oil along with 8.5 mg (15% yield) of **16d**. Compound **19d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H, H3), 7.68 (s, 1H, H2), 7.49 (s, 1H, H8), 6.92 (d, J=1 Hz, 1H, H6), 4.46 (s, 2H, CH_2O), 3.40 (s, 3H, CH_3O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1 (C9), 136.0 (C7), 134.1 (C3), 126.3 (C5), 113.9 (C8), 111.6 (C6), 111.4 (C2), 73.1 (CH_2O), 53.4 (CH_3O); HRMS (CI) *m/z* 197.0489 (calculated 197.0482, $C_9H_9ClN_2O$).

4.4.8. 7-(But-3-enyl)-5-chloro-imidazo[1,2-*a*]pyridine (19e). Following the general procedure above with **9e** in CH_2Cl_2, 2 mg (8% yield) of **19e** was obtained as a yellow oil along with 2.5 mg (10% yield) of **22e**. Compound **19e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.66 (s, 1H), 7.42 (d, J=0.9 Hz, 1H), 6.80 (d, J=0.9 Hz, 1H), 5.83 (ddt, J=16.8, 10.5, 6 Hz), 5.09–5.00 (m, 2H), 2.77 (t, J=7.2 Hz, 2H), 2.41 (q, J=7.2 Hz, 2H); HRMS (CI) *m/z* 207.0689 (calculated 207.0689, $C_{11}H_{12}N_2Cl$). Compound **22e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J=2.4 Hz, 1H), 8.27 (d, J=2.4 Hz, 1H), 6.81 (s, 1H), 5.93 (m, 1H), 5.19 (dt, J=17.4, 1 Hz, 1H), 5.09 (dt, J=10.5, 1 Hz, 1H), 4.37 (d, J=9.9 Hz, 1H), 3.70 (d, J=9.9 Hz, 1H), 2.6–2.4 (m, 4H); HRMS (CI) *m/z* 185.1074 (calculated 185.1079, $C_{12}H_{13}N_2$).

4.5. General procedure for thermolysis in DMF

4.5.1. (*Z*)-1-(2-Chlorovinyl)-2-(3-methoxyprop-1-ynyl)-1*H*-imidazole (20d) and 2-[(*Z*)-2-chloro-3-methoxyprop-1-enyl]-1-[(*Z*)-2-chlorovinyl]-1*H*-imidazole (21d). To a solution of **9d** (25 mg, 0.155 mmol) in dry, degassed DMF (5 ml) was added tetramethylammonium chloride (48 mg, 0.44 mmol) and TFA (32 µl, 0.44 mmol). The mixture was stirred at 80 °C overnight. Upon disappearance of **9d** (by TLC), the solvent was evaporated and the residue diluted with CH_2Cl_2 (5 ml) and washed with satd $NaHCO_3$ solution (2×5 ml) and brine (5 ml). The organic extracts were combined, dried and the solvent evaporated. The residue was purified by flash chromatography (0–70% EtOAc/hexanes) to afford 3 mg (10% yield) of **20d** as a yellow oil and 13 mg (36% yield) of **21d** as a yellow oil. Compound **20d**: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.87 (d, J=1.6 Hz, 1H), 7.26 (d, J=6.8 Hz, 1H), 7.10 (br s, 1H), 6.02 (d, J=6.2 Hz, 1H), 4.35 (s, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 132.1, 130.4, 123.4, 119.7, 108.6, 91.1, 75.3, 60.4, 58.1; HRMS *m/z* 197.0483 (calculated 197.0482, $C_9H_{10}ClN_2O$). Compound **21d**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.52 (d, J=1 Hz, 1H), 7.20 (br s, 1H), 6.98 (d, J=6 Hz, 1H), 6.63 (t, J=1.5 Hz, 1H), 6.18 (d, J=6 Hz, 1H), 4.14 (d, J=1.5 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 142.4, 136.1, 129.9, 123.9, 119.5, 113.3, 112.3, 76.1, 58.7; HRMS *m/z* 233.0235 (calculated 233.0242, $C_9H_{11}Cl_2N_2O$).

4.5.2. (*Z*)-1-(2-Chlorovinyl)-2-(2-phenylethynyl)-1*H*-imidazole (20b). Following the general procedure above with **9b** and employing 1.2 equiv of conc HCl in place of Me_4NCl and TFA, 18 mg (69% yield) of **20b** was obtained as a yellow oil: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.92 (d, J=1.5 Hz, 1H), 7.58–7.55 (m, 2H), 7.41–7.32 (m, 4H), 7.19 (d, J=1.5 Hz, 1H), 6.00 (d, J=6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 131.8, 130.03, 129.5, 128.5, 123.0, 121.2, 119.2, 107.9, 94.5, 77.7; HRMS (CI) *m/z* 229.0533 (calculated 229.0531, $C_{10}H_{12}ClN_2$)

4.5.3. (*Z*)-1-(2-Chlorovinyl)-2-(pent-1-ynyl)-1*H*-imidazole (20c). Following the general procedure above with **9b** and employing 1.2 equiv of conc HCl in place of Me_4NCl and TFA, 20 mg (56% yield) of **20c** was obtained as a yellow oil along with 5 mg (14% yield) of **19c**. Compound **20c**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.84 (d, J=1.5 Hz, 1H), 7.25 (d, J=6.6 Hz, 1H), 7.03 (d, J=1.2 Hz, 1H), 5.96 (d, J=6 Hz, 1H), 2.45, (t, J=6.9 Hz, 2H), 1.67 (quintet, J=7.5 Hz, 2H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 133.5, 129.9, 123.5, 118.9, 107.4, 96.6, 70.1, 22.1, 21.6,

13.7; HRMS (CI) *m/z* 195.0686 (calculated 195.0689, $C_{10}H_{12}ClN_2$).

4.6. General procedure for deuteration of dialkynylimidazoles

4.6.1. [^2H]-1-Ethynyl-2-(3-methoxyprop-1-ynyl)-1*H*-imidazole ([^2H]-9d). A solution of **9d** (101 mg, 0.63 mmol) in dry ether (7 ml) was cooled to −78 °C using a dry-ice acetone bath and a 1.4 M solution of *n*-BuLi in hexanes (0.495 ml, 0.69 mmol) was added slowly drop wise. The resultant suspension was stirred for 15 min and 3 ml of D_2O was added. The reaction mixture was allowed to slowly warm to room temperature over 0.5–1 h and extracted with CH_2Cl_2. The organic extracts were combined, dried, and purified by flash chromatography (5–10% Et_2O/hexanes) to yield 95 mg (94%) of [^2H]-**9d** as a light brown oil. Isotopic purity > 95% by ^1H NMR: ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J= 1.6 Hz, 1H), 7.01 (d, J=1.2 Hz, 1H), 4.36 (s, 2H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 129.6, 122.5, 90.2, 74.5, 70.4, 61.6 (t, J_{C-D}=40.5 Hz), 59.9, 57.8; HRMS (CI) *m/z* 162.0774 (calculated 162.0777, $C_9H_8N_2DO$).

4.6.2. [^2H]-2-Ethynyl-1-phenylethynyl-1*H*-imidazole ([^2H]-9a). Following the procedure above starting with **9a**, 59 mg (94% yield) of [^2H]-**9a** was obtained as light brown solid. Isotopic purity was >95% by ^1H NMR: mp 108.5–109 °C; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.57–7.52 (m, 2H), 7.42–7.37 (m, 3H), 7.24 (d, J=1.5 Hz, 1H), 7.05 (d, J=1.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 134.3, 132.0, 121.9, 129.5, 128.9, 123.2, 121.2, 82.1 (t, J=39 Hz), 77.5, 73.6, 71.9 (t, J=7.5 Hz); HRMS (CI) *m/z* 194.0826 (calculated 194.0828, $C_{13}H_8N_2D$).

4.6.3. Diethyl-(7-methoxymethyl-imidazo[1,2-*a*]pyridin-5-yl)-amine (23d). A solution of **9d** (22 mg, 0.138 mmol) in benzene (1.8 ml) and diethylamine (285 μl, 2.76 mmol) was heated at 80 °C for 14 h. The reaction mixture was allowed to cool, the solvent was evaporated, and the residue was purified by flash chromatography (3:0:7–3:1:6 hexanes/CH_3OH/CH_2Cl_2) to afford 20 mg (60% yield) of **23d** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.60, (s, 1H, H3), 7.57 (s, 1H, H2), 7.30 (s, 1H, H8), 6.36 (s, 1H, H6), 4.49 (s, 2H, CH_2O), 3.39 (s, 3H, CH_3O), 3.19 (q, J=7 Hz, 4H, CH_2N), 1.11 (t, J=7 Hz, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (C9), 144.2 (C5), 136.6 (C7), 133.0 (C2), 110.12 (C3), 110.0 (C8), 102.0 (C6), 74.2 (CH_2O), 58.2 (CH_3O), 44.8 (CH_2N), 12.1 (CH_3); HRMS (CI) *m/z*, 234.1599 (calculated 234.1606, $C_{13}H_{20}N_3O$).

Acknowledgements

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Synthesis of ynamides from formamides

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Abstract—*N*-Formyl-tosylamides can be efficiently converted to *N*-ethynyl-tosylamides in two steps via the corresponding dichlorovinylamides.

1. Introduction

The chemistry of ynamines has been studied extensively in the past.[1] However, their sensitivity and difficulties in their preparation prevented broader application in synthetic chemistry so far.[2] Ynamides,[3] however, are electron deficient and hence possess a significantly higher stability, which makes them valuable synthetic building blocks.[4,5] In recent years, the chemistry of ynamides has attracted many chemists resulting in a multitude of publications demonstrating the synthetic potential of ynamides for various applications such as cycloadditions[6,7] and cycloisomerizations,[8] transition metal-catalyzed coupling reactions,[9,10] radical cyclizations,[11] ring-closing metatheses,[12,13] acid-catalyzed hydroarylations,[14] hydrohalogenations,[15] carbometallations[16] and rearrangement reactions.[17,18]

Among the practical and commonly used syntheses of ynamides[4] are the reaction of a deprotonated amide with a hypervalent iodine salt,[6,19] N-alkynylation of amides by alkynyl bromides,[20] and the base-catalyzed isomerization of propargyl amides.[12,21]

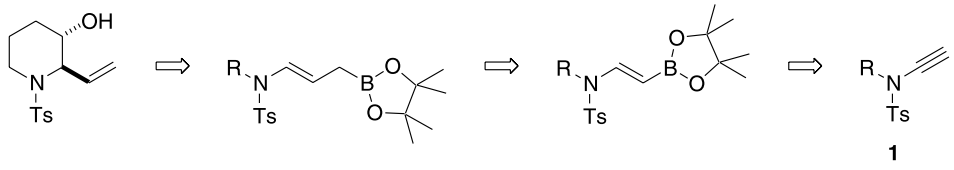
We report here the synthesis of *N*-ethynyl-tosylamides **1** from formamides in two steps employing cheap, readily available reagents, which might be advantageous to larger scales. Since our first publication[22] this method has already been utilized by other groups.[8,10,13,18,23]

2. Results and discussion

In the course of our research into intramolecular allylborations aiming at the stereoselective formation of substituted piperidine rings,[24] we envisaged to start the synthesis of the mandatory allylboronic ester from an ynamide **1** (see Scheme 1). At that time we thought of trying to synthesize the desired ynamides in a novel manner.

Inspired by the well-known conversion of aldehydes to alkynes developed by Corey and Fuchs[25] we planned to transfer this method to the conversion of formamides **3** to ynamides **1** (see Scheme 2).

As only a few *N*-formyl-tosylamides **3** had been described before,[26,27] we explored new and general methods to synthesize these mixed imides. Two strategies proved to be successful: formylation of substituted tosylamides **4** and alkylation of *N*-formyl-toluenesulfonamide[26] (**6**), respectively (Scheme 3 and Table 1).[28]



Scheme 1. Retrosynthetic path from allylboronic esters to ynamides.

Keywords: Ynamides; Formamides; Alkenation; Enamides; Mixed imides.
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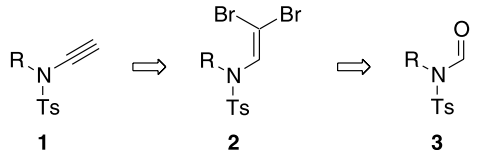
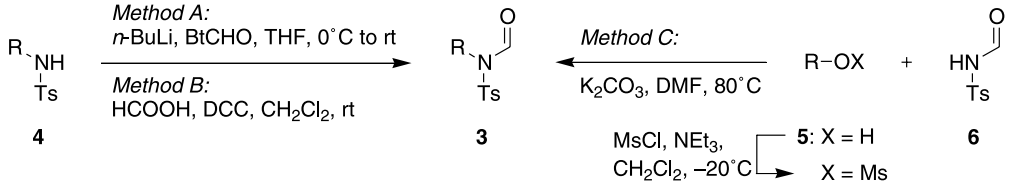


Scheme 2. Synthetic plan towards ynamides.

formic acid in the presence of dicyclohexylcarbodiimide[30] provided the *N*-formylated tosylamide **3f** in excellent yield (Scheme 3, Method B). Preparation of formamides **3** directly from an alcohol is also possible as shown in entry 4 (Table 1). Here, alkylation of **6** with the mesylate generated from alcohol **5d** afforded formamide **3d** in moderate yield (Scheme 3, Method C).[31]



Scheme 3. Different preparations of *N*-formyl-tosylamides **3**.

Table 1. Preparation of *N*-formyl-tosylamides **3**

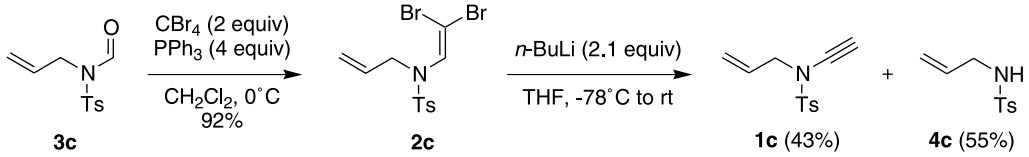
Entry	R	Method	3	Yield (%)[a]
1	*n*-Bu	A	**a**	95
2	*i*-Pr	A	**b**	85
3	$-CH_2CH_2=CH_2$	A	**c**	93
4	$-CH_2C(CH_3)=CH_2$	C	**d**	49
5	Bn	A	**e**	90
6	Ph	B	**f**	99

[a] Isolated yield of analytically pure product.

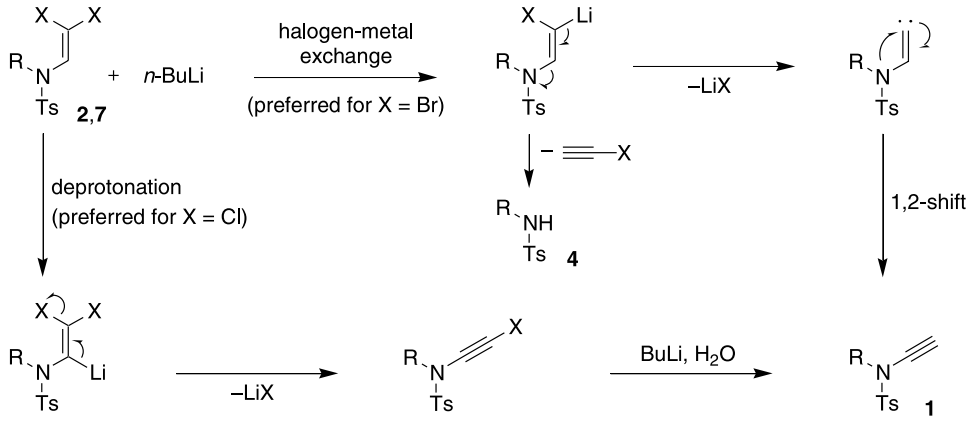
Formylation of **4a–c,e** succeeded with high yields by deprotonating the amide with *n*-butyllithium in THF followed by treatment with formylbenzotriazole (BtCHO),[29] which is easy to prepare and to handle (Scheme 3, Method A). In the case of phenyl toluenesulfonamide **4f** (Table 1, entry 6) this method gave unsatisfactory conversion (53%), possibly because of its lower nucleophilicity. Here, reaction with

The required formamides in hand, we applied the protocol for dibromomethylenation described by Corey and Fuchs.[25] Reaction of **3c** with triphenylphosphine and CBr_4 afforded the dibromoenamide **2c** in very good yield. However, the following step—treatment with *n*-butyllithium—resulted in a mixture of the desired ynamide **1c** and tosylamide **4c** (see Scheme 4).

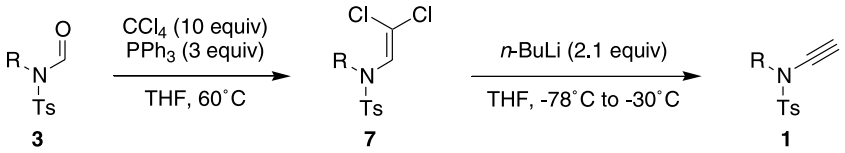
A possible explanation of this result is given in Scheme 5. The initial bromo–lithium exchange is followed by two competing eliminations, that of lithiumbromide or of bromoacetylene, respectively, resulting in a mixture of **1** and **4** (in which the *E*/*Z*-selectivity of the bromo–lithium exchange certainly will have an impact on the **1**:**4**-ratio). But a second reaction sequence is conceivable as well. If the initial step is a deprotonation, an elimination of lithium halogenide should follow leading to the triple bond. A cleavage of the C–N bond appears to be unlikely here. We hoped to promote the second pathway by switching



Scheme 4. Synthesis of ynamides via dibromovinylamides.



Scheme 5. Proposed mechanism of the reaction of dihalovinylamides with *n*-BuLi.



Scheme 6. Synthesis of ynamides via dichlorovinylamides.

from bromine to chlorine as the chlorine-lithium exchange is significantly slower.

The dichloromethylenation of esters and lactones to 2,2-dichlorovinylethers is a well-studied reaction,[32] however, the corresponding conversion of formamides to dichlorovinylamines had not been described yet. Nevertheless, treatment of formamides **3** with triphenylphosphine (3 equiv) and excess tetrachloromethane (10 equiv, slow addition) in tetrahydrofuran at 60 °C proceeded very well and lead to the dichlorovinylamides **7a–f** in excellent yields (Scheme 6 and Table 2). Subsequent dehalogenation of **7** with *n*-butyllithium (2.1 equiv) in tetrahydrofuran at −78 °C and quenching at −30 °C with methanol afforded the desired ynamides **1a–f** in very good yields (Table 2). Formation of undesired tosylamides **4** was not observed supporting the proposed reaction mechanism (Scheme 5). *N*-Ethynyl-tosylamides **1** are nearly colorless crystalline solids that can be purified by chromatography on aluminum oxide or silica gel (the latter can slightly diminish the yield). As shown in Table 2, both steps gave good to excellent yields for a variety of substituents with diverse steric demands and electronic properties.

Table 2. Conversion of formamides to dichlorovinylamides **7** and ynamides **1**

Entry	3	R	7	Yield (%)[a]	1	Yield (%)[a]
1	**a**	*n*-Bu	**a**	99	**a**	86
2	**b**	*i*-Pr	**b**	96	**b**	93
3	**c**	$-CH_2CH_2{=}CH_2$	**c**	97	**c**	81
4	**d**	$-CH_2C(CH_3){=}CH_2$	**d**	97	**d**	95
5	**e**	Bn	**e**	96	**e**	80
6	**f**	Ph	**f**	81	**f**	97

[a] Isolated yield of analytically pure product.

This procedure may also be applied to the synthesis of ynolethers[22] serving as an alternative to Greene's one-pot synthesis.[33]

3. Conclusion

A facile, reliable and high-yielding procedure for the preparation of *N*-ethynyl-tosylamides has been developed that employs non-expensive, readily available starting materials allowing for easy scale up.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. All starting materials were purchased from commercial sources and used without further purification. Solvents were dried prior to use by standard methods. Boiling range of petroleum ether (PE): 40–60 °C. All temperatures quoted are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on Bruker ARX-200 and AC-300 spectrometers. Flash chromatography was performed on silica gel Si60 (40–60 μm; E. Merck KGaA, Darmstadt).

4.2. Syntheses of formamides 3

4.2.1. *N*-Formyl-*N*-isopropyl-4-methyl-benzenesulfonamide (3b) (representative procedure for the formylation of tosylamides 4, Method A). A solution of **4b** (213 mg, 1 mmol) in THF (5 mL) at 0 °C was treated with *n*-BuLi (670 μL, 1.64 M in hexane, 1.1 mmol). After 5 min, a solution of formylbenzotriazole (177 mg, 1.2 mmol) in THF (2 mL) was added and the mixture stirred for 2 h at rt. Dilution with *tert*-butyl methyl ether (TBME, 20 mL) and workup with satd $NaHCO_3$ (15 mL) followed by flash chromatography on silica gel (pentane/TBME 5:1) afforded formamide **3b** (205 mg, 85%) as a colorless crystalline solid. R_f 0.52 (PE/EtOAc 5:1); mp 38–39 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.26$ (d, $J=6.9$ Hz, 6H), 2.47 (s, 3H), 4.11 (septd, $J=6.9$, 1.3 Hz, 1H), 7.36–7.42 (m, 2H), 7.74–7.79 (m, 2H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=19.5$, 21.6, 50.0, 127.4 (2C), 130.2 (2C), 135.6, 143.2, 161.6. Anal. Calcd for $C_{11}H_{15}NO_3S$: C 54.75, H 6.27, N 5.80; Found: C 54.82, H 6.11, N 5.92.

4.2.2. *N*-Butyl-*N*-formyl-4-methyl-benzenesulfonamide (3a). According to Method A starting from compound **4a**, yield 95% (1 mmol scale, 241 mg), colorless oil. R_f 0.31 (PE/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.86$ (t, $J=7.3$ Hz, 3H), 1.18–1.37 (m, 2H), 1.45–1.57 (m, 2H), 2.46 (s, 3H), 3.38–3.45 (m, 2H), 7.35–7.40 (m, 2H), 7.71–7.77 (m, 2H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=13.9$, 20.3, 22.0, 30.7, 43.0, 127.8 (2C), 130.6 (2C), 135.6, 145.8, 161.7. Anal. Calcd for $C_{12}H_{17}NO_3S$: C 56.45, H 6.71, N 5.49; Found: C 56.39, H 6.73, N 5.70.

4.2.3. *N*-Allyl-*N*-formyl-4-methyl-benzenesulfonamide (3c). According to Method A starting from compound **4c**, yield 93% (0.74 mmol scale, 165 mg), colorless crystalline solid. R_f 0.26 (PE/EtOAc 5:1); mp 43 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.46$ (s, 3H), 4.11 (dt, $J=6.0$, 1.3 Hz, 2H), 5.08 (dq, $J=10.2$, 1.0 Hz, 1H), 5.15 (dq, $J=17.2$, 1.0 Hz, 1H), 5.60 (ddt, $J=17.0$, 10.3, 6.0 Hz, 1H), 7.36 (d, $J=8.1$ Hz, 2H), 7.74 (d, $J=8.3$ Hz, 2H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=21.6$, 44.6, 119.0, 127.5 (2C), 130.2 (2C), 130.7, 135.2, 145.5, 160.9. Anal. Calcd for $C_{11}H_{13}NO_3S$: C 55.21, H 5.48, N 5.85; Found: C 55.06, H 5.21, N 5.81.

4.2.4. *N*-Benzyl-*N*-formyl-4-methyl-benzenesulfonamide (3e). According to Method A starting from compound **4e**, yield 90% (2 mmol scale, 518 mg), colorless crystalline solid. R_f 0.38 (PE/EtOAc 5:1); mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.40 (s, 3H), 4.72 (s, 2H), 7.17–7.20 (m, 5H), 7.20–7.25 (m, 2H), 7.53–7.59 (m, 2H), 9.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.6, 45.7, 127.3, 127.7, 128.36, 128.42, 130.0, 134.6, 135.3, 145.2, 161.5. Anal. Calcd for $C_{15}H_{15}NO_3S$: C 62.26, H 5.23, N 4.84; Found: C 62.16, H 5.28, N 4.90.

4.2.5. *N*-Formyl-*N*-phenyl-4-methyl-benzenesulfonamide (3f) (Method B). Tosylamide **4f** (247 mg, 1 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated successively with formic acid (75 μL, 2 mmol) and DCC (516 mg, 2.5 mmol). The temperature rose to 40 °C. The mixture was stirred for 24 h, diluted with CH_2Cl_2 (10 mL) and filtered over a short pad of Celite. After removal of the solvent the residue was purified by flash chromatography on silica gel (pentane/TBME 4:1) to give formamide **3f** (274 mg, 99%) as colorless crystals. R_f 0.60 (CH_2Cl_2+2% acetone); mp 117–118 °C (lit.[27] mp 133 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.45 (s, 3H), 6.90–6.95 (m, 2H), 7.27–7.45 (m, 5H), 7.54–7.59 (m, 2H), 9.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.7, 128.0 (2C), 129.4 (2C), 129.86, 129.88 (2C), 130.0 (2C), 132.0, 134.2, 145.7, 161.1. Anal. Calcd for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09; Found: C 60.96, H 4.89, N 5.20.

4.2.6. *N*-Formyl-*N*-(2-methyl-allyl)-4-methyl-benzenesulfonamide (3d) (Method C). A solution of 2-methyl-allylalcohol (**5d**) (505 μL, 6 mmol) and triethylamine (1.25 mL, 9 mmol) in CH_2Cl_2 (20 mL) was cooled to −20 °C. Methanesulfonyl chloride (604 μL, 7.8 mmol) was added and the mixture stirred for 1.5 h. Dilution with diethylether (20 mL) and aqueous workup with satd NH_4Cl (20 mL) furnished the crude mesylate, which was dissolved in DMF (3 mL). *N*-Formyltoluenesulfonamide[26] (**6**) (598 mg, 3 mmol) and K_2CO_3 (622 mg, 4.5 mmol) were added and the mixture heated to 80 °C for 14 h. Workup with TBME (3×20 mL) and satd $NaHCO_3$ (20 mL) followed by flash chromatography on silica gel (pentane/TBME 6:1) furnished formamide **3d** (370 mg, 49%) as a colorless crystalline solid. R_f 0.31 (PE/EtOAc 5:1); mp 49 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.55 (s, 3H), 2.46 (s, 3H), 4.08 (s, 2H), 4.77–4.79 (m, 1H), 4.80–4.83 (m, 1H), 7.33–7.35 (m, 2H), 7.35–7.38 (m, 2H), 9.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.8, 21.6, 47.5, 113.5, 127.6 (2C), 130.1 (2C), 135.1, 138.2, 145.5, 161.2. Anal. Calcd for $C_{12}H_{15}NO_3S$: C 56.90, H 5.97, N 5.53; Found: C 57.05, H 6.14, N 5.75.

4.2.7. *N*-Formyltoluenesulfonamide (6).[26] Toluenesulfonyl amide (8.56 g, 50 mmol) was added to a solution of sodium methylate (1.50 g, 65 mmol) in methanol (100 mL). The solution was warmed to 40 °C for 30 min before ethyl formate (20.2 mL, 250 mmol) was added dropwise. Stirring at 40 °C was continued overnight. Subsequently, the mixture was acidified (pH 3–4) with 2 M HCl, solvents removed in vacuo, the residue taken up in water (50 mL), and the acidified (2 M HCl) mixture extracted with MTBE (5×50 mL). To remove not converted starting material, the crude product was dissolved in MTBE (50 mL) and thoroughly washed with satd $NaHCO_3$ (100 mL). The aqueous phase was acidified (2 M HCl) and extracted with MTBE (4×50 mL) to give **6** (8.7 g, 87%) as a colorless crystalline solid. R_f 0.20 (CH_2Cl_2/MTBE 5:1); mp 102–103 °C (MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.46 (s, 3H), 7.37 (m, 2H), 7.80 (m, 2H), 8.50 (br s, 1H), 8.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.6, 127.0, 130.2, 136.1, 145.6, 162.0.

4.3. Syntheses of dihaloenamides 2 and 7

4.3.1. *N*-Allyl-*N*-(2,2-dibromovinyl)-4-methyl-benzenesulfonamide (2c). A solution of PPh_3 (6.03 g, 23 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and CBr_4 (3.81 g, 11.5 mmol) was added. After 1 h formamide **3c** (1.38 g, 5.75 mmol) dissolved in CH_2Cl_2 (8 mL) was added. Stirring was continued for 3 h at 0 °C and 4 h at rt. PE (25 mL) was added and the mixture was filtered, the solid residue dissolved in CH_2Cl_2 (15 mL) and precipitated by addition of pentane (15 mL). Filtration–dissolution–precipitation was repeated once more. The combined filtrates were concentrated and the crude product was purified by flash chromatography on silica gel (pentane/TBME 8:1) to give dibromovinylamide **2c** (2.10 g, 92%) as a colorless crystalline solid. R_f 0.30 (PE/EtOAc 5:1); mp 100 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.42 (s, 3H), 3.98 (dt, J=6.3, 1.3 Hz, 2H), 5.10–5.23 (m, 2H), 5.69 (ddt, J=16.9, 10.2, 6.5 Hz, 1H), 6.68 (s, 1H), 7.31 (m, 2H), 7.69 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.6, 51.8, 95.7, 119.5, 127.4 (2C), 129.9 (2C), 131.3, 131.8, 135.6, 144.2. Anal. Calcd for $C_{12}H_{13}Br_2NO_2S$: C 36.48, H 3.32, N 3.54; Found: C 36.50, H 3.46, N 3.41.

4.3.2. *N*-(2,2-Dichlorovinyl)-*N*-isopropyl-4-methyl-benzenesulfonamide (7b) (representative procedure for the dichloromethylenation of formamides 3). Formamide **3b** (172 mg, 0.71 mmol) and PPh_3 (559 mg, 2.13 mmol) were dissolved in THF (7 mL). CCl_4 (687 μL, 7.1 mmol) was added via syringe over a period of 6 h at 60 °C. After stirring for an additional hour, the mixture was diluted with TBME (15 mL). Aqueous workup with satd $NaHCO_3$ (15 mL) afforded after flash chromatography on silica gel (pentane/TBME 6:1) dichlorovinylamide **7b** (210 mg, 96%) as a pale yellow crystalline solid. R_f 0.62 (PE/EtOAc 5:1); mp 86–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.02 (d, J=6.7 Hz, 6H), 2.43 (s, 3H), 4.21 (sept, J=6.7 Hz, 1H), 6.08 (s, 1H), 7.30–7.33 (m, 2H), 7.70–7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.3, 21.5, 52.5, 121.0 (*C*=CCl_2), 127.3 (2C), 129.7 (2C), 132.7 (C=*C*Cl_2), 136.7, 143.8. Anal. Calcd for $C_{12}H_{15}NO_2SCl_2$: C 46.76, H 4.91, N 4.54; Found: C 46.77, H 4.95, N 4.53.

4.3.3. *N*-Butyl-*N*-(2,2-dichlorovinyl)-4-methyl-benzenesulfonamide (7a). As described for compound **7b** starting from compound **3a**, yield 99% (1.46 mmol scale, 464 mg), yellowish crystalline solid. R_f 0.43 (PE/EtOAc 5:1); mp 66 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.90 (t, J=7.1 Hz, 3H), 1.42 (m, 4H), 2.43 (s, 3H), 3.31 (t, J=7.1 Hz, 2H), 6.26 (s, 1H), 7.32 (d, J=8.1 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.6, 19.7, 21.5, 30.4, 48.9, 124.4, 124.9, 127.2, 129.8, 135.5, 144.0. Anal. Calcd for $C_{13}H_{17}Cl_2NO_2S$: C 48.45, H 5.32, N 4.35; Found: C 48.64, H 5.43, N 4.52.

4.3.4. *N*-Allyl-*N*-(2,2-dichlorovinyl)-4-methyl-benzenesulfonamide (7c). As described for compound **7b** starting from compound **3c**, yield 97% (3.93 mmol scale, 1.17 g), colorless crystalline solid. R_f 0.41 (PE/EtOAc 5:1); mp 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.43 (s, 3H), 4.00 (d, J=6.3 Hz, 2H), 5.15 (dq, J=10.0, 1.0 Hz, 1H), 5.18 (dq, J=17.1, 1.2 Hz, 1H), 5.68 (ddt, J=17.0, 10.2, 6.3 Hz, 1H), 6.31 (s, 1H), 7.32 (d, J=8.1 Hz, 2H), 7.69 (d, J=8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.6, 51.7, 119.4, 124.3, 124.8, 127.4 (2C), 129.9 (2C), 131.9, 135.7, 144.2. Anal. Calcd for $C_{12}H_{13}Cl_2NO_2S$: C 47.07, H 4.28, N 4.57; Found: C 47.01, H 4.27, N 4.42.

4.3.5. *N*-(2,2-Dichlorovinyl)-*N*-(2-methyl-allyl)-4-methyl-benzenesulfonamide (7d). As described for compound **7b** starting from compound **3d**, yield 97% (1.13 mmol scale, 350 mg), colorless crystalline solid. R_f 0.43 (PE/EtOAc 5:1); mp 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.76 (s, 3H), 2.44 (s, 3H), 3.88 (s, 2H), 4.84–4.87 (m, 1H), 4.90–4.93 (m, 1H), 6.20 (s, 1H), 7.31–7.36 (m, 2H), 7.67–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.8, 21.5, 55.2, 115.1, 124.7, 125.2, 127.2 (2C), 129.8 (2C), 135.4, 139.4, 144.2. Anal. Calcd for $C_{13}H_{15}Cl_2NO_2S$: C 48.76, H 4.72, N 4.37; Found: C 48.95, H 4.89, N 4.23.

4.3.6. *N*-(2,2-Dichlorovinyl)-*N*-benzyl-4-methyl-benzenesulfonamide (7e). As described for compound **7b** starting from compound **3e**, yield 96% (1.76 mmol scale, 600 mg), colorless crystalline solid. R_f 0.40 (PE/EtOAc 5:1); mp 126 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.43 (s, 3H), 4.53 (s, 2H), 6.21 (s, 1H), 7.28 (m, 5H), 7.34 (d, J=8.3 Hz, 2H), 7.72 (d, J=8.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.5, 52.6, 124.7, 125.6, 127.2, 127.9, 128.3, 128.5, 129.8, 135.0, 135.6, 144.2. Anal. Calcd for $C_{16}H_{15}Cl_2NO_2S$: C 53.94, H 4.24, N 3.93; Found: C 53.83, H 4.12, N 3.87.

4.3.7. *N*-(2,2-Dichlorovinyl)-*N*-phenyl-4-methyl-benzenesulfonamide (7f). As described for compound **7b** starting from compound **3f**, yield 81% (1 mmol scale, 276 mg), colorless crystalline solid. Mp 115–116 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.43 (s, 3H), 6.97 (s, 1H), 7.06 (m, 2H), 7.28 (m, 5H), 7.47 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.6, 118.2, 126.2, 127.7, 128.0, 128.3, 128.9, 129.6, 134.1, 138.2, 144.6. Anal. Calcd for $C_{15}H_{13}Cl_2NO_2S$: C 52.64, H 3.83, N 4.09; Found: C 52.83, H 3.93, N 3.95.

4.4. Syntheses of ynamides 1

4.4.1. *N*-Ethynyl-*N*-isopropyl-4-methyl-benzenesulfonamide (1b) (representative procedure for the synthesis of ynamides 1). A solution of dichlorovinylamide **7b** (205 mg, 0.66 mmol) in THF (3.3 mL) was cooled to −78 °C and treated with *n*-BuLi (0.96 mL, 1.53 M in hexane, 1.46 mmol). The mixture was warmed to −30 °C within 2 h and then MeOH (135 μL) was added. Dilution with TBME (10 mL) and workup using satd $NaHCO_3$ (5 mL) gave a yellow crude product, which was purified by flash chromatography on basic alox (pentane/TBME 6:1) to yield the desired ynamide **1b** (146 mg, 93%) as a pale yellow crystalline solid. R_f 0.58 (PE/EtOAc 5:1); mp 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (d, J=6.6 Hz, 6H), 2.45 (s, 3H), 2.80 (s, 1H), 4.13 (sept, J=6.6 Hz, 1H), 7.32–7.37 (m, 2H), 7.79–7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.4, 21.5, 52.0, 61.0 (C≡*C*H), 72.9 (*C*≡CH), 127.3 (2C), 129.7 (2C), 135.9, 144.5. Anal. Calcd for $C_{12}H_{15}NO_2S$: C 60.73, H 6.37, N 5.90; Found: C 60.88, H 6.48, N 5.99.

4.4.2. *N*-Butyl-*N*-ethynyl-4-methyl-benzenesulfonamide (1a). As described for compound **1b** starting from compound **7a**, yield 86% (1.18 mmol scale, 255 mg), yellow oil. R_f 0.41 (PE/EtOAc 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.83 (t, J=7.3 Hz, 3H), 1.21–1.51 (m, 4H), 2.37 (s, 3H), 2.65 (s, 1H), 3.22 (t, J=7.2 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 7.72 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.5, 19.4, 21.6, 29.6, 50.9, 58.9, 76.4, 127.6, 129.7, 134.6, 144.6.

4.4.3. *N*-Allyl-*N*-ethynyl-4-methyl-benzenesulfonamide (1c). As described for compound **1b** starting from compound **7c**, yield 81% (3.78 mmol scale, 721 mg), colorless crystalline solid. R_f 0.25 (PE/EtOAc 5:1); mp 68–70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.37 (s, 3H), 2.65 (s, 1H), 3.88 (dt, J=6.2, 1.2 Hz, 2H), 5.11–5.24 (m, 2H), 5.66 (ddt, J=17.1, 10.1, 6.3 Hz, 1H), 7.29 (m, 2H), 7.74 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.5, 53.9, 59.2, 75.8, 120.0, 127.7 (2C), 129.7 (2C), 130.5, 134.6, 144.8. Anal. Calcd for $C_{12}H_{13}NO_2S$: C 61.25, H 5.57, N 5.95; Found: C 61.35, H 5.41, N 5.89.

4.4.4. *N*-Ethynyl-*N*-(2-methyl-allyl)-4-methyl-benzenesulfonamide (1d). As described for compound **1b** starting from compound **7d**, yield 95% (1.09 mmol scale, 257 mg), colorless crystalline solid. R_f 0.34 (PE/EtOAc 5:1); mp 69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.72 (s, 3H), 2.46 (s, 3H), 2.71 (s, 1H), 3.86 (s, 2H), 4.91–4.94 (m, 1H), 4.95–4.98 (m, 1H), 7.33–7.38 (m, 2H), 7.79–7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.5, 21.6, 57.5, 59.0, 75.8, 115.8, 127.7 (2C), 129.7 (2C), 134.5, 138.4, 144.7. Anal. Calcd for $C_{13}H_{15}NO_2S$: C 62.62, H 6.06, N 5.62; Found: C 62.32, H 5.90, N 5.77.

4.4.5. *N*-Benzyl-*N*-ethynyl-4-methyl-benzenesulfonamide (1e). As described for compound **1b** starting from compound **7e**, yield 80% (1.61 mmol scale, 367 mg), colorless crystalline solid. R_f 0.34 (PE/EtOAc 5:1); mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.44 (s, 3H), 2.67 (s, 1H), 4.49 (s, 2H), 7.27–7.35 (m, 7H), 7.73–7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.6, 55.2, 59.6, 76.2, 127.6, 128.3, 128.5, 128.6, 129.7, 134.2, 134.6, 144.7. Anal. Calcd for $C_{16}H_{15}NO_2S$: C 67.34, H 5.30, N 4.91; Found: C 67.02, H 5.32, N 5.06.

4.4.6. *N*-Ethynyl-*N*-phenyl-4-methyl-benzenesulfonamide (1f). As described for compound **1b** starting from compound **7f**, yield 97% (1.52 mmol scale, 401 mg), pale yellow crystalline solid. R_f 0.30 (PE/EtOAc 5:1); mp 86–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.44 (s, 3H), 2.84 (s, 1H), 7.21–7.37 (m, 7H), 7.54–7.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ=21.6, 58.9, 76.4, 126.1, 128.1, 128.3, 129.0, 129.5, 132.7, 138.1, 145.1. Anal. Calcd for $C_{15}H_{13}NO_2S$: C 66.40, H 4.83, N 5.16; Found: C 66.25, H 4.61, N 5.07.

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[2+2] Cycloaddition of ketenes with ynamides. A general method for the synthesis of 3-aminocyclobutenone derivatives

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Abstract—Ynamides react with ketenes in [2+2] cycloadditions leading to a variety of substituted 3-aminocyclobut-2-en-1-ones. The ynamides employed in these reactions are readily available via the copper-promoted N-alkynylation of carbamates and sulfonamides with alkynyl bromides and iodides. The scope of the [2+2] cycloaddition with regard to both the ketene and ynamide component is described.

1. Introduction

Cyclobutenones are valuable synthetic intermediates that participate in a variety of novel and useful synthetic transformations.[1] The most direct and convenient approach to the synthesis of cyclobutenones employs the [2+2] cycloaddition of ketenes with alkynes.[2] Unfortunately, unactivated alkynes only engage in efficient cycloadditions with highly electrophilic ketenes such as dichloroketene.[3] Electron-rich alkynes (e.g., alkoxy-[4] and silyloxy-substituted acetylenes[5]) combine with a wider range of ketenes and provide access to 3-alkoxycyclobutenones, generally in good yield. Ynamines[6] also combine readily with ketenes; however, these reactions often lead to mixtures of the desired cyclobutenones accompanied by allenyl amides.[7] The formation of these allene byproducts is believed to result from initial addition of the ynamine across the ketene carbonyl group via a stepwise pathway to form an alkylideneoxete. Electrocyclic ring opening then transforms this strained intermediate to the allenyl carboxamide.

In connection with our interest in benzannulation strategies based on the reaction of alkynes with aryl- and vinylketenes,[8] we undertook a study of the reactions of various ynamine derivatives with ketenes. In order to suppress the 'abnormal' reaction leading to oxetes and allenes, we have focused our attention on reactions of ynamides, in which the nucleophilicity of the aminoalkyne is attenuated by the electron-withdrawing substituent on the nitrogen atom. Herein, we report the results of our systematic investigation of the [2+2] cycloaddition of several classes of ketenes with ynamides.

2. Results and discussion

2.1. Synthesis of ynamides

Recent advances in copper-promoted amide coupling reactions have provided the basis for the efficient and convenient synthesis of a variety of ynamides. The ynamides employed in the present study were prepared as described in Table 1 using the N-alkynylation method recently developed in our laboratory.[9] The terminal ynamide **9** was obtained in 70% yield by desilylation of **7** as shown in Scheme 1. The conditions shown in Table 1 and detailed in Section 4 represent a minor modification of our original procedure. In this revised protocol, we now employ THF as the reaction solvent with 25 equiv of pyridine, use only a small excess of the alkynyl halide, and utilize an improved workup procedure. Although this protocol requires the use of 1 equiv of CuI, coupling proceeds smoothly at rt and this method thus accommodates the synthesis of a wide range of alkyne derivatives including thermally unstable systems. For many of these ynamides, similar results can be obtained by using the method of Hsung, which employs catalytic CuCN or $CuSO_4$ in conjunction with diamine ligands and requires reaction at elevated temperatures.[10] We have found both methods to be reliable and reproducible for reactions on both small and large (i.e., multigram) scale.

Recently, Tam and co-workers have reported an alternative N-alkynylation protocol that involves a melding of the

Keywords: Ynamides; Ketenes; Cyclobutenones; [2+2] Cycloadditions.
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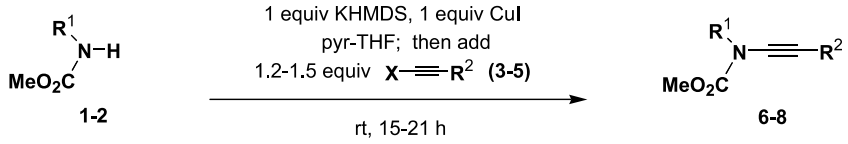
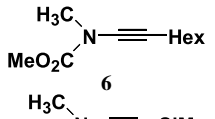
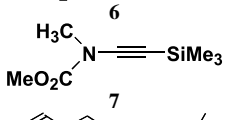
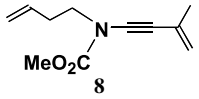
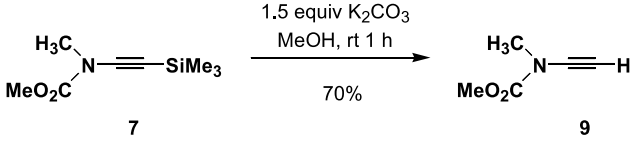
Table 1. Synthesis of ynamides by alkynylation of carbamates



Entry	Carbamate	Halo alkyne	Ynamide	Yield (%)[a]
1	**1** $R^1=CH_3$	**3** X=Br, R^2=Hex	 **6**	61
2	**1** $R^1=CH_3$	**4** X=I, $R^2=SiMe_3$	 **7**	64
3	**2** $R^1=(CH_2)_2CH=CH_2$	**5** X=Br, $R^2=C(CH_3)=CH_2$	 **8**	68

[a] Isolated yields of products purified by column chromatography.



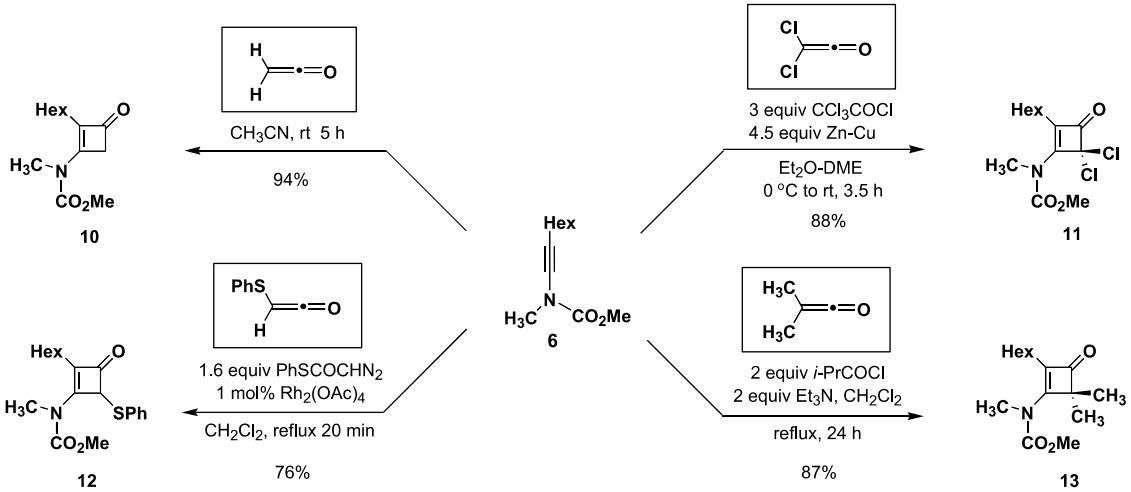
Scheme 1. Synthesis of ynamide **9**.

procedures previously developed in our laboratory and that of Hsung.[11] Tam was motivated to introduce this variant following difficulties he encountered in reproducing results previously reported by both our group and that of Hsung. For example, Tam reported obtaining none of the desired ynamide from the reaction of 1-bromo-2-phenylacetylene with $BnNHCO_2Me$ using either our method[9] or the method of Hsung.[10b] Hsung had previously reported obtaining this ynamide in 73% yield, and we had reported the synthesis of the corresponding Boc derivative in 61% yield.

We have investigated the coupling of $BnNHCO_2Me$ with 1-bromo-2-phenylacetylene in some detail in an attempt to identify the experimental variables that might be responsible for Tam's unsuccessful results. We obtained the expected ynamide (*N*-benzyl-*N*-methoxycarbonyl-2-phenylethynylamine) in 63% yield using our method, and in 79% yield by employing the method of Hsung.[10a] In our experience, both procedures have proved to be highly reproducible. We have noted, however, that results employing our method are affected by the quality of the pyridine used in the reaction. Thus, the yields reported here were obtained using pyridine freshly distilled from CaH_2 or KOH as recommended in our original report.[9] When pyridine (Alfa Aesar, 99%, 0.1% water content) from a freshly opened bottle (without distillation) was used instead, the yield of ynamide product declined to 52%. Most significantly, when distilled pyridine that had then been exposed to the atmosphere for several days was used for the N-alkynylation, none of the desired ynamide was formed.

2.2. Cycloaddition studies

N-Methoxycarbonyl-*N*-methyl-1-octynylamine (**6**) was employed as an initial test substrate to investigate the reactivity of ynamides with different classes of ketenes. As shown in Scheme 2, we found that this ynamide combines



Scheme 2.

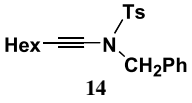
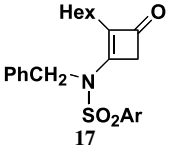
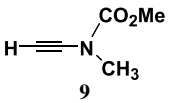
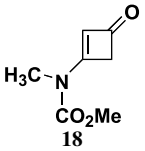
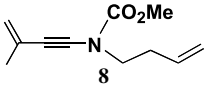
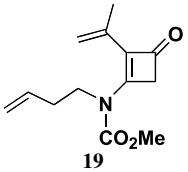
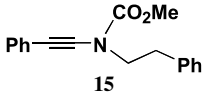
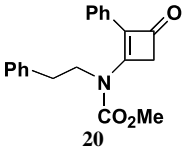
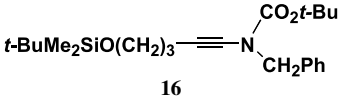
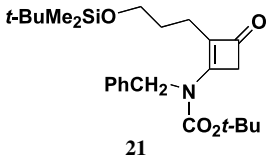
readily with ketene itself to afford the expected cyclobutenone **10** in high yield after purification by column chromatography. For this reaction, ketene was generated by pyrolysis of acetone in a Hurd 'ketene lamp' as described previously[12] and bubbled into a 0.5 M solution of the ynamide in acetonitrile. Although reactions of ketene with alkoxyacetylenes are well known,[4a,c,d] to our knowledge only a few examples of reactions with ynamines,[7c,13] and none with ynamides, have previously been reported. In contrast to the reactions of ynamines, no evidence for the formation of oxete or allene byproducts was detected in the reaction of ynamide **6** with ketene.

Dichloroketene is considerably more reactive in [2+2] cycloadditions than ketene itself,[14] and its reaction with a variety of alkynes has previously been described.[3] As shown in Scheme 2, generation of dichloroketene via reductive dechlorination of trichloroacetyl chloride with zinc–copper couple[3c] in the presence of ynamide **6** provides the 3-amino-4,4-dichlorocyclobutenone **11** in 88% yield. As noted previously, the 1,2-dechlorination protocol constitutes the superior method for the generation of dichloroketene for cycloaddition with alkynes. In the present case, when dichloroketene was generated via the dehydrohalogenation of dichloroacetyl chloride with Et_3N, cyclobutenone **11** was obtained in only 35% yield. To our knowledge, no previous examples of the addition of dichloroketene to ynamines or ynamides have previously been reported.

Reaction of ynamide **6** with (phenylthio)ketene also proceeded smoothly to furnish **12** in 76% yield when this ketene was generated in situ by our $Rh_2(OAc)_4$-catalyzed 'thia-Wolff rearrangement' beginning with $PhSCOCHN_2$.[15] Finally, addition of dimethylketene to ynamide **6** also proceeded in excellent yield when the ketene was prepared in situ via the triethylamine-promoted dehydrohalogenation of isobutyryl chloride. Best results were obtained using CH_2Cl_2 as solvent; in Et_2O the desired cyclobutenone was obtained in only 11% yield. Previously, the cycloaddition of dimethylketene (generated by pyrolysis of tetramethylcyclobutane-1,3-dione) with ynamines has been reported to occur in only low to moderate yield.[7a] As expected, allene byproducts were not detected in any of the above reactions. It should also be noted that the yields in the above cycloadditions are all based on the ynamide component and these reactions were all conducted employing the ketenophile as the limiting reactant. In many ketene cycloadditions, satisfactory yields are only obtained when the ketenophile reaction partner is used in significant excess.

Table 2 presents the results of our investigation of the reaction of ketene with several types of ynamides. In the case of most ynamides, these cycloadditions proceed smoothly in acetonitrile (0.5 M), and CH_2Cl_2, THF, and toluene can also be used with similar results. The [2+2] cycloaddition of ynamides **8** and **15** with ketene proved sluggish under these standard conditions; we believe that the

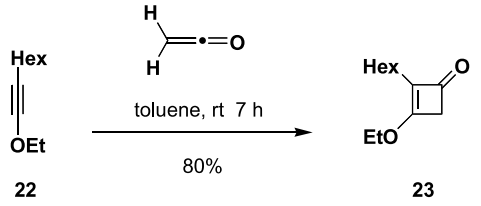
Table 2. [2+2] Cycloadditions of ynamides with ketene

Entry	Ynamide	Cycloadduct	Yield (%)[a]
1	 **14**	 **17**	79
2	 **9**	 **18**	80
3	 **8**	 **19**	65
4	 **15**	 **20**	67 (83)[b]
5	 **16**	 **21**	86

[a] Isolated yields of products purified by column chromatography.
[b] Yield based on recovered starting material.

reactivity of these ynamides is attenuated by the inductive effect of the sp^2 unsaturated substituents attached to the alkyne. These cycloadditions did proceed at a reasonable rate when conducted in the absence of solvent, and under these conditions the desired cyclobutenones **19** and **20** could be obtained in good yield. It is noteworthy that the addition of ketene to ynamide **8** occurs exclusively at the triple bond; no products could be detected resulting from addition of ketene to either the conjugated double bond or the terminal olefin of the butenyl substituent.

As discussed earlier, alkoxyacetylenes function as excellent ketenophiles in reactions with ketene itself. For example, addition of ketene to 1-ethoxyoctyne (**22**) proceeds in 80% yield to afford cyclobutenone **23** after purification by column chromatography on triethylamine-deactivated silica gel (Scheme 3). In order to compare the reactivity of ynamides and alkoxyalkynes in [2+2] cycloadditions, we carried out a competition experiment in which a solution of equal amounts of ynamide **6** and 1-ethoxyoctyne in benzene-d_6 were reacted with excess ketene in the presence of 1,4-dibromobenzene as an internal standard. As shown in Figure 1, analysis of aliquots by ^{1}H NMR indicated that the ynamide reacts with ketene at a similar but slightly slower rate as compared to the alkoxyacetylene.



Scheme 3. Cycloaddition of ketene with 1-ethoxyoctyne.

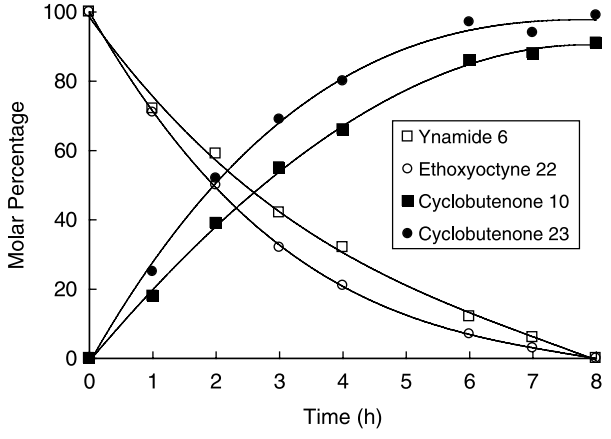


Figure 1. Comparison of rate of [2+2] cycloaddition of ketene with 1-ethoxyoctyne (**22**) and ynamide **6** in benzene-d_6 at 25 °C.

3. Conclusions

3-Aminocyclobutenones have previously been prepared via addition–elimination reactions of amines with 3-alkoxy- and 3-acyloxycyclobutenones,[4d,16] and by the reaction of cyclobutane-1,3-diones with primary amines.[17] Although a few examples of [2+2] cycloadditions of ketenes with ynamines have been reported previously,[7,13] these reactions are often complicated by the formation of allene byproducts arising from stepwise addition pathways. We have shown here that the cycloaddition of several classes of ketenes with ynamide derivatives proceeds in good yield to provide access to a variety of substituted 3-aminocyclobutenones.

4. Experimental

4.1. General

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin-layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230–400 mesh).

4.2. Materials

Commercial grade reagents and solvents were used without further purification except as indicated below. CH_2Cl_2, Et_2O and THF were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Benzene-d_6 was degassed by purging with argon for 10 min prior to use. Et_3N, CH_3CN, and pyridine were distilled under argon from CaH_2 prior to use. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). DME was predried over sodium and then distilled from sodium–benzophenone ketyl prior to use. Trichloroacetyl chloride and isobutyryl chloride were distilled at atmospheric pressure under argon. Zinc–copper couple was prepared from Zn and $CuSO_4 \cdot 5H_2O$.[3c] $PhSCOCHN_2$ was prepared from phenyl thioacetate by diazo transfer as described previously.[15]

4.3. Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance-400 (400 MHz) and Varian Inova-500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were recorded on Bruker Avance-400 (100 MHz) and Varian Inova-500 (125 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High-resolution

mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 T Fourier transform mass spectrometer.

4.4. General procedure for the synthesis of ynamides

4.4.1. *N*-Methoxycarbonyl-*N*-methyl-1-octynylamine (6). A 250 mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and an addition funnel fitted with a rubber septum was charged with carbamate **1**[18] (1.20 g, 13.5 mmol), 60 mL of THF, and 27.3 mL of pyridine. The colorless solution was cooled at 0 °C and a solution of KHMDS (0.91 M in THF, 14.8 mL, 13.5 mmol) was added dropwise via syringe over 4 min. After 15 min, CuI (2.57 g, 13.5 mmol) was added and the resulting green reaction mixture was allowed to warm to rt (ca. 40 min) and stirred for a total of 2 h. A solution of bromo alkyne **3**[9] (3.06 g, 16.2 mmol) in 16 mL of THF was added via the addition funnel over 1 h and the reaction mixture was stirred for 20 h. The resulting red mixture was diluted with 50 mL of Et_2O and washed with three 100-mL portions of a 2:1 mixture of brine and concentrated aqueous NH_4OH solution. The combined aqueous phases were extracted with two 100-mL portions of Et_2O, and the combined organic phases were washed with two 100-mL portions of 3 M HCl solution and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 5.87 g of dark red oil. Column chromatography on 100 g of silica gel (gradient elution with 0–20% EtOAc–hexanes) provided 1.62 g (61%) of ynamide **6** as an orange liquid: IR (neat) 3584, 2956, 2930, 2858, 2265, 1729, 1446, and 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.14 (s, 3H), 2.29 (t, $J=7.2$ Hz, 2H), 1.49–1.55 (m, 2H), 1.36–1.42 (m, 2H), 1.26–1.35 (m, 4H), 0.90 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 54.1, 38.2, 31.8, 31.6, 29.2, 28.7, 22.8, 18.7, 14.4, and 14.3; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{11}H_{19}NO_2$, 220.1308; found 220.1310.

4.4.2. *N*-Methoxycarbonyl-*N*-methyl-2-(trimethylsilyl)-ethynylamine (7). Reaction of a solution of carbamate **1**[18] (1.48 g, 16.6 mmol) in 66 mL of THF with KHMDS (18 mL, 16.6 mmol), pyridine (33 mL, 415 mmol), CuI (3.20 g, 16.6 mmol), and alkynyl iodide **4**[19] (5.20 g, 23.3 mmol) in 20 mL of THF according to the general procedure gave 4.5 g of black oil. Column chromatography on 60 g of silica gel (gradient elution with 0–5% EtOAc–hexanes) afforded 1.96 g (64%) of ynamide **7** as a dark yellow oil: IR (CH_2Cl_2) 2959, 2179, 1733, 1447, and 1344 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.12 (s, 3H), and 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 96.8, 71.2, 54.2, 37.9, and 0.29; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_8H_{15}NO_2Si$, 208.0674; found 208.0674.

4.4.3. *N*-Methoxycarbonyl-*N*-(3-butenyl)-3-methyl-3-buten-1-ynylamine (8). Reaction of a solution of carbamate **2**[20] (0.994 g, 7.70 mmol) in 30 mL of THF with KHMDS (8.5 mL, 7.70 mmol), pyridine (15 mL, 193 mmol), CuI (1.47 g, 7.70 mmol), and alkynyl bromide **5**[9] (1.84 g, 12.6 mmol) in 12 mL of THF according to the general procedure gave 4.2 g of dark brown oil. Column chromatography on 55 g of silica gel (gradient elution with 0–5% EtOAc–hexanes) afforded 1.02 g (68%) of ynamide **8** as a yellow oil: IR (CH_2Cl_2) 2955, 2235, 1732, 1615, 1445 and 1308 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76–5.83 (m, 1H), 5.07–5.20 (m, 4H), 3.81 (s, 3H), 3.57 (t, $J=7.0$ Hz, 2H), 2.43 (app q, $J=7.1$ Hz, 2H), and 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 134.3, 126.5, 119.6, 117.6, 82.2, 72.4, 54.2, 49.4, 32.3, and 23.9; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{11}H_{13}NO_2$, 216.0995; found 216.0999.

4.4.4. *N*-Methoxycarbonyl-*N*-methylethynylamine (9). A 100 mL, one-necked, round-bottomed flask fitted with an argon inlet adapter was charged with ynamide **7** (1.08 g, 5.84 mmol) and 30 mL of methanol. K_2CO_3 (1.21 g, 8.76 mmol) was added in one portion and the reaction mixture was stirred at rt for 1 h. The resulting cloudy mixture was diluted with 30 mL of H_2O and 30 mL of Et_2O. The aqueous layer was separated and extracted with three 30-mL portions of Et_2O and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 0.456 g (69%) of **9** as a flaky yellow solid: IR (CH_2Cl_2) 2959, 2145, 1729, 1448, and 1341 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.11 (s, 3H), and 2.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 105.2, 58.0, 54.4, and 37.7; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_5H_7NO_2$, 136.0369; found 136.0372. A sample recrystallized from hexane had mp 43–45 °C.

4.5. General procedure for the [2+2] cycloaddition of ketene with ynamides[21]

4.5.1. 2-Hexyl-3-[*N*-(methoxycarbonyl)-*N*-methyl-amino]-2-cyclobuten-1-one (10). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[12] A two-necked, 25 mL, pear flask fitted with a rubber septum and an argon inlet adapter was charged with ynamide **6** (0.152 g, 0.77 mmol) in 1.5 mL of CH_3CN. The argon inlet adapter was replaced with an adapter fitted with a glass pipette connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the reaction mixture at rt over a period of 5 h. The reaction mixture was then concentrated to afford 0.279 g of brown oil. Purification by column chromatography on 16 g of silica gel (elution with 25% EtOAc–hexanes) gave 0.184 g (94%) of **10** as a yellow oil: IR (CH_2Cl_2) 2957, 2930, 2858, 1738, 1611, 1382, 1326, and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.44 (s, 2H), 3.39 (s, 3H), 2.15 (t, $J=7.8$ Hz, 2H), 1.45–1.49 (m, 2H), 1.25 (app s, 6H), and 0.85 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 160.4, 153.9, 127.3, 54.5, 51.0, 35.4, 32.0, 29.6, 29.4, 24.1, 23.0, and 14.5; HRMS-EI *m/z* $[M]^+$ calcd for $C_{13}H_{21}NO_3$, 239.1516; found 239.1524.

4.5.2. 2-Hexyl-3-{*N*-benzyl-*N*-[4-(methylphenyl)sulfonyl]-amino}-2-cyclobuten-1-one (17). Reaction of ynamide **14**[9] (0.124 g, 0.34 mmol) in 0.7 mL of CH_3CN with ketene over 6 h according to the general procedure[21] afforded 0.138 g of reddish-brown oil, which was dissolved in 1 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 15% EtOAc–hexanes to provide 0.109 g (79%) of **17** as a pale yellow oil: IR (neat) 2928, 2856, 1753,

1602, 1380, and 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, $J=7.9$ Hz, 2H), 7.27–7.33 (m, 5H), 7.20 (d, $J=7.3$ Hz, 2H), 5.05 (s, 2H), 3.50 (s, 2H), 2.42 (s, 3H), 1.80 (t, $J=7.6$ Hz, 2H), 1.15 (app q, $J=7.1$ Hz, 4H), 0.98–1.08 (m, 4H), and 0.79 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 157.7, 145.3, 136.0, 135.4, 130.3, 129.0, 128.0, 127.5, 126.8, 126.2, 52.6, 50.3, 31.4, 29.2, 28.3, 23.7, 22.5, 21.7, and 14.1; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{24}H_{29}NO_3S$, 434.1760; found 434.1770.

4.5.3. 3-(*N*-Methoxycarbonyl-*N*-methylamino)-2-cyclobuten-1-one (18). Reaction of ynamide **9** (0.456 g, 4.03 mmol) in 8 mL of CH_3CN with ketene for 10 h according to the general procedure afforded 1.49 g of dark brown liquid. Column chromatography on 20 g of silica gel (elution with 50% EtOAc–hexanes) yielded 0.496 g (80%) of cyclobutenone **18** as a reddish-brown solid: mp 52–53 °C; IR (CH_2Cl_2) 2960, 1741, 1570, 1445, 1365, and 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 1H), 3.71 (s, 3H), 3.42 (s, 2H), and 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 166.4, 153.1, 112.2, 49.9, and 34.7; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_7H_9NO_3$, 178.0475; found 178.0472.

4.5.4. 3-[*N*-(3-Butenyl)-*N*-(methoxycarbonyl)amino]-2-isopropenyl-2-cyclobuten-1-one (19). Reaction of ynamide **8** (0.109 g, 0.564 mmol) with ketene in the absence of solvent for 44 h according to the general procedure[21] provided 0.166 g of dark red oil, which was purified by column chromatography on 10 g of silica gel (gradient elution with 0–20% EtOAc–hexanes) to furnish 0.087 g (65%) of **19** as a pale yellow oil: IR (neat) 2958, 1737, 1642, 1595, 1416, 1390, 1368, and 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66–5.75 (m, 1H), 5.17 (qn, $J=1.6$ Hz, 1H), 5.08–5.10 (m, 1H), 5.06 (app t, $J=1.4$ Hz, 1H), 4.89–4.91 (m, 1H), 3.87–3.91 (m, 2H), 3.86 (s, 3H), 3.51 (s, 2H), 2.31–2.36 (m, 2H), and 1.94 (dd, $J=1.5$, 1.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.8, 157.9, 153.3, 134.6, 133.6, 127.9, 117.9, 117.8, 54.2, 51.1, 46.6, 32.9, and 22.3; HRMS-EI *m/z* $[M]^+$ calcd for $C_{13}H_{17}NO_3$, 236.1281; found 236.1291.

4.5.5. 3-[*N*-Methoxycarbonyl-*N*-(2-phenylethyl)amino]-2-phenyl-2-cyclobuten-1-one (20). Reaction of ynamide **15** (0.100 g, 0.377 mmol) with ketene in the absence of solvent for 42 h according to the general procedure[21] provided 0.125 g of dark red oil, which was purified by column chromatography on 6 g of silica gel (gradient elution with 0–20% EtOAc–hexanes) to furnish 0.078 g (67%) of **20** as a pale yellow solid: mp 99–101 °C; IR (CH_2Cl_2) 3028, 2956, 2361, 1749, 1735, 1619, 1590, and 1399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.41 (m, 3H), 7.31 (app d, $J=0.9$ Hz, 2H), 7.16 (t, $J=2.6$ Hz, 3H), 6.67 (dd, $J=5.8$, 2.4 Hz, 2H), 3.94 (t, $J=7.8$ Hz, 2H), 3.83 (s, 3H), 3.59 (s, 2H), and 2.74 (t, $J=7.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 158.8, 153.4, 137.3, 129.6, 129.3, 128.9, 128.7, 128.6, 128.3, 127.0, 126.4, 54.4, 51.8, 49.4, and 34.9; HRMS-EI *m/z* $[M]^+$ calcd for $C_{20}H_{19}NO_3$, 322.1438; found 322.1446.

4.5.6. 3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]-2-(3-*tert*-butyldimethylsiloxybutyl)-2-cyclobuten-1-one (21). Reaction of ynamide **16** (0.100 g, 0.248 mmol) in 0.5 mL of CH_3CN with ketene for 10 h according to the general procedure[21] provided 0.114 g of dark red oil, which was purified by column chromatography on 6 g of silica gel (gradient elution with 0–10% EtOAc–hexanes) to furnish 0.095 g (86%) of **21** as an orange oil: IR (neat) 2955, 2930, 2857, 1756, 1732, 1606, 1370, 1239, and 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (app t, $J=7.4$ Hz, 2H), 7.29 (app d, $J=7.3$ Hz, 1H), 7.18 (d, $J=7.2$ Hz, 2H), 4.96 (s, 2H), 3.56 (t, $J=1.6$ Hz, 2H), 3.51 (t, $J=6.1$ Hz, 2H), 2.07 (t, $J=7.6$ Hz, 2H), 1.60–1.66 (m, 2H), 1.46 (s, 9H), 0.84 (s, 9H), and −0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 160.7, 151.5, 137.0, 129.0, 127.7, 126.0, 125.7, 84.3, 62.6, 51.4, 50.9, 31.4, 28.1, 26.1, 20.5, 18.5, and −5.1; HRMS-EI *m/z* $[M]^+$ calcd for $C_{25}H_{39}NO_4Si$, 446.2721; found 446.2737.

4.5.7. 4,4-Dichloro-2-hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-2-cyclobuten-1-one (11). A one-necked, 10 mL, pear flask fitted with a rubber septum and an argon inlet needle was charged with ynamide **6** (0.100 g, 0.507 mmol) in 1.7 mL of Et_2O and cooled to 0 °C. Zinc–copper couple (0.149 g, 2.28 mmol) was then added in one portion followed by a solution of trichloroacetyl chloride (0.17 mL, 0.276 g, 1.52 mmol) in 0.5 mL of DME dropwise via syringe over 15 min. The reaction mixture was allowed to warm to rt over 3.5 h, diluted with 10 mL of Et_2O, and then extracted with 4 mL of ice-cold 0.5 M HCl solution followed by 4 mL of ice-cold 5% NaOH solution. The combined aqueous layers were extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.165 g of dark yellow oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc–hexanes) afforded 0.138 g (88%) of cyclobutenone **11** as a yellow oil: IR ($CDCl_3$) 2958, 2931, 1785, 1754, 1601, 1448, 1384, and 1295 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.61 (s, 3H), 2.35 (t, $J=6.7$ Hz, 2H), 1.55–1.56 (m, 2H), 1.26–1.32 (m, 6H), 0.88 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 163.0, 152.9, 133.1, 88.6, 54.7, 35.1, 31.5, 29.7, 29.2, 24.9, 22.6, and 14.1; HRMS-EI *m/z* $[M]^+$ calcd for $C_{13}H_{19}Cl_2NO_3$, 307.0737; found 307.0749.

4.5.8. 2-Hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-4-phenylsulfanyl-2-cyclobuten-1-one (12). A 25 mL, two-necked, pear flask equipped with a rubber septum and a reflux condenser fitted with an argon inlet adapter was charged with ynamide **6** (0.100 g, 0.507 mmol), 6 mL of CH_2Cl_2, and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol). The rubber septum was replaced with a 5 mL addition funnel, which was then charged with a solution of $PhSCOCHN_2$ (0.145 g, 0.811 mmol) in 1.5 mL of CH_2Cl_2. The green reaction mixture was heated at reflux and the diazo thiol ester solution was added dropwise over 1 h (the funnel was rinsed with 0.5 mL of CH_2Cl_2). The resulting mixture was heated at reflux for an additional 20 min and then allowed to cool to rt. The reaction mixture was concentrated and the resulting brown oil was filtered through a column of 2 g of silica gel with the aid of 40 mL of CH_2Cl_2. The filtrate was concentrated to give 0.244 g of orange oil, which was purified by column chromatography on 10 g of silica gel (elution with 10% EtOAc–hexanes) to give 0.133 g (76%) of **12** as an orange oil: IR (neat) 2956, 2929, 1758, 1738, 1612, and 1379 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J=7.0 Hz, 2H), 7.27–7.33 (m, 3H), 4.85 (s, 1H), 3.88 (s, 3H), 3.20 (s, 3H), 1.93 (t, 2H), 1.05–1.28 (m, 8H), and 0.86 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0, 161.2, 153.3, 136.4, 132.3, 129.1, 129.0, 128.7, 66.0, 54.4, 35.1, 31.5, 29.2, 28.2, 23.7, 22.5, and 14.1; HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{19}H_{25}NO_3S$, 370.1447; found 370.1440.

4.5.9. 4,4-Dimethyl-2-hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-2-cyclobuten-1-one (13). A 10 mL, one-necked, pear flask equipped with a rubber septum and an argon inlet needle was charged with ynamide **6** (0.100 g, 0.507 mmol), 2 mL of CH_2Cl_2, and isobutyryl chloride (0.108 g, 0.106 mL, 1.01 mmol). A solution of Et_3N (0.113 g, 0.156 mL, 1.12 mmol) in 0.3 mL of CH_2Cl_2 was transferred into the reaction mixture via cannula over 3 min (the flask was rinsed with 0.2 mL of CH_2Cl_2). The septum was replaced with a cold finger condenser and the pink solution was heated at reflux for 24 h. The resulting heterogeneous orange mixture was allowed to cool to rt, diluted with 20 mL of CH_2Cl_2, and washed with 10 mL of 1 M HCl solution and 15 mL of H_2O. The combined aqueous phases were extracted with two 10-mL portions of CH_2Cl_2 and the combined organic phases were washed with 20 mL of 10% K_2CO_3 solution and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.161 g of orange oil. Column chromatography on 10 g of silica gel (elution with 20% EtOAc–hexanes) provided 0.118 g (87%) of cyclobutenone **13** as a yellow liquid: IR (neat) 2957, 2928, 2361, 1751, 1602, 1449, 1379, and 1198 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.40 (s, 3H), 2.17 (t, J=7.6 Hz, 2H), 1.46–1.52 (m, 2H), 1.31 (s, 6H), 1.24–1.34 (m, 6H), and 0.87 (t, J=3.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 169.5, 152.8, 124.6, 62.3, 53.9, 35.5, 31.7, 29.3, 29.1, 23.8, 22.7, 21.5, and 14.2; HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{15}H_{25}NO_3$, 290.1727; found, 290.1725.

4.5.10. 3-Ethoxy-2-hexyl-2-cyclobuten-1-one (23). Reaction of 1-ethoxyoctyne (**22**)[22] (0.078 g, 0.51 mmol) in 2 mL of toluene with ketene for 7 h according to the general procedure[21] afforded 0.157 g of brown oil, which was dissolved in 2 mL of CH_2Cl_2 and several drops of Et_3N and concentrated onto 0.6 g of silica gel. This material was added to the top of a column of 8 g of silica gel and eluted with 0–30% EtOAc–hexanes containing 1% Et_3N to give 0.080 g (80%) of **23** as a pale yellow oil: IR (neat) 2956, 2928, 2857, 1758, 1635, 1379, and 1340 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, J=7.1 Hz, 2H), 3.16 (t, J=1.8 Hz, 2H), 2.02 (app tt, J=7.6, 1.8 Hz, 2H), 1.44–1.52 (m, 2H), 1.44 (t, J=7.0 Hz, 3H), 1.23–1.34 (m, 6H), and 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 175.8, 122.3, 69.0, 46.8, 31.6, 29.3, 27.9, 22.7, 22.4, 15.5, and 14.2; HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{12}H_{20}O_2$, 219.1356; found 219.1362.

4.6. Competition experiment

A solution of ynamide **6** (0.081 g, 0.41 mmol) and 1-ethoxyoctyne (**22**) (0.063 g, 0.41 mmol) in 1.6 mL of benzene-d_6 containing 1,4-dibromobenzene (0.096 g, 0.41 mmol) as an internal standard was treated with ketene according to the general procedure. Aliquots (ca. 0.1 mL) of the reaction mixture were taken at intervals, diluted with benzene-d_6, and examined by ^{1}H NMR (500 MHz) with relaxation time $d1$=20 s to ensure accurate integration and auto phasing or manual phasing to ensure a level baseline. In this experiment, chemical shifts are expressed in parts per million downfield from tetramethylsilane with the C_6H_6 peak at 7.16 ppm used as the standard. For cyclobutenone **10**, the average of the resonances at 3.21, 3.17, and 2.68 ppm were used; for cyclobutenone **23**, the resonance at 2.80 ppm was integrated. For alkoxyacetylene **22**, the methylene at 3.63 ppm was used, and for ynamide **6**, the relative amount was determined by integration of the overlapping methylenes for **6** and **22** at 2.18 ppm (after correcting for the amount of **22** determined by integration of the resonance at 3.63 ppm).

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Ruthenium-catalyzed [2+2] cycloadditions of bicyclic alkenes and ynamides

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Abstract—Ruthenium-catalyzed [2+2] cycloadditions between bicyclic alkenes and ynamides were investigated. The ynamide moiety was found to be compatible with the ruthenium-catalyzed cycloaddition conditions giving the corresponding cyclobutene cycloadducts in moderate to good yields (up to 97%). Diastereoselective cycloaddition utilizing chiral cyclic ynamides were also examined and a low to moderate level of asymmetric induction was observed.

1. Introduction

Ynamines and ynamides (electron-deficient ynamines) have been shown to be useful building blocks in organic synthesis.[1] However, their inaccessibility had limited their synthetic usefulness until recent developments and improvements in their synthesis were published by Danheiser,[2] Hsung,[3] Cossy,[4] Sato,[5] and Witulski.[6] Ynamides have been the main focus of research in this area due to their greater stability over ynamines. Accordingly, the interest in the application of ynamides in organic synthesis has increased remarkably. Recent studies on the synthetic value of ynamides include: Pauson–Khand [2+2+1] cycloadditions,[7] thermal and transition metal-catalyzed [4+2] cycloadditions,[8] Lewis acid catalyzed [2+2] cycloadditions,[9] Rh-catalyzed [2+2+2] cycloadditions,[10] ring-closing metathesis (RCM),[11] transition metal-catalyzed coupling reactions,[12] rearrangement reactions,[13] hydrometalation and hydrohalogenation reactions,[14] and cyclization reactions.[15]

We have studied various types of cycloaddition reactions of bicyclic alkenes, and are especially interested in those catalyzed by transition metals.[16,17] Transition metal-catalyzed cycloadditions have demonstrated their utility as efficient methods in the formation of rings and complex molecules.[18] We and others have studied various aspects of transition metal-catalyzed [2+2] cycloadditions between an alkene and an alkyne for the synthesis of cyclobutene rings, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsymmetrical substrates, and asymmetric induction studies using chiral auxilliary on the alkyne component.[17,19–21] The alkynes employed in transition metal-catalyzed [2+2] cycloadditions usually contain carbon substituents such as alkyl, aryl, ester, and ketone functionalities. However, we recently showed that heteroatom substituted acetylenes such as alkynyl halides[17g] and ynamides[17h] were also suitable substrates. We now report a full account on the ruthenium-catalyzed [2+2] cycloaddition reactions of bicyclic alkenes with ynamides.

2. Results and discussion

2.1. Synthesis of ynamides

To begin this study, several acyclic ynamides were prepared (Table 1). Screening of various methods for the synthesis of ynamides found the methods by Danheiser[2] and Hsung[3] to be the most reliable. However, fine-tuning of the reaction conditions was required in order to optimize yields for some of the desired ynamides. For example, using Hsung's catalytic $CuSO_4$ method[3c] did not result in the formation of ynamide **3a** (entry 1), and only homo-coupling of alkynyl bromide **1a** was observed. Similarly, Danheiser's stoichiometric CuI method[2] only produced ynamide **3a** in a low yield of 16% (entry 2). Re-examination of Buchwald's amidation of aryl bromide[22] suggested that the rate of

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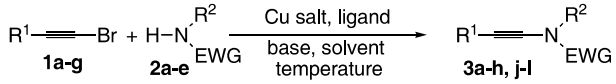
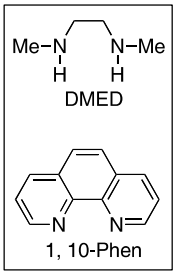
Table 1. Synthesis of acyclic ynamides **3a–h**, **3j–l**





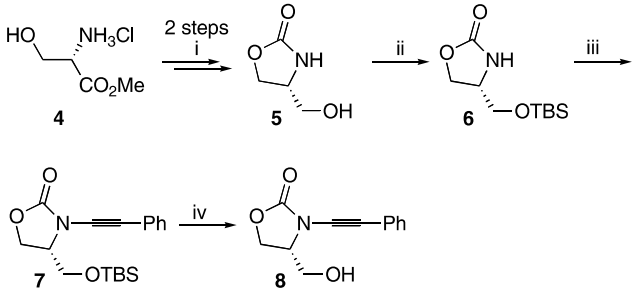
3a: R^1=Ph, EWG=COOMe, R^2=Cy
3b: R^1=Ph, EWG=COOMe, R^2=CH_2CH_2Ph
3c: R^1=Ph, EWG=COOMe, R^2=CH_2Ph
3d: R^1=Ph, EWG=COO^tBu, R^2=CH_2Ph
3e: R^1=Ph, EWG=COOMe, R^2=Ph
3f: R^1=*p*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3g: R^1=*o*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3h: R^1=*m*-F-C_6H_5, EWG=COOMe, R^2=Ph
3j: R^1=CH_2OTBS, EWG=COOMe, R^2=Ph
3k: R^1=CH_2CH_2OTBS, EWG=COOMe, R^2=Ph
3l: R^1=$^iPr_3Si$, EWG=COOMe, R^2=Ph

Entry	Ynamide **3**	Alkyne **1** (equiv)	Amide **2** (equiv)	Cu (equiv)	Base (equiv)	Ligand (equiv)	Solvent/ Temperature (°C)	Yield (%)[a]
1	**3a**	**1a** (2)	**2a** (1)	$CuSO_4$ (0.1)	K_2CO_3 (2.0)	Phen (0.2)	Toluene/60	0
2		**1a** (2)	**2a** (1)	CuI (1.0)	KHMDS (0.1)	—	Pyridine/25	16
3[b]		**1a** (2)	**2a** (1)	CuI (0.06)	KHMDS (1.2)	Phen (0.14)	Toluene/90	43
4[b]		**1a** (2)	**2a** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	Toluene/90	65
5[b]	**3b**	**1a** (1)	**2b** (1.1)	CuI (0.06)	KHMDS (1.1)	DMED (0.1)	Toluene/90	17
6		**1a** (1)	**2b** (1.2)	CuI (0.06)	K_2CO_3 (2.0)	DMED (0.1)	Toluene/60	38
7[b]		**1a** (3)	**2b** (1)	CuI (0.08)	KHMDS (1.2)	Phen (0.12)	Toluene/90	52
8	**3c**	**1a** (2)	**2c** (1)	CuI (1.0)	KHMDS (1.0)	—	Pyridine/25	0
9		**1a** (1)	**2c** (1)	CuCN (0.06)	K_3PO_4 (2.0)	DMED (0.1)	Toluene/110	0
10[b]		**1a** (2)	**2c** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	Toluene/90	61
11[b]	**3d**	**1a** (1)	**2d** (1.7)	CuI (0.2)	KHMDS (1.0)	Phen (0.22)	Toluene/90	68
12[b]	**3e**	**1a** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	Toluene/90	65
13[b]	**3f**	**1b** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.27)	Toluene/90	48
14[b]	**3g**	**1c** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	Toluene/90	39
15[b]	**3h**	**1d** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.1)	Phen (0.28)	Toluene/90	54
16[b]	**3j**	**1e** (1)	**2e** (1.4)	CuI (0.4)	KHMDS (1.7)	Phen (0.46)	Toluene/90	59
17[b]	**3k**	**1f** (1.4)	**2e** (1)	CuI (0.25)	KHMDS (1.0)	Phen (0.23)	Toluene/90	26
18[b]	**3l**	**1g** (1.2)	**2e** (1)	CuI (0.3)	KHMDS (1.3)	Phen (0.36)	Toluene/90	90

[a] Yield of isolated cycloadducts after column chromatography.
[b] The base was added slowly to the reaction mixture at the indicated temperature through a syringe pump over 3–4 h. See text for details.

deprotonation of the amide had to match the rate of the amidation reaction in order for the coupling reaction to be successful. Buchwald suggested that the formation of excess deprotonated amide deactivates the Cu-catalyst by forming an unreactive cuprate complex. With this insight, Hsung's catalytic CuI method[3b] was modified by adding the base (KHMDS) slowly to the reaction mixture over 3–4 h using a syringe pump. To our delight, we could improve the yield of ynamide **3a** up to 65% (entry 4). Similarly, several reaction conditions were attempted for the syntheses of ynamides **3b** and **3c** and it was found that our modified conditions gave the best results. By using the modified reaction conditions (0.2–0.3 equiv of CuI, 0.22–0.36 equiv of the 1,10-phen ligand, and adding 1.2 equiv of the base KHMDS slowly over 3–4 h in toluene at 90 °C), ynamides **3d–3l** were obtained in moderate to good yields (entries 11–18).

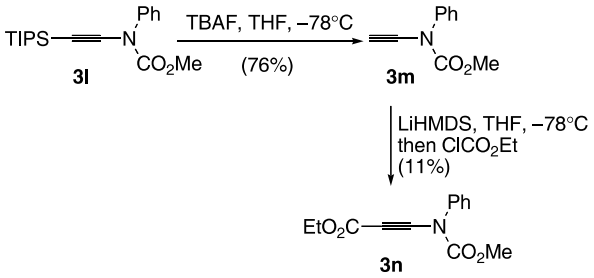
This methodology was also effective for the synthesis of the chiral ynamide **8** (Scheme 1). The synthesis first required the preparation of **5** from (*S*)-4-hydroxymethyloxazolidin-2-one **4** following a method developed by Sibi et al.[23] Direct coupling of **5** with bromophenylacetylene **1a** did not produce the desired product. However, when the alcohol group was protected using TBSCl, the coupled product **7** was obtained in 46% yield. Deprotection of **7** afforded **8** in a yield of 40%.



Scheme 1. Synthesis of (*S*)-4-hydroxymethyl-3-phenylethynyl-oxazolidin-2-one (**8**). Reagents and conditions: (i) see Ref. 34; (ii) TBSCl, DMAP, Et_3N, CH_2Cl_2, 25 °C (80%); (iii) **1a**, CuI, KHMDS, 1,10-phen, toluene, 90 °C (46%); (iv) TBAF, THF, −78 °C (40%).

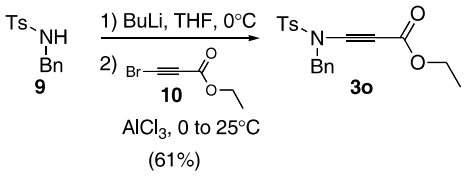
Our attention was then directed towards the synthesis of ynamides bearing an electron-withdrawing group at the acetylenic position. To date, no method to couple amides or sulfonamides with electron-deficient haloacetylenes has been published. Indeed, all our attempts to couple **2e** with ethyl 3-bromopropynoate **10** utilizing different copper-based coupling methodologies failed. Instead, **3n** was synthesized from **3l** in two steps (Scheme 2).

Electron-poor ynamide **3o** was also prepared. Unlike all previous cases, it was obtained through an unprecedented



Scheme 2. Synthesis of *N*-ethoxycarbonylethynyl-*N*-phenylcarbamic acid methyl ester **3n**.

conjugate addition/elimination process. Sulfonamide **9** was first deprotonated with butyllithium, and was then added to the bromoester **10** in presence of aluminium chloride, yielding to **3o** in 61% (Scheme 3). Intrigued by this expedient synthesis, we attempted to apply this methodology to the preparation of **3n** from the amide **2e**. Unfortunately, this methodology is thus far only applicable to sulfonamides.



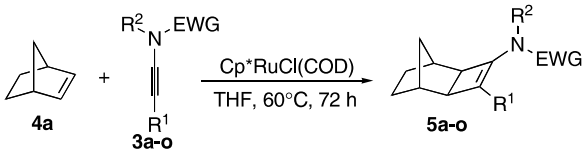
Scheme 3. Synthesis of **3o**.

2.2. Ruthenium-catalyzed [2+2] cycloadditions of ynamides

With these acyclic ynamides in hand, we studied their Ru-catalyzed [2+2] cycloadditions with norbornene **4a** and the results are shown in Table 2. Unlike alkynes with electron-withdrawing groups attached to the acetylenic carbon (e.g., COOEt[17a] or halides[17g]), which undergo Ru-catalyzed [2+2] cycloadditions with bicyclic alkenes at room temperature, ynamides were found to be less reactive and usually required an elevated temperature (60 °C) and a longer reaction time in order for the reaction to go to completion. Moderate to good yields of the Ru-catalyzed [2+2] cycloadditions were obtained with most of the ynamides. Interestingly, Hsung previously observed an unusual *endo* cycloaddition of ynamides with bicyclic alkenes in the Co-catalyzed [2+2+1] Pauson–Khand cycloadditions.[7e] We did not observe such an unusual change in stereochemistry with our Ru-catalyzed [2+2] cycloadditions with ynamides.[24] In all cases single stereoisomers, the *exo* cycloadducts **5** were formed.

Several trends were observed in the Ru-catalyzed [2+2] cycloadditions of acyclic ynamides (Table 2). With ynamides **3a–e** (R^1=Ph, entries 1–6), an increase in the steric bulk of the substituents (R^2 and EWG) on the nitrogen led to a decrease in the yield (compare entries 1 and 2, R^2=2° alkyl group vs 1° alkyl group; and compare entries 3 and 4, EWG=COOMe vs COO^{t}Bu). For ynamides **3e–h** (R^2=Ph, EWG=COOMe and R^1=aromatic groups, entries 6–9), both the electron-withdrawing aromatic group (*m*-F–C_6H_5, entry 9) and sterically bulky aromatic group (*o*-Me–C_6H_5, entry 8) led to a decrease in the yield in

Table 2. Ru-catalyzed [2+2] cycloaddition between norbornene and acyclic ynamides



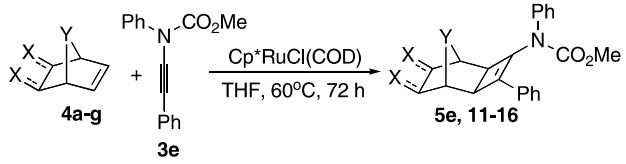
Entry	Ynamide	R^1	EWG	R^2	Yield (%)[a]
1	**3a**	Ph	COOMe	Cy	55[b]
2	**3b**	Ph	COOMe	CH_2CH_2Ph	73
3	**3c**	Ph	COOMe	CH_2Ph	91
4	**3d**	Ph	COO^{t}Bu	CH_2Ph	39 (5)
5		Ph	COO^{t}Bu	CH_2Ph	75 (9)[c]
6	**3e**	Ph	COOMe	Ph	97
7	**3f**	*p*-Me–C_6H_5	COOMe	Ph	85[b]
8	**3g**	*o*-Me–C_6H_5	COOMe	Ph	49 (32)[b]
9	**3h**	*m*-F–C_6H_5	COOMe	Ph	58[d]
10	**3i**	CH_2OH	COOMe	Ph	32[d]
11	**3j**	CH_2OTBS	COOMe	Ph	25[d]
12	**3k**	CH_2CH_2OTBS	COOMe	Ph	78
13	**3l**	$^i Pr_3Si$	COOMe	Ph	0 (93)
14	**3m**	H	COOMe	Ph	0[d]
15	**3n**	COOEt	COOMe	Ph	0 (34)[d]
16	**3o**	COOEt	SO_2Tol	Bn	0 (47)

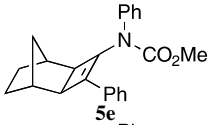
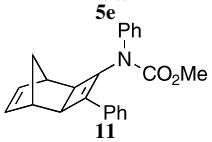
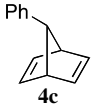
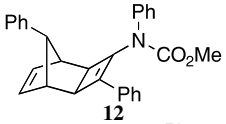
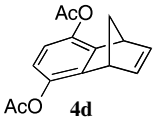
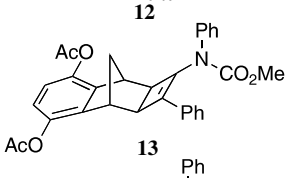
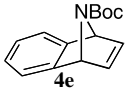
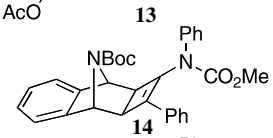
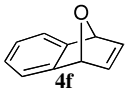
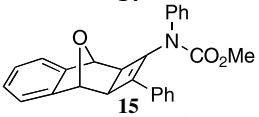
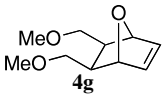
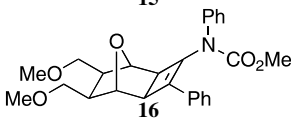
[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.
[b] The reaction was stirred at 60 °C for 168 h.
[c] The reaction was stirred at 25 °C for 168 h.
[d] Polymeric materials were also obtained on the top of the column.

the cycloaddition. Ynamides containing propargylic alcohol and propargylic silyl ether groups (entries 10 and 11) gave low yields in the cycloadditions, which may be explained by the observance of polymeric materials. Terminal ynamide **3m** (R^1=H, entry 14) gave only polymeric materials under the cycloaddition conditions. Also, ynamide **3l**, with a very bulky group on the alkyne (R^1=Si^{i}Pr$_3$, entry 13) and ynamide **3n**, containing an electron-withdrawing group (R^1=COOEt, entry 15), were both inert in the Ru-catalyzed [2+2] cycloaddition. In the case of R^1 being an electron-withdrawing group, changing the electronics of the nitrogen (EWG=SO_2Tol, entry 16) did not improve the reactivity.

The scope of the reaction of ynamide **3e** with different bicyclic alkenes was also investigated (Table 3). In general, moderate to excellent yields were obtained (entries 1, 4–7), with the exception of norbornadienes **4b** and **4c** (entries 2 and 3). This was surprising since previous examples using these norbornadiene substrates suggested that the Ru-catalyzed [2+2] cycloaddition reaction was feasible with other alkynes.[17a–g] Furthermore, the presence of an extra double bond of the norbornadienes usually enhances the rate of the Ru-catalyzed [2+2] cycloaddition. In the present cases, we believe that the alkyne moiety of the ynamide fails to displace the alkene that chelates, in a bidentate fashion, to the ruthenium catalyst. Therefore, the relatively stable complex stays inert in the reaction conditions. As mentioned previously, higher temperature and longer reaction time are usually required with ynamides, which can be related to their lower affinity to complex to the ruthenium catalyst. Thus, utilizing **4d** (entry 4) as the alkene partner, where one of the double bonds is substituted by an aryl group,

Table 3. Ruthenium-catalyzed [2+2] cycloaddition bicyclic alkenes and ynamide **3e**



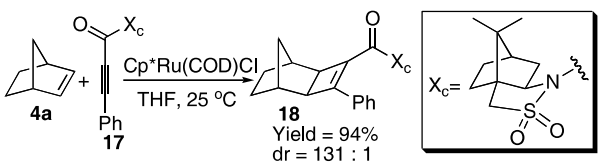
Entry	Alkene	Product	Yield (%)[a]
1	 **4a**	 **5e**	97
2	 **4b**	 **11**	0 (97)
3	 **4c**	 **12**	0 (98)
4	 **4d**	 **13**	90
5	 **4e**	 **14**	46
6	 **4f**	 **15**	83
7	 **4g**	 **16**	94

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.

the reaction proceeded smoothly and a 90% yield of the cycloadduct **13** was obtained. Similarly to **4d**, alkenes **4e**, **4f**, and **4g** containing a heteroatom-based group at the bridgehead position, also underwent cycloaddition with ynamide **3e** (entries 5–7).

2.3. Asymmetric ruthenium-catalyzed [2+2] cycloadditions of chiral ynamides

We have recently reported the first two examples of asymmetric induction studies of Ru-catalyzed [2+2] cycloadditions between an alkene and an alkyne using a chiral auxilliary attached to the alkyne component.[17d,e] With the excellent level of asymmetric induction obtained in the case of the chiral acetylenic acyl sultams

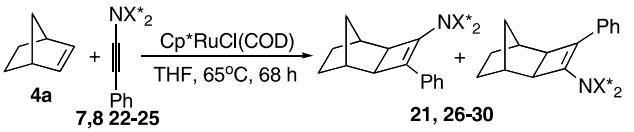


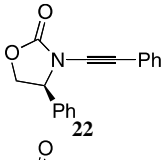
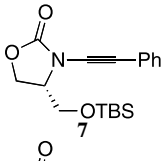
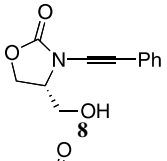
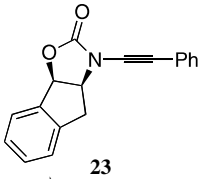
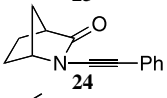
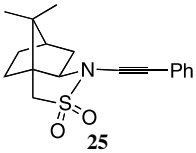
Scheme 4. Ru-catalyzed [2+2] cycloadditions between **4a** and **17**.

(Scheme 4) and good reactivity of acyclic ynamides in the Ru-catalyzed [2+2] cycloadditions, we decided to explore the chiral cyclic ynamides. Since the chiral functional group would be closer to the reaction center, a greater degree of asymmetric induction was anticipated. On the other hand, this could also mean increased steric congestion, which could potentially decrease the rate of the reaction or even suppress the formation of the cycloadduct since the acetylenic electron-withdrawing carbonyl group is not present anymore.

Several known (**22**, **23**) and new chiral cyclic ynamides (**7**, **8**, **24**, **25**) were synthesized and the results of the Ru-catalyzed [2+2] cycloadditions of these chiral cyclic ynamides are shown in Table 4. Good yields of the cycloadditions were obtained with chiral cyclic ynamides **7**, **8**, **22** and **23** (entries 1–5), however, the diastereoselectivity was only low to moderate. The diastereomeric ratios (dr) were determined by 400 MHz ^{1}H NMR and the peaks were compared to the 1:1 mixture of the diastereomers, which were synthesized using Buchwald's Cu-catalyzed amidation of vinyl iodide **19** (Scheme 5).[25]

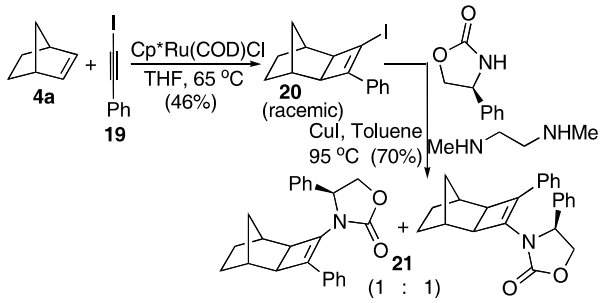
Table 4. Ru-catalyzed [2+2] cycloaddition between norbornene and chiral cyclic ynamides



Entry	Ynamide	Product (% yield)[a]	dr (%)[b]
1	 22	**21** (83)	72:28
2[c]	 7	**26** (72)	58:42
3[c]	 8	**27** (81)[d]	71:29
4	 23	**28** (82)	74:26
5[e]		**28** (60)[d]	75:25
6[c]	 24	**29** (0)[d]	NA
7	 25	**30** (0)[d]	NA

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.
[b] Diastereomeric ratios (dr) measured by 400 MHz ^{1}H NMR.
[c] The reaction was stirred for 168 h.
[d] 16–94% of starting material recovered.
[e] The reaction was stirred at 25 °C for 216 h.

A decrease in the reaction temperature led to a corresponding decrease in the yield and no improvement of the diastereoselectivity was observed (entries 4 and 5). Ynamides attached to bicyclic frameworks were too bulky and were found to be inert in the Ru-catalyzed [2+2] cycloadditions (entries 6 and 7). It is worth noting that ynamide **25** was unreactive in the Ru-catalyzed [2+2] cycloaddition, but that amide **17** (Scheme 4), with an extra carbonyl group between the nitrogen atom and the acetylenic carbon, gave excellent yield and excellent diastereoselectivity in the cycloaddition.



Scheme 5. Synthesis of 1:1 diastereomers of **23**.

3. Conclusion

In summary, we have demonstrated that the ynamide moiety is compatible with the Ru-catalyzed [2+2] cycloadditions and that the reactivity of ynamide functionality is generally lower than other electron-deficient alkynes. We also found that diverse bicyclic alkenes could be utilized, with the exception of norbornadienes. Moderate to good yields of the cycloadditions were obtained with various acyclic and cyclic ynamides. However, only low to moderate levels of asymmetric induction was observed in the Ru-catalyzed [2+2] cycloadditions with chiral cyclic ynamides. Futher investigations on the mechanism of the cycloaddition, improvement of the asymmetric induction using other chiral ynamides, and the studies on regioselectivity of the Ru-catalyzed [2+2] cycloadditions between unsymmetrical bicyclic alkenes and ynamides are currently in progress in our laboratory.

4. Experimental

All reactions were carried out in an atmosphere of dry nitrogen at ambient temperature unless otherwise stated. Standard column chromatography was performed on 230–400 mesh silica gel (obtained from Silicycle) using flash column chromatography techniques.[26] Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. All glassware was flame dried under an inert atmosphere of dry nitrogen. Infrared spectra were taken on a Bomem MB-100 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-300, 400 or 600 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). High resolution mass spectra were done by McMaster Regional Centre for Mass Spectrometry at McMaster University, Hamilton, Ontario. Elemental analyses were performed by Canadian Microanalytical Service Ltd, British Columbia or by Quantitative Technologies Inc., New Jersey. Unless stated otherwise, commercial reagents were used without purification. Solvents were purified by distillation under dry nitrogen: from CaH_2 (pyridine); from sodium (toluene); and from potassium/benzophenone (THF). Ynamides **22** and **23**,[27] and Cp*RuCl(COD)[28] were prepared according to literature procedures.

Special note: for some of the acyclic ynamides as well as their corresponding [2+2] cycloadducts, some of the ^{13}C NMR signals (especially those of acetylenic, olefinic and carbonyl carbons, which are directly attached to the nitrogen) are severely broadened and virtually lost

(or very hard to detect) in 1-D ^{13}C NMR spectra. This is due to the system undergoing chemical exchange near the coalescence point, and in these cases, 2-D HMBC spectra were obtained in which the 'missing peaks' can be detected.[29]

4.1. Synthesis of ynamides

General procedure (A) for the synthesis of the ynamides. A mixture of the amide (1.0 equiv), alkynyl halide (2.0 equiv), copper iodide (0.2 equiv), 1,10-phenanthroline (0.25 equiv), and toluene (~0.6 M w.r.t. the amide) was prepared in an oven-dried round-bottomed flask, equipped with a condenser, under nitrogen. The mixture was heated at 90 °C and potassium bis(trimethylsilyl)amide (KHMDS, 1.2 equiv, 0.5 M in toluene) was added slowly via a syringe pump over 3–4 h. The reaction mixture was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was diluted with diethyl ether and subsequently washed three times with 2:1 mixture of saturated sodium chloride solution and concentrated NH_4OH. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (hexanes or ethyl acetate/hexanes mixture) using silica gel pre-treated with triethylamine.

General procedure (B) for the synthesis of the ynamides. To a cold solution (0 °C) of the amide (1.0 equiv) in pyridine (0.4 M) was added dropwise potassium bis(trimethylsilyl)-amide (KHMDS, 1 equiv, 0.5 M in toluene). The reaction was stirred for 15 min then a solution of copper iodide (1.0 equiv) in pyridine was added via a cannula. The resulting mixture was allowed to warm up to 25 °C and stirred for 2 h. A solution of alkynyl halide (2.0 equiv) in THF was added via cannula over 30 min and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with diethyl ether and washed three times with 2:1 mixture of saturated sodium chloride solution and concentrated NH_4OH. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (hexanes or ethyl acetate/hexanes mixture) using silica gel treated with triethylamine.

General procedure (C) for the synthesis of the ynamides. To a cold solution (0 °C) of the sulfonamide (1.0 equiv) in THF (~0.4 M w.r.t. the amide) prepared in an oven-dried round-bottomed flask under nitrogen was added dropwise a solution of butyllithium in THF (2.5 M, 1.01 equiv). The mixture was stirred at 0 °C for 15 min and aluminium chloride (0.1 equiv) was added. The reaction mixture was then added via cannula to a cold solution (0 °C) of bromoalkyne (1.1 equiv) in THF (~0.8 M w.r.t. the bromoalkyne). The reaction mixture was stirred 30 min at 0 °C and then allowed to warm to room temperature until completion. The reaction mixture was quenched with water and diluted with diethyl ether, and the water was subsequently removed using Na_2SO_4. The organic layer was filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (ethyl acetate/hexanes mixture) using silica.

4.1.1. *N*-Cyclohexyl-*N*-phenylethynylcarbamic acid methyl ester (3a). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (298.9 mg, 1.651 mmol) and *N*-cyclohexylcarbamic acid methyl ester **2a** (127.4 mg, 0.8106 mmol), copper iodide (8.9 mg, 0.047 mmol), 1,10-phenanthroline (20.7 mg, 0.115 mmol), and KHMDS (0.5 M in toluene, 2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide **3a** (89.3 mg, 0.347 mmol, 43%) as a yellow oil. R_f 0.47 (EtOAc/hexanes=1:4); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.43 (m, 2H), 7.24–7.35 (m, 3H), 3.99 (br t, 1H, J=12.0 Hz), 3.84 (s, 3H), 1.82–1.89 (m, 4H), 1.58–1.68 (m, 3H), 1.33–1.43 (m, 2H), 1.11–1.19 (m, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 155.4, 131.1, 128.2, 127.4, 123.4, 80.6, 72.3, 56.5, 53.9, 30.5, 25.3, 25.1. This is a known compound and the spectral data are identical to those reported in the literature.[31]

4.1.2. *N*-Phenylethyl-*N*-phenylethynylcarbamic acid methyl ester (3b). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (662 mg, 3.657 mmol) and *N*-phenylcarbamic acid methyl ester **2b** (209.5 mg, 1.169 mmol), copper iodide (16.7 mg, 0.088 mmol), 1,10-phenanthroline (24.7 mg, 0.137 mmol), and KHMDS (2.8 mL, 1.4 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:99) to provide **3b** (171 mg, 0.6121 mmol, 52%) as an orange oil. R_f 0.43 (EtOAc/hexanes=1:9); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.47 (m, 10H), 3.87 (t, 2H, J=7.8 Hz), 3.84 (s, 3H), 3.09 (t, 2H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 137.9, 131.3, 128.9, 128.5, 128.2, 127.6, 126.6, 123.1, 82.7, 71.0, 54.0, 51.3, 34.1. This is a known compound and the spectral data are identical to those reported in the literature.[2]

4.1.3. *N*-Benzyl-*N*-phenylethynylcarbamic acid methyl ester (3c). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (476 mg, 2.623 mmol) and *N*-benzylcarbamic acid methyl ester **2c** (208.7 mg, 1.263 mmol), copper iodide (47.6 mg, 0.250 mmol), 1,10-phenanthroline (59.8 mg, 0.332 mmol), and KHMDS (3.0 mL, 1.5 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide **3c** (205.7 mg, 0.7753 mmol, 61%) as a yellow oil. R_f 0.31 (EtOAc/hexanes=1:9); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.42 (m, 10H), 4.71 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 135.8, 131.1, 128.5, 128.1, 128.0, 127.5, 123.0, 82.9, 71.1, 54.1. This is a known compound and the spectral data are identical to those reported in the literature.[32]

4.1.4. *N*-Phenyl-*N*-phenylethynylcarbamic acid methyl ester (3e). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (478.1 mg, 2.641 mmol) and *N*-phenylcarbamic acid methyl ester **2a** (209.2 mg, 1.384 mmol), copper iodide (57.3 mg, 0.301 mmol), 1,10-phenanthroline (60.9 mg, 0.338 mmol), and KHMDS (3.2 mL, 1.6 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to

provide **3e** (225.6 mg, 0.8978 mmol, 65%) as a yellow oil. R_f 0.32 (EtOAc/hexanes=1:9); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.56 (m, 10H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 139.5, 131.4, 129.0, 128.2, 127.8, 127.0, 124.6, 122.8, 82.7, 70.1, 54.4. This is a known compound and the spectral data are identical to those reported in the literature.[33]

4.1.5. *N*-Phenyl-*N*-*p*-tolylethynylcarbamic acid methyl ester (3f). Following the above general procedure (A) with 1-bromoethynyl-4-methylbenzene **1b**[30] (596 mg, 3.040 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (231 mg, 1.528 mmol), copper iodide (64.2 mg, 0.337 mmol), 1,10-phenanthroline (74.9 mg, 0.416 mmol), and KHMDS (3.6 mL, 1.8 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3f** (196.1 mg, 0.7391 mmol, 48%) as an orange solid (mp 59–63 °C). R_f 0.39 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3045 (w), 2955 (w), 2252 (m), 1738 (s), 1595 (w), 1492 (m), 1439 (m), 1362 (m), 1289 (s), 1124 (w), 1052 (w), 738 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.63 (m, 2H), 7.40–7.47 (m, 4H), 7.32 (m, 1H), 7.15–7.17 (m, 2H), 3.93 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 139.5, 137.7, 131.2, 128.9, 128.8, 126.7, 124.4, 119.5, 81.9, 70.0, 54.1, 21.2. HRMS calcd for $C_{17}H_{15}NO_2$: *m*/*z* 265.1103, found *m*/*z* 265.1113. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found C, 76.80; H, 5.86.

4.1.6. *N*-Phenyl-*N*-*o*-tolylethynylcarbamic acid methyl ester (3g). Following the above general procedure (A) with 1-bromoethynyl-2-methylbenzene **1c**[17g] (321.4 mg, 1.648 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (129.6 mg, 0.8579 mmol), copper iodide (36.4 mg, 0.191 mmol), 1,10-phenanthroline (40.9 mg, 0.227 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3g** (89.5 mg, 0.337 mmol, 39%) as an orange oil. R_f 0.39 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2987 (w), 2305 (w), 2250 (w), 1738 (m), 1491 (w), 1439 (w), 1360 (w), 1266 (s), 896 (w), 739 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.46 (m, 2H), 7.25–7.30 (m, 3H), 7.15 (m, 1H), 6.99–7.06 (m, 3H), 3.77 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 139.5, 139.5, 131.1, 129.3, 128.9, 127.6, 126.9, 125.4, 124.4, 122.6, 86.6, 69.3, 54.3, 20.6. HRMS calcd for $C_{17}H_{15}NO_2$: *m*/*z* 265.1103, found *m*/*z* 265.1109.

4.1.7. *N*-(*m*-Fluorophenylethynyl)-*N*-phenylcarbamic acid methyl ester (3h). Following the above general procedure (A) with 1-bromoethynyl-3-fluorobenzene **1d**[17g] (335 mg, 1.683 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (133.7 mg, 0.8851 mmol), copper iodide (37.5 mg, 0.197 mmol), 1,10-phenanthroline (44.8 mg, 0.249 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:19) to provide **3h** (129.4 mg, 0.4805 mmol, 54%) as an orange solid (mp 26–27 °C). R_f 0.37 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3065 (w), 2955 (w), 2252 (s), 1738 (s), 1579 (m), 1490 (m), 1439 (m), 1363 (m), 1290 (s), 1053 (w), 940 (w), 738 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80–7.39 (m, 9H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (d, J=246.2 Hz), 154.5, 139.2, 129.7 (d, J=8.7 Hz), 129.0, 127.1, 127.0 (d, J=2.4 Hz), 124.7, 124.6, 117.9 (d, J=22.8 Hz), 114.9 (d, J=21.2 Hz), 83.7, 69.1 (d, J=3.0 Hz), 54.4. HRMS calcd for $C_{16}H_{12}NO_2F$: *m*/*z* 269.0852, found *m*/*z* 269.0845. Anal. Calcd for $C_{16}H_{12}NO_2F$: C, 71.37; H, 4.49. Found C, 71.48; H, 4.30.

4.1.8. *N*-(3-Hydroxy-1-propynyl)-*N*-phenylcarbamic acid methyl ester (3i). A solution of **3j** (79.4 mg, 0.249 mmol) in THF (0.5 mL) was cooled to −78 °C under nitrogen in a dry round-bottom flask. A solution of TBAF (1 M in THF, 0.46 mL, 0.46 mmol) was added dropwise and the resulting mixture was stirred for 1 h. The reaction was quenched with water at −20 °C and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=2:3) to provide **3i** (33.4 mg, 0.163 mmol, 65%) as a white solid (mp 81–84 °C). R_f 0.48 (EtOAc/hexanes=2:3); IR (CH_2Cl_2, NaCl) 3052 (w), 2987 (w), 2305 (w), 2253 (w), 1740 (m), 1487 (w), 1442 (w), 1266 (s), 1016 (w), 888 (w), 739 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.45 (m, 4H), 7.28 (m, 1H), 4.43 (s, 2H), 3.85 (s, 3H), 2.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0, 139.2, 129.0, 127.2, 124.8, 79.4, 68.6, 54.4, 51.1. HRMS calcd for $C_{11}H_{11}NO_3$: *m*/*z* 205.0739, found *m*/*z* 207.0745.

4.1.9. *N*-[3-(*tert*-Butyldimethylsilyloxy)-1-propynyl]-*N*-phenylcarbamic acid methyl ester (3j). Following the above general procedure (A) with (3-bromoprop-2-ynyloxy)-*tert*-butyldimethylsilane **1e**[34] (146.4 mg, 0.5874 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (120.6 mg, 0.7984 mmol), copper iodide (49.7 mg, 0.261 mmol), 1,10-phenanthroline (49.6 mg, 0.275 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (Et_2O/pentane=1:9) to provide **3j** (51.4 mg, 0.161 mmol, 35%) as an orange oil. R_f 0.48 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3054 (w), 2987 (w), 2955 (w), 2859 (w), 2305 (w), 2253 (w), 1739 (m), 1596 (w), 1440 (w), 1266 (s), 1075 (w), 896 (w), 735 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.46 (m, 2H), 7.35–7.41 (m, 2H), 7.26 (m, 1H), 4.49 (s, 2H), 3.86 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 139.3, 128.8, 127.0, 124.6, 78.4, 68.9, 54.1, 51.8, 25.8, 18.2, −5.2. HRMS calcd for $C_{17}H_{25}NO_3Si$: *m*/*z* 319.1604, found *m*/*z* 319.1611.

4.1.10. *N*-[4-(*tert*-Butyldimethylsilyloxy)-1-butynyl]-*N*-phenylcarbamic acid methyl ester (3k). Following the above general procedure (A) with **1f**[17g] (156.1 mg, 0.5930 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (66.1 mg, 0.438 mmol), copper iodide (20.8 mg, 0.109 mmol), 1,10-phenanthroline (18.4 mg, 0.102 mmol), and KHMDS (0.75 mL, 0.38 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3k** (37.8 mg, 0.113 mmol, 26%) as a yellow oil. R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2956 (w), 2930 (w), 2857 (w), 1737 (m), 1492 (w), 1440 (m), 1298 (m), 1266 (s), 1104 (w), 838 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (m, 2H), 7.30 (m, 2H), 7.19 (m, 1H), 3.78 (s, 3H), 3.67 (t, 2H, J=7.0 Hz), 2.48 (t, 2H, J=7.0 Hz), 0.81 (s, 9H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 139.8, 128.8, 126.7,

124.6, 74.6, 66.8, 62.0, 54.1, 25.8, 22.9, 18.3, −5.3. HRMS calcd for $C_{18}H_{27}NO_3Si$: *m/z* 333.1760, found *m/z* 333.1752.

4.1.11. *N*-Phenyl-*N*-triisopropylsilylethynylcarbamic acid methyl ester (3l). Following the above general procedure (A) with bromoethynyltriisopropylsilane **1g**[35] (2.9332 g, 11.226 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (1.4324 g, 9.4823 mmol), copper iodide (0.5808 g, 3.050 mmol), 1,10-phenanthroline (615.7 mg, 3.417 mmol), and KHMDS (24.0 mL, 12.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3l** (2.8186 g, 8.5017 mmol, 90%) as a yellow oil. R_f 0.53 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (w), 2949 (m), 2865 (m), 2305 (w), 2178 (m), 1740 (m), 1596 (w), 1492 (w), 1440 (m), 1266 (s), 1055 (w), 881 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (m, 2H), 7.41 (m, 2H), 7.29 (m, 1H), 3.90 (s, 3H), 1.14 (s, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 139.2, 128.7, 126.5, 123.9, 96.2, 68.9, 54.0, 18.5, 11.3. HRMS calcd for $C_{19}H_{29}NO_2Si$: *m/z* 331.1968, found *m/z* 331.1977. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82. Found C, 68.72; H, 8.99.

4.1.12. *N*-Ethynyl-*N*-phenylcarbamic acid methyl ester (3m). A solution of **3l** (2.6024 g, 7.8497 mmol) in THF (15 mL) was cooled to −78 °C under nitrogen in a dry round-bottom flask. A solution of TBAF (1 M in THF, 15.0 mL, 15.0 mmol) was added dropwise and the resulting mixture was stirred for 1 h. The reaction was quenched with water at −20 °C and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=1:24) to provide **3m** (1.0451 g, 5.9658 mmol, 76%) as a white solid (mp 48–50 °C). R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3312 (w), 3055 (w), 2987 (w), 2306 (w), 2148 (w), 1742 (w), 1493 (w), 1440 (w), 1299 (w), 1266 (s), 896 (w), 738 (s), 705 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 7.34 (m, 2H), 7.29 (m, 1H), 3.89 (s, 3H), 2.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 138.8, 129.0, 127.2, 124.6, 76.2, 58.5, 54.4. HRMS calcd for $C_{10}H_9NO_2$: *m/z* 175.0633, found *m/z* 175.0631.

4.1.13. *N*-Ethoxycarbonylethynyl-*N*-phenylcarbamic acid methyl ester (3n). In a dry round-bottom flask, at −78 °C and under a flow of nitrogen, LiHMDS (1 M in THF, 1.85 mL, 1.85 mmol) was added dropwise to a solution of **3m** (186.4 mg, 1.064 mmol) in THF (8.5 mL). The reaction mixture was allowed to warm slowly to −40 °C and then stirred for 1 h. The reaction mixture was then added to a solution of ethyl chloroformate (0.165 mL, 1.73 mmol) in THF (2.9 mL) at −40 °C via a cannula. The reaction was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=1:9) to provide **3n** (29.1 mg, 0.118 mmol, 11%) as a white solid (mp 82–84 °C). R_f 0.36 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3056 (w), 2981 (w), 2955 (w), 2237 (s), 1754 (s), 1705 (s), 1595 (w), 1492 (w), 1440 (m), 1288 (m), 1266 (s), 1197 (m), 1158 (m), 1025 (w), 896 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.45 (m, 4H), 7.34 (m, 1H), 4.24 (q, 2H, J=7.1 Hz), 3.93 (s, 3H), 1.30 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 154.0, 137.7, 129.3, 128.1, 125.0, 81.4, 65.8, 61.7, 55.0, 14.1. HRMS calcd for $C_{13}H_{13}NO_4$: *m/z* 247.0845, found *m/z* 247.0852.

4.1.14. Ethyl [benzyl-(toluene-4-sulfonyl)-amino]-propynoate (3o). Following the above general procedure (C) with sulfonamide **9** (204.1 mg, 0.781 mmol), THF (2.0 mL), BuLi (0.37 mL, 0.93 mmol), $AlCl_3$ (11.1 mg, 0.0832 mmol), alkynyl bromide **10**[36] (190.3 mg, 1.075 mmol) and THF (1.0 mL). The reaction mixture was stirred at 25 °C for 1.5 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes=1:19–3:7) to provide ynamide **3o** (171.0 mg, 0.4784 mmol, 61%) as a colorless oil. R_f 0.26 (EtOAc/hexanes=3:7); IR (CH_2Cl_2, NaCl) 3090 (w), 3066 (w), 3034 (w), 2983 (m), 2937 (m), 2219 (vs), 1704 (vs), 1374 (vs), 1165 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, J=8.4 Hz), 7.27–7.34 (m, 7H), 4.63 (s, 2H), 4.19 (q, 2H, J=7.1 Hz), 2.45 (s, 3H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 153.9, 145.4, 134.2, 133.5, 129.8, 128.6, 127.7, 82.6, 68.0, 61.5, 55.4, 21.6, 14.1. HRMS (EI) calcd for $C_{19}H_{19}NO_4S$ (M^+): 357.1035; found: 357.1039.

4.1.15. (*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)oxazolidin-2-one (6). To a solution of (*S*)-4-hydroxymethyloxazolidin-2-one **5**[23] (1.16 g, 9.91 mmol) in CH_2Cl_2 (15 mL) were successively added triethylamine (1.50 mL, 10.8 mmol), 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 70.3 mg, 0.575 mmol) and *tert*-butyl(chloro)dimethylsilane (TBSCl, 2.04 g, 13.5 mmol). The reaction mixture was stirred for 16 h at 25 °C under N_2 then quenched with of water (1 mL). Magnesium sulfate was added and the mixture was filtered, and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (EtOAc/hexanes=3:2) to give the product **6** (1.84 g, 7.95 mmol, 80%) as a semi-solid. $[\alpha]_D^{23}$ +26 (*c* 0.59, CH_2Cl_2); R_f 0.55 (EtOAc); IR (neat) 3327 (s), 2956 (s), 2936 (s), 1748 (s), 1253 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (br s, 1H), 4.42 (app t, 1H, J=8.6 Hz), 4.18 (dd, 1H, J=8.7, 4.8 Hz), 3.89–3.92 (m, 1H), 3.59 (d, 2H, J=5.4 Hz), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 160.0, 67.1, 64.6, 53.6, 25.7, 18.1, −5.6. HRMS (*m/z*) for $C_{10}H_{21}NO_3Si$ calcd 231.1291, found 231.1299.

4.1.16. (*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-phenylethnyloxazolidin-2-one (7). Following the above general procedure (A) with alkynyl bromide **1a** (1.095 g, 6.049 mmol) and **6** (900.3 mg, 3.891 mmol), copper iodide (303.3 mg, 1.593 mmol), 1,10-phenanthroline (295.7 mg, 1.641 mmol), and KHMDS (0.5 M in toluene, 12.4 mL, 6.2 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:4) to give the ynamide **7** (592.6 mg, 1.788 mmol, 46%) as a semi-solid. $[\alpha]_D^{23}$ −94 (*c* 0.30, CH_2Cl_2); R_f 0.56 (EtOAc/hexanes=2:3); IR (neat) 2961 (m), 2937 (m), 2251 (m), 1777 (s), 1414 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H), 7.30 (m, 3H), 4.48 (app t, 1H, J=8.6 Hz), 4.43 (dd, 1H, J=8.5, 5.2 Hz), 4.10–4.13 (m, 1H), 4.04 (dd, 1H, J=11.3, 3.0 Hz), 3.72 (d, 1H, J=11.3 Hz), 0.89

(s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 155.8, 131.6, 128.2, 128.1, 122.1, 77.8, 72.2, 65.4, 60.5, 58.6, 25.6, 18.0, −5.6. HRMS (*m/z*) for $C_{18}H_{25}NO_3Si$ calcd 331.1604, found 331.1620.

4.1.17. (*S*)-4-Hydroxymethyl-3-phenylethynyl-oxazolidin-2-one (8). To a cold solution (−78 °C) of **7** (500.1 mg, 1.508 mmol) in THF (3 mL) under N_2 was slowly added a solution of tetrabutylammonium fluoride (1 M in THF, 3.0 mL, 3.0 mmol). After 30 min, the reaction was quenched with saturated NH_4Cl solution (3 mL) and diluted with EtOAc. Layers were separated and aqueous layer was extracted three times with EtOAc. Organics were combined, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes=2:3) to give ynamide **8** (142.3 mg, 0.6551 mmol, 48%) as a solid (mp 109–112 °C). $[\alpha]_D^{23}$ −63 (*c* 0.40, CH_2Cl_2); R_f 0.13 (EtOAc/hexanes=2:3); IR (neat) 2942 (w), 2978 (w), 2253 (m), 1753 (s), 1414 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.26 (m, 2H), 7.29–7.33 (m, 3H), 4.46–4.56 (m, 2H), 4.16–4.22 (m, 1H), 4.11 (dd, 1H, *J*=12.2, 3.5 Hz), 3.81 (d, 1H, *J*=11.8 Hz), 2.06 (br s, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 156.1, 131.5, 128.3, 121.9, 77.4, 72.5, 65.5, 60.1, 58.6. HRMS (*m/z*) for $C_{12}H_{11}NO_3$ calcd 217.0739, found 217.0729.

4.1.18. (+)-3-Phenylethynyl-3,3a,8,8a-tetrahydroindeno[1,2-*d*]oxazol-2-one (24). Following the above general procedure (B) with bromoethynylbenzene **1a** (631.2 mg, 3.487 mmol) and (+)-2-azabicyclo[2.2.1]heptan-3-one[37] (199.3 mg, 1.861 mmol), copper iodide (354.1 mg, 1.859 mmol), and KHMDS (0.5 M in toluene, 3.6 mL, 1.8 mmol). The crude mixture was the purified by column chromatography (EtOAc/hexanes=1:4) affording the ynamide **24** (181.9 mg, 0.8615 mmol, 46%) as a solid (mp 73–77 °C). $[\alpha]_D^{23}$ +52 (*c* 0.37, CH_2Cl_2); R_f 0.45 (EtOAc/hexanes=3:7); IR (neat) 3052 (w), 2987 (w), 2246 (m), 1727 (s), 1397 (s), 1266 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.40 (m, 2H), 7.20–7.27 (m, 3H), 4.15 (br s, 1H), 2.85 (m, 1H), 2.03 (dm, 1H, *J*=9.9 Hz), 1.81–1.97 (m, 3H), 1.67–1.74 (m, 1H), 1.47 (dm, 1H, *J*=9.9 Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 177.7, 131.2, 128.1, 127.6, 122.7, 79.4, 72.2, 64.4, 44.1, 39.0, 27.6, 24.1. HRMS (*m/z*) for $C_{14}H_{13}NO$ calcd 211.0997, found 211.0991. Anal. Calcd for $C_{14}H_{13}NO$=C, 79.59%; H, 6.20%; found C, 79.70%; H, 6.08%.

4.1.19. (−)-10,10-Dimethyl-4-phenylethynyl-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-3,3-dioxide (25). Following the above general procedure (B) with bromoethynylbenzene **1a** (69.4 mg, 0.383 mmol) and (1*S*)-(−)-2,10-camphorsultam (41.1 mg, 0.191 mmol), copper iodide (37.4 mg, 0.196 mmol), and KHMDS (0.5 M in toluene, 0.38 mL, 0.19 mmol). The crude mixture was the purified by column chromatography (EtOAc/hexanes=1:4) affording the ynamide **10f** (41.5 mg, 0.132 mmol, 69%) as a pale yellow oil. $[\alpha]_D^{23}$ −146 (*c* 0.52, CH_2Cl_2); R_f 0.41 (EtOAc/hexanes=3:7); IR (neat) 3058 (w), 3000 (m), 2962 (s), 2237 (s), 1336 (s), 1146 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.44 (m, 2H), 7.27–7.29 (m, 3H), 3.68 (dd, 1H, *J*=8.1, 4.1 Hz), 3.29 (s, 2H), 2.29 (dd, 1H, *J*=13.4, 3.0 Hz), 1.98 (m, 1H), 1.89–1.93 (m, 2H), 1.82 (dd, 1H, *J*=13.4, 8.2 Hz), 1.43–1.46 (m, 1H), 1.33–1.36 (m, 1H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 131.7, 128.1, 127.8, 122.6, 76.7, 72.6, 67.2, 51.2, 49.8, 48.0, 44.4, 34.4, 31.6, 27.0, 20.2, 19.9. HRMS (*m/z*) for $C_{18}H_{21}NO_2S$ calcd 315.1293, found 315.1273. Anal. Calcd for $C_{18}H_{21}NO_2S$=C, 68.54%; H, 6.71%; found C, 68.79%; H, 6.66%.

4.2. Ruthenium-catalyzed [2+2] cycloaddition

General procedure (D) for the Ru-catalyzed [2+2] cycloaddition between bicyclic alkenes and ynamides. A mixture of bicyclic alkene (2.5–5 equiv), ynamide (1 equiv) and THF (0.2–0.5 M w.r.t. the ynamide) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (weighed out from a dry box, 5–10 mol%) under nitrogen. The reaction mixture was stirred in the dark at 25 or 65 °C for 68–168 h. The crude product was purified by column chromatography to give the cycloadduct.

4.2.1. Cycloadduct 5a. Following the above general procedure (D) with norbornene **4a** (15.8 mg, 0.168 mmol), ynamide **3a** (16.6 mg, 0.0645 mmol), THF (0.3 mL), and Cp*RuCl(COD) (6.2 mg, 0.016 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5a** (12.4 mg, 0.0354 mmol, 55%) as a slightly yellow oil. R_f 0.48 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (m), 2987 (w), 2942 (w), 2305 (w), 1693 (m), 1442 (m), 1422 (m), 1266 (s), 894 (w), 740 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.29 (m, 4H), 7.20 (m, 1H), 3.93 (m, 1H), 3.59 (s, 3H), 2.74 (d, 1H, *J*=3.5 Hz), 2.60 (d, 1H, *J*=3.5 Hz), 2.30 (br s, 1H), 2.09 (br s, 1H), 1.90 (m, 1H), 1.72–1.82 (m, 4H), 1.51–1.66 (m, 5H), 1.26–1.37 (m, 2H), 1.06–1.19 (m, 3H), 0.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.7, 136.8, 133.7, 131.3, 128.1, 127.3, 126.4, 57.4, 52.7, 52.4, 43.9, 35.2, 34.2, 32.0, 31.1, 30.8, 28.6, 28.4, 26.0, 25.9, 25.5. HRMS calcd for $C_{23}H_{29}NO_2$: *m/z* 351.2198, found *m/z* 351.2189.

4.2.2. Cycloadduct 5b. Following the above general procedure (D) with norbornene **4a** (43.4 mg, 0.461 mmol), ynamide **3b** (26.9 mg, 0.0963 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.5 mg, 0.012 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5b** (26.1 mg, 0.0698 mmol, 73%) as a yellow oil. R_f 0.34 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 2950 (w), 2865 (w), 1711 (m), 1648 (w), 1493 (w), 1447 (m), 1390 (w), 1313 (w), 1203 (w), 765 (w), 694 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.34 (m, 10H), 3.80 (m, 1H), 3.68 (s, 3H), 3.60 (m, 1H), 2.83–2.99 (m, 2H), 2.74 (br s, 1H), 2.59 (d, 1H, *J*=3.2 Hz), 2.32 (s, 1H), 2.14 (br s, 1H), 1.61–1.70 (m, 3H), 1.07–1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.1, 138.6, 134.1, 132.3, 130.7, 128.8, 128.4, 128.0, 126.9, 126.3, 52.6, 50.0, 48.6, 44.0, 35.4, 35.2, 34.5, 30.6, 28.4, 28.2. HRMS calcd for $C_{25}H_{27}NO_2$: *m/z* 373.2042, found *m/z* 373.2051.

4.2.3. Cycloadduct 5c. Following the above general procedure (D) with norbornene **4a** (31.7 mg, 0.337 mmol), ynamide **3c** (31.9 mg, 0.120 mmol), THF (0.3 mL), and

Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5c** (39.4 mg, 0.110 mmol, 91%) as an orange solid (mp 55–60 °C). R_f 0.34 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2953 (m), 2871 (w), 2305 (w), 1710 (s), 1648 (m), 1494 (w), 1447 (m), 1265 (s), 974 (w), 896 (w), 738 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.33 (m, 10H), 4.83 (d, 1H, J=15.3 Hz), 4.62 (d, 1H, J=15.4 Hz), 3.70 (s, 3H), 2.71 (br s, 1H), 2.54 (d, 1H, J=3.4 Hz), 2.26 (s, 1H), 2.00 (br s, 1H), 1.53–1.64 (m, 2H), 1.40 (m, 1H), 1.06–1.17 (m, 2H), 0.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.6, 138.1, 134.3, 132.2, 130.5, 128.3, 128.0, 127.4, 127.2, 126.9, 52.9, 50.1, 50.0, 44.1, 35.2, 34.4, 30.4, 28.4, 28.1. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1892.

4.2.4. Cycloadduct 5d. Following the above general procedure (D) with norbornene **4a** (72.6 mg, 0.771 mmol), ynamide **3c** (32.5 mg, 0.106 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.3 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 25 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5d** (31.8 mg, 0.0792 mmol, 75%) as a colorless oil. R_f 0.63 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 2949 (m), 2865 (w), 1698 (s), 1383 (m), 1364 (m), 1313 (m), 1248 (w), 1161 (m), 688 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.25 (m, 10H), 4.79 (d, 1H, J=15.0 Hz), 4.46 (d, 1H, J=15.4 Hz), 2.68 (br s, 1H), 2.43 (br s, 1H), 2.23 (br s, 1H), 1.93 (br s, 1H), 1.50–1.54 (m, 2H), 1.36 (d, 1H, J=10.1 Hz), 1.28 (s, 9H), 1.02–1.08 (m, 2H), 0.84 (d, 1H, J=10.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.8, 138.7, 135.0, 132.6, 129.6, 128.3, 127.8, 127.3, 127.0, 126.6, 80.9, 50.2, 49.4, 44.3, 35.6, 34.3, 30.4, 28.5, 28.2, 28.1. HRMS calcd for $C_{27}H_{31}NO_2$: m/z 401.2355, found m/z 401.2330. Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78. Found C, 80.65; H, 7.89.

4.2.5. Cycloadduct 5e. Following the above general procedure (D) with norbornene **4a** (36.6 mg, 0.389 mmol), ynamide **3e** (32.5 mg, 0.129 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.2 mg, 0.014 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5e** (43.3 mg, 0.125 mmol, 97%) as a pale yellow solid (mp 66–69 °C). R_f 0.36 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2955 (w), 2865 (w), 2363 (w), 2305 (w), 1715 (m), 1596 (w), 1493 (w), 1442 (w), 1266 (s), 894 (w), 741 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.38 (m, 10H), 3.73 (s, 3H), 2.70 (d, 1H, J=3.4 Hz), 2.64 (d, 1H, J=3.5 Hz), 2.35 (d, 1H, J=3.6 Hz), 1.95 (d, 1H, J=3.5 Hz), 1.55–1.73 (m, 2H), 0.92–1.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.0, 154.4, 139.6, 133.6, 131.7, 128.9, 127.9, 127.0, 126.8, 126.7, 126.6, 53.0, 49.8, 44.0, 35.5, 34.3, 30.8, 28.4, 28.2. HRMS calcd for $C_{23}H_{23}NO_2$: m/z 345.1729, found m/z 345.1722.

4.2.6. Cycloadduct 5f. Following the above general procedure (D) with norbornene **4a** (60.2 mg, 0.639 mmol), ynamide **3f** (41.5 mg, 0.156 mmol), THF (0.3 mL), and Cp*RuCl(COD) (8.7 mg, 0.023 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide cycloadduct **5f** (48.0 mg, 0.134 mmol, 85%) as a yellow solid (mp 69–75 °C). R_f 0.36 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (m), 2954 (m), 2871 (m), 2350 (w), 2298 (w), 1714 (s), 1597 (m), 1492 (m), 1440 (m), 1266 (s), 1062 (m), 894 (w), 734 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.31 (m, 4H), 7.18 (m, 1H), 6.99–7.06 (m, 4H), 3.65 (s, 3H), 2.59 (d, 1H, J=3.5 Hz), 2.54 (d, 1H, J=3.6 Hz), 2.26 (s, 3H), 2.25 (br s, 1H), 1.84 (d, 1H, J=3.6 Hz), 1.43–1.65 (m, 3H), 0.94–1.13 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 139.8, 136.9, 132.0, 130.8, 130.6, 128.9, 128.7, 126.7, 126.5, 53.0, 49.7, 43.8, 35.4, 34.3, 30.8, 28.5, 28.2, 21.3. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1896.

4.2.7. Cycloadduct 5g. Following the above general procedure (D) with norbornene **4a** (38.7 mg, 0.411 mmol), ynamide **3g** (38.6 mg, 0.146 mmol), THF (0.3 mL), and Cp*RuCl(COD) (6.3 mg, 0.017 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:9) to provide cycloadduct **5g** (26.7 mg, 0.0742 mmol, 51%) as pale yellow oil. R_f 0.53 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3054 (m), 2954 (m), 1718 (m), 1597 (w), 1491 (w), 1440 (m), 1348 (m), 1266 (s), 896 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.25 (m, 2H), 7.13–7.18 (m, 3H), 6.99–7.04 (m, 4H), 3.48 (s, 3H), 2.70 (d, 1H, J=3.0 Hz), 2.60 (d, 1H, J=3.4 Hz), 2.25 (s, 3H), 2.17 (br s, 1H), 1.85 (br s, 1H), 1.74 (d, 1H, J=10.1 Hz), 1.48–1.56 (m, 2H), 1.00–1.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 139.0, 136.0, 135.4, 132.9, 129.6, 128.6, 127.7, 127.6, 127.0, 126.5, 124.8, 52.7, 49.7, 46.9, 35.6, 34.9, 30.6, 28.2, 28.1, 20.5. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1880.

4.2.8. Cycloadduct 5h. Following the above general procedure (D) with norbornene **4a** (35.0 mg, 0.372 mmol), ynamide **3h** (31.0 mg, 0.115 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.6 mg, 0.015 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:19) to provide cycloadduct **5h** (24.3 mg, 0.0668 mmol, 58%) as a yellow oil. R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (m), 2954 (m), 2872 (w), 2298 (w), 1718 (m), 1610 (w), 1596 (w), 1581 (w), 1494 (w), 1440 (m), 1348 (m), 1266 (s), 1062 (w), 851 (w), 739 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.28 (m, 2H), 7.14–7.20 (m, 3H), 7.07 (m, 1H), 6.66–6.82 (m, 3H), 3.64 (s, 3H), 2.63 (d, 1H, J=3.6 Hz), 2.50 (d, 1H, J=3.6 Hz), 2.22 (d, 1H, J=3.5 Hz), 1.86 (d, 1H, J=3.4 Hz), 1.47–1.59 (m, 3H), 0.96–1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.5 (d, J=244.8 Hz), 154.1, 139.4, 135.8 (d, J=7.2 Hz), 133.1, 129.2 (d, J=7.4 Hz), 129.0, 128.8, 127.0, 126.9, 122.4, 113.6 (d, J=21.4 Hz), 113.4 (d, J=21.7 Hz), 53.1, 50.0, 44.2, 35.5, 34.3, 30.7, 28.4, 28.2. HRMS calcd for $C_{23}H_{22}NO_2F$: m/z 363.1635, found m/z 363.1643.

4.2.9. Cycloadduct 5i. Following the above general procedure (D) with norbornene **4a** (44.6 mg, 0.474 mmol), ynamide **3i** (24.5 mg, 0.119 mmol), THF (0.3 mL), and

Cp*RuCl(COD) (7.3 mg, 0.019 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to provide cycloadduct **5i** (11.6 mg, 0.0387 mmol, 32%) as a yellow oil. R_f 0.35 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2, NaCl) 3052 (m), 2955 (m), 2871 (w), 1712 (m), 1596 (w), 1493 (w), 1442 (m), 1313 (m), 1266 (s), 1055 (w), 894 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.42 (m, 3H), 7.20–7.22 (m, 2H), 3.74 (m, 1H), 3.70 (s, 3H), 3.66 (m, 1H), 2.50 (br s, 1H), 2.27 (d, 1H, J = 3.3 Hz), 2.08 (d, 1H, J = 3.3 Hz), 1.77 (br s, 1H), 1.43–1.52 (m, 3H), 0.07–1.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.6, 139.2, 132.9, 129.2, 128.0, 127.9, 125.4, 57.6, 53.3, 49.3, 44.2, 35.0, 34.1, 30.3, 28.1, 27.9. HRMS calcd for $C_{18}H_{21}NO_3$: *m/z* 299.1521, found *m/z* 299.1530.

4.2.10. Cycloadduct 5j. Following the above general procedure (D) with norbornene **4a** (24.8 mg, 0.263 mmol), ynamide **3j** (21.0 mg, 0.0657 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.9 mg, 0.016 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:9) to provide cycloadduct **5j** (6.8 mg, 0.016 mmol, 25%) as a yellow oil. R_f 0.58 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2, NaCl) 3052 (w), 2981 (w), 2949 (w), 2305 (w), 1719 (w), 1442 (w), 1422 (w), 1266 (s), 1036 (w), 894 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.40 (m, 2H), 7.33 (m, 1H), 7.20–7.22 (m, 2H), 3.70 (s, 3H), 3.48 (d, 1H, J = 13.6 Hz), 3.38 (d, 1H, J = 13.6 Hz), 2.73 (br s, 1H), 2.29 (d, 1H, J = 3.1 Hz), 2.07 (br s, 1H), 2.02 (br s, 1H), 1.51–1.53 (m, 3H), 0.96–1.04 (m, 3H), 0.81 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.1, 139.8, 132.3, 130.5, 129.2, 128.1, 127.6, 57.4, 52.9, 49.7, 44.2, 35.3, 34.4, 30.4, 28.1, 28.1, 25.9, 18.3, −5.4. HRMS calcd for $C_{24}H_{35}NO_3Si$: *m/z* 413.2386, found *m/z* 413.2391.

4.2.11. Cycloadduct 5k. Following the above general procedure (D) with norbornene **4a** (36.0 mg, 0.382 mmol), ynamide **3k** (37.8 mg, 0.113 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:24) to provide cycloadduct **5k** (37.7 mg, 0.0881 mmol, 78%) as a yellow oil. R_f 0.48 (EtOAc/hexanes = 1:9); IR (CH_2Cl_2, NaCl) 3052 (w), 2954 (m), 2871 (w), 1716 (m), 1442 (m), 1351 (w), 1266 (s), 1087 (w), 1055 (w), 836 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.39 (m, 2H), 7.29 (m, 1H), 7.21–7.22 (m, 2H), 3.70 (s, 3H), 3.43 (t, 2H, J = 7.2 Hz), 2.75 (br s, 1H), 2.18 (d, 1H, J = 3.1 Hz), 2.00 (br s, 1H), 1.98 (br s, 1H), 1.48–1.73 (m, 5H), 0.95–1.05 (m, 3H), 0.84 (s, 9H), −0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.2, 140.0, 133.4, 129.0, 128.0, 127.3, 125.1, 61.1, 52.8, 50.2, 45.4, 35.1, 34.1, 30.4, 30.4, 28.2, 28.0, 25.9, 18.2, −5.3. HRMS calcd for $C_{25}H_{37}NO_3Si$: *m/z* 427.2543, found *m/z* 427.2548.

4.2.12. Cycloadduct 13. Following the above general procedure (D) with alkene **4d** (73.6 mg, 0.285 mmol), ynamide **3e** (29.9 mg, 0.119 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.1 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to provide cycloadduct **13** (54.6 mg, 0.107 mmol, 90%) as a white solid (mp 112–114 °C). R_f 0.13 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2, NaCl) 3054 (w), 3027 (w), 2985 (w), 2954 (w), 1760 (vs), 1722 (vs), 1204 (vs), 1155 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.40 (m, 10H), 6.80 (AB_q, 2H, J = 9.0, 2.4 Hz), 3.76 (s, 3H), 3.27 (br s, 1H), 2.94–2.96 (m, 2H), 2.87 (br s, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 2.13 (d, 1H, J = 9.8 Hz), 1.78 (d, 1H, J = 9.7 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 169.1, 169.0, 154.1, 142.34, 142.29, 141.0, 140.7, 139.4, 132.9, 132.6, 129.6, 129.0, 127.9, 127.3, 127.05, 127.02, 126.8, 120.10, 120.06, 53.1, 47.2, 41.5, 40.8, 39.1, 20.9, 20.7. HRMS (CI) calcd for $C_{31}H_{27}NO_6$ ($(M+H)^+$): 510.1917; found: 510.1923. Anal. Calcd for $C_{31}H_{27}NO_6$ = C, 73.07%; H, 5.34%; found = C, 73.40%; H, 5.21%.

4.2.13. Cycloadduct 14. Following the above general procedure (D) with alkene **4e** (32.9 mg, 0.135 mmol), ynamide **3e** (22.7 mg, 0.0903 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.1 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 3:7) to provide cycloadduct **14** (20.4 mg, 0.0412 mmol, 46%) as a white solid (mp 152–153 °C). R_f 0.42 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2, NaCl) 3060 (w), 2968 (w), 1729 (s), 1691 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05–7.41 (m, 12H), 6.66–6.93 (m, 2H), 5.11 (m, 2H), 3.77 (s, 3H), 3.19 (br d, 1H, J = 3.5 Hz), 2.74 (br s, 1H), 1.36 (s, 3H), 1.25 (s, 6H). HRMS (CI) calcd for $C_{31}H_{30}N_2O_4$ ($(M+H)^+$): 495.2284; found: 495.2280. Anal. Calcd for $C_{31}H_{30}N_2O_4$ = C, 75.28%; H, 6.11%; found = C, 75.55%; H, 6.01%.

4.2.14. Cycloadduct 15. Following the above general procedure (D) with alkene **4f** (47.0 mg, 0.326 mmol), ynamide **3e** (26.5 mg, 0.105 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.6 mg, 0.012 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19–1:4) to provide cycloadduct **15** (37.2 mg, 0.0872 mmol, 83%) as a white solid (mp 164–166 °C). R_f 0.22 (EtOAc/hexanes = 1:9); IR (CH_2Cl_2, NaCl) 3055 (m), 3026 (m), 2993 (m), 2952 (m), 1727 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, 2H, J = 7.8 Hz), 7.06–7.46 (m, 12H), 5.30 (s, 1H), 5.17 (s, 1H), 3.91 (s, 3H), 3.39 (d, 1H, J = 3.6 Hz), 3.01 (d, 1H, J = 3.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 145.3, 139.5, 133.4, 132.4, 128.8, 127.8, 127.5 (br), 127.1, 126.7, 126.63, 126.57, 126.5, 119.9, 119.6, 77.2, 76.1, 53.4, 45.9, 43.3. HRMS (CI) calcd for $C_{26}H_{21}NO_3$ ($(M+H)^+$): 396.1600; found: 396.1609. Anal. Calcd for $C_{26}H_{21}NO_3$ = C, 79.97%; H, 5.35%; found = C, 79.11%; H, 5.30%.

4.2.15. Cycloadduct 16. Following the above general procedure (D) with alkene **4g** (47.2 mg, 0.256 mmol), ynamide **3e** (27.1 mg, 0.108 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19–2:3) to provide cycloadduct **16** (47.0 mg, 0.102 mmol, 94%) as a white solid (mp 130–133 °C). R_f 0.30 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2, NaCl) 3061 (w), 2981

(m), 2928 (m), 2892 (m), 2875 (m), 2811 (w), 1722 (vs), 1302 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, 2H, J= 7.8 Hz), 7.21–7.27 (m, 2H), 7.02–7.13 (m, 4H), 6.85–6.94 (m, 2H), 4.40 (s, 1H), 4.21 (s, 1H), 3.79 (s, 3H), 3.34–3.48 (m, 5H), 3.36 (s, 3H), 3.34 (s, 3H), 2.94 (d, 1H, J=3.7 Hz), 2.10–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 139.7, 132.3, 131.7, 128.9, 128.7, 127.7, 126.9, 126.1, 125.9, 77.3, 75.7, 71.00, 70.97, 58.85, 58.75, 53.3, 50.8, 45.4, 44.8, 44.2. HRMS (CI) calcd for $C_{26}H_{29}NO_5$ ($(M+H)^+$): 436.2124; found: 436.2130. Anal. Calcd for $C_{26}H_{29}NO_5$=C, 71.70%; H, 6.71%; found=C, 71.44%; H, 6.98%.

4.2.16. Cycloadduct 21. Following the above general procedure (D) with norbornene **4a** (54.1 mg, 0.575 mmol), ynamide **22** (54.6 mg, 0.207 mmol), THF (0.60 mL), and Cp*RuCl(COD) (5.0 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:7) to give the cycloadducts **21** as an inseparable mixture of diastereoisomers (60.4 mg, 0.169 mmol, 83%, dr=72:28 measured by 400 MHz ^1H NMR) as pale yellow oil. R_f 0.37 (EtOAc/hexanes=3:7); IR (neat) 3065 (w), 3032 (w), 2949 (m), 2872 (w), 1762 (s), 1648 (w), 1395 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.18–7.36 (m, 8H), 7.08–7.17 (m, 0.56H), 6.93–6.97 (m, 1.44H), 5.11–5.15 (m, 1H), 4.74 (app t, 0.28H, J=8.8 Hz), 4.73 (app t, 0.72H, J= 8.8 Hz), 4.22 (dd, 0.72H, J=8.8, 5.8 Hz), 4.18 (dd, 0.28H, J=8.8, 5.8 Hz), 2.86 (br d, 0.72H, J=3.6 Hz), 2.57 (br d, 0.56H), 2.50 (br d, 0.72H, J=3.6 Hz), 2.18 (br s, 0.72H), 2.06 (br s, 0.72H), 2.02 (br s, 0.56H), 1.46–1.58 (m, 2H), 1.27 (d, 0.28H, J=10.4 Hz), 1.14–1.23 (m, 2H), 0.85 (d, 0.72H, J=10.4 Hz), 0.79 (d, 0.28H, J=10.4 Hz), 0.74 (d, 0.72H, J=10.4 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 154.94, 154.91, 138.6, 134.9, 133.5, 130.3, 129.3, 128.8, 128.7, 128.6, 128.04, 127.97, 127.94, 127.89, 127.84, 127.76, 127.43, 127.35, 127.1, 126.9, 126.5, 126.2, 70.4, 70.2, 59.6, 58.7, 55.9, 48.6, 48.5, 46.3, 44.8, 35.4, 35.0, 34.1, 34.0, 30.3, 29.8, 28.10, 28.07, 28.03, 28.0. HRMS (m/z) for $C_{24}H_{23}NO_2$ calcd 357.1729, found 357.1720. Anal. Calcd for $C_{24}H_{23}NO_2$=C, 80.64%; H, 6.49%; found C, 80.78%; H, 6.30%.

The 1:1 diastereomeric mixture of **21** was prepared as follow: to a flask under nitrogen containing K_3PO_4 (52.4 mg, 0.247 mmol), CuI (3.3 mg, 0.017 mmol) and (*R*)-(−)-4-phenyl-2-oxazolidinone (23.4 mg, 0.129 mmol) was added a solution of **20**[17g] (32.5 mg, 0.101 mmol) in toluene (0.4 mL) via cannula. *N*,*N*′-dimethylethylenediamine (15 μL, 0.14 mmol), prior to heat the reaction mixture at 90 °C for 20 h. The crude mixture was then cooled to room temperature and purified by column chromatography to give **21** as an inseparable mixture of diastereoisomers (25.1 mg, 0.0702 mmol, 70%, dr=53:47 measured by 400 MHz ^1H NMR).

4.2.17. Cycloadduct 26. Following the above general procedure (D) with norbornene **4a** (29.7 mg, 0.315 mmol), ynamide **7** (28.1 mg, 0.0848 mmol), THF (0.40 mL), and Cp*RuCl(COD) (3.4 mg, 0.0089 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:4) to give the cycloadducts **26** as an inseparable mixture of diastereoisomers (26.1 mg, 0.0611 mmol, 72%, dr=58:42 measured by 400 MHz ^1H NMR) as pale yellow oil. R_f 0.49 (EtOAc/hexanes=1:4); IR (neat) 3055 (w), 3026 (w), 2952 (s), 2868 (m), 1760 (vs), 1650 (m), 1404 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.34 (m, 2H), 7.21–7.24 (m, 3H), 4.43 (d, 0.42H, J= 8.6 Hz), 4.41 (d, 0.58H, J=8.6 Hz), 4.33 (dd, 0.42H, J= 8.4, 3.6 Hz), 4.28 (dd, 0.58H, J=8.6, 4.4 Hz), 4.17–4.21 (m, 1H), 3.50 (dd, 0.42H, J=10.4, 5.2 Hz), 3.46 (dd, 0.58H, J=10.6, 4.7 Hz), 3.40 (dd, 0.58H, J=10.4, 3.0 Hz), 3.29 (dd, 0.42H, J=10.6, 2.4 Hz), 3.02 (br d, 0.58H, J=3.5 Hz), 2.79 (br d, 0.42H, J=3.5 Hz), 2.72 (br d, 0.42H, J= 3.4 Hz), 2.59 (d, 0.58H, J=3.6 Hz), 2.48 (br s, 0.42H), 2.41 (br s, 0.58H), 2.19 (br s, 0.58H), 2.02 (br s, 0.42H), 1.53–1.64 (m, 3H), 1.12–1.18 (m, 2H), 1.06 (d, 0.58H, J= 10.3 Hz), 1.02 (d, 0.42H, J=10.2 Hz), 0.83 (s, 3.78H), 0.81 (s, 5.22H), −0.06 (s, 1.26H), −0.08 (s, 1.74H), −0.09 (s, 1.26H), −0.10 (s, 1.74H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) major diastereomer: δ 155.0, 134.8, 128.1, 128.0, 127.2, 126.99, 126.3, 65.1, 55.5, 48.8, 46.4, 45.2, 36.3, 34.3, 30.6, 28.26, 28.1, 25.6, −5.6; minor diastereomer: δ 155.1, 133.8, 128.7, 128.2, 127.5, 127.1, 125.2, 65.1, 60.9, 55.9, 48.5, 45.2, 35.5, 34.5, 30.5, 28.35, 27.8, 25.6, −5.8. HRMS (m/z) for $C_{25}H_{35}NO_3Si$ calcd 425.2386, found 425.2367. Anal. Calcd for $C_{25}H_{35}NO_3Si$=C, 70.55%; H, 8.29%; found C, 70.40%; H, 8.44%.

4.2.18. Cycloadduct 27. Following the above general procedure (D) with norbornene **4a** (62.6 mg, 0.665 mmol), ynamide **8** (46.8 mg, 0.215 mmol), THF (0.50 mL), and Cp*RuCl(COD) (7.3 mg, 0.019 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:2) to give the cycloadducts **27** as an inseparable mixture of diastereoisomers (54.6 mg, 0.174 mmol, 81%, dr=71:29 measured by 400 MHz ^1H NMR) as a pale yellow oil. R_f 0.47 (EtOAc/hexanes=3:2); IR (neat) 3058 (w), 2953 (m), 2870 (m), 1739 (s), 1649 (m), 1409 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.31 (m, 5H), 4.43–4.47 (m, 2H), 4.20–4.23 (m, 1H), 3.50–3.63 (m, 1H), 3.38–3.48 (m, 1H), 2.99 (br s, 0.71H), 2.77 (br s, 0.29H), 2.73 (br s, 0.29H), 2.62 (br s, 0.71H), 2.40 (br s, 1H), 2.16 (br s, 0.71H), 2.08 (br s, 0.29H), 1.99 (br s, 0.29H), 1.89 (br s, 0.71H), 1.52–1.69 (m, 3H), 1.02–1.25 (m, 3H); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) major diastereomer: δ 155.1, 134.3, 128.5, 128.2, 127.42, 127.38, 127.1, 64.9, 60.9, 55.6, 48.8, 46.0, 36.0, 34.1, 30.4, 28.2, 28.1; minor diastereomer: δ 155.2, 133.4, 128.3, 128.06, 128.01, 127.34, 127.24, 65.1, 60.8, 56.1, 48.8, 45.1, 35.3, 34.4, 30.5, 28.3, 27.9. HRMS (m/z) for $C_{19}H_{21}NO_3$ calcd 311.1521, found 311.1530. Anal. Calcd for $C_{19}H_{21}NO_3$=C, 73.29%; H, 6.80%; found C, 73.44%; H, 6.71%.

4.2.19. Cycloadduct 28. Following the above general procedure (D) with norbornene **4a** (74.3 mg, 0.789 mmol), ynamide **23** (65.2 mg, 0.237 mmol), THF (0.40 mL), and Cp*RuCl(COD) (5.4 mg, 0.014 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:7) to give an inseparable mixture cycloadducts **28** as an inseparable mixture of diastereoisomers (72.0 mg, 0.195 mmol, 82%, dr=74:26 measured by 400 MHz ^1H NMR) as a pale yellow oil. R_f 0.51 (EtOAc/hexanes=3:7); IR (neat) 3065 (m), 2953 (s), 2871 (m), 1751 (s), 1651 (s),

1385 (s), 1266 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.38–7.39 (m, 1H), 7.24–7.33 (m, 5H), 7.18–7.22 (m, 1H), 7.10–7.14 (m, 1H), 7.04–7.06 (m, 1H), 5.58 (d, 0.26H, J= 6.5 Hz), 5.57 (d, 0.74H, J=7.3 Hz), 5.35–5.41 (m, 1H), 3.33–3.41 (m, 2H), 3.12 (br d, 0.74H, J=3.6 Hz), 2.86 (br d, 0.26H, J=3.6 Hz), 2.73 (br d, 0.26H, J=3.5 Hz), 2.68 (br d, 0.74H, J=3.6 Hz), 2.60 (br s, 0.26H), 2.48 (br d, 0.74H, J=3.1 Hz), 2.13 (br d, 0.74H, J=2.9 Hz), 2.11 (br s, 0.26H), 1.57–1.70 (m, 3H), 1.14–1.23 (m, 2H), 1.08 (d, 0.26H, J=10.3 Hz), 1.00 (d, 0.74H, J=10.4 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 154.1, 154.0, 140.04, 139.93, 139.0, 138.6, 134.6, 133.5, 129.5, 129.4, 128.5, 128.2, 127.9, 127.7, 127.63, 127.55, 127.4, 127.3, 127.2, 127.1, 127.0, 126.6, 125.6, 125.33, 125.26, 78.1, 77.8, 63.3, 63.2, 49.1, 49.0, 46.2, 44.9, 38.6, 38.1, 36.2, 35.6, 34.3, 34.1, 30.6, 30.3, 28.3, 28.2, 28.0, 27.8. HRMS (m/z) for $C_{25}H_{23}NO_2$ calcd 369.1729, found 369.1717. Anal. Calcd for $C_{25}H_{23}NO_2$=C, 81.27%; H, 6.27%; found C, 81.36%; H, 6.14%.

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Click chemistry with ynamides

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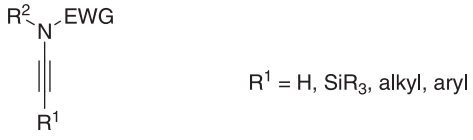
Abstract—A series of diversely 1-substituted 4-amino 1,2,3-triazoles were synthesized by [3+2] cycloaddition between azides and ynamides. This copper catalyzed process represents the first examples of a 'click reaction' employing ynamides and should expand the scope of the ynamide chemistry both synthetically and industrially. Various azides (even highly functionalized) were allowed to react with *N*-benzyl, *N*-tosyl ynamide to give the corresponding triazole adducts in high yield and with very high levels of regioselectivity.

1. Introduction

Over the last decade, the chemistry of electron deficient variants of ynamines (ynamides) has exploded. This is mainly due to the emergence of straightforward synthetic protocols to obtain this particular synthon[1] in which the nitrogen atom is a member of an electron-withdrawing group (Scheme 1) providing superior stability when compared to the parent ynamines.



Scheme 1. Stabilized ynamines.

Having in hand robust protocols to synthesize ynamides, numerous transformations of these compounds have been reported among which the metal catalyzed transformations are the more abundant. We can for instance mention the reactions in which internal ynamides are involved in carbometallation,[2] RCM,[3] Ru-catalyzed cycloadditions[4] or titanation.[5] Focussing on terminal alkynes ($R^1=H$ in Scheme 1), similar reactivity has been evidenced including RCM,[6] [4+2] cycloaddition,[7] cyclotrimerizations,[8] Pauson–Khand reaction[9,10], hydro-[11a] and carboboration,[11b] hydro- or silylstannation,[12a–d] Bu_3SnH-induced radical cyclization,[12e] titanium-mediated couplings,[13] platinum dichloride-catalyzed cycloisomerisation,[14] Negishi-coupling,[15] Glaser-type homocoupling[16] as well as Sonogashira cross-couplings.[17]

2. Results and discussion

Surprisingly, to the best of our knowledge, no [3+2] dipolar cycloaddition of ynamides with azides has been reported. This synthetic route would open access to amino triazole, a scaffold found in bioactive molecules.[18] In addition, the recent discovery of copper catalysis[19] of this 1,3-dipolar cyclization has revitalized interest of the synthetic community in this coupling strategy.[20] Indeed, addition of copper(I) salts allows, besides clean reaction and an increase of the reaction rate, a complete control of the regioselectivity observed in this process (1,4-disubstituted 1,2,3-isomer is obtained as the sole product). Therefore, encouraged by the reported relative stability of terminal ynamides towards copper(I) salts,[17] we decided to explore the feasibility of the 'click chemistry' with compounds of the general formula depicted in Scheme 1 ($R^1=H$).[21] Using two sets of previously described conditions for successful 'click' reactions, preliminary experiments were conducted with *N*-benzyl *N*-tosyl ynamide, an imidazolidinone based ynamide as well as the *N*-ethynyl 1,3-oxazolidinone in the presence of *N*-Boc 2-azido ethylamine (Scheme 2).

Whilst the reactions with the two heterocyclic based ynamides **1** and **3** resulted in extensive degradation of the starting material, the same conditions applied to *N*-tosyl *N*-benzyl ynamide **2** cleanly afforded the expected cyclized product with only minor by-products. Therefore, we decided to select ynamide **2** as one of the coupling partner in 'click

Keywords: Ynamides; Click chemistry; Cyclization; Azide.
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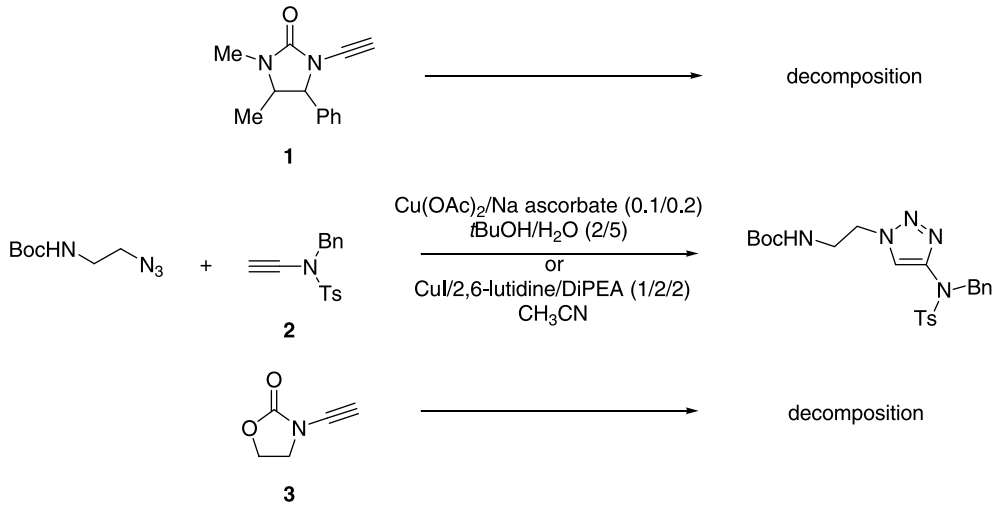


Scheme 2. Preliminary attempts of 'click chemistry' with ynamides.

chemistry'. A wide range of azides were tested for [3+2] cyclization with **2** and the results are summarized in Table 1.

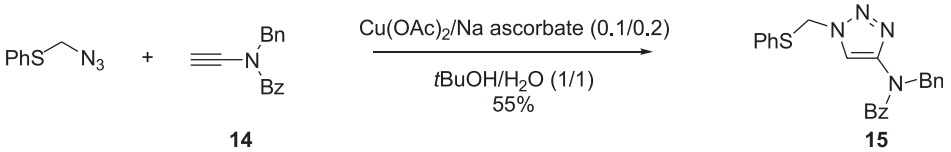
As already mentioned in numerous reports, the click conditions can be applied to structures that bear a wide variety of functional groups. For instance, in our case the first example was conducted with an azide bearing a carbamate (entry 1). It is, however, noteworthy that the amino group of an amine does not need to be protected to give successful cyclization (entry 2). Obviously very simple azides (benzylic or aliphatic) can be reacted with ynamide **2** affording benzyl- or homobenzyl-substituted triazoles (entries 3 and 4) despite a lower yield for compound **6**. One should keep in mind that deprotection of the 1-benzyl group of compound **6** by hydrogenolysis should afford a free amino group that could serve as a starting point for further introduction of functional diversity on triazoles. A slightly different aromatic azide bearing a thio ether group has also proven to be a good candidate for such reaction (entry 5). In an effort to improve the complexity of starting azides, a phenol derivative bearing amide functionality was also cyclized with **2** (entry 6). In order to target our approach to potentially bioactive compounds, ynamide **2** was reacted with carbohydrates based azides with excellent yields (entries 7 and 8). Even an amino-acid based azide has been clicked with **2** to yield a new heteroaromatic alanine derivative (entry 9). Finally, AZT could also be coupled with **2** to furnish compound **13** with a moderate yield (entry 10). It is quite clear from the above results that ynamides can react with various azides in [3+2] cycloaddition. Even highly functionalized azides (entries 6–10) are good partners for ynamides in copper catalyzed 1,3-dipolar cycloadditions.

As mentioned above, in order to diversify the functional groups on the triazole scaffold it is mandatory to have easily removable protective groups. This is something that can be hardly achieved with *N*-tosyl group present in ynamide **2**. Therefore, we also tried to involve ynamide **14** in the 1,3-dipolar cycloaddition (Scheme 3).

Despite the unsuccessful cyclization previously encountered with ynamides **1** and **3** (Scheme 2), erroneously first assigned to a lack of reactivity of carbamates or urea derived ynamides, we were pleased to observe a clean conversion of compound **14** as checked by ^{1}H NMR of the crude reaction mixture. Purification afforded compound **15** with a satisfactory yield (55%).

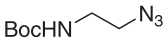
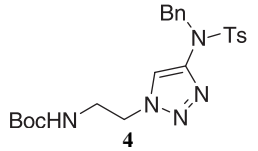
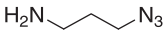
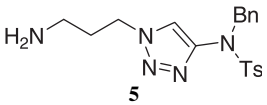
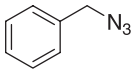
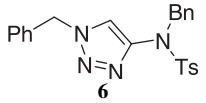
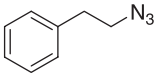
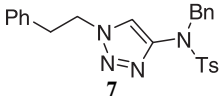
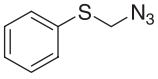
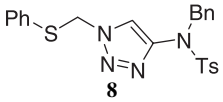
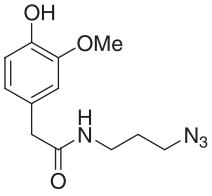
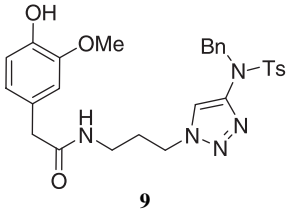
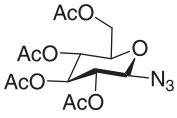
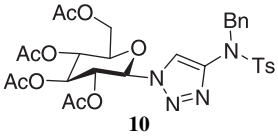
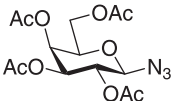
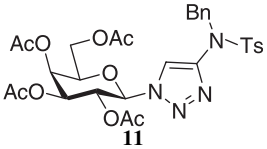
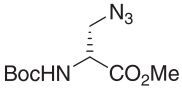
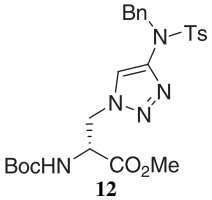
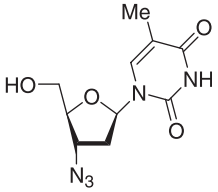
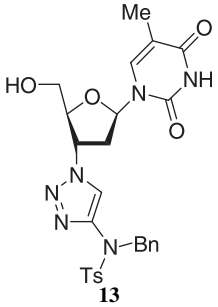
Although the complete mechanism of the 'click chemistry' has not been unambiguously elucidated,[22] it seems quite clear that the first step involves the formation of a copper acetylide. Since such a species has already been evoked in the Glaser[16] or Sonogashira couplings of ynamides,[17] we assume that the same intermediate can be postulated as the key reactive intermediate for the cycloaddition described here; hence the presence of a sulfonamide or carbamate protected amino group on the alkyne moiety does not alter the reactivity of the terminal alkyne in this synthetic transformation.

We should finally point out that there are many reports about the bioactivity of 4-amino imidazoles.[23] In search for potentially more active analogs, the most obvious transformation is the conversion of the imidazole ring into a triazole.[24] The synthetic protocol described in this paper should allow a quick and efficient access to such compounds.



Scheme 3. 'Click chemistry' of *N*-benzyl *N*-benzoyl ynamide.

Table 1. 'Click chemistry' of *N*-benzyl *N*-tosyl ynamide[a]

Entry	Azide	Product	Yield (%)
1		 **4**	58
2		 **5**	58
3		 **6**	38
4		 **7**	77
5		 **8**	68
6		 **9**	62
7		 **10**	96
8		 **11**	85
9		 **12**	43
10		 **13**	59

[a] For the exact conditions used in this reaction see the Section 4.

3. Conclusion

In conclusion, we have demonstrated that ynamides can be good partners for [3+2] cycloaddition affording a novel extension to the 'click chemistry' concept. Two ynamides bearing different protecting groups were successfully clicked with a wide range of azides. Starting from either very simple or highly functionalized azides afforded diversely 1-substituted 4-amino 1,2,3-triazoles. Further work is in progress to improve the yields of this reaction and to expand this approach to other ynamides.

4. Experimental

4.1. General considerations

Most of the azides used in the Huisgen cycloaddition described in this report are either commercially available and were used without further purification or were prepared according to standard protocols. Copper acetate[25] and sodium ascorbate were purchased from Aldrich. Reactions were run under air atmosphere and yields in Table 1 refer to isolated compounds (column chromatography) of greater than 95% purity as determined by ^{1}H NMR, the regiochemistry has been assigned based on the usually observed regioselectivity in similar click reactions. All new compounds were fully characterized by spectroscopic methods (^{1}H, ^{13}C NMR, MS, IR), HRMS.

4.1.1. *tert*-Butyl *N*-[2-(4-benzyl[(4-methylphenyl)sulfonyl]amino-1*H*-1,2,3-triazol-1-yl)ethyl] carbamate (4). To a stirred solution of **2** (100 mg, 0.35 mmol) and *N*-Boc 2-azido ethylamine (65 mg, 0.35 mmol) in ^{t}BuOH (2 mL) and $CHCl_3$ (0.3 mL) was added a premixed solution of $Cu(OAc)_2$ (13 mg, 70 μmol) and sodium ascorbate (30 mg, 0.14 mmol) in H_2O (5 mL). After vigorous stirring overnight the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Purification using flash chromatography (20% EtOAc in cyclohexane) afforded compound **4** as a white solid (95 mg, 0.20 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8.0 Hz, 2H), 7.52 (s, 1H), 7.35 (d, J=7.6 Hz, 2H), 7.26–7.18 (m, 5H), 4.89 (s, 2H), 4.74 (br s, 1H), 4.35 (t, J=3.4 Hz, 2H), 3.51 (q, J=5.6 Hz, 2H), 2.45 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 144.0, 144.0, 135.8, 135.3, 129.7, 128.6, 128.3, 127.6, 127.4, 120.6, 80.0, 52.5, 50.2, 40.3, 28.2, 21.5; IR ν (cm^{-1}) 3396, 3154, 2978, 1712, 1550, 1514, 1360, 1167; MS (ESI): 416 (–^{t}Bu), 438 (–^{t}Bu+23), 494.

4.1.2. *N*1-[1-(3-Aminopropyl)-1*H*-1,2,3-triazol-4-yl]-*N*1-benzyl-4-methyl-1-benzenesulfonamide (5). Using the conditions as described before **2** (50 mg, 0.18 mmol) and a solution of 3-amino propylazide (0.80 mL, 2.2% in toluene) were combined. After purification using flash chromatography (2% MeOH in CH_2Cl_2) **5** (39 mg, 0.10 mmol, 58%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (d, J=8.2 Hz, 2H) 7.39–7.33 (m, 3H), 7.27–7.19 (m, 5H), 4.67 (s, 2H), 4.41 (t, J=6.0 Hz, 2H), 3.21 (t, J=5.7 Hz, 2H), 2.44 (s, 3H), 1.97 (p, J=5.7 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 144.1, 135.8, 129.3, 128.1, 127.9, 127.6, 127.3, 53.6, 43.7, 38.4, 20.6, 20.1; IR ν (cm^{-1}) 3393, 2975, 2515, 1729, 1630, 1453, 1339, 1289, 1161, 1091; MS (ESI): 385. HRMS (ESI-MS): for $C_{19}H_{22}N_5O_2S$ (M−1) calcd 384.1494, found 384.1468.

4.1.3. *N*1-Benzyl-*N*1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-1-benzenesulfonamide (6). Using the previously described conditions **2** (50 mg, 0.17 mmol) was combined with benzylazide (26 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **6** (27.4 mg, 66 μmol, 38%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8.4 Hz, 2H), 7.44 (s, 1H), 7.37–7.31 (m, 5H), 7.27–7.22 (m, 5H), 7.11–7.08 (m, 2H), 5.41 (s, 2H), 4.89 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 144.0, 135.7, 135.1, 134.2, 129.6, 129.0, 128.7, 128.6, 128.2, 127.6, 127.4, 120.1, 54.5, 52.5, 21.5; IR ν (cm^{-1}) 3138, 3034, 2954, 1753, 1552, 1341, 1164, 1089; MS (ESI): (M+23) 441. HRMS (ESI-MS): for $C_{23}H_{23}N_4O_2S$ (M+1) calcd 419.1542, found 419.1541.

4.1.4. *N*1-Benzyl-*N*1-(1-phenethyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-1-benzenesulfonamide (7). Using the previously described conditions **2** (50 mg, 0.17 mmol) was combined with 2-azido ethyl benzene (29 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **7** (58.0 mg, 0.13 mmol, 77%) was obtained as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J=1.6, 8.4 Hz, 2H), 7.35–7.21 (m, 11H), 6.98–6.95 (m, 2H), 4.87 (s, 2H), 4.48 (t, J=7.1 Hz, 2H), 3.12 (t, J=7.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.5, 136.6, 135.8, 135.2, 129.6, 128.7, 128.6, 128.5, 125.3, 127.9, 127.7, 127.6, 127.3, 127.0, 120.5, 52.4, 52.0, 36.3, 21.5; IR ν (cm^{-1}) 3122, 3032, 2924, 1701, 1599, 1543; 1455, 1354, 1165; MS: (M+1) 433 (M+23) 455. HRMS (ESI-MS): for $C_{24}H_{25}N_4O_2S$ (M+1) calcd 433.1698, found 433.1683.

4.1.5. *N*1-Benzyl-*N*1-1-[(phenylsulfanyl)methyl]-1*H*-1,2,3-triazol-4-yl-4-methyl-1-benzenesulfonamide (8). Using the previously described conditions azidomethylsulfanyl benzene (140 mg, 0.85 mmol) was combined with **2** (361 mg, 1.27 mmol). Further purification (50% EtOAc in hexanes) yielded **8** as a yellowish oil (261 mg, 0.58 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.49 (d, J=8.0 Hz, 2H), 7.33–7.13 (m, 14H), 5.41 (s, 2H), 4.85 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 135.7, 135.0, 133.0, 131.1, 129.7, 129.4, 128.9, 128.6, 128.3, 127.7, 127.4, 120.0, 54.6, 52.5, 21.5; IR ν (cm^{-1}) 3650, 3296, 3154, 3063, 3032, 2926, 1754, 1676, 1598, 1553, 1454, 1355, 1225, 1165, 1091; MS: (M+23) 473. HRMS (ESI-MS): for $C_{23}H_{23}N_4O_2S_2$ (M+1) calcd 451.1262, found 451.1286.

4.1.6. *N*1-[3-(4-Benzyl[(4-methylphenyl)sulfonyl]amino-1*H*-1,2,3-triazol-1-yl)propyl]-2-(4-hydroxy-3-methoxyphenyl) acetamide (9). Using the previously described conditions, **2** (50 mg, 0.17 mmol) was combined in 48 h with *N*-(3-azidopropyl)-2-(4-hydroxy 3-methoxyphenyl) acetamide (45 mg, 0.17 mmol). After further purification using flash chromatography (gradient from 30 to 100% EtOAc in hexanes) **9** (59.4 mg, 0.11 mmol, 62%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.57 (d, J=8.2 Hz, 2H), 7.51 (s, 1H), 7.32 (d, J=7.0 Hz, 2H), 7.27–7.18 (m, 5H), 6.88 (d, J=7.9 Hz, 1H), 6.76 (s, 1H), 6.71 (d, J=7.9 Hz, 1H), 5.73 (br s, 1H), 4.86 (s, 2H), 4.19 (t, J=6.8 Hz, 2H), 3.86 (s, 3H), 3.44 (s, 2H), 3.09 (q, J=6.3 Hz, 2H), 2.41 (s, 3H), 1.98 (p, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 146.9, 145.0, 144.1, 144.0, 135.7, 135.2, 129.7, 128.6, 128.3, 127.6, 127.3, 126.4, 122.0, 120.2, 114.8, 111.7, 55.9, 52.5, 48.0, 43.3, 36.3, 29.7, 21.5; IR ν (cm^{-1}) 3297, 2925, 1653, 1547, 1515, 1455, 1354, 1275, 1163; MS: (M+23) 572. HRMS (ESI-MS): for $C_{28}H_{32}N_5O_5S$ (M+1) calcd 550.2124, found 550.2159.

4.1.7. 1-{4-(Benzyl-toluene-4-sulfonyl)-amino-(1,2,3)-triazol-1-yl}-1-deoxy-β-D-glucopyranoside tetraacetate (10). Using the previously described conditions 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate (161 mg, 0.432 mol) and **2** (135 mg, 0.474 mol) were combined. Further purification using flash chromatography (50% EtOAc in cyclohexane) yielded a white solid (271.6 mg, 0.422 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.35 (d, J=7.6 Hz, 2H), 7.32–7.19 (m, 5H), 5.67 (d, J=8.4 Hz, 1H), 5.39–5.33 (m, 2H), 5.26 (t, J=8.4 Hz, 1H), 4.89 (s, 2H), 4.31 (dd, J=4.4, 12.4 Hz), 4.15 (d, J=13.2 Hz, 2H), 3.95 (d, J=10 Hz, 1H), 2.41 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.72 (s, 3H); IR ν (cm^{-1}) 3124, 2950, 1753, 1555, 1459, 1369, 1228, 1165, 1036; MS: (M+1) 659 (M+23) 681. HRMS (ESI-MS): for $C_{30}H_{34}N_4O_{11}NaS$ (M+23) calcd 681.1842, found 681.1868.

4.1.8. 1-{4-(Benzyl-toluene-4-sulfonyl)-amino-(1,2,3)-triazol-1-yl}-1-deoxy-β-D-galactopyranoside tetraacetate (11). Using the previously described conditions 1-azido-1-deoxy-β-D-galactopyranoside tetraacetate (250 mg, 0.777 mmol) was combined with **2** (331 mg, 1.16 mmol). After further purification using flash chromatography (50% EtOAc in hexanes) **11** (480 mg, 0.666 mmol, 85%) was obtained as a white fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.59 (d, J=8.4 Hz, 2H) 7.35 (d, J=7.0 Hz, 2H), 7.28–7.18 (m, 5H), 5.67 (d, J=9.1 Hz, 1H), 5.52 (d, J=3.6 Hz, 1H), 5.49 (t, J=10.0 Hz, 1H), 5.21 (dd, J=3.6, 10.0 Hz, 1H), 4.90 (s, 2H), 4.18 (s, 1H), 4.21–4.08 (m, 2H), 2.41 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.0, 169.7, 168.5, 144.5, 144.0, 135.6, 135.0, 129.7, 128.6, 128.3, 127.6, 1274, 118.2, 86.8, 74.1, 70.5, 67.8, 66.7, 61.1, 52.1, 21.5, 20.6, 20.5, 20.4, 20.0; IR ν (cm^{-1}) 3646, 3487, 3152, 3033, 2940, 1757, 1677, 1557, 1458, 1370, 1224, 1166, 1092, 1061; MS: (M+23) 681. HRMS (ESI-MS): for $C_{30}H_{34}N_4O_{11}NaS$ (M+23) calcd 681.1842, found 681.1862.

4.1.9. Methyl 3-(4-benzyl[(4-methylphenyl)sulfonyl]-amino-1*H*-1,2,3-triazol-1-yl)-2*R*-[(*tert*-butoxycarbonyl)-amino] propanoate (12). Using the conditions as described before **2** (100 mg, 0.35 mmol) and (*R*)-2-Boc-amino-3-azido-propionic acid methyl ester (77 mg, 0.35 mmol) were combined. After further purification using a gradient from 20% EtOAc to 100% in hexane a white solid (77 mg, 43%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8.1 Hz, 2H), 7.48 (s, 1H), 7.34 (d, J=7.9 Hz, 2H), 7.29–7.21 (m, 5H), 5.22 (br d, J=7.0 Hz, 1H), 4.86 (dd, J=4.4, 18.4 Hz, 2H), 4.77–4.61 (m, 3H), 3.69 (s, 3H), 2.41 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 154.8, 144.0, 135.7, 135.0, 129.7, 128.7, 128.3, 127.6, 127.3, 121.3, 80.8, 65.7, 52.9, 52.4, 28.2, 21.5; IR ν (cm^{-1}) 3392, 1747, 1686, 1517, 1351, 1160; MS: (M+1) 530 (M+23) 552. HRMS (ESI-MS): for $C_{25}H_{32}N_5O_6S$ (M+1) calcd 530.2073, found 530.2078.

4.1.10. *N*1-Benzyl-*N*1-1-[2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-3-furanyl]-1*H*-1,2,3-triazol-4-yl-4-methyl-1-benzenesulfonamide (13). Using the conditions as previously described, AZT (40 mg, 0.15 mmol) and **2** (45 mg, 0.16 mmol) were combined. Further purification using flash chromatography (66% EtOAc in hexanes) resulted in a white solid (47.0 mg, 85 μmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.58 (d, J=8.2 Hz, 2H), 7.40 (s, 1H), 7.32 (d, J=6.7 Hz, 2H), 7.29–7.19 (m, 5H), 6.18 (t, J=6.5 Hz, 1H), 5.34–5.29 (m, 1H), 4.88 (s, 2H), 4.29–4.27 (m, 1H), 3.97–3.92 (m, 1H), 3.72–3.67 (m, 1H), 2.90–2.85 (m, 2H), 2.40 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 163.8, 150.4, 144.3, 137.6, 135.6, 135.1, 129.8, 128.5, 128.3, 127.7, 127.3, 119.8, 111.2, 88.2, 84.9, 61.3, 60.4, 59.5, 52.5, 37.3, 21.5, 20.9, 14.1, 12.3; IR ν 3443, 3126, 2927, 1713, 1683, 1545, 1469, 1357, 1275, 1165, 1092; MS: (M+1) 553, (M+23) 575. HRMS (ESI-MS): for $C_{26}H_{29}N_6O_6S$ (M+1) calcd 553.1869, found 553.1880.

4.1.11. *N*1-Benzyl-*N*1-1-[(phenylsulfanyl)methyl]-1*H*-1,2,3-triazol-4-yl benzamide (15). Using the previously described conditions **14** (50 mg, 0.17 mmol) was combined with azidomethylsulfanyl benzene (29 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **15** (46.5 mg, 11.6 μmol, 55%) was obtained as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=7.1 Hz, 2H), 7.36–7.20 (m, 14H), 5.43 (br s, 2H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 136.9, 135.2, 132.4, 130.2, 129.4, 128.7, 128.4, 128.2, 127.9, 127.8, 127.4, 54.5, 52.0; IR ν (cm^{-1}) 3178, 3052, 1636, 1545, 1412, 1255, 1148, 973; MS: (M+23): 423. HRMS (ESI-MS): for $C_{23}H_{20}N_4ONaS$ (M+23) calcd 423.1256, found 423.1244.

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Coupling and cycloaddition of ynamides: homo- and Negishi coupling of tosylynamides and intramolecular [4+2] cycloaddition of *N*-(*o*-ethynyl)phenyl ynamides and arylynamides

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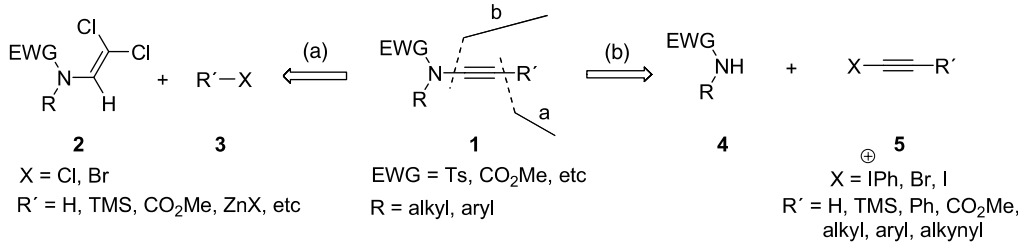
Abstract—*N*,*N*′-aryl- and *N*,*N*′-alkyl-buta-1,3-diyne-1,4-ditosylamides have been synthesized for the first time, in good to excellent yields, by copper-catalyzed dimerization of the corresponding *N*-aryl or *N*-alkyl tosylynamides. Negishi coupling of *N*-ethynylzinc tosylamides derivatives with (hetero)aryl iodides in the presence of Pd_2dba_3 and triphenylphosphine affords *N*-aryl and *N*-alkyl arylynamides in yields of up to 90%. Intramolecular [4+2] cycloaddition reactions of *N*-ethynylphenyl ynamides and arylynamides allow the synthesis of carbazoles and benzannulated and heteroannulated carbazoles in moderate-to-good yields.

1. Introduction

Ynamides **1** have emerged as potentially more useful than other ynamines for organic synthesis because of their superior thermal stability.[1,2,3] Typically, ynamides withstand aqueous work-up and chromatographic purification on silica gel, and are often crystalline solids that are stable in air. These features have allowed their recent use in an array of procedures such as Pauson–Khand reactions,[4] hydroboration,[5] Rh(I)- and Ru(II)-catalyzed [2+2+2] cycloadditions,[6] Ni(0)- and Rh(I)-catalyzed [4+2] cycloadditions,[7] ring-closing metatheses,[8] radical cyclizations,[9] Pt-catalyzed cycloisomerizations,[10] Heck reactions[11] and pericyclic reactions.[12]

Although not all possible ynamides are currently accessible, many can be obtained by subjecting to elimination reactions dichloroenamides **2** (Scheme 1, route a) or by direct alkynylation of amide derivatives **4** (route b). Brückner's elimination protocol,[13] based on Viehe's pioneer work,[14] is really a tandem process, a base-promoted elimination followed by lithium–halogen exchange.[15,16] Direct alkynylation was initially developed by Stang[2d] and Feldman[17] to prepare 'push–pull'-type ynamines (R′=CO_2R, SO_2Ar, etc), and consists in the reaction of metalated amides with alkynyl(phenyl)iodonium salts **5** (X=IPh).[18] Though extended by Witulski and Rainier to the preparation of ynamides **1** in which R′=H, TMS, or phenyl,[4,6] this approach is of limited use for synthesis of alkyl ynamides (R′= alkyl), and also gives relatively low yields with some amide substrates.[1a] A second direct alkynylation approach, based on the methods developed by Buchwald and Hartwig for nitrogen–carbon bond formation,[19] involves the



Scheme 1. General approaches to ynamides.

Keywords: Alkynylation; Carbazoles; Coupling; Cycloaddition; Ynamides.
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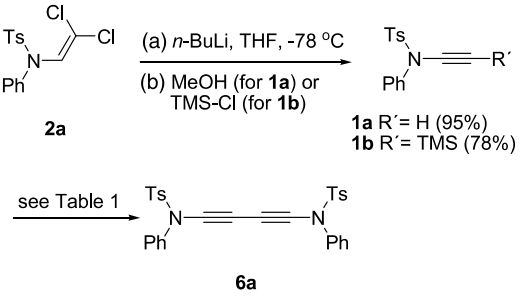
Cu(I)-catalyzed cross-coupling of amide derivatives **4** with readily available alkynyl halides **5** (X=Br, I).[20] This latter strategy was first developed by Hsung[21] and Danheiser,[22] for acyclic and cyclic carbamates, and cyclic ureas and was extended to sulfonamides and heteroaromatic substrates by Hsung[23] (using $CuSO_4$ as catalyst) and Sato.[24] Another straightforward protocol for the synthesis of ynamides involves base-induced isomerization of propargylic amides.[25]

In the course of our research on the synthesis of heterocyclic compounds we required several *N*-aryl ynamides (**1**; R= aryl, R′=H or protecting group) and arylynamides (**1**; R, R′=aryl).[26] To our surprise, only one such compound had previously been synthesized.[23] Here we describe the preparation of *N*-aryl and *N*-alkyl tosylynamides by Brückner's method; their homocoupling reactions; the preparation of *N*-aryl and *N*-alkyl arylynamides by Negishi coupling between the corresponding *N*-ethynylzinc tosylamides and appropriate aryl iodides, the preparation of *N*-ethynylphenyl ynamides and arylynamides by combinations of Sonogashira reactions[27] and Stang's[18] ethynyl(phenyl)iodonium salt approach; and the intramolecular [4+2] cycloaddition reactions of *N*-ethynylphenyl ynamides and arylynamides, which afford carbazoles and benzannulated and heteroannulated carbazoles.

2. Results and discussion

2.1. Preparation and homocoupling of *N*-aryl and *N*-alkyl tosylynamides[16a]

Our interest in the metal-catalyzed cyclization of diynes[28] led us to search the literature for methods for homodimerization of ynamides.[29] Finding none, we decided to evaluate the performance of common alkyne dimerization methods[30] when applied to selected ynamides, starting with aniline ynamides. Aniline ynamide **1a** was prepared as per Brückner[13a] by sequential treatment of the dichlorovinylamide **2a** with *n*-butyllithium and methanol (Scheme 2); similarly, trimethylsilyl ynamide **1b** was obtained in 78% yield by trapping the lithium acetylide with trimethylsilyl chloride.



Scheme 2. Preparation of *N*-phenyltosylynamides **1a**,**b**.

In our first attempt to dimerize ynamide **1a** (Table 1, entry 1) we used a palladium catalyst that had proved useful for other alkyne dimerizations in our laboratory.[31] However, in the presence of this catalyst **1a** gave a mixture from which the dimer **6a** could only be isolated in 40% yield, and similar results were obtained with other terminal alkynes.[32] We then tried copper catalysts.

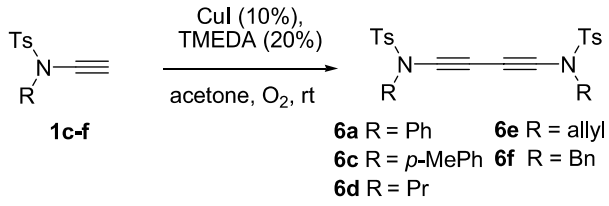
Table 1. Dimerization of *N*-phenyl tosylynamides **1a** and **1b**

Entry	Ynamide	Conditions[a]	Time	Yield **6a** (%)
1	**1a**	$PdCl_2(PPh_3)_2$, CuI, I_2, *i*-Pr_2NH, THF, rt	1 min	See text
2	**1a**	CuCl, TMEDA, acetone, O_2, rt	3 h	63
3	**1a**	$Cu(OAc)_2$, Py, rt	0.5 h	See text
4	**1a**	CuI, TMEDA, acetone, O_2, rt	3 h	91
5	**1a**	CuI, TMEDA, acetone, O_2, rt	1 h	88
6	**1b**	CuCl, DMF, 60 °C	0.5 h	88

[a] Amounts of catalyst: entry 1, 5% $PdCl_2(PPh_3)_2$, 5% CuI; entries 2 and 4, 10% CuX, 20% TMEDA; entry 3, 250% $Cu(OAc)_2$; entry 5, 50% CuI, 100% TMEDA; entry 6, 100% CuCl.

Classical Hay[33] conditions (CuCl, TMEDA, acetone, O_2) afforded dimer **6a** in 63% isolated yield as an air-stable white solid (entry 2). Copper(II) acetate in pyridine (entry 3) also brought about fast, clean conversion of the starting material (as shown by TLC monitoring), but the reaction product could not be isolated due to its decomposition in the presence of Cu_2SO_4 (5%) or HCl (5%) during work-up.[34] By contrast, the conditions reported by Pericàs[35] for the synthesis of 1,4-dialkoxy-1,3-butadiynes, which use 10% CuI instead of CuCl, afforded **6a** in 91% yield (entry 4). Furthermore, increasing the amount of catalyst to 50% shortened the reaction time to 1 h with minimal reduction of yield (entry 5). Trimethylsilyl ynamide **1b** was efficiently dimerized in DMF at 60 °C in the presence of CuCl (entry 6).[36]

We next applied the Pericàs conditions to ynamides **1c–f** (Scheme 3), all of which were prepared following Brückner's procedure.[13a] All these substrates afforded high yields of the corresponding Glaser adduct **6** (Table 2).



Scheme 3. Homocoupling of *N*-aryl and *N*-alkyl tosylynamides **1c–f**.

Table 2. Dimerization of *N*-substituted tosylynamides **1a**,**c**,**d**,**e** and **f**[a]

Entry	Ynamide, R	Product, yield (%)
1	**1a**, Ph	**6a**, 91
2	**1c**, *p*-MePh	**6c**, 84
3	**1d**, Pr	**6d**, 100
4	**1e**, Allyl	**6e**, 86
5	**1f**, Bn	**6f**, 91

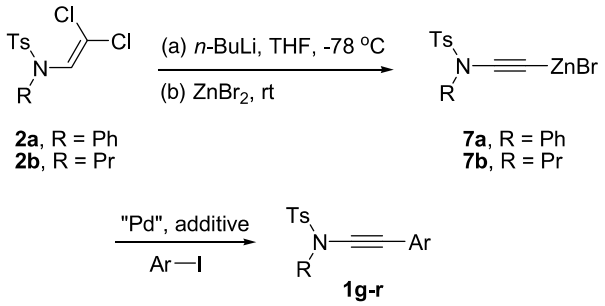
[a] Conditions: CuI (10%), TMEDA (20%), acetone, O_2, rt, 3 h.

All the *N*,*N*′-substituted-buta-1,3-diyne-1,4-ditosylamides **6** were isolated as air-stable white solids that withstood aqueous work-up procedures and chromatographic purification on silica gel. They have been stored at rt for weeks with no appreciable decomposition. Note that dimer **6f**, obtained in 91% yield from benzyl ynamide **1f**, can be

considered as masked 1,3-butadiyne-1,4-diamine, the tosyl and benzyl groups being easily removable under standard conditions.[37]

2.2. Synthesis of *N*-aryl and *N*-alkyl arylynamides by Negishi coupling[16b]

In our first experiments on using the Negishi approach[38] to obtain arylynamides, sequential treatment of *N*-phenyl ynamide **1a** with *n*-BuLi and $ZnBr_2$, followed by addition of $PdCl_2(PPh_3)_2$ and iodobenzene, led only to a low yield of dimer **6a**. When Pd_2dba_3 was used as palladium source, the cross-coupled product was obtained as well as **6a**, but the yield was very poor and the catalyst was contaminated by the starting ynamide. Finally, however, complete formation of zinc acetylide **7a** was achieved by treating the precursor of **1a**, dichlorovinylamide **2a**, with 2 equiv of *n*-BuLi followed by $ZnBr_2$ (Scheme 4).



Scheme 4. Preparation of *N*-aryl and *N*-alkyl arylynamides **1g–r** by Negishi coupling.

With zinc acetylide **7a** in hand we explored its palladium-catalyzed coupling with *p*-iodoanisole. $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ showed no catalytic activity (Table 3, entries 1 and 2) and, when used alone, Pd_2dba_3 produced only small amounts of the desired coupled ynamide **1g** (entry 3).[39] However, when 20 mol% of PPh_3 was added the yield increased to 48% and was accompanied by an 18% yield of the dimer **6g** (entry 4). Using triphenylarsine or P(*o*-Tol)$_3$ instead of PPh_3 gave lower yields of **1g** with or without increased production of dimer **6g** (entries 5 and 6), and there was no reaction when PPh_3 was added without palladium (entry 7). The lithium analogue of **7a** slowly decomposed under the reaction conditions, affording only small amounts of **6g**.[39]

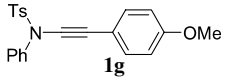
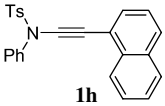
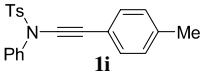
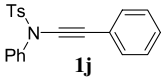
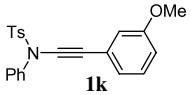
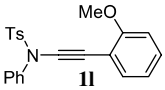
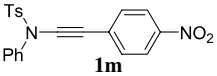
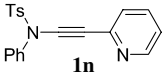
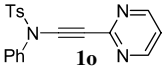
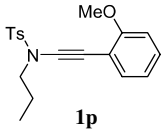
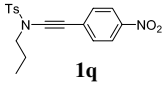
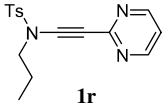
Table 3. Optimization of Negishi coupling of alkynylzinc **7a** and *p*-iodoanisole[a]

Entry	Catalyst (5%)	Additive (20%)	**1g** (%)	**6g** (%)[b]
1	$PdCl_2(PPh_3)_2$	None	0	ND
2	Pd $(PPh_3)_4$	None	0	ND
3	Pd_2dba_3	None	<5	ND
4	Pd_2dba_3	PPh_3	48	18
5	Pd_2dba_3	$AsPh_3$	38	18
6	Pd_2dba_3	P(*o*-Tol)$_3$	35	33
7	None	PPh_3	0	0
8[c]	Pd_2dba_3	PPh_3	0	ND

[a] Catalyst amount=5%, additive amount=20%; rt, 2 h.
[b] ND=not determined.
[c] Reaction with the lithium analogue of zinc acetylide **7a**.

The optimized conditions (5% Pd_2dba_3, 20% PPh_3) were then employed for the synthesis of the new *N*-phenyl aryl and heteroarylynamides **1h–o** (Table 4). The 1-naphthyl, 4-methylphenyl and phenyl derivatives **1h–j**, were obtained in quite good yields (entries 2–4). The *m*-anisole derivative **1k** was obtained in the same yield as its *para* analogue **1g** had been (entries 1 and 5), and the yield of the *ortho* analogue **1l** was only 25% (entry 6). As expected, however, coupling partners with an electron-withdrawing group (entry 7) or with electronegative heteroatoms (entries 8 and 9) afforded higher yields (81–92% after purification). Finally, the *N*-propyl arylynamides **1p–r** were also synthesized, in yields very similar to those of their *N*-phenyl counterparts **1l**, **1m** and **1o** (Table 4, entries 10–12).

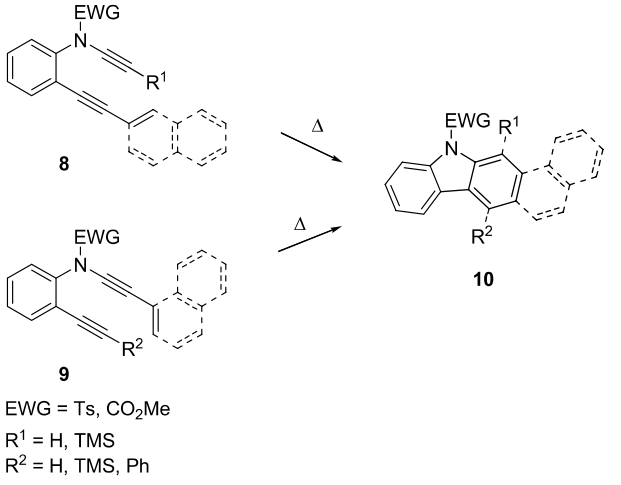
Table 4. Synthesis of arylynamides **1g–r** by Negishi cross-coupling

Entry	Vinyl-amide	I-Ar	Ynamide	Yield (%)[a]
1	**2a**	I-benzene	 **1g**	48
2	**2a**	2-I-naphthalene	 **1h**	63
3	**2a**	4-I-toluene	 **1i**	68
4	**2a**	4-I-anisole	 **1j**	69
5	**2a**	3-I-anisole	 **1k**	48
6	**2a**	2-I-anisole	 **1l**	25
7	**2a**	4-I-nitrobenzene	 **1m**	83
8	**2a**	2-I-pyridine	 **1n**	92
9	**2a**	2-I-pyrimidine	 **1o**	81
10	**2b**	2-I-anisole	 **1p**	24
11	**2b**	4-I-nitrobenzene	 **1q**	81
12	**2b**	2-I-pyrimidine	 **1r**	85

[a] Isolated yields of products purified by column chromatography.

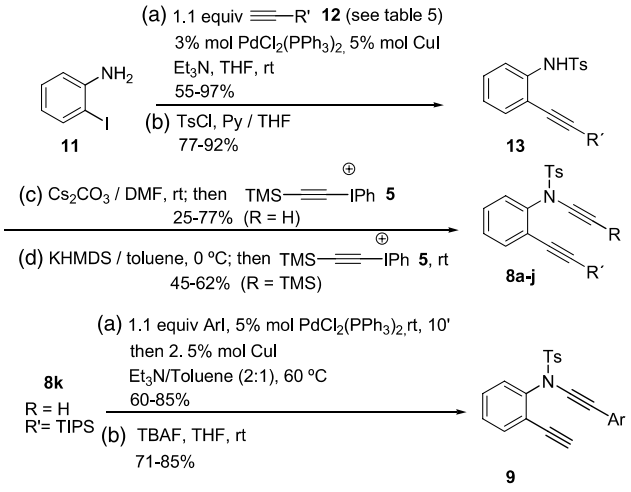
2.3. Intramolecular [4+2] cycloadditions of *N*-aryl ynamides 8 and *N*-aryl arylynamides 9[26]

In this section we report our approach to the synthesis of carbazoles[40] and benzannulated carbazoles **10** by means of intramolecular dehydro Diels–Alder (IDDA) reactions,[41] specifically, the intramolecular [4+2] cycloaddition of *N*-aryl ynamides **8** and *N*-aryl arylynamides **9** (Scheme 5).[42] Carbazoles constitute an important class of alkaloid displaying a wide variety of biological activities,[43] and their derivatives are also widely used as building blocks for new organic materials.[44]



Scheme 5. Carbazoles by intramolecular [4+2] cycloaddition of *N*-aryl ynamides **8** and *N*-aryl arylynamides **9**.

N-Aryl ynamides **8** and *N*-aryl arylynamides **9** were prepared in three and five steps, respectively, starting from commercially available *o*-iodoaniline (**11**) (Scheme 6). Sonogashira reactions between **11** and terminal alkynes **12**, followed by N-tosylation,[45] gave alkynes **13** (which were also obtained by Sonogashira reactions of tosylated **11** with **12**), and N-ethynylation of alkynes **13** with (trimethylsilyl)ethynyliodonium salt **5** then gave the desired *N*-aryl ynamides **8** (Table 5), generally, in good overall yields. Using Cs_2CO_3 as the base in the last step afforded terminal acetylenes **8** (R=H), using KHMDS retained the TMS group.[6c] *N*-aryl arylynamides **9** were synthesized in good yields by Sonogashira cross-coupling of aryl iodides with ynamide **8k**[27] (R=H, R′=TIPS) followed by desilylation.



Scheme 6. Preparation of *N*-aryl ynamides **8** and *N*-aryl arylynamides **9**.

Heating ynamides **8** in toluene at 150 °C (conditions A) generally gave poor to moderate yields of the desired intramolecular [4+2] cycloaddition.[41] Not unexpectedly, in most cases better results were obtained in a mixture of toluene and Et_3N (Table 5, conditions B).[41b,d] For example, for ynamide **8a** the change of medium raised the yield of 2-methylcarbazole **10a** from a poor 16% to an acceptable 40% (Table 5, entry 1). Remarkably, however, access to the interesting tetrahydro-5*H*-benzo[*b*]carbazole nucleus **10b** was achieved in 55% yield using toluene alone (entry 2).[46] This nucleus was also obtained using a carbamate instead of a tosylamide as substrate (**10c**, entry 3). Thus our metal-free IDDA approach to carbazoles nicely complements the intermolecular Rh(I)-catalyzed [2+2+2] cycloaddition of ynamides with alkynes,[6c] which is unable to create fused cyclohexyl rings.

Benzannulated carbazole ring systems are found only rarely in nature but are of considerable interest because of their potential antitumoral and other pharmacological properties,[40] and as building blocks for organic materials.[44] Several synthetic approaches to benzo[*b*]carbazoles (2-deazaellipticines) have been developed over the past half century,[40] including benzannulation of indoles,[47] Fischer indolization of phenylhydrazones,[48] Diels–Alder reactions of pyrano[3,4-*b*]indol-3-ones,[49] 4*H*-furo[3,4-*b*]indoles[50] and 2,4-dihydropyrrolo[3,4-*b*]indoles,[51] and cycloaromatization of *N*-[2-(1-alkynyl)phenyl]keteneimines;[52] yields have varied between 22 and 98%. The main failing of these methods is their lack of flexibility, since they almost exclusively allow the synthesis of the parent benzo[*b*]carbazole nucleus but not that of benz[*b*]annulated analogues. In this work, the 30% yield of benzo[*b*]carbazole **10d** that was obtained by heating **8d** in toluene was surprisingly reduced to 12–15% in basic or protic media (Table 5, entry 4).[41] Indeed, when a mixture of toluene and AcOH was used, hydrolysis of the ynamide group occurred giving **14d** in 68% yield (Fig. 1). However, the carbamate substrate **8e** gave more satisfactory yields of up to 50% (entry 5). Gratifyingly, unlike the methods mentioned above, the ynamide IDDA approach allowed uneventful preparation of benz[*b*]annulated carbazoles with additional benzene rings: heating ynamides **8f–h** in conditions B gave the known naphtho[1,2-*b*]carbazole[47d] **10f** in 90% yield (entry 6) and the hitherto unknown naphtho[2,1-*b*]carbazole **10g** (30% yield, entry 7) and dibenzo[*a*,*c*]carbazole **10h** (58% yield, entry 8).

We then investigated whether benzo[*c*]carbazoles might be prepared through rearrangement of the cyclic allene intermediate that would be formed in the course of the IDDA reaction of silylynamide **8i**.[53] Unfortunately, all attempts at IDDA reaction of **8i** led to its decomposition (entry 9), even when we tried to trap the putative initial cyclic allene in the presence of MeOH (entry 9). By contrast, silylynamide **8j**, in which the terminal phenyl of **8i** was replaced by a cyclohexenyl ring, smoothly cyclized in very good yields to the 6-(trimethylsilyl)tetrahydrobenzo[*b*]carbazole **10j** (entry 10).

Table 5. Results of intramolecular [4+2] cycloaddition of ynamides **8**

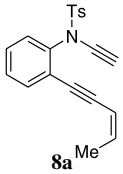
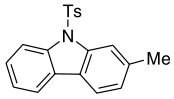
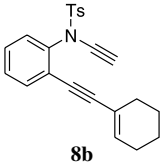
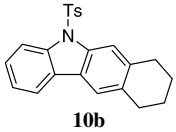
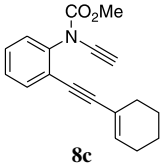
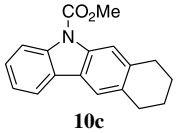
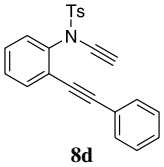
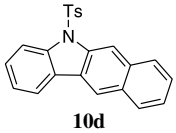
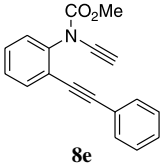
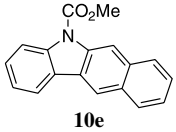
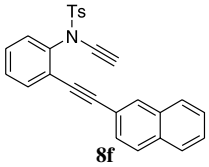
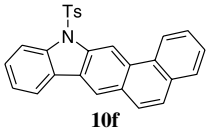
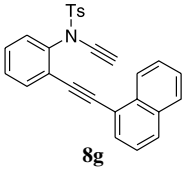
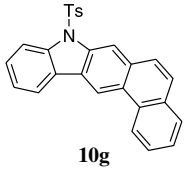
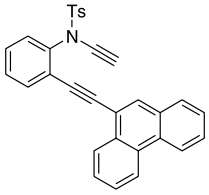
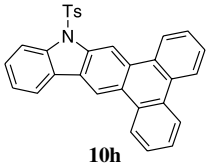
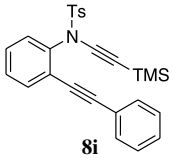
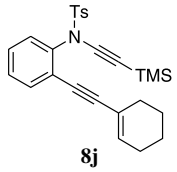
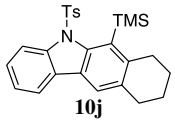
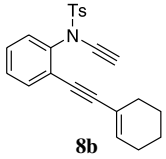
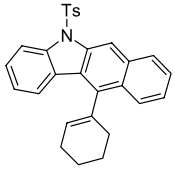
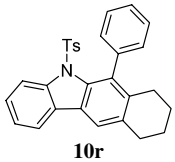
Entry	Ynamide	Carbazole	Yield (%)
1	 **8a**	 **10a**	16,[a] 40[b]
2	 **8b**	 **10b**	55[a]
3	 **8c**	 **10c**	35,[a] 43[b]
4	 **8d**	 **10d**	30,[a] 12,[b] 15[c]
5	 **8e**	 **10e**	42,[a] 50[b]
6	 **8f**	 **10f**	21,[a] 90[b]
7	 **8g**	 **10g**	10,[a] 30[b]
8	 **8h**	 **10h**	27,[a] 58[b]
9	 **8i**	decomp.[a,c]	

Table 5 (*continued*)

Entry	Ynamide	Carbazole	Yield (%)
10	 **8j**	 **10j**	72,[b] 85[c]
11[d]	 **8b**	 **10q** +  **10r**	8+16

[a] Experimental conditions. A: **8** (0.01 M), toluene (typically, 6 mL), 150 °C, sealed tube (normal).
[b] Conditions B: conditions A plus 0.5 mL of Et_3N.
[c] Conditions C: conditions A plus 0.5 mL of MeOH or ^{i}PrOH.
[d] PhI (1.1 equiv), 5% $Pd(PPh_3)_4$, 2% CuI, 2:1 Et_3N/toluene, 60 °C.

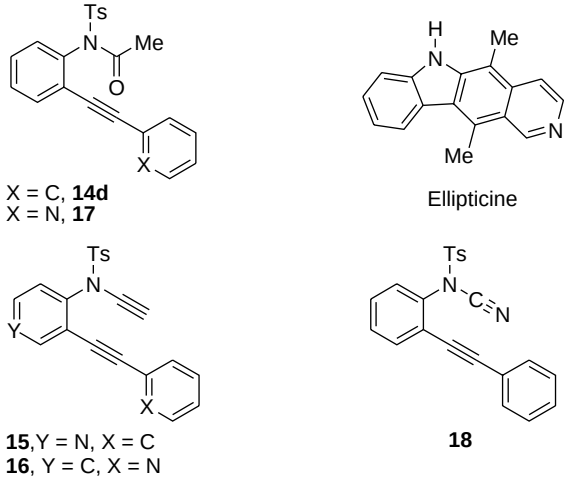


Figure 1.

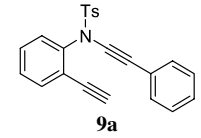
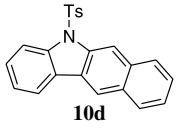
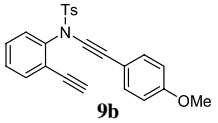
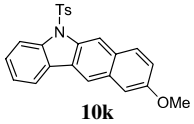
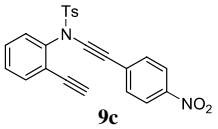
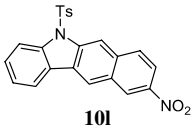
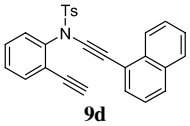
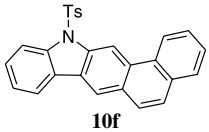
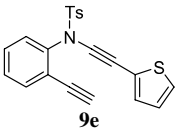
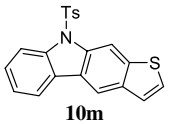
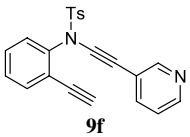
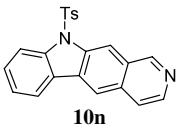
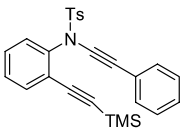
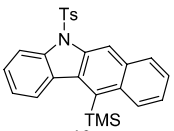
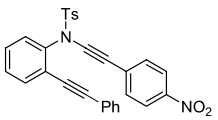
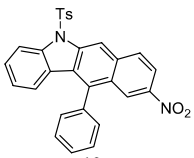
We were also unsuccessful in our attempts to prepare pyrido[4,3-*b*]benzo[*f*]indoles, pyrido[3,2-*b*]carbazoles or indolo[2,3-*b*]quinolines, which we sought as isomers of the skeleton of the interesting antitumoral agent ellipticine (Fig. 1).[40] Heating **15**[54] or **16** in toluene at 150 °C led to their decomposition, giving at best traces of the desired cyclized products; heating **16** in the presence of AcOH resulted in its 85% conversion into the hydrolysis product **17**; and heating cyanamide **18**[55] had no effect, a result that contrasts with the exceptionally easy photocyclizations of the related aryldiimides.[56]

When we investigated the intramolecular [4+2] cycloaddition reactions of arylynamides **9** we found that in toluene/Et_3N a much better yield of the benzo[*b*]carbazole **10d** was obtained from **9a** than from **8d**, 50% (Table 6, entry 1) as against 12% (Table 5, entry 4). This exemplifies a trend noted by Danheiser,[22b] that conjugated enynamides (in our case, **9a**) give better results than ynamides lacking such conjugation, such as **8d**, and in the case of **8d** may be due to the cyclic allene intermediate undergoing ring-opening reactions.[41,57] However, naphthylynamide **9d** gave a lower yield of naphthocarbazole **10f** than did **8f**, 73% (Table 6, entry 4) as against 90% (Table 5, entry 7). Surprisingly, the yields of the IDDA reactions of arylynamides **9** did not seem to be influenced by the electronic nature of the arylynamide moiety (Table 6, entries 2 and 3).

Unlike ynamides **15** and **16**, heteroarylynamides **9e** and **9f** responded to IDDA conditions, giving moderate yields of thienocarbazole **10m** and pyridocarbazole **10n** (Table 6, entries 5 and 6).[58] Also, the silylated benzo[*b*]carbazole **10o** was obtained in 31% yield from phenylynamide **9g** (Table 6, entry 7), silylynamide **8i** had failed to react (Table 5, entry 9).

Finally, we examined the regioselectivity of the dehydro Diels–Alder reaction by installing a second phenyl ring in the aryl *N*-substituent of the starting arylynamide: heating **9h** gave the 2-nitro-11-phenylbenzo[*b*]carbazole **10p** regioselectively,[59] (though in rather poor yield), showing that the cycloaddition occurred selectively on the conjugated arenynamide moiety (Table 6, entry 8). Interestingly, however when ynamide **8b** was subjected to Sonogashira conditions in the presence of iodobenzene, two carbazoles were isolated, 11-cyclohexenylbenzo[*b*]carbazole **10q** in 8% yield and 6-phenyltetrahydrobenzo[*b*]carbazole **10r** in 16% yield, suggesting that after initial phenylation of **8b**[27] the two possible cycloadditions had occurred in roughly 1:2 ratio (Table 5, entry 11).

Table 6. Results of intramolecular [4+2] cycloaddition of arylynamides **9**

Entry	Arylynamide	Carbazole	Yield (%)[a]
1	 **9a**	 **10d**	50
2	 **9b**	 **10k**	50
3	 **9c**	 **10l**	60
4	 **9d**	 **10f**	73
5	 **9e**	 **10m**	34
6	 **9f**	 **10n**	21
7	 **9g**	 **10o**	31
8	 **9h**	 **10p**	16

[a] Experimental conditions: **9** (0.01 M), toluene (typically, 6 mL) plus 0.5 mL of Et_3N, 150 °C, sealed tube.

3. Conclusions

The catalytic system CuI/TMEDA promotes dimerization of *N*-aryl- and *N*-alkyl tosylynamides in high yield. The resulting *N*,*N*′-substituted-buta-1,3-diyne-1,4-ditosylamides are air-stable solids. The use of these diynes in metal-catalyzed cyclization reactions is currently being explored in our laboratories.

Negishi coupling allows one-pot synthesis of *N*-aryl and *N*-alkyl arylynamides starting from readily available dichlorovinylamides, and intramolecular [4+2] cycloaddition reactions of *N*-ethynylphenyl ynamides and arylynamides afford carbazoles and benzannulated and heteroannulated carbazoles in relatively good yields. These results open new perspectives for the application of ynamides in the field of poly- and heterocyclic aromatic chemistry.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere with magnetic stirring. The solvents were purified and dried using standard procedures. All reagents were purchased and used without further purification. Melting points were measured using a Koefler melting point apparatus, and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Brucker DPX-250 (250 and 63 MHz), AMX-300 (300 and 75 MHz) and Brucker WM-500 (500 and 125 MHz) spectrometers using $CDCl_3$ as solvent with tetramethylsilane as internal standard. Mass spectra were recorded on either a Hewlett-Packard HP5988A and Micromass Autospec MS (EI and HRMS) or an Applied 'API 4000' (ESI). Microanalyses were performed on a Thermo Finnigan Flash 112 at the University of Santiago de Compostela, Spain. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel.

4.2. Typical procedure for the homocoupling of tosylynamides

4.2.1. *N*,*N*′-1,3-Butadiyn-1,4-diyl-*N*,*N*′-diphenyl ditosylamide 6a. TMEDA (5 μL, 0.033 mmol) was added to a suspension of CuI (3 mg, 0.017 mmol) in dry acetone (4 mL) under O_2 atmosphere, at rt. After 15 min, a solution of **1a** (45 mg, 0.177 mmol) in acetone (4 mL) was added and the mixture was vigorously stirred until TLC showed complete comsuption of the starting material (3 h). After removal of the solvent, the crude residue was purified by column chromatography on silica gel using a mixture of hexanes/EtOAc 1:3 as eluent, yielding 41 mg (91%) of **6a** as white prisms, mp 157–159 °C (dec). ^1H NMR (250 MHz, $CDCl_3$) δ: 7.62–7.56 (m, 4H, ArH), 7.36–7.26 (m, 10H, ArH), 7.25–7.17 (m, 4H, ArH), 2.44 (s, 6H, 2×CH_3). ^{13}C NMR+DEPT (62.83 MHz, $CDCl_3$) δ: 145.3 (2×C), 138.2 (2×C), 133.1 (2×C), 129.7 (4×CH), 129.2 (4×CH), 128.7 (2×CH), 128.1 (4×CH), 126.4 (4×CH), 75.7 (2×C), 58.5 (2×C), 21.7 (2×CH_3). MS (70 eV) *m*/*z* (%): 545 (M^+-CH_3, 29), 369 (57), 322 (55), 278 (97), 247 (63), 218 (82), 139 (100), 91 (60). Elemental analysis calcd (%) for $C_{30}H_{24}N_2O_4S_2$: C 66.65, H 4.47, N 5.18, S 11.86; found: C 66.21, H 4.21, N 5.27, S 11.67.

4.2.2. *N*,*N*′-1,3-Butadiyn-1,4-diyl-*N*,*N*′-di-4-methylphenyl ditosylamide 6c. Brown powder, mp 125 °C (dec). ^1H NMR ($CDCl_3$) δ: 7.59 (d, J=8.2 Hz, 4H, ArH), 7.29 (d, J=8.2 Hz, 4H, ArH), 7.12 (d, J=8.5 Hz, 4H, ArH), 7.05 (d, J=8.5 Hz, 4H, ArH), 2.44 (s, 6H, CH_3), 2.34 (s, 6H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 145.2 (2×C), 138.8 (2×C), 135.5 (2×C), 133.0 (2×C), 129.8 (4×CH), 128.0 (4×CH), 126.3 (4×CH), 75.8 (2×C), 58.2 (2×C), 21.6 (2×CH_3), 21.0 (2×CH_3).

4.2.3. *N*,*N*′-1,3-Butadiyn-1,4-diyl-*N*,*N*′-dipropyl ditosylamide 6d. White powder, mp 90–92 °C. ^1H NMR ($CDCl_3$) δ: 7.79 (d, J=8.2 Hz, 4H, ArH), 7.37 (d, J=8.2 Hz, 4H,

ArH), 3.31 (t, J=7.2 Hz, 4H, CH_2), 2.47 (s, 6H, CH_3), 1.71–1.60 (m, 4H, CH_2), 0.89 (t, J=7.4 Hz, 6H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (2×C), 134.5 (2×C), 128.8 (4×CH), 127.4 (4×CH), 75.1 (2×C), 59.3 (2×C), 53.2 (2×CH_2), 21.5 (2×CH_3), 21.1 (2×CH_2), 10.6 (2×CH_3). MS (70 eV) m/z (%): 472 (M^+, 8), 248 (85), 206 (88), 162 (100).

4.2.4. *N*,*N*′-1,3-Butadiyn-1,4-diyl-*N*,*N*′-di-2-propenyl ditosylamide 6e. White powder, mp 109–111 °C. ^{1}H NMR ($CDCl_3$) δ: 7.79 (d, J=8.3 Hz, 4H, ArH), 7.36 (d, J=8.3 Hz, 4H, ArH), 5.49–5.63 (m, 2H, C*H*=CH_2), 5.24 (t, J=8.6 Hz, 4H, CH=CH_2), 4.00 (d, J=6.3 Hz, 4H, CH_2), 2.47 (s, 6H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 145.0 (2×C), 134.5 (2×C), 130.3 (2×CH), 129.8 (4×CH), 127.6 (4×CH), 120.4 (2×CH_2), 75.2 (2×C), 59.5 (2×C), 54.3 (2×CH_2), 21.6 (2×CH_3).

4.2.5. *N*,*N*′-1,3-Butadiyn-1,4-diyl-*N*,*N*′-dibenzyl ditosylamide 6f. White needles, mp 153 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 7.68 (d, J=8.4 Hz, 4H, ArH), 7.30–7.21 (m, 14H, ArH), 4.52 (s, 4H, CH_2), 2.45 (s, 6H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (2×C), 134.6 (2×C), 134.1 (2×C), 129.8 (4×CH), 128.5 (4×CH), 128.4 (4×CH), 128.3 (2×CH), 127.6 (4×CH), 75.9 (2×C), 60.0 (2×C), 55.8 (2×CH_2), 21.7 (2×CH_3). MS (70 eV) m/z (%): 568 (M^+, 22), 413 (100), 139 (62).

4.3. Typical procedure for the preparation of arylynamides by Negishi coupling of zinc acetylides and aromatic iodides

4.3.1. *N*-Phenyl-*N*-(pyrimidin-2-yl)ethynyl tosylamide 1o. *n*-BuLi (0.56 mL, 1.6 M in hexanes) was slowly added to a solution of **2a** (0.15 g, 0.43 mmol) in dry THF (8 mL) cooled at −78 °C and the mixture was stirred for 5 min. A solution of $ZnBr_2$ (0.31 mL, 1.5 M in THF) was added via syringe and, after stirring for 20 additional minutes at rt, the reaction mixture was transferred via cannula to a solution of Pd_2dba_3 (22 mg, 0.02 mmol), PPh_3 (22 mg, 0.09 mmol) and 2-iodopyrimidine (0.11 g, 0.51 mmol) in dry THF (4 mL). After 3 h TLC showed complete consumption of the intermediate acetylide. The volatiles were removed and the resulting residue was solved in EtOAc (20 mL) and washed with brine (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using hexane/EtOAc 1:2 as eluent to yield **1o** (0.12 g, 81%) as colorless prisms, mp 107–109 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.68–8.63 (m, 2H, ArH), 7.75–7.67 (m, 2H, ArH), 7.38–7.24 (m, 7H, ArH), 7.19–7.12 (m, 1H, ArH), 2.43 (s, 3H, CH_3). ^{13}C NMR+DEPT (62.83 MHz, $CDCl_3$) δ: 157.0 (2×CH), 153.2 (C), 145.3 (C), 137.7 (C), 132.8 (C), 129.6 (2×CH), 129.2 (2×CH), 128.7 (CH), 128.2 (2× CH), 126.5 (2×CH), 119.0 (CH), 82.3 (C), 71.4 (C), 21.6 (CH_3). Elemental analysis calcd (%) for $C_{19}H_{15}N_3O_2S$ (349.41): C 65.31, H 4.33, N 12.03, S 9.18; found: C 65.62, H 4.21, N 11.90, S 9.38.

4.3.2. *N*-(4-Methoxyphenyl)ethynyl-*N*-phenyl tosylamide 1g. White powder, mp 106–108 °C. ^{1}H NMR ($CDCl_3$) δ: 7.62 (d, J=8.3 Hz, 2H, ArH), 7.35–7.26 (m, 9H, ArH), 6.83 (d, J=8.3 Hz, 2H, ArH), 3.80 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 159.6 (C), 144.8 (C), 139.1 (C), 133.4 (CH), 133.0 (C), 129.4 (2×CH), 129.0 (2×CH), 128.3 (2×CH), 128.1 (2×CH), 126.2 (2×CH), 114.5 (C), 113.9 (2×CH), 81.5 (C), 70.2 (C), 55.3 (OCH_3), 21.7 (CH_3). MS (70 eV) m/z (%): 377 (M^+, 71), 222 (100), 119 (20).

4.3.3. *N*-(1-Naphthyl)ethynyl-*N*-phenyl tosylamide 1h. Clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.87–7.83 (m, 1H, ArH), 7.80 (d, J=7.5 Hz, 1H, ArH), 7.69 (d, J=8.4 Hz, 2H, ArH), 7.60 (dd, J=7.2, 1.2 Hz, 1H, ArH), 7.56–7.52 (m, 2H, ArH), 7.43–7.38 (m, 7H, ArH), 7.28 (d, J=8.4 Hz, 2H, ArH), 2.43 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 145.0 (C), 143.3 (C), 149.0 (C), 133.2 (C), 133.1 (C), 133.0 (C), 129.8 (CH), 129.6 (2×CH), 129.2 (2×CH), 128.9 (CH), 128.4 (CH), 128.3 (2×CH), 128.2 (CH), 126.7 (CH), 126.3 (CH), 126.2 (2×CH), 126.2 (CH), 125.2 (CH), 80.0 (C), 69.0 (C), 21.7 (CH_3). MS (70 eV) m/z (%): 397 (M^+, 15), 242 (100), 139 (13).

4.3.4. *N*-(4-Methylphenyl)ethynyl-*N*-phenyl tosylamide 1i. Pale brown powder, mp 113–115 °C. ^{1}H NMR ($CDCl_3$) δ: 7.61 (d, J=8.3 Hz, 2H, ArH), 7.32–7.25 (m, 9H, ArH), 7.10 (d, J=8.0 Hz, 2H, ArH), 2.43 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 139.0 (C), 138.1 (C), 132.9 (C), 131.5 (2×CH), 129.4 (2×CH), 129.0 (3×CH), 128.2 (2×CH), 128.1 (2×CH), 126.2 (2×CH), 119.4 (C), 82.2 (C), 70.5 (C), 21.7 (CH_3), 21.4 (CH_3). MS (70 eV) m/z (%): 361 (M^+, 96), 297 (10), 206 (100).

4.3.5. *N*-Phenyl-*N*-(phenyl)ethynyl tosylamide 1j. Pale brown powder, mp 68–70 °C. ^{1}H NMR ($CDCl_3$) δ: 7.64 (d, J=7.9 Hz, 2H, ArH), 7.43–7.39 (m, 4H, ArH), 7.34–7.29 (m, 8H, ArH), 2.44 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 138.8 (C), 132.8 (C), 131.3 (2×CH), 129.4 (2×CH), 129.0 (2×CH), 128.9 (CH), 128.3 (2×CH), 128.2 (2×CH), 127.9 (CH), 126.2 (2×CH), 122.5 (C), 82.9 (C), 70.4 (C), 21.6 (CH_3). MS (70 eV) m/z (%): 347 (M^+, 22), 192 (100), 89 (18).

4.3.6. *N*-(3-Methoxyphenyl)ethynyl-*N*-phenyl tosylamide 1k. Clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.62 (d, J=8.4 Hz, 2H, ArH), 7.34–7.27 (m, 7H, ArH), 7.20 (t, J=7.9 Hz, 1H, ArH), 6.98 (d, J=7.6 Hz, 1H, ArH), 6.91 (dd, J=2.6, 1.1 Hz, 1H, ArH), 6.84 (ddd, J=8.3, 2.6, 1.0 Hz, 1H, ArH), 3.79 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 159.3 (C), 145.0 (C), 138.9 (C), 133.0 (C), 129.5 (2×CH), 129.3 (CH), 129.5 (2×CH), 128.3 (2×CH), 128.28 (CH), 126.3 (2×CH), 123.9 (CH), 123.6 (C), 116.3 (CH), 114.4 (CH), 82.8 (C), 70.5 (C), 55.3 (OCH_3), 21.7 (CH_3). MS (70 eV) m/z (%): 377 (M^+, 100), 222 (61), 119 (27).

4.3.7. *N*-(2-Methoxyphenyl)ethynyl-*N*-phenyl tosylamide 1l. Clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, J=8.3 Hz, 2H, ArH), 7.38–7.23 (m, 9H, ArH), 6.91–6.85 (m, 2H, ArH), 3.87 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 160.0 (C), 144.7 (C), 139.1 (C), 133.1 (CH), 133.0 (C), 129.3 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 128.0 (2×CH), 126.1 (2×CH), 120.4 (CH), 112.0 (C), 110.7 (CH), 86.6 (C), 67.0 (CH_3), 21.7 (CH_3). MS (70 eV) m/z (%): 377 (M^+, 24), 222 (100), 119 (27).

4.3.8. *N*-(4-Nitrophenyl)ethynyl-*N*-phenyl tosylamide 1m. Pale brown needles, mp 129–131 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.17 (d, J=8.7 Hz, 2H, ArH), 7.62 (d, J=8.2 Hz, 2H, ArH), 7.48 (d, J=8.7 Hz, 2H, ArH), 7.39–7.26 (m, 7H, ArH), 2.45 (s, 3H, CH_3). ^{13}C NMR/DEPT (62.83 MHz, $CDCl_3$) δ: 146.3 (C), 145.4 (C), 138.1 (C), 132.7 (C), 131.0 (2×CH), 130.0 (C), 129.7 (2×CH), 129.3 (2×CH), 128.7 (CH), 128.1 (2×CH), 126.3 (2×CH), 123.5 (2×CH), 89.7 (C), 69.8 (C), 21.7 (CH_3). MS (70 eV) *m*/*z* (%): 392 (M^+, 14), 237 (74), 91 (100).

4.3.9. *N*-Phenyl-*N*-(pyridin-2-yl)ethynyl tosylamide 1n. Clear oil. ^{1}H NMR (DMSO) δ: 8.55–8.51 (m, 1H, ArH), 7.79 (dt, J=7.9, 1.8 Hz, 1H, ArH), 7.67–7.60 (m, 2H, ArH), 7.52–7.42 (m, 6H, ArH), 7.36 8 (ddd, J=7.6, 4.8, 1.2 Hz, 1H, ArH), 7.30–7.25 (m, 2H, ArH), 2.42 (s, 3H, CH_3). ^{13}C NMR/DEPT (DMSO) δ: 150.0 (CH), 145.8 (C), 141.9 (C), 137.7 (CH), 136.7 (CH), 132.0 (C), 130.1 (2×CH), 129.7 (2×CH), 129.0 (C), 127.8 (2×CH), 126.5 (CH), 126.0 (2×CH), 123.0 (CH), 82.2 (C), 70.5 (C), 21.1 (CH_3). MS (70 eV) *m*/*z* (%): 348 (M^+, 14), 283 (100), 193 (10).

4.3.10. *N*-(4-Nitrophenylethynyl)-*N*-propyl tosylamide 1q. Clear oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.15 (d, J=8.7 Hz, 2H, ArH), 7.83 (d, J=8.0 Hz, 2H, ArH), 7.40 (d, J=8.7 Hz, 2H, ArH), 7.37 (d, J=8.0 Hz, 2H, ArH), 3.41 (t, J=7.2 Hz, 2H, CH_2N), 2.46 (s, 3H, CH_3), 1.78–1.70 (m, 2H, CH_2), 0.96 (t, J=7.4 Hz, 2H, CH_3). ^{13}C NMR/DEPT (62.83 MHz, $CDCl_3$) δ: 146.1 (C), 145.0 (C), 134.3 (C), 130.7 (2×CH), 130.3 (C), 129.9 (2×CH), 127.4 (2×CH), 123.5 (2×CH), 88.4 (C), 70.4 (C), 53.0 (CH_2), 21.6 (CH_3), 21.3 (CH_2), 10.7 (CH_3). MS (70 eV) *m*/*z* (%): 358 (M^+, 7), 150 (37), 91 (100).

4.4. Typical procedure for the preparation of ynamides 8

To a stirred solution of *N*-tosylaniline **13** (1 mmol) (or the corresponding carbamate) in dry DMF (20 mL) at rt was added Cs_2CO_3 (1.3 equiv). After 30 min, a solution of **5** (1.3 mmol) in dry CH_2Cl_2 (8 mL) was added dropwise. Stirring was continued until starting materials disappeared (TLC monitoring, typically 5 h). Then, ether was added (10 mL) and the combined organic layers were extracted with water and brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the residue by flash chromatography on silica gel using a gradient mixture of EtOAc/hexanes as eluent afforded ynamides **8** in good yields.

Ynamides **15** and **16** have been prepared following the same procedure.

4.4.1. *N*-Ethynyl-*N*-2-[(*Z*)-pent-3-en-1-ynyl]phenyl tosylamide 8a. Obtained in 68% yield as a clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.71 (d, J=8.3 Hz, 2H, ArH), 7.47–7.44 (m, 1H, ArH), 7.35–7.21 (m, 5H, ArH), 6.07–5.94 (m, 1H, C=CH), 5.47 (dd, J=10.7, 1.6 Hz, 1H, C=CH), 3.83 (s, 1H, C≡CH), 2.41 (s, 3H, CH_3), 1.90 (dd, J=6.9, 1.6 Hz, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 139.4 (CH), 137.8 (C), 134.2 (C), 133.4 (CH), 129.5 (2×CH), 129.1 (2×CH), 128.7 (CH), 128.3 (2×CH), 123.5 (C), 110.4 (C), 109.7 (CH), 92.2 (C), 89.0 (C), 75.8 (CH), 58.6 (C), 21.6 (CH_3), 16.2 (CH_3). MS (70 eV) *m*/*z* (%): 335 (M^+, 2), 156 (31), 123 (51), 91 (100). HRMS ($C_{20}H_{17}NO_2S$): calcd: 335.0980, found: 335.0979.

4.4.2. *N*-Ethynyl-*N*-2-[2-cyclohexen-1-ynyl]phenyl tosylamide 8b. Obtained in 80% yield as a clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.55 (d, J=8.2 Hz, 2H, ArH), 7.28–7.24 (m, 1H, ArH), 7.14–7.11 (m, 5H, ArH), 5.92 (br s, 1H, ArH), 2.70 (s, 1H, CCH), 2.27 (s, 3H, CH_3), 1.95–1.89 (m, 4H, CH_2), 1.46–1.44 (m, 4H, CH_2). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.6 (C), 137.8 (C), 135.8 (CH), 134.4 (C), 133.0 (CH), 129.4 (CH), 129.2 (2×CH), 128.9 (CH), 128.3 (CH), 128.2 (2×CH), 123.3 (C), 120.4 (C), 97.3 (C), 82.1 (C), 75.7 (CH), 58.7 (C), 28.5 (CH_2), 25.7 (CH_2), 22.1 (CH_2), 21.5 (CH_3), 21.4 (CH_2). MS (70 eV) *m*/*z* (%): 375 (M^+, 17), 180 (74), 123 (100). HRMS ($C_{23}H_{21}NO_2S$): calcd: 375.1293, found: 375.1290.

4.4.3. Methyl *N*-ethynyl-*N*-2-[2-cyclohexen-1-ynyl]-phenyl carbamate 8c. Clear oil, 10% yield. ^{1}H NMR ($CDCl_3$) δ: 7.45 (dd, J=6.5, 2.4 Hz, 1H, ArH), 7.41–7.24 (m, 3H, ArH), 6.22 (br s, 1H, ArH), 3.82 (s, 3H, CH_3), 2.82 (s, 1H, C≡CH), 2.21–2.18 (m, 4H, CH_2), 1.71–1.60 (m, 4H, CH_2). ^{13}C NMR/DEPT ($CDCl_3$) δ: 139.5 (C), 136.1 (CH), 132.4 (CH), 128.6 (CH), 128.3 (CH), 126.9 (CH), 122.4 (C), 120.4 (C), 97.3 (C), 81.9 (C), 76.3 (CH), 57.5 (C), 54.4 (CH_3), 29.0 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 21.5 (CH_2).

4.4.4. *N*-Ethynyl-*N*-2-(2-phenylethynyl)phenyl tosylamide 8d. Obtained in 77% yield as a clear oil. ^{1}H NMR ($CDCl_3$) δ: 7.68 (d, J=7.8 Hz, 2H, ArH), 7.51–7.30 (m, 9H, ArH), 7.07 (d, J=7.8 Hz, 2H, ArH), 2.94 (s, 1H, C≡CH), 2.15 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 138.0 (C), 134.2 (C), 133.1 (CH), 131.4 (2×CH), 129.7 (CH), 129.5 (2×CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 128.1 (2×CH), 127.9 (2×CH), 122.6 (C), 122.5 (C), 95.3 (C), 84.6 (C), 75.6 (CH), 59.1 (C), 21.3 (CH_3). MS (FAB) m/z: 372 (M^++1, 3), 231 (61), 154 (79), 137 (100). HRMS FAB ($C_{23}H_{17}NO_2S$): calcd: (M+1) 372.1058, found: 372.1052.

4.4.5. Methyl *N*-ethynyl-*N*-2-(2-phenylethynyl)phenyl carbamate 8e. White solid, 20% yield, mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ: 7.61 (dd, J=7.6, 1.7 Hz, 1H, ArH), 7.57–7.54 (m, 2H, ArH), 7.44–7.39 (m, 2H, ArH), 7.38–7.34 (m, 4H, ArH), 3.85 (s, 3H, CH_3), 2.88 (s, 1H, C≡CH). ^{13}C NMR/DEPT ($CDCl_3$) δ: 139.9 (C), 132.7 (CH), 131.7 (2×CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 128.3 (2×CH), 127.2 (CH), 122.7 (C), 121.9 (C), 95.3 (C), 84.6 (C), 76.3 (CH), 57.7 (C), 54.5 (CH_3).

4.4.6. *N*-Ethynyl-*N*-2-[2-(naphthalen-2-yl)ethynyl]-phenyl tosylamide 8f. Clear oil, 31% yield. ^{1}H NMR ($CDCl_3$) δ: 7.80–7.71 (m, 6H, ArH), 7.54–7.37 (m, 7H, ArH), 7.05 (d, J=8.2 Hz, 2H, ArH), 2.98 (s, 1H, C≡CH), 2.01 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 138.3 (C), 134.5 (C), 133.3 (CH), 132.9 (C), 132.7 (C), 131.5 (CH), 130.0 (CH), 129.6 (CH), 129.5 (2×CH), 129.2 (CH), 129.0 (CH), 128.3 (2×CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 126.8 (CH), 126.6 (CH), 122.6 (C), 120.1 (C), 95.8 (C), 85.2 (C), 75.9 (CH), 59.2 (C), 21.3 (CH_3). MS (FAB) *m*/*z* (%): 422 (M^++1, 13), 397 (74), 243 (100).

4.4.7. *N*-Ethynyl-*N*-2-[2-(naphthalen-1-yl)ethynyl]phenyl tosylamide 8g. Clear oil, 25% yield. ^{1}H NMR ($CDCl_3$) δ: 8.35–8.31 (m, 1H, ArH), 7.84 (d, J=7.9 Hz, 2H, ArH), 7.69–7.39 (m, 10H, ArH), 6.87 (d, J=7.9 Hz, 2H, ArH), 3.02 (s, 1H, C≡CH), 1.83 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 138.1 (C), 134.3 (C), 133.6 (CH), 132.94 (C), 132.89 (C), 130.7 (CH), 130.1 (CH), 129.4 (2×CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.2 (2×CH), 128.0 (CH), 126.7 (CH),126.6 (CH), 126.4 (CH), 125.0 (CH), 122.9 (C), 120.5 (C), 93.4 (C), 89,4 (C), 76.1 (CH), 59.1 (C), 21.1 (CH_3). MS (FAB) *m/z* (%): 422 (M^++1, 5), 301 (13), 282 (100). HRMS FAB ($C_{27}H_{19}NO_2S$): calcd (M+1): 422.1214, found: 422.1212.

4.4.8. *N*-Ethynyl-*N*-2-[2-(phenanthren-10-yl)ethynyl]-phenyl tosylamide 8h. Clear oil, 69% yield. ^{1}H NMR ($CDCl_3$) δ: 8.71–8.67 (m, 3H, ArH), 8.44 (d, J=7.5 Hz, 1H, ArH), 7.87–7.85 (m, 2H, ArH), 7.72–7.63 (m, 6H, ArH), 7.47–7.43 (m, 3H, ArH), 6.86 (d, J=8.0 Hz, 2H, ArH), 3.05 (s, 1H, C≡CH), 1.74 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 138.2 (C), 134.3 (C), 133.6 (CH), 132.2 (CH), 130.9 (C), 130.6 (C), 130.2 (C), 130.0 (CH), 129.7 (C), 129.34 (2×CH), 129.28 (CH), 129.2 (CH), 128.5 (CH), 128.2 (2×CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 126.9 (2×CH), 122.8 (C), 122.5 (CH), 122.4 (CH), 119.2 (C), 93.6 (C), 89.1 (C), 76.2 (CH), 59.2 (C), 20.9 (CH_3). FAB *m/z* (%): 472 (M^++1, 13), 293 (100), 137 (67). HRMS FAB ($C_{31}H_{21}NO_2S$): calcd (M+1): 472.1371, found: 472.1369.

4.4.9. *N*-(Trimethylsilyl)ethynyl-*N*-2-(2-phenylethynyl)-phenyl tosylamide 8i. To a stirred solution of *N*-tosylaniline **13** (1 mmol) in dry toluene (10 mL) at 0 °C was added KHMDS dropwise (1.2 equiv). After 15 min a solution of **5** (1.4 mmol) in dry CH_2Cl_2 (4 mL) was added and stirring was continued overnight. The reaction mixture was concentrated, dissolved in ether (10 mL), extracted with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the residue by flash chromatography on silica gel using a mixture of 10% EtOAc in hexanes as eluent afforded ynamide **8i** as a white powder in 62% yield, mp 124–126 °C. ^{1}H NMR ($CDCl_3$) δ: 7.85 (d, J=8.2 Hz, 2H, ArH), 7.66–7.61 (m, 9H, ArH), 7.24 (d, J=8.2 Hz, 2H, ArH), 2.32 (s, 3H, CH_3), 0.24 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.8 (C), 138.5 (C), 134.4 (C), 133.2 (CH), 131.6 (2×CH), 129.8 (CH), 129.4 (2×CH), 128.9 (2×CH), 128.8 (CH), 128.5 (2×CH), 127.9 (2×CH), 122.7 (C), 122.5 (C), 95.4 (C), 94.3 (C), 85.0 (C), 73.1 (C), 21.4 (CH_3), 0.0 ($Si(CH_3)_3$). MS (70 eV) *m/z* (%): 443 (M^+, 6), 304 (32), 288 (100); HRMS ($C_{26}H_{25}NO_2SSi$): calcd: 443.1375, found: 443.1368.

4.4.10. *N*-(Trimethylsilyl)ethynyl-*N*-2-[2-cyclohexen-1-ynyl]phenyl tosylamide 8j. Clear oil, 45% yield. ^{1}H NMR ($CDCl_3$) δ: 7.71 (d, J=8.4 Hz, 2H, ArH), 7.42–7.40 (m, 1H, ArH), 7.31–727 (m, 5H, ArH), 6.1 (s, 1H, C=CH), 2.43 (s, 3H, CH_3), 2.09–2.08 (br s, 2H, CH_2), 2.02–2.01 (br s, 2H, CH_2), 1.62–1.58 (m, 4H, CH_2), 0.13 (s, 3H, $Si(CH_3)_3$). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.5 (C), 138.2 (C), 135.9 (CH), 134.6 (C), 133.2 (CH), 129.3 (3×CH), 128.9 (CH), 128.7 (2×CH), 128.3 (CH), 123.4 (C), 120.5 (C), 97.4 (C), 94.4 (C), 82.4 (C), 72.8 (C), 28.7 (CH_2), 25.7 (CH_2), 22.2 (CH_2), 21.7 (CH_3), 21.5 (CH_2), 0.0 ($Si(CH_3)_3$).

4.4.11. *N*-Ethynyl-*N*-3-(2-phenylethynyl)pyridyl tosylamide 15. Clear oil, 12% yield. ^{1}H NMR ($CDCl_3$) δ: 8.75 (s, 1H, ArH), 8.59 (d, J=5.3 Hz, 1H, ArH), 7.69 (d, J=8.1 Hz, 2H, ArH), 7.42–7.27 (m, 6H, ArH), 7.13 (d, J=8.1 Hz, 2H, ArH), 2.99 (s, 1H, C≡CH), 2.20 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 154.3 (CH), 149.4 (CH), 145.5 (C), 145.2 (C), 133.9 (C), 131.5 (2×CH), 129.8 (2×CH), 129.1 (CH), 128.2 (2×CH), 128.1 (2×CH), 123.5 (CH), 122.1 (C), 118.7 (C), 98.9 (C), 81.7 (C), 74.4 (CH), 60.6 (C), 21.5 (CH_3). MS (70 eV) *m/z* (%): 372 (M^+, 2), 308 (59), 217 (100). HRMS ($C_{22}H_{16}N_2O_2S$): calcd: 372.0925, found: 372.0932.

4.4.12. *N*-Ethynyl-*N*-2-[2-(pyrid-2-yl)ethynyl)]phenyl tosylamide 16. Clear oil, 50% yield. ^{1}H NMR ($CDCl_3$) δ: 8.58 (d, J=4.4 Hz, 1H, ArH); 7.70 (d, J=8.2 Hz, 2H, ArH), 7.64–7.60 (m, 2H, ArH), 7.40–7.39 (m, 3H, ArH), 7.27–7.22 (m, 1H, ArH), 7.12 (d, J=8.1 Hz, 2H, ArH), 2.94 (s, 1H, C≡CH), 2.22 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 149.7 (CH), 145.0 (C), 142.9 (C), 138.6 (C), 135.8 (CH), 134.1 (C), 133.8 (CH), 129.7 (CH), 129.6 (2×CH+CH), 129.2 (CH), 128.2 (2×CH), 127.5 (CH), 122.9 (CH), 94.1 (C), 84.4 (C), 75.8 (CH), 59.1 (C), 21.5 (CH_3). MS (70 eV) *m/z* (%): 372 (M^+, 100), 217 (36), 190 (14). HRMS ($C_{22}H_{16}N_2O_2S$): calcd: 372.0932, found: 372.0943.

4.5. Typical procedure for the preparation of aryl ynamides 9

A solution of 1 mmol of ynamide **8k**, 1.1 mmol of iodoarene and 0.05 mmol of $Pd(PPh_3)_4$ in 7.5 mL of Et_3N and 3.7 mL of toluene was stirred at rt for 10 min. Then, 0.02 mmol of CuI was added and the reaction mixture was heated at 60 °C until starting material disappeared (TLC monitoring, 4–8 h). The mixture was diluted with EtOAc, filtered through silica, and concentrated to dryness. Purification of the residue by flash chromatography on silica gel using a gradient mixture of EtOAc/hexanes as eluent afforded TIPS-protected arylynamides **9a–f′** in good yields.

Excess of tetrabutylammonium fluoride (1.0 M solution in THF) was added to a solution of TIPS-protected arylynamides **9a–f′** (0.1 mmol) in THF (10 mL), and the resulting mixture was stirred at rt for 10 min. After solvent removal, the residue was dissolved in EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel using a gradient mixture of EtOAc/hexanes as eluent giving arylynamides **9a–f** in good yields.

4.5.1. *N*-2-Ethynylphenyl-*N*-2-phenylethynyl tosylamide 9a. Clear oil, 60% yield (overall). ^{1}H NMR ($CDCl_3$) δ: 7.77 (d, J=8.3 Hz, 2H, ArH), 7.53 (dd, J=6.3, 3.3 Hz, 1H, ArH), 7.41–7.26 (m, 10H, ArH), 3.09 (s, 1H, C≡CH), 2.44 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.9 (C), 139.7 (C), 134.1 (CH+CH), 133.7 (C), 131.3 (2×CH), 129.5 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 128.1 (2×CH), 127.7 (CH), 122.6 (C), 122.0 (C), 83.1 (C), 82.5 (C), 78.7 (CH), 70.1 (C), 21.5 (CH_3). FAB *m/z* (%): 372 (M^++1) (1), 154 (89), 137 (100). HRMS ($C_{23}H_{18}NO_2S$): calcd: 372.1058, found: 372.1064.

4.5.2. *N*-2-Ethynylphenyl-*N*-2-(4-methoxyphenyl)-ethynyl tosylamide 9b. Clear oil, 44% yield (overall). ^{1}H NMR ($CDCl_3$) δ: 7.75 (d, J=8.4 Hz, 2H, ArH), 7.52 (dd, J=6.9, 2.4 Hz, 1H, ArH), 7.39–7.27 (m, 7H, ArH), 6.81 (d, J=8.9 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.06 (s, 1H, C≡CH), 2.46 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 159.5 (C), 144.8 (C), 140.1 (C), 134.2 (CH), 134.1 (C), 133.5 (2×CH), 129.5 (CH), 129.5 (2×CH), 129.1 (CH), 128.8 (CH), 128.6 (2×CH), 122.2 (C), 114.7 (C), 113,8 (2×CH), 82.9 (C), 81.2 (C), 79.0 (CH), 69.9 (C), 55.2 (CH_3), 27.7 (CH_3).

4.5.3. *N*-2-Ethynylphenyl-*N*-2-(4-nitrophenyl)ethynyl tosylamide 9c. Clear oil, 65% yield (overall). ^{1}H NMR ($CDCl_3$) δ: 8.14 (d, J=8.9 Hz, 2H, ArH), 7.75 (d, J=8.3 Hz, 2H, ArH), 7.55 (dd, J=6.6, 2.7 Hz, 1H, ArH), 7.48–7.34 (m, 7H, ArH), 3.05 (s, 1H, C≡CH), 2.47 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 146.2 (C), 145.4 (C), 138.9 (C), 134.2 (CH), 130.9 (2×CH), 130.2 (C), 129.7 (2×CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 128.4 (2×CH), 123.4 (2×CH), 121.9 (C), 88.3 (C), 83.3 (CH), 78.4 (C), 70.0 (C), 60.3 (C), 21.6 (CH_3).

4.5.4. *N*-2-(2-Triisopropylsilylethynyl)phenyl-*N*-2-(naphthalen-1-yl)ethynyl tosylamide 9d′. Clear oil, 62% yield. ^{1}H NMR ($CDCl_3$) δ: 8.26 (d, J=8.0 Hz, 1H, ArH), 7.86–7.72 (m, 4H, ArH), 7.63 (t, J=7.1 Hz, 1H, ArH), 7.52 (d, J=6.0 Hz, 2H, ArH), 7.44–7.17 (m, 6H, ArH), 6.98 (d, J=8.0 Hz, 1H, ArH), 2.45 (s, 3H, CH_3), 1.09 (br s, 21H, $Si(CH(CH_3)_2)_3$). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.8 (C), 144.7 (C), 139.5 (C), 136.6 (C), 134.7 (C), 134.6 (CH), 133.1 (C), 133.06 (C), 129.7 (2×CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.4 (2×CH), 128.0 (CH), 127.8 (CH), 126.4 (CH), 126.2 (CH), 125.0 (CH), 102.0 (C), 98.1 (C), 87.7 (C), 68.5 (C), 21.6 (CH_3), 18.6 (CH_3), 11.3 (CH).

4.5.5. *N*-2-(2-Triisopropylsilylethynyl)phenyl-*N*-2-(thien-2-yl)ethynyl tosylamide 9e′. Clear oil, 80% yield. ^{1}H NMR ($CDCl_3$) δ: 7.77 (d, J=8.3 Hz, 2H, ArH), 7.58 (dd, J=7.0, 2,0 Hz, 1H, ArH), 7.34–7.22 (m, 5H, ArH), 7.13 (dd, J=3.6, 1.1 Hz, 1H, ArH), 7.04 (dd, J=7.5, 1.7 Hz, 1H, ArH), 6.93 (dd, J=5.2, 3.6 Hz, 1H, ArH), 2.46 (s, 3H, CH_3), 1.16 (br s, 21H, $Si(CH(CH_3)_2)_3$). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.7 (C), 139.4 (C), 134.6 (C), 134.4 (CH), 132.8 (CH), 129.6 (2×CH), 129.0 (CH), 128.9 (CH), 128.3 (2×CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 124.2 (C), 123.0 (C), 102.0 (C), 97.8 (C), 86.3 (C), 63.2 (C), 21.7 (CH_3), 18.7 (CH_3), 11.3 (CH).

4.5.6. *N*-2-Ethynylphenyl-*N*-2-(pyridin-3-yl)ethynyl tosylamide 9f. Clear oil, 55% yield (overall). ^{1}H NMR ($CDCl_3$) δ: 8.59 (s, 1H, ArH), 8.49 (d, J=4.8 Hz, 1H, ArH), 7.76 (d, J=8.4 Hz, 2H, ArH), 7.66 (dt, J=7.9, 1.7 Hz, 1H, ArH), 7.55 (dd, J=6.9, 2.3 Hz, 1H, ArH), 7.44–7.32 (m, 5H, ArH), 7.22 (dd, J=7.8, 4.8 Hz, 1H, ArH), 3.05 (s, 1H, C≡CH), 2.48 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 152.0 (CH), 148.1 (CH), 145.2 (C), 139.4 (C), 138.2 (CH), 134.3 (2×CH +C), 133.9 (C), 129.6 (2×CH+CH), 129.2 (CH), 129.1 (CH), 128.5 (CH), 122.9 (CH), 122.0 (C), 85.5 (C), 83.2 (CH), 78.6 (C), 67.3 (C), 21.7 (CH_3). FAB *m/z* (%): 373 (M^++1, 100), 218 (90). HRMS ESI-TOF: ($C_{22}H_{17}N_2O_2S$): calcd: 373.1005, found: 373.1013.

4.5.7. *N*-2-(2-Trimethylsilylethynyl)phenyl-*N*-2-phenylethynyl tosylamide 9g. Obtained as a white powder in 80% yield by silylation of **9a**. ^{1}H NMR ($CDCl_3$) δ: 7.75 (d, J=8.3 Hz, 2H, ArH), 7.52–7.50 (m, 1H, ArH), 7.36–7.24 (m, 10H, ArH), 2.45 (s, 3H, CH_3), 0.08 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR/DEPT ($CDCl_3$) δ: 144.7 (C), 139.2 (C), 134.5 (C), 134.1 (CH), 131.0 (2×CH), 129.6 (2×CH), 129.1 (2×CH), 128.7 (CH), 128.5 (2×CH), 128.1 (2×CH), 127.4 (CH), 123.0 (C), 122.8 (C), 101.3 (C), 98.8 (C), 82.5 (C), 70.6 (C), 21.7 (CH_3), −0.4 ($Si(CH_3)_3$). MS (ESI-TOF) *m/z* (%): 466 (M^++Na, 16). HRMS ($C_{26}H_{25}NO_2SSiNa$): calcd: 466.1267, found: 466.1282.

4.5.8. *N*-2-(2-Phenylethynyl)phenyl-*N*-2-(4-nitrophenyl)-ethynyl tosylamide 9h. Clear oil, 46% yield. ^{1}H NMR ($CDCl_3$) δ: 8.10 (d, J=8.5 Hz, 2H, ArH), 7.73 (d, J=8.5 Hz, 2H, ArH), 7.57–7.52 (m, 2H, ArH), 7.46–7.41 (m, 4H, ArH), 7.28–7.10 (m, 7H, ArH), 2.18 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 146.1 (C), 145.3 (C), 138.0 (C), 134.0 (C), 133.4 (CH), 131.3 (2×CH), 130.8 (2×CH), 130.3 (C), 129.9 (CH), 129.7 (2×CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.2 (2×CH), 127.9 (2×CH), 123.5 (2×CH), 122.4 (C), 122.3 (C), 95.6 (C), 88.4 (C), 84.4 (C), 70.6 (C), 21.4 (CH_3). MS (70 eV) *m/z* (%): 492 (M^+, 29), 337 (100), 281 (59). HRMS ($C_{29}H_{20}N_2O_4S$): calcd: 492.1143, found: 492.1127.

Obtained by Negishi coupling of **2** (EWG=Ts, R=2-(2-phenylethynyl)phenyl) with *p*-nitroiodobenzene.

4.5.9. *N*-2-[2-(Pyrid-2-yl)ethynyl)]phenyl tosylacetamide 17. Clear oil, 50% yield. ^{1}H NMR ($CDCl_3$) δ: 8.56 (d, J=4.5 Hz, 1H, ArH), 8.01 (d, J=8.2 Hz, 2H, ArH), 7.75–7.71 (m, 1H, ArH), 7.57–7.47 (m, 4H, ArH), 7.25–7.20 (m, 1H, ArH), 7.14 (d, J=8.2 Hz, 2H, ArH), 6.97 (d, J=7.8 Hz, 1H, ArH), 2.21 (s, 3H, CH_3), 1.98 (s, 3H, CH_3). MS (70 eV) *m/z* (%): 390 (M^+, 1), 348 (70), 283 (100).

4.5.10. *N*-2-(2-Phenylethynyl)phenyl tosylcyanamide 18. White solid, 51% yield. ^{1}H NMR ($CDCl_3$) δ: 7.97 (d, J=8.1 Hz, 2H, ArH), 7.53–7.34 (m, 4H, ArH), 7.21–7.05 (m, 5H, ArH), 6.70 (d, J=8.1 Hz, 2H, ArH), 2.09 (s, 3H, CH_3). ^{13}C NMR/DEPT ($CDCl_3$) δ: 162.0 (C), 145.6 (C), 136.9 (C), 135.1 (C), 132.8 (CH), 131.2 (CH), 131.1 (2×CH), 130.7 (2×CH), 129.7 (CH), 129.3 (CH), 128.9 (2×CH), 128.6 (CH), 127.9 (2×CH), 122.8 (C), 121.5 (C), 95.1 (C), 85.2 (C), 21.4 (CH_3).

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59. Previously misidentified as the other regioisomer in Ref. 26 Table 1, entry 23.

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Radical cascade cyclizations and platinum(II)-catalyzed cycloisomerizations of ynamides

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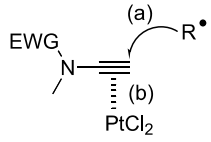
Abstract—Ynamides are tested as new partners in radical and organometallic transformations. A radical cascade involving a 5-*exo-dig* cyclization followed by a 6-*endo-trig* radical trapping transforms ynamides into hetero-polycyclic compounds such as isoindoles, isoindolinones and pyrido-isoindolones. Various ene–tosylynamides react with platinum(II) chloride and lead to bicyclic nitrogenated heterocycles. This unprecedented and easily operated process can be coupled with a hydrolysis of the intermediate cyclic tosylenamides in a one-pot transformation, which provides cyclobutanones.

1. Introduction

As a coincidence, the pioneer works on ynamines were reviewed 30 years ago in our university by late Professor Jacqueline Ficini.[1] She, and other groups successfully prepared and studied a moiety bearing a very high organic synthetic potential, the triple bond, attached to a nitrogen atom whose both electron donating ability and natural abundance are seminal for chemical processes and target oriented strategies.[2–4] However, the reactivity of ynamines has not been developed until recently due to their high sensitivity towards hydrolysis and to their difficult preparation.[5] Interestingly, the substitution of the nitrogen atom with an electron withdrawing group helps stabilizing the yne–nitrogen association under the form of an ynamide, which reaches a compromise between reactivity and stability. The most frequently reported ynamides are sulfonamides, cyclic carbamates and lactams. Since the first preparation of ynamides by Viehe in 1972, numerous methods have been described in the literature.[6–21] Very recently copper-mediated *N*-alkynylations as synthetic preparations of ynamides were reported by Danheiser and Hsung to obtain carbamates, sulfonamides and lactams mainly.[22,23] The growing development of several efficient methods for the synthesis of ynamides is due to their original and very diverse reactivity and to the synthetic importance of these versatile building blocks. Indeed ynamides can undergo metal-catalyzed [2+2+2][24] and [2+2+1][14,15,25] cycloadditions, [2+2][12,26] and [4+2][12,27] cycloadditions, ring-closing metatheses,[28] addition reactions,[29] palladium-catalyzed cross-couplings,[30] electrocyclic processes[31] and carbometallation reactions.[32] Being deeply involved both in radical and organometallic mechanistical studies as well as synthetic processes, we examined ynamides as new partners in the two types of approaches.

First, our interest in radical cyclization cascades[33] and in the discovery of new radical reaction partners[34] together with the emergence of radical chemistry in the field of heterocyclic synthesis[35] prompted us into the study of ynamides radical transformations (pathway (a) in scheme 1).[36] Second, we investigated the platinum(II) dichloride catalyzed cycloisomerization of ene–tosylynamides (pathway (b) in Scheme 1), targeting the promotion of charge controlled processes on the nitrogen substituted triple bond by $PtCl_2$.



Scheme 1.

Keywords: Cycloisomerization; Heterocycles; Platinum; Radical Cascades; Radical cyclization; (Tosyl)-ynamides.
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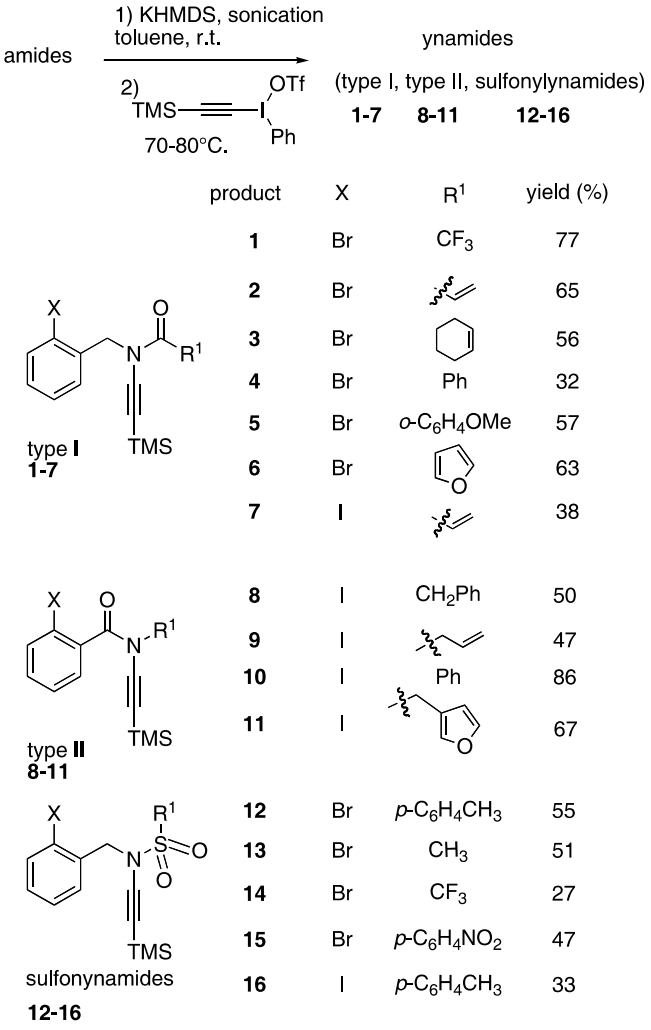


product	X	R^1	yield (%)
1	Br	CF_3	77
2	Br		65
3	Br		56
4	Br	Ph	32
5	Br	*o*-C_6H_4OMe	57
6	Br		63
7	I		38
8	I	CH_2Ph	50
9	I		47
10	I	Ph	86
11	I		67
12	Br	*p*-$C_6H_4CH_3$	55
13	Br	CH_3	51
14	Br	CF_3	27
15	Br	*p*-$C_6H_4NO_2$	47
16	I	*p*-$C_6H_4CH_3$	33

Scheme 2.

2. Radical cyclization cascades of ynamides

2.1. Synthesis of precursors

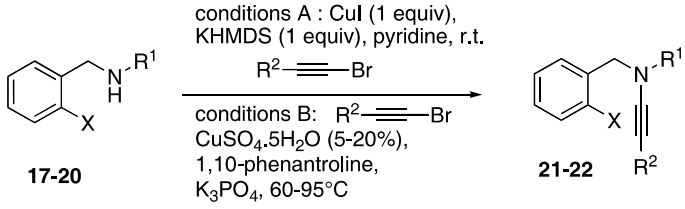
We report herein the first use of ynamides in radical cyclizations leading to polycyclic nitrogen heterocycles. Initially, the silylated carboxamides precursors **1**–**11** of type **I** and **II** were easily prepared according to Witulski's[14] method, which involves the Michael addition of an amide to an alkynyliodonium salt, whilst sulfonylynamides **12**–**16** were obtained in less satisfying yields (Scheme 2).

We have tested other preparation methods, especially following Hsung's and Danheiser's procedures.[22,23] For instance, coupling of 2-bromobenzyltosylamide **18** with phenylethynylbromide succeeds in a yield of 75 and 80%, respectively, in the presence of copper(I) iodide in pyridine and with copper (II) sulfate and 1,10-phenantroline. This result is comparable with the transformation of benzyltosylamide **17** reported in the literature.[22,23,37] When we submitted conjugated carboxamides such as **19** or **20** to the same set of experimental conditions, we could only recover the starting material. (Scheme 3) This lack of reactivity may be due to the deactivation of the copper catalyst by the amide as reported by Riddell[26] and Buchwald.[38]

Therefore, we rather prepared the carboxamides precursors **1**–**11** by reacting them as depicted in scheme 2, whilst further desilylation[14] and subsequent alkylation[17a] of compounds **2**, **3**, **7** and **9** gave an easy access to various substituted ynamides **23**–**28** (Scheme 4).

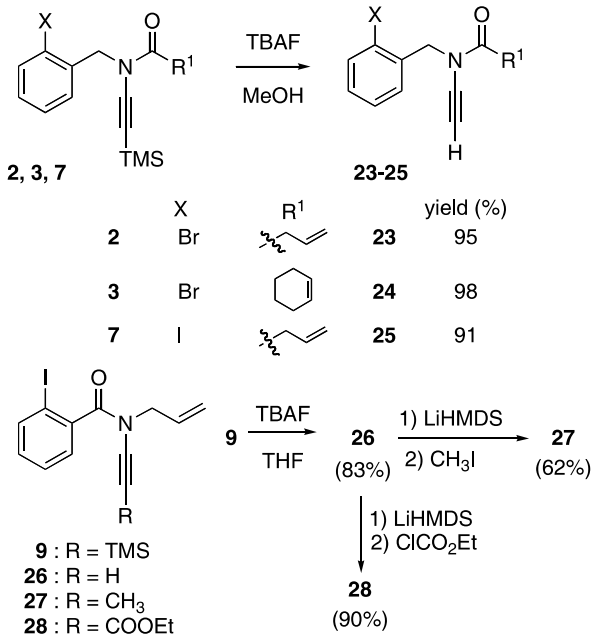
2.2. Radical cyclization

We first examined the 5-*exo-dig* cyclization with differently protected ynamides (sulfonylynamides **12**–**17**, type **I**



substrate	R^1	X	R^2	conditions	yield (%)
17	Ts	H	Ph	A	78
17	Ts	H	Ph	B	96
18	Ts	Br	Ph	A	75
18	Ts	Br	Ph	B	80
19		H	Ph	A or B	0
20		Br	Ph or TMS	A or B	0

Scheme 3.

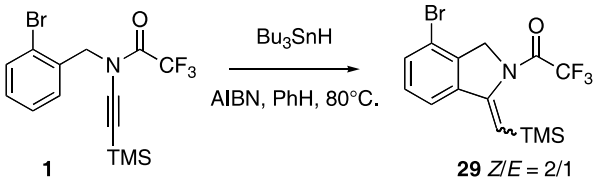


Scheme 4.

compounds **1**–**7** and type **II** compounds **7**–**11**) obtained either from the corresponding amides (Scheme 1) or by desilylation of the triple bond and further substitution if necessary (Scheme 4).

Since radical cyclization of various sulfonamides has been well studied in the literature,[35] in our first attempts we submitted sulfonylynamides **12**–**17** to tributyltin hydride/AIBN initiation conditions in benzene. Cyclization failed and the results could not be improved upon changing the halogen atom or the electronic properties of the sulfonyl group. These precursors reacted slowly and sluggishly to give only trace amounts of the 5-*exo-dig* products in the case of the methanesulfonyl- and the trifluoromethanesulfonyl-protected ynamides. The outbreak of a deep purple colour in the reaction mixture leads us in speculating about the formation of a persistent radical, which would not allow the cascade process to evolve and proceed.

Next, we turned our attention to the trifluoroacetamide **1**, which cyclized in refluxing benzene in the presence of tin hydride and AIBN in 78% yield to give the isoindole **29** as a mixture of two diastereomers on the double bond in a 2/1 ratio (Scheme 5). NOE experiments have shown that the *Z* diastereomer was the main compound, suggesting that the reduction of the vinylic radical was governed by its stability and therefore by allylic strain.



Scheme 5.

With this preliminary result in hands, we next assumed that the intermediate vinylic radical could be trapped by another insaturation. Gratifyingly, we could assist to the radical cyclization cascade with good yields when reacting type **I** precursors, which contain an activated double bond (Table 1).

In the case of bromobenzyl precursors (entries 1–3 and 6–9), the cyclization products could be observed only with silylated ynamides (entries 1, 2 and 6–8). Slow addition of tin hydride was necessary to obtain the cascade products in good yields (entries 2 and 7).

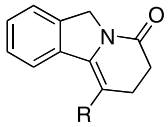
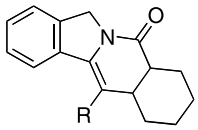
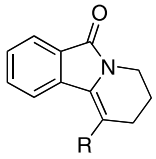
For iodobenzyl compounds, the cyclization products were obtained in good yields without slow addition and in the case of silylated and monosubstituted triple bonds (Table 1, entries 4 and 5). This suggests that the addition of the tributylstannyl radical[39] to the triple bond is competitive with the bromine atom abstraction and is the major pathway when the ynamide is monosubstituted. The use of tristrimethylsilylsilane[40] as the reductor in order to try to avoid this side reaction did not allow us to isolate any cyclization product in the case of the cyclohexenyl precursor (entries 8 and 9). The observed products were issued from a radical cascade, which involves a 5-*exo-dig* cyclization followed by radical trapping in a 6-*endo-trig* mode for an activated terminal or endocyclic double bond. This cascade shows an excellent regioselectivity in the case of type **I** precursors, which contain activated acceptors.

The same 5-*exo-dig*/6-*endo-trig* regioselectivity was observed when reacting type **II** compounds with non-activated acceptors (Table 1). The substitution on the triple bond was studied on type **II** compounds. In order to avoid the addition of tin on the triple bond, we have also chosen an iodo-precursor. We obtained good yields for mono- and di-substituted ynamides.(Table 1) The yield decreased when the triple bond was activated with an ester group. The addition of tin became then possible and the yield could not be improved with slow addition of the hydride.

In the case of ynamides **4**, **5**, **8** and **10**, an aromatic acceptor is either conjugated with the amide or linked to it through a methylene group (Table 2). We observed that type **I** precursors **4** and **5** react differently than type **II** compounds **8** and **10**. When compound **4** reacts with tributyltinhydride, azabisisobutyronitrile in benzene at 80 °C, the aromatized tetracyclic product **37** is isolated after 2 h in 67% yield (entry 1). The formation of compound **37** under reducing conditions and the absence of traces of the reduced vinylsilane indicate that the cascade process is faster than the reduction of the intermediate vinyl radical. This could also be observed for the methoxysubstituted ynamide **5**, which cyclizes slightly less rapidly for 16 h and gives compound **38** in a lower yield of 54% (entry 2). No product issued from an *ipso* cyclization followed by a rearrangement was isolated.[35d,41]

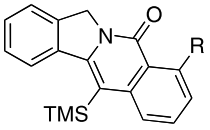
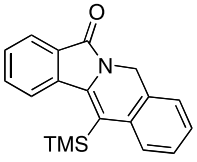
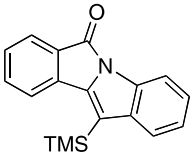
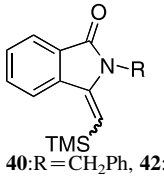
Reaction (under the same classical radical conditions mentionned above) of type **II** ynamide **8** gives a 1/1 mixture of the two diastereomeric forms of compound **40** in a yield of 57% whilst traces of the tetracyclic compound **39** could be identified in the crude material (entry 3). Compound **10** was transformed into a mixture of the tetracyclic isoindolinone **41** (23%) and the two

Table 1

	Entry	Ynamide	R	Yield (%)[a]		Product
Type **I**	1	**2**	TMS	42	**30**	
	2	**2**	TMS	70[b]	**30**	
	3	**23**	H	0[b]		
	4	**7**	TMS	83	**30**	
	5	**25**	H	54	**31**	
	6	**3**	TMS	45	**32**	
	7	**3**	TMS	75[b]	**32**	
	8	**3**	TMS	54[c]	**32**	
	9	**24**	H	0,[b] 0[c]		
Type **II**	10	**9**	TMS	90	**33**	
	11	**26**	H	78	**34**	
	12	**27**	CH_3	84	**35**	
	13	**28**	CO_2Et	45	**36**	

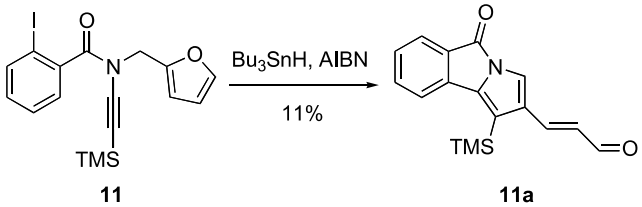
[a] A benzene solution (15 mL) of ynamide (0.25 mmol), tin hydride (2 equiv) and AIBN (0.5 equiv) was refluxed until the starting material disappeared.
[b] Slow addition of the hydride was performed.
[c] Tristrimethylsilylsilane was used as reductor.

Table 2

	Entry	Ynamide	Yield (%)[a]	Product
Type **I**	1	**4**	67	**37**
	2	**5**	54	**38**
	3	**8**	57	**40** (*Z*/*E*:1/1)
Type **II**	4	**10**	94	**41** (23%)+**42** (71%) (*Z*/*E*: 2:1)
	5	**8**	46[a]	**39**
	6	**10**	62[a]	**41**
	 **37**:R=H, **38**:R=OMe	 **39**	 **41**	 **40**:R=CH_2Ph, **42**:R=Ph

[a] Photolysis of hexabutylditin in toluene is used in the reaction.

diastereomers (*Z*/*E*: 2:1) of compound **42** (71%) (entry 4). Slow addition of tributyltin hydride (0.25 mmol h^{-1}) neither increased the formation of compound **39** nor significantly modified the ratio of compounds **41** and **42**. When we carried out the reaction under atom transfer conditions (photochemical homolytic cleavage of hexabutylditin in toluene) in order to try to avoid the intermediate reduction products, the type **II** precursors gave only the tetracyclic products **39** and **41**, respectively, in a yield of 46 (40 h) and 62% (7 h) (entries 5 and 6). The difference in behaviour between type **I** and type **II** ynamides bearing an aromatic moiety, which plays the role of trapping the intermediate vinyl radical speaks for the importance of the place of the amide function. When the ynamide bears an heteroaromatic ring as the acceptor moiety such as a furanyl substituent the reaction developed differently in the case of type **I** and **II** compounds. We failed in initiating the radical transformation of compound **6** whilst compound **11** was transformed into a compound that we could identify as the highly conjugated aldehyde **11a** probably via an *ipso*[42] cyclisation and an oxidative fragmentation process.(Scheme 6)



11 **11a**

Scheme 6.

We have demonstrated that ynamides are excellent partners for radical chemistry. We have described a new radical cyclization cascade process, which leads to isoindole, isoindolinones and pyrido-isoindolones in good yields. These results bring new perspectives for the development of ynamides and the application of their reactivity in the field of heterocyclic chemistry.

3. Platinum(II) chloride catalyzed cycloisomerization of ynamides

The transition metal catalyzed cycloisomerization of enyne systems is a powerful synthetic tool that has witnessed intense development.[43] Nevertheless, there is still room for the implementation of new partners in this process. Among all potential candidates, ene–tosylynamides are highly appealing substrates. Because of the presence of the nitrogen atom directly attached to the triple bond, one can anticipate charge controlled processes.[5,24a,31b] This led us to the use of platinum(II) dichloride as catalyst, since this versatile reagent is known to promote charge build-up on enyne systems.[44,45] In addition, the resulting products should incorporate valuable nitrogen heterocycles. This has also been demonstrated by Hsung with the development of a $PtCl_2$-catalyzed keteniminium Pictet–Spengler cyclization.[46] Herein, we describe our results of a versatile organometallic process, which transforms different ene–tosylynamides, in the presence of $PtCl_2$, into bicyclic nitrogenated heterocycles.

3.1. Synthesis of precursors

The precursors we have used in this part were prepared following the Brückner's alternative transformation of formamides.[7] After a Mitsonobu transformation, the alkylated tosylamines are formylated with Katritsky's reagent: *N*-formylbenzotriazole.[47] Dichloroolefination and a butyllithium-triggered Fritsch–Buttenberg–Wiechell rearrangement sets the alkyne function. This procedure allowed us to obtain various ene–tosylynamides, which are utilized in this work as precursors of original $PtCl_2$-catalyzed cycloisomerizations (Scheme 7).

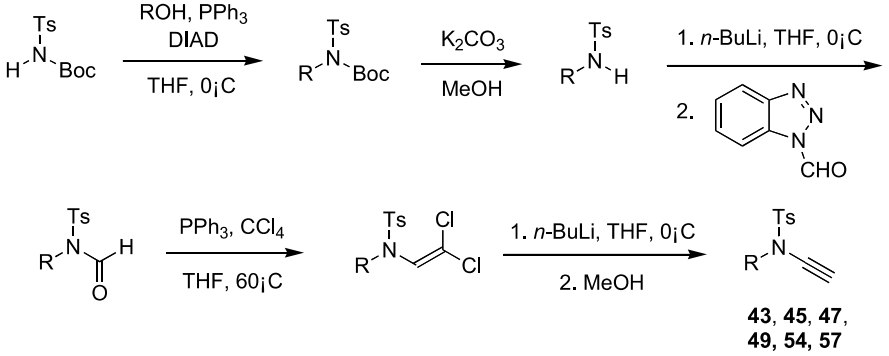
3.2. Cycloisomerizations

Our first attempt consisted in exposing ene–ynamide **43** to $PtCl_2$ (5 mol%) in toluene at 80 °C and led to the metathesis product **44** in 98% yield, whose structure was secured by comparing to Mori's data. (Scheme 8). Mori has indeed investigated the ring-closing metathesis transformation of **43** and found out that this reaction was accelerated in the presence of the second generation Grubb's catalyst.[28b] Moreover, she performed efficient ring-closing metathesis with several precursors bearing a different carbon tether between the amide function and the carbon–carbon double bond like precursors **45** and **47**. We show here a completely distinct and original reactivity of these substrates in the presence of platinum dichloride. Thus, in the case of ene–tosylynamide **45**, cyclization occurred and yielded the bicyclic[4.2.0] compound **46**.[48] This fragile structure, partially degrading during the purification process, was obtained in 34% yield, which we had some difficulty to reproduce since these reactions proved to be sensitive to moisture. The bicyclic derivative **48** was similarly obtained by reacting the β-dimethyl-substituted ene–ynamide **47** with 5 mol equiv of $PtCl_2$ in 71% yield. The structural assignment for **46** and **48** was based on the following data: ^1H NMR spectra show no stereogenic centre and ^{13}C NMR spectra display no CH signal, indicating that the double bond is shared by the two cycles. Quaternary carbon signals around 122 and 135 ppm confirm the structure of the bicyclic product. These platinum(II)-catalyzed cyclizations could not easily be monitored by TLC because of close R_f for the product and the starting material which, in addition, reveal as faint spots. Therefore, we followed the consumption of the ene–ynamide by IR spectroscopy and checked the vanishing of the triple bond band.

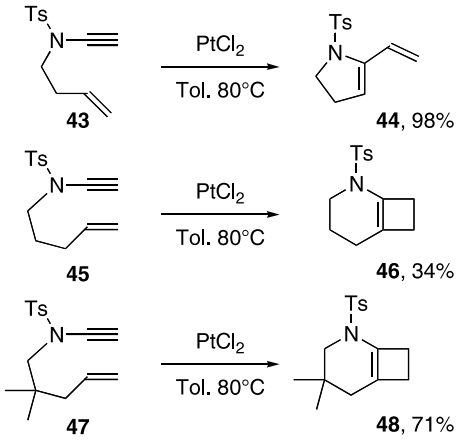
Because of the general lability of the final products,[49] we decided to transform the crude bicyclic products directly into more stable compounds through a second reaction in a one-pot process.

First, we performed ozonolysis, which provided easily isolated keto-lactams **50–52**, that could be useful building blocks in total synthesis of more complex alkaloid natural products. Nevertheless, the moderate yields (Table 3), yet consistent with literature,[50] drove us to switch to a hydrolysis reaction as the second step. Thus, after cycloisomerization reaction in presence of 10 mol% of $PtCl_2$, addition of a 1 M HCl solution to the crude cycloisomerized product gave cyclobutanones formed by hydrolysis of the intermediate enamines. The results of this cyclization–hydrolysis sequence are summarized in Table 3.

The four atom-tethered substrates **45** and **47** are transformed in good yields into the corresponding cyclobutanones **53**, **56**. Alkyl substitution is tolerated both on the alkyne partner (precursor **59**) and on the alkene one (precursors **54** and **57**). In the case of **57**, the non-opened bicyclic aminal **58**, presumably cis[51] was obtained in 76% yield. As anticipated,



Scheme 7.



Scheme 8.

Table 3

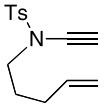
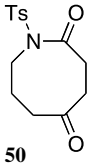
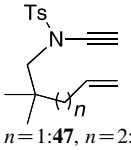
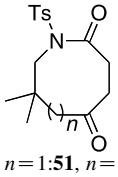
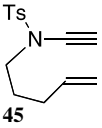
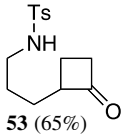
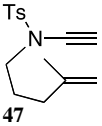
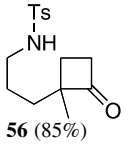
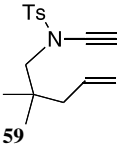
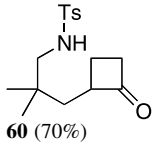
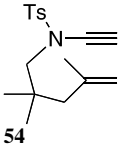
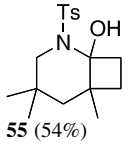
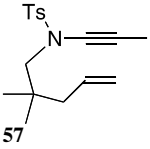
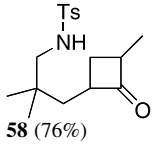
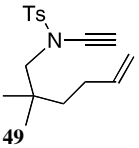
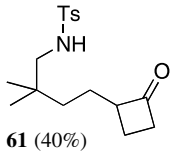
Ynamides	Keto-lactams	Yield (%)
 **45**	 **50**	20
 $n=1$:**47**, $n=2$:**49**	 $n=1$:**51**, $n=2$:**52**	37,24

Table 4

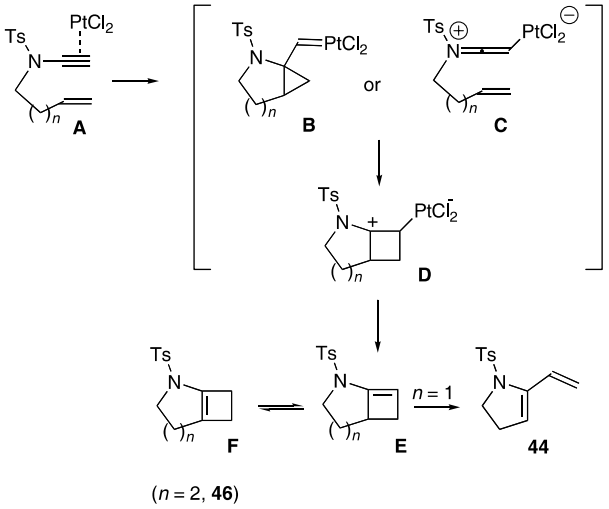
Ynamides	Cyclobutanones
 **45**	 **53** (65%)
 **47**	 **56** (85%)
 **59**	 **60** (70%)
 **54**	 **55** (54%)
 **57**	 **58** (76%)
 **49**	 **61** (40%)

introduction of a *gem*-dimethyl group in the tether resulted in improved yields (substrate **45** and **47** vs **54** and **57**).[52]

Lengthening the tether up to five atoms, corresponding to an intermediate [5,2,0]-bicyclic adduct still gave a satisfactory yield of cyclobutanone **61**. In this case, some aminal could also be observed in the crude product but was not isolated after separation on silica gel (Table 4).

3.3. Mechanism

The original results summarized in Scheme 8 and in both Tables 3 and 4 show two types of products whose formation would be dependent from the tether length. For $n=1$, which corresponds to a 1,6-enyne precursor, the formal metathesis diene (**44**) is isolated; for $n=2$, bicyclo[$n+2.0.2$] products are obtained. Although the formation of 1,3-dienes does not necessarily transit via a cyclobutene,[53] the proposition of a common reaction pathway involving bicyclic intermediate **E** with two distinct evolutions appears appropriate. Ring strain associated with the cyclobutene moiety would direct the fate of this intermediate. Presumably, for $n=1$, the severe ring strain would promote the electrocyclic ring opening of **E** to provide the diene **44**. With a six-membered ring fused to the cyclobutene, the strain is reduced and isomerization of the double bond from *exo* to *endo* at the ring junction would be favourable, giving products **F**. This is supported by the isolation of **46** and **48**. However, in the case of precursors **54** and **57**, intermediate **F** is not attainable. Instead, intermediate of type **E**[54] could also lead to the hydrolysis products **55** and **58** (Scheme 9).



Scheme 9.

Several mechanistic scenarios are possible for the generation of key intermediate **E**. All begin with the electrophilic activation of the yne partner by the π-Lewis acid (complex **A**). Then, as supported by DFT calculations of Soriano,[51] and consitent with Echavarren modelizations,[55] evolution of a cyclopropylplatina carbene intermediate **B** could lead to **D**. Alternatively, a ketenimium intermediate **C**, as proposed by Hsung[46] would undergo a [2+2] cycloaddition and ensure the construction of the cyclobutyl ring. Both pathways could transit via stabilized carbocation **D** to provide **E**. 'Homoallyl-cyclopropylmethyl-cyclobutyl' cation **D** could also originate from Fürstner's cationic manifold proposal.[44d]

4. Conclusion

We herein report the first use of ene–ynamides as versatile partners for radical cyclizations and $PtCl_2$-catalyzed cycloisomerization reactions. Efficient and original new accesses to nitrogenated polycyclic derivatives have been worked out. The radical approach implies two main classes of ynamides, which were designed to be precursors to an aryl radical that is suitably placed for cyclization onto the ynamide. On type **I** and **II** *N*-alkynylcarboxamides, 5-*exo* cyclization was easily and efficiently carried out, and examples of tandem 5-*exo*, 6-*endo*-cyclizations have led to nitrogen-containing heterocyclic compounds. The key factors that affected the success of these reactions were shown to be the starting halide, and the degree of substitution of the alkyne. The extension of this cascade process to substrates in which the final cyclization would occur onto an aryl or an heteroaryl ring completes this study and opens it towards future synthetic developments in the field of medicinal chemistry. In the case of the Pt(II) chemistry,[56] a formal [2+2] cycloaddition gives birth to versatile cyclobutenyl bicyclic substrates that we could ozonolyse to provide medium-sized nitrogen heterocycles, and hydrolyze to give various cyclobutanone derivatives. In the latter case, the reaction corresponds to an intramolecular addition of a ketene on the alkene partner via a nitrogen tether. These preliminary elements of reactivity confirm the high synthetic potential of the introduction of ene–ynamides in organometallic chemistry and pave the way for important applications we will disclose in due course.

5. Experimental

^1H and ^{13}C NMR spectra were recorded at rt at 400 and 100 MHz, respectively, on an ARX 400 Bruker spectrometer. Chemical shifts are reported in parts per million referenced to the residual proton resonances of the solvents. Coupling constants are expressed in Hertz. We use (I), (II), (III) and (IV) to caracterize primary, secondary, tertiary and quaternary carbons.

Infrared (IR) spectra were recorded with a Bruker tensor 27 (ATR diamond spectrometer). Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254. Silica gel Merck Geduran SI (40–63 μm) was used for column chromatography using Still's method.

All melting points are uncorrected. THF and Et_2O are distilled from sodium benzophenone ketyl, CH_2Cl_2, pentane and toluene are distilled, respectively, from CaH_2 and Na/K.

5.1. General procedure for the formation of ynamides

To a solution of amide (2 mmol) in toluene (60 mL) was added at ambient temperature KHMDS (powder, 2.2 mmol), the resulting mixture was sonicated for 30–60 min. The reaction medium was then heated to 70–80 °C and the iodonium salt (2.5 mmol) was added under vigorous stirring. After 30 min the temperature was raised to rt and silica (10 g) was added. The solvent was then removed under reduced pressure and chromatography on silica gel (9:1 petroleum ether/ethyl acetate) of the crude residue afforded ynamides.

5.1.1. *N*-(2-Bromo-benzyl)-2,2,2-trifluoro-*N*-trimethylsilanylethynyl-acetamide 1. Yield=77%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.62 (d, J=7.6 Hz, 1H), 7.36–7.23 (m, 3H), 4.91 (s, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 158.3 (q, 1C, IV, J=36.4 Hz), 133.2 (III), 132.99 (IV), 130.9 (III), 130.22 (III), 127.7 (III), 124.46 (IV), 117.1–114.2 (q, 1C, IV, J=287.2 Hz), 90.9 (IV), 78.0 (IV), 53.30 (II), −0.4 (3C, I); ^{19}F NMR ($CDCl_3$, 376 MHz): −71.5; IR (neat) cm^{-1}: 3064, 2187, 1725, 1251, 1154.

5.1.2. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-acrylamide 2. Yield=65%. Pale yellow solid; mp 40–43 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.58 (d, J=8.0 Hz, 1H), 7.31 (m, 2H), 7.17 (t, J=8.0 Hz, 1H), 7.14 (dd, J=16.8, 10.2 Hz, 1H), 6.54 (dd, J=16.8, 1.6 Hz, 1H), 5.88 (dd, J=10.2, 1.6 Hz, 1H), 4.89 (s, 2H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.3 (IV), 134.7 (IV), 132.8 (III), 131.3 (II), 130.3 (III), 129.4 (III), 127.5 (III), 126.5 (III), 124.1 (IV), 95.6 (IV), 76.5 (IV), 51.3 (II), −0.1 (3C, I); IR (neat) cm^{-1}: 3065, 3032, 2173, 1685, 1625, 1244. Anal. Calcd for $C_{15}H_{18}BrNOSi$ (336.29): C, 53.57; H, 5.39; N, 4.16. Found: C, 53.42; H, 5.45; N, 4.08.

5.1.3. Cyclohex-1-enecarboxylic acid (2-bromo-benzyl)-trimethylsilanylethynyl-amide 3. Yield=56%. Pale yellow solid; mp 37–39 °C; ^1H NMR ($CDCl_3$, 200 MHz): 7.55 (d, J=7.4 Hz, 1H), 7.28 (m, 3H), 7.15 (m, 1H), 6.52 (h, J=2.0 Hz, 1H), 4.79 (s, 2H), 2.34 (m, 2H), 2.14 (m, 2H), 1.64 (m, 4H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.2 (IV), 135.2 (IV), 134.7 (III), 132.9 (III), 132.6 (IV), 130.3 (III), 129.3 (III), 127.4 (III), 124.1 (IV), 97.6 (IV), 74.7 (IV), 52.0 (II), 25.3 (II), 25.0 (II), 22.0 (II), 21.6 (II), 0.1 (3C, I); IR (neat) cm^{-1}: 3064, 3032, 2164, 1679, 1278. Anal. Calcd for $C_{19}H_{24}BrNOSi$ (390.38): C, 58.46; H, 6.20; N, 3.53. Found: C, 58.47; H, 6.08; N, 3.53.

5.1.4. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-benzamide 4. Yield=32%. Pale yellow solid; mp 51–53 °C; ^1H NMR (C_6D_6, 400 MHz): 8.04 (dd, J=6.6, 2.0 Hz, 2H), 7.39 (td, J=8.1, 1.5 Hz, 2H), 7.15 (m, 3H), 6.98 (td, J=7.6, 1.5 Hz, 1H), 6.75 (td, J=8.1, 2.0 Hz, 1H), 5.03 (s, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.7 (IV), 135.1 (IV), 133.2 (IV), 133.0 (III), 131.7 (III), 130.6 (III), 129.6 (III), 129.1 (2C, III), 127.4 (2C, III), 127.5 (III), 124.3 (IV), 97.4 (IV), 75.9 (IV), 52.6 (II), −0.2 (3C, I); IR (neat) cm^{-1}: 3086, 3067, 3029, 3006, 2171, 1673, 1286.

Anal. Calcd for $C_{19}H_{20}BrNOSi$ (386.36): C, 59.07; H, 5.22; N, 3.63. Found: C, 59.15; H, 5.21; N, 3.52.

5.1.5. *N*-(2-Bromo-benzyl)-2-methoxy-*N*-trimethylsilanylethynyl-benzamide 5. Yield=57%. Pale yellow solid; mp 96–98 °C; ^{1}H NMR (C_6D_6, 200 MHz): 7.65 (dd, J=7.6, 1.3 Hz, 1H), 7.50 (dd, J=7.6, 1.3 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.08 (td, J=7.5, 1.1 Hz, 1H), 6.80 (m, 2H), 6.56 (d, J=8.2 Hz, 1H), 5.14 (s, 2H), 3.45 (s, 3H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 170.8 (IV), 156.6 (IV), 135.1 (IV), 132.9 (III), 131.6 (III), 129.6 (III), 129.3 (III), 128.5 (III), 127.6 (III), 124.7 (IV), 123.7 (IV), 120.5 (III), 110.9 (III), 97.1 (IV), 74.27 (IV), 55.8 (I), 51.6 (II), 0.00 (3C, I); IR (neat) cm^{-1}: 3065, 3029, 3009, 2178, 1681, 1273. Anal. Calcd for $C_{20}H_{22}BrNO_2Si$ (416.38): C, 57.69; H, 5.33; N, 3.36. Found: C, 57.71; H, 5.37; N, 3.53.

5.1.6. Furan-2-carboxylic acid (2-bromo-benzyl)-trimethylsilanylethynyl-amide 6. Yield=63%. Pale yellow solid; mp 113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.66 (d, 1H, J=3.5 Hz), 7.64 (d, J=1.0 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.38 (dd, J=7.6, 1.5 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.20 (td, J=1.5, 7.1 Hz, 1H), 6.54 (dd, J=3.5, 1.5 Hz, 1H), 5.01 (s, 2H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 158.6 (IV), 146.1 (III), 145.3 (IV), 134.7 (IV), 132.9 (III), 132.8 (IV), 130.6 (III), 128.5 (III), 127.5 (III), 124.3 (IV), 119.1 (III), 111.5 (III), 96.8 (IV), 76.7 (IV), 52.6 (II), −0.1 (3C, I); IR (neat) cm^{-1}: 2958, 2164, 1662, 1465, 1294, 839, 744. Elemental Anal. Calcd for $C_{17}H_{18}BrNO_2Si$ (376.32): C, 54.26; H, 4.82; N, 3.72. Found: C, 54.16; H, 4.90; N, 3.64.

5.1.7. *N*-(2-Iodo-benzyl)-*N*-trimethylsilanylethynyl-acrylamide 7. Yield=38%. Pale yellow solid; mp 34–36 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (dd, J=7.8, 1.0 Hz, 1H), 7.32 (m, 2H), 7.11 (dd, J=16.9, 10.4 Hz, 1H), 7.00 (td, J=7.8, 1.9 Hz, 1H), 6.55 (dd, J=16.9, 1.9 Hz, 1H), 5.89 (dd, J=10.4, 1.9 Hz, 1H), 4.83 (s, 2H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.4 (IV), 139.5 (III), 137.8 (IV), 131.3 (II), 129.6 (III), 129.5 (III), 128.3 (III), 126.5 (III), 99.4 (IV), 95.5 (IV), 76.7 (IV), 55.7 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3058, 2172, 1685, 1236. Anal. Calcd for $C_{15}H_{18}INOSi$ (383.29): C, 47.00; H, 4.73; N, 3.65. Found: C, 47.14; H, 4.78; N, 3.58.

5.1.8. *N*-Benzyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 8. Yield=50%. Pale yellow solid; mp 46–48 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.58 (m, 3H), 7.25 (m, 2H), 7.18 (m, 1H), 7.08 (dd, J=7.5, 1.6 Hz, 1H), 6.88 (td, J=7.5, 1.0 Hz, 1H), 6.57 (td, J=7.8, 1.6 Hz, 1H), 4.83 (s, 2H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.2 (IV), 141.3 (IV), 138.8 (III), 135.3 (IV), 130.7 (III), 129.2 (2C, III), 128.4 (2C, III), 128.1 (III), 127.8 (III), 127.7 (III), 96.3 (IV), 92.2 (IV), 79.2 (IV), 51.6 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3066, 3023, 2170, 1686, 1297, Anal. Calcd for $C_{19}H_{20}INOSi$ (433.36): C, 52.66; H, 4.65; N, 3.23. Found: C, 52.40; H, 4.87; N, 3.18.

5.1.9. *N*-Allyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 9. Yield=47%. Pale yellow solid; mp 36–38 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.59 (d, J=7.5 Hz, 1H), 7.13 (dd, J=7.5, 1.5 Hz, 1H), 6.91 (t, J=7.5 Hz, 1H), 6.60 (t, J=7.5 Hz, 1H), 6.01 (m, 1H), 5.34 (dd, J=17.1, 1.2 Hz, 1H), 5.19 (dd, J=10.3, 1.0 Hz, 1H), 4.28 (d, J=6.0 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.2 (IV), 141.4 (IV), 138.8 (III), 130.8 (III), 130.7 (III), 127.7 (III), 127.7 (III), 119.4 (II), 96.1 (IV), 92.2 (IV), 75.6 (IV), 50.2 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3085, 3053, 3021, 2170, 1685, 1644, 1291. Anal. Calcd for $C_{15}H_{18}INOSi$ (383.29): C, 47.00; H, 4.73; N, 3.65. Found: C, 47.08; H, 4.65; N, 3.62.

5.1.10. 2-Iodo-*N*-phenyl-*N*-trimethylsilanylethynyl-benzamide 10. Yield=86%. Pale yellow solid; mp 86–88 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.89 (d, J=7.5 Hz, 2H), 7.59 (dd, J=8.0, 1.0 Hz, 1H), 7.21 (m, 2H), 7.15 (dd, J=7.5, 1.5 Hz, 1H), 7.05 (t, J=7.5 Hz, 1H), 6.92 (td, J=7.5, 1.0 Hz, 1H), 6.62 (td, J=7.8, 1.5 Hz, 1H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 141.5 (IV), 138.8 (III), 138.2 (IV), 130.9 (III), 129.2 (2C, III), 127.9 (III), 127.9 (III), 127.7 (III), 124.8 (III), 95.9 (IV), 92.4 (IV), 75.5 (IV), −0.2 (3C, I); IR (neat) cm^{-1}: 3075, 3058, 3028, 2172, 1697, 1301. Anal. Calcd for $C_{18}H_{18}INOSi$ (419.33): C, 51.56; H, 4.33; N, 3.34. Found: C, 51.54; H, 4.14; N, 3.27.

5.1.11. *N*-Furan-2-ylmethyl-2-iodo-*N*-trimethylsilanylethynyl-benzamide 11. Yield=67%. ^{1}H NMR (C_6D_6, 400 MHz): 7.58 (d, 1H, J=7.6 Hz, 1H), 7.15 (d, J=1.0 Hz, 1H), 7.08 (dd, J=7.6, 2.0 Hz, 1H), 6.87 (dt, J=7.6, 1.0 Hz, 1H), 6.57 (dt, J=7.6, 2.0 Hz, 1H), 6.42 (d, J=3.0 Hz, 1H), 6.13 (dd, J=3.0, 2.0 Hz, 1H), 4.81 (s, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 148.6 (IV), 142.7 (III), 141.0 (IV), 138.8 (III), 130.8 (III), 127.8 (III), 127.7 (III), 110.5 (III), 110.2 (III), 95.7 (IV), 92.1 (IV), 76.2 (IV), 44.2 (II), −0.3 (3C, I); IR (neat) cm^{-1}: 2171, 1685.

5.1.12. 3-(5-Oxo-1-trimethylsilanyl-5*H*-pyrrolo[2,1-*a*]-isoindol-2-yl)-propenal 11a. Yield=11%. ^{1}H NMR (C_6D_6, 400 MHz): 9.60 (d, J=7.6 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.24 (m, 1H), 7.19 (d, J=15.7 Hz, 1H), 6.99 (s, 1H), 6.97 (t, J=7.6 Hz, 1H), 6.73 (t, J=7.6 Hz, 1H), 6.35 (dd, J=7.6, 15.7 Hz, 1H), 0.32 (s, 9H).

5.1.13. *N*-(2-Bromo-benzyl)-4-methyl-*N*-trimethylsilanylethynyl-benzenesulfonamide 12. Yield=55%. Pale yellow solid; mp 70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.85 (d, J=8.6 Hz, 2H), 7.55 (dd, J=8.1, 1.0 Hz, 1H), 7.43 (dd, J=7.6, 1.0 Hz, 1H), 7.38 (d, J=8.1 Hz, 2H), 7.31 (dd, J=8.6, 1.0 Hz, 1H), 7.18 (dt, J=7.6, 1.0 Hz, 1H), 4.59 (s, 2H), 2.44 (s, 3H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.9 (IV), 134.2 (IV), 133.8 (IV), 132.8 (III), 130.5 (III), 129.7 (2C, III), 127.9 (3C, III), 127.5 (III), 123.7 (IV), 95.0 (IV), 73.8 (IV), 55.0 (II), 21.7 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2956, 2160, 1679, 1594, 1442, 1368, 1248. Elemental Anal. Calcd for $C_{19}H_{22}BrNO_2SSi$ (436.44): C, 52.29; H, 5.08; N, 3.21. Found: C, 52.42; H, 5.26; N, 3.11.

5.1.14. *N*-(2-Bromo-benzyl)-*N*-trimethylsilanylethynyl-methanesulfonamide 13. Yield=51%. Pale yellow solid; mp 63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.61 (d, J=7.6 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.23 (td, J=8.1, 1.5 Hz, 1H), 4.77 (s, 2H), 3.17 (s, 3H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 133.9 (IV), 133.0 (III), 132.2 (IV), 130.9 (III), 130.0 (III), 127.7 (III), 124.0 (IV),

94.0 (IV), 74.6 (IV), 54.8 (II), 38.7 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2950, 2161, 1600, 1353, 1166, 952.

5.1.15. *N*-(2-Bromo-benzyl)-C,C,C-trifluoro-*N*-trimethylsilanylethynyl-methanesulfonamide 14. Yield=27%. ^1H NMR ($CDCl_3$, 400 MHz): 7.30–7.20 (m, 2H), 6.90 (td, $J=7.5$, 1.2 Hz, 1H), 6.73 (td, $J=7.8$, 1.6 Hz, 1H), 4.65 (s, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 133.5 (III), 132.6 (IV), 131.3 (III), 130.9 (III), 128.2 (III), 124.7 (IV), 120.0 (q, $J=322.6$ Hz, IV), 90.1 (IV), 75.6 (IV), 57.0 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 2900, 2180, 1411, 1228, 1198, 1134, 841.

5.1.16. *N*-(2-Bromo-benzyl)-4-nitro-*N*-trimethylsilanylethynyl-benzenesulfonamide 15. Yield=47%. ^1H NMR ($CDCl_3$, 400 MHz): 7.70–7.0 (m, 4H), 7.8 (dd, $J=7.6$, 1.5 Hz, 1H), 7.28 (m, 1H), 6.88 (td, $J=7.6$, 1.0 Hz, 1H), 6.69 (td, $J=7.6$, 1.5 Hz, 1H), 4.62 (s, 2H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.7 (IV), 142.6 (IV), 133.0 (III), 130.9 (III), 130.2 (III), 129.1 (2C, III+IV), 128.4 (III), 127.7 (III), 124.3 (2C, III), 124.1 (IV), 93.7 (IV), 75.0 (IV), 55.5 (II), −0.0 (3C, I); IR (neat) cm^{-1}: 3103, 2956, 2897, 2166, 1529, 1345, 1000, 842.

5.1.17. *N*-(2-Iodo-benzyl)-4-methyl-*N*-trimethylsilanylethynyl-benzenesulfonamide 16. Yield=33%. Pale yellow solid; mp 115 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.37 (m, 5H), 7.01 (m, 1H), 4.57 (s, 2H), 2.49 (s, 3H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 145.0 (IV), 139.5 (III), 136.8 (IV), 134.3 (IV), 128.9 (III), 129.8 (2C, III), 128.4 (2C, III), 128.1 (2C, III), 99.0 (IV), 95.0 (IV), 74.0 (IV), 59.6 (II), 21.8 (I), 0.0 (3C, I); IR (neat) cm^{-1}: 2954, 2159, 1364, 1247, 1164, 836, 745.

5.2. General procedure for Danheiser's method[22]

Copper iodide was purified with THF for 24 h in a Soxhlet extractor. Pyridine was distilled and degassed with argon. The amide **17** or **18** (1 mmol) was introduced in a reaction vessel, and three vacuum-argon cycles were done. Degassed pyridine (4.5 mL) was added via syringe and the temperature was lowered to 0 °C. KHMDS (0.5 M solution in toluene, 2 mL, 1 mmol, 1 equiv) was added via syringe over 4 min and the mixture was stirred during 10 min. Copper iodide (1 mmol, 1 equiv) in pyridine (2 mL) was then added in one batch through a canula, which was then rinsed with pyridine (1 mL). The temperature was raised to rt and after 2 h of stirring, the bromoalkyne (2 M solution in toluene, 1 mL, 2 equiv) was added over 1 h. The reaction was monitored by thin-layer chromatography (petroleum ether/ethylacetate 80:20). After 20 h, the reaction mixture was diluted in ether (30 mL) and washed trice with a solution of saturated aq ammonium chloride and ammonia (NH_4Cl/NH_4OH 2:1, 3×10 mL). The aqueous layer was extracted trice with ether (3×10 mL). The combined organic layers were washed with a 5% solution of copper sulfate (to remove the pyridine) and washed with brine. An acidic wash may also be done but is not compatible with certain substrates (tosylated amines for example). The organic layers were dried on magnesium sulfate and concentrated under reduced pressure to give a brown oil, which was purified on a silica gel to give the product as an oil: compounds **21**[22,23,37] or **22**, respectively, in 78 or 75% yield.

5.3. General procedure for Hsung's method[23]

The bromoalkyne (1.1 mmol, 1.1 equiv) was diluted in toluene (0.5 mL) and then the amide **17** or **18** (1 mmol, 1 equiv), potassium carbonate (2 equiv), copper sulfate pentahydrate (10 mol%) and phenantroline (20 mol%) were added. The reaction mixture was then sonicated and heated at 65 °C. The reaction was monitored by thin-layer chromatography (petroleum ether/ethylacetate 80:20). After 50 h, the reaction mixture was diluted in chloroform (30 mL), filtered through Celite and concentrated under reduced pressure to give an orange oil, which was purified on silica gel to give the product as an oil: compounds **21**[22,23,37] or **22**, respectively, in 96 and 80% yield.

5.3.1. *N*-(2-Bromobenzyl)-4-methyl-*N*-(phenylethynyl)-benzenesulfonamide 22. Yellow oil; ^1H NMR ($CDCl_3$) 400 MHz 7.55 (dd, $J=8.1$, 1.2 Hz, 1H), 7.49 (dd, $J=7.8$, 1.5 Hz, 1H), 7.37 (d, $J=8.3$ Hz, 2H), 7.31 (dt, $J=7.6$, 1.0 Hz, 1H), 7.24 (br s, 5H), 7.18 (dt, $J=7.6$, 1.5 Hz, 1H), 4.73 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) 100 MHz: 145.0 (IV), 134.5 (IV), 134.0 (IV), 133.0 (III), 131.2 (III, 2C), 130.5 (III), 130.0 (III, 2C), 129.8 (III), 128.3 (III, 2C), 128.0 (III, 2C), 127.8 (III), 127.7 (III), 123.8 (IV), 122.8 (IV), 82.5 (IV), 71.3 (IV), 55.4 (II), 21.8 (I); IR (neat) cm^{-1}: 3063, 2924, 2237, 1702, 1357, 1167.

5.3.2. *N*-(2-Bromo-benzyl)-*N*-ethynyl-acrylamide 23. Yield=95%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.59 (d, $J=8.6$ Hz, 1H), 7.29 (m, 2H), 7.17 (m, 2H), 6.56 (dd, $J=16.7$, 1.7 Hz, 1H), 5.90 (dd, $J=10.4$, 1.7 Hz, 1H), 4.91 (s, 2H), 2.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.6 (IV), 134.5 (IV), 132.9 (III), 131.6 (II), 129.4 (III), 127.6 (III), 126.3 (III), 123.6 (IV), 76.8 (IV), 62.4 (III), 51.3 (II); IR (neat) cm^{-1}: 3223, 3052, 3035, 2135, 1671, 1620. Anal. Calcd for $C_{12}H_{10}BrNO$ (264.12): C, 54.57; H, 3.82; N, 5.30. Found: C, 54.202; H, 4.29; N, 5.32.

5.3.3. Cyclohex-1-enecarboxylic acid (2-bromo-benzyl)-ethynyl-amide 24. Yield=98%. Pale yellow solid; mp 38–40 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.59 (d, $J=7.6$ Hz, 1H), 7.32 (m, 2H), 7.18 (m, 1H), 6.57 (h, $J=1.5$ Hz, 1H), 4.85 (s, 2H), 2.79 (s, 1H), 2.37 (m, 2H), 2.20 (m, 2H), 1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.4 (IV), 135.0 (IV), 134.9 (III), 133.0 (III), 132.4 (IV), 129.6 (III), 129.3 (III), 127.5 (III), 123.7 (IV), 78.4 (IV), 60.90 (III), 52.1 (II), 25.4 (II), 25.1 (II), 22.0 (II), 21.5 (II); IR (neat) cm^{-1}: 3231, 3061, 3032, 2136, 1659. Anal. Calcd for $C_{16}H_{16}BrNO$ (318.21): C, 60.39; H, 5.07; N, 4.40. Found: C, 60.48; H, 5.12; N, 4.29.

5.3.4. *N*-Ethynyl-*N*-(2-iodo-benzyl)-acrylamide 25. Yield=91%. Paste; ^1H NMR ($CDCl_3$, 400 MHz): 7.86 (dd, $J=8.1$, 1.0 Hz, 1H), 7.34 (td, $J=7.7$, 1.0 Hz, 1H), 7.25 (dd, $J=7.7$, 1.5 Hz, 1H), 7.14 (dd, $J=16.9$, 10.4 Hz, 1H), 7.00 (td, $J=7.7$, 1.5 Hz, 1H), 6.57 (dd, $J=16.9$, 1.8 Hz, 1H), 5.91 (dd, $J=10.4$, 1.8 Hz, 1H), 4.84 (s, 2H), 2.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.6 (IV), 139.6 (III), 137.5 (IV), 131.7 (II), 129.5 (III), 128.7 (III), 128.5 (III),

126.3 (III), 98.7 (IV), 76.7 (IV), 62.7 (III), 55.8 (II); IR (neat) cm^{-1}: 3294, 3058, 2139, 1681, 1623. Anal. Calcd for $C_{12}H_{10}INO$ (311.12): C, 46.33; H, 3.24; N, 4.50. Found: C, 46.41; H, 3.24; N, 4.34.

5.3.5. *N*-Allyl-*N*-ethynyl-2-iodo-benzamide 26. Yield=83%. Pale yellow solid; mp 43–45 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.1 Hz, 1H), 7.40 (td, J=7.4, 1.1 Hz, 1H), 7.32 (dd, J=7.5, 1.1 Hz, 1H), 7.13 (td, J=7.5, 1.6 Hz, 1H), 6.02 (ddt, J=6.2, 10.2, 17.0 Hz, 1H), 5.44 (dd, J=17.0, 1.0 Hz, 1H), 5.35 (d, J=10.2 Hz, 1H), 4.32 (d, J=6.2 Hz, 2H), 2.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171 (IV), 141.0 (IV), 139.1 (III), 131.0 (III), 130.7 (III), 127.9 (III), 127.7 (III), 119.6 (II), 92.1 (IV), 76.7 (IV), 61.4 (I), 50.5 (II); IR (neat) cm^{-1}: 3237, 3096, 3052, 3012, 2141, 1669, 1646. Anal. Calcd for $C_{12}H_{10}INO$ (297.09): C, 46.33; H, 3.24; N, 4.50. Found: C, 46.52; H, 3.57; N, 4.27.

5.3.6. *N*-Allyl-2-iodo-*N*-prop-1-ynyl-benzamide 27. Yield=62%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.1 Hz, 1H), 7.40 (td, J=7.3, 1.0 Hz, 1H), 7.33 (dd, J=7.7, 1.8 Hz, 1H), 7.10 (td, J=7.7, 1.5 Hz, 1H), 6.00 (ddt, J=6.0, 10.6, 16.9 Hz, 1H), 5.42 (dd, J=16.9, 1.3 Hz, 1H), 5.32 (dd, J=10.1, 1.0 Hz, 1H), 4.30 (d, J=6.0 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0 (IV), 141.6 (IV), 138.9 (III), 131.3 (III), 130.7 (III), 127.8 (III), 127.7 (III), 119.0 (II), 92.3 (IV), 73.7 (IV), 68.2 (IV), 50.6 (II), 3.1 (I); IR (neat) cm^{-1}: 3080, 3013, 2263, 1731, 1674.

5.3.7. [Allyl-(2-iodo-benzoyl)-amino]-propynoic acid ethyl ester 28. Yield=90%. Clear oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.87 (dd, J=8.4, 1.0 Hz, 1H), 7.44 (td, J=7.6, 1.0 Hz, 1H), 7.33 (dd, J=7.6, 1.5 Hz, 1H), 7.18 (td, J=7.6, 1.8 Hz, 1H), 5.98 (ddd, J=16.9, 10.2, 6.3 Hz, 1H), 5.46 (d, J=16.9 Hz, 1H), 5.38 (d, J=10.2 Hz, 1H), 4.35 (d, J=5.6 Hz, 2H), 4.06 (q, J=7.1 Hz, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.9 (IV), 153.8 (IV), 139.7 (IV), 139.3 (III), 131.6 (III), 130.0 (III), 128.0 (III), 127.8 (III), 120.4 (II), 92.0 (IV), 82.4 (IV), 68.9 (IV), 61.5 (II), 50.7 (II), 14.0 (I); IR (neat) cm^{-1}: 3085, 2225, 1693.

Standard cyclization conditions. A degassed solution of ynamide (0.25 mmol), tributyltin hydride (0.5 mmol, 2 equiv) and AIBN (0.12 mmol, 0.5 equiv) in benzene (15 mL) was refluxed until the monitoring of the reaction by TLC showed total consumption of the starting material. Once the mixture was back to rt, aq NaOH (1 M, 15 mL) was added and stirred for 30 min. The organic phase was extracted with ethyl acetate (2×20 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by silica gel flash chromotography (pentane/ethyl acetate/triethylamine 80:20:1) afforded cyclization products. In case of ynamides in Table 2 the eluent was pentane/ethyl acetate/triethylamine 70:30:1.

Slow addition conditions. A degassed solution of tin hydride (0.5 mmol, 2 equiv) and AIBN (0.12 mmol, 0.5 equiv) in benzene (5 mL) was added over a period of 2 h via a syringe pump to a refluxing degassed solution of ynamide (0.25 mmol) in benzene (10 mL). When the addition was finished, the precedent treatment was applied to afford cyclization product.

Atom transfer conditions. A degassed solution of ynamide (0.25 mmol) and hexabutylditin (0.375 mmol, 1.5 equiv) in toluene 15 mL was refluxed and irradiated with a sun lamp (300 W) until the monitoring of the reaction by TLC showed total consumption of the starting material. The precedent treatment was applied to afford cyclization products.

5.3.8. 2,2,2-Trifluoro-1-(1-trimethylsilanylmethylene-1,3-dihydro-isoindol-2-yl)-acetamide 29. Yield=78%. Two diastereomers *Z*/*E*: 2:1; pale yellow solid; mp 56–58 °C; ^1H NMR (C_6D_6, 400 MHz): 7.80 (d, J=7.5 Hz, 1Hm), 7.56 (se, 1Hm), 7.25 (m, 1HM), 7.10 (m, 2HM+2Hm), 6.69 (m, 1HM+1Hm), 5.92 (s, 1HM), 4.39 (s, 2Hm), 4.34 (s, 2HM), 0.54 (s, 9HM), 0.42 (s, 9Hm); ^{13}C NMR (C_6D_6, 100 MHz): major compound 155.3 (q, 1C, IV, J=26.29 Hz), 148.0 (IV), 136.2 (IV), 134.8 (IV), 129.1 (III), 128.1 (III), 122.3 (III), 120.5 (III), 117.9 (q, 1C, IV, J=287.00 Hz), 109.7 (III), 52.2 (II), 1.5 (3C, I); minor compound 155.2 (q, 1C, IV, J=26.2 Hz), 149.6 (IV), 136.7 (IV), 135.0 (IV), 129.1 (III), 127.6 (III), 123.2 (III), 122.5 (III), 117.7 (q, 1C, IV, J=287.2 Hz), 109.9 (III), 51.9 (II), −0.9 (3C, I); ^{19}F NMR ($CDCl_3$, 376 MHz): −72.5 (m), −73.2 (M); IR (neat) cm^{-1}: 3043, 3024, 1696, 1248, 1132.

5.3.9. 1-Trimethylsilanyl-2,6-dihydro-3*H*-pyrido[2,1-*a*]-isoindol-4-one 30. Yield=70%. White solid; mp 136–138 °C; ^1H NMR (C_6D_6, 400 MHz): 7.79 (d, J=7.7 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 7.05 (t, J=7.7 Hz, 1H), 6.87 (d, J=7.3 Hz, 1H), 4.75 (s, 2H), 2.32 (m, 2H), 2.23 (m, 2H), 0.35 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 168.2 (IV), 146.8 (IV), 139.1 (IV), 135.0 (IV), 128.4 (III), 126.8 (III), 123.8 (III), 123.3 (III), 105.5 (IV), 50.0 (II), 30.8 (II), 26.0 (II), 0.1 (3C, I); IR (neat) cm^{-1}: 3078, 3051, 3034, 1672, 1241. Anal. Calcd for $C_{15}H_{19}NOSi$: C, 69.99; H, 7.44; N, 5.44. Found: C, 69.49; H, 7.61; N, 5.08.

5.3.10. 2,6-Dihydro-3*H*-pyrido[2,1-*a*]isoindol-4-one 31. Yield=54%. Paste; ^1H NMR (C_6D_6, 400 MHz): 7.23 (d, J=7.3 Hz, 1H), 7.07 (m, 2H), 6.82 (d, J=7.4 Hz, 1H), 5.14 (t, J=4.3 Hz, 1H), 4.69 (s, 2H), 2.40 (t, J=8.3 Hz, 2H), 2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.8 (IV), 140.5 (IV), 136.7 (IV), 133.8 (IV), 129.0 (III), 127.9 (III), 123.3 (III), 120.4 (III), 94.9 (III), 50.3 (II), 30.8 (II), 21.0 (II); IR (neat) cm^{-1}: 3071, 1727, 1644.

5.3.11. 12-Trimethylsilanyl-2,3,4,4a,7,12a-hexahydro-1*H*-isoindolo[2,1-*b*]isoquinolin-5-one 32. Yield=75%. White solid; mp 120–123 °C; ^1H NMR (C_6D_6, 400 MHz): 7.83 (d, J=7.6 Hz, 1H), 7.13 (t, J=7.6 Hz, 1H), 7.06 (t, J=7.1 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 4.85 (AB, J_{AB}=17.0 Hz, 2H), 2.94 (m, 1H), 2.54 (m, 2H), 1.9–1.2 (m, 7H), 0.42 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 169.9 (IV), 145.7 (IV), 139.4 (IV), 135.3 (IV), 132.4 (IV), 128.5 (III), 127.0 (III), 123.9 (III), 123.5 (III), 50.2 (II), 40.8 (III), 40.3 (III), 28.8 (II), 26.7 (II), 25.0 (II), 22.8 (II), 0.4 (3C, I); IR (neat) cm^{-1}: 3070, 3034, 1730, 1669, 1249; MS (C.I.), m/z 312 (MH+), 269, 182.

5.3.12. 1-Trimethylsilanyl-3,4-dihydro-2*H*-pyrido[2,1-*a*]-isoindol-6-one 33. White solid; mp 128–130 °C; ^1H NMR (C_6D_6, 400 MHz): 8.09 (d, J=7.3 Hz, 1H), 7.82

(d, J=7.8 Hz, 1H), 7.21 (td, J=7.3, 1.2 Hz, 1H), 7.12 (td, J=7.3, 0.7 Hz, 1H), 3.65 (t, J=5.8 Hz, 2H), 2.03 (t, J=6.0 Hz, 2H), 1.39 (m, 2H), 0.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.1 (IV), 140.2 (IV), 135.0 (IV), 131.1 (III), 131.1 (IV), 128.7 (III), 123.5 (III), 123.3 (III), 119.9 (IV), 38.9 (II), 28.6 (II), 22.1 (II), 0.3 (3C, I); IR (neat) cm^{-1}: 3082, 3058, 3022, 1685, 1281.

5.3.13. 3,4-Dihydro-2*H*-pyrido[2,1-*a*]isoindol-6-one 34. Paste; ^{1}H NMR (C_6D_6, 400 MHz): 8.00 (dt, J=7.6, 1.0 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.21 (td, J=8.6, 1.3 Hz, 1H), 7.14 (td, J=7.6, 1.0 Hz, 1H), 5.34 (t, J=4.6 Hz, 1H), 3.58 (m, 2H), 1.86 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 164.9 (IV), 135.5 (IV), 135.0 (IV), 130.8 (III), 130.6 (IV), 128.6 (III), 128.1 (III), 123.0 (III), 119.2 (III), 102.7 (III), 38 (II), 22.1 (II), 21.2 (II); IR (neat) cm^{-1}: 3053, 1690, 1664.

5.3.14. 1-Methyl-3,4-dihydro-2*H*-pyrido[2,1-*a*]isoindol-6-one 35. Yield=84%. White solid; mp 98–100 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.14 (d, J=7.4 Hz, 1H), 7.53 (d, J=7.6 Hz, 1H), 7.25 (m, 1H), 7.16 (t, J=7.3 Hz, 1H), 3.61 (m, 2H), 1.80 (s, 3H), 1.76 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 164.4 (IV), 135.4 (IV), 131.2 (IV), 130.7 (III), 129.4 (IV), 127.7 (III), 123.3 (III), 122.6 (III), 116.8 (IV), 37.7 (II), 30.3 (II), 21.2 (II), 18.5 (I); IR (neat) cm^{-1}: 3058, 3029, 1662.

5.3.15. 6-Oxo-2,3,4,6-tetrahydro-pyrido[2,1-*a*]isoindole-1-carboxylic acid ethyl ester 36. Yield=45%. White solid; mp 62–65 °C; ^{1}H NMR (C_6D_6, 400 MHz): 9.15 (d, J=8.2 Hz, 1H), 7.98 (dt, J=7.6, 1.0 Hz, 1H), 7.33 (td, J=8.1, 1.3 Hz, 1H), 7.14 (td, J=7.3, 0.7 Hz, 1H), 4.17 (q, J=7.3 Hz, 2H), 3.44 (m, 2H), 2.33 (t, J=6.0 Hz, 2H), 1.27 (m, 2H), 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz): 166.5 (IV), 165.5 (IV), 141.6 (IV), 134.4 (IV), 132.1 (III), 130.9 (IV), 130.1 (III), 127.3 (III), 122.7 (III), 109.6 (IV), 60.2 (II), 38.1 (II), 25.3 (II), 20.1 (II), 14.1 (I); IR (neat) cm^{-1}: 3073, 1693, 1603.

5.3.16. 12-Trimethylsilanyl-7*H*-isoindolo[2,1-*b*]isoquinolin-5-one 37. Yield=67%. Yellow solid; mp 132–134 °C; ^{1}H NMR (C_6D_6, 400 MHz): 9.01 (dd, J=8.1, 1.5 Hz, 1H), 7.87 (dd, J=7.1, 3.0 Hz, 2H), 7.42 (td, J=6.6, 1.5 Hz, 1H), 7.31 (t, J=7.1 Hz, 1H), 7.10 (m, 2H), 6.93 (d, J=7.6 Hz, 1H), 4.85 (s, 2H), 0.56 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 161.1 (IV), 149.8 (IV), 142.8 (IV), 140.3 (IV), 136.1 (IV), 131.1 (III), 129.7 (III), 128.7 (III), 128.2 (III), 127.1 (III), 126.7 (III), 126.2 (III), 123.7 (III), 107.3 (IV), 52.5 (II), 3.7 (3C, I); IR (neat) cm^{-1}: 3053, 3035, 1644, 1603, 1249.

5.3.17. 4-Methoxy-12-trimethylsilanyl-7*H*-isoindolo-[2,1-*b*]isoquinolin-5-one 38. Yield=54%. Yellow solid; mp 135–136 °C; ^{1}H NMR (C_6D_6, 200 MHz): 8.68 (d, 1H, J=8.0 Hz), 7.99 (d, 1H, J=8.0 Hz), 7.32–6.92 (m, 4H), 6.69 (d, 1H, J=7.8 Hz), 4.88 (s, 2H), 3.41 (s, 3H), 0.52 (s, 9H); ^{13}C NMR (C_6D_6, 50 MHz): 160.6 (IV), 155.9 (IV), 149.7 (IV), 139.8 (IV), 136.4 (IV), 134.1 (IV), 129.5 (III), 126.8 (III), 126.5 (III), 126.4 (III), 123.3 (III), 119.9 (III), 111.5 (III), 104.1 (IV), 54.1 (I), 52.3 (II), 3.1 (3C, I); IR (neat) cm^{-1}: 3069, 3033, 1713, 1645, 1234. Anal. Calcd for $C_{20}H_{21}NO_2Si$ (335.47): C, 71.60; H, 6.31; N, 4.18. Found: C, 71.49; H, 6.41; N, 4.09.

5.3.18. 12-Trimethylsilanyl-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one 39. Yield=46%. Yellow solid; mp 126–128 °C; ^{1}H NMR (C_6D_6, 400 MHz): 7.98 (d, 1H, J=7.1 Hz), 7.75 (d, 1H, J=7.6 Hz), 7.34 (d, 1H, J=7.0 Hz), 7.15 (m, 3H), 7.02 (td, 1H, J=7.6, 1.3 Hz), 6.86 (d, 1H, J=7.6 Hz), 4.73 (s, 2H), 0.50 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz): 165.9 (IV), 144.1 (IV), 136.9 (IV), 135.7 (IV), 131.0 (IV), 130.5 (III), 130.0 (IV), 129.3 (III), 128.4 (III), 126.8 (III), 126.8 (III), 126.6 (III), 124.5 (III), 123.4 (III), 117.2 (IV), 42.8 (II), 2.0 (3C, I); IR (neat) cm^{-1}: 3058, 3016, 1691, 1251.

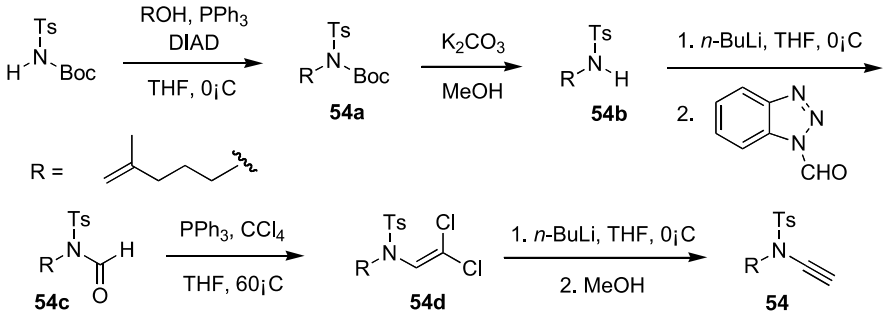
5.3.19. 2-Benzyl-3-trimethylsilanylmethylene-2,3-dihydro-isoindol-1-one 40. Yield=57%. Two diastereomers (1/1): paste; ^{1}H NMR (C_6D_6, 400 MHz): 8.05 (d, J=7.3 Hz, 1H), 7.95 (d, J=7.6 Hz, 1H), 7.81 (d, J=7.8 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.30–7.00 (m, 14H), 5.58 (s, 1H), 5.28 (s, 1H), 5.19 (s, 2H), 4.95 (s, 2H), 0.27 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.4 (IV), 167.1 (IV), 146.6 (IV), 145.8 (IV), 138.1 (IV), 137.1 (IV), 136.7 (IV), 136.3 (IV), 132.1 (III), 131.7 (III), 130.5 (IV), 129.4 (III), 129.3 (III), 128.6 (4C, III), 128.4 (IV), 127.2 (III), 127.1 (2C, III), 127.0 (III), 125.8 (2C, III), 123.5 (III), 123.1 (III), 122.9 (III), 120.0 (III), 106.8 (III), 102.8 (III), 44.0 (II), 42.7 (II), 1.2 (3C, I), 0.3 (3C, I); IR (neat) cm^{-1}: 3087, 3063, 3031, 1705, 1606, 1249.

5.3.20. 11-Trimethylsilanyl-isoindolo[2,1-*a*]indol-6-one 41. Yield=62%. Yellow solid; mp 139–142 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.26 (d, J=7.8 Hz, 1H), 7.65 (m, 2H), 7.47 (d, J=7.6 Hz, 1H), 7.18 (td, J=7.6, 1.0 Hz, 1H), 7.08 (td, J=8.0, 1.0 Hz, 1H), 7.01 (td, J=7.5, 1.0 Hz, 1H), 6.83 (t, J=7.3 Hz, 1H), 0.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.5 (IV), 144.3 (IV), 139.1 (IV), 135.5 (IV), 134.3 (IV), 133.9 (IV), 133.6 (III), 128.6 (III), 126.1 (III), 125.3 (III), 123.6 (III), 123.5 (III), 122.6 (III), 116.0 (IV), 113.2 (III), 0.6 (3C, I); IR (neat) cm^{-1}: 3051, 1763, 1725, 1245.

5.3.21. 2-Phenyl-3-trimethylsilanylmethylene-2,3-dihydro-isoindol-1-one 42. Yield=71%. Two diastereomers *Z*/*E*: 2:1; yellow solid; mp 136–138 °C; ^{1}H NMR (C_6D_6, 400 MHz): 8.06 (d, J=7.6 Hz, 1Hm), 7.97 (d, J=7.6 Hz, 1HM), 7.93 (d, J=7.8 Hz, 1Hm), 7.43 (d, J=7.8 Hz, 1HM), 7.32–7.30 (m, 2HM+2Hm), 7.24–7.08 (m, 5HM+5Hm), 5.59 (s, 1HM), 5.45 (s, 1Hm), 0.29 (s, 9Hm), −0.07 (s, 9HM); ^{13}C NMR (C_6D_6, 100 MHz): major compound 167.3 (IV), 147.7 (IV), 138.5 (IV), 136.9 (IV), 132.0 (III), 129.4 (2C, III), 129.1 (2C, III), 127.9 (2C, III), 123.3 (III), 119.9 (III), 102.8 (III), 0.1 (3C, I); IR (neat) cm^{-1}: 3062, 3043, 1713, 1609, 1247; minor compound 165.8 (IV), 148.3 (IV), 136.4 (IV), 135.1 (IV), 131.6 (III), 129.5 (2C, III), 129.3 (2C, III), 129.2 (2C, III), 123.8 (III), 123.0 (III), 105.1 (III), 0.0 (3C, I); IR (neat) cm^{-1}: 3062, 3043, 1713, 1609, 1247. IEMS: *m*/*z* (%)=293 [(M^+), 3], 276 [M^+−17, 100], 232 [M^+−63, 17].

5.4. Svnthesis of cycloisomerization precursors: a representative example (Scheme 10)

5.4.1. *N-tert*-Butoxycarbonyl-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54a. Ts-NH–Boc (12.25 g,



Scheme 10.

45.2 mmol, 1 equiv), PPh_3 (11.86 g, 45.2 mmol, 1 equiv) and 4-methylpent-4-en-1-ol (4.52 g, 45.2 mmol, 1 equiv) were introduced in 100 mL of THF. The mixture was cooled to 0 °C and 8.96 mL (45.2 mmol, 1 equiv) of DIAD were added dropwise. After stirring for 5 min, the mixture was allowed to warm up to rt and stirred for 1 h. The solvent was removed and the residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1–4:1) to give **54a** (14.43 g, 90%) as a yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.79 (d, $J=8.2$ Hz, 2H), 7.31 (d, $J=8.2$ Hz, 2H), 4.76 (br s, 2H), 3.83 (t, $J=7.6$ Hz, 2H), 2.44 (s, 3H), 2.08–2.12 (m, 2H), 1.91–1.95 (m, 2H), 1.77 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.9 (IV), 144.4 (IV), 144.0 (IV), 137.5 (IV), 129.2 (2C, III), 127.7 (2C, III), 110.4 (II), 83.9 (IV), 46.9 (II), 34.7 (II), 31.8 (II), 27.8 (3C, I), 22.2 (I), 21.5 (I); IR (neat) cm^{-1}: 2984, 1718, 1649, 1350, 1152. Anal. Calcd for $C_{18}H_{27}O_4NS$ (353.28): C, 61.17; H, 7.69; N, 3.96. Found: C, 61.00; H, 7.77; N, 4.10.

5.4.2. *N*-(4-Methylpent-4-enyl)-4-methylbenzenesulfonamide 54b. Consistent with literature (Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172).

In a flask containing a solution of **54a** (13.94 g, 39.49 mmol, 1 equiv) in methanol (400 mL) was added K_2CO_3 (27.29 g, 197.45 mmol, 5 equiv). After refluxing for 3 h, water (100 mL) was introduced and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give **54b** (9.99 g, 100%) as a yellow oil.

5.4.3. *N*-Formyl-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54c. Under argon, *n*-BuLi (18.8 mL, 2.3 M solution in hexane, 43.16 mmol, 1.1 equiv) was added to a solution of **54b** (9.93 g, 39.23 mmol, 1 equiv) in THF (200 mL) at 0 °C. After stirring for 5 min, *N*-formylbenzotriazole (6.92 g, 47.08 mmol, 1.2 equiv) was added, and the mixture was stirred at rt for 1 h. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1–4:1) to give **54c** (9.85 g, 89%) as a colourless oil; ^1H NMR ($CDCl_3$, 200 MHz): 9.09 (s, 1H), 7.74 (d, $J=8.0$ Hz, 2H), 7.36 (d, $J=8.0$ Hz, 2H), 4.69 (br s, 1H), 4.62 (br s, 1H), 3.40 (t, $J=7.8$ Hz, 2H), 2.44 (s, 3H), 1.95 (t, $J=8.3$ Hz, 2H), 1.58–1.70 (m, 2H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): 161.2 (IV), 145.4 (IV), 144.0 (IV), 135.0 (IV), 130.3 (2C, III), 127.3 (2C, III), 110.6 (II), 42.4 (II), 34.6 (II), 25.7 (II), 22.1 (I), 21.6 (I); IR (neat) cm^{-1}: 3072, 2935, 1697, 1650, 1596, 1355, 1161. Anal. Calcd for $C_{14}H_{19}O_3NS$ (281.37): C, 59.77; H, 6.80; N, 4.98. Found: C, 59.67; H, 6.89; N, 5.15.

5.4.4. *N*-(2,2-Dichlorovinyl)-*N*-(4-methylpent-4-enyl)-4-methylbenzenesulfonamide 54d. To a solution of **54c** (9.79 g, 34.83 mmol, 1 equiv) and PPh_3 (27.41 g, 104.49 mmol, 3 equiv) in THF (350 mL) at 60 °C was added 33.7 mL of CCl_4 (348.29 mmol, 10 equiv) over 6 h. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O 9:1, then PE/EA 9:1–4:1) to give **54d** (12.12 g, 100%) as a yellow solid; mp 85 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.67 (d, $J=8.1$ Hz, 2H), 7.31 (d, $J=8.1$ Hz, 2H), 6.25 (s, 1H), 4.71 (br s, 1H), 4.65 (br s, 1H), 3.29 (t, $J=7.3$ Hz, 2H), 2.42 (s, 3H), 2.01 (t, $J=7.5$ Hz, 2H), 1.68 (s, 3H), 1.60–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.4 (IV), 144.2 (IV), 135.4 (IV), 130.0 (2C, III), 127.3 (2C, III), 125.0 (III), 124.8 (IV), 110.7 (II), 49.0 (II), 34.6 (II), 26.4 (II), 22.4 (I), 21.6 (I); IR (neat) cm^{-1}: 3067, 2969, 1650, 1598, 1353, 1164.

5.4.5. Ynamide 54. Under argon, *n*-BuLi (9.57 mL, 2.3 M solution in hexane, 22 mmol, 2.2 equiv) was added to a solution of **54d** (3.48 g, 10 mmol, 1 equiv) in anhydrous THF (50 mL) at −78 °C and the mixture was stirred during 45 min, 80 μL (2 mmol, 0.2 equiv) of MeOH were then added and the mixture was allowed to warm up to rt over 1 h 30. After addition of saturated $NaHCO_3$ aq, the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (pentane/EA/NEt_3 90:10:1) to give **54** (1.97 g, 71%) as a yellow solid; mp 49 °C; ^1H NMR ($CDCl_3$, 400 MHz): 7.77 (d, $J=7.8$ Hz, 2H), 7.33 (d, $J=7.8$ Hz, 2H), 4.70 (s, 1H), 4.64 (s, 1H), 3.27 (t, $J=6.4$ Hz, 2H), 2.74 (s, 1H), 2.41 (s, 3H), 1.98–2.01 (m, 2H), 1.72–1.80 (m, 2H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.7 (IV), 144.0 (IV), 134.4 (IV), 129.7 (2C, III), 127.5 (2C, III), 110.6 (II), 75.9 (IV), 59.1 (III), 50.7 (II), 34.0 (II), 25.4 (II), 22.4 (I), 21.5 (I); IR (neat) cm^{-1}: 3294, 3073, 2933, 2132, 1650, 1596, 1362, 1166. Anal. Calcd for $C_{15}H_{19}O_2NS$ (277.38): C, 64.95; H, 6.90; N, 5.05. Found: C, 64.82; H, 7.05; N, 5.09.

Ynamides **45**, **47**, **49** and **57** were prepared according to this method.

5.4.6. Ynamide 45. Consistent with literature (Ref. 28b). Yield=82%.

Anal. Calcd for $C_{14}H_{17}O_2NS$ (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.70; N, 5.38.

5.4.7. Ynamide 47. Consistent with literature (Ref. 28b). Yield=69%. White solid; mp 53 °C.

5.4.8. Ynamide 49. Yield=56%. White solid; mp 38 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.82 (d, J=4.2 Hz, 2H), 7.37 (d, J=4.2 Hz, 2H), 5.81 (ddt, J=17.0, 10.1, 6.4 Hz, 1H), 4.92–5.07 (m, 2H), 3.15 (s, 2H), 2.70 (s, 1H), 2.46 (s, 3H), 1.99–2.11 (m, 2H), 1.41–1.50 (m, 2H), 1.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): 144.7 (IV), 138.9 (III), 134.3 (IV), 129.7 (2C, III), 127.8 (2C, III), 114.2 (II), 78.7 (IV), 61.5 (II), 58.3 (III), 38.8 (II), 35.7 (IV), 28.2 (II), 25.2 (2C, I), 21.6 (I); IR (neat) cm^{-1}: 3276, 3081, 2968, 2133, 1643, 1598, 1355, 1168. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 66.67; H, 7.78; N, 4.62.

5.4.9. Ynamide 57. Yield=66%. White solid; mp 77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.80 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.88 (br s, 1H), 4.67 (br s, 1H), 3.16 (s, 2H), 2.68 (s, 1H), 2.45 (s, 3H), 2.07 (s, 2H), 1.78 (s, 3H), 1.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.8 (IV), 142.5 (IV), 134.5 (IV), 129.9 (2C, III), 128.0 (2C, III), 115.3 (II), 79.0 (IV), 63.0 (II), 58.5 (III), 48.0 (II), 36.7 (IV), 25.6 (3C, I), 21.8 (I); IR (neat) cm^{-1}: 3274, 3070, 2964, 2133, 1638, 1597, 1355, 1168. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 67.00; H, 7.82; N, 4.38.

5.4.10. Ynamide 59. To a solution of LiHMDS (343 mg, 2.13 mmol, 1.3 equiv) in THF (8 mL) at −78 °C was added *n*-BuLi (0.92 mL, 2.3 M solution in hexane, 2.13 mmol, 1.3 equiv). The mixture was stirred for 10 min, then a solution of ynamide **47** (476 mg, 1.64 mmol, 1 equiv) in THF (8 mL) was canulated. The reaction medium was allowed to warm up to −40 °C and was stirred for 1 h, and then MeI (0.51 mL, 8.18 mmol, 5 equiv) was slowly added. The mixture was stirred for 30 min at −40 °C, then allowed to warm up to rt and stirred for 20 h. To the mixture was added saturated $NaHCO_3$ aq, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (pentane/EA 95:5) to give **59** (420 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.2 Hz, 2H), 5.80 (ddt, J=16.9, 10.4, 7.3 Hz, 1H), 4.99–5.06 (m, 2H), 3.06 (s, 2H), 2.44 (s, 3H), 2.08 (d, J=7.6 Hz, 2H), 1.84 (s, 3H), 0.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.3 (IV), 134.7 and 134.6 (IV+III), 129.7 (2C, III), 127.8 (2C, III), 117.8 (II), 74.9 (IV), 64.8 (IV), 61.8 (II), 44.5 (II), 35.8 (IV), 25.2 (2C, I), 21.7 (I), 3.3 (I); IR (neat) cm^{-1}: 3074, 2966, 2259, 1638, 1597, 1363, 1170. Anal. Calcd for $C_{17}H_{23}O_2NS$ (305.44): C, 66.85; H, 7.59; N, 4.59. Found: C, 67.21; H, 7.69; N, 4.26.

5.5. General procedure for cycloisomerizations

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed by the freeze-pump-thaw method and the reaction vessel was plunged in a pre-heated oil bath (80 °C). $PtCl_2$ (7 mg, 0.025 mmol, 0.05 equiv) was then added, and the mixture was stirred until the IR spectrum indicated the vanishing of the triple bond. The solvent was removed and the residue was purified by flash chromatography (PE/Et_2O/NEt_3 85:15:1) to give the desired cyclization product.

5.5.1. Dienamide 44. Consistent with literature (Ref. 28b). Yield=98%.

5.5.2. Bicyclic enamide 46. Yield=44%. Pale yellow oil; ^{1}H NMR (C_6D_6, 400 MHz): 7.72 (d, J=8.1 Hz, 2H), 6.77 (d, J=8.1 Hz, 2H), 3.20–3.22 (m, 2H), 3.09 (quint., J=3.2 Hz, 2H), 2.15–2.18 (m, 2H), 1.86 (s, 3H), 1.35–1.38 (m, 2H), 1.18–1.21 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): 141.3 (IV), 136.8 (IV), 134.2 (IV), 129.8 (2C, III), 127.6 (2C, III), 122.3 (IV), 45.7 (II), 33.1 (II), 28.7 (II), 22.5 (II), 22.0 (II), 21.1 (I); IR (neat) cm^{-1}: 3074, 2920, 1691, 1597, 1353, 1166.

5.5.3. Bicyclic enamide 48. Yield=71%. Pale yellow oil; ^{1}H NMR (C_6D_6, 400 MHz): 7.76 (d, J=4.2 Hz, 2H), 6.79 (d, J=8.2 Hz, 2H), 3.11 (m, J=2.8 Hz, 2H), 2.94 (s, 2H), 2.20 (br s, 2H), 1.84 (s, 3H), 1.31 (br s, 2H), 0.69 (s, 6H); ^{13}C NMR (C_6D_6, 100 MHz): 143.1 (IV), 137.2 (IV), 132.6 (IV), 129.8 (2C, III), 127.6 (2C, III), 118.9 (IV), 55.9 (II), 36.6 (II), 32.0 (II), 31.6 (IV), 28.5 (II), 26.6 (2C, I), 21.1 (I); IR (neat) cm^{-1}: 2958, 2927, 1696, 1598, 1356, 1163.

5.6. General one-pot procedure (cycloisomerization–ozonolysis)

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed by the freeze-pump-thaw method and the reaction vessel was plunged in a pre-heated oil bath (80 °C). $PtCl_2$ (7 mg, 0.025 mmol, 0.05 equiv) was then added, and the mixture was stirred until the IR spectrum indicated the end of the reaction. The solvent was removed and CH_2Cl_2 (20 mL) was added. The mixture was cooled down to −78 °C and O_3 was allowed to bubble in the solution until the mixture becomes blue. One millilitre of SMe_2 was then added and the mixture was allowed to warm up to rt over 2 h. The solvent was removed and the residue was purified by flash chromatography (pentane/EA 9:1–1:1) to give the desired lactam.

5.6.1. Ketolactam 50. Yield=20%. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.91 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.00 (t, J=5.7 Hz, 2H), 2.68–2.76 (m, 4H), 2.54 (t, J=6.4 Hz, 2H), 2.46 (s, 3H), 2.13–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 211.4 (IV), 172.3 (IV), 145.3 (IV), 135.6 (IV), 129.4 (2C, III), 129.3 (2C, III), 46.6 (II), 46.6 (II), 37.8 (II), 33.0 (II), 27.9 (II), 21.9 (I); IR (neat) cm^{-1}: 2924, 2854, 1694, 1597, 1340, 1157; HRMS: m/z calcd for $C_{14}H_{17}O_4NS$ (MH^+) 318.0776; found 318.0792.

5.6.2. Ketolactam 51. Yield=37%. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.84 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 3.87 (br s, 2H), 2.65 (s, 4H), 2.44 (s, 2H), 2.42 (s, 3H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz):

208.5 (IV), 172.7 (IV), 145.0 (IV), 136.1 (IV), 129.3 (2C, III), 129.2 (2C, III), 56.5 (II), 51.0 (II), 43.7 (II), 37.5 (IV), 32.5 (II), 27.2 (2C, I), 21.8 (I); IR (neat) cm^{-1}: 2966, 1698, 1597, 1345, 1167.

5.6.3. Ketolactam 52. Yield=24%. Pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.79 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 3.74 (s, 2H), 2.60–2.67 (m, 4H), 2.47 (t, J=6.7 Hz, 2H), 2.40 (s, 3H), 1.66 (t, J=6.7 Hz, 2H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.6 (IV), 174.3 (IV), 144.9 (IV), 136.2 (IV), 129.4 (2C, III), 129.1 (2C, III), 54.7 (II), 39.7 (II), 36.9 (II), 36.6 (IV), 33.9 (II), 31.3 (II), 26.8 (2C, I), 21.8 (I); IR (neat) cm^{-1}: 2957, 2871, 1688, 1596, 1348, 1164.

5.7. General one-pot procedure (cycloisomerization–hydrolysis)

In a dry schlenk under argon was introduced 0.5 mmol of ynamide in 20 mL of anhydrous toluene. The reaction medium was degassed during 10 min. 7 mg of $PtCl_2$ (0.025 mmol, 0.05 equiv) were added and the reaction vessel was plunged in a pre-heated oil bath (80 °C). At the end of 10 min, 7 mg of $PtCl_2$ (0.025 mmol, 0.05 equiv) were added. The mixture was stirred until the IR spectrum indicated the end of the reaction. Then, the mixture was quickly cooled to rt with a water bath, and 2.5 mL (2.5 mmol, 5 equiv) of HCl 1 M were added with 20 mL of ethyl acetate. The resulting mixture was stirred during 2 h. The mixture was then neutralized with a saturated solution of $NaHCO_3$, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/EA 6:4) to give the desired cyclobutanone.

5.7.1. Cyclobutanone 53. Yield=65%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=8.5 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 4.63 (t, J=6.3 Hz, 1H), 3.22 (m, 1H), 2.83–3.08 (m, 4H), 2.42 (s, 3H), 2.16 (m, 1H), 1.47–1.66 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.1 (IV), 143.4 (IV), 136.8 (IV), 129.7 (2C, III), 127.0 (2C, III), 59.6 (III), 44.4 (II), 42.8 (II), 27.1 (II), 26.4 (II), 21.5 (I), 16.8 (I); IR (neat) cm^{-1}: 3282, 2925, 1772, 1598, 1325, 1157.

5.7.2. Cyclobutanone 55. Yield=54%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=7.9 Hz, 2H), 7.29 (d, J=7.9 Hz, 2H), 5.22 (t, J=6.1 Hz, 1H), 2.85–3.02 (m, 4H), 2.41 (s, 3H), 1.81 (m, 1H), 1.68 (m, 1H), 1.37–1.56 (m, 4H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 215.7 (IV), 143.4 (IV), 136.9 (IV), 129.7 (2C, III), 127.1 (2C, III), 63.4 (IV), 43.3 (II), 42.2 (II), 32.8 (II), 24.7 (II), 24.0 (II), 21.5 (I), 20.4 (I); IR (neat) cm^{-1}: 3277, 2925, 1769, 1598, 1325, 1155. Anal. Calcd for $C_{15}H_{21}O_3NS$ (295.40): C, 60.99; H, 7.17; N, 4.74. Found: C, 61.01; H, 7.27; N, 4.55.

5.7.3. Cyclobutanone 56. Yield=85%. ^1H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J=8.1 Hz, 2H), 7.30 (d, J=4.1 Hz, 2H), 5.22 (t, J=7.2 Hz, 1H), 3.25 (m, 1H), 3.04 (m, 1H), 2.85 (m, 1H), 2.66 (ABX, 1H), 2.58 (ABX, 1H), 2.22 (m, 1H), 1.73 (dd, J=14.6, 6.8 Hz, 1H), 1.58 (m, 1H), 1.30 (dd, J=14.6, 6.4 Hz, 1H), 0.91 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.6 (IV), 143.3 (IV), 137.3 (IV), 129.8 (2C, III), 127.1 (2C, III), 56.4 (III), 52.6 (II), 44.7 (II), 39.0 (II), 34.1 (IV), 26.1 (I), 24.9 (I), 21.6 (I), 18.9 (II); IR (neat) cm^{-1}: 3281, 3064, 2959, 1772, 1598, 1327, 1157. Anal. Calcd for $C_{16}H_{23}O_3NS$ (309.42): C, 62.11; H, 7.48; N, 4.53. Found: C, 61.97; H, 7.58; N, 4.51.

5.7.4. Aminal 58. Yield=76%. ^1H NMR ($CDCl_3$, 400 MHz): 7.81 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 3.33 (s, 1H), 3.01 (d, J=12.9 Hz, 1H), 2.81 (m, 1H), 2.75 (d, J=12.9 Hz, 1H), 2.45 (s, 3H), 2.35 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.35 (d, J=14.4 Hz, 1H), 1.27 (d, J=14.4 Hz, 1H), 1.17 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 143.4 (IV), 137.8 (IV), 129.5 (2C, III), 127.7 (2C, III), 87.3 (IV), 52.1 (II), 45.7 (II), 44.2 (IV), 33.8 (II), 31.4 (IV), 29.2 (I), 28.1 (II), 27.8 (I), 24.7 (I), 21.6 (I); IR (neat) cm^{-1}: 3506, 3027, 2958, 1603, 1347, 1163.

5.7.5. Cyclobutanone 60. Yield=70%. ^1H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.2 Hz, 2H), 5.25 (t, J=7.1 Hz, 1H), 3.14–3.30 (m, 2H), 2.65 (ABX, 1H), 2.60 (ABX, 1H), 2.41 (s, 3H), 1.82 (t, J=8.1 Hz, 2H), 1.69 (dd, J=14.5, 7.1 Hz, 1H), 1.37 (dd, J=14.5. 7.1 Hz. 1H), 1.18 (d, J=7.6 Hz, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 216.8 (IV), 143.3 (IV), 137.1 (IV), 129.7 (2C, III), 127.0 (2C, III), 53.5 (III), 52.7 (II), 52.2 (III), 39.8 (II), 34.2 (II), 31.2 (II), 25.8 (I), 24.9 (I), 21.6 (I), 15.3 (I); IR (neat) cm^{-1}: 3283, 2960, 1768, 1599, 1327, 1158.

5.7.6. Cyclobutanone 61. Yield=40%. ^1H NMR ($CDCl_3$, 400 MHz): 7.73 (d, J=4.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.78 (t, J=6.9 Hz, 1H), 3.18 (m, 1H), 3.00 (m, 1H), 2.87 (m, 1H), 2.59–2.70 (ABX, 2H), 2.42 (s, 3H), 2.15 (m, 1H), 1.56 (m, 1H), 1.51 (m, 1H), 1.35 (m, 1H), 1.23–1.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.5 (IV), 143.4 (IV), 137.1 (IV), 129.9 (2C, III), 127.2 (2C, III), 60.7 (III), 52.6 (II), 44.6 (II), 36.4 (II), 33.8 (IV), 25.0 (I), 23.8 (II), 21.7 (I), 16.9 (II); IR (neat) cm^{-1}: 3284, 2958, 1773, 1598, 1326, 1158.

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Synthesis of cyclic dienamide using ruthenium-catalyzed ring-closing metathesis of ene–ynamide

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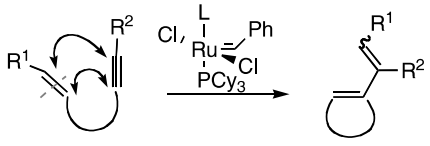
Abstract—Ring-closing metathesis of ene–ynamide, which has alkene and ynamide moieties in a molecule, using a second-generation ruthenium carbene complex produced nitrogen-containing heterocycles, which have a dienamide moiety, in high yields. Diels–Alder reaction of the cyclized product with dienophile proceeded smoothly to give an indole or quinoline derivative in high yield.

1. Introduction

A transition metal carbene complex-catalyzed olefin, enyne, and diyne metatheses are recognized as powerful and useful methodologies in synthetic organic chemistry.[1] Ring-closing metathesis (RCM), ring-opening metathesis (ROM), and cross-metathesis (CM) are now widely used for the synthesis of complex molecules, including natural products and biologically active substances. An intramolecular enyne metathesis is a particularly interesting reaction because carbon–carbon bond formation occurs between the double and triple bonds and the double bond of the enyne is cleaved, and the cleaved alkylidene part of the double bond migrates to the alkyne carbon to afford a cyclized compound having a diene moiety (Scheme 1).[2] We have recently developed enyne metathesis using a Grubbs' ruthenium carbene complex **1** and have reported some applications, including natural product synthesis.[3]



Scheme 1. Ring-closing enyne metathesis.

Ynamide is an interesting moiety because nitrogen is conjugated with an alkyne part.[4] Thus, the metathesis of ene–ynamide, which has an electron-rich ynamide moiety and an alkene moiety in a molecule, is interesting. If the reaction of ene–ynamide **I** with ruthenium carbene complex **1** proceeds, ruthenacyclobutene **III** would be formed and ring opening of **III** would give ruthenium carbene complex **IV**, whose ruthenium carbene would react with an alkene intramolecularly to give ruthenacyclobutane **V**. Ring opening of this would give cyclic dienamide **II**, which should be reactive toward an electron-deficient agent or a dienophile in the Diels–Alder reaction (Scheme 2).[5]

The starting ene–ynamides were synthesized according to the procedure shown in Scheme 3.[6] Coupling reaction of *N*-tosylformamide **2a** and alcohol **3** in the presence of DEAD and PPh_3 followed by treatment with CCl_4 and PPh_3 gave **4a** or **6a**, which was treated with BuLi to give desired ene–ynamides **5a** and **7a** in high yields, respectively. In a similar manner, ene–ynamide **7b** was synthesized from **2a** and alcohol **3c**. Ene–ynamides **5b**, **7c**, and **7d** having an aryl group on an alkyne were synthesized using Negishi-coupling reaction of the alkynylzinc of the terminal alkyne and ArX in the presence of palladium catalyst.[7] An ethoxycarbonyl group on the alkyne of ene–ynamide **5c** was introduced by treatment of **4a** with BuLi and then $ClCO_2Et$. Ene–ynamides *E*-**5d** and *Z*-**5d** having a substituent on the alkene were prepared from **2b** and alcohol *E*-**3d** or *Z*-**3d** by a procedure similar to that used for the synthesis of **5a**, **7a** and **7b**.[8]

Keywords: Ene–ynamide; Dienamide; Enyne metathesis; Indole; Quinoline; Ethylene.
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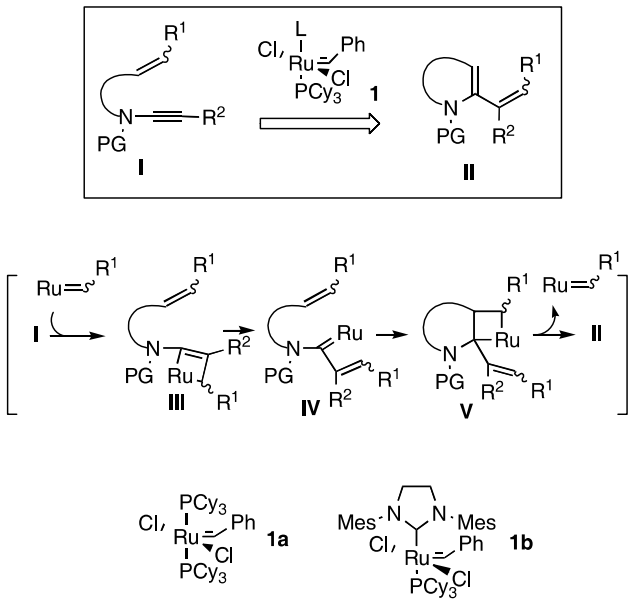


Scheme 2. Plan for synthesis of cyclic dienamide using RCM.

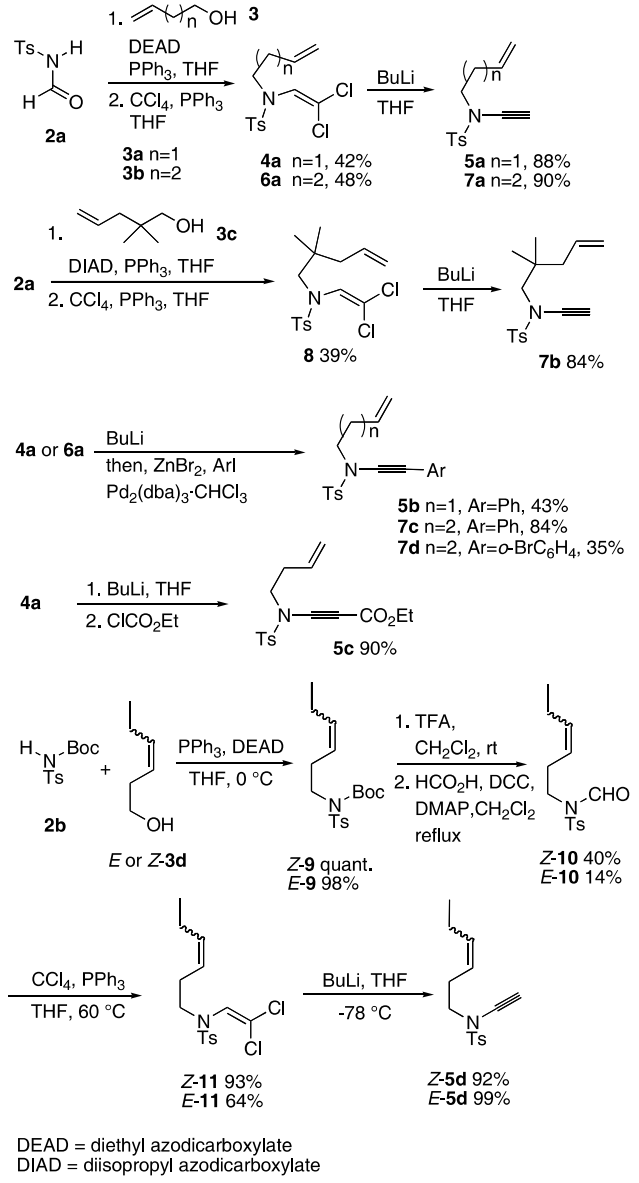
2. Results and discussion

2.1. Synthesis of dihydropyrrolidine derivatives using RCM of ene–ynamide

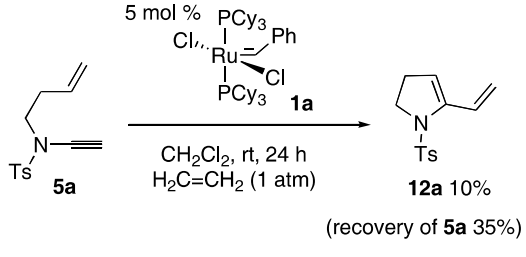
When a CH_2Cl_2 solution of ene–ynamide **5a** was stirred in the presence of 5 mol% of the first-generation ruthenium carbene complex **1a**[9a] under ethylene gas[3e] at rt for 24 h, desired cyclic compound **12a** having a dienamide moiety was obtained in 10% yield along with the starting material in 35% yield. Although the yield was low, it is clear that cyclic dienamide **12a** was obtained from **5a** using RCM (Scheme 4).

To improve the yield of the desired compound, the reaction was carried out under various conditions. The yield of **12a** was further decreased when the CH_2Cl_2 solution was refluxed overnight (entry 2). However, interestingly, the use of the second-generation ruthenium carbene complex **1b**[9b] instead of **1a** improved the yield of **12a** to 66% and the reaction time was shortened (entry 3). Toluene can be used as a solvent, and the reaction was carried out at 80 °C for only 15 min to give **12a** in 83% yield (entry 4).[10] The yield was slightly decreased when the reaction was carried out under argon gas (entry 5) (Table 1).[11]

The substituent effect on the enyne, especially that on the alkyne, was interesting. The substituent effect on the alkyne was first examined. Ene–ynamide **5b** having a phenyl group on the alkyne gave cyclic dienamide **12b** in 85% yield when the reaction was carried out using 10 mol% of **1b** at 80 °C in toluene under ethylene gas. (Table 2, entry 1). Even 5 mol% of the catalyst gave a good result (entry 2). In this case, ethylene gas was effective because the yield was decreased to 31% when the reaction was carried out under argon (entry 3). The electron-withdrawing group on the alkyne tolerates in this reaction and desired cyclic compound **12c** was obtained from **5c** having an ethoxycarbonyl group on the alkyne in 87% yield after only 30 min.



Scheme 3. Synthesis of various ene–ynamides.



Scheme 4. Synthesis of cyclic dienamide.

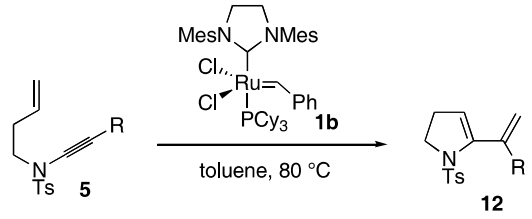
Next, the substituent effect on the alkene was examined. When a toluene solution of ene–ynamide *Z*-**5d** was warmed at 80 °C for 15 min under ethylene gas, surprisingly, cyclic dienamide **12a**, which was previously obtained from **5a**, was obtained in 66% yield. Presumably, the methylidene carbene complex generated from **1b** and ethylene reacts with an alkyne part of *Z*-**5d** to give ruthenacyclobutene **VI**,

Table 1. Ring-closing metathesis of **5a** using **1a** or **1b**[a]

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield of **12a** (%)
1	**1a**	CH_2Cl_2	rt	24	10[b]
2	**1a**	CH_2Cl_2	Reflux	24	7[b]
3	**1b**	CH_2Cl_2	Reflux	4	66
4	**1b**	Toluene	80	0.25	83
5[c]	**1b**	Toluene	80	0.5	76

[a] All reactions were carried out using 5 mol% of the catalyst under ethylene atmosphere except entry 5.
[b] Starting material **5a** was recovered in 35% (run 1) and 36% (run 2) yields, respectively.
[c] The reaction was carried out under Ar.

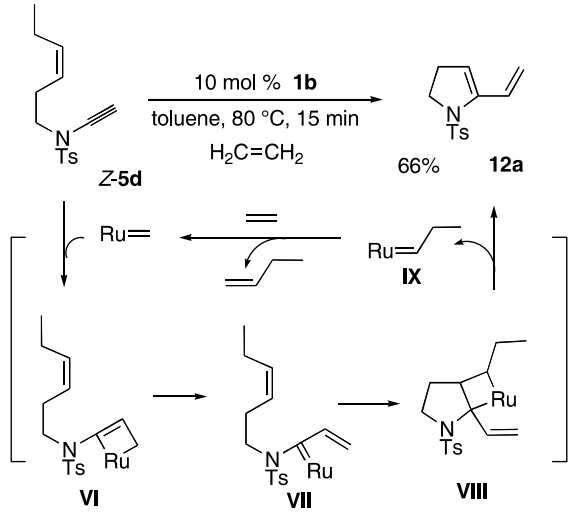
Table 2. Synthesis of various cyclic using **1b**



Entry	R		**1b** (mol%)	Atmosphere	Time (h)	Yield of **12** (%)
1	Ph	**5b**	10	$CH_2{=}CH_2$	0.25	85
2	Ph	**5b**	5	$CH_2{=}CH_2$	0.5	78
3	Ph	**5b**	5	Ar	22	31[a]
4	CO_2Et	**5c**	5	$CH_2{=}CH_2$	0.5	87

[a] Starting material was recovered in 47% yield.

which converts into ruthenium carbene complex **VII**. Then intramolecular reaction occurs to give ruthenacyclobutane **VIII**, whose ring opening gives **12a** and propylidene carbene complex **IX**. However, this complex **IX** would react with ethylene to form methylidene ruthenium carbene complex and propene. Thus, the real species in this reaction would be methylidene ruthenium carbene complex, not propylidene carbene complex **IX**, and **12a** would therefore be formed from *Z*-**5d** (Scheme 5).



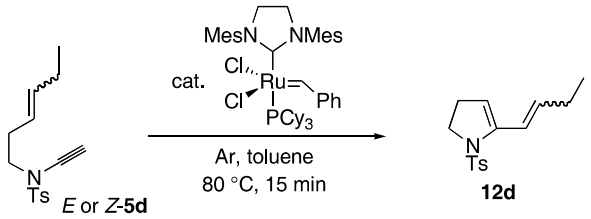
Scheme 5. Synthesis of cyclic dienamide from ene–ynamide having a substituent on alkene.

Thus, the reaction of *Z*-**5d** and **1b** was carried out under argon gas, and a mixture of desired cyclic dienamides *E*-**12d** and *Z*-**12d** was obtained in 39% yield in a ratio to 1 to 1 (Table 3, entry 1). The use of a smaller amount of the catalyst increased the yield of **12d**, and the ratio to *E*- to *Z*- was 1–4.1 (entry 2). However, a longer reaction time did not improve the yield of **12d** (entry 3). From *E*-**5d**, the same compound **12d** was obtained in 48% yield, and the isomeric ratio was 1.5–1. In this case, the use of 5 mol% of the catalyst also increased the yield of **12d** to 57% with a ratio to 1–2.6. These results indicated that a smaller amount of the catalyst improved the yield and that the ratio of the *Z*-isomer of the product was raised, but the reason for this is not clear.

2.2. Synthesis of piperidine derivatives using metathesis of ene–ynamide

Since the synthesis of dihydropyrrole derivative **12** from ene–ynamide **5** was achieved, the reaction of ene–ynamide **7**, which has a one-carbon elongated substituent on nitrogen, using **1b** was carried out. In this case, tetrahydropiperidine derivative **13** would be produced. When a toluene solution of **7a** was warmed in the presence of 5 mol% of **1b** under ethylene gas at 80 °C for 20 h, desired piperidine derivative **13a** was obtained, though the yield was low (entry 1). A lower reaction temperature decreased the yield of **13a** (entry 2). When the solvent was changed from toluene to CH_2Cl_2, the yield of desired compound **13a** was slightly improved (entry 3), and an increase of the amount of the catalyst **1b** to 10 mol% increased the yield of **13a** to 85% (entry 4). The same reaction was carried out under argon gas to afford **13a** in almost the same yield (entry 5). Cyclic dienamide **13b** was obtained from ene–ynamide **7b** using these reaction conditions under ethylene gas in 61% yield (entry 6). Ene–ynamide **7c** having a phenyl group on the alkyne was treated in a similar manner to give cyclic dienamide **13c** in 76% yield (entry 7). In this case, the use of toluene as a solvent improved the yield of **13c** (entry 8).

Table 3. Reaction of *E*-**5d** or *Z*-**5d** with **1b**



Entry	Substrate	cat. (mol%)	Yield (%)	Ratio of **12d** (*E*/*Z*)
1	*Z*-**5d**	10	39	1:1
2	*Z*-**5d**	5	48	1:4.1
3[a]	*Z*-**5d**	5	41	1:5.9
4	*E*-**5d**	10	48	1.5:1
5	*E*-**5d**	5	57	1:2.6

[a] Reaction time, 30 min.

However, ene–ynamide **7d** having an *ortho*-bromophenyl group on the alkyne did not give a good result even when 20 mol% of the catalyst was used due to the steric hindrance (entry 9) (Table 4).

Thus, a cyclic dienamide could be synthesized from ene–ynamide using ring-closing enyne metathesis.

2.3. Synthesis of indole and quinoline derivatives from cyclic dienamide by Diels–Alder reaction

Since the products obtained by the present RCM reaction have a dienamide moiety, they should be good Diels–Alder precursors. A toluene solution of **12a** was warmed at 60 °C in the presence of dimethyl but-2-ynedioate (DMAD) to give tetrahydroindole derivatives **14a** and **14b** in 52% yield in a ratio of 1.3–1. Compound **14b** is an isomerization product of the double bond of **14a**. Since the cyclic dienamide is unstable, a one-pot reaction from ene–ynamide **5a** was examined. A toluene solution of **5a** and 10 mol% of **1b** was stirred under ethylene gas at 80 °C for 15 min, and then DMAD was added after cooling. The toluene solution was warmed at 60 °C for 12 h under argon to give desired indole derivative **14a** in 80% yield. Furthermore, when 1-phenyl-1*H*-pyrrole-2,5-dione was used as a dienophile, tricyclic compound **15** was obtained in 68% yield. In a similar manner, *Z*-**5d** was stirred in the presence of **1b** in toluene, and then to the toluene solution was added DMAD and the whole solution was warmed at 100 °C for 3 h. The resultant product was treated with DDQ in toluene at 80 °C for 20 h to give indoline **16** and indole **17** derivatives in 20 and 12% yields, respectively, via three steps (Scheme 6).

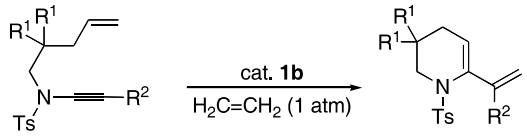
Furthermore, synthesis of quinoline derivatives was examined. A toluene solution of cyclic dienamide **13a** and DMAD was heated at 100 °C for 12 h to give quinoline derivative **18b** in 71% yield. On the other hand, to a toluene solution of the reaction product **13a**, obtained from **7a** using 10 mol% of **1b**, was added DMAD and the solution was heated at 100 °C for 12 h to give quinoline derivative **18a** in 57% yield (Scheme 7).

These results indicated that indole and quinoline derivatives, which are important skeletons in natural products or biologically active substances, could be synthesized from ene–ynamide using RCM followed by Diels–Alder reaction as a one-pot reaction. The reason why the reaction of the isolated product **12a** or **13a** gave isomerization product **14b** or **18b** of the double bond is not clear.

3. Conclusions

Since an alkyne part of ynamide is conjugated with nitrogen, the reactivity of ynamide is very interesting. It was expected that metathesis of enyne containing ynamide would give a cyclic dienamide, whose reactivity is also interesting. Thus, metathesis of enyne containing ynamide was examined. As a result, cyclic dienamides were obtained from ene–ynamide using the second-generation ruthenium carbene

Table 4. Ring-closing metathesis of **7** using catalyst **1b**

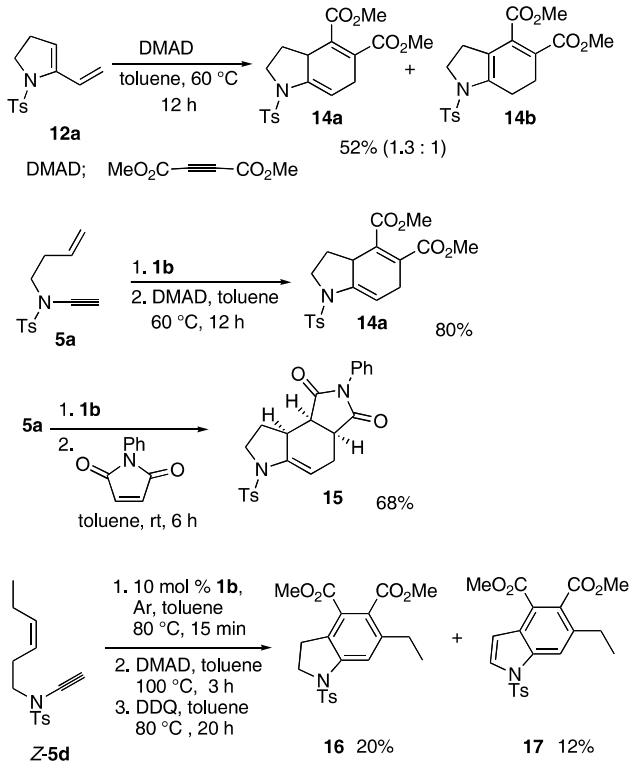


7a R^1=R^2=H
7b R^1=Me, R^2=H
7c R^1=H, R^2=Ph
7d R^1=H, R^2=*o*-BrC_6H_4

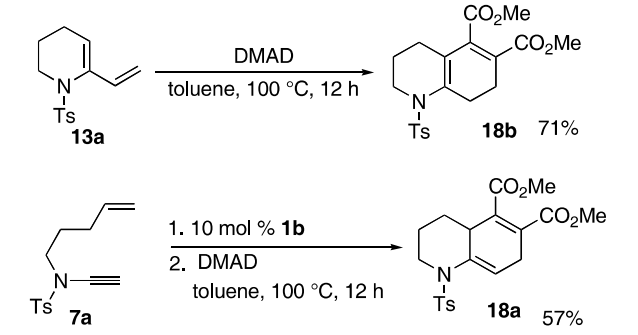
13

Entry	Substrate	**1b** (mol%)	Solvent	Temperature (°C)	Product	Time (h)	Yield (%)
1	**7a**	5	Toluene	80	**13a**	20	22
2	**7a**	5	Toluene	60	**13a**	20	19[a]
3	**7a**	5	CH_2Cl_2	Reflux	**13a**	27	36[a]
4	**7a**	10	CH_2Cl_2	Reflux	**13a**	6	85
5[b]	**7a**	10	CH_2Cl_2	Reflux	**13a**	5	82
6	**7b**	10	CH_2Cl_2	Reflux	**13b**	6	61
7	**7c**	10	CH_2Cl_2	Reflux	**13c**	70	76
8	**7c**	5	Toluene	80	**13c**	0.5	88
9	**7d**	20	Toluene	80	**13d**	41	34[a]

[a] Starting material was recovered in 20% (run 2), 38% (run 3) and 23% (run 9) yields, respectively.
[b] The reaction was carried out under Ar.



Scheme 6. Synthesis of indole derivatives.



Scheme 7. Synthesis of quinoline derivatives.

complex. The cyclic dienamide is good precursor toward the Diels–Alder reaction and afforded an indole or quinoline derivative under mild conditions in high yield. These compounds are important skeletons of natural products or biologically active substances. Further investigations of RCM of ene–ynamide should give various interesting compounds.

4. Experimental

4.1. General

The metathesis reactions were carried out under an atmosphere of ethylene (1 atm) unless otherwise mentioned. All other manipulations were carried out under an atmosphere of argon unless otherwise mentioned. Solvents were distilled under an atmosphere of argon from sodium–benzophenone (toluene) or CaH_2 (CH_2Cl_2). Ethylene gas was purified by passage through the aqueous CuCl solution (2 g of CuCl in 180 mL of saturated NH_4Cl solution) and concentrated H_2SO_4 and then KOH tubes. Ruthenium complexes were purchased from Strem Chemicals or Aldrich Chemical Company. All other solvents and reagents were purified when necessary using standard procedure.

4.2. Typical procedure for the metathesis reaction

A solution of **5a** (91.5 mg, 0.37 mmol) and **1b** (15.6 mg, 0.018 mmol) in toluene was stirred at 80 °C for 15 min under ethylene atmosphere (1 atm). After the solution was cooled to rt, a few drops of ethyl vinyl ether was added. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane/Et_2O/Et_3N 100:5:1) to give **12a** (76.2 mg, 83%) as colorless oil.

4.3. Spectral data of metathesis products

4.3.1. 1-*p*-Toluenesulfonyl-5-vinyl-2,3-dihydro-1*H*-pyrrole (12a). IR (neat) ν 1647, 1589, 1343, 1147 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.10 (ddd, J=8.4, 8.4, 3.0 Hz, 2H), 2.40 (s, 3H), 3.77 (dd, J=8.4, 8.4 Hz, 2H), 5.20 (d, J=10.8 Hz, 1H), 5.35 (dd, J=3.0, 3.0 Hz, 1H), 5.53 (d, J=17.6 Hz, 1H), 6.60 (dd, J=17.6, 10.8 Hz, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.5, 27.5, 50.5, 103.9, 113.5, 117.0, 127.9, 128.8, 129.5, 133.9, 143.6; EI-LRMS m/z 249 (M^+), 184, 155, 91; EI-HRMS m/z calcd for $C_{13}H_{15}O_2NS$ (M^+) 249.0823, found 149.0831.

4.3.2. 5-(1-Phenyl-vinyl)-1-*p*-toluenesulfonyl-2,3-dihydro-1*H*-pyrrole (12b). IR (KBr) ν 1597 (w), 1350 (m), 1167 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.12 (dt, J=2.9, 8.3 Hz, 2H), 2.42 (s, 3H), 3.95 (t, J=8.3 Hz, 2H), 5.48 (t, J=2.9 Hz, 1H), 5.50 (s, 2H), 7.25–7.43 (m, 7H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.5, 28.0, 51.2, 116.5, 119.8, 127.1, 127.7, 127.8, 128.1, 129.4, 134.6, 138.9, 142.2, 143.6, 144.5; EI-LRMS m/z 325 (M^+), 260, 246, 186, 168, 103, 91; EI-HRMS m/z calcd for $C_{19}H_{19}O_2NS$ (M^+) 325.1137, found 325.1147.

4.3.3. Ethyl 2-(1-*p*-toluenesulfonyl-4,5-dihydro-1*H*-pyrrol-2-yl)-acrylate (12c). IR (KBr) ν 1721 (s), 1598 (m), 1352 (s), 1164 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (t, J=7.1 Hz, 3H), 2.18 (dt, J=2.8, 8.7 Hz, 2H), 2.43 (s, 3H), 3.85 (t, J=8.7 Hz, 2H), 4.31 (q, J=7.1 Hz, 2H), 5.44 (t, J=2.8 Hz, 1H), 5.88 (d, J=1.3 Hz, 1H), 6.29 (d, J=1.3 Hz, 1H), 7.30 (d, J=8.2 Hz, 2H), 7.66 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 21.5, 28.0, 50.2, 61.2, 118.4, 127.2, 127.8, 129.5, 133.9, 134.8, 140.6, 143.7, 165.2; EI-LRMS m/z 321 (M^+), 276, 182, 166, 155, 120, 92; EI-HRMS m/z calcd for $C_{16}H_{19}O_4NS$ (M^+) 321.1035, found 321.1010.

4.3.4. 5-But-1-enyl-1-*p*-toluenesulfonyl-2,3-dihydro-1*H*-pyrrole (12d). IR (neat) ν 2964, 1598, 1351, 1164 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.03 (t, J=7.4 Hz, 1.5H), 1.09 (t, J=7.4 Hz, 1.5H), 2.08–2.31 (m, 4H), 2.42 (s, 3H), 3.76 (t, J=8.2 Hz, 1H), 3.78 (t, J=7.8 Hz, 1H), 5.10 (t, J=2.8 Hz, 0.5H), 5.22 (t, J=2.8 Hz, 0.5H), 5.73 (dt, J=11.5, 7.1 Hz, 0.5H), 6.07 (dt, J=15.8, 6.3 Hz, 0.5H), 6.24

(m, 1H), 7.27 (m, 2H), 7.69 (m, 2H); EI-LRMS *m/z* 277 (M^+), 198, 184, 155, 122, 91; EI-HRMS *m/z* calcd for $C_{15}H_{19}O_2NS$ (M^+) 277.1136, found 277.1144.

4.3.5. 1-*p*-Toluenesulfonyl-6-vinyl-1,2,3,4-tetrahydropyridine (13a). IR (neat) ν 1654, 1343, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.30 (m, 2H), 1.90–1.97 (m, 2H), 2.42 (s, 3H), 3.58–3.63 (m, 2H), 5.04 (d, J=10.7 Hz, 1H), 5.39 (d, J=17.2 Hz, 1H), 5.50 (dd, J=4.0, 4.0 Hz, 1H), 6.51 (dd, J=17.2, 10.7, 1 Hz), 7.27 (d, J=8.5 Hz, 2H), 7.63 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.6, 22.8, 46.4, 112.8, 116.0, 127.2, 129.4, 136.4, 136.5, 137.6, 143.3; EI-LRMS *m/z* 263 (M^+), 198, 155, 108, 91; EI-HRMS *m/z* calcd for $C_{14}H_{17}O_2NS$ (M^+) 263.0980, found 263.0965.

4.3.6. 3,3-Dimethyl-1-*p*-toluenesulfonyl-6-vinyl-1,2,3,4-tetrahydro-pyridine (13b). IR (neat) ν 1635, 1598, 1349, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 6H), 1.83 (d, J=3.8 Hz, 2H), 2.41 (s, 3H), 3.34 (s, 2H), 4.98 (d, J=10.6 Hz, 1H), 5.13 (t, J=3.8 Hz, 1H), 5.32 (d, J=16.9 Hz, 1H), 6.47 (dd, J=16.9, 10.6 Hz, 1H), 7.26 (d, J=8.0 Hz, 2H), 7.68 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.4, 29.5, 37.5, 56.9, 110.0, 114.3, 127.0, 129.4, 134.3, 136.4, 138.2, 143.0; EI-LRMS *m/z* 291 (M^+), 276, 262, 248, 155, 136, 91; EI-HRMS *m/z* calcd for $C_{16}H_{21}O_2NS$ (M^+) 291.1293, found 291.1289.

4.3.7. 6-(1-Phenyl-vinyl)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-pyridine (13c). IR (KBr) ν 1599 (w), 1357 (m), 1166 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.52–1.62 (m, 2H), 2.12 (dt, J=3.8, 6.8 Hz, 2H), 2.37 (s, 3H), 3.48–3.53 (m, 2H), 5.30 (d, J=1.6 Hz, 1H), 5.35 (d, J=1.6 Hz, 1H), 5.61 (t, J=3.8 Hz, 1H), 7.14 (d, J=8.2 Hz, 2H), 7.27–7.33 (m, 5H), 7.40 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.5, 21.3, 22.8, 46.2, 113.8, 120.6, 127.2, 127.3, 127.3, 127.8, 129.2, 136.5, 138.5, 139.6, 143.1, 149.1; EI-LRMS *m/z* 339 (M^+), 274, 184, 170, 156, 142, 130, 103, 91; EI-HRMS *m/z* calcd for $C_{20}H_{21}O_2NS$ (M^+) 339.1293, found 339.1292.

4.3.8. 6-[1-(2-Bromo-phenyl)-vinyl]-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-pyridine (13d). IR (neat) ν 1598 (m), 1348 (s), 1165 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.48–1.58 (m, 2H), 2.06 (dt, J=4.0, 6.9 Hz, 2H), 2.39 (s, 3H), 3.42–3.46 (m, 2H), 5.17 (d, J=1.3 Hz, 1H), 5.60 (d, J=1.3 Hz, 1H), 5.71 (t, J=4.0 Hz, 1H), 7.15 (ddd, J=1.8, 7.4, 7.9 Hz, 1H), 7.18 (d, J=8.2 Hz, 2H), 7.29 (ddd, J=1.3, 7.4, 7.5 Hz, 1H), 7.42 (d, J=8.2 Hz, 2H), 7.51 (dd, J=1.8, 7.5 Hz, 1H), 7.54 (dd, J=1.3, 7.9 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.3, 21.5, 22.8, 46.2, 117.1, 122.9, 123.4, 127.1, 127.6, 128.6, 129.4, 132.7, 133.6, 136.8, 138.6, 140.9, 143.4, 148.3; EI-LRMS *m/z* 419 (M^+, ^{81}Br), 417 (M^+, ^{79}Br), 338, 274, 262, 182, 91; EI-HRMS *m/z* calcd for $C_{20}H_{20}O_2NS^{81}Br$ (M^+) 419.0378, found 419.0361, *m/z* calcd for $C_{20}H_{20}O_2NS^{79}Br$ (M^+) 417.0398, found 419.0362.

4.4. Procedure for the synthesis of 5 and 7

4.4.1. *N*-But-3-enyl-*N*-(2,2-dichlorovinyl)-*p*-toluenesulfonamide (4a). To a solution of **2a** (2.9 g, 14 mmol) in THF (29 mL) were added PPh_3 (4.9 g, 19 mmol), **3a** (1.5 mL, 17 mmol) and DEAD (2.7 mL, 17 mmol) at 0 °C, and the mixture was stirred at rt for 14 h. After the solvent was evaporated, the residue was purified by short column chromatography on silica gel (hexane/AcOEt 10:1) to give an inseparable mixture of *N*-alkylated product and *O*-alkylated product (2.9 g, in the ratio of 1.3:1). To a solution of the above mixture (2.9 g) in THF (38 mL) were added PPh_3 (9.0 g, 35 mmol) and CCl_4 (11 mL, 115 mmol) at rt, and the mixture was stirred at 60 °C for 6 h. To the mixture was added saturated $NaHCO_3$ solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 20:1) to give **4a** (1.9 g, 42%, two steps) as a colorless crystal. Mp 53–55 °C; IR (Nujol) ν 1642, 1597, 1357, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (dt, J=6.8, 7.3 Hz, 2H), 2.44 (s, 3H), 3.41 (t, J=7.3 Hz, 2H), 5.05 (d, J=10.2 Hz, 1H), 5.08 (d, J=17.0 Hz, 1H), 5.70 (ddt, J=17.0, 10.2, 6.8 Hz, 1H), 6.31 (s, 1H), 7.32 (d, J=8.1 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 32.9, 48.5, 117.4, 124.1, 124.7, 127.1, 129.7, 133.9, 135.3, 144.0; EI-LRMS *m/z* 319 (M^+), 278, 223, 164, 155, 91; EI-HRMS *m/z* calcd for $C_{13}H_{15}O_2NS^{35}Cl_2$ (M^+) 319.0200, found 319.0190.

4.4.2. *N*-But-3-enyl-*N*-ethynyl-*p*-toluenesulfonamide (5a). To a solution of **4a** (200 mg, 0.64 mmol) in THF (12 mL) was added BuLi (1.58 M solution in hexane, 0.87 mL, 1.37 mmol) at −78 °C, and the solution was stirred for 1 h. To the solution was added saturated NH_4Cl solution, and the aqueous solution was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 5:1) to give **5a** (137.1 mg, 88%) as colorless oil. IR (Nujol) ν 3260, 2150, 1374, 1167 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.40 (dt, J=7.3, 7.6 Hz, 2H), 2.46 (s, 3H), 2.75 (s, 1H), 3.38 (t, J=7.6 Hz, 2H), 5.05 (d, J=10.2 Hz, 1H), 5.10 (d, J=17.3 Hz, 1H), 5.71 (ddt, J=17.3, 10.2, 7.3 Hz, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.81 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.6, 32.0, 50.5, 59.4, 75.9, 117.8, 127.6, 129.8, 133.4, 134.6, 144.7; EI-LRMS *m/z* 248 (M^+-H), 184, 155, 96, 55; EI-HRMS *m/z* calcd for $C_{13}H_{14}O_2NS$ (M^+-H) 248.0745, found 248.0736.

4.4.3. *N*-(2,2-Dichloro-vinyl)-*N*-pent-4-enyl-*p*-toluenesulfonamide (6a). A crude product, which was obtained from **2a** (3.44 g, 17 mmol), PPh_3 (6.34 g, 24 mmol), **3b** (2.4 mL, 23 mmol) and DEAD (10.2 mL, 22 mmol), was purified by short column chromatography on silica gel (hexane/AcOEt 5:1) to give an inseparable mixture of *N*-alkylated product and *O*-alkylated product (4.46 g, in the ratio of 1.8:1). To a solution of the above mixture (4.46 g) and PPh_3 (11.32 g, 43 mmol) in THF (38 mL) was added CCl_4 (14 mL, 142 mmol) at 60 °C for 3 h, and the mixture was stirred continuously at 60 °C for 12 h. To the mixture was added saturated $NaHCO_3$ solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 10:1) to give

6a (2.79 g, 48%, two steps) as a colorless crystal. Mp 73–75 °C; IR (Nujol) ν 1638, 1597, 1351, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (tt, J=7.4, 7.4 Hz, 2H), 2.08 (dt, J=6.8, 7.4 Hz, 2H), 2.44 (s, 3H), 3.32 (t, J=7.4 Hz, 2H), 4.99 (d, J=10.2 Hz, 1H), 5.02 (d, J=16.9 Hz, 1H), 5.75 (ddt, J=16.9, 10.2, 6.8 Hz, 1H), 6.26 (s, 3H), 7.32 (d, J=8.1 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 27.5, 30.5, 48.6, 115.3, 124.6, 124.7, 127.0, 129.7, 135.0, 136.9, 144.0; EI-LRMS m/z 333 (M^+), 318, 298, 278, 237, 178, 91; EI-HRMS m/z calcd for $C_{14}H_{17}O_2NS^{35}Cl_2$ (M^+) 333.0357, found 333.0354.

4.4.4. *N*-Ethynyl-*N*-pent-4-enyl-*p*-toluenesulfonamide (7a). In a similar manner to that for the synthesis of **5a** from **4a**, **7a** (262 mg, 99%) was synthesized from **6a** (347 mg, 1.0 mmol) and BuLi (1.66 M solution in hexane, 1.4 mL, 2.3 mmol). IR (neat) ν 3297, 2132, 1641, 1597, 1364, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (tt, J=7.2, 7.2 Hz, 2H), 2.09 (dt, J=6.6, 7.2 Hz, 2H), 2.45 (s, 3H), 2.73 (s, 1H), 3.31 (*t*, J=7.2 Hz, 2H), 4.99 (d, J=10.1 Hz, 1H), 5.02 (d, J=16.9 Hz, 1H), 5.75 (ddt, J=16.9, 10.1, 6.6 Hz, 1H), 7.35 (d, J=8.3 Hz, 2H), 7.80 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 26.8, 30.2, 50.6, 59.1, 75.9, 115.5, 127.4, 129.6, 134.3, 136.8, 144.6; FAB-LRMS m/z 264 (M^++H), 237, 198, 155, 108, 91; FAB-HRMS m/z calcd for $C_{14}H_{18}O_2NS$ 264.1058 (M^++H), found 264.1034.

4.4.5. *N*-(2,2-Dichloro-vinyl)-*N*-(2,2-dimethyl-pent-4-enyl)-*p*-toluenesulfonamide (8). To a solution of **2a** (1.6 g, 8.0 mmol) in THF (26 mL) were added PPh_3 (2.5 g, 20 mmol), **3c** (1.1 g, 9.6 mmol) and DIAD (1.9 mL, 9.7 mmol) at 0 °C, and the mixture was stirred at 50 °C for 16 h. After the solvent was evaporated, the residue was purified by short column chromatography on silica gel (hexane/AcOEt 10:1) to give an inseparable mixture of *N*-alkylated product and *O*-alkylated product (1.5 g, in the ratio of 1:1.4). To a solution of the above mixture (1.5 g) in THF (17 mL) were added PPh_3 (1.0 g, 15 mmol) and CCl_4 (4.9 mL, 51 mmol) at rt, and the mixture was stirred at 60 °C for 24 h. To the mixture was added saturated $NaHCO_3$ solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 20:1) to give **8** (675 mg, 23%, two steps) as colorless oil. IR (Nujol) ν 1638, 1598, 1358, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 6H), 2.03 (d, J=7.3 Hz, 2H), 2.44 (s, 3H), 3.02 (s, 2H), 5.02 (d, J=16.9 Hz, 1H), 5.05 (d, J=9.2 Hz, 1H), 5.77 (ddt, J=16.9, 9.2, 7.3 Hz, 1H), 7.32 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.3, 35.4, 44.6, 59.8, 117.7, 127.2, 127.3, 127.7, 129.7, 134.1, 135.1, 143.9.

4.4.6. *N*-(2,2-Dimethyl-pent-4-enyl)-*N*-ethynyl-*p*-toluenesulfonamide (7b). In a similar manner to that for the synthesis of **5a** from **4a**, **7b** (247 mg, 84%) was synthesized from **8** (366 mg, 1.0 mmol) and BuLi (1.66 M solution in hexane, 1.4 mL, 2.3 mmol). IR (neat) ν 3302, 2134, 1638, 1597, 1367, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 6H), 2.10 (d, J=7.5 Hz, 2H), 2.23 (s, 3H), 2.68 (s, 1H), 3.13 (s, 2H), 5.03 (d, J=10.3 Hz, 1H), 5.04 (d, J=16.9 Hz, 1H), 5.81 (ddt, J=16.9, 10.3, 7.5 Hz, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.79 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 25.1, 35.9, 44.4, 58.3, 61.6, 78.6, 117.9, 127.6, 129.5, 135.1, 134.2, 144.6; EI-LRMS m/z 291 (M^+), 290, 276, 262, 250, 155, 136, 91; EI-HRMS m/z calcd for $C_{16}H_{21}O_2NS$ (M^+) 291.1293, found 291.1287.

4.4.7. *N*-But-3-enyl-*N*-phenylethynyl-*p*-toluenesulfonamide (5b). To a solution of **4a** (300 mg, 0.94 mmol) in THF (6 mL) was added BuLi (1.58 M solution in hexane, 1.3 mL, 2.1 mmol) at −78 °C, and the mixture was stirred for 1 h. Then, a solution of $ZnBr_2$ (253 mg, 1.12 mmol) in THF (4 mL) was added via syringe and the solution was stirred at rt for 30 min. The whole mixture was transferred via cannula to a solution of $Pd_2dba_3\cdot CHCl_3$ (48.5 mg, 0.05 mmol), PPh_3 (49.1 mg, 0.19 mmol) and iodobenzene (0.13 mL, 1.12 mmol) in THF (5 mL), and the solution stirred at rt for 18 h. The volatiles were removed and the residue was dissolved in AcOEt (30 mL). The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt/Et_3N 250:50:3) to give **5b** (130.4 mg, 43%). IR (neat) ν 2235 (s), 1598 (m), 1367 (s), 1171 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.41–2.50 (m, 2H), 2.45 (s, 3H), 3.47 (t, J=7.3 Hz, 2H), 5.06 (dd, J=1.4, 10.2 Hz, 1H), 5.11 (dd, J=1.4, 17.1 Hz, 1H), 5.75 (ddt, J=10.2, 17.1, 6.9 Hz, 1H), 7.27–7.39 (m, 7H), 7.84 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.6, 32.2, 50.9, 70.9, 82.1, 117.7, 122.8, 127.7, 127.8, 128.2, 129.7, 131.3, 133.6, 134.5, 144.6; EI-LRMS m/z 325 (M^+), 260, 233, 186, 170, 155, 128, 105, 91; EI-HRMS m/z calcd for $C_{19}H_{19}O_2NS$ (M^+) 325.1137, found 325.1138.

4.4.8. *N*-Pent-4-enyl-*N*-phenylethynyl-*p*-toluenesulfonamide (7c). In a similar manner to that for the synthesis of **5b** from **4a**, **7c** (260 mg, 84%) was synthesized from **6a** (303 mg, 0.91 mmol), BuLi (1.58 M solution in hexane, 1.3 mL, 2.0 mmol), $ZnBr_2$ (245 mg, 1.08 mmol), $Pd_2dba_3\cdot CHCl_3$ (46.9 mg, 0.05 mmol), PPh_3 (47.9 mg, 0.18 mmol) and iodobenzene (0.12 mL, 1.09 mmol). IR (neat) ν 2236 (s), 1598 (m), 1367 (s), 1171 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.75–1.87 (m, 2H), 2.08–2.18 (m, 2H), 2.45 (s, 3H), 3.41 (t, J=7.2 Hz, 2H), 4.97–5.09 (m, 2H), 5.78 (ddt, J=10.2, 16.8, 6.6 Hz, 1H), 7.26–7.39 (m, 7H), 7.84 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.6, 27.1, 30.2, 51.0, 70.6, 82.3, 115.6, 122.8, 127.6, 127.7, 128.2, 129.7, 131.3, 134.4, 137.0, 144.6; EI-LRMS m/z 339 (M^+), 274, 184, 170, 142, 130, 116, 105, 91; EI-HRMS m/z calcd for $C_{20}H_{21}O_2NS$ (M^+) 339.1293, found 339.1317.

4.4.9. *N*-(2-Bromo-phenylethynyl)-*N*-pent-4-enyl-*p*-toluenesulfonamide (7d). In a similar manner to that for the synthesis of **5b** from **4a**, **7d** (142.5 mg, 35%) was synthesized from **6a** (329.6 mg, 0.99 mmol), BuLi (1.60 M solution in hexane, 1.4 mL, 2.17 mmol), $ZnBr_2$ (266.5 mg, 1.18 mmol), $Pd_2dba_3\cdot CHCl_3$ (51.0 mg, 0.05 mmol), PPh_3 (51.7 mg, 0.20 mmol) and 2-bromo-iodobenzene (0.15 mL, 1.18 mmol). IR (neat) ν 2236 (s), 1597 (m), 1369 (s), 1172 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.86 (tt, J=7.1, 7.3 Hz, 2H), 2.14 (dt, J=6.6, 7.3 Hz, 2H), 2.45 (s, 3H), 3.45 (t, J=7.1 Hz, 2H), 4.99 (d, J=10.2 Hz, 1H), 5.05

(d, J=16.8 Hz, 1H), 5.78 (ddt, J=10.2, 16.8, 6.6 Hz, 1H), 7.11 (dd, J=7.6, 7.9 Hz, 1H), 7.24 (dd, J=7.6, 7.6 Hz, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.39 (d, J=7.6 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.88 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.7, 27.0, 30.3, 51.1, 70.0, 86.8, 115.6, 124.6, 125.2, 126.9, 127.7, 128.6, 129.8, 132.3, 132.5, 134.6, 137.1, 144.7; EI-LRMS m/z 419 (M^+, ^{81}Br), 417 (M^+, ^{79}Br), 354, 338, 274, 262, 182, 91; EI-HRMS m/z calcd for $C_{20}H_{20}O_2NS^{81}Br$ (M^+) 419.0378, found 419.0367, m/z calcd for $C_{20}H_{20}O_2NS^{79}Br$ (M^+) 417.0398, found 419.0389.

4.4.10. Ethyl (but-3-enyl-*p*-toluenesulfonyl-amino)-propiolate (5c). To a solution of **4a** (220.4 mg, 0.69 mmol) in THF (14 mL) was added BuLi (1.58 M solution in hexane, 0.96 mL, 1.51 mmol) at −78 °C. After the stirring for 1 h, $ClCO_2Et$ (0.13 mL, 1.38 mmol) was added, and the mixture was stirred at −50 °C for 0.5 h. To the mixture was added saturated NH_4Cl solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt/Et_3N 80:20:1) to give **5c** (199.5 mg, 90%). IR (neat) ν 2218 (s), 1705 (s), 1597 (m), 1376 (s), 1175 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H), 2.41 (dt, J=6.8, 7.4 Hz, 2H), 2.47 (s, 3H), 3.49 (t, J=7.4 Hz, 2H), 4.23 (q, J=7.1 Hz, 2H), 5.05 (dd, J=1.4, 10.2 Hz, 1H), 5.09 (dd, J=1.4, 17.0 Hz, 1H), 5.67 (ddt, J=10.2, 17.0, 6.8 Hz, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.82 (d, J=8.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 21.6, 32.1, 50.5, 61.4, 67.9, 82.1, 118.3, 127.7, 130.0, 132.8, 134.1, 145.5, 154.0; EI-LRMS m/z 321 (M^+), 276, 256, 242, 228, 184, 155, 91; EI-HRMS m/z calcd for $C_{16}H_{19}O_4NS$ (M^+) 321.1035, found 321.1059.

4.4.11. (*Z*)-*N*-Formyl-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*Z*)-10). To a solution of (*Z*)-**9** (1.98 g, 5.60 mmol) in CH_2Cl_2 (11 mL) was added TFA (2.1 mL, 27.7 mmol) at 0 °C, and the mixture was stirred at rt for 3 h. The mixture was extracted with AcOEt, and the organic layer was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 3:1) to give (*Z*)-*N*-hex-3-enyl-*p*-toluenesulfonamide (1.36 g, 96%) as colorless oil. To a solution of (*Z*)-*N*-hex-3-enyl-*p*-toluenesulfonamide (1.26 g, 4.97 mmol), DMAP (0.218 mg, 1.78 mmol) and formic acid (0.39 mL, 10.4 mmol) in CH_2Cl_2 (26 mL) was added DCC (2.66 g, 13.2 mL) at 0 °C, and the mixture was refluxed for 18 h. Undissolved materials were removed by filtration through the Celite pad, and filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 5:1) to give (*Z*)-**10** (0.59 g, 40%, two steps) as colorless oil along with recovered (*Z*)-*N*-hex-3-enyl-*p*-toluenesulfonamide (0.70 g, 56%). IR (neat) ν 2934, 1701, 1597, 1359, 1166 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, J=7.5 Hz, 3H), 2.00 (dq, J=6.7, 7.5 Hz, 2H), 2.27 (dt, J=7.5, 7.9 Hz, 2H), 2.46 (s, 3H), 3.40 (t, J=7.9 Hz, 2H), 5.19 (dt, J=10.7, 6.7 Hz, 1H), 5.45 (dt, J=10.7, 7.5 Hz, 1H), 7.37 (d, J=8.2 Hz, 2H), 7.75 (d, J=8.2 Hz, 2H), 9.10 (s, 1H); EI-LRMS m/z 281 (M^+), 184, 155, 126, 91, 82; EI-HRMS m/z calcd for $C_{14}H_{19}O_3NS$ (M^+) 281.1086, found 281.1104.

4.4.12. (*E*)-*N*-Formyl-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*E*)-10). In a similar manner to that for the synthesis of (*Z*)-**10** from (*Z*)-**9**, (*E*)-**10** (0.21 g, 14%, two steps) was synthesized from (*E*)-**9** (2.51 g, 7.10 mmol), TFA (2.5 mL, 34.1 mmol), DMAP (0.12 g, 1.01 mmol), Formic acid (0.57 mL, 15.2 mmol) and DCC (3.09 g, 15.2 mmol), and (*E*)-*N*-hex-3-enyl-*p*-toluenesulfonamide (0.94 g, 73%) was recovered. Colorless oil; IR (neat) ν 2934, 1705, 1597, 1360, 1166 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, J=7.5 Hz, 3H), 1.95 (dq, J=6.9, 7.5 Hz, 2H), 2.20 (dt, J=6.2, 7.7 Hz, 2H), 2.46 (s, 3H), 3.45 (t, J=7.7 Hz, 2H), 5.22 (dt, J=15.3, 6.9 Hz, 1H), 5.45 (dtt, J=15.3, 6.2 Hz, 1H), 7.37 (d, J=8.5 Hz, 2H), 7.74 (d, J=8.5 Hz, 2H), 9.08 (s, 1H); EI-LRMS m/z 281 (M^+), 184, 155, 126, 91, 82; EI-HRMS m/z calcd for $C_{14}H_{19}O_3NS$ (M^+) 281.1086, found 281.1106.

4.4.13. (*Z*)-*N*-(2,2-Dichloro-vinyl)-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*Z*)-11). To a solution of (*Z*)-**10** (0.59 g, 2.10 mmol) and PPh_3 (1.72 g, 6.57 mmol) in THF (18 mL) was added CCl_4 (2.11 mL, 21.9 mmol) at 60 °C for 6 h, and the mixture was stirred continuously at 60 °C for 18 h. To the mixture was added saturated $NaHCO_3$ solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt 7:1) to give (*Z*)-**11** (0.67 g, 93%) as a colorless needle. Mp 68–70 °C; IR (KBr) ν 2967, 1597, 1355, 1165 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H), 2.01 (dq, J=6.7, 7.4 Hz, 2H), 2.29 (dt, J=6.8, 7.4 Hz, 2H), 2.44 (s, 3H), 3.38 (t, J=7.4 Hz, 2H), 5.22 (dt, J=12.1, 6.7 Hz, 1H), 5.46 (dt, J=12.1, 6.8 Hz, 1H), 6.37 (s, 1H), 7.32 (d, J=8.2 Hz, 2H), 7.69 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 20.6, 21.6, 26.6, 48.7, 123.5, 123.8, 124.8, 127.2, 129.8, 134.7, 135.7, 144.1; EI-LRMS m/z 347 (M^+), 319, 278, 155, 91; EI-HRMS m/z calcd for $C_{15}H_{19}O_2NS^{35}Cl_2$ (M^+) 347.0514, found 347.0483.

4.4.14. (*E*)-*N*-(2,2-Dichloro-vinyl)-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*E*)-11). In a similar manner to that for the synthesis of (*Z*)-**11** from (*Z*)-**10**, (*E*)-**11** (0.37 g, 64%) was synthesized from (*E*)-**10** (0.47 g, 1.67 mmol), PPh_3 (1.31 g, 5.01 mmol) and CCl_4 (1.61 mL, 16.7 mmol). A colorless needle; mp 60–65 °C; IR (KBr) ν 2969, 1598, 1357, 1161 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (t, J=7.5 Hz, 3H), 1.98 (dq, J=6.6, 7.5 Hz, 2H), 2.21 (dt, J=6.5, 7.5 Hz, 2H), 2.44 (s, 3H), 3.38 (t, J=7.5 Hz, 2H), 5.26 (dt, J=15.3, 6.6 Hz, 1H), 5.52 (dt, J=15.3, 6.5 Hz, 1H), 6.32 (s, 1H), 7.32 (d, J=8.5 Hz, 2H), 7.69 (d, J=8.5 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.6, 21.6, 25.6, 31.9, 49.1, 123.8, 124.3, 124.9, 127.2, 129.8, 135.4, 135.7, 144.1; EI-LRMS m/z 347 (M^+), 319, 278, 155, 91; EI-HRMS m/z calcd for $C_{15}H_{19}O_2NS^{35}Cl_2$ (M^+) 347.0514, found 347.0517.

4.4.15. (*Z*)-*N*-Ethynyl-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*Z*)-5d). In a similar manner to that for the synthesis of **5a** from **4a**, (*Z*)-**5d** (0.46 g, 92%) was synthesized from (*Z*)-**11** (0.63 g, 1.81 mmol) and BuLi (1.58 M solution in hexane, 3.6 mL, 5.70 mmol). A pale yellow oil; IR (neat) ν 3301, 2964, 2137, 1597, 1370, 1171 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (t, J=7.5 Hz, 3H), 2.01

(dq, J=7.2, 7.5 Hz, 2H), 2.38 (dt, J=7.7, 7.5 Hz, 2H), 2.45 (s, 3H), 2.75 (s, 1H), 3.31 (t, J=7.5 Hz, 2H), 5.22 (dt, J=12.1, 7.2 Hz, 1H), 5.46 (dt, J=12.1, 7.7 Hz, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.80 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 20.6, 21.6, 25.7, 50.9, 59.2, 75.9, 123.3, 127.6, 129.8, 134.6, 135.1, 144.7; EI-LRMS *m/z* 276 (M^+), 198, 184, 155, 122, 91; EI-HRMS *m/z* calcd for $C_{15}H_{19}O_2NS$ (M^+) 277.1136, found 277.1122.

4.4.16. (*E*)-*N*-Ethynyl-*N*-hex-3-enyl-*p*-toluenesulfonamide ((*E*)-5d). In a similar manner to that for the synthesis of **5a** from **4a**, (*E*)-**5d** (0.21 g, 99%) was synthesized from (*E*)-**11** (0.27 g, 0.78 mmol) and BuLi (1.58 M solution in hexane, 1.3 mL, 2.10 mmol). Colorless oil; IR (neat) ν 3299, 2963, 2136, 1597, 1369, 1170 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (t, J=7.4 Hz, 3H), 1.96 (dq, J=6.8, 7.4 Hz, 2H), 2.33 (dt, J=7.0, 7.2 Hz, 2H), 2.45 (s, 3H), 2.75 (s, 1H), 3.33 (t, J=7.2 Hz, 2H), 5.26 (dt, J=15.2, 6.8 Hz, 1H), 5.53 (dt, J=15.2, 7.0 Hz, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.80 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.5, 21.6, 25.5, 30.9, 51.1, 59.3, 75.9, 123.6, 127.6, 129.8, 134.7, 135.6, 144.6; EI-LRMS *m/z* 276 (M^+), 198, 184, 155, 91; EI-HRMS *m/z* calcd for $C_{15}H_{19}NO_2S$ (M^+) 277.1136, found 277.1147.

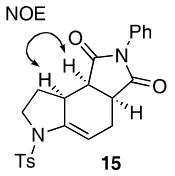
4.5. Typical procedure for the Diels–Alder reaction

A solution of **5a** (55 mg, 0.22 mmol) and **1b** (10 mg, 0.012 mmol) in toluene (7 mL) was refluxed for 30 min under ethylene gas (1 atm). After the reaction solution was cooled to rt, the atmosphere of ethylene gas was replaced by argon gas. To this solution was added DMAD (0.14 mL, 1.2 mmol), and the resulting mixture was stirred at 60 °C for 12 h. After the volatiles were removed under reduce pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt 3:1) to give **14a** (69 mg, 80%, two steps) as colorless oil. (Scheme 6, Eq. 2).

4.6. Spectral data of Diels–Alder products

4.6.1. Dimethyl 1-*p*-toluenesulfonyl-2,3,3a,6-tetrahydro-1*H*-indole-4,5-dicarboxylate (14a). IR (neat) ν 1733, 1646, 1597, 1359, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (dddd, J=11.8, 11.8, 11.3, 8.2 Hz, 1H), 2.15 (ddd, J=11.8, 6.0, 6.0 Hz, 1H), 2.43 (s, 3H), 2.94 (m, 1H), 3.08 (ddd, J=22.5, 11.3, 2.2 Hz, 1H), 3.24 (ddd, J=22.5, 7.0, 5.6 Hz, 1H), 3.35 (ddd, J=10.0, 6.0, 6.0 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.79 (dd, J=10.0, 8.2 Hz, 1H), 5.79 (dd, J=5.6, 2.2 Hz, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.69 (d, J=8.2 Hz, 2H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 21.6, 27.3, 28.8, 39.5, 48.9, 52.3, 52.4, 101.4, 127.2, 133.4, 134.3, 134.7, 136.4, 144.1, 167.3, 167.4; EI-LRMS *m/z* 391 (M^+), 236, 159, 91; EI-HRMS *m/z* calcd for $C_{19}H_{21}O_6NS$ (M^+) 391.1080, found 391.1089.

4.6.2. (3a*S,8a*S**,8b*R**)-2-Phenyl-6-*p*-toluenesulfonyl-4,6,7,8,8a,8b-hexahydro-3a*H*−2,6-diaza-as-indacene-1,3-dione (15).** IR (Nujol) ν 1707, 1348, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (m, 1H), 2.26 (m, 1H), 2.35 (s, 3H), 2.60 (m, 1H), 2.82 (m, 1H), 2.89 (ddd, J=15.6, 7.8, 1.5 Hz, 1H), 3.20 (ddd, J=10.7, 7.3, 1.5 Hz, 1H), 3.29 (dd, J=9.3, 7.3 Hz, 1H), 3.61–3.71 (m, 2H), 5.65 (ddd, J=7.8, 2.0, 2.0 Hz, 1H), 6.95 (d, J=8.3 Hz, 2H), 7.21 (br d, J=8.3 Hz, 2H), 7.34–7.42 (m, 3H), 7.68 (br d, J=8.3 Hz, 2H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 21.3, 21.5, 21.6, 29.4, 39.5, 42.1, 49.0, 115.1, 126.2, 127.3, 128.6, 129.1, 129.9, 131.6, 134.2, 138.8, 143.9, 174.5, 177.1; EI-LRMS *m/z* 422 (M^+), 267, 155, 120, 91; EI-HRMS *m/z* calcd for $C_{23}H_{22}O_4N_2S$ (M^+) 422.1300, found 422.1301. The stereochemistry of **15** was determined by NOE experiment.



15

4.6.3. Dimethyl 6-ethyl-1-*p*-toluenesulfonyl-2,3-dihydro-1*H*-indole-4,5-dicarboxylate (16) and dimethyl 6-ethyl-1-*p*-toluenesulfonyl-1*H*-indole-4,5-dicarboxlate (17). To a solution of diastereoisomeric mixture (22.7 mg, 54.1 μmol) in toluene (2 mL), which was prepared from (*Z*)-**5d**, **1b** and DMAD according to typical procedure, was added DDQ (113 mg, 0.497 mmol), and the mixture was stirred at 80 °C for 20 h. After the volatiles were removed under reduce pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt 3:1) to give **16** (13.7 mg, 20%, three steps) as a colorless crystal and **17** (7.9 mg, 12%, three steps) as pale yellow oil. **16**: IR (KBr) ν 2967, 1729, 1598, 1364, 1167 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, J=7.5 Hz, 3H), 2.39 (s, 3H), 2.68 (q, J=7.5 Hz, 2H), 3.15 (t, J=8.8 Hz, 2H), 3.81 (s, 3H), 3.87 (s, 3H), 3.93 (t, J=8.8 Hz, 2H), 7.26 (d, J=8.1 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H), 7.68 (s, 1H); EI-LRMS *m/z* 417 (M^+), 385, 327, 262, 230, 198, 91; EI-HRMS *m/z* calcd for $C_{21}H_{23}O_6NS$ (M^+) 417.1246, found 417.1259. Compound **17**: IR (neat) ν 2953, 1732, 1597, 1378, 1168 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, J=7.5 Hz, 3H), 2.35 (s, 3H), 2.76 (q, J=7.5 Hz, 2H), 3.92 (s, 6H), 7.13 (d, J=3.7 Hz, 1H), 7.23 (d, J=8.6 Hz, 2H), 7.65 (d, J=3.7 Hz, 1H), 7.70 (d, J=8.6 Hz, 2H), 8.07 (s, 1H); EI-LRMS *m/z* 415 (M^+), 383, 325, 228, 91; EI-HRMS *m/z* calcd for $C_{21}H_{21}O_6NS$ (M^+) 415.1090, found 415.1084.

4.6.4. Dimethyl 1-*p*-toluenesulfonyl-1,2,3,4,4a,7-hexahydro-quinoline-5,6-dicarboxylate (18a). Mp 129 °C (decomp.); IR (Nujol) ν 1724, 1594, 1346, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.55 (m, 2H), 1.75 (br d, J=13.3 Hz, 1H), 1.87 (m, 1H), 2.43 (s, 3H), 2.77 (m, 1H), 3.03 (m, 1H), 3.05 (ddd, J=23.7, 8.3, 3.7 Hz, 1H), 3.20 (ddd, J=23.7, 8.1, 3.8 Hz, 1H), 3.75 (s, 6H), 4.17 (br d, J=13.4 Hz, 1H), 5.83 (ddd, J=3.6, 3.6, 1.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 24.0, 27.7, 30.5, 36.6, 47.8, 52.1, 52.3, 119.5, 126.9, 127.8, 129.6, 133.2, 137.8, 138.4, 143.4, 166.6, 168.0; EI-LRMS *m/z* 405 (M^+), 374, 282, 218, 131, 91; EI-HRMS *m/z* calcd for $C_{20}H_{23}O_6NS$ (M^+) 405.1246, found 405.1226.

4.6.5. Dimethyl 1-*p*-toluenesulfonyl-1,2,3,4,7,8-hexahydro-quinoline-5,6-dicarboxylate (18b). IR (neat) ν 1734, 1708, 1635, 1596, 1343, 1162 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.45–1.54 (m, 2H), 1.96–2.02 (m, 2H), 2.44 (s, 3H), 2.48–2.55 (m, 2H), 2.75–2.85 (m, 2H), 3.63–3.68 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 7.31 (d, $J=8.3$ Hz, 2H), 7.65 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.6, 22.8 (2C), 26.6, 46.5, 52.0, 52.3, 115.3, 120.8, 128.9, 129.8, 136.7, 139.2, 142.0, 144.0, 166.0, 168.8; EI-LRMS *m/z* 405 (M^+), 374, 250, 218, 190, 158; EI-HRMS *m/z* calcd for $C_{20}H_{23}O_6NS$ (M^+) 405.1246, found 405.1234.

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11. When ene–ynamide was used as the substrate, the enyne metathesis of terminal alkyne proceeded smoothly under argon for the first time (cf. Ref. 3e). Recently, RCM of electron-rich terminal alkynes using **1** without ethylene gas has been reported (Ref. 2e,h). We continued to examine the reaction under ethylene gas, since the yield of the cyclized product that was obtained from the reaction under ethylene gas is higher than that of the cyclized product obtained from the reaction under argon.

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Synthesis of 3-(arylmethylene)isoindolin-1-ones from ynamides by Heck–Suzuki–Miyaura domino reactions. Application to the synthesis of lennoxamine

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Abstract—Substituted 3-(arylmethylene)isoindolin-1-ones can be efficiently synthesized from various ynamides and boronic acids by palladium-catalyzed Heck–Suzuki–Miyaura domino reactions. This methodology has been applied to the total synthesis of lennoxamine and a concise route to this isoindolobenzazepine alkaloid was achieved in eight steps from 2,3-dimethoxybenzoic acid via a key intermediate ynamide.

1. Introduction

Substituted 3-methyleneisoindolin-1-ones of type **A**, and in particular those in which R^3 is an aromatic substituent (R^3 = Ar), are encountered in a number of naturally occurring products such as enterocarpam II, a member of the aristolactam alkaloids family[1] or the secophthalide–isoquinoline ene-lactam fumaridine[2] (Fig. 1).

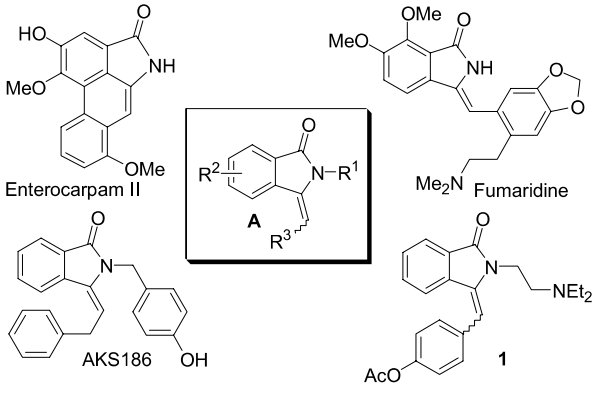

Figure 1. Naturally occurring and/or biologically active substituted 3-methyleneisoindolin-1-ones.

Isoindolin-1-ones of type **A** are also found as the structural feature of biologically active compounds such as AKS186 that displays vasorelaxant properties[3] or compound **1** whose hydrochloride was claimed to exhibit local anesthetic activity superior to that of procaine[4] (Fig. 1).

The synthesis of isoindolin-1-ones of type **A** has elicited considerable synthetic interest as several representative general strategies have been developed (Scheme 1). In the earliest routes [routes (a), Scheme 1], phthalimides of type **B** were often considered as starting materials and were converted to isoindolin-1-ones of type **A** by Wittig reaction with stabilized phosphoranes[5] or addition of organometallic reagents followed by dehydration of the resulting 3-hydroxyphthalimidines.[3,6] However, this approach can lead to a mixture of regioisomers in the case of an unsymmetrical substrate.[3,6] Furthermore, the synthesis of 3-(arylmethylene)-isoindolin-1-ones of type **A** where R^3 = Ar by the latter route requires the use of benzylic Grignard reagents as nucleophiles whose preparation is not always trivial. More recently, an interesting alternative benzylation procedure of phthalimides of type **B**, based on the photodecarboxylation of arylacetates, has been developed.[7] Phthalides of type **C** (or the corresponding open-chain keto-benzoic acids) are also useful precursors since they can be readily converted to compounds of type **A** by treatment with primary amines, followed by dehydration [route (b), Scheme 1].[8] Another general route towards substituted 3-methyleneisoindolin-1-ones of type **A** relies on an ortholithiation–anionic cyclization sequence initiated by treatment of *N*-acyl-2-bromobenzamides of type **D** with

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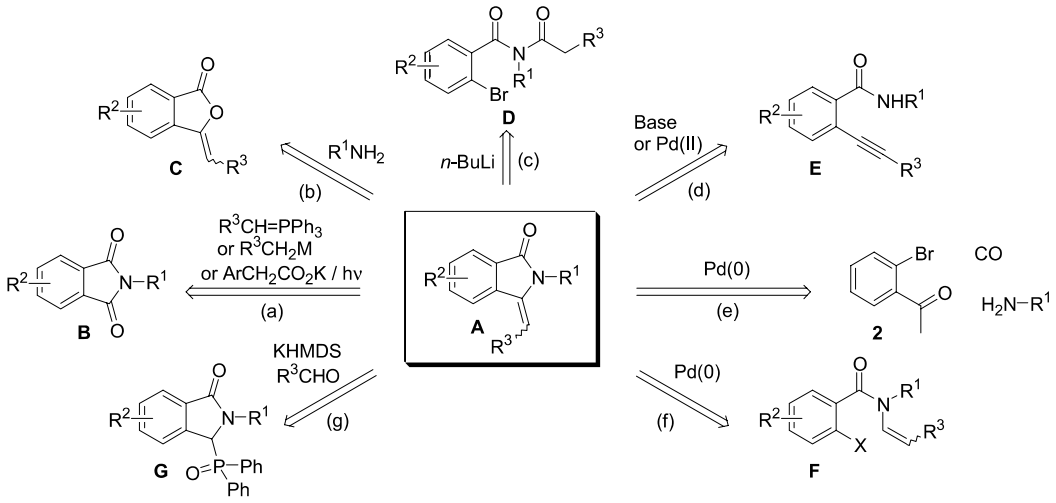
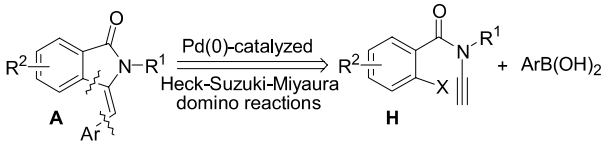


Scheme 1. Representative synthetic strategies towards substituted 3-methyleneisoindolin-1-ones of type **A**.

n-butyllithium, followed by dehydration of the resulting 3-hydroxyphthalimidines [route (c), Scheme 1].[9] Efficient syntheses of isoindolin-1-ones of type **A** have also been achieved by cyclization of 2-alkynylbenzamides of type **E** induced by treatment with a base or a palladium(II) catalyst [route (d), Scheme 1].[10,11] Interestingly, the disubstituted alkynes of type **E** are readily available by Sonogashira cross-coupling reactions involving 2-halobenzamides as substrates and, in some cases, both transformations leading to isoindolin-1-ones of type **A** have been carried out in a one-pot sequence.[10c] A palladium(0)-catalyzed three-component reaction involving 2-bromoacetophenone **2** and a variety of primary amines under carbon monoxide pressure can also be used to synthesize 3-methyleneisoindolin-1-ones of type **A** ($R^3=H$) [route (e), Scheme 1].[12] A related process has been described from 2-bromoaryl ketones wherein a titanium–isocyanate complex was used as the nitrogen donor.[13] Alternative palladium(0)-catalyzed processes towards compounds of type **A** exploit the synthetic potential of intramolecular Heck reactions of enamide derivatives of type **F** [route (f), Scheme 1].[14] Finally, the Horner condensation of 3-(diphenylphosphinoyl)isoindolin-1-ones of type **G** with a variety of aldehydes constitutes a particularly interesting entry to isoindolin-1-ones of type **A** that has culminated with several applications to natural products synthesis [route (g), Scheme 1].[15] Besides these main representative strategies, other reactions leading to isoindolin-1-ones of type **A** have also been reported.[16]

In recent years, the synthetic application of ynamides has expanded enormously.[17] Indeed, these stable electron-deficient variants of ynamines can participate in several transformations usually carried out with alkynes such as thermal, metal- or Lewis acid-catalyzed cycloadditions,[18–21] platinum(II)-catalyzed cycloisomerization,[22] ring-closing metathesis,[23] titanium(II)-mediated coupling reactions,[24] carbocupration,[25] hydroboration[26] and hydrohalogenation[27] followed by cross-coupling reactions, as well as sigmatropic rearrangements.[28] Some radical cyclization cascades involving ynamides as substrates have also been reported as a route to various nitrogen heterocycles, including substituted isoindolin-1-ones of type **A**.[29]

We became interested in the development of an alternative synthetic strategy towards a variety of (*E*)-3-(arylmethylene)isoindolin-1-ones of type **A** that proceeds from ynamides of type **H** and arylboronic acids and relies on Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions (Scheme 2).

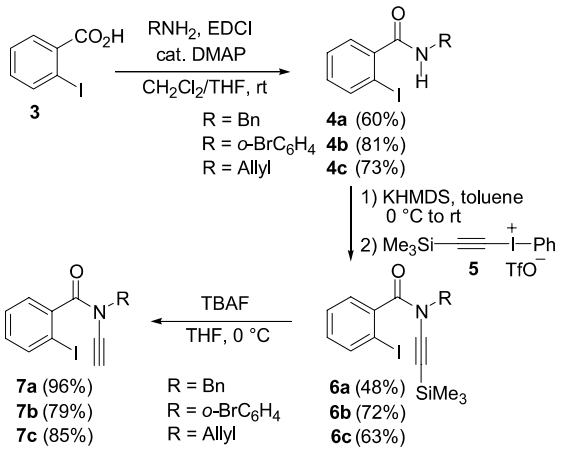


Scheme 2. Synthesis of 3-(arylmethylene)isoindolin-1-ones of type **A** by Heck–Suzuki–Miyaura domino reactions from ynamides of type **H**.

When we began our investigations on this project, hydrostannation[30] and an heteroannulation strategy towards 2-aminoindoles, based on the nucleophilic addition of amines to the triple bond of ynamides activated by an intramolecular arylpalladium(II) complex,[31] were the only reported examples of palladium-catalyzed processes involving ynamides as substrates. Herein, we report a full account of our work on the synthesis of 3-(arylmethylene)-isoindoloin-1-ones by Heck–Suzuki–Miyaura domino reactions involving ynamides,[32] as well as its application to the total synthesis of the natural product lennoxamine.

2. Results and discussion

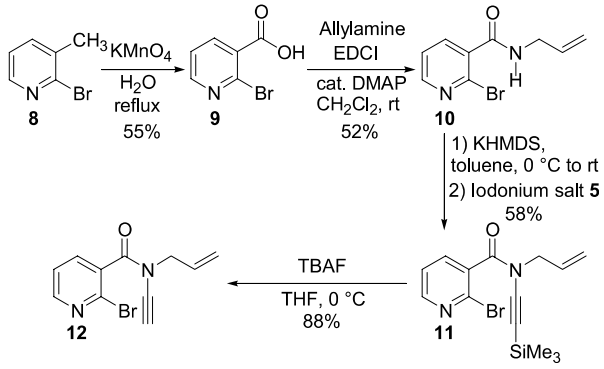
In order to investigate the feasibility of the Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions as a route to isoindolinones of type **A**, several ynamides of type **H** were prepared from 2-iodobenzoic acid **3**. This carboxylic acid was coupled with benzylamine, 2-bromobenzylamine and allylamine *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), cat. DMAP, CH_2Cl_2 or CH_2Cl_2/THF, rt] to afford the corresponding 2-iodobenzamides **4a** (60%), **4b** (81%) and **4c** (73%), respectively. After formation of the potassium amides (KHMDS, toluene, 0 °C to rt) and addition of the alkynyliodonium salt **5**,[33] the trimethylsilyl-substituted ynamides **6a** (48%), **6b** (72%) and **6c** (63%) were obtained in acceptable yields.[18a] Subsequent



Scheme 3. Preparation of ynamides **7a**–**7c**.

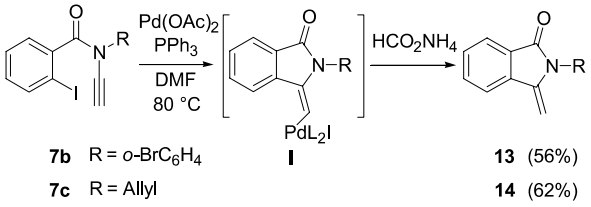
desilylation by using tetra(*n*-butyl)ammonium fluoride (TBAF) in THF finally provided the ynamides **7a** (96%), **7b** (79%) and **7c** (85%), respectively (Scheme 3).

A structurally related ynamide possessing a pyridine ring was also prepared from 2-bromo-3-methylpyridine **8**. This latter compound was oxidized with potassium permanganate to generate 2-bromonicotinic acid **9**[34] (55%) which was coupled with allylamine (EDCI, cat. DMAP, CH_2Cl_2, rt) to afford the corresponding amide **10** (52%). After deprotonation with KHMDS and condensation with trimethylsilyliodonium salt **5**,[33] the resulting ynamide **11** (58%) was desilylated (TBAF, THF, 0 °C) to deliver the terminal ynamide **12** (88%) (Scheme 4).



Scheme 4. Synthesis of ynamide **12** containing a pyridine ring.

Since the planned strategy towards 3-(arylmethylene)-isoindolin-1-ones of type **A** from ynamides of type **H** involved two different Pd(0)-catalyzed steps, it was of interest to initially examine the feasibility of the Heck reaction.[35] Thus, ynamides **7b** and **7c** (Scheme 3) were treated with a catalytic amount of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) in DMF at 80 °C and the reaction was carried out in the presence of ammonium formate (1.5 equiv) as the reducing agent, in order to regenerate the Pd(0) catalyst from the intermediate σ-vinylpalladium complexes of type **I**.[35] Under these conditions, the desired 3-methyleneisoindolin-1-ones **13** and **14**[12] were generated and isolated in 56% and 62% yield, respectively. It is noteworthy that the presence of an arylbromide in substrate **7b** did not alter the course of the reaction, and the carbon–bromine bond in the final product **13** was also unaffected (Scheme 5).



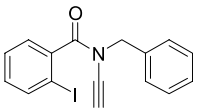
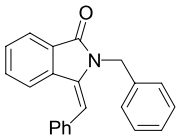
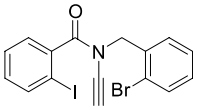
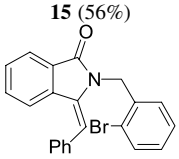
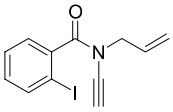
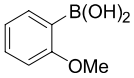
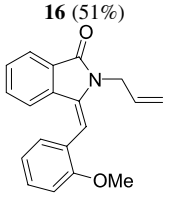
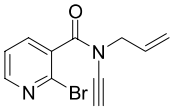
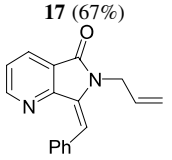
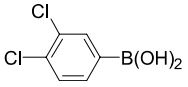
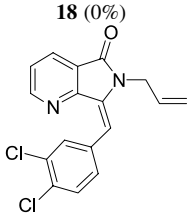
Scheme 5. Reductive Heck reaction applied to ynamides of type **H**.

Having demonstrated that ynamides were viable substrates in carbopalladation processes, the Suzuki–Miyaura coupling reactions[36] of the intermediate σ-vinylpalladium complexes of type **I** could be next examined, with the goal of achieving both processes in a domino fashion from the starting ynamides (Table 1). When ynamide **7a** was treated with benzeneboronic acid in the presence of aqueous sodium hydroxide as the base and a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) in refluxing 1,2-dimethoxyethane (DME), the corresponding 3-benzylideneisoindolin-1-one **15** was obtained in acceptable yield (48%) as a single geometric isomer. Additional experiments revealed that THF was also a suitable solvent for this reaction and other palladium catalysts were then screened. Thus, the use of $Pd(dba)_2$ led to a slightly increased yield of **15** (59%) but the optimal result (70% yield) was obtained when a combination of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) was used to catalyze the reaction. Interestingly, the heterogeneous catalyst Pd/C was also effective and led to the isoindolinone **15** albeit in slightly diminished yield (56%) (Table 1).

The Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions were applied to ynamide **7b** in the presence of benzeneboronic acid and ynamide **7c** in the presence of 2-methoxybenzeneboronic acid, under optimized conditions [$Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), aqueous NaOH, THF, reflux]. The resulting 3-(arylmethylene)-isoindolin-1-ones **16** (51%) and **17** (67%) were obtained in moderate to good yields, as single geometric isomers. Subjecting the ynamide **12**, containing a pyridine ring, to the Heck–Suzuki–Miyaura domino reactions with benzeneboronic acid and 3,4-dichlorobenzeneboronic acid, under the previously optimized conditions, afforded the pyrrolopyridinones **18** (52%) and **19** (68%), respectively. It is worth mentioning that the use of the heterogeneous catalyst Pd/C was unsatisfactory in the case of ynamide **12**, presumably due to poisoning of the catalyst by the nitrogen atom of the pyridine ring (Table 1).

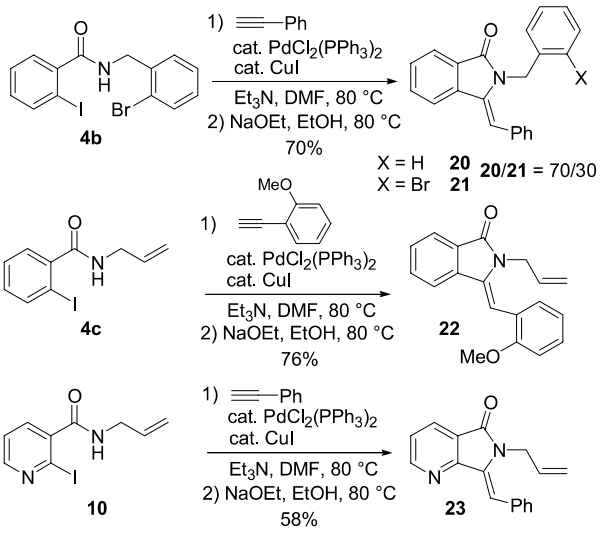
Apparently, in the case of ynamides **7a**–**c** and **12**, the Heck–Suzuki–Miyaura domino reactions afforded the corresponding 3-(arylmethylene)isoindolin-1-ones **15**, **16** and **17** or the pyrrolopyridinones **18** and **19** as single geometric isomers. The (*E*)-configuration of the known isoindolin-1-one **15** was readily assigned by NMR and comparison with the literature data.[8a,10c] In order to unambiguously assign the configuration of the isoindolinones **16** and **17** as well as that of the pyrrolopyridinone **19**, authentic samples of their corresponding geometric isomers

Table 1. Heck–Suzuki–Miyaura domino reactions involving ynamides

Ynamides	Reagents: boronic acid, Pd catalyst (5 mol%), base, solvent	Product (yield)
	$PhB(OH)_2$	
	$Pd(PPh_3)_4$, aqueous NaOH, DME	**15** (48%)
7a	$Pd(dba)_2$, aqueous NaOH, THF	**15** (59%)
	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**15** (70%)
	Pd (10%)/C, aqueous NaOH, THF	**15** (56%)
	$PhB(OH)_2$	
7b	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**16** (51%)
		
7c	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**17** (67%)
	$PhB(OH)_2$	
12	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**18** (52%)
	Pd (10%)/C, aqueous NaOH, THF	**18** (0%)
12		
	$Pd(OAc)_2+2PPh_3$, aqueous NaOH, THF	**19** (68%)

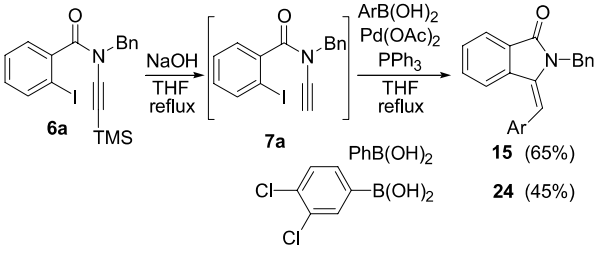
having a trisubstituted double bond of (*Z*) configuration were prepared by a different route.[10c] According to this latter strategy, the *N*-(2-bromobenzyl)-2-iodobenzamide **4b** was subjected to a Sonogashira coupling reaction with phenylacetylene in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (3.5 mol%), CuI (8 mol%) and Et_3N (4 equiv) in DMF at 80 °C. After work-up, the resulting 2-alkynylbenzamide was not purified but directly cyclized under alkaline conditions (NaOEt, EtOH, reflux), the latter reaction having been demonstrated to involve an *anti*-addition across the carbon–carbon triple bond.[10] Under these conditions, the amide **4b** led to a 70/30 mixture of the known (*Z*)-3-benzylideneisoindolin-1-one **20**[8a,10c] and the desired (*Z*)-3-(2-bromobenzylidene)isoindolin-1-one **21**. Substantial reduction of the carbon–bromine bond of the 2-bromobenzyl nitrogen substituent also took place as a side-reaction during the Sonogashira coupling reaction. It is noteworthy that such a side-reaction was not observed when ynamide **7b** was converted to the 3-(arylmethylene)isoindolin-1-one **16** by Heck–Suzuki–Miyaura domino reactions. Similarly, the *N*-allyl-2-iodobenzamide **4c** and the *N*-allyl-2-bromonicotinamide **10** were coupled with (2-methoxyphenyl)acetylene and with phenylacetylene, respectively. The resulting intermediate disubstituted alkynes underwent subsequent ring-closure by treatment with sodium ethoxide in refluxing ethanol, to afford the (2-methoxybenzylidene)isoindolin-1-one **22** (76%) and the pyrrolopyridinone **23** (58%) with high (*Z*) stereoselectivity ((*Z*):(*E*)≥95:5) (Scheme 6). Comparison of the spectral data of compounds **20–23** with those of isoindolin-1-ones **15–17** and the pyrrolopyridinone **18** confirmed that the latter products were obtained as single geometric isomers of (*E*) configuration. The configuration of the other 3-(arylmethylene)isoindolinones described in this study was attributed on the basis of these results. The observed stereochemical outcome was in agreement with the fact that carbopalladation of alkynes involves a *syn*-addition process and cross-coupling reactions of σ-vinylpalladium complexes are known to generally proceed with retention of the olefinic configuration.[35] Some exceptions to both trends have been reported but they appear limited to particular classes of substrates.[37,38]

As the Suzuki–Miyaura cross-coupling reactions require the presence of a base,[36] and because alkynylsilanes are known to be deprotected under these conditions, it was envisaged to carry out a one-pot sequence starting from the



Scheme 6. Preparation of the (*Z*)-3-benzylideneisoindolin-1-ones **20**–**22** and the (*Z*)-pyrrolopyridinone **23**.

trimethylsilylynamide **6a**. Indeed, treatment of **6a** with aqueous NaOH in THF at reflux generated the terminal ynamide **7a** in situ that underwent the subsequent Heck–Suzuki–Miyaura domino reactions by addition of benzeneboronic acid or 3,4-dichlorobenzeneboronic acid and the palladium catalyst. Under these conditions, the 3-(arylmethylene)isoindolinones **15** and **24** were obtained in 65% and 45% overall yield, respectively (Scheme 7).



Scheme 7. One-pot desilylation and Heck–Suzuki–Miyaura reactions from ynamide **6a**.

Having demonstrated that ynamides could efficiently participate in palladium(0)-catalyzed Heck–Suzuki–Miyaura reactions, it was envisaged to highlight the interest of this methodology by an application to the synthesis of the natural product lennoxamine.

3. Synthesis of lennoxamine

Polycyclic nitrogen containing heterocycles are encountered in naturally occurring alkaloids and numerous physiologically active drugs.[39] Lennoxamine, an isoindolobenzazepine alkaloid belonging to the *aporhoedane* series, was extracted from the Chilean plant *Berberis darwinii*. This natural product exists as a racemate (Fig. 2).[40]

Although this compound has no important biological activity, its unique structural feature, five- and seven-membered rings fused with an aromatic moiety, has elicited considerable synthetic interest and several total syntheses of

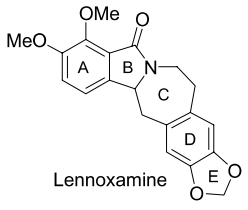
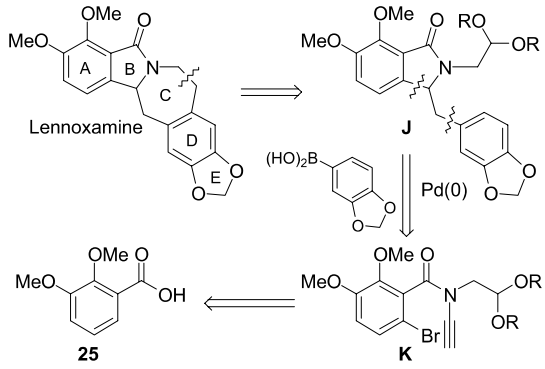


Figure 2. Structure of lennoxamine.

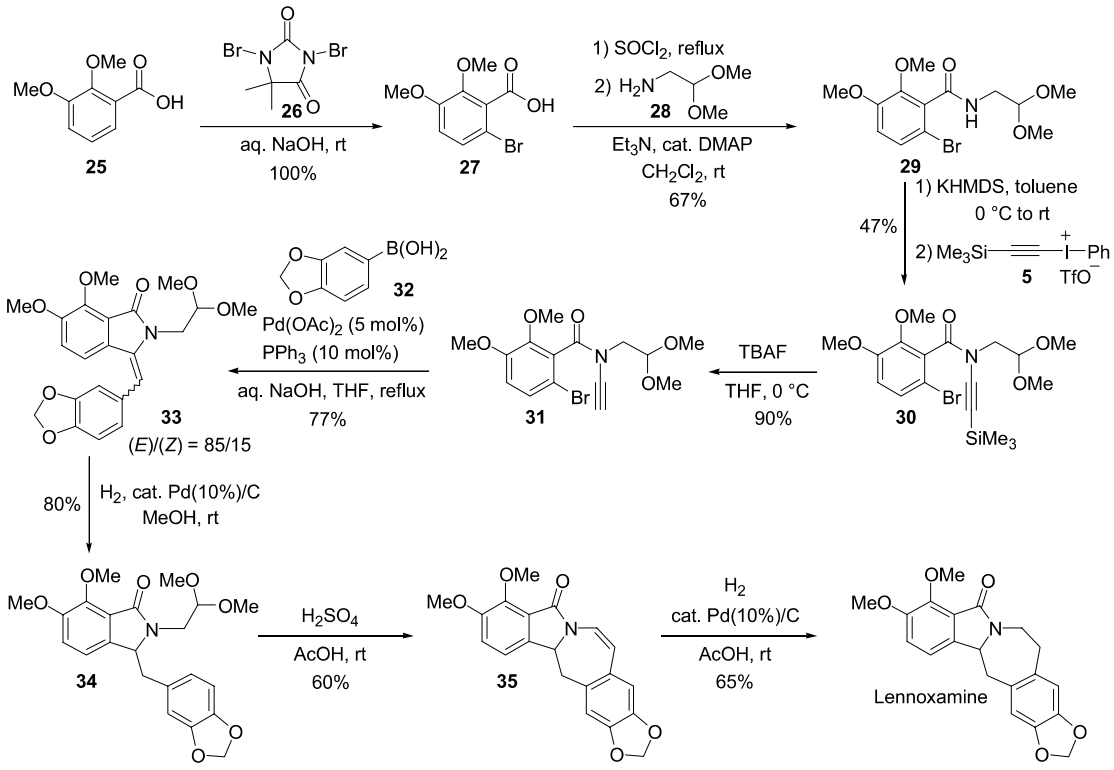
this natural product have been reported relying on the construction of ring B or/and ring C as the key steps.[15b,41] As previous syntheses of lennoxamine indicate that the seven-membered ring can arise from the cyclization of an isoindolinone of type **J** under acidic conditions followed by catalytic hydrogenation,[15b,41o] it was envisaged to apply the Heck–Suzuki–Miyaura reactions to an ynamide of type **K**. The latter compound should be prepared from 2,3-dimethoxybenzoic acid **25** (Scheme 8).



Scheme 8. Retrosynthetic analysis of lennoxamine.

The synthesis of lennoxamine (Scheme 9) started with the bromination of 2,3-dimethoxybenzoic acid **25** with 1,3-dibromo-5,5-dimethylhydantoin **26** (aqueous NaOH, rt) which led to 2,3-dimethoxy-6-bromobenzoic acid **27** in quantitative yield.[42] Initial attempts to couple the carboxylic acid **27** with aminoacetaldehyde dimethyl acetal **28** (EDCI, cat. DMAP, CH_2Cl_2, rt) provided the corresponding secondary amide **29** in low yield (35%). Therefore, the carboxylic acid **27** was converted to the corresponding acyl chloride ($SOCl_2$, reflux) and the latter was coupled with aminoacetaldehyde dimethyl acetal **28** (Et_3N, cat. DMAP, CH_2Cl_2, rt) to afford the secondary amide **29** (67% overall yield, one-pot process). After formation of the potassium amide (KHMDS, toluene, 0 °C to rt) and condensation with the alkynyliodonium salt **5**, the ynamide **30** was obtained in relatively modest yield (47%).[43] The trimethylsilyl group was then removed by treatment of **30** with TBAF in THF to afford the terminal ynamide **31** (90%). The next key stage of our synthetic strategy was to construct ring B and hence elaborate the isoindolinone core of lennoxamine by the palladium-catalyzed Heck–Suzuki–Miyaura domino reactions.

The terminal ynamide **31** was treated with a catalytic amount of $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and a base (aqueous NaOH) in the presence of the commercially available boronic acid **32** that incorporates both the D and E rings of the natural product (THF, reflux). Under these



Scheme 9. Synthesis of lennoxamine.

conditions, the Heck–Suzuki–Miyaura domino reactions proceeded smoothly and the resulting 3-(arylmethylene)-isoindolin-1-one **33** was isolated in 77% yield but as a mixture of two geometric isomers [(*E*):(*Z*)=85:15] (Scheme 9). The (*E*) configuration of the major isomer was readily assigned by comparison with the spectroscopic data reported for this compound.[15b]

This latter result was in sharp contrast with our initial observation that 3-(arylmethylene)isoindolin-1-ones of type **A** were obtained with high (*E*) stereoselectivity by Heck–Suzuki–Miyaura domino reactions from ynamides of type **H**. Although we cannot rule out that an isomerization may have occurred during the palladium-catalyzed domino reactions,[37] the particular structure of the 3-(arylmethylene) isoindolin-1-one **33**, which bears a rather electron-rich enamide moiety, may explain a possible isomerization subsequent to its formation. The latter could take place through a reversible protonation of the double bond or a hydration–dehydration pathway.[6–8,15e] A photochemical process could also not be excluded due to the light sensitivity of compound **33**.

However, this lack of stereoselectivity in the synthesis of compound **33** had no consequence for the total synthesis of lennoxamine since the mixture of geometric isomers was subsequently hydrogenated (cat. Pd (10%)/C, 1 atm H_2, MeOH, rt) to afford the 3-(arylmethyl)isoindolin-1-one **34** in 60% yield. Completion of the total synthesis was achieved from compound **34**, as previously reported,[15b] by treatment under acidic conditions (H_2SO_4 in AcOH, rt) that served to elaborate the seven-membered ring (ring C) and generate dehydrolennoxamine **35** (60%). This latter compound was finally hydrogenated (cat. Pd (10%)/C, 1 atm H_2, AcOH, rt) to afford lennoxamine in 65% yield (Scheme 9). The spectroscopic and analytical data of this compound were in perfect agreement with those reported in the literature.[41]

4. Conclusion

We have reported an efficient and stereoselective access to (*E*)-3-(arylmethylene)isoindolin-1-ones by using Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions involving ynamides and arylboronic acids. The interest of this methodology, which further expands the synthetic utility of ynamides, has been highlighted by its application to the preparation of the natural product lennoxamine. A concise route to this isoindolobenzazepine alkaloid was achieved from 2,3-dimethoxybenzoic acid (eight steps, 7% overall yield) via an intermediate ynamide from which the isoindolone core of the natural product was elaborated by Heck–Suzuki–Miyaura domino reactions.

5. Experimental

5.1. General procedures

Infrared (IR) spectra were recorded on a Perkin-Elmer 298 or a Bruker Tensor 27 (IR-FT), wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC 300 at 300 MHz in $CDCl_3$ (unless otherwise specified) and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet or overlap of non-equivalent resonances),

integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz in $CDCl_3$ and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s, quaternary C; d, CH; t, CH_2; q, CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column)—5971 MS (70 eV). Mass spectra with chemical ionization (CI^+) and high-resolution mass spectra (HRMS) were performed by the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm (Paris). Elemental analyses were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, CH_3CN, toluene, Et_3N, DMF were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on Merck $60F_{254}$ silica gel plates visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/H_2SO_4/AcOH in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed with SDS 60 silica gel (230–400 mesh).

5.2. Preparation of ynamides of type H

5.2.1. *N*-Benzyl-2-iodobenzamide (4a). To a solution of 2-iodobenzoic acid **3** (5.00 g, 20.2 mmol) in a mixture of CH_2Cl_2 (200 mL) and THF (50 mL) at 0 °C were successively added DMAP (493 mg, 4.03 mmol, 0.2 equiv), benzylamine (2.4 mL, 22 mmol, 1.1 equiv) and EDCI (5.40 g, 28.2 mmol, 1.4 equiv) portionwise. After 12 h, the reaction mixture was hydrolyzed with water and extracted with CH_2Cl_2. The combined organic extracts were successively washed with a 1 M aqueous solution of hydrochloric acid, a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallization from absolute EtOH to afford 4.08 g (60%) of **4a** as a white powder; mp 126 °C; IR 3420, 1660, 1585, 1510, 1300, 1015, 750 cm^{-1}; ^1H NMR δ 7.78 (d, J=7.7 Hz, 1H), 7.35–7.25 (m, 7H), 7.04 (m, 1H), 6.43 (br s, 1H, NH), 4.53 (d, J=5.5 Hz, 2H); ^{13}C NMR δ 169.1 (s), 141.9 (s), 139.7 (d), 137.5 (s), 131.0 (d), 128.6 (d, 2C), 128.1 (d), 128.0 (d, 3C), 127.5 (d), 92.4 (s), 44.0 (t); MS-EI *m/z* (relative intensity) 337 (M^+, 92), 336 (19), 231 (100), 210 (45), 203 (32), 192 (13), 132 (15), 105 (22), 104 (16), 91 (31), 77 (19), 76 (25).

5.2.2. *N*-(2-Bromobenzyl)-2-iodobenzamide (4b). This compound was synthesized from 2-bromobenzylamine (2.1 g, 11 mmol), 2-iodobenzoic acid (2.5 g, 10 mmol) in the presence of EDCI (2.3 g, 12 mmol) and DMAP (244 mg, 2 mmol) in CH_2Cl_2 (100 mL), as described for the preparation of **4a** from benzylamine. After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 3.36 g (81%) of **4b** were obtained as white solid; mp 154 °C; IR 3277, 1644, 1585, 1540, 1305, 1242, 1027, 1013, 986, 743, 719, 684, 666 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.98 (t, J=5.9 Hz, 1H, NH), 7.91 (d, J=7.7 Hz, 1H), 7.64 (dd, J=7.7, 1.1 Hz, 1H), 7.56–7.38 (m, 4H), 7.27–7.16 (m, 2H), 4.47 (d, J=5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 169.1 (s), 142.7 (s), 139.2 (d), 137.4 (s), 132.4 (d), 130.9 (d), 129.0 (d), 128.9 (d), 128.2 (d), 128.0 (d), 127.7 (d), 122.3 (s), 93.5 (s), 43.0 (t); MS-EI *m/z* (relative intensity) 337 ($M+H-Br^+$, 15), 336 ($M-Br^+$, 100), 231 (27), 203 (13), 107 (14), 76 (12). Anal. Calcd for $C_{14}H_{11}BrINO$: C, 40.42; H, 2.66; N, 3.37. Found: C, 40.12; H, 2.66; N, 2.90.

5.2.3. *N*-Allyl-2-iodobenzamide (4c). This compound was synthesized from allylamine (1.7 mL, 22 mmol), 2-iodobenzoic acid (5.00 g, 20.2 mmol) in the presence of EDCI (4.90 g, 25.4 mmol) and DMAP (493 mg, 4.03 mmol) in CH_2Cl_2/THF (80 mL/110 mL), as described for the preparation of **4a** from benzylamine. After purification by flash chromatography (petroleum ether/EtOAc: 60:40), 4.22 g (73%) of **4c** were obtained as a white powder; mp 106 °C; IR 3410, 3350, 1645, 1580, 1510, 1300, 1260, 1010, 990, 730 cm^{-1}; ^1H NMR δ 7.83 (d, J=7.7 Hz, 1H), 7.36–7.32 (m, 2H), 7.07 (m, 1H), 6.16 (br s, 1H, NH), 5.93 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.29 (dq, J=17.3, 1.5 Hz, 1H), 5.17 (dq, J=10.3, 1.5 Hz, 1H), 4.02 (dt, J=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 169.0 (s), 142.0 (s), 139.7 (d), 133.5 (d), 131.0 (d), 128.1 (d), 128.0 (d), 116.8 (t), 92.3 (s), 42.3 (t); MS-EI *m/z* (relative intensity) 287 (M^+, 10), 272 (3), 232 (8), 231 (100), 203 (21), 160 (11), 105 (4), 77 (6), 76 (17).

5.2.4. *N*-Benzyl-2-iodo-*N*-trimethylsilylethynyl-benzamide (6a). To a solution of **4a** (2.84 g, 8.43 mmol) in toluene (100 mL) at 0 °C was added KHMDS (15.3 mL, 15% in toluene, 10.1 mmol, 1.2 equiv). After 2 h at 0 °C, the iodonium salt **5** (4.55 g, 10.1 mmol, 1.2 equiv) was added. After 24 h at rt, the reaction mixture was filtered through Celite (toluene/ether: 80:20). The filtrate was evaporated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 90:10–60:40) to afford 1.75 g (48%) of **6a** as a white powder; mp 57 °C; IR 2180, 1680, 1580, 1430, 1370, 1290, 1250, 820, 760, 745 cm^{-1}; ^1H NMR δ 7.79 (dd, J=7.7, 0.7 Hz, 1H), 7.50–7.45 (m, 2H), 7.40–7.31 (m, 4H), 7.28 (dd, J=7.7, 1.8 Hz, 1H), 7.08 (apparent td, J=7.7, 1.8 Hz, 1H), 4.82 (s, 2H), −0.11 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.3 (s), 138.7 (d), 135.2 (s), 130.6 (d), 129.2 (d, 2C), 128.4 (d, 2C), 128.1 (d), 127.8 (d), 127.6 (d), 96.3 (s), 92.1 (s), 76.1 (s), 51.6 (t), −0.43 (q, 3C); MS-EI *m/z* (relative intensity) 433 (M^+, 8), 418 ($M-Me^+$, 5), 306 (4), 232 (7), 231 (55), 203 (15), 92 (8), 91 (100), 76 (7).

5.2.5. *N*-(2-Bromobenzyl)-2-iodo-*N*-trimethylsilylethynylbenzamide (6b). This compound was prepared from **4b** (1.50 g, 3.60 mmol), KHMDS (14.4 mL, 0.5 M in toluene, 7.20 mmol, 2 equiv) and iodonium salt **5** (3.25 g, 7.20 mmol, 2 equiv) in toluene (85 mL), as described for the preparation of **6a** from **4a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5) to afford 1.32 g (72%) of **6b** as a yellow solid; mp 140 °C; IR 2180, 1685, 1585, 1570, 1370, 1295, 1250, 1025, 985, 850, 750, 700 cm^{-1}; ^1H NMR δ 7.83 (d, J=8.1 Hz, 1H), 7.60 (dd, J=7.7, 1.1 Hz, 1H), 7.55 (dd, J=7.7, 1.5 Hz, 1H), 7.40–7.32 (m, 3H), 7.20 (apparent td, J=7.7, 1.5 Hz, 1H), 7.12 (m, 1H), 5.00 (s, 2H), 0.13 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.1 (s), 138.8 (d), 134.3 (s), 132.8 (d), 130.8 (d), 130.5 (d), 129.5 (d), 127.9 (d), 127.6 (d), 127.4 (d), 124.1 (s), 95.6 (s), 92.2 (s), 76.5 (s), 51.2 (t), −0.44 (q, 3C); MS-EI *m/z* (relative intensity) 513 ($M[^{81}Br]^+$, 4), 511 ($M[^{79}Br]^+$, 4),

498 (6), 496 (6), 432 (7), 232 (10), 231 (100), 203 (30), 172 (7), 171 (88), 170 (8), 169 (91), 90 (13), 89 (9), 76 (15).

5.2.6. *N*-Allyl-2-iodo-*N*-trimethylsilylethynyl-benzamide (6c). This compound was prepared from **4c** (2.50 g, 8.71 mmol), KHMDS (30.7 mL, 0.5 M in toluene, 15.3 mmol, 1.8 equiv) and iodonium salt **5** (7.53 g, 16.7 mmol, 1.9 equiv) in toluene (200 mL), as described for the preparation of **6a** from **4a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5–90:10) to afford 2.10 g (63%) of **6c** as a white waxy solid; mp <45 °C; IR 2180, 1665, 1585, 1360, 1290, 1250, 840, 760, 740 cm^{-1}; ^1H NMR δ 7.81 (dd, J=8.1, 0.9 Hz, 1H), 7.41–7.27 (m, 2H), 7.10 (ddd, J=8.1, 7.4, 0.9 Hz, 1H), 5.98 (ddt, J=16.5, 10.3, 6.2 Hz, 1H), 5.41 (dq, J=16.5, 1.5 Hz, 1H), 5.32 (dq, J=10.3, 1.5 Hz, 1H), 4.27 (dt, J=6.2, 1.5 Hz, 2H), −0.07 (s, 9H); ^{13}C NMR δ 171.1 (s), 141.4 (s), 138.7 (d), 130.8 (d), 130.6 (d), 127.6 (d, 2C), 119.3 (t), 96.0 (s), 92.1 (s), 75.6 (s), 50.1 (t), −0.29 (q, 3C); MS-EI m/z (relative intensity) 383 (M^+, 9), 368 ($M-Me^+$, 17), 294 (6), 256 (13), 231 (100), 203 (28), 180 (6), 76 (17). Anal. Calcd for $C_{15}H_{18}INOSi$: C, 47.00; H, 4.73; N, 3.65. Found: C, 47.11; H, 4.74; N, 3.63.

5.2.7. *N*-Benzyl-*N*-ethynyl-2-iodobenzamide (7a). To a solution of **6a** (70 mg, 0.16 mmol) in THF (5 mL) at 0 °C was added tetra(*n*-butyl)ammonium fluoride (TBAF) (0.21 mL, 1 M in THF, 0.21 mmol, 1.3 equiv). After 10 min at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 56 mg (96%) of **7a** as a pale yellow solid; mp 100–102 °C; IR 3290, 2140, 1680, 1580, 1355, 1320, 1285, 1250, 1140, 760, 730, 710, 695 cm^{-1}; ^1H NMR δ 7.81 (dd, J=8.1, 0.7 Hz, 1H), 7.52–7.46 (m, 2H), 7.42–7.28 (m, 5H), 7.10 (ddd, J=8.1, 7.4, 1.8 Hz, 1H), 4.87 (s, 2H), 2.60 (s, 1H); ^{13}C NMR δ 170.9 (s), 138.9 (s), 135.0 (s), 130.8 (d), 128.9 (d, 2C), 128.4 (d, 2C), 128.4 (s), 128.1 (d), 127.8 (d, 2C), 91.9 (s), 76.6 (s), 61.7 (d), 51.7 (t); MS-EI m/z (relative intensity) 361 (M^+, 2), 232 (7), 231 (43), 203 (16), 91 (100), 76 (12).

5.2.8. *N*-(2-Bromobenzyl)-*N*-ethynyl-2-iodobenzamide (7b). This compound was synthesized from ynamide **6b** (600 mg, 1.17 mmol) by treatment with TBAF (1.53 mL, 1 M in THF, 1.53 mmol, 1.3 equiv) in THF (15 mL), as described for the preparation of **7a** from **6a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 408 mg (79%) of **7b** as an orange solid; mp 105–106 °C; IR 3300, 2150, 1690, 1585, 1350, 1295, 1030, 980, 770, 750 cm^{-1}; ^1H NMR δ 7.86 (br d, J=8.1 Hz, 1H), 7.62 (br d, J=8.1 Hz, 1H), 7.56 (dd, J=7.7, 1.5 Hz, 1H), 7.43–7.35 (m, 3H), 7.23 (dd, J=7.7, 1.5 Hz, 1H), 7.15 (m, 1H), 5.04 (s, 2H), 2.55 (s, 1H); ^{13}C NMR δ 171.0 (s), 140.8 (s), 139.2 (d), 134.2 (s), 133.0 (d), 131.2 (d), 130.3 (d), 129.6 (d), 127.9 (d), 127.8 (d), 127.5 (d), 124.0 (s), 92.2 (s), 76.5 (s), 62.2 (d), 51.4 (t); MS-EI m/z (relative intensity) 271 ($M+H-CH_2(C_6H_4Br)^+$, 100), 243 (5), 242 (5), 215 (3), 116 (32), 89 (36), 88 (13), 63 (7), 62 (8). Anal. Calcd for $C_{16}H_{11}BrINO$: C, 43.67; H, 2.52; N, 3.18. Found: C, 43.89; H, 2.65; N, 3.06.

5.2.9. *N*-Allyl-*N*-ethynyl-2-iodobenzamide (7c). This compound was synthesized from ynamide **6c** (1.50 g, 3.90 mmol) by treatment with TBAF (5.1 mL, 1 M in THF, 5.1 mmol, 1.3 equiv) in THF (50 mL), as described for the preparation of **7a** from **6a**. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 70:30) to afford 1.03 g (85%) of **7c** as a white powder; mp 55–57 °C; IR 3300, 2140, 1580, 1360, 1290, 1255, 1015, 935, 770, 740 cm^{-1}; ^1H NMR δ 7.83 (dd, J=8.0, 0.7 Hz, 1H), 7.42–7.30 (m, 2H), 7.11 (apparent td, J=7.7, 1.8 Hz, 1H), 5.99 (ddt, J=16.6, 10.3, 6.3 Hz, 1H), 5.43 (dq, J=16.6, 1.5 Hz, 1H), 5.34 (dq, J=10.3, 1.5 Hz, 1H), 4.31 (dt, apparent br d, J=6.3, 1.5 Hz, 2H), 2.64 (s, 1H); ^{13}C NMR δ 170.8 (s), 140.9 (s), 138.9 (d), 130.9 (d), 130.6 (d), 127.7 (d), 127.5 (d), 119.4 (t), 92.0 (s), 76.6 (s), 61.3 (d), 50.4 (t); MS-EI m/z (relative intensity) 311 (M^+, 4), 271 (15), 232 (8), 231 (100), 203 (33), 182 (5), 76 (24). Anal. Calcd for $C_{12}H_{10}INO$: C, 46.33; H, 3.24; N, 4.50. Found: C, 46.68; H, 3.47; N, 4.29.

5.2.10. *N*-Allyl-2-bromonicotinamide (10). This compound was synthesized from 2-bromonicotinic acid **9**[34] (2.0 g, 9.9 mmol) and allylamine (0.93 mL, 12.4 mmol, 1.25 equiv) in the presence of EDCI (2.3 g, 12 mmol, 1.2 equiv) and DMAP (0.12 g, 0.99 mmol, 0.1 equiv) in CH_2Cl_2 (200 mL) as described for the preparation of **4a** from benzylamine and 2-iodobenzoic acid. After purification by flash chromatography (diethyl ether), 1.25 g (52%) of **10** were obtained as a white solid; mp 97–98 °C; IR 1660, 1580, 1395, 1300, 1055, 990, 930, 820 m^{-1}; ^1H NMR δ 8.31 (dd, J=4.8, 1.8 Hz, 1H), 7.75 (dd, J=7.7, 1.8 Hz, 1H), 7.27 (dd, J=7.7, 4.8 Hz, 1H), 6.79 (br s, 1H, NH), 5.86 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.25 (dq, J=17.3, 1.5 Hz, 1H), 5.14 (dq, J=10.3, 1.5 Hz, 1H), 3.99 (ddt, apparent tt, J=5.9, 1.5 Hz, 2H); ^{13}C NMR δ 165.6 (s), 150.7 (d), 138.3 (s), 138.0 (d), 134.7 (s), 133.0 (d), 122.6 (d), 116.9 (t), 42.4 (t); MS-EI m/z (relative intensity) 242 ($M[^{81}Br]^+$, 5), 240 ($M[^{79}Br]^+$, 5), 227 (20), 225 (20), 186 (97), 184 (100), 161 (23), 158 (30), 156 (31), 76 (17), 56 (6), 51 (7).

5.2.11. *N*-Allyl-2-bromo-*N*-trimethylsilylethynyl-nicotinamide (11). This compound was synthesized from **10** (800 mg, 3.32 mmol), KHMDS (10.6 mL, 0.5 M in toluene, 5.3 mmol, 1.6 equiv) and iodonium salt **5** (2.39 g, 5.30 mmol, 1.6 equiv) in toluene (50 mL), as described for the preparation of **6a** from **4a**. After purification by flash chromatography (petroleum ether/EtOAc: 90:10), 643 mg (58%) of **11** were obtained as a yellow oil; IR 2180, 1685, 1645, 1575, 1555, 1390, 1365, 1295, 1250, 1205, 1165, 1120, 1055, 990, 920, 840, 760, 705, 640 cm^{-1}; ^1H NMR δ 8.42 (dd, J=4.8, 1.9 Hz, 1H), 7.64 (dd, J=7.7, 1.9 Hz, 1H), 7.32 (dd, J=7.7, 4.8 Hz, 1H), 5.93 (ddt, J=17.2, 10.3, 6.2 Hz, 1H), 5.40 (dq, J=17.2, 1.1 Hz, 1H), 5.32 (dq, J=10.3, 1.1 Hz, 1H), 4.27 (dt, J=6.2, 1.1 Hz, 2H), −0.06 (s, 9H); ^{13}C NMR δ 168.0 (s), 150.5 (d), 138.5 (s), 136.5 (d), 134.5 (s), 130.3 (d), 122.1 (d), 119.6 (t), 95.4 (s), 76.3 (s), 50.2 (t), −0.35 (q, 3C); MS-EI m/z (relative intensity) 338 ($M[^{81}Br]^+$, 15), 336 ($M[^{79}Br]^+$, 15), 323 (58), 321 (57), 257 (56), 249 (14), 247 (14), 186 (97), 185 (14), 184 (100), 180 (14), 158 (48), 156 (49), 139 (20), 137 (20), 84 (14), 76 (19), 73 (18). Anal. Calcd for $C_{14}H_{17}BrN_2OSi$: C, 49.85; H, 5.08; N, 8.31. Found: C, 49.89; H, 5.27; N, 8.27.

5.2.12. *N*-Allyl-2-bromo-*N*-ethynylnicotinamide (12). This compound was synthesized from **11** (500 mg, 1.48 mmol) by treatment with TBAF (1.4 mL, 1 M in THF, 1.4 mmol, 1.25 equiv) in THF (18 mL). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 345 mg (88%) of **12** were obtained as a yellow oil; IR 3305, 2150, 1685, 1580, 1560, 1395, 1365, 1290, 1055, 810, 760, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (dd, J=4.8, 2.0 Hz, 1H), 7.67 (dd, J=7.7, 2.0 Hz, 1H), 7.34 (dd, J=7.7, 4.8 Hz, 1H), 5.95 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.42 (dq, J=17.3, 1.5 Hz, 1H), 5.35 (dq, J=10.3, 1.5 Hz, 1H), 4.31 (dt, J=5.9, 1.5 Hz, 2H), 2.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.7 (s), 150.8 (d), 138.3 (s), 136.5 (d), 134.0 (s), 130.1 (d), 122.2 (d), 119.8 (t), 76.1 (s), 61.7 (d), 50.4 (t); MS-EI *m/z* (relative intensity) 266 ($M[^{81}Br]^+$, 29), 264 ($M[^{79}Br]^+$, 29), 199 (33), 197 (34), 186 (96), 184 (100), 158 (62), 156 (65), 77 (20), 76 (49), 50 (20). HRMS (CI^+, CH_4) calcd for $C_{11}H_{10}ON_2^{79}Br$ ($M+H^+$): 264.9976. Found: 264.9974.

5.3. Reductive Heck reaction of ynamides

5.3.1. 2-(2-Bromobenzyl)-3-methylene-2,3-dihydro-1*H*-isoindol-1-one (13) (representative procedure). To a solution of ynamide **7b** (80 mg, 0.18 mmol) in DMF (8 mL) were successively added ammonium formate (17 mg, 0.27 mmol, 1.5 equiv), $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.05 equiv) and PPh_3 (4.8 mg, 0.018 mmol, 0.1 equiv). After 1 h at 80 °C, the reaction mixture was cooled to rt, diluted with water and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95:5) to afford 34 mg (56%) of **13** as a pale yellow solid; mp 110 °C; IR 1705, 1640, 1395, 1025, 980, 845, 770, 755 cm^{-1}; ^1H NMR δ 7.92 (apparent br d, J=7.5 Hz, 1H), 7.72 (apparent dt, J=7.5, 1.1 Hz, 1H), 7.63 (apparent td, J=7.5, 1.1 Hz, 1H), 7.61–7.53 (m, 2H), 7.24–7.09 (m, 2H), 6.98 (apparent br d, J=7.5 Hz, 1H), 5.18 (d, J=2.6 Hz, 1H), 5.18 (br s, 2H), 4.74 (d, J=2.6 Hz, 1H); ^{13}C NMR δ 167.2 (s), 141.3 (s), 136.4 (s), 135.4 (s), 132.8 (d), 132.3 (d), 129.6 (d), 129.1 (s), 128.8 (d), 127.7 (d, 2C), 123.5 (d), 122.4 (s), 120.0 (d), 90.2 (t), 43.2 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 316 ($M[^{81}Br]+H^+$, 100), 314 ($M[^{79}Br]+H^+$, 100), 234 (17). HRMS (CI^+, CH_4) calcd for $C_{16}H_{13}ON^{79}Br$ ($M+H^+$): 314.0181. Found: 314.0178.

5.3.2. 2-Allyl-3-methylene-2,3-dihydro-1*H*-isoindol-1-one (14).[12] This compound was synthesized from ynamide **7c** (70 mg, 0.22 mmol) in the presence of ammonium formate (21 mg, 0.34 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 0.05 equiv) and PPh_3 (5.9 mg, 0.022 mmol, 0.10 equiv) in DMF (9 mL), according to the representative procedure (2 h at 80 °C). After purification by flash chromatography (petroleum ether/EtOAc: 90:10), 21 mg (62%) of **14** were obtained as an orange oil; IR 1710, 1640, 1390, 1340, 1095, 925, 840, 770, 730, 715, 700 cm^{-1}; ^1H NMR δ 7.85 (ddd, apparent dt, J=7.7, 1.1 Hz, 1H), 7.69 (ddd, apparent dt, J=7.7, 1.1 Hz, 1H), 7.59 (ddd, apparent td, J=7.7, 1.1 Hz, 1H), 7.50 (ddd, apparent td, J=7.7, 1.1 Hz, 1H), 5.87 (ddt, J=16.9, 10.3, 5.1 Hz, 1H), 5.22–5.13 (m, 2H), 5.20 (d, J=2.2 Hz, 1H), 4.87 (d, J=2.2 Hz, 1H), 4.43 (dt, J=5.1, 1.6 Hz, 2H); ^{13}C NMR δ 166.7 (s), 141.5 (s), 136.2 (s), 132.2 (d), 131.8 (d), 129.3 (d), 129.1 (s), 123.1 (d), 119.7 (d), 116.6 (t), 89.3 (t), 41.6 (t); MS-EI *m/z* (relative intensity) 186 ($M+H^+$, 13), 185 (M^+, 100), 184 (67), 170 (35), 156 (33), 130 (13), 129 (16), 115 (14), 103 (14), 102 (14), 77 (13), 76 (13).

5.4. Palladium-catalyzed Heck–Suzuki–Miyaura domino reactions involving ynamides

5.4.1. 2-Benzyl-3-(*E*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (15) (representative procedure). To a solution of ynamide **7a** (40 mg, 0.11 mmol) in THF (5 mL) were added a 1 M aqueous solution of NaOH (0.17 mL, 0.17 mmol, 1.5 equiv) and benzeneboronic acid (16 mg, 0.14 mmol, 1.2 equiv). To the resulting degassed mixture [argon bubbling, 10 min] were added PPh_3 (3.0 mg, 0.011 mmol, 0.1 equiv) and $Pd(OAc)_2$ (1.3 mg, 0.0055 mmol, 0.05 equiv). After 1.5 h at reflux, the reaction mixture was cooled to rt, hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 75:25) to afford 25 mg (70%) of **15** as a yellow oil; IR 3020, 1695, 1635, 1405, 1335, 1175, 1150, 1115, 970, 820, 765, 735, 695 cm^{-1}; ^1H NMR δ 7.91–7.21 (m, 14H), 6.46 (s, 1H), 5.13 (s, 2H); ^{13}C NMR δ 166.7 (s), 136.7 (s), 135.9 (s), 135.0 (s), 134.9 (s), 131.6 (d), 130.1 (s), 129.4 (d, 2C), 129.2 (d), 128.7 (d, 2C), 128.5 (d, 2C), 127.7 (d), 127.3 (d), 126.9 (d, 2C), 123.4 (d), 123.1 (d), 111.5 (d), 43.1 (t); MS-EI *m/z* (relative intensity) 312 ($M+H^+$, 23), 311 (M^+, 100), 310 ($M-H^+$, 31), 282 (10), 234 (15), 232 (27), 220 (22), 167 (17), 165 (16), 91 (72), 65 (9).

5.4.2. 2-(2-Bromobenzyl)-3-(*E*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (16). This compound was synthesized from ynamide **7b** (61 mg, 0.14 mmol) and benzeneboronic acid (20 mg, 0.16 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (1.5 mg, 0.007 mmol, 0.05 equiv), PPh_3 (3.6 mg, 0.014 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.20 mL, 1 M, 0.20 mmol, 1.5 equiv) in THF (6 mL), according to the representative procedure (2 h at reflux). After purification by flash chromatography (pentane/EtOAc gradient: 95:5–80:20), 27 mg (51%) of **16** were obtained as a yellow solid; mp 178 °C; IR 1700, 1635, 1440, 1410, 1270, 1220, 1175, 1025, 970, 860, 830, 770, 755, 730 cm^{-1}; ^1H NMR δ 7.94 (dt, J=7.3, 1.1 Hz, 1H), 7.61 (dd, J=7.7, 1.1 Hz, 1H), 7.49 (m, 1H), 7.45–7.32 (m, 7H), 7.25 (ddd, apparent td, J=7.3, 1.1 Hz, 1H), 7.15 (ddd, apparent td, J=7.3, 1.8 Hz, 1H), 7.06 (dd, J=7.7, 1.5 Hz, 1H), 6.37 (s, 1H), 5.21 (s, 2H); ^{13}C NMR δ 166.7 (s), 135.6 (s), 135.3 (s), 135.0 (s), 134.8 (s), 132.7 (d), 131.7 (d), 130.0 (s), 129.3 (d, 2C), 129.2 (d), 128.7 (d), 128.5 (d, 2C), 127.7 (d), 127.6 (d), 127.5 (d), 123.4 (d), 123.1 (d), 122.2 (s), 111.7 (d), 43.3 (t).

5.4.3. 2-Allyl-3-(*E*)-(2-methoxybenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (17). This compound was synthesized from ynamide **7c** (116 mg, 0.372 mmol) and 2-methoxybenzeneboronic acid (85 mg, 0.56 mmol, 1.5 equiv) in the presence of $Pd(OAc)_2$ (4.2 mg,

0.018 mmol, 0.05 equiv), PPh_3 (10 mg, 0.037 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.56 mL, 0.56 mmol, 1.5 equiv) in THF (10 mL), according to the representative procedure (0.75 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc gradient: 90:10–70:30), 73 mg (67%) of **16** were obtained as a light brown solid; mp 110 °C; IR 1690, 1645, 1600, 1250, 1025, 760, 750 cm^{-1}; ^1H NMR δ 7.85 (br d, $J=7.2$ Hz, 1H), 7.49–7.26 (m, 5H), 7.02–6.95 (m, 2H), 6.49 (s, 1H), 5.94 (ddt, $J=17.0$, 10.2, 5.3 Hz, 1H), 5.25 (dq, $J=17.0$, 1.5 Hz, 1H), 5.23 (dq, $J=10.2$, 1.5 Hz, 1H), 4.57 (dt, $J=5.3$, 1.5 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR δ 166.3 (s), 157.6 (s), 135.5 (s), 135.3 (s), 132.6 (d), 131.4 (d), 131.2 (d), 130.2 (s), 129.6 (d), 129.0 (d), 123.9 (s), 123.1 (d), 123.0 (d), 120.4 (d), 116.9 (t), 110.8 (d), 107.9 (d), 55.6 (q), 41.9 (t); MS-EI *m/z* (relative intensity) 292 ($M+H^+$, 21), 291 (M^+, 100), 290 ($M-H^+$, 23), 276 (13), 262 (17), 260 (18), 232 (18), 219 (32), 206 (14), 190 (14), 185 (31), 184 (43), 182 (18), 170 (39), 165 (19).

5.4.4. 6-Allyl-7-(*E*)-benzylidene-6,7-dihydropyrrolo-[3,4-*b*]pyridin-5-one (18). This compound was synthesized from ynamide **12** (154 mg, 0.58 mmol) and benzeneboronic acid (84.5 mg, 0.68 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (6.4 mg, 0.028 mmol, 0.05 equiv), PPh_3 (15 mg, 0.058 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (0.85 mL, 0.85 mmol, 1.5 equiv) in THF (25 mL), according to the representative procedure (5 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 78.5 mg (52%) of **18** were obtained as a brown oil; IR 3060, 1695, 1640, 1605, 1575, 1395, 1340, 1280, 1265, 1170, 1100, 920, 795, 770, 735, 695 cm^{-1}; ^1H NMR δ 8.77 (dd, $J=4.8$, 1.8 Hz, 1H), 8.18 (dd, $J=7.7$, 1.8 Hz, 1H), 8.04–7.99 (m, 2H), 7.45–7.32 (m, 4H), 6.57 (s, 1H), 5.95 (ddt, $J=17.2$, 10.3, 5.1 Hz, 1H), 5.30–5.21 (m, 2H), 4.62 (dt, $J=5.1$, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 164.0 (s), 154.8 (s), 152.7 (d), 134.0 (s), 133.8 (s), 132.3 (d), 131.1 (d), 130.9 (d, 2C), 128.3 (d), 127.9 (d, 2C), 124.1 (s), 123.5 (d), 117.2 (t), 115.7 (d), 41.8 (t); MS-EI *m/z* (relative intensity) 262 (M^+, 67), 261 ($M-H^+$, 100), 233 (18), 221 (15), 220 (15), 192 (16), 185 (11), 166 (12), 139 (5), 89 (5), 77 (6). HRMS (CI^+, CH_4) calcd for $C_{17}H_{15}ON_2$ ($M+H^+$): 263.1184. Found: 263.1179.

5.4.5. 6-Allyl-7-(*E*)-(3,4-dichlorobenzylidene)-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (19). This compound was synthesized from ynamide **12** (204 mg, 0.754 mmol) and 3,4-dichlorobenzeneboronic acid (173 mg, 0.905 mmol, 1.2 equiv) in the presence of $Pd(OAc)_2$ (8.5 mg, 0.38 mmol, 0.05 equiv), PPh_3 (20 mg, 0.076 mmol, 0.1 equiv) and a 1 M aqueous solution of NaOH (1.1 mL, 1.1 mmol, 1.5 equiv) in THF (30 mL), according to the representative procedure (1.5 h at reflux). After purification by flash chromatography (petroleum ether/EtOAc: 80:20), 170 mg (68%) of **16** were obtained as a yellow solid; mp 127 °C; IR 1700, 1640, 1610, 1580, 1475, 1400, 1340, 1030, 925, 880, 795, 695, 640 cm^{-1}; ^1H NMR δ 8.78 (dd, $J=4.8$, 1.8 Hz, 1H), 8.21 (br d, $J=2.2$ Hz, 1H), 8.18 (dd, $J=7.7$, 1.8 Hz, 1H), 7.82 (m, 1H), 7.45 (br d, $J=8.1$ Hz, 1H), 7.43 (dd, $J=7.7$, 4.8 Hz, 1H), 6.40 (s, 1H), 5.92 (ddt, $J=17.3$, 10.4, 5.1 Hz, 1H), 5.28 (apparent br d, $J=10.4$ Hz, 1H), 5.24 (apparent br d, $J=17.3$ Hz, 1H), 4.59 (dt, $J=5.1$, 1.8 Hz, 2H); ^{13}C NMR δ 164.0 (s), 154.5 (s), 152.8 (d), 135.4 (s), 133.9 (s), 132.5 (d), 132.0 (d), 131.9 (s), 131.8 (s), 131.3 (d), 130.2 (d), 129.7 (d), 124.1 (s), 124.0 (d), 117.3 (t), 112.6 (d), 41.8 (t); MS-EI *m/z* (relative intensity) 334 ($M[^{37}Cl_2]^+$, 12), 333 ($M[^{37}Cl_2]-H^+$, 20), 332 ($M[^{35}Cl^{37}Cl]^+$, 67), 331 ($M[^{35}Cl^{37}Cl]-H^+$, 67), 330 ($M[^{35}Cl_2]^+$, 100), 329 ($M[^{35}Cl_2]-H^+$, 78), 315 (13), 303 (23), 301 (33), 295 (18), 267 (16), 256 (22), 254 (68), 191 (22), 185 (57), 171 (35). HRMS (CI^+, CH_4) calcd for $C_{17}H_{13}ON_2^{35}Cl_2$ ($M+H^+$): 331.0405. Found: 331.0407.

5.5. Attribution of the configuration of the isoindolin-1-ones 15–17 and the pyrrolopyridinone 18. Synthesis of the geometric isomers of (*Z*) configuration

5.5.1. 2-(2-Bromobenzyl)-3-(*Z*)-benzylidene-2,3-dihydro-1*H*-isoindol-1-one (21). To a solution of **4b** (416 mg, 1.00 mmol) in DMF (5 mL) were successively added $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol, 0.035 equiv), CuI (15 mg, 0.080 mmol, 0.08 equiv) and Et_3N (0.56 mL, 4.02 mmol, 4 equiv). After 1 h at rt, phenylacetylene (0.13 mL, 1.2 mmol, 1.2 equiv) was added and the resulting mixture was heated at 80 °C. After 1 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was added to a solution of sodium ethoxide in absolute ethanol [prepared by adding Na (70 mg, 3.0 mmol, 3 equiv) in EtOH (20 mL)]. After 2 h at reflux, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the resulting mixture was evaporated under reduced pressure. The residue was portioned between EtOAc and water and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography (petroleum ether/EtOAc: 90:10) afforded 275 mg (70%) of an inseparable mixture of the known (*Z*)-3-benzylideneisoindolin-1-one **20**[8a,10c] and **21** (70/30 ratio). An analytically pure sample of **21** was obtained after separation by preparative TLC (toluene/ether=96:4) for individual characterization; IR 1705, 1645, 340, 1110, 1025, 980, 955 cm^{-1}; ^1H NMR δ 7.94 (br d, $J=7.0$ Hz, 1H), 7.80 (br d, $J=7.5$ Hz, 1H), 7.67 (td, $J=7.5$, 1.1 Hz, 1H), 7.56 (td, $J=7.5$, 1.1 Hz, 1H), 7.35–6.99 (m, 6H), 6.90 (m, 2H), 6.80 (s, 1H), 6.73 (br d, $J=8.3$ Hz, 1H), 4.81 (s, 2H); ^{13}C NMR δ 168.6 (s), 138.2 (s), 135.7 (s), 134.3 (s), 133.7 (s), 132.35 (d), 132.3 (d), 129.2 (d), 128.7 (d), 128.1 (d, 2C), 128.0 (s), 127.9 (d, 2C), 127.5 (d), 127.1 (d), 126.5 (d), 123.6 (d), 122.2 (s), 119.6 (d), 107.8 (d), 45.8 (t); MS-EI *m/z* (relative intensity) 391 ($M[^{81}Br]^+$, 5), 389 ($M[^{79}Br]^+$, 5), 311 ($M+H-Br^+$, 25), 310 ($M-Br^+$, 100), 232 (11), 170 (8), 168 (8), 165 (11), 90 (7), 89 (6).

5.5.2. 2-Allyl-3-(*Z*)-(2-methoxybenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (22). This compound was synthesized from **4c** (287 mg, 1.00 mmol) by a Sonogashira coupling with 2-methoxyphenylacetylene[44] (158 mg, 1.2 mmol, 1.2 equiv) in the presence of $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol, 0.035 equiv), CuI (15 mg, 0.080 mmol, 0.08 equiv) and Et_3N (0.56 mL, 4.0 mmol, 4 equiv) in DMF (5 mL) (1.5 h at 80 °C). The resulting crude disubstituted alkyne was cyclized by treatment with a solution of EtONa in EtOH [Na (70 mg) in EtOH (20 mL),

2 h at reflux]. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 90:10) to afford 222 mg (76%) of **22** as a waxy orange solid; IR 1707, 1656, 1595, 1578, 1487, 1460, 1328, 1248, 1216, 1103, 1017, 954, 910, 748, 698 cm^{-1}; ^1H NMR δ 7.85 (d, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H), 7.58 (apparent td, J=7.5, 1.1 Hz, 1H), 7.47 (apparent td, J=7.5, 1.1 Hz, 1H), 7.32 (apparent br td, J=8.1, 1.5 Hz, 1H), 7.25 (br d, J=7.5 Hz, 1H), 6.96 (dd, apparent t, J=7.5 Hz, 1H), 6.89 (br d, J=8.1 Hz, 1H), 6.70 (s, 1H), 5.44 (ddt, J=17.1, 10.3, 5.4 Hz, 1H), 4.85 (dq, J=10.3, 1.5 Hz, 1H), 4.54 (dq, J=17.1, 1.5 Hz, 1H), 4.31 (dt, J=5.4, 1.5 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR δ 168.6 (s), 157.6 (s), 138.5 (s), 134.8 (s), 132.6 (s), 131.9 (d), 131.6 (d), 129.3 (d), 128.8 (d), 128.2 (s), 123.7 (s), 123.2 (d), 119.9 (d), 119.6 (d), 116.1 (t), 110.4 (d), 103.6 (d), 55.4 (q), 43.7 (t); MS-EI *m/z* (relative intensity) 291 (M^+, 100), 290 ($M-H^+$, 24), 276 ($M-Me^+$, 11), 262 (17), 260 ($M-OMe^+$, 18), 232 (18), 219 (21), 206 (15), 185 (30), 184 (42), 182 (15), 185 (30), 184 (42), 182 (15), 170 (37), 165 (21), 152 (10), 102 (9).

5.5.3. 6-Allyl-7-(*Z*)-benzylidene-6,7-dihydropyrrolo-[3,4-*b*]pyridin-5-one (23). This compound was synthesized according to the experimental procedure described for the preparation of **22** from amide **4c**, by a Sonogashira coupling between amide **10** (114 mg, 0.473 mmol) and phenylacetylene (0.063 mL, 0.57 mmol, 1.2 equiv) in the presence of $PdCl_2(PPh_3)_2$ (12 mg, 0.016 mmol, 0.035 equiv), CuI (7.2 mg, 0.038 mmol, 0.08 equiv) and Et_3N (0.26 mL, 1.9 mmol, 4 equiv) in DMF (2.5 mL) (2 h at 80 °C). The resulting crude disubstituted alkyne was cyclized by treatment with a solution of EtONa in EtOH (2 h at reflux) and after purification of the crude material by flash chromatography (petroleum ether/EtOAc gradient: 80:20–70:30), 68 mg (58%) of **23** were obtained as a viscous oil; IR 1700, 1655, 1600, 1585, 1170, 780 cm^{-1}; ^1H NMR δ 8.80 (dd, J=4.9, 1.5 Hz, 1H), 8.15 (dd, J=7.9, 1.5 Hz, 1H), 7.45–7.29 (m, 7H), 5.48 (ddt, J=17.3, 10.5, 5.3 Hz, 1H), 4.93 (dq, J=10.5, 1.5 Hz, 1H), 4.63 (dq, J=17.3, 1.5 Hz, 1H), 4.35 (dt, J=5.3, 1.5 Hz, 2H); ^{13}C NMR δ 166.3 (s), 156.6 (s), 153.3 (d), 134.4 (s), 133.6 (s), 132.2 (d), 131.3 (d), 129.6 (d, 2C), 128.0 (d, 2C), 127.9 (d), 123.7 (d), 121.8 (s), 116.6 (t), 109.4 (d), 43.6 (t); MS-EI *m/z* (relative intensity) 262 (M^+, 67), 261 (100), 233 (17), 221 (17), 220 (13), 192 (15), 185 (10), 166 (10), 139 (5), 89 (5), 77 (6).

5.6. One-pot desilylation–Heck–Suzuki–Miyaura domino reactions from trimethylsilylynamides. 2-Benzyl-3-(*E*)-(3,4-dichlorobenzylidene)-2,3-dihydro-1*H*-isoindol-1-one (24)

To a solution of **7a** (300 mg, 0.692 mmol) in THF (30 mL) was added a 1 M aqueous solution of NaOH (1.7 mL, 1.7 mmol, 2.5 equiv). After 0.5 h at reflux, the resulting mixture was cooled to rt and benzeneboronic acid (158 mg, 0.828 mmol, 1.2 equiv), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol, 0.05 equiv), PPh_3 (18.5 mg, 0.069 mmol, 0.1 equiv) were successively added. After 1.5 h at reflux, the reaction mixture was worked-up as usual. Purification by flash chromatography (petroleum ether/EtOAc: 90:10) gave 119 mg (45%) of **24** as an orange solid; mp 136 °C; IR 1700, 1635, 1470, 1410, 1340, 1315, 770, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (d, J=7.0 Hz, 1H), 7.80–7.05 (m, 11H), 6.27 (s, 1H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 166.7 (s), 137.1 (s), 136.5 (s), 135.2 (s), 134.7 (s), 132.8 (s), 132.0 (d), 131.8 (s), 131.3 (d), 130.6 (d), 130.2 (s), 129.8 (d), 129.0 (d), 128.8 (d), 128.2 (d), 127.5 (d), 126.9 (d, 2C), 123.7 (d), 123.0 (d), 108.4 (d), 43.3 (t); MS-EI *m/z* (relative intensity) 384 ($M[^{37}Cl_2]+H^+$, 1), 383 ($M[^{37}Cl_2]^+$, 6), 382 ($M[^{37}Cl^{35}Cl]+H^+$, 9), 381 ($M[^{37}Cl^{35}Cl]^+$, 32), 380 ($M[^{35}Cl^{35}Cl]+H^+$, 19), 379 ($M[^{35}Cl_2]^+$, 48), 378 (12), 300 (7), 253 (8), 235 (10), 207 (14), 190 (7), 92 (8), 91 (100), 65 (10). HRMS (CI^+, CH_4) calcd for $C_{22}H_{16}ON^{35}Cl_2$ ($M+H^+$): 380.0609. Found: 380.0605.

5.7. Synthesis of lennoxamine

5.7.1. 6-Bromo-2,3-dimethoxybenzoic acid (27).[42] To a solution of 2,3-dimethoxybenzoic acid (2.50 g, 13.7 mmol) in a 0.7 M aqueous solution of NaOH (21 mL) at 0 °C, was added 1,3-dibromo-5,5-dimethylhydantoin (2.16 g, 7.55 mmol, 0.55 equiv). After 6 h at rt, the reaction was quenched by addition of solid sodium sulfite until the yellow color disappeared. The reaction mixture was diluted with ether and acidified to pH=2 by addition of a 1 M aqueous solution of hydrochloric acid. After extraction with ether, the combined extracts were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting viscous oil was dried under reduced pressure to afford 3.58 g (100%) of **27** as a white solid, which was directly engaged in the next step without further purification; mp 110–112 °C; IR 3220 (br), 1734, 1575, 1470, 1416, 1294, 1236, 1177, 1161, 1043, 988, 814, 790, 702, 634 cm^{-1}; ^1H NMR δ 9.53 (br s, 1H), 7.27 (d, J=8.9 Hz, 1H), 6.86 (d, J=8.9 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR δ 170.8 (s), 152.1 (s), 147.0 (s), 130.4 (s), 128.2 (d), 114.9 (d), 108.6 (s), 61.9 (q), 56.1 (q).

5.7.2. 6-Bromo-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxybenzamide (29). To the carboxylic acid **27** (2.86 g, 10.9 mmol) was added thionyl chloride (6 mL) and the resulting mixture was heated at reflux. After 3 h, the reaction mixture was cooled to rt and excess $SOCl_2$ was distilled off under reduced pressure (15 mmHg). The residue was dissolved in CH_2Cl_2 (30 mL) and a solution of aminoacetaldehyde dimethyl acetal **28** (1.80 mL, 16.5 mmol, 1.5 equiv), Et_3N (2.30 mL, 16.5 mmol, 1.5 equiv), and DMAP (67 mg, 0.55 mmol, 0.05 equiv) in CH_2Cl_2 (30 mL) was added at 0 °C. After 5 h at rt, the reaction mixture was hydrolyzed with a 0.5 M aqueous solution of hydrochloric acid and extracted with ether. The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 60:40–50:50) to afford 2.57 g (67%) of **29** as a pale yellow solid; mp 90 °C; IR 3420, 3330, 1665, 1570, 1515, 1470, 1410, 1295, 1265, 1080, 1005, 915, 855, 805 cm^{-1}; ^1H NMR δ 7.20 (d, J=8.8 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 6.04 (br t, J=5.5 Hz, 1H, NH), 4.50 (t, J=5.5 Hz, 1H), 3.83 (s, 3H) 3.82 (s, 3H) 3.56 (t, J=5.5 Hz, 2H), 3.39 (s, 6H); ^{13}C NMR δ 165.5 (s), 152.0 (s), 146.7 (s), 133.7 (s), 127.9 (d), 114.0 (d), 109.4 (s), 102.4 (d), 61.8 (q), 55.9 (q), 54.2 (q), 54.1 (q), 41.2 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 348 ($M[^{81}Br]+H^+$, 95), 346 ($M[^{79}Br]+H^+$, 95), 319 ($M[^{81}Br]-MeO^+$, 35), 318 ($M[^{81}Br]-MeOH^+$, 100), 317 ($M[^{79}Br]-MeO^+$, 35), 316

($M[^{79}Br]-MeOH^+$, 100). HRMS (CI^+, CH_4) calcd for $C_{13}H_{19}O_5N^{81}Br$ ($M+H^+$): 348.0447. Found: 348.0440.

5.7.3. 6-Bromo-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxy-*N*-trimethylsilylethynylbenzamide (30). To a solution of amide **29** (1.00 g, 2.87 mmol) in toluene (50 mL) at 0 °C, was added KHMDS (11.5 mL, 0.5 M in toluene, 5.74 mmol, 2 equiv). After 2 h at 0 °C, the iodonium salt **5** (2.59 g, 5.74 mmol, 2 equiv) was added to the reaction mixture. After 48 h at rt, the reaction mixture was filtered through Celite (toluene/diethyl ether: 80:20) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc gradient: 90:10–80:20) to afford 596 mg (47%) of **30** as a yellow oil; IR 2180, 1690, 1585, 1575, 1470, 1410, 1355, 1315, 1295, 1250, 1180, 1125, 1090, 1060, 1005, 845, 760, 720, 705, 670, 665, 655, 620 cm^{-1}; ^1H NMR δ 7.21 (d, J=8.8 Hz, 1H), 6.83 (d, J=8.8 Hz, 1H), 4.78 (apparent t, J=5.9 Hz, 1H), 3.89 (s, 3H) 3.85 (s, 3H), 3.84 (dd, ABX syst., J=13.6, 5.9 Hz, 1H), 3.75 (dd, ABX syst., J=13.6, 5.9 Hz, 1H), 3.43 (s, 6H), −0.08 (s, 9H); ^{13}C NMR δ 168.2 (s), 151.9 (s), 146.8 (s), 132.4 (s), 127.4 (d), 114.6 (d), 109.3 (s), 100.8 (d), 96.2 (s), 74.4 (s), 61.4 (q), 56.2 (q), 53.6 (q), 53.5 (q), 48.0 (t), −0.30 (q, 3C); MS (CI^+, CH_4) *m/z* (relative intensity) 446 ($M[^{81}Br]+H^+$, 45), 444 ($M[^{79}Br]+H^+$, 44), 414 (60), 412 (58), 351 (25), 350 (100), 334 (25), 260 (20). HRMS calcd for $C_{18}H_{27}O_5NSi^{81}Br$ ($M+H^+$): 446.0824. Found: 446.0823.

5.7.4. 6-Bromo-*N*-ethynyl-*N*-(2,2-dimethoxyethyl)-2,3-dimethoxybenzamide (31). To a solution of **30** (500 mg, 1.12 mmol) in THF (15 mL) at 0 °C, was added TBAF (1.5 mL, 1 M in THF, 1.5 mmol, 1.3 equiv). After 10 min, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 70:30) to afford 376 mg (90%) of **31** as a pale yellow solid; mp 100–101 °C; IR 3300, 2150, 1690, 1475, 1415, 1355, 1295, 1270, 1090, 1050, 1000, 805, 670, 640 cm^{-1}; ^1H NMR δ 7.23 (d, J=8.5 Hz, 1H), 6.83 (d, J=8.5 Hz, 1H), 4.79 (t, J=5.7 Hz, 1H), 3.89 (s, 3H) 3.85 (s, 3H), 3.85 (dd, ABX syst., J=13.9, 5.7 Hz, 1H), 3.81 (dd, ABX syst., J=13.9, 5.7 Hz, 1H), 3.44 (s, 6H), 2.63 (s, 1H); ^{13}C NMR δ 167.8 (s), 151.7 (s), 146.6 (s), 131.8 (s), 127.4 (d), 114.5 (d), 108.9 (s), 100.7 (d), 77.1 [(NC≡C), the signal corresponding to the other ynamide carbon could not be unambiguously assigned presumably due to overlap], 61.4 (q), 55.9 (q), 53.8 (q), 53.7 (q), 48.5 (t); MS-EI *m/z* (relative intensity) 374 ($M[^{81}Br]+H^+$, 0.4), 373 ($M[^{81}Br]^+$, 3), 372 ($M[^{79}Br]+H^+$, 0.5), 371 ($M[^{79}Br]^+$, 3), 342 (6), 340 (6), 245 (77), 243 (79), 232 (8), 230 (6), 228 (10), 202 (11), 201 (5), 200 (12), 199 (5), 157 (5), 97 (6), 75 (100). HRMS calcd for $C_{15}H_{18}NO_5^{79}Br$ ($M+H^+$): 372.0447. Found: 372.0448.

5.7.5. 3-[(*E*)-(1-Benzo[1,3]dioxol-5-yl)methylidene]-2-(2,2-dimethoxyethyl)-6,7-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (33). To a solution of ynamide **31** (561 mg, 1.51 mmol) in THF (60 mL) were successively added the arylboronic acid **32** (300 mg, 1.81 mmol, 1.2 equiv), a 1 M aqueous solution of NaOH (2.3 mL, 2.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (17 mg, 0.075 mmol, 0.05 equiv) and PPh_3 (40 mg, 0.15 mmol, 0.1 equiv). After 2 h at reflux, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 480 mg (77%) of **33**[15b] as a yellow oil and as a 85/15 mixture of (*E*)/(*Z*) geometric isomers; IR 1690, 1640, 1500, 1430, 1330, 1270, 1235, 1120, 1095, 1035, 935, 825, 740 cm^{-1}; ^1H NMR (only the signals corresponding to the (*E*) major isomer could all be attributed unambiguously) δ 7.09 (d, J=8.5 Hz, 1H), 6.90–6.75 (m, 4H), 6.48 (s, 1H), 6.00 (s, 2H) 4.67 (t, J=5.1 Hz, 1H) 4.06 (s, 3H), 3.94 (d, J=5.1 Hz, 2H), 3.84 (s, 3H), 3.43 (s, 6H); ^{13}C NMR (only the signals corresponding to the major (*E*) isomer could all be attributed unambiguously) δ 164.7 (s), 153.2 (s), 147.7 (s), 146.9 (s), 146.4 (s), 135.5 (s), 129.0 (s), 128.7 (s), 123.0 (d), 122.0 (s), 118.8 (d), 115.8 (d) 109.6 (d), 108.7 (d), 108.4 (d), 102.2 (d), 101.1 (t), 62.2 (q), 56.4 (q), 54.4 (q, 2C), 41.7 (t); MS-EI *m/z* (relative intensity) 414 ($M+H^+$, 3), 413 (M^+, 42), 398 (3), 381 (8), 350 (6), 338 (14), 325 (11), 308 (9), 294 (7), 280 (8), 264 (6), 207 (20), 75 (100).

5.7.6. (1-Benzo[1,3]dioxol-5-yl)methyl-2-(2,2-dimethoxyethyl)-6,7-dimethoxy-2,3-dihydroisoindol-1-one (34). A mixture of **33** (231 mg, 0.559 mmol) and Pd (10%)/C (30 mg, 0.028 mmol, 0.05 equiv) in MeOH (8 mL) was stirred under an atmospheric pressure of hydrogen. After 4 h, the reaction mixture was filtered through Celite (MeOH) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 187 mg (80%) of **34**[15b] as a white solid; mp 125–126 °C; IR 1682, 1490, 1440, 1404, 1266, 1245, 1192, 1122, 1094, 1036, 981, 927, 811, 782, 730, 662, 609 cm^{-1}; ^1H NMR δ 6.97 (d, J=8.4 Hz, 1H), 6.65 (d, J=8.4 Hz, 1H), 6.62 (dd, J=8.1, 0.7 Hz, 1H), 6.47–6.41 (m, 2H), 5.90 (d, J=1.4 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 4.80 (dd, J=8.1, 3.7 Hz, 1H), 4.54 (dd, J=6.6, 3.6 Hz, 1H), 4.18 (dd, J=14.3, 3.6 Hz, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.31 (dd, J=13.8, 3.8 Hz, 1H), 3.19 (dd, J=14.3, 6.6 Hz, 1H), 2.65 (dd, J=13.8, 8.0 Hz, 1H); ^{13}C NMR δ 166.7 (s), 152.3 (s), 147.5 (s), 147.0 (s), 146.4 (s), 138.9 (s), 129.6 (s), 124.1 (s), 122.7 (d), 118.0 (d), 116.0 (d), 109.7 (d), 108.1 (d), 103.4 (d), 100.9 (t), 62.4 (q), 60.2 (d), 56.7 (q), 55.4 (q), 54.7 (q), 42.2 (t), 37.8 (t); MS-EI *m/z* (relative intensity) 414 ($M-H^+$, 0.1), 384 (5), 281 (16), 280 (100), 249 (12), 248 (79), 206 (6), 205 (4), 190 (5), 176 (4), 162 (4), 135 (9), 77 (6), 75 (12).

5.7.7. Dehydrolennoxamine (35).[15b] To a solution of **34** (115 mg, 0.277 mmol) in AcOH (3 mL) was slowly added H_2SO_4 (0.12 mL, 2.4 mmol, 8.5 equiv). After 3 h at rt, the reaction mixture was neutralized by dropwise addition of 28% aqueous NH_4OH at 0 °C. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 60:40) to afford 58 mg (60%) of **35** as a yellow solid; mp 224–225 °C; IR 1689, 1650, 1491, 1450, 1357, 1266, 1237, 1216, 1032, 928, 854, 828, 814, 792, 769 cm^{-1}; ^1H NMR δ 7.18 (s, 2H), 7.10 (d, J=10.5 Hz, 1H), 6.70

(apparent s, 2H), 5.96 (apparent br s, 2H), 5.66 (d, J= 10.5 Hz, 1H), 4.68 (d, J=9.4 Hz, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 3.34 (d, J=15.7 Hz, 1H), 3.00 (dd, J=15.1, 9.4 Hz, 1H); ^{13}C NMR δ 163.6 (s), 152.8 (s), 147.6 (s), 146.7 (s), 146.4 (s), 137.4 (s), 130.0 (s), 129.2 (s), 123.0 (s), 120.0 (d), 117.4 (d), 117.2 (d), 110.5 (d), 110.0 (d), 109.2 (d), 101.2 (t), 62.5 (q), 59.7 (d), 56.8 (q), 42.2 (t); MS-EI *m/z* (relative intensity) 352 ($M+H^+$, 20), 351 (M^+, 100), 350 ($M-H^+$, 9), 336 (8), 322 (8), 207 (11), 160 (48), 130 (18), 102 (14).

5.7.8. Lennoxamine.[15b,41] A mixture of **35** (58 mg, 0.16 mmol) and Pd (10%)/C (17.5 mg, 0.016 mmol, 0.05 equiv) in AcOH (15 mL) was stirred under an atmospheric pressure of hydrogen. After 14 h at rt, the reaction mixture was filtered through Celite (AcOH) and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chomatography (petroleum ether/EtOAc: 50:50) to afford 37 mg (65%) of lennoxamine as a white solid; mp 226–228 °C; IR 1679, 1483, 1424, 1263, 1196, 1172, 1035, 934, 834 cm^{-1}; ^{1}H NMR δ 7.16 (d, J=8.3 Hz, 1H), 7.11 (d, J=8.3 Hz, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 5.94 (d, J=1.5 Hz, 1H), 5.93 (d, J=1.5 Hz, 1H), 4.78–4.67 (m, 1H), 4.28 (dd, J= 10.5, 1.5 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.09 (dd, J=14.7, 1.9 Hz, 1H), 2.93–2.75 (m, 4H); ^{13}C NMR δ 165.2 (s), 152.6 (s), 147.3 (s), 146.4 (s), 146.1 (s), 138.2 (s), 134.8 (s), 131.0 (s), 124.2 (s), 117.0 (d), 116.2 (d), 110.4 (d), 110.3 (d), 101.1 (t), 62.5 (q), 60.2 (d), 56.7 (q), 42.7 (t), 41.1 (t), 35.9 (t); MS (CI^+, CH_4) *m/z* (relative intensity) 354 ($M+H^+$, 100), 353 (8), 318 (10), 316 (10). HRMS calcd for $C_{20}H_{20}NO_5$ ($M+H^+$): 354.1341. Found: 354.1337.

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44. This compound was prepared in two steps from 2-methoxybenzaldehyde by dibromomethylenation (PPh_3, CBr_4, CH_2Cl_2, 0 °C) and subsequent treatment of the dibromoolefin with *n*-BuLi (2 equiv), THF, −78 °C (73% overall yield), see: Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

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Practical preparation of *N*-(1-alkynyl)sulfonamides and their synthetic utility in titanium alkoxide-mediated coupling reactions

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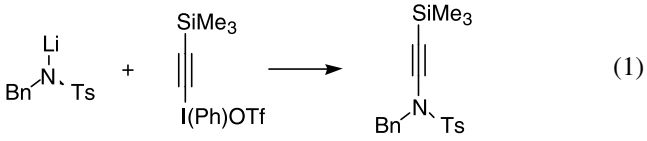
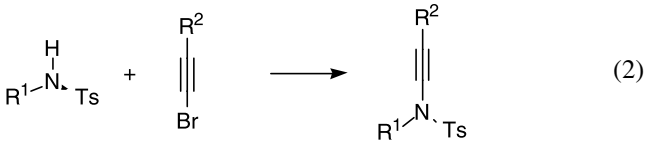
Abstract—Aliphatic and aromatic sulfonamides were alkynylated with 1-bromo-1-alkynes in the catalytic presence of CuI to give *N*-(1-alkynyl)sulfonamides in good to excellent yields. Racemization of optically active sulfonamides was not observed during this alkynylation. The acetylene–titanium complexes generated from the resultant *N*-(1-alkynyl)sulfonamides and Ti(O–*i*-Pr)$_4$/2 *i*-PrMgCl underwent regio-, olefinic stereo-, and diastereoselective addition to aldehydes to give virtually single allyl alcohols. Alternatively, inter- or intramolecular coupling reaction between *N*-(1-alkynyl)sulfonamides and another acetylene or olefin with the above titanium alkoxide reagent generated the corresponding titanacycles, hydrolysis of which furnished stereo-defined (sulfonylamino)dienes or cyclic compounds.

1. Introduction

Acetylenes are versatile starting materials for transition metal-mediated coupling reactions with other unsaturated compounds.[1] As far as the group 4 metal-mediated coupling reactions are concerned,[2–4] functionalized acetylenes such as alkoxycarbonyl-, chloro-, alkoxy-, sulfur-, or phosphorus-functionalized ones were utilized to effect unique transformations.[5] However, (protected) amino-substituted acetylenes had not yet been studied, until we reported the first example 2 years ago.[6,7] There are a wide variety of methods to prepare amino-substituted acetylenes,[8] among which the displacement of alkynyliodonium salts with amino-nucleophiles has been one of the most dependable methods (Eq. 1).[9] However, as the prior preparation of alkynyliodonium salts needs additional steps, a more straightforward synthesis of these acetylenes is called for. The recent success in the transition-metal catalyzed displacement at an sp^2 or sp-carbon center bearing a leaving group with a heteroatom nucleophile[10,11] led us to examine a new and facile preparation of *N*-(1-alkynyl)sulfonamides from sulfonamides and haloacetylenes (Eq. 2) and, eventually, their application to titanium-mediated coupling reactions.



(1)



(2)

2. Results and discussion

2.1. Preparation of *N*-(1-alkynyl)sulfonamides

Considering the broad applicability of palladium-catalyzed coupling reactions between aryl or vinyl halides and amino-nucleophiles,[10] we first attempted N-alkynylation of sulfonamide **1**[12] with 1-bromo-1-octyne (**2**) under palladium catalysis. A few selected conditions are summarized in Table 1, which did not show a fruitful result. During the course of our study along this line, copper-catalyzed alkynylation of amides by Hsung and co-workers[11b] and the copper-mediated alkynylation of sulfonamides by Danheiser's group[11c] appeared. In addition to these pioneering works, we report here our results on a copper-catalyzed coupling reaction between 1-halo-1-alkynes and sulfonamides to give various *N*-(1-alkynyl)-sulfonamides.[6b] Some typical conditions are summarized

Keywords: Alkynylation; Copper catalyst; Sulfonamides; Titanium alkoxide; Titanacycle; Ynamide; Enamide.
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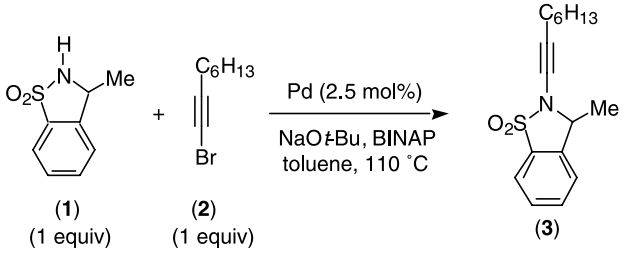
Table 1. Attempted Pd-catalyzed alkynylation of benzosultam **1**

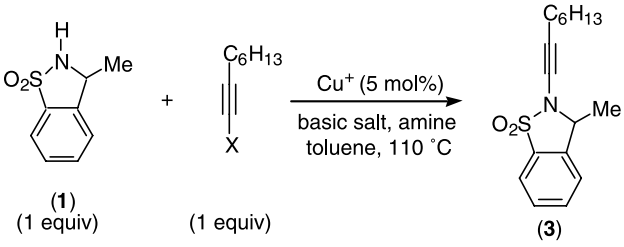


(**1**) (1 equiv) (**2**) (1 equiv) (**3**)

Entry	Pd	Yield (%)[a]
1	$Pd(PPh_3)_4$	<1
2	$PdCl_2(C_6H_5CN)_2$	<1
3	$Pd_2(dba)_3$	<1

[a] Yield determined by ^1H NMR spectroscopy with $CHCl{=}CCl_2$ as an internal standard.

Table 2. Optimum conditions for the alkynylation of benzosultam **1**



(**1**) (1 equiv) (1 equiv) (**3**)

Entry	X	Cu^+	Basic salt	Amine	Yield (%)[a]
1	Br	CuI	Cs_2CO_3	$(CH_2NHMe)_2$	68
2	Br	CuI	K_2CO_3	$(CH_2NHMe)_2$	94 (68)
3	Br	CuCN	K_3PO_4	$(CH_2NHMe)_2$	87
4	Br	CuSPh	K_3PO_4	$(CH_2NHMe)_2$	93
5	Br	CuI	K_3PO_4	$(CH_2NH_2)_2$	62
6	Br	CuI	K_3PO_4	$(CH_2NHMe)_2$	97 (79)
7	I	CuI	K_3PO_4	$(CH_2NHMe)_2$	77

[a] Yield determined by ^1H NMR spectroscopy with $CHCl{=}CCl_2$ as an internal standard. Isolated yield in parantheses.

in Table 2. The best yield was obtained in entry 6 with alkynyl bromide rather than iodide (cf. entry 7), with K_3PO_4 rather than K_2CO_3 or Cs_2CO_3 (entries 1 and 2), and with *N*,*N*′-dimethylethylenediamine rather than ethylenediamine (entry 5). Under the optimum conditions, a virtually quantitative yield of the desired product **3** was attained.

Table 3 shows the generality of this transformation. Open-chain sulfonamide **4** was alkynylated with 1-bromo-1-octyne (**2**) to give **12** in good yield (entry 1). This compound was previously prepared via a stepwise sequence, involving (i) coupling of (silylethynyl)iodonium salt with *N*-benzyl-*p*-toluenesulfonamide (**4**) (to give **13**, see Eq. 1), (ii) desilylation of **13** to the terminal acetylene, and (iii) its alkylation.[6a] Thus, the one-step synthesis from **4** to **12** proved to be advantageous over the conventional method shown in Eq. 1. The trimethylsilyl group of bromide **10** survived the reaction conditions to give *N*-(silylethynyl)-sulfonamide **13** in good yield, which is a precursor of the versatile terminal acetylene as mentioned above (entry 2). Another open-chain sulfonamide **5** afforded the coupling products **14** and **15**, although the yield was not satisfactory under the standard conditions and thus the excess use of the alkynylating agent is required (entry 3). It should be noted that the product **15** (and also **14**) were hardly obtained by the alkynyliodonium method (Scheme 1). Sterically more congested benzosultams **6**–**8** were successfully alkynylated to afford the desired products (entries 7–12). The enantiopurity of optically active sultam **7** was completely retained in the product (**19**, entry 9). In addition to aromatic sulfonamides **1** and **4**–**8**, an aliphatic cyclic sulfonamide **9**, a useful chiral auxiliary known as Oppolzer's camphorsultam,[13] underwent this coupling reaction to give **23** or **24**. In the latter case, the product yield was improved by the use of excess alkylating agent (entry 14).

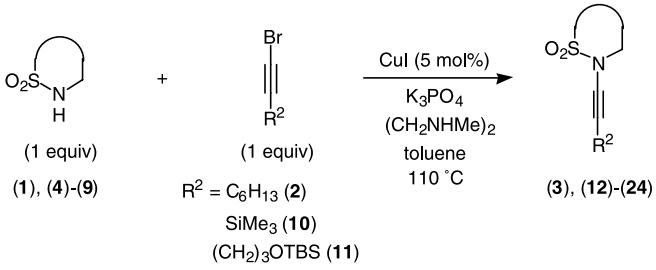
2.2. Coupling of *N*-(1-alkynyl)sulfonamides with aldehyde

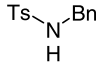
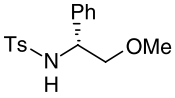
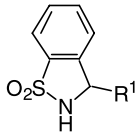
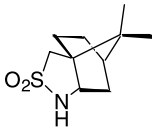
With *N*-(1-alkynyl)sulfonamides in hand, we began to investigate the generation and synthetic application of a new class of *N*-(1-alkynyl)sulfonamide–titanium alkoxide complexes. As the aminoacetylenes having a chiral element were conveniently prepared as shown in Table 3, the titanation of these acetylenes followed by the aldehyde addition should lead to an interesting approach for asymmetric synthesis (Table 4). Thus, *N*-(silylethynyl)-sultam **16** was first treated with a titanium(II) alkoxide reagent, Ti(O–*i*-Pr)$_4$/2 *i*-PrMgCl (**25**),[4] to generate the acetylene–titanium complex **26**, to which was added benzaldehyde as **27**. After hydrolysis, the adduct **29** was obtained in good yield, showing virtually complete regio- and olefinic stereoselectivities[6a,14,15] and with high 1,5-diastereoselectivity (ds=96:4) (entry 1). The excellent level of the remote asymmetric induction (=1,5-diastereoselectivity) is noteworthy.[16] Other sultams **18**, **20**, and **24** having the same acetylenic moiety gave the analogous adducts with benzaldehyde in the following yields and diastereoselectivities: 73%, 97:3; 62%, 79:21; and 46%, 84:16, which revealed that sultam **16** is the most effective one. The structure of **29** was established by spectroscopic means as well as appropriate derivatization. The deuteriolysis confirmed the presence of the remaining vinyl–titanium bond in the intermediate oxatitanacycle **28**, which may serve for further transformations.[17] Other types of aldehydes gave the adducts **30**–**34** in good to excellent diastereoselectivities (entries 2–6).

Chart 1 shows a proposed stereochemical course of the above reaction. The intermediate shown below, which fulfills (i) the least hindered conformation of the sultam moiety to the substituent (Me_3Si) of the titanated acetylene, (ii) the approach of the aldehyde from the less hindered side (opposite the Me group on the sultam), and (iii) the less hindered orientation of the side chain (R) of the aldehyde, may account for the observed stereochemistry of the products in entries 1–6.

On the other hand, when the same reaction between the sultams having an *N*-octynyl group and aldehydes is performed, benzosultam **19** with a *tert*-butyl side chain was found to be the substrate of choice and its titanation and subsequent addition to aldehydes afforded the coupling

Table 3. Alkynylation of various sulfonamides

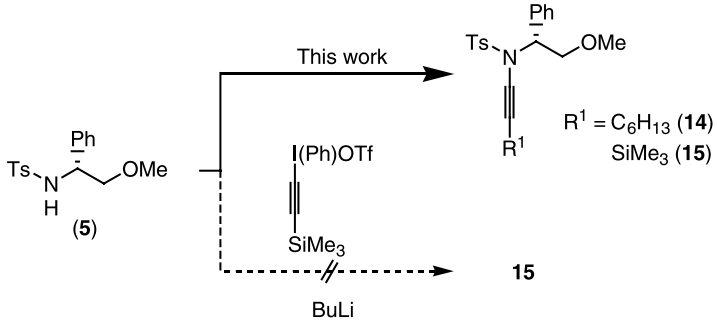


Entry	Starting sulfonamide		Bromoalkyne	Product		
				R^2		Yield (%)[a]
1		(**4**)	**2**	C_6H_{13}	(**12**)	93
2		(**4**)	**10**	$SiMe_3$	(**13**)	84
3		(**5**)	**2**	C_6H_{13}	(**14**)	28, 44,[b] 57,[c] 67[d]
4		(**5**)	**10**	$SiMe_3$	(**15**)	23
5		R^1=Me (**1**)	**2**	C_6H_{13}	(**3**)	79
6		Me (**1**)	**10**	$SiMe_3$	(**16**)	71
7		Bu (**6**)	**2**	C_6H_{13}	(**17**)	84
8		Bu (**6**)	**10**	$SiMe_3$	(**18**)	66
9		*t*-Bu (**7**)[e]	**2**	C_6H_{13}	(**19**)[e]	94
10		*t*-Bu (**7**)	**10**	$SiMe_3$	(**20**)	71
11		*t*-Bu (**7**)	**11**	-$(CH_2)_3$OTBS	(**21**)	81
12		Ph (**8**)	**11**	-$(CH_2)_3$OTBS	(**22**)	91
13		(**9**)	**2**	C_6H_{13}	(**23**)	95
14		(**9**)	**10**	$SiMe_3$	(**24**)	58, 95[f]

[a] Isolated yield.
[b] Compound **2** (2 equiv) was used.
[c] Compound **2** (3 equiv) was used.
[d] Compound **2** (4 equiv) was used.
[e] The enantiopurity of (*S*)-**7** (96% ee) was completely preserved in the product (*S*)-**19** (96% ee).
[f] Compound **10** (2 equiv) was used.

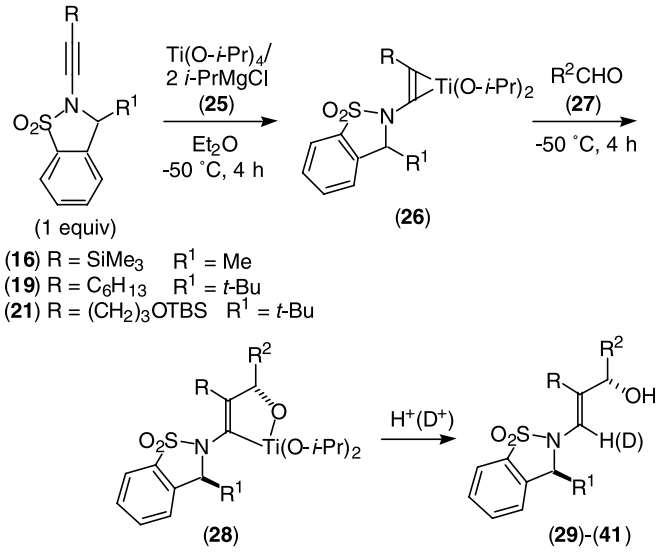
products **35**–**40**, again with exclusive regio- and olefinic stereoselectivities and good to excellent 1,5-diastereoselectivities (entries 7–12). Benzosultam **21** with a different acetylenic side chain also showed a similar result (entry 13). When the reaction was started with chiral alkynylsultam ((*S*)-**19**, 96% ee, prepared in entry 9 of Table 3), the optically active products **38** and **40** were obtained without loss of the enantiopurity (entries 10 and 12).

Chart 2 shows a proposed stereochemical course of the reaction discussed above. The intermediate shown below,



Scheme 1.

Table 4. Remote diastereoselective addition of *N*-alkynylsultams to aldehydes



Entry	Sultam	Aldehyde		Product		
		R^2	Equiv		Yield (%)[a]	1,5-Ds[b]
1	**16**	Ph	0.8	(**29**)	87 (97%D)[c]	96:4[d]
2	**16**	*p*-ClC$_6$H$_4$–	1	(**30**)	54	96:4
3	**16**	(*E*)-C$_5$H$_{11}$CH=CH–	0.8	(**31**)	73	94:6
4	**16**	(*E*)-MeCH=CH–	1	(**32**)	52	95:5
5	**16**	C$_8$H$_{17}$	0.8	(**33**)	94	88:12
6	**16**	*c*-C$_6$H$_{11}$	0.8	(**34**)	89	68:32
7	**19**	Ph	1	(**35**)	74	88:12
8	**19**	(*E*)-MeCH=CH–	1	(**36**)	59	81:19
9	**19**	C$_8$H$_{17}$	1	(**37**)	62	88:12
10[e]	**19**[f]	*i*-Pr	1	(**38**)[f]	88 (96%D)[c]	93:7
11	**19**	*c*-C$_6$H$_{11}$	0.8	(**39**)	79	93:7
12	**19**[f]	*t*-Bu	0.8	(**40**)[f]	93	98.2
13	**21**	*i*-Pr	1.5	(**41**)	84	>95:5[g]

[a] Isolated yields.
[b] Diasterioselectivity.
[c] Result of deuteriolysis.
[d] Isomerically pure sample of **29** could be obtained by recrystallization from hexane–CH_2Cl_2.
[e] In this case, a small amount of a regioisomer (less than 4%) was detected and was easily separated from **38** by silica gel chromatography. In other entries, we were unable to identify the regioisomeric product(s).
[f] The enantiopurity of (*S*)-**19** (96% ee) was retained in the product **38** (95% ee) or **40** (96% ee).
[g] We were unable to identify the characteristic peaks of minor diastereoisomer by ^{1}H NMR spectroscopy, and deduced that the diastereoselectivity of **41** was > 95:5.

which fulfills (i) the least hindered conformation of the sultam moiety to the substituent (C_6H_{13}) of the titanated acetylene, (ii) the approach of the aldehyde from the less hindered side (opposite the *t*-Bu group on the sultam), and (iii) the less hindered orientation of the side chain (R) of the aldehyde, may account for the observed stereochemistry of the products of entries 7–13.

Some derivatizations based on the coupling products obtained in Table 4 demonstrated their synthetic utility.

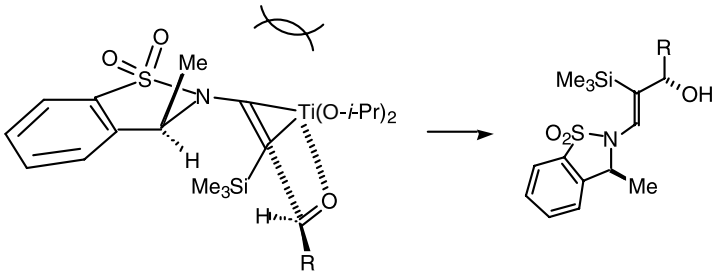


Chart 1.

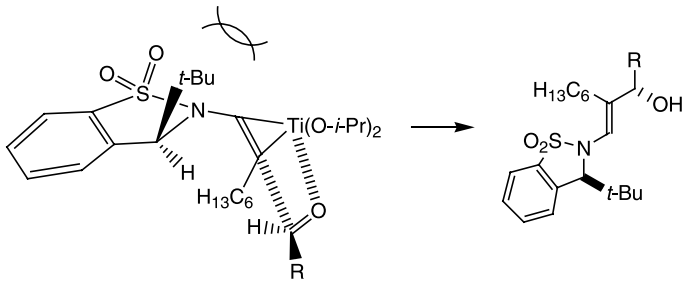
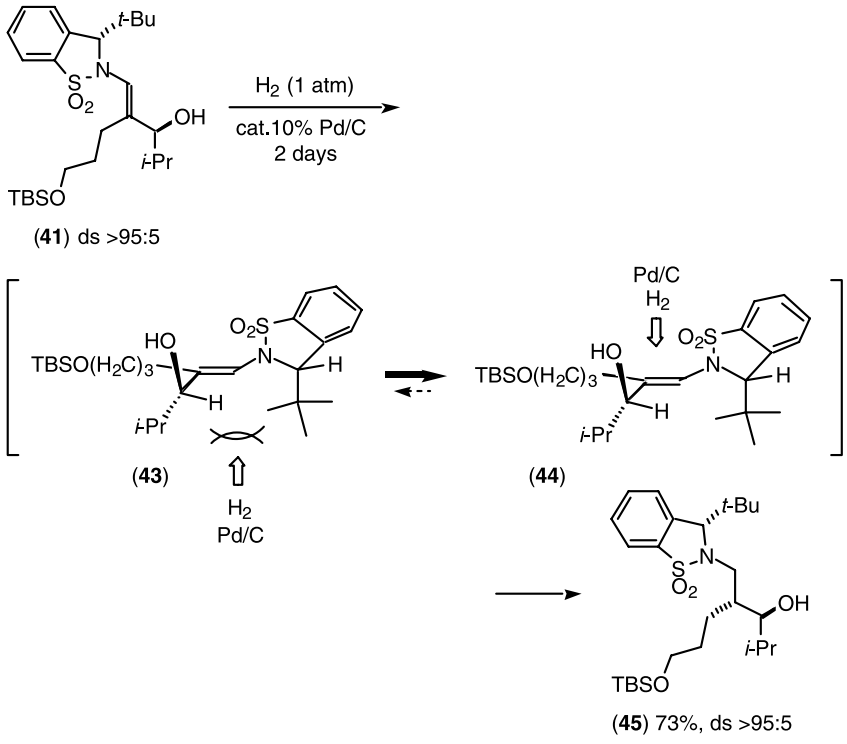
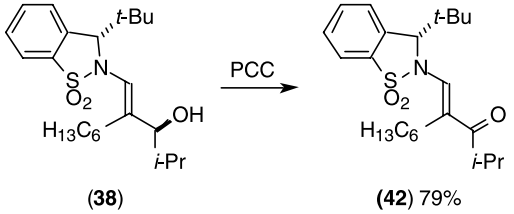


Chart 2.



Scheme 2.

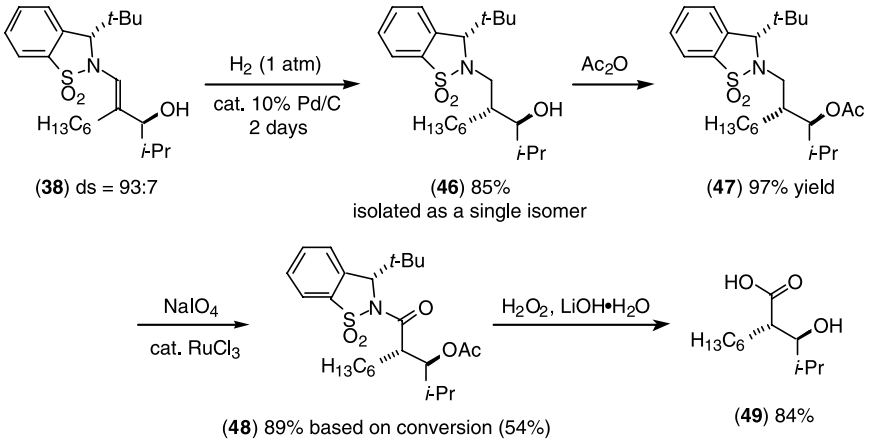
Oxidation of alcohol **38** afforded an α,β-unsaturated ketone **42** having a chiral amino group at its β-position (Eq. 3).[18] On the other hand, hydrogenation of **41** on Pd/C produced γ-aminoalcohol **45** in a highly stereoselective manner (Scheme 2). The stereochemical outcome of the hydrogenation could be interpreted in terms of the less hindered approach of hydrogen on Pd/C to the depicted conformation of **44**[19] rather than **43**. After protection of its hydroxy group, a similar hydrogenated product **46** prepared from **38** was oxidized at the methylene group adjacent to the benzosultam with $RuCl_3$–$NaIO_4$ to afford chiral amide **48**, which, in turn, was smoothly hydrolyzed to afford hydroxy ester **49** (Scheme 3).



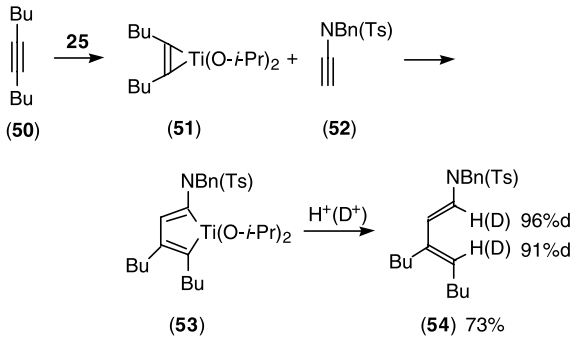
(3)

2.3. Coupling of *N*-(1-alkynyl)sulfonamides with another acetylene or olefin

One of the most characteristic features of acetylene–titanium alkoxide complexes is their capability of undergoing the coupling reaction with another acetylene. When this reaction is successfully applied to the *N*-(1-alkynyl)-sulfonamides, stereoselective construction of aminodienes, which are versatile compounds for the preparation of nitrogen-functionalized cyclic systems via a concerted process such as the Diels–Alder reaction, will be readily achieved.[20] Acetylene–titanium complex **51**, generated from 5-decyne (**50**) and **25**[4] by a known procedure,[21] was found to undergo a coupling reaction with the amino-substituted acetylene **52** (prepared by desilylation of **13** as described in Section 2.1) at −50 °C in a regio- and stereoselective manner to give single dienamide **54** after hydrolytic workup (Scheme 4).[22,23] Its structure was verified by ^{1}H NMR spectroscopy. In addition to the simple hydrolysis, deuteriolysis gave bis-deuterated dienamide **54**-d_2, confirming the presence of titanacyclopentadiene **53** as the intermediate.



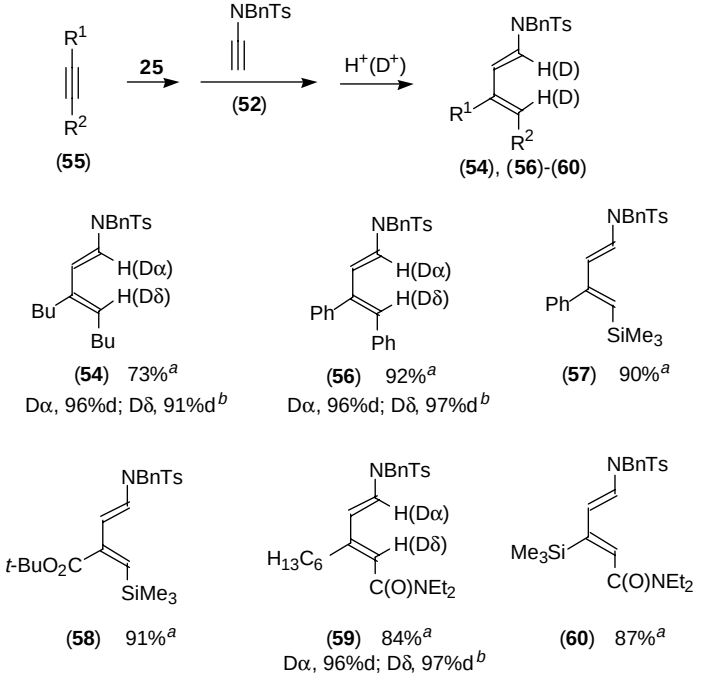
Scheme 3.



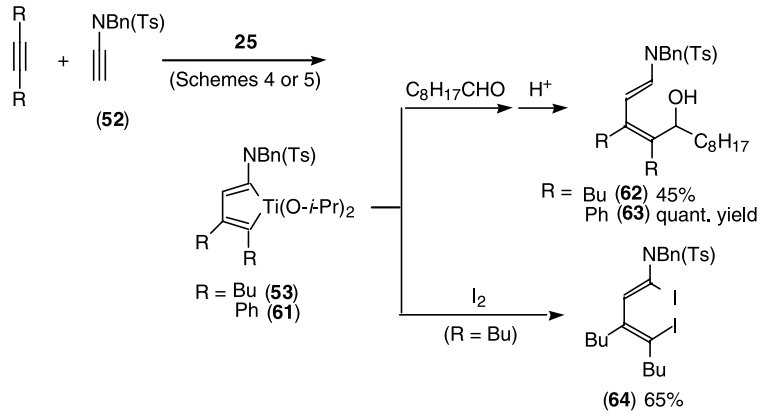
Scheme 4. Preparation of dienamide.

The generality of this reaction is shown in Scheme 5. As the first acetylene **55**, dialkylacetylene, diphenylacetylene, silylacetylene, and acetylenic esters and amides participated in the coupling reaction to give a variety of dienamides **54** and **56–60** in good to excellent yields. All reactions afforded the products as a single regio- as well as stereoisomer. In addition, further carbon-chain elongation and functionalization of the intermediate titanacycles **53** and **61** were exemplified by the regio- and stereoselective aldehyde addition to furnish **62** and **63** or by iodinolysis of **53** to give diiodide **64** (Scheme 6).[17]

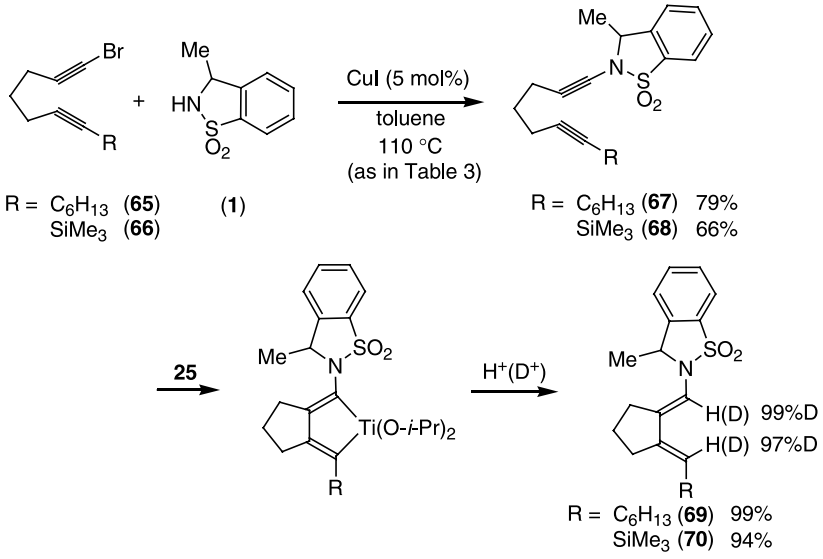
Intramolecular coupling of two acetylenic moieties is an attractive method to prepare cyclic compounds (Scheme 7). The starting diynes **67** and **68** were readily prepared by the standard protocol, copper-catalyzed *N*-alkynylation of sulfonamide **1** with bromodiynes **65** and **66** without any complication. The resultant dinynes **67** and **68** were then cyclized with the titanium reagent to give, upon hydrolysis or deuteriolysis, the desired



Scheme 5. Preparation of various dienamides according to Scheme 4. Isomeric products were not observed. The stereochemistry was unambiguously determined in several representative cases. [a]Isolated yields. [b]Results of deuteration.



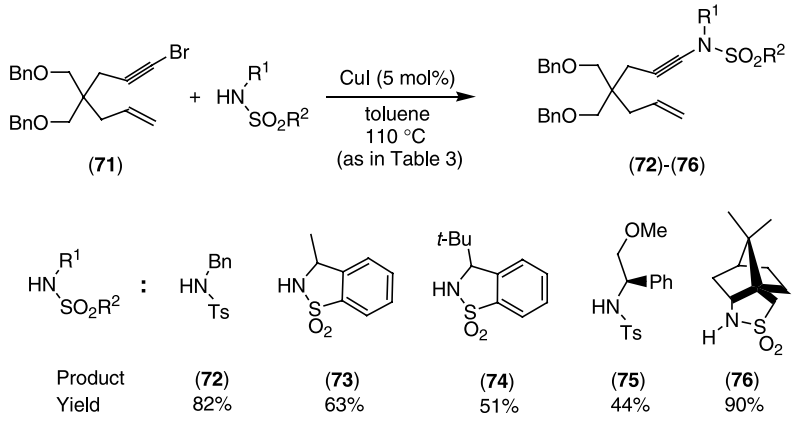
Scheme 6. Synthetic utility of the titanacycle.



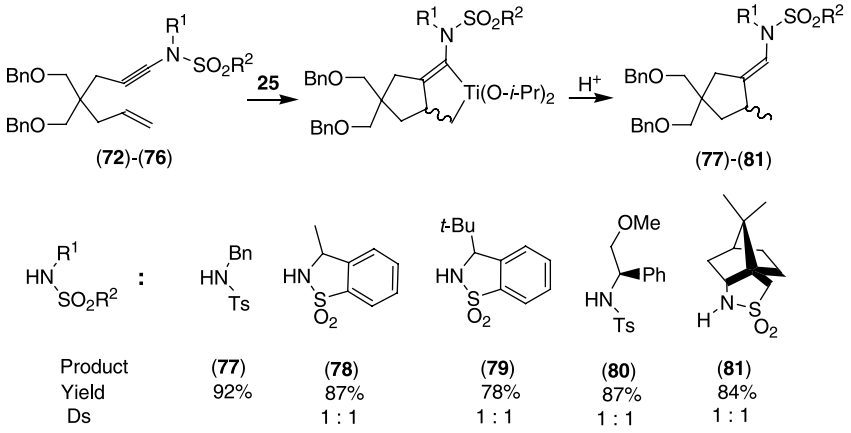
Scheme 7. Preparation of *N*-alkadiynylsulfonamides and its intramolecular cyclization with titanium reagent **25**.

amino-substituted, *exo*-cyclic dienes **69** and **70** in excellent yields.

In contrast to the above successful inter- and intramolecular coupling reactions between two acetylenes, the attempted intermolecular coupling of an *N*-(1-alkynyl)sulfonamides with an olefin failed. Accordingly, we moved to investigate an intramolecular version, that is, enyne cyclization,[24] and were glad to find that this type of reaction was, in fact, viable (Schemes 8 and 9). The copper-catalyzed alkynylation of sulfonamides with bromoenyne **71** proceeded as usual, unaffected by the neighboring olefinic moiety in the



Scheme 8. Preparation of *N*-alkadiynylsulfonamides having an olefin moiety.



Scheme 9. Intramolecular enyne cyclization of *N*-alkynylsulfonamides.

same molecule, to give the starting *N*-(1-alkynyl)sulfonamides **72–76** having an olefinic appendix (Scheme 8). Although the observed diastereoselectivities of the subsequent titanium alkoxide-mediated coupling reaction fell in an unsatisfactory range, the desired cyclic products **77–81** were obtained in good yields (Scheme 9).

3. Conclusion

A variety of *N*-(1-alkynyl)sulfonamides are now conveniently prepared from readily available starting materials and reagents. This improved synthesis enhanced the utility of these amino-substituted acetylenes to promising compounds that serve for the stereoselective construction of enamides and dienamide. Further application of the present transformation as well as the resultant amino-substituted compounds in organic synthesis will be reported in due course.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively. $CDCl_3$ was used as the solvent, unless otherwise specified. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. When a sample was dissolved in C_6D_6 for ^{1}H NMR spectroscopy, the peak of the residual proton of the solvent is the internal standard (δ 7.20 ppm). Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in Hertz. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). Optical rotation was measured on JASCO DIP-370 digital polarimeter. All reactions were carried out under argon. Dry solvents were purchased from Kanto Chemicals Co. (Japan). Chemicals were purified or dried in a standard manner, if necessary.

4.1.1. Typical procedure for Table 3. *N*-(1-Octynyl)-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (19). To a heterogeneous mixture of 3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**7**) (90.1 mg, 0.400 mmol), powdered K_3PO_4 (170 mg, 0.80 mmol), and CuI (3.8 mg, 0.020 mmol) in 1 mL of toluene was added 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol) in 3 mL of toluene followed by *N*,*N*′-dimethylethylenediamine (0.010 mL) under argon. After the mixture was stirred overnight in an oil bath maintained at 110 °C, it was cooled to room temperature and was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (125.2 mg, 94%) as an oil. ^{1}H NMR δ 0.87 (t, J=6.9 Hz, 3H), 1.10 (s, 9H), 1.19–1.45 (m, 6H), 1.46–1.58 (m, 2H), 2.32 (t, J=7.2 Hz, 2H), 4.45 (s, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 13.87, 18.53, 22.39, 26.74, 28.53, 28.69, 31.17, 38.23, 71.13, 72.63, 75.26, 121.84, 125.77, 129.49, 132.54, 134.13, 135.59; IR (neat) 2958, 2931, 2858, 2256, 1472, 1328, 1276, 1178, 1139, 1041, 1015, 897, 758, 709 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16. Found: C, 68.54; H, 8.23.

4.1.2. *N*-(1-Octynyl)-3-methyl-1,2-benzisothiazoline 1,1-dioxide (3). ^{1}H NMR δ 0.87 (t, J=6.9 Hz, 3H), 1.21–1.47 (m, 6H), 1.48 –1.61 (m, 2H), 1.64 (d, J=6.6 Hz, 3H), 2.35 (t, J=6.9 Hz, 2H), 4.76 (q, J=6.6 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.66 (t, J=7.5 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 13.82, 18.53, 19.01, 22.34, 28.32, 28.66, 31.11, 58.96, 66.96, 74.29, 121.56, 123.93, 129.53, 132.68, 133.59, 137.33; IR (neat) 2968, 2935, 2911, 2862, 2250, 1377, 1324, 1273, 1178, 1138, 1070, 903, 760, 717, 653 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26. Found: C, 66.11; H, 7.09.

4.1.3. *N*-Benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide (12). ^{1}H NMR δ 0.85 (t, J=6.9 Hz, 3H), 1.10–1.41 (m, 8H), 2.14 (t, J=6.9 Hz, 2H), 2.41 (s, 3H), 4.42 (s, 2H), 7.22–7.30 (m, 7H), 7.73 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 13.84, 18.15, 21.38, 22.34, 28.07, 28.52, 31.12, 55.43, 70.77, 73.27, 127.66, 128.06, 128.36, 128.68, 129.54, 134.74, 134.85, 144.30; IR (Nujol) 3091, 3063, 3040, 2921, 2845, 2250, 1454, 1354, 1303, 1170, 1093, 1055, 812, 735, 698 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.36. Found: C, 71.45; H, 7.02. Mp 47–48 °C.

4.1.4. *N*-Benzyl-*N*-[2-(trimethylsilyl)ethynyl]-*p*-toluenesulfonamide (13). ^{1}H NMR δ 0.08 (s, 9H), 2.44 (s, 3H), 4.48 (s, 2H), 7.24–7.34 (m, 7H), 7.73 (d, J=8.4 Hz, 2H); ^{13}C NMR δ −0.22, 21.48, 55.37, 73.84, 95.32, 127.85, 128.28, 128.40, 128.96, 129.56, 134.42, 134.65, 144.64; IR (Nujol) 3090, 3062, 3045, 3038, 2924, 2862, 2168, 1454, 1374, 1253, 1175, 1090, 1049, 946, 892, 842, 748 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_2SSi$: C, 63.83; H, 6.48. Found: C, 63.92; H, 6.33. Mp 76–77 °C.

4.1.5. (*R*)-*N*-(*p*-Toluenesulfonyl)-*N*-(1-octynyl)-(2-methoxy-1-phenylethyl)amine (14). ^{1}H NMR δ 0.88 (t, J=6.9 Hz, 3H), 1.19–1.36 (m, 6H), 1.39–1.51 (m, 2H), 2.29 (t, J=6.9 Hz, 2H), 2.39 (s, 3H), 3.25 (s, 3H), 3.62 (d/d, J=5.1, 10.5 Hz, 1H), 3.84 (d/d, J=9.6, 10.5 Hz, 1H), 5.18 (d/d, J=5.1, 9.6 Hz, 1H), 7.14–7.21 (m, 2H), 7.22–7.33 (m, 5H), 7.61–7.69 (m, 2H); ^{13}C NMR δ 13.91, 18.52, 21.41, 22.46, 28.32, 28.77, 31.24, 58.61, 61.60, 70.64, 72.41, 73.08, 127.39, 127.96, 128.22, 128.43, 129.03, 135.66, 136.67, 143.83; IR (neat) 3095, 3065, 3033, 2960, 2935, 2862, 2250, 1457, 1363, 1261, 1168, 1133, 1092, 976, 764, 715 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_3S$: C, 69.70; H, 7.56. Found: C, 69.51; H, 7.31; $[\alpha]_D^{24}$ 69.3 (c 1.39, $CHCl_3$).

4.1.6. (*R*)-*N*-(*p*-Toluenesulfonyl)-*N*-[2-(trimethylsilyl)-ethynyl]-(2-methoxy-1-phenylethyl)amine (15). ^{1}H NMR δ 0.16 (s, 9H), 2.40 (s, 3H), 3.23 (s, 3H), 3.62 (d/d, J=4.8, 10.5 Hz, 1H), 3.82 (d/d, J=9.6, 10.5 Hz, 1H), 5.13 (d/d, J=4.8, 9.6 Hz, 1H), 7.15–7.21 (m, 2H), 7.22–7.32 (m, 5H), 7.60–7.68 (m, 2H); ^{13}C NMR δ −0.08, 21.46, 58.65, 62.07, 72.33, 76.34, 93.05, 127.42, 128.11, 128.40, 128.47, 129.03, 135.34, 136.32, 144.17; IR (neat) 3058, 3017, 2957, 2919, 2895, 2158, 1597, 1457, 1364, 1249, 1168, 971, 844, 760, 698, 665 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_3SSi$: C, 62.81; H, 6.78. Found: C, 63.12; H, 6.87; $[\alpha]_D^{24}$ 70.2 (c 1.06, $CHCl_3$).

4.1.7. *N*-[2-(Trimethylsilyl)ethynyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (16). ^{1}H NMR δ 0.21 (s, 9H), 1.67 (d, J=6.6 Hz, 2H), 4.86 (q, J=6.6 Hz, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.79 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −0.04, 19.16, 59.06, 77.40, 88.66, 121.66, 124.02, 129.70, 132.54, 133.82, 137.01; IR (neat) 2960, 2903, 2166, 1474, 1328, 1250, 1181, 1139, 1067, 1029, 844, 749, 694 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2SSi$: C, 55.88; H, 6.13. Found: C, 55.90; H, 6.36.

4.1.8. *N*-(1-Octynyl)-3-butyl-1,2-benzisothiazoline 1,1-dioxide (17). ^{1}H NMR δ 0.85 (t, J=7.2 Hz, 3H), 0.89 (t, J=6.9 Hz, 3H), 0.93–1.07 (m, 1H), 1.22–1.48 (m, 9H), 1.49–1.64 (m, 2H), 1.91–2.07 (m, 1H), 2.08–2.23 (m, 1H), 2.37 (t, J=6.9 Hz, 2H), 4.83 (t, J=4.5 Hz, 1H), 7.38 (d, J=7.5 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.66 (t, J=7.5 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 13.62, 13.88, 18.61, 22.27, 22.41, 24.77, 28.37, 28.72, 31.20, 31.84, 63.07, 67.23, 74.15, 121.76, 123.96, 129.48, 133.41, 133.46, 135.94; IR (neat) 2968, 2935, 2895, 2845, 2250, 1466, 1327, 1279, 1189, 1140, 1050, 903, 764 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16. Found: C, 68.51; H, 8.17.

4.1.9. *N*-[2-(Trimethylsilyl)ethynyl]-3-butyl-1,2-benzisothiazoline 1,1-dioxide (18). ^{1}H NMR δ 0.21 (s, 9H), 0.86 (t, J=7.2 Hz, 3H), 0.96–1.13 (m, 1H), 1.21–1.44 (m, 3H), 1.92–2.07 (m, 1H), 2.08–2.24 (m, 1H), 4.91 (t, J=4.5 Hz, 1H), 7.39 (d, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −0.04, 13.58, 22.15, 24.84, 32.08, 63.22, 77.21, 89.09, 121.77, 124.02, 129.62, 133.18, 133.68, 135.65; IR (neat) 2959, 2935, 2854, 2169, 1451, 1321, 1250, 1179, 1138, 1048, 840, 757, 697 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2SSi$: C, 59.77; H, 7.21. Found: C, 59.57; H, 7.05.

4.1.10. (*S*)-3-(*tert*-Butyl)-1,2-benzisothiazoline 1,1-dioxide (96% ee) ((*S*)-7). This was prepared according to the following literature: Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett*. **1991**, *32*, 4893–4896. $[\alpha]_D^{25}$ −51.7 (c 1.0, $CHCl_3$) for a sample of 96% ee. Lit. $[\alpha]_D^{18}$ −54.0 (c 1.0, $CHCl_3$) for an enantiopure (*S*)-sample [Ahn, K. H.; Ham, C.; Kim, S. -K.; Cho, C. -W. *J. Org. Chem*. **1997**, *62*, 7047–7048]; $[\alpha]_D^{20}$ −53.9 (c 1, $CHCl_3$) for a pure (*S*)-sample [Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett*. **1991**, *32*, 4893–4896; however, the nomenclature of *R*/*S* in this reference is wrong].

4.1.11. (*S*)-*N*-(1-Octynyl)-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (96% ee) ((*S*)-19) prepared from (*S*)-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (96% ee) ((*S*)-7). For ^{1}H and ^{13}C NMR, IR, and elemental analyses, see the racemic sample listed above. $[\alpha]_D^{29}$ −21.1 (c 1.06, $CHCl_3$) for a sample of 96% ee. The enantiopurity was determined to be 96% ee by HPLC analysis [CHIRALCEL OD-H column (silica gel, 0.46ϕ×15.25 cm), *i*-PrOH/hexane (1:10 v/v) at a rate of 0.5 mL/min: retention time=13.8 min for (*R*) and 16.0 min for (*S*)]. Thus, no racemization was observed during this copper-catalyzed coupling reaction.

4.1.12. *N*-[2-(Trimethylsilyl)ethynyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (20). ^{1}H NMR δ 0.18 (s, 9H), 1.11 (s, 9H), 4.54 (s, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.79 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −0.10, 26.72, 38.50, 75.36, 75.66, 92.72, 121.91, 125.86, 129.64, 132.75, 134.00, 135.26; IR (Nujol) 2922, 2845, 2161, 1464, 1376, 1333, 1245, 1175, 1010, 846, 746, 671 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2SSi$: C, 59.77; H, 7.21. Found: C, 59.81; H, 7.26. Mp 73–74 °C.

4.1.13. *N*-[5-((*tert*-Butyl)dimethylsiloxy)-1-pentynyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (21). To a heterogeneous mixture of 3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**7**) (1.13 g, 5.00 mmol), powdered K_3PO_4 (2.12 g, 10.0 mmol), and CuI (47.6 mg, 0.250 mmol) in 10 mL of toluene was added 1-bromo-[5-(*tert*-butyl)dimethylsiloxy]-1-pentyne (**11**) (1.39 g, 5.00 mmol) in 40 mL of toluene followed by *N*,*N*′-dimethylethylenediamine (0.125 mL) under argon. After the mixture was stirred overnight in an oil bath maintained at 110 °C, it was cooled to room temperature and was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (1.70 g, 81%) as an oil. ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 1.10 (s, 9H), 1.72 (quintet, J=6.6 Hz, 2H), 2.40 (t, J=6.6 Hz, 2H), 3.69 (t, J=6.6 Hz, 2H), 4.44 (s, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.49–7.64 (m, 2H), 7.77 (d, J=7.8 Hz, 1H); ^{13}C NMR δ −5.25, 15.18, 18.33, 25.96, 26.89, 31.99, 38.34, 61.59, 71.27,

72.09, 75.23, 121.64, 125.58, 129.30, 132.35, 133.88, 135.30; IR (neat) 3074, 2955, 2903, 2845, 2256, 1472, 1331, 1252, 1179, 1140, 1104, 1010, 836, 777, 709 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_3SSi$: C, 62.66; H, 8.37. Found: C, 62.53; H, 8.50.

4.1.14. *N*-[5-((*tert*-Butyl)dimethylsiloxy)-1-pentynyl]-3-phenyl-1,2-benzisothiazoline 1,1-dioxide (22). ^1H NMR δ 0.00 (s, 6H), 0.86 (s, 9H), 1.59 (quintet, $J=6.6$ Hz, 2H), 2.29 (t, $J=6.6$ Hz, 2H), 3.53 (t, $J=6.6$ Hz, 2H), 5.67 (s, 1H), 7.08–7.16 (m, 1H), 7.28–7.43 (m, 5H), 7.50–7.61 (m, 2H), 7.79–7.88 (m, 1H); ^{13}C NMR δ −5.61, 14.79, 18.06, 25.73, 31.57, 61.16, 67.17, 67.23, 74.18, 121.39, 125.32, 128.00 (2 peaks), 129.03, 129.31, 129.75, 132.39, 133.66, 136.27; IR (neat) 3074, 3025, 2928, 2895, 2862, 2250, 1466, 1325, 1270, 1189, 1115, 838, 772, 707 cm^{-1}.

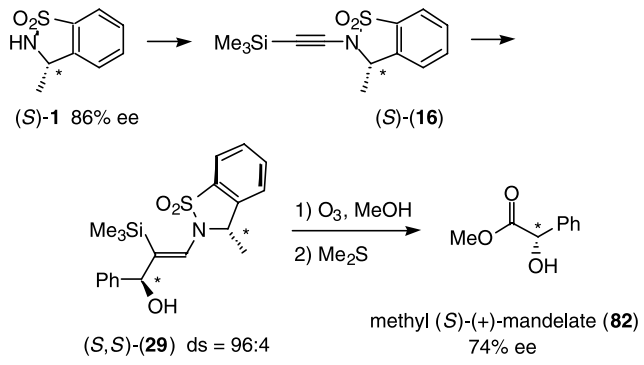
4.1.15. (1*S*,2*S*)-*N*-(1-Octynyl)-2,10-camphorsultam (23). ^1H NMR δ 0.84 (t, $J=6.9$ Hz, 3H), 0.89 (s, 3H), 1.06 (s, 3H), 1.17–1.58 (m, 10H), 1.70 (d/d, $J=8.1$, 13.2 Hz, 1H), 1.76–1.94 (m, 3H), 2.13 (d/d/d, $J=13.2$, 6.6, 3.9 Hz, 1H), 2.25 (t, $J=6.9$ Hz, 2H), 3.18 (s, 2H), 3.47 (d/d, $J=4.2$, 8.1 Hz, 1H); ^{13}C NMR δ 13.78, 18.37, 19.68, 19.93, 22.27, 26.80, 28.19, 28.65, 31.04, 31.34, 34.17, 44.16, 47.68, 49.27, 50.63, 67.00, 67.29, 72.27; IR (neat) 2960, 2935, 2250, 1457, 1335, 1224, 1166, 1144, 1116, 1068, 875, 833, 772, 669 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04. Found: C, 66.83; H, 8.70; $[\alpha]_D^{29}$ −99.9 (*c* 1.02, $CHCl_3$).

4.1.16. (1*S*,2*S*)-*N*-[2-(Trimethylsilyl)ethynyl]-2,10-camphorsultam (24). ^1H NMR δ 0.16 (s, 9H), 0.93 (s, 3H), 1.09 (s, 3H), 1.20–1.46 (m, 2H), 1.76 (d/d, $J=8.1$, 13.2 Hz, 1H), 1.83–1.99 (m, 3H), 2.20 (d/d/d, $J=13.2$, 6.6, 3.9 Hz, 1H), 3.23 (s, 2H), 3.59 (d/d, $J=4.2$, 8.1 Hz, 1H); ^{13}C NMR δ 0.08, 19.82, 20.02, 26.92, 31.49, 34.12, 44.28, 47.88, 49.79, 51.07, 66.87 (2 peaks), 75.53; IR (neat) 2952, 2927, 2895, 2166, 1344, 1246, 1156, 1075, 851, 822, 781, 748, 668 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_2SSi$: C, 57.83; H, 8.09. Found: C, 57.75; H, 7.97; $[\alpha]_D^{29}$ −119.0 (*c* 1.01, $CHCl_3$).

4.1.17. Typical procedure for Table 4. (*RS*)-*N*-[(*RS*)-(*Z*)-3-Hydroxy-3-phenyl-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (29). To a stirred solution of *N*-[2-(trimethylsilyl)ethynyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (**16**) (34.4 mg, 0.123 mmol) and $Ti(O\text{–}i\text{-}Pr)_4$ (0.073 mL, 0.246 mmol) in 1.2 mL of Et_2O was added *i*-PrMgCl (1.46 M in Et_2O, 0.337 mL, 0.492 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned black. After stirring at −50 °C for an additional 4 h, benzaldehyde (0.010 mL, 0.098 mmol) was added at −50 °C and the solution was stirred for another 4 h. Then, the reaction was terminated by the addition of H_2O (0.123 mL) and the reaction mixture was allowed to warm to room temperature, stirred for 30 min, and was filtered through Celite with the aid of ether. The combined filtrates were concentrated in vacuo to give a crude oil, careful analysis of which by ^1H NMR spectroscopy showed the presence of a 96:4 mixture of diastereoisomers. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (33.3 mg, 87%) as a colorless solid and as a 96:4 mixture of diastereoisomers. ^1H NMR δ 0.02 (s, 9H), 1.61 (d, $J=6.6$ Hz, 3H), 1.91 (br s, 1H, OH), 4.60 (q, $J=6.6$ Hz, 1H), 5.48 (s, 1H), 6.71 (s, 1H), 7.22–7.58 (m, 7H), 7.66 (t, $J=7.5$ Hz, 1H), 7.80 (d, $J=7.5$ Hz, 1H). Irradiation of proton at δ 4.60 ppm (CHN) showed 12% NOE enhancement to the peak at δ 6.71 ppm (CH=C). Irradiation of proton at δ 5.48 ppm (C*H*OH) showed 4% NOE enhancement to the peak at δ 6.71 ppm (CH=C). Irradiation of proton at δ 6.71 ppm (CH=C) showed 12% NOE enhancement to the peak at δ 4.60 ppm (CHN) and 4% NOE enhancement to the peak at δ 5.48 ppm (C*H*OH). Thus, the regio- and stereochemistries have been confirmed. ^1H NMR (C_6D_6) δ 0.22 (s, 9H), 1.14 (d, $J=6.6$ Hz, 3H), 1.35 (br s, 1H, OH), 4.00 (q, $J=6.3$ Hz, 1H), 5.33 (s, 1H), 6.59 (d, $J=7.5$ Hz, 1H), 6.72 (t, $J=7.5$ Hz, 1H), 6.76 (s, 1H), 6.88 (t, $J=7.5$ Hz, 1H), 7.00–7.24 (m, 3H), 7.36 (d, $J=7.5$ Hz, 1H), 7.53 (d, $J=7.8$ Hz, 2H). A characteristic peak of the minor diastereoisomer: ^1H NMR (C_6D_6) δ 5.26 (s, 1H). ^{13}C NMR δ 0.23, 19.05, 60.20, 77.21, 121.48, 123.53, 127.94, 128.32, 128.69, 129.11, 130.63, 133.11, 134.40, 138.77, 141.60, 149.50; IR (Nujol) 3509, 2952, 2923, 2854, 1597, 1457, 1375, 1297, 1172, 974, 844, 757 cm^{-1} for a 96:4 mixture of diastereoisomers. Anal. Calcd for $C_{20}H_{25}NO_3SSi$: C, 61.98; H, 6.50. Found: C, 61.61; H, 6.48 for a 96:4 mixture of diastereoisomers. Mp 165–168 °C (recrystallized from CH_2Cl_2–hexane).

4.1.18. (*RS*)-*N*-[(*RS*)-(*Z*)-1-Deuterio-3-hydroxy-3-phenyl-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (29-*d*$_1$). ^1H NMR δ 0.02 (s, 9H), 1.61 (d, $J=6.6$ Hz, 3H), 1.91 (br s, 1H, OH), 4.60 (q, $J=6.6$ Hz, 1H), 5.48 (s, 1H), 7.22–7.58 (m, 7H), 7.66 (t, $J=7.5$ Hz, 1H), 7.80 (d, $J=7.5$ Hz, 1H). The peak at δ 6.71 ppm (CH=C) of (*RS*)-*N*-[(*RS*)-(*Z*)-3-hydroxy-3-phenyl-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (**29**) disappeared to show 97% deuterium incorporation.

4.1.19. Structural determination of adduct 29. (*S*)-*N*-[(*S*)-(*Z*)-3-Hydroxy-3-phenyl-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide ((*S*,*S*)-29). For determination of the relative stereochemistry of the (racemic) adduct **29**, optically active (*S*)-**16** prepared from known benzosultam (*S*)-**1** (86% ee, $[\alpha]_D^{25}$ −25.8 (*c* 1.00, $CHCl_3$). Lit. $[\alpha]_D^{20}$ −30 (*c* 1.21, $CHCl_3$) for a pure (*S*)-sample [Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett*. **1990**, *31*, 4117–4120]) was allowed to react with benzaldehyde to give (*S*,*S*)-**29** (ds=96:4). The olefinic bond of (*S*,*S*)-**29** was oxidatively cleaved by ozonolysis in methanol, affording directly (*S*)-methyl mandelate (**82**), the absolute stereochemistry and ee value of which were determined to be *S* and 74% ee, respectively, by ^1H NMR analyses of the derived MTPA esters in comparison with an authentic sample of methyl (*S*)-(+)-mandelate. The ee value of the methyl mandelate (74% ee) derived from the adduct (*S*,*S*)-**29** was in good agreement with the expected value (79% ee) based on the ee value of the starting **29** (86% ee) and the diastereoselectivity (ds=96:4). Thus, the relative stereochemistry of adduct **29** has been established.



4.1.20. Methyl (*S*)-(+)-mandelate (82) from (*S*,*S*)-29. Adduct (*S*,*S*)-**29** (153.2 mg, 0.305 mmol) dissolved in dry MeOH (2.35 mL) was cooled to −78 °C, and ozone was bubbled into this solution. After the blue color of ozone appeared, argon was bubbled for 10 min in place of ozone and then methyl sulfide (0.427 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The solution was concentrated to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (14.4 mg, 29%) as an oil. ^{1}H NMR δ 3.46 (br s, 1H, OH), 3.76 (s, 3H), 5.18 (s, 1H), 7.29–7.47 (m, 5H).

$[\alpha]_D^{25}$ +111.3 (*c* 0.96, $CHCl_3$) for a sample of 74% ee. Lit. $[\alpha]_D^{20}$ +144 (*c* 1.00, MeOH) for a sample of 98% ee [Aldrich Handbook of Fine Chemicals and Laboratory Equipment; Sigma–Aldrich: 2003–2004, p 1255].

4.1.21. The MTPA ester of methyl (*S*)-(+)-mandelate (82). A characteristic peak of the (*R*)-MTPA ester prepared from (*S*)-MTPACl and **82**: ^{1}H NMR δ 6.12 (s, 1H, CHOMTPA). A characteristic peak of the (*S*)-MTPA ester prepared from (*R*)-MTPACl and **82**: ^{1}H NMR δ 6.10 (s, 1H, CHOMTPA).

4.1.22. (*RS*)-*N*-[(*RS*)-(*Z*)-3-(*p*-Chlorophenyl)-3-hydroxy-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (30). ^{1}H NMR δ 0.03 (s, 9H), 1.59 (d, *J*=6.6 Hz, 3H), 2.18 (br s, 1H, OH), 4.58 (q, *J*=6.6 Hz, 1H), 5.44 (s, 1H), 6.65 (s, 1H), 7.30–7.46 (m, 5H) 7.55 (t, *J*=7.5 Hz, 1H), 7.66 (t, *J*=7.5 Hz, 1H), 7.79 (d, *J*=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 4.51 (q, *J*=6.6 Hz, 1H), 6.41 (s, 1H). ^{13}C NMR δ 0.01, 18.88, 60.21, 75.78, 121.63, 123.73, 128.96, 129.34, 129.46, 131.57, 133.37, 134.17, 134.48, 138.95, 140.47, 149.54; IR (Nujol) 3482, 2952, 2919, 2862, 2723, 1458, 1376, 1290, 1175, 1134, 1083, 854 cm^{-1} for a 96:4 mixture of diastereoisomers. Anal. Calcd for $C_{20}H_{24}ClNO_3SSi$: C, 56.92; H, 5.73. Found: C, 57.17; H, 5.70 for a 96:4 mixture of diastereoisomers.

4.1.23. (*RS*)-*N*-[(*RS*)-(1*Z*,4*E*)-3-Hydroxy-2-(trimethylsilyl)-1,4-decadien-1-yl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (31). ^{1}H NMR δ 0.22 (s, 9H), 0.88 (t, *J*=7.2 Hz, 3H), 1.10–1.48 (m, 6H), 1.54 (d, *J*=6.6 Hz, 3H), 1.69 (br s, 1H, OH), 2.06 (q, *J*=6.9 Hz, 2H), 4.52 (q, *J*=6.6 Hz, 1H), 4.87 (d, *J*=7.2 Hz, 1H), 5.53 (d/d, *J*=7.2, 15.3 Hz, 1H), 5.79 (d/t, *J*=15.3, 6.9 Hz, 1H), 6.50 (s, 1H), 7.40 (d, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 1H), 7.63 (t, *J*=7.5 Hz, 1H), 7.78 (d, *J*=7.5 Hz, 1H). A characteristic peak of the minor diastereoisomer: ^{1}H NMR δ 6.45 (s, 1H). ^{13}H NMR δ 0.31, 13.90, 18.51, 22.38, 28.57, 31.37, 32.13, 59.87, 74.94, 121.59, 123.67, 129.24, 130.28, 132.00, 133.19, 134.69, 134.94, 139.02, 151.39; IR (neat) 3486, 2968, 2926, 2895, 2856, 1606, 1456, 1377, 1313, 1245, 1174, 973, 843, 759 cm^{-1} for a 94:6 mixture of diastereoisomers. Anal. Calcd for $C_{21}H_{33}NO_3SSi$: C, 61.87; H, 8.16. Found: C, 62.05; H, 7.93 for a 94:6 mixture of diastereoisomers.

4.1.24. (*RS*)-*N*-[(*RS*)-(1*Z*,4*E*)-3-Hydroxy-2-(trimethylsilyl)-1,4-hexadien-1-yl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (32). ^{1}H NMR δ 0.21 (s, 9H), 1.54 (d, *J*=6.6 Hz, 3H), 1.67 (br s, 1H, OH), 1.73 (d/d, *J*=1.5, 6.6 Hz, 3H), 4.52 (q, *J*=6.6 Hz, 1H), 4.86 (d, *J*=7.2 Hz, 1H), 5.55 (d/d/q, *J*=7.2, 15.3, 1.5 Hz, 1H), 5.80 (d/q, *J*=15.3, 6.6 Hz, 1H), 6.49 (s, 1H), 7.40 (d, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 1H), 7.63 (t, *J*=7.5 Hz, 1H), 7.78 (d, *J*=7.5 Hz, 1H). A characteristic peak of the minor diastereoisomer: ^{1}H NMR δ 6.44 (s, 1H). ^{13}C NMR δ 0.26, 17.60, 18.50, 59.83, 74.78, 121.56, 123.66, 129.22, 129.46, 130.22, 133.20, 133.31, 134.64, 139.00, 151.36; IR (Nujol) 3509, 2951, 2923, 2854, 2723, 1600, 1457, 1376, 1300, 1165, 1096, 1067, 973, 843, 761 cm^{-1} for a 95:5 mixture of diastereoisomers. Anal. Calcd for $C_{17}H_{25}NO_3SSi$: C, 58.08; H, 7.17. Found: C, 58.06; H, 6.93 for a 95:5 mixture of diastereoisomers.

4.1.25. (*RS*)-*N*-[(*RS*)-(*Z*)-3-Hydroxy-2-(trimethylsilyl)-1-undecenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (33). ^{1}H NMR δ 0.24 (s, 9H), 0.88 (distorted t, *J*=6.9 Hz, 3H), 1.18–1.43 (br m, 12H), 1.53 (d, *J*=6.6 Hz, 3H), 1.58–1.90 (m, 3H), 4.44 (q, *J*=3.6 Hz, 1H), 4.52 (q, *J*=6.6 Hz, 1H), 6.44 (s, 1H), 7.40 (d, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.5 Hz 1H), 7.63 (t, *J*=7.5 Hz, 1H), 7.78 (d, *J*=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 4.36 (q, *J*=3.6 Hz, 1H), 4.79 (q, *J*=6.6 Hz, 1H), 6.43 (s, 1H). ^{13}C NMR δ 0.32, 13.97, 18.47, 22.55, 25.51, 29.16, 29.38, 29.47, 31.76, 37.95, 59.87, 74.24, 121.57, 123.68, 129.24, 130.14, 133.18, 134.62, 139.00, 153.29; IR (neat) 3503, 3072, 2960, 2923, 2854, 1608, 1456, 1376, 1308, 1247, 1173, 1134, 1067, 1027, 842, 759, 689 cm^{-1} for an 88:12 mixture of diastereoisomers. Anal. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80. Found: C, 62.44; H, 9.10 for an 88:12 mixture of diastereoisomers.

4.1.26. (*RS*)-*N*-[(*RS*)-(*Z*)-3-Cyclohexyl-3-hydroxy-2-(trimethylsilyl)-1-propenyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (34). ^{1}H NMR δ 0.23 (s, 9H), 0.78–1.38 (m, 9H), 1.46–2.03 (m, 6H), 4.21 (d, *J*=4.8 Hz, 1H), 4.51 (q, *J*=6.6 Hz, 1H), 6.33 (s, 1H), 7.39 (d, *J*=7.5 Hz, 1H), 7.51 (t, *J*=7.5 Hz, 1H), 7.62 (t, *J*=7.5 Hz, 1H), 7.76 (d, *J*=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 7.38 (d, *J*=7.5 Hz, 1H), 7.50 (t, *J*=7.5 Hz, 1H), 7.61 (t, *J*=7.5 Hz, 1H). ^{13}C NMR δ 0.30, 18.57, 25.92, 26.02, 26.27, 26.43, 30.60, 42.38, 59.92, 78.87, 121.49, 123.64, 129.20, 131.00, 133.18, 134.52, 138.95, 151.29; IR (neat) 3515 (OH), 2922, 2854, 2659, 1603, 1313, 1246, 1130, 1027, 853, 755, 721 cm^{-1} for a 68:32 mixture of diastereoisomers. Anal. Calcd for $C_{20}H_{31}NO_3SSi$: C, 61.03; H, 7.94. Found: C, 60.97; H, 7.66 for a 68:32 mixture of diastereoisomers.

4.1.27. (*RS*)-*N*-[(*RS*)-(*E*)-2-Hexyl-3-hydroxy-3-phenyl-1-propenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (35). ^{1}H NMR δ 0.84 (t, J=7.2 Hz, 3H), 1.09 (s, 9H), 1.15–1.31 (m, 6H), 1.37–1.49 (m, 2H), 2.01–2.14 (m, 2H, including OH), 2.55–2.63 (m, 1H), 4.24 (s, 1H), 5.28 (s, 1H), 5.87 (s, 1H), 7.27–7.39 (m, 4H), 7.45–7.60 (m, 4H), 7.79 (d, J=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 4.17 (s, 1H), 5.34 (s, 1H), 5.80 (s, 1H). ^{13}C NMR δ 13.90, 22.42, 27.16, 27.23, 28.83, 29.54, 31.43, 38.13, 75.61, 76.20, 121.76, 125.50, 125.75, 127.46, 128.11, 128.70, 129.21, 132.08, 137.08, 138.15, 141.24, 141.84; IR (neat) 3464, 3064, 3028, 2956, 2927, 2871, 1654, 1602, 1454, 1312, 1179, 1049, 911, 760, 731, 701 cm^{-1} for an 88:12 mixture of diastereoisomers. Anal. Calcd for $C_{26}H_{35}NO_3S$: C, 70.71; H, 7.99. Found: C, 70.94; H, 8.37 for an 88:12 mixture of diastereoisomers.

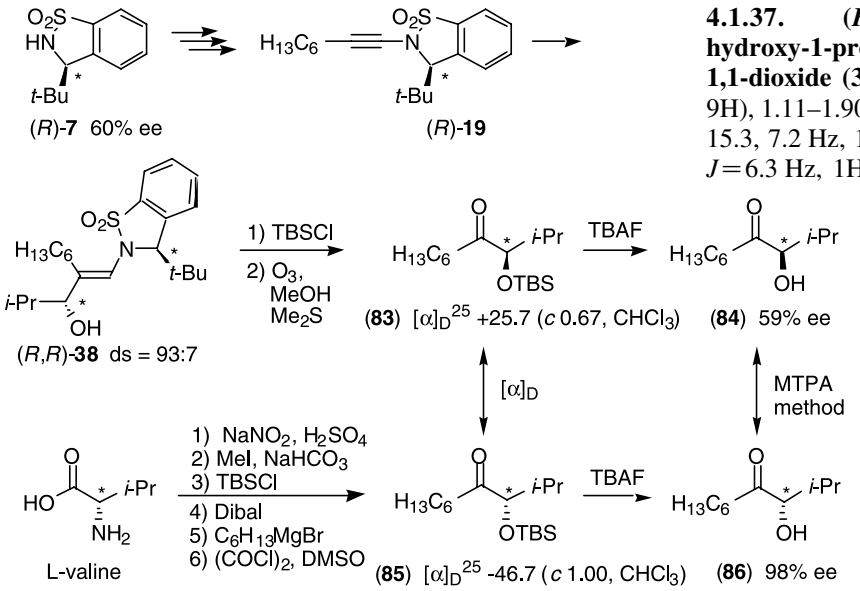
4.1.28. (*RS*)-*N*-[(*RS*)-(1*E*,4*E*)-2-Hexyl-3-hydroxy-1,4-hexadien-1-yl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (36). ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 1.06 (s, 9H), 1.22–1.42 (m, 6H), 1.48–1.60 (m, 2H), 1.71 (d/d, J=1.5, 6.3 Hz, 3H), 1.75 (br s, 1H, OH), 2.30 (d/t, J=14.7, 8.1 Hz, 1H), 2.62 (d/t, J=14.7, 8.1 Hz, 1H), 4.18 (s, 1H), 4.64 (d, J=7.2 Hz, 1H), 5.54 (d/d/q, J=7.2, 15.3, 1.5 Hz, 1H), 5.70 (s, 1H), 5.81 (d/q, J=15.3, 6.3 Hz, 1H), 7.42–7.60 (m, 3H), 7.77 (d, J=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 4.17 (s, 1H), 4.67 (d, J=7.2 Hz, 1H), 5.44 (d/d/q, J=6.9, 15.3, 1.5 Hz, 1H), 5.72 (s, 1H). ^{13}C NMR δ 13.94, 17.62, 22.49, 27.14, 27.42, 28.87, 29.65, 31.53, 38.10, 73.65, 76.08, 121.74, 124.54, 125.70, 128.90, 129.15, 132.01, 132.16, 136.17, 137.07, 142.13; IR (neat) 3482 (OH), 2968, 2927, 2870, 1662, 1471, 1367, 1314, 1179, 1135, 966, 911, 756, 740 cm^{-1} for an 81:19 mixture of diastereoisomers. Anal. Calcd for $C_{23}H_{35}NO_3S$: C, 68.11; H, 8.70. Found: C, 68.38; H, 8.87 for an 81:19 mixture of diastereoisomers.

4.1.29. (*RS*)-*N*-[(*RS*)-(*E*)-2-Hexyl-3-hydroxy-1-undecenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (37). ^{1}H NMR δ 0.82–0.95 (m, 6H), 1.06 (s, 9H), 1.18–1.45 (m, 18H), 1.55 (m, 4H), 1.78 (br s, 1H, OH), 2.37 (d/t, J=10.2, 6.3 Hz, 1H), 2.54 (d/t, J=10.2, 6.3 Hz, 1H), 4.16 (s, 1H), 4.19 (t, J=6.6 Hz, 1H), 5.63 (s, 1H), 7.45–7.61 (m, 3H), 7.78 (d, J=7.5 Hz, 1H). A characteristic peak of the minor diastereoisomer: ^{1}H NMR δ 5.65 (s, 1H). ^{13}C NMR δ 13.97, 22.55, 25.28, 26.49, 27.15, 27.97, 28.60, 29.16, 29.46, 29.51, 29.59, 29.86, 31.57, 31.78, 35.51, 38.14, 73.81, 76.07, 121.79, 125.08, 125.70, 129.20, 132.04, 136.16, 137.00, 143.51; IR (Nujol) 3498, 2960, 2935, 2862, 1646, 1468, 1367, 1313, 1179, 1135, 1050, 910, 757, 731, 707 cm^{-1} for an 88:12 mixture of diastereoisomers. Anal. Calcd for $C_{28}H_{47}NO_3S$: C, 70.39; H, 9.92. Found: C, 70.41; H, 9.75 for an 88:12 mixture of diastereoisomers.

4.1.30. (*RS*)-*N*-[(*RS*)-(*E*)-2-Hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (38). ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 0.92 (d, J=6.3 Hz, 3H), 0.95 (d, J=6.3 Hz, 3H), 1.06 (s, 9H), 1.22–1.42 (m, 6H), 1.50–1.70 (m, 2H), 1.78 (br s, 1H, OH), 1.94 (octet, J=6.6 Hz, 1H), 2.29 (d/t, J=14.4, 8.1 Hz, 1H), 2.61 (d/t, J=14.4, 8.1 Hz, 1H), 3.92 (d, J=6.6 Hz, 1H), 4.17 (s, 1H), 5.61 (s, 1H), 7.42–7.60 (m, 3H), 7.76 (d, J=7.5 Hz, 1H). Irradiation of proton at δ 5.61 ppm (C=CH) showed 7% NOE enhancement to the peak at δ 3.92 ppm (C*H*OH) and 15% NOE enhancement to the peak at δ 4.17 ppm (NCH). Irradiation of proton at δ 3.92 ppm (C*H*OH) showed 9% NOE enhancement to the peak at δ 5.61 ppm (CH=C). Thus, the regio- and stereochemistries have been confirmed. ^{1}H NMR (C_6D_6) δ 0.88–0.93 (m, 12H), 1.16 (d, J=6.6 Hz, 6H), 1.26–1.58 (m, 7H, including OH), 1.70–1.85 (m, 2H), 1.95 (octet, J=6.6 Hz, 1H), 2.54 (d/t, J=14.4, 8.1 Hz, 1H), 2.92 (d/t, J=14.4, 8.1 Hz, 1H), 3.72 (s, 1H), 3.89 (d, J=6 Hz, 1H), 5.56 (s, 1H), 6.72–6.78 (m, 1H), 6.84–6.92 (m, 2H), 7.42 (d, J=7.8 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR (C_6D_6) δ 3.67 (s, 1H), 3.96 (d, J=6 Hz, 1H), 5.62 (s, 1H). ^{13}C NMR δ 13.94, 16.60, 19.45, 22.53, 27.15, 27.81, 28.97, 29.84, 31.39, 31.56, 38.06, 76.11, 78.59, 121.74, 125.53, 125.70, 129.15, 132.02, 136.15, 137.05, 142.43; IR (Nujol) 3502, 2968, 2923, 2854, 1457, 1377, 1304, 1169, 1135, 1042, 1024, 830, 707 cm^{-1} for a 93:7 mixture of diastereoisomers. Anal. Calcd for $C_{23}H_{37}NO_3S$: C, 67.77; H, 9.15. Found: C, 67.53; H, 9.30 for a 93:7 mixture of diastereoisomers.

4.1.31. (*RS*)-*N*-[(*RS*)-(*E*)-1-Deuterio-2-hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (38-d_1). ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 0.92 (d, J=6.3 Hz, 3H), 0.95 (d, J=6.3 Hz, 3H), 1.06 (s, 9H), 1.22–1.42 (m, 6H), 1.50–1.70 (m, 2H), 1.78 (br s, 1H, OH), 1.94 (octet, J=6.6 Hz, 1H), 2.29 (d/t, J=14.4, 8.1 Hz, 1H), 2.61 (d/t, J=14.4, 8.1 Hz, 1H), 3.92 (d, J=6.6 Hz, 1H), 4.17 (s, 1H), 7.42–7.60 (m, 3H), 7.76 (d, J=7.5 Hz, 1H). The peak at δ 5.61 ppm (CH=C) of (*RS*)-*N*-[(*SR*)-(*E*)-2-hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**38**) disappeared to show 96% deuterium incorporation.

4.1.32. Structural determination of adduct 38. (*R*)-*N*-[(*R*)-(*E*)-2-Hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide ((*R*,*R*)-38). For determination of the relative stereochemistry of the (racemic) adduct **38**, optically active (*R*)-**19** prepared from known benzosultam (*R*)-**7** (60% ee, $[\alpha]_D^{25}$ +32.1 (*c* 1.00, $CHCl_3$); Lit. see (*S*)-**7**) was allowed to react with benzaldehyde to give (*R*,*R*)-**38** (ds=93:7). After protection as a TBS ether, the olefinic bond of (*R*,*R*)-**38** was oxidatively cleaved by ozonolysis in methanol to afford siloxy ketone (**83**), which was desilylated to give hydroxy ketone **84**. The absolute configuration and ee value of this ketone **84** were determined to be *R* and 59% ee, respectively, by ^{1}H NMR analyses of the derived MTPA esters in comparison with an authentic antipode **86** prepared from L-valine. The ee value of hydroxy ketone **84** (59% ee) prepared from (*R*,*R*)-**38** was in good agreement with the expected value (52% ee) based on the ee value of (*R*)-**7** (60% ee) and the diastereoselectivity of (*R*,*R*)-**38** (ds=93:7). The comparison between the samples of **83** and **85** at the stage of α-siloxyketones was also consistent with the above assignment.



4.1.33. (*R*)-3-[(*tert*-Butyl)dimethylsiloxy]-2-methyl-4-decanone (83) derived from (*R*,*R*)-38. ^{1}H NMR δ 0.00 (s, 3H), 0.03 (s, 3H), 0.81–0.91 (m, 9H), 0.93 (s, 9H), 1.18–1.35 (m, 6H), 1.44–1.64 (m, 2H), 1.92 (octet, J=6.9 Hz, 1H), 2.43 (d/t, J=18.0, 7.5 Hz, 1H), 2.54 (d/t, J=18.0, 7.5 Hz, 1H), 3.71 (d, J=5.4 Hz, 1H); ^{13}C NMR δ −5.21, −4.94, 13.91, 17.37, 18.03, 18.83, 22.40, 22.92, 25.68, 28.92, 31.59, 32.51, 37.75, 83.70, 214.04; $[\alpha]_D^{25}$ +25.7 (c 0.67, $CHCl_3$) for a sample of 59% ee.

4.1.34. (*R*)-3-Hydroxy-2-methyl-4-decanone (84). ^{1}H NMR δ 0.69 (d, J=6.9 Hz, 3H), 0.86 (distorted t, J=6.9 Hz, 3H), 1.10 (d, J=6.9 Hz, 3H), 1.20–1.38 (m, 6H), 1.50–1.68 (m, 2H), 2.15 (heptet/d, J=6.9, 2.7 Hz, 1H), 2.43 (t, J=6.9 Hz, 2H), 3.40 (d, J=5.1 Hz, 1H, OH), 4.05 (d/d, J=2.7, 5.1 Hz, 1H); ^{13}C NMR δ 13.84, 14.57, 19.91, 22.32, 23.44, 28.79, 31.08, 31.40, 38.04, 80.62, 212.56.

4.1.35. The MTPA ester of (*R*)-3-hydroxy-2-methyl-4-decanone (84). A characteristic peak of the (*R*)-MTPA ester prepared from (*S*)-MTPACl and **84**: ^{1}H NMR δ 3.61 (s, 3H, OCH_3). A characteristic peak of the (*S*)-MTPA ester prepared from (*R*)-MTPACl and **84**: ^{1}H NMR δ 3.57 (s, 3H, OCH_3).

4.1.36. (*S*)-*N*-[(*S*)-(*E*)-2-Hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide ((*S*,*S*)-38) (95% ee). This was prepared from (*S*)-**19** (96% ee). For ^{1}H and ^{13}C NMR, IR, and elemental analyses, see the racemic sample **38** listed above. $[\alpha]_D^{25}$ −11.7 (c 0.81, $CHCl_3$) for a 93:7 mixture of diastereoisomers, in which the major diastereoisomer is 95% ee. The ee value of the major diastereoisomer was determined by ^{1}H NMR chiral shift study and integration of the separated peaks: (+)-Eu(hfc)$_3$, 0 mol%: δ 5.61 (s, 1H, C=CH) ppm; 2.5 mol%: major enantioisomer 5.66, minor enantioisomer 5.67; 5 mol%: major enantioisomer 5.73, minor enantioisomer 5.75; 7.5 mol%: major enantioisomer 5.80, minor enantioisomer 5.84; 10 mol%: major enantioisomer 5.86, minor enantioisomer 5.93.

4.1.37. (*RS*)-*N*-[(*RS*)-(*E*)-3-Cyclohexyl-2-hexyl-3-hydroxy-1-propenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (39). ^{1}H NMR δ 0.79–0.93 (m, 5H), 1.05 (s, 9H), 1.11–1.90 (m, 17H), 2.00 (br s, 1H, OH), 2.30 (d/t, J=15.3, 7.2 Hz, 1H), 2.60 (d/t, J=15.3, 7.2 Hz, 1H), 3.92 (d, J=6.3 Hz, 1H), 4.17 (s, 1H), 5.59 (s, 1H), 7.43–7.61 (m, 3H), 7.77 (d, J=7.5 Hz, 1H); ^{1}H NMR (C_6D_6) δ 0.86–0.98 (m, 12H), 1.04–1.94 (m, 19H), 2.37 (br s, 1H, OH), 2.60 (d/t, J=15.3, 7.2 Hz, 1H), 2.91 (d/t, J=15.3, 7.2 Hz, 1H), 3.74 (s, 1H), 3.93 (d, J=6 Hz, 1H), 5.58 (s, 1H), 6.68–6.80 (m, 1H), 6.80–6.90 (m, 2H), 7.42 (d, J=7.8 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR (C_6D_6) δ 3.70 (s, 1H), 3.98 (d, J=6 Hz, 1H), 5.61 (s, 1H). ^{13}C NMR δ 13.96, 22.54, 25.92, 26.22, 26.39, 26.48, 27.16, 27.90, 29.04, 29.76, 29.87, 31.57, 38.08, 41.31, 76.12, 78.02, 121.78, 125.63, 125.70, 129.17, 132.03, 136.14, 137.04, 142.22; IR (Nujol) 3498, 2952, 2927, 2845, 1458, 1377, 1299, 1170, 1045, 1020, 757, 733 cm^{-1} for a 93:7 mixture of diastereoisomers. Anal. Calcd for $C_{26}H_{41}NO_3S$: C, 69.76; H, 9.23. Found: C, 70.04; H, 9.20 for a 93:7 mixture of diastereoisomers.

4.1.38. (*RS*)-*N*-[(*RS*)-(*E*)-4,4-Dimethyl-2-hexyl-3-hydroxy-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (40). ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 0.97 (s, 9H), 1.07 (s, 9H), 1.20–1.42 (m, 6H), 1.48–1.72 (m, 3H, including OH), 2.04–2.20 (m, 1H), 2.78–3.05 (m, 1H), 3.98 (s, 1H), 4.21 (s, 1H), 5.65 (s, 1H), 7.44–7.60 (m, 3H), 7.76 (d, J=7.5 Hz, 1H). Characteristic peaks of the minor diastereoisomer: ^{1}H NMR δ 3.94 (s, 1H), 4.14 (s, 1H). ^{13}C NMR δ 14.17, 22.68, 26.10, 27.32, 27.58, 29.80, 31.60, 31.75, 36.33, 38.22, 76.26, 79.34, 121.57, 125.57, 126.66, 128.98, 131.83, 135.92, 136.70, 140.72; IR (Nujol) 3506, 2960, 2919, 2854, 1464, 1377, 1169, 1136, 1096, 1015, 855, 755, 723, 707 cm^{-1} for a 98:2 mixture of diastereoisomers. Anal. Calcd for $C_{24}H_{39}NO_3S$: C, 68.37; H, 9.32. Found: C, 68.29; H, 9.62 for a 98:2 mixture of diastereoisomers.

4.1.39. (*S*)-*N*-[(*S*)-(*E*)-4,4-Dimethyl-2-hexyl-3-hydroxy-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide ((*S*,*S*)-40) (96% ee). This was prepared from (*S*)-**19** (96% ee). For ^{1}H and ^{13}C NMR, IR, and elemental analyses, see the racemic sample **40** listed above. $[\alpha]_D^{28}$ −9.4 (c 0.96, $CHCl_3$) for a 98:2 mixture of diastereoisomers, in which the major diastereoisomer is 96% ee. The ee value of the major diastereoisomer was determined by ^{1}H NMR chiral shift study and integration of the separated peaks: (+)-Eu(hfc)$_3$,

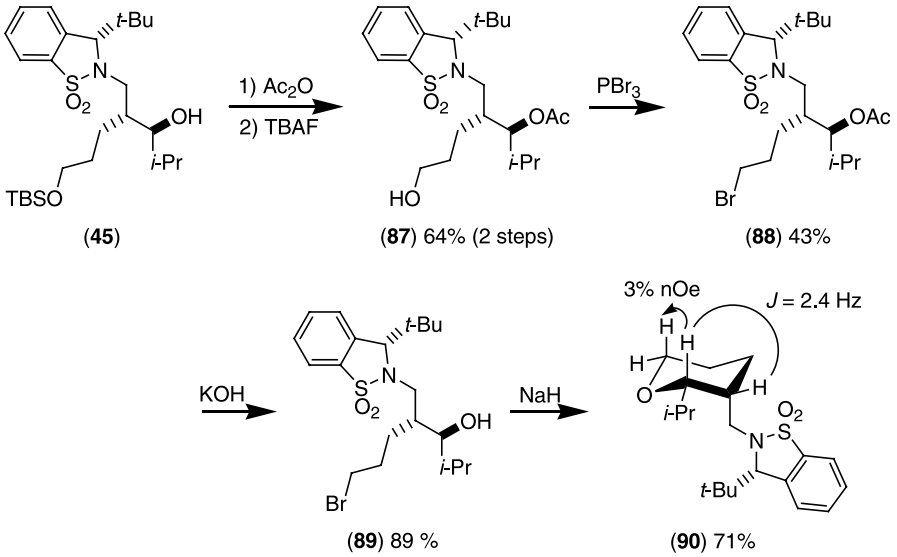
0 mol%: δ 5.65 (s, 1H, C=CH) ppm; 7.5 mol%: major enantioisomer 5.73, minor enantioisomer 5.76; 10 mol%: major enantioisomer 5.76, minor enantioisomer 5.80; 12.5 mol%: major enantioisomer 5.79, minor enantioisomer 5.83; 15 mol%: major enantioisomer 5.81, minor enantioisomer 5.86; 17.5 mol%: major enantioisomer 5.84, minor enantioisomer 5.89.

4.1.40. (*RS*)-*N*-[(*RS*)-(*E*)-2-(3-(*tert*-Butyl)dimethylsiloxypropyl)-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (41). To a stirred solution of *N*-[5-((*tert*-butyl)dimethylsiloxy)-1-pentynyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**21**) (713 mg, 1.69 mmol) and Ti(O–*i*-Pr)$_4$ (0.998 mL, 3.38 mmol) in 17 mL of Et_2O was added *i*-PrMgCl (1.50 M in Et_2O, 4.51 mL, 6.76 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned black. After stirring at −50 °C for an additional 4 h, isobutyraldehyde (0.230 mL, 2.54 mmol) was added at −50 °C and the solution was stirred for another 4 h. Then, the reaction was terminated by the addition of H_2O (1.7 mL) and the reaction mixture was allowed to warm to room temperature, stirred for 30 min, and was filtered through Celite with the aid of ether. The combined filtrates were concentrated in vacuo to give a crude oil, ^{1}H NMR analysis of which did not show the peaks corresponding to the minor diastereoisomer within the limits of detection. Thus the diastereoselectivity was judged to be >95:5. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (700 mg, 84%) as a colorless solid. ^{1}H NMR δ 0.07 (s, 6H), 0.90 (s, 9H), 0.97 (d, J=6.9 Hz, 6H), 1.06 (s, 9H), 1.66–2.05 (m, 4H), 2.30–2.45 (m, 1H), 2.58–2.73 (m, 1H), 3.68 (d/t, J=10.2, 6.0 Hz, 1H), 3.74 (d/t, J=10.2, 6.0 Hz, 1H), 3.90 (d, J=6.3 Hz, 1H), 4.17 (s, 1H), 5.63 (s, 1H), 7.42–7.68 (m, 3H), 7.77 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −5.13, 17.09, 18.47, 19.62, 25.45, 26.09, 27.35, 31.26, 31.61, 38.21, 63.63, 76.15, 78.91, 121.64, 125.53, 125.72, 129.01, 131.89, 135.85, 136.84, 142.05; IR (Nujol) 3492 (OH), 3278, 3066, 2925, 2854, 1457, 1377, 1298, 1168, 1134, 1107, 836, 759 cm^{-1} for a >95:5 mixture of diastereoisomers. Anal. Calcd for $C_{26}H_{45}NO_4SSi$: C, 62.99; H, 9.15. Found: C, 62.61; H, 8.82 for a >95:5 mixture of diastereoisomers. Mp 114–116 °C.

4.1.41. *N*-[(*E*)-2-Hexyl-4-methyl-3-oxo-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (42). ^{1}H NMR δ 0.88 (t, J=6.9 Hz, 3H), 1.07 (s, 9H), 1.09 (d, J=6.9 Hz, 3H), 1.11 (d, J=6.9 Hz, 3H), 1.20–1.76 (m, 8H), 2.58–2.80 (m, 2H), 3.09 (septet, J=6.9 Hz, 1H), 4.31 (s, 1H), 6.50 (s, 1H), 7.46–7.66 (m, 3H), 7.80 (d, J=7.2 Hz, 1H); ^{13}C NMR δ 13.95, 18.80, 19.31, 22.53, 27.07, 27.68, 27.93, 29.55, 31.49, 35.65, 38.26, 76.73, 121.86, 125.66, 129.54, 132.46, 135.82, 136.07, 136.51, 136.82, 205.34; IR (neat) 2960, 2927, 2870, 1668 (C=O), 1627, 1468, 1325, 1266, 1198, 1181, 1136, 1050, 872, 755, 700 cm^{-1}.

4.1.42. (*RS*)-*N*-[(2*SR*,3*RS*)-2-(3-(*tert*-Butyl)dimethylsiloxypropyl)-3-hydroxy-4-methyl-1-pentyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (45). A solution of (*RS*)-*N*-[(*RS*)-(*E*)-2-(3-(*tert*-butyl)dimethylsiloxypropyl)-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**41**) (399 mg, 0.805 mmol) and 10% Pd/C (12 mg) in 8 mL of EtOH was stirred at room temperature under 1 atm of hydrogen gas for 2 days. Then, the reaction mixture was filtered through Celite with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, ^{1}H NMR analysis of which did not show the peaks corresponding to the minor diastereoisomer within the limits of detection. Thus the diastereoselectivity was judged to be > 95:5. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (293 mg, 73%) as a colorless solid. ^{1}H NMR δ 0.05 (s, 6H), 0.89 (s, 9H), 0.95 (d, J=6.0 Hz, 3H), 0.97 (d, J=6.0 Hz, 3H), 1.06 (s, 9H), 1.44–1.94 (m, 5H), 1.98–2.12 (m, 1H), 2.31–2.46 (m, 1H), 3.18 (t, J=12.0 Hz, 1H), 3.33 (d/d, J=3.0, 8.4 Hz, 1H), 3.52–3.74 (m, 3H), 4.07 (s, 1H), 7.39–7.57 (m, 3H), 7.70–7.76 (m, 1H); ^{13}C NMR δ −5.48, −5.44, 18.28, 18.93, 19.49, 24.59, 25.92, 27.12, 29.63, 30.55, 38.02, 39.54, 52.00, 63.65, 75.32, 76.66, 121.41, 125.87, 129.19, 131.78, 136.63, 137.62; IR (Nujol) 3511 (OH), 2952, 2923, 2862, 1458, 1377, 1295, 1173, 1108, 963, 835, 763 cm^{-1}. Anal. Calcd for $C_{26}H_{47}NO_4SSi$: C, 62.73; H, 9.52. Found: C, 62.68; H, 9.51. Mp 117–119 °C.

The stereochemistry of the title compound was unambiguously determined by the following derivatization (**45**→**87**→**88**→**89**→**90**).



4.1.43. (*RS*)-*N*-[((2*SR*,3*RS*)-3-Oxa-2-isopropyl-1-cyclohexyl)methyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (90). ^{1}H NMR δ 0.95 (d, J=6.6 Hz, 6H), 1.07 (s, 9H), 1.20–1.36 (m, 4H), 1.56–1.72 (m, 1H), 2.55–2.67 (m, 1H), 2.94 (d/d, J=2.4, 10.2 Hz, 1H), 3.36–3.57 (m, 3H), 4.07 (s, 1H), 4.09 (d/d, J=6.6, 17.4 Hz, 1H), 7.38–7.45 (m, 1H), 7.46–7.60 (m, 2H), 7.72–7.79 (m, 1H). Decoupling experiment was carried out as follows: Irradiation of the peak at δ 1.56–1.72 ppm (C*H*(CH$_3$)$_2$) changed the doublet–doublet peak at δ 2.94 ppm (*i*-PrC*H*O–) to a doublet peak (d, J=2.4 Hz). Irradiation of proton at δ 3.36–3.57 ppm (CH$_2$O–) showed 3% NOE enhancement to the peak at δ 2.94 ppm (*i*-PrC*H*O–). These coupling constants and NOE experiment established the depicted structure of **90** and, hence, that of **45**. ^{13}C NMR δ 17.89, 21.20, 24.35, 27.23, 29.61, 29.73, 33.25, 49.13, 69.95, 75.24, 77.20, 86.82, 121.48, 125.60, 125.75, 129.25, 131.80, 137.82; IR (neat) 2960, 2923, 2845, 1457, 1308, 1172, 1066, 757 cm^{-1}.

4.1.44. (*RS*)-*N*-[(2*SR*,3*RS*)-2-Hexyl-3-hydroxy-4-methylpentyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (46). A solution of (*RS*)-*N*-[(*RS*)-(*E*)-2-hexyl-3-hydroxy-4-methyl-1-pentenyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**38**) (100 mg, 0.244 mmol, a 93:7 mixture of diastereoisomer) and 10% Pd/C (5 mg) in 2 mL of EtOH was stirred at room temperature under 1 atm of hydrogen gas for 2 days. Then, the reaction mixture was filtered through Celite with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, ^{1}H NMR analysis of which showed the presence of a 93:7 mixture of diastereoisomers. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to give the isomerically pure title compound (84.8 mg, 85%) as an oil. ^{1}H NMR δ 0.87 (t, J=6.9 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 1.06 (s, 9H), 1.18–1.52 (m, 9H), 1.60–1.85 (m, 2H), 1.87–2.05 (m, 1H), 2.30–2.45 (symmetric m, 1H), 3.18 (t, J=12.6 Hz, 1H), 3.31 (d/d, J=2.7, 8.4 Hz, 1H), 3.57 (d/d, J=3.6, 12.6 Hz, 1H), 4.07 (s, 1H), 7.38–7.58 (m, 3H), 7.69–7.78 (m, 1H); ^{13}C NMR δ 13.97, 19.00, 19.30, 22.47, 26.59, 27.09, 28.27, 29.32, 30.67, 31.72, 37.99, 39.32, 51.87, 75.14, 76.95, 121.35, 125.84, 129.15, 131.73, 136.64, 137.61; IR (neat) 3535 (OH), 3278, 3066, 2956, 2927, 2870, 1471, 1367, 1301, 1171, 1107, 1001, 928, 759, 707 cm^{-1}. Anal. Calcd for C$_{23}$H$_{39}$NO$_3$S: C, 67.44; H, 9.60. Found: C, 67.12; H, 9.81.

4.1.43. (*RS*)-*N*-[(2*SR*,3*RS*)-3-Acetoxy-2-hexyl-4-methylpentyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (47). A solution of (*RS*)-*N*-[(2*SR*,3*RS*)-2-hexyl-3-hydroxy-4-methylpentyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**46**) (398 mg, 0.800 mmol), NEt$_3$ (0.450 mL, 3.20 mmol), Ac$_2$O (0.150 mL, 1.60 mmol), and DMAP (5 mg, 0.04 mmol) in CH$_2$Cl$_2$ (8 mL) was stirred at room temperature overnight. The organic layer was washed with water, dried, and concentrated to give an oil, which was chromatographed on silica gel to afford the title compound (419 mg, 97%). This sample was directly used in the next step.

4.1.46. (*RS*)-*N*-[(2*RS*,3*RS*)-3-Acetoxy-2-hexyl-4-methylpentanoyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (48). To a stirred solution of (*RS*)-*N*-[(2*SR*,3*RS*)-3-acetoxy-2-hexyl-4-methylpentyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**47**) (67.5 mg, 0.149 mmol) in 0.3 mL of CCl$_4$, 0.3 mL of CH$_3$CN, and 0.45 mL of H$_2$O were added NaIO$_4$ (95.9 mg, 0.448 mmol) and RuCl$_3$ (3.1 mg, 0.015 mmol) at room temperature. After being stirred overnight, the reaction mixture was filtered through Celite with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (33.6 mg, 89% based on conversion (54%)) as an oil. ^{1}H NMR δ 0.74–1.04 (m, 18H), 1.16–2.10 (m, 14H), 3.88 (d/d/d, J=4.2, 6.9, 9.0 Hz, 1H), 5.31 (d/d, J=3.0, 9.0 Hz, 1H), 5.67 (s, 1H), 7.45–7.85 (m, 4H); ^{13}C NMR δ 13.90, 15.65, 19,97, 20.76, 22.42, 25.86, 27.15, 28.72, 29.31, 30.51, 31.44, 38.22, 48.85, 66.12, 75.93, 121.91, 126.07, 129.53, 132.96, 135.35, 135.73, 170.63, 173.38; IR (neat) 2976, 2928, 2870, 1733 (OC=O), 1711 (NC=O), 1456, 1322, 1123, 1025, 830 cm^{-1}. Anal. Calcd for C$_{25}$H$_{39}$NO$_5$S: C, 64.48; H, 8.44. Found: C, 64.17; H, 8.78.

4.1.47. (2*RS*,3*RS*)-2-Hexyl-3-hydroxy-4-methylpentanoic acid (49). To a stirred solution of (*RS*)-*N*-[(2*RS*,3*RS*)-3-acetoxy-2-hexyl-4-methylpentanoyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (**48**) (36.0 mg, 0.077 mmol) in 1.2 mL of THF and 1.2 mL of H$_2$O were added H$_2$O$_2$ (35%, 0.027 mL, 0.309 mmol) and LiOH·H$_2$O (6.4 mg, 0.155 mmol) at 0 °C. After the reaction mixture was stirred overnight at room temperature, most of the THF was evaporated. The aqueous solution was extracted with CH$_2$Cl$_2$ and the organic layer was discarded. Then the aqueous solution was acidified with 1 N HCl until pH~1 and extracted a few times with CH$_2$Cl$_2$. The combined CH$_2$Cl$_2$ solution was dried over Na$_2$SO$_4$ and concentrated to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (14.0 mg, 84%) as an oil. ^{1}H NMR δ 0.87 (t, J=6.6 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 1.18–1.42 (m, 9H), 1.53–1.82 (m, 3H), 2.60 (d/t, J=9.0, 5.4 Hz, 1H), 3.38 (d/d, J=5.4, 6.3 Hz, 1H), 3.56 (br s, 1H); ^{13}C NMR δ 17.44, 19.42, 22.46, 27.15, 29.04, 29.61, 29.82, 31.51, 31.90, 47.90, 77.30, 179.03; IR (neat) 3409 (OH), 2960, 2925, 2854, 1700, 1559, 1457 cm^{-1}. Anal. Calcd for C$_{12}$H$_{24}$O$_3$: C, 66.63; H, 11.18. Found: C, 66.99; H, 10.71.

4.1.48. Typical procedure for Schemes 4 and 5. *N*-Benzyl-*N*-[(1*E*,3*E*)-3-butyl-1,3-octadienyl]-*p*-toluenesulfonamide (54). To a stirred solution of 5-decyne (**50**) (0.021 mL, 0.117 mmol) and Ti(O–*i*-Pr)$_4$ (0.043 mL, 0.146 mmol) in 2 mL of Et$_2$O was added *i*-PrMgCl (1.44 M in Et$_2$O, 0.203 mL, 0.292 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned black. After stirring at −50 °C for 2 h, pulverized *N*-benzyl-*N*-ethynyl-*p*-toluenesulfonamide (**52**) (27 mg, 0.094 mmol) was added in one portion to the reaction mixture at −50 °C. After being stirred for 4 h at the same temperature, the reaction was terminated by the addition of H$_2$O (0.2 mL) and the heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was concentrated in vacuo to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude

product was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (29 mg, 73%) as a colorless oil. ^{1}H NMR δ 0.86 (t, J=6.9 Hz, 3H), 0.92 (t, J=6.9 Hz, 3H), 1.23–1.33 (m, 8H), 2.00 (q, J=7.2 Hz, 2H), 2.13 (t, J=7.2 Hz, 2H), 2,42 (s, 3H), 4.53 (s, 2H), 5.10 (t, J=7.2 Hz, 1H), 5.31 (d, J=14.4 Hz, 1H), 6.80 (d, J=14.4 Hz, 1H), 7.23–7.33 (m, 7H), 7.68 (d, J=8.1 Hz, 2H). Irradiation of proton at δ 5.10 ppm (C=C*H*(Bu)) showed 12% NOE enhancement to the peak at δ 5.31 ppm (C*H*=CHN). Thus, the stereochemistry has been confirmed. ^{13}C NMR δ 13.82, 13.97, 21.42, 22.33, 22.78, 26.62, 27.67, 31.02, 31.84, 49.44, 117.42, 123.74, 127.01 (2 peaks), 127.42, 128.64, 129.86, 130.50, 135.92, 136.07, 136.12, 143.84; IR (neat) 3088, 3065, 3030, 2957, 2928, 2871, 2859, 1638, 1620, 1598, 1496, 1465, 1456, 1401, 1358, 1322, 1307, 1289, 1265, 1210, 1185, 1165, 1119, 1093, 1044, 1025, 1018, 1003, 938, 887, 812, 778, 735, 704, 696, 663 cm^{-1}. Anal. Calcd for $C_{26}H_{35}NO_2S$: C, 73.37; H, 8.29. Found: C, 73.57; H, 7.92.

4.1.49. *N*-Benzyl-*N*-[(1*E*,3*E*)-3-butyl-1,4-dideuterio-1,3-octadienyl]-*p*-toluenesulfonamide (54-d_2). ^{1}H NMR δ 0.86 (t, J=6.9 Hz, 3H), 0.92 (t, J=6.9 Hz, 3H), 1.23–1.33 (m, 8H), 2.00 (t, J=7.2 Hz, 2H), 2.13 (t, J=7.2 Hz, 2H), 2.42 (s, 3H), 4.53 (s, 2H), 5.31 (s, 1H), 7.23–7.33 (m, 7H), 7.68 (d, J=8.1 Hz, 2H). The peak at δ 5.10 ppm (C=C*H*(Bu)) of **54** disappeared to show 91% deuterium incorporation. The peak at δ 6.80 ppm (CH=C*H*(N)) of **54** disappeared to show 96% deuterium incorporation.

4.1.50. *N*-Benzyl-*N*-[(1*E*,3*Z*)-3,4-diphenyl-1,3-butadienyl]-*p*-toluenesulfonamide (56). ^{1}H NMR δ 2.44 (s, 3H), 4.61 (s, 2H), 5.77 (d, J=14.1 Hz, 1H), 6.25 (s, 1H), 6.51 (d, J=14.1 Hz, 1H), 6.74–6.77 (m, 2H), 7.01–7.03 (m, 3H), 7.08–7.12 (m, 2H), 7.29–7.42 (m, 10H), 7.54 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 21.44, 49.65, 118.33, 126.36, 126.95, 127.00, 127.61, 127.76, 127.92, 128.22, 128.78, 128.98, 129.03, 129.45, 129.78, 129.87, 135.66, 135.83, 136.99, 138.02, 139.82, 144.05; IR (Nujol) 3089, 3065, 3032, 2953, 2924, 2854, 1629, 1594, 1456, 1377, 1364, 1341, 1312, 1286, 1273, 1239, 1211, 1200, 1184, 1163, 1117, 1089, 1078, 1042, 1028, 1017, 1000, 972, 951, 932, 911, 897, 867, 852, 835, 809, 799, 775, 759, 751, 733, 694, 674, 654 cm^{-1}. Anal. Calcd for $C_{30}H_{27}NO_2S$: C, 77.39; H, 5.84. Found: C, 77.19; H, 5.63. Mp 127–129 °C.

4.1.51. *N*-Benzyl-*N*-[(1*E*,3*Z*)-3,4-diphenyl-1,4-dideuterio-1,3-butadienyl]-*p*-toluenesulfonamide (56-d_2). ^{1}H NMR δ 2.44 (s, 3H), 4.61 (s, 2H), 5.77 (s, 1H), 6.74–6.77 (m, 2H), 7.01–7.03 (m, 3H), 7.08–7.12 (m, 2H), 7.29–7.42 (m, 10H), 7.54 (d, J=8.1 Hz, 2H). The peak at δ 6.25 ppm (C=C*H*(Ph)) of **56** disappeared to show 97% deuterium incorporation. The peak at δ 6.51 ppm (CH=C*H*(N)) of **56** disappeared to show 96% deuterium incorporation.

4.1.52. *N*-Benzyl-*N*-[(1*E*,3*Z*)-3-phenyl-4-(trimethylsilyl)-1,3-butadienyl]-*p*-toluenesulfonamide (57). ^{1}H NMR δ −0.28 (s, 9H), 2.43 (s, 3H), 4.55 (s, 2H), 5.45 (s, 1H), 5.65 (d, J=14.4 Hz, 1H), 6.45 (d, J=14.4 Hz, 1H), 7.04–7.07 (m, 2H), 7.26–7.36 (m, 10H), 7.50 (d, J=8.4 Hz, 2H). Irradiation of proton at δ −0.28 ppm ($SiMe_3$) showed 5% NOE enhancement to the peak at δ 5.45 ppm (C=C*H*($SiMe_3$)). Irradiation of proton at δ 5.45 ppm (C=C*H*($SiMe_3$)) showed 10% NOE enhancement to the peak at δ 5.65 ppm (C*H*=CH(N)). Thus, the regio- and stereochemistries have been confirmed. ^{13}C NMR δ −0.33, 21.44, 49.55, 119.11, 126.92, 126.98, 127.56, 128.00, 128.76, 129.27, 129.87, 130.39, 130.63, 135.66, 135.92, 140.32, 144.06, 154.42; IR (neat) 3078, 3064, 3029, 2953, 2926, 2898, 2857, 1623, 1598, 1559, 1491, 1456, 1442, 1400, 1363, 1316, 1260, 1247, 1215, 1185, 1167, 1107, 1090, 1039, 1028, 945, 864, 837, 775, 739, 703, 664 cm^{-1}. Anal. Calcd for $C_{27}H_{31}NO_2SSi$: C, 70.24; H, 6.77; N, 3.03. Found: C, 70.10; H, 6.73; N, 2.82.

4.1.53. *tert*-Butyl (3*E*)-4-[benzyl(*p*-toluenesulfonyl)-amino]-2-[(*Z*)-(trimethylsilyl)methylene]-3-butenoate (58). ^{1}H NMR δ 0.09 (s, 9H), 1.53 (s, 9H), 2.42 (s, 3H), 4.54 (s, 2H), 5.40 (d, J=14.7 Hz, 1H), 5.72 (s, 1H), 7.24–7.32 (m, 7H), 7.35 (d, J=14.7 Hz, 1H), 7.67 (d, J=8.4 Hz, 2H). Irradiation of proton at δ 0.09 ppm ($SiMe_3$) showed 8% NOE enhancement to the peak at δ 5.72 ppm (C=C*H*($SiMe_3$)). Irradiation of proton at δ 5.72 ppm (C=C*H*($SiMe_3$)) showed 5% NOE enhancement to the peak at δ 0.09 ppm ($SiMe_3$) and 14% NOE enhancement to the peak at δ 5.40 ppm (C*H*=CH(N)). Thus, the regio- and stereochemistries have been confirmed. ^{13}C NMR δ −0.54, 21.43, 28.07, 49.29, 81.93, 111.82, 126.87, 127.02, 127.59, 128.75, 129.06, 130.03, 135.27, 136.05, 136.46, 144.22, 145.56, 167.21; IR (Nujol) 3087, 3063, 3032, 2952, 2924, 2854, 1715 (C=O), 1653, 1624, 1596, 1569, 1559, 1539, 1507, 1495, 1457, 1375, 1319, 1259, 1228, 1169, 1090, 1026, 971, 939, 894, 860, 845, 803, 755, 729, 694, 661 cm^{-1}. Anal. Calcd for $C_{26}H_{35}NO_4SSi$: C, 64.29; H, 7.26; N, 2.88. Found: C, 64.16; H, 7.29; N, 2.71. Mp 101–103 °C.

4.1.54. (2*E*,4*E*)-*N*,*N*-Diethyl-5-[benzyl(*p*-toluenesulfonyl)-amino]-3-hexyl-2,4-pentadienamide (59). ^{1}H NMR δ 0.89 (t, J=6.9 Hz, 3H), 1.06 (t, J=7.2 Hz, 3H), 1.09 (t, J=7.2 Hz, 3H), 1.25–1.33 (m, 6H), 1.40 (m, 2H), 2.42 (s, 3H), 3.23 (q, J=7.2 Hz, 2H), 3.36 (q, J=7.2 Hz, 2H), 4.60 (s, 2H), 5.27 (d, J=14.4 Hz, 1H), 5.60 (s, 1H), 7.17 (d, J=14.4 Hz, 1H), 7.23–7.31 (m, 7H), 7.66 (d, J=8.4 Hz, 2H). Irradiation of proton at δ 5.60 ppm (C=CH(C=O)) showed 13% NOE enhancement to the peak at δ 5.27 ppm (C*H*=CH(N)). Thus, the regio- and stereochemistries have been confirmed. ^{13}C NMR δ 12.90, 13.98, 14.08, 21.43, 22.51, 28.39, 29.29, 29.43, 31.65, 39.26, 42.26, 49.31, 114.14, 119.11, 126.84, 127.00, 127.58, 128.70, 128.88, 130.00, 135.29, 135.92, 144.27, 147.69, 167.24; IR (neat) 3089, 3065, 3032, 2958, 2930, 2871, 2858, 1634 (C=O), 1618, 1598, 1496, 1456, 1428, 1362, 1321, 1281, 1272, 1220, 1185, 1165, 1140, 1119, 1090, 1046, 1028, 1017, 1002, 944, 911, 863, 813, 785, 734, 704, 696, 663 cm^{-1}. Anal. Calcd for $C_{29}H_{40}N_2O_3S$: C, 70.12; H, 8.12. Found: C, 70.11; H, 7.78.

4.1.55. (2*E*,4*E*)-*N*,*N*-Diethyl-5-[benzyl(*p*-toluenesulfonyl)-amino]-2,5-dideuterio-3-hexyl-2,4-pentadienamide (59-d_2). ^{1}H NMR δ 0.89 (t, J=6.9 Hz, 3H), 1.06 (t, J=7.2 Hz, 3H), 1.09 (t, J=7.2 Hz, 3H), 1.25–1.33 (m, 6H), 1.40 (m, 2H), 2.42 (s, 3H), 3.23 (q, J=7.2 Hz, 2H), 3.36 (q, J=7.2 Hz, 2H), 4.60 (s, 2H), 5.27 (s, 1H), 7.23–7.31 (m, 7H), 7.66 (d, J=8.4 Hz, 2H). The peak at δ 5.60 ppm (C=CH(C=O)) of **59** disappeared to show 97% deuterium

incorporation. The peak at δ 7.17 ppm (CH=C*H*(N)) of **59** disappeared to show 96% deuterium incorporation.

4.1.56. *N*-Benzyl-*N*-[(1*E*,3*Z*)-4-(*N*,*N*-diethylcarbamoyl)-3-(trimethylsilyl)]-*p*-toluenesulfonamide (60). ^{1}H NMR δ 0.01 (s, 9H), 1.12 (t, *J*=7.2 Hz, 3H), 1.16 (t, *J*=7.2 Hz, 3H), 2.43 (s, 3H), 3.33 (q, *J*=7.2 Hz, 2H), 3.36 (q, *J*=7.2 Hz, 2H), 4.54 (s, 2H), 5.42 (d/d, *J*=1.2, 13.8 Hz, 1H), 6.47 (d, *J*=1.2 Hz, 1H), 6.98 (d, *J*=13.8 Hz, 1H), 7.24–7.33 (m, 7H), 7.68 (d, *J*=8.4 Hz, 2H). Irradiation of proton at δ 0.01 ppm ($SiMe_3$) showed 7% NOE enhancement to the peak at δ 5.42 ppm (C*H*=CH(N)) and 6% NOE enhancement to the peak at δ 6.98 ppm (CH=C*H*(N)). Irradiation of proton at δ 6.47 ppm (C=CH(C=O)) showed 1% NOE enhancement to the peak at δ 3.33 ppm (NCH_2CH_3), 4% NOE enhancement to the peak at δ 5.42 ppm (C*H*=CHN), and 13% NOE enhancement to the peak at δ 6.98 ppm (CH=C*H*(N)). Thus, the regio- and stereochemistries have been confirmed. ^{13}C NMR δ −0.48, 12.90, 14.18, 21.44, 39.84, 42.48, 49.69, 116.59, 126.47, 126.93, 127.03, 127.59, 128.71, 129.25, 129.97, 135.35, 135.93, 144.18, 151.11, 167.41; IR (neat) 3087, 3065, 3031, 2973, 2933, 2899, 2873, 1633, 1622, 1616, 1563, 1558, 1496, 1475, 1456, 1446, 1429, 1379, 1361, 1314, 1290, 1261, 1221, 1185, 1165, 1103, 1090, 1040, 1028, 1017, 1002, 944, 841, 812, 780, 734, 705, 696, 660 cm^{-1}. Anal. Calcd for $C_{26}H_{36}N_2O_3SSi$: C, 64.42; H, 7.49; N, 5.78. Found: C, 64.18; H, 7.68; N, 5.49.

4.1.57. Typical procedure for Scheme 6. *N*-Benzyl-*N*-[(1*E*,3*Z*)-5-hydroxy-3,4-dibutyl-1,3-tridecadienyl]-*p*-toluenesulfonamide (62). To a stirred solution of 5-decyne (**50**) (0.016 mL, 0.088 mmol) and Ti(O–*i*-Pr)$_4$ (0.032 mL, 0.110 mmol) in 1 mL of Et_2O was added *i*-PrMgCl (1.47 M in Et_2O, 0.149 mL, 0.219 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned black. After stirring at −50 °C for 2 h, pulverized *N*-benzyl-*N*-ethynyl-*p*-toluenesulfonamide (**52**) (20 mg, 0.070 mmol) was added in one portion to the reaction mixture at −50 °C and the solution was stirred for another 4 h. Then, nonanal (0.023 mL, 0.131 mmol) was added and the reaction mixture was subsequently allowed to warm to room temperature. After being stirred for 5 h at the same temperature, the reaction was terminated by the addition of H_2O (0.2 mL) and the heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was concentrated in vacuo to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (18 mg, 45%) as a colorless oil. ^{1}H NMR δ 0.88 (t, *J*=6.9 Hz, 3H), 0.89 (t, *J*=6.9 Hz, 3H), 0.92 (t, *J*=6.9 Hz, 3H), 1.11–1.34 (m, 20H), 1.59 (br s, 2H), 1.96 (m, 3H), 2.12 (t, *J*=8.7 Hz, 2H), 2.43 (s, 3H), 4.16 (t, *J*=7.8 Hz, 1H), 4.45 (d, *J*=15.6 Hz, 1H), 4.64 (d, *J*=15.6 Hz, 1H), 5.64 (d, *J*=14.4 Hz, 1H), 6.86 (d, *J*=14.4 Hz, 1H), 7.23–7.36 (m, 7H), 7.70 (d, *J*=8.1 Hz, 2H). Irradiation of proton at δ 5.64 ppm (C*H*=CH(N)) showed 20% NOE enhancement to the peak at δ 4.16 ppm (C*H*OH). Thus, the stereochemistry has been confirmed. ^{13}C NMR δ 13.74, 13.91, 13.97, 21.42, 22.56, 22.98, 23.37, 25.92, 28.13, 29.03, 29.18, 29.45, 29.54, 31.43, 31.80, 33.04, 35.87, 49.61, 71.95, 111.28, 125.53, 126.92, 127.04, 127.57, 128.73, 129.81, 129.94, 132.11, 135.77, 138.68, 143.97; IR (neat) 3303 (OH), 3089, 3065, 3032, 2956, 2927, 2871, 2857, 1598, 1496, 1456, 1402, 1339, 1306, 1290, 1239, 1163, 1120, 1092, 1060, 926, 814, 738, 698, 663 cm^{-1}. Anal. Calcd for $C_{35}H_{53}NO_3S$: C, 74.03; H, 9.41. Found: C, 74.21; H, 9.16.

4.1.58. *N*-Benzyl-*N*-[(1*E*,3*E*)-5-hydroxy-3,4-diphenyl-1,3-tridecadienyl]-*p*-toluenesulfonamide (63). ^{1}H NMR δ 0.90 (t, *J*=6.9 Hz, 3H), 1.12–1.39 (m, 14H), 1.58 (br s, 1H, OH), 2.45 (s, 3H), 4.47 (d, *J*=15.6 Hz, 1H), 4.47 (br s, 1H), 4.74 (d, *J*=15.5 Hz, 1H), 6.06 (d, *J*=14.4 Hz, 1H), 6.46 (d, *J*=14.4 Hz, 1H), 6.85 (d/t, *J*=1.8, 7.8 Hz, 4H), 6.99–7.12 (m, 6H), 7.29–7.38 (m, 7H), 7.50 (d, *J*=8.4 Hz, 2H). Irradiation of proton at δ 6.06 ppm (C*H*=CH(N)) showed 26% NOE enhancement to the peak at δ 4.47 ppm (C*H*OH). Thus, the stereochemistry has been confirmed. ^{13}C NMR δ 14.00, 21.46, 22.56, 25.83, 29.17, 29.44 (2 peaks), 31.78, 36.37, 49.84, 71.26, 111.80, 126.26, 126.54, 126.92, 127.01, 127.38, 127.54, 127.75, 128.89, 129.91, 130.41, 130.60, 131.65, 135.65, 135.71, 136.98, 138.58, 139.50, 139.94, 144.10; IR (neat) 3553 (OH), 3077, 3056, 3028, 2926, 2855, 1625, 1598, 1490, 1456, 1441, 1399, 1362, 1318, 1289, 1268, 1212, 1186, 1167, 1119, 1091, 1073, 1038, 1029, 1018, 1009, 946, 911, 833, 813, 768, 736, 701, 666 cm^{-1}. Anal. Calcd for $C_{39}H_{45}NO_3S$: C, 77.06; H, 7.46. Found: C, 76.91; H, 7.54.

4.1.59. Typical procedure for Scheme 6. *N*-Benzyl-*N*-[(1*Z*,3*Z*)-3-butyl-1,4-diiodo-1,3-octadienyl]-*p*-toluenesulfonamide (64). To a stirred solution of 5-decyne (**50**) (0.022 mL, 0.120 mmol) and Ti(O–*i*-Pr)$_4$ (0.044 mL, 0.150 mmol) in 1 mL of Et_2O was added *i*-PrMgCl (1.46 M in Et_2O, 0.213 mL, 0.311 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned black. After stirring at −50 °C for 2 h, pulverized *N*-benzyl-*N*-ethynyl-*p*-toluenesulfonamide (**52**) (27 mg, 0.096 mmol) was added in one portion and the mixture was stirred for 4 h at the same temperature. Then, iodine (91 mg, 0.359 mmol) in 1.0 mL of Et_2O was added. After 30 min, to the cold reaction mixture was added an aqueous solution of $Na_2S_2O_3$ (0.2 mL). The resulting heterogeneous solution was filtered through Celite with the aid of ether. The organic phase was concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (42 mg, 65%) as a colorless oil. Its stereochemistry was assigned based on that of the protonated and deuterated products. ^{1}H NMR δ 0.86 (t, *J*=6.9 Hz, 3H), 0.88 (t, *J*=6.9 Hz, 3H), 1.13–1.50 (m, 8H), 2.15 (t, *J*=7.5 Hz, 2H), 2.44 (t, *J*=7.5 Hz, 2H), 2.46 (s, 3H), 4.44 (s, 2H), 6.47 (s, 1H), 7.23–7.41 (m, 7H), 7.79 (d, *J*=8.1 Hz, 2H); ^{13}C NMR δ 13.68, 13.81, 21.53, 22.52, 30.00, 31.45, 33.13, 39.99, 54.11, 102.69, 107.28, 128.08, 128.71 (2 peaks), 129.59, 129.70, 134.84, 134.94, 142.58, 144.45, 149.24; IR (neat) 3087, 3064, 3031, 2956, 2927, 2870, 2858, 1598, 1495, 1456, 1359, 1305, 1291, 1259, 1216, 1185, 1168, 1140, 1091, 1041, 946, 838, 813, 774, 742, 697, 662 cm^{-1}. Anal. Calcd for $C_{26}H_{33}I_2NO_2S$: C, 46.10; H, 4.91. Found: C, 46.38; H, 5.24.

4.1.60. Typical procedure for Scheme 7. *N*-(1,6-Tridecadiyn-1-yl)-3-methyl-1,2-benzisothiazoline 1,1-dioxide (67). To a heterogeneous mixture of 3-methyl-1,2-benzisothiazoline 1,1-dioxide (**1**) (293 mg, 1.60 mmol), powdered K_3PO_4 (679 mg, 3.20 mmol), and CuI (15.2 mg, 0.080 mmol) in 4 mL of toluene was added 1-bromo-1,6-tridecadiyne (**65**) (408 mg, 1.60 mmol) in 12 mL of toluene, followed by *N*,*N*′-dimethylethylenediamine (0.040 mL) under argon. The mixture was stirred overnight in an oil bath maintained at 110 °C. The reaction mixture was cooled to room temperature and was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (455 mg, 79%) as an oil. ^{1}H NMR δ 0.89 (t, J=6.9 Hz, 3H), 1.26–1.54 (m, 8H), 1.67 (d, J=6.6 Hz, 3H), 1.76 (quintet, J=6.9 Hz, 2H), 2.15 (t/t, J=6.9, 2.4 Hz, 2H), 2.30 (t/t, J=6.9 Hz, 2.4 Hz, 2H), 2.51 (t, J=6.9 Hz, 2H), 4.79 (q, J=6.6 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.83 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 13.39, 17.84, 17.93, 18.65, 19.15, 22.46, 28.38, 28.47, 28.98, 31.28, 59.05, 67.45, 73.61, 78.94, 81.11, 121.81, 123.91, 129.62, 132.86, 133.62, 137.41; IR (neat) 3074, 3025, 2863, 2241, 1453, 1328, 1178, 1091, 928, 736, 699 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_2S$: C, 70.55; H, 7.61. Found: C, 70.42; H, 7.48.

4.1.61. *N*-[7-(Trimethylsilyl)-1,6-tridecadiyn-1-yl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (68). ^{1}H NMR δ 0.15 (s, 9H), 1.67 (d, J=6.6 Hz, 3H), 1.79 (quintet, J=7.2 Hz, 2H), 2.37 (t, J=7.2 Hz, 2H), 2.51 (t, J=7.2 Hz, 2H), 4.79 (q, J=6.6 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.82 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −0.02, 17.81, 18.95, 19.15, 27.82, 59.03, 67.64, 73.33, 85.20, 106.28, 121.78, 123.93, 129.62, 132.79, 133.65, 137.36; IR (Nujol) 2923, 2854, 2731, 2266, 2184, 1457, 1376, 1303, 1180, 1033, 848, 763, 715 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2SSi$: C, 62.57; H, 6.71. Found: C, 62.40; H, 6.49. Mp 88–90 °C.

4.1.62. Typical procedure for Scheme 7. *N*-[(*E*)-((*E*)-2-Heptylidene-1-cyclopentylidene)methyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (69). To a stirred solution of *N*-(1,6-tridecadiyn-1-yl)-3-methyl-1,2-benzisothiazoline 1,1-dioxide (**67**) (38 mg, 0.106 mmol) and Ti(O–*i*-Pr)$_4$ (0.063 mL, 0.212 mmol) in 1.1 mL of Et_2O was added *i*-PrMgCl (1.50 M in Et_2O, 0.283 mL, 0.424 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned red. After stirring at −50 °C for 3 h, the reaction was terminated by the addition of H_2O (0.11 mL) and the heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was concentrated in vacuo to give a crude oil. Careful analysis of the crude product by ^{1}H NMR spectroscopy did not show the presence of any isomeric products. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (37 mg, 99%) as a colorless oil. ^{1}H NMR δ 0.88 (t, J=6.9 Hz, 3H), 1.20–1.46 (m, 8H), 1.52 (d, J=6.6 Hz, 3H), 1.57–1.86 (m, 2H), 2.04–2.13 (m, 2H), 2.34–2.44 (m, 2H), 2.56–2.69 (m, 2H), 4.59 (q, J=6.6 Hz, 1H), 5.93–6.00 (m, 1H), 6.07 (t, J=1.8 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.63 (t, J=7.5 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 14.09, 19.23, 22.61, 23.71, 29.12, 29.24, 29.79, 29.86, 31.58, 31.75, 58.73, 108.83, 121.44, 122.43, 123.60, 129.07, 132.91, 134.48, 138.75, 138.87, 148.30; IR (neat) 2976, 2927, 2862, 2837, 1660, 1455, 1308, 1262, 1172, 1132, 761 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_2S$: C, 70.15; H, 8.13. Found: C, 69.91; H, 8.10.

4.1.63. *N*-[(*E*)-[(*E*)-2-(Trimethylsilyl)methylidene-1-cyclopentylidene]methyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (70). ^{1}H NMR δ 0.14 (s, 9H), 1.53 (d, J=6.6 Hz, 3H), 1.60–1.75 (m, 1H), 1.75–1.96 (m, 1H), 2.45–2.53 (m, 2H), 2.63–2.68 (m, 2H), 4.69 (q, J=6.6 Hz, 1H), 6.02 (t, J=2.1 Hz, 1H), 6.27 (t, J=2.1 Hz, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H). NOESY experiments showed the correlation between the peaks at δ 4.69 ppm (NCH) and at δ 6.02 ppm (vinylic H), and that between the peaks at δ 6.02 ppm (vinylic H) and at δ 6.27 ppm (vinylic H). Thus, the stereochemistry of the olefinic bond has been confirmed. ^{13}C NMR δ −0.57, 19.57, 24.04, 30.78, 33.44, 58.72, 112.44, 118.33, 121.55, 123.73, 129.26, 133.12, 134.42, 138.88, 145.69, 155.48; IR (Nujol) 2952, 2924, 2854, 1653, 1457, 1376, 1303, 1172, 1134, 879, 836, 757 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2SSi$: C, 62.21; H, 7.25. Found: C, 61.96; H, 7.11.

4.1.64. Typical procedure for Scheme 8. *N*-[4,4-Bis(benzyloxymethyl)-6-hepten-1-yn-1-yl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (73). To a heterogeneous mixture of 3-methyl-1,2-benzisothiazoline 1,1-dioxide (**1**) (293 mg, 1.60 mmol), powdered K_3PO_4 (679 mg, 3.20 mmol), and CuI (15.2 mg, 0.080 mmol) in 4 mL of toluene was added 4,4-bis(benzyloxymethyl)-1-bromo-6-hepten-1-yne (**71**) (617 mg, 1.60 mmol) in 12 mL of toluene, followed by *N*,*N*′-dimethylethylenediamine (0.040 mL) under argon. The mixture was stirred overnight in an oil bath maintained at 110 °C. The reaction mixture was cooled to room temperature and was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate) to give the title compound (515 mg, 63%) as an oil. ^{1}H NMR δ 1.60 (d, J=6.6 Hz, 3H), 2.28 (d, J=7.2 Hz, 2H), 2.49 (s, 2H), 3.44 (s, 4H), 4.52 (s, 4H), 4.72 (q, J=6.6 Hz, 1H), 5.06 (d, J=9.9 Hz, 1H), 5.12 (d, J=17.1 Hz, 1H), 5.76–5.89 (m, 1H), 7.25–7.33 (m, 10H), 7.39 (d, J=7.8 Hz, 1H), 7.57 (t, J=7.8 Hz, 1H), 7.68 (t, J=7.8 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H); ^{13}C NMR δ 19.20, 22.49, 36.43, 42.45, 59.00, 71.32, 72.05 (2 peaks), 73.34 (2 peaks), 77.21, 118.24, 121.79, 123.91, 123.91, 127.41, 127.54, 128.33, 129.62, 132.96, 133.60, 133.97, 137.41, 138.97; IR (neat) 3058, 3025, 2968, 2919, 2258, 1453, 1325, 1270, 1179, 1107, 1025, 911, 797, 736, 715 cm^{-1}. Anal. Calcd for $C_{31}H_{33}NO_4S$: C, 72.20; H, 6.45. Found: C, 72.01; H, 6.57.

4.1.65. *N*-Benzyl-*N*-[4,4-bis(benzyloxymethyl)-6-hepten-1-yn-1-yl]-*p*-toluenesulfonamide (72). ^{1}H NMR δ 1.99 (d, J=7.5 Hz, 2H), 2.24 (s, 2H), 2.41 (s, 3H), 3.20 (s, 4H), 4.38 (s, 4H), 4.43 (s, 2H), 4.86–4.90 (m, 2H), 5.55–5.72 (m, 1H), 7.22–7.30 (m, 17H), 7.72 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.46, 21.98, 35.96, 42.29, 55.26, 67.64, 71.64 (2 peaks),

73.02 (2 peaks), 74.73, 117.83, 127.14, 127.21, 127.52, 128.00, 128.12, 128.36, 128.46, 129.52, 133.73, 134.65, 134.71, 138.71, 144.21; IR (neat) 3041, 2919, 2860, 2250, 1496, 1453, 1364, 1169, 1092, 1034, 928, 854, 813, 756, 698 cm^{-1}. Anal. Calcd for $C_{37}H_{39}NO_4S$: C, 74.84; H, 6.62. Found: C, 74.83; H, 6.51.

4.1.66. *N*-[4,4-Bis(benzyloxymethyl)-6-hepten-1-yn-1-yl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide (74). ^1H NMR δ 1.10 (s, 9H), 2.28 (d, $J=7.5$ Hz, 2H), 2.47 (s, 2H), 3.44 (s, 4H), 4.39 (s, 1H), 4.53 (s, 4H), 5.07 (d, $J=9.9$ Hz, 1H), 5.13 (d, $J=17.4$ Hz, 1H), 5.75–5.89 (m, 1H), 7.25–7.34 (m, 10H), 7.47 (d, $J=7.5$ Hz, 1H), 7.54–7.65 (m, 2H), 7.82 (d, $J=6.6$ Hz, 1H); ^{13}C NMR δ 22.36, 26.77 (*t*-Bu), 36.30, 38.16, 42.50, 69.45, 71.98 (2 peaks), 72.92, 73.22 (2 peaks), 75.19, 118.11, 121.89, 125.79, 127.34, 127.45 (2 peaks), 128.27, 129.53, 132.54, 134.03, 135.57, 138.95; IR (neat) 3082, 3025, 2960, 2919, 2862, 2250, 1466, 1328, 1254, 1181, 1115, 1091, 936, 736, 707 cm^{-1}. Anal. Calcd for $C_{34}H_{39}NO_4S$: C, 73.22; H, 7.05. Found: C, 73.09; H, 6.87.

4.1.67. (*R*)-*N*-(*p*-Toluenesulfonyl)-*N*-[4,4-bis(benzyloxymethyl)-6-hepten-1-yn-1-yl]-*N*-(2-methoxy-1-phenylethyl)amine (75). ^1H NMR δ 1.99 (d, $J=7.8$ Hz, 2H), 2.35 (s, 3H), 2.38 (s, 2H), 3.22 (s, 3H), 3.33 (s, 4H), 3.60 (d/d, $J=4.8$, 9.9 Hz, 1H), 3.80 (t, $J=9.9$ Hz, 1H), 4.44 (s, 4H), 5.01 (m, 2H), 5.21 (d/d, $J=4.8$, 9.9 Hz, 1H), 5.73 (m, 1H), 7.11 (d, $J=8.4$ Hz, 2H), 7.22–7.34 (m, 15H), 7.64 (d, $J=8.4$ Hz, 2H); ^{13}C NMR δ 21.44, 22.34, 36.20, 42.54, 58.65, 61.58, 70.04, 72.02 (2 peaks), 72.30, 72.39, 73.24 (2 peaks), 118.05, 127.36, 127.39, 127.44, 128.00, 128.27, 128.35, 128.54, 129.16, 134.00, 135.76, 136.72, 138.91, 143.91; IR (neat) 3066, 3025, 2927, 2861, 2258, 1597, 1491, 1453, 1363, 1181, 1092, 1034, 958, 928, 813, 748, 701 cm^{-1}. Anal. Calcd for $C_{39}H_{43}NO_5S$: C, 73.44; H, 6.80. Found: C, 73.18; H, 6.57; $[\alpha]_D^{28}$ +51.2 (*c* 3.36, $CHCl_3$).

4.1.68. (1*S*,2*S*)-*N*-[4,4-Bis(benzyloxymethyl)-6-hepten-1-yn-yl]-2,10-camphorsultam (76). ^1H NMR δ 0.99 (s, 3H), 1.09 (s, 3H), 1.28–1.31 (m, 1H), 1.38–1.44 (m, 1H), 1.64 (d/d, $J=5.1$, 8.1 Hz, 1H), 1.85–1.92 (m, 3H), 2.05–2.15 (m, 1H), 2.24 (d, $J=7.5$ Hz, 2H), 2.40 (s, 2H), 3.21 (s, 2H), 3.41 (s, 4H), 3.46 (t, $J=7.8$ Hz, 1H), 4.51 (s, 4H), 5.05 (d, $J=10.4$ Hz, 1H), 5.10 (d, $J=17.4$ Hz, 1H), 5.72–5.86 (m, 1H), 7.24–7.36 (m, 10H); ^{13}C NMR δ 19.79, 20.04, 22.24, 26.87, 31.44, 34.28, 36.30, 42.31, 44.27, 47.78, 49.44, 50.80, 67.04, 69.28, 69.37, 71.99 (2 peaks), 73.25 (2 peaks), 118.11, 127.35, 127.43, 128.28, 133.96, 138.94; IR (neat) 3066, 2959, 2895, 2854, 2250, 1638, 1453, 1338, 1320, 1270, 1140, 1095, 919, 737, 699 cm^{-1}. Anal. Calcd for $C_{33}H_{41}NO_4S$: C, 72.36; H, 7.54. Found: C, 72.51; H, 7.59; $[\alpha]_D^{28}$ +8.3 (*c* 0.936, $CHCl_3$).

4.1.69. Typical procedure for Scheme 9. *N*-[[(*E*)-4,4-Bis(benzyloxymethyl)-2-methyl-1-cyclopentylidene]-methyl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide as a 1:1 mixture of diastereoisomers (78). To a stirred solution of *N*-[4,4-bis(benzyloxymethyl)-6-hepten-1-yn-1-yl]-3-methyl-1,2-benzisothiazoline 1,1-dioxide (**73**) (47 mg, 0.097 mmol) and Ti(O–*i*-Pr)$_4$ (0.057 mL, 0.193 mmol) in 1.0 mL of Et_2O was added *i*-PrMgCl (1.50 M in Et_2O, 0.257 mL, 0.386 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned red. After stirring at −50 °C for 3 h, the reaction was terminated by the addition of H_2O (0.10 mL) and the heterogeneous mixture was filtered through Celite with the aid of ether. The organic phase was concentrated in vacuo to give a crude oil, ^1H NMR analysis of which showed the diastereoselectivity to be 1:1. The crude product was chromatographed on silica gel (hexane–ethyl acetate) to afford the title compound (53 mg, 87%) as a colorless oil. ^1H NMR δ 1.15–1.21 (m, 4H), 1.43 (d, $J=6.6$ Hz, 1.5H) 1.45 (d, $J=6.6$ Hz, 1.5H), 2.04 (d/d, $J=10.2$, 13.8 Hz, 1H), 2.58 (br s, 2H), 2.77 (m, 1H), 3.35–3.43 (m, 4H), 4.46–4.51 (m, 5H), 5.55 (q, $J=2.4$ Hz, 0.5H), 5.64 (q, $J=2.4$ Hz, 0.5H), 7.26–7.33 (m, 10H), 7.37 (d, $J=7.5$ Hz, 1H), 7.52 (t, $J=7.5$ Hz, 1H), 7.62 (t, $J=7.5$ Hz, 1H), 7.80 (d, $J=7.5$ Hz, 1H). Irradiation of proton at δ 5.55–5.64 ppm (vinylic H) showed 3% NOE enhancement to the peak at δ 2.77 ppm (C=CC*H*Me). Irradiation of proton at δ 2.77 ppm (C=CC*H*Me) showed 3% NOE enhancement to the peak at δ 5.55–5.64 ppm (vinylic H). Thus, the stereochemistry has been confirmed. ^{13}C NMR δ 17.74, 18.55, 18.64, 19.87, 36.21, 36.74, 39.95, 40.36, 45.71, 46.25, 58.17, 58.33, 72.84, 73.22, 73.38, 74.65, 74.82, 77.21, 111.52, 111.99, 121.51, 123.63, 123.67, 127.41, 127.49, 127.52, 127.55, 128.28, 128.32, 128.35, 129.10, 132.89, 132.95, 134.72, 138.90, 139.16, 157.28, 157.84. (Peaks of diastereoisomers may be overlapping.) IR (neat) 3025, 2960, 2927, 2856, 1496, 1453, 1363, 1304, 1279, 1172, 1148, 1099, 1034, 910, 735, 699 cm^{-1} for a 1:1 mixture of diastereoisomers. Anal. Calcd for $C_{31}H_{35}NO_4S$: C, 71.92; H, 6.81. Found: C, 71.64; H, 6.56 for a 1:1 mixture of diastereoisomers.

4.1.70. *N*-Benzyl-*N*-[[(*E*)-4,4-bis(benzyloxymethyl)-2-methyl-1-cyclopentylidene]methyl]-*p*-toluenesulfonamide (77). ^1H NMR δ 0.96 (d, $J=6.0$ Hz, 3H), 1.22–1.36 (m, 1H), 1.82–1.92 (m, 1H), 2.18 (s, 2H), 2.44 (s, 3H), 2.40–2.54 (m, 1H), 2.99–3.14 (m, 4H), 4.18 (d, $J=3.9$ Hz, 2H), 4.32–4.50 (m, 4H), 4.97–5.05 (m, 1H), 7.16–7.40 (m, 17H), 7.70 (d, $J=8.1$ Hz, 2H); ^{13}C NMR δ 19.19, 21.51, 35.50, 37.00, 39.67, 45.73, 54.44, 72.48, 73.03 (2 peaks), 74.46, 117.36, 127.25, 127.50, 128.18, 129.05, 129.50, 135.20, 136.09, 138.89, 143.27, 155.85. Peaks of aromatic carbons may be overlapping. IR (neat) 3029, 2968, 2927, 2855, 1598, 1496, 1453, 1355, 1165, 1099, 815, 739, 697 cm^{-1}. Anal. Calcd for $C_{37}H_{41}NO_4S$: C, 74.59; H, 6.94. Found: C, 74.75; H, 6.93.

4.1.71. *N*-[[(*E*)-4,4-Bis(benzyloxymethyl)-2-methyl-1-cyclopentylidene]methyl]-3-(*tert*-butyl)-1,2-benzisothiazoline 1,1-dioxide as a 1:1 mixture of diastereoisomers (79). ^1H NMR δ 1.04 (s, 9H), 1.08 (d, $J=6.6$ Hz, 1.5H) 1.15 (d, $J=6.6$ Hz, 1.5H), 1,25–1,29 (m, 1H), 1.97–2.08 (m, 1H), 2.51–2.63 (m, 1H), 2.65–2.85 (m, 2H), 3.29–3.59 (m, 4H), 4.12 (s, 0.5H), 4.17 (s, 0.5H), 4.42–4.62 (m, 4H), 5.31 (d, $J=1.8$ Hz, 0.5H), 5.44 (d, $J=1.8$ Hz, 0.5H), 7.24–7.36 (m, 10H), 7.43–7.58 (m, 3H), 7.76–7.82 (m, 1H). ^{13}C NMR δ 17.10, 21.95, 27.13, 29.66, 35.82, 35.86, 37.00, 37.11, 38.06, 38.24, 39.69, 40.53, 45.98, 47.33, 72.19, 73.08, 73.19, 73.75, 7452, 74.79, 75.13, 75.38, 119.13, 120.45, 121.62, 121.65, 125.51, 127.20, 127.26, 127.41, 127.45, 128.15, 128.21, 128.94, 128.97, 131.75, 131.79, 136.19, 136.88, 136.97, 138.83, 147.25, 148.35. (Peaks of

diastereoisomers may be overlapping.) IR (neat) 3025, 2956, 2919, 2862, 1453, 1313, 1262, 1178, 1099, 919, 736, 699 cm^{-1} for a 1:1 mixture of diastereoisomers. Anal. Calcd for $C_{34}H_{41}NO_4S$: C, 72.95; H, 7.38. Found: C, 72.86; H, 7.59 for a 1:1 mixture of diastereoisomers.

4.1.72. (*R*)-*N*-(*p*-Toluenesulfonyl)-*N*-[[(*E*)-4,4-bis(benzyloxymethyl)-2-methyl-1-cyclopentylidene]methyl]-(2-methoxy-1-phenylethyl)amine as a 1:1 mixture of diastereoisomers (80). ^{1}H NMR δ 0.96–1.06 (m, 3H), 1.22–1.37 (m, 1H), 1.70–2.03 (m, 1H), 2.22 (d, J=15.6 Hz, 1H), 2.28 (d/d, J=15.6 Hz, 1H), 2.37 (s, 3H), 2.50–2.67 (m, 1H), 3.00–3.27 (m, 7H), 3.57–3.74 (m, 2H), 4.36–4.51 (m, 4H), 5.04 (q, J=2.1 Hz, 0.5H), 5.11 (q, J=2.1 Hz, 0.5H), 5.26–5.34 (m, 1H), 7.08–7.38 (m, 17H), 7.65 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 19.02, 19.42, 19.49, 21.40, 35.89, 36.02, 36.58, 36.76, 39.63, 40.18, 45.73, 45.77, 58.48, 60.78, 60.86, 71.05, 71.26, 72.58, 73.02, 73.07, 73.14, 74.61, 74.74, 113.32, 113.69, 127.22, 127.27, 127.31, 127.75, 127.92, 128.10, 128.14, 128.19, 128.60, 126.63, 128.99, 129.02, 136.15, 136.47, 137.33, 137.39, 138.79, 138.85, 138.90, 142.73, 142.78, 159.51, 159.98. (Peaks of diastereoisomers may be overlapping.) IR (neat) 3031, 2952, 2927, 2858, 1598, 1496, 1453, 1345, 1197, 1159, 1096, 1028, 1001, 813, 777, 738, 698, 661 cm^{-1} for a 1:1 mixture of diastereoisomers. Anal. Calcd for $C_{39}H_{45}NO_5S$: C, 73.21; H, 7.09. Found: C, 73.02; H, 6.86 for a 1:1 mixture of diastereoisomers.

4.1.73. (1*S*,2*S*)-*N*-[[(*E*)-4,4-Bis(benzyloxymethyl)-2-methyl-1-cyclopentylidene]methyl]-2,10-camphorsultam as a 1:1 mixture of diastereoisomers (81). ^{1}H NMR δ 0.92 (s, 3H), 1.07–1.19 (m, 8H), 1.42–1.60 (m, 2H), 1.78–2.05 (m, 5H), 2.54 (s, 2H), 2.58–2.72 (m, 1H), 3.15 (d, J= 1.8 Hz, 2H), 3.16–3.25 (m, 1H), 3.28–3.41 (m, 4H), 4.49 (s, 2H), 4.50 (s, 2H), 5.11 (q, J=2.1 Hz, 0.5H), 5.19 (q, J= 2.1 Hz, 0.5H), 7.22–7.38 (m, 10H); ^{13}C NMR δ 17.70, 20.05, 20.15, 20.50, 27.06, 32.10, 35.04, 35.17, 36.03, 36.22, 36.37, 36.61, 39.77, 40.61, 44.49, 45.59, 46.19, 47,61, 49.48, 49.85, 49.87, 67.73, 67.78, 72.77, 73.09, 73.12, 73.17, 73.34, 74.46, 74.83, 112.53, 113.34, 127.27, 127.41, 128.17, 138.76, 138.84, 155.41, 155.73. (Peaks of diastereoisomers may be overlapping.) IR (neat) 3033, 2955, 2870, 1453, 1319, 1254, 1197, 1135, 1115, 1034, 816, 737, 698 cm^{-1} for a 1:1 mixture of diastereoisomers. Anal. Calcd for $C_{33}H_{43}NO_4S$: C, 72.10; H, 7.88. Found: C, 72.23; H, 7.98 for a 1:1 mixture of diastereoisomers.

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Synthesis of vinylpyrroles, vinylfurans and vinylindoles via a Brønsted acid catalyzed highly regio- and stereoselective cis-hydroarylation of ynamides☆

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Abstract—A highly regio- and stereoselective Brønsted acid-catalyzed coupling of ynamides and aromatic heterocycles, such as pyrroles, furans, and indoles is described. This process is the equivalent of hydroarylation of ynamides, and leads to the efficient syntheses of an array of vinylheterocycles. Diels–Alder reaction between the vinylindoles and DMAD afforded carbazole derivatives in good yields.

1. Introduction

Serving as a powerful electrophile, iminium ions have been extensively investigated in organic synthesis. These efforts have led to the discovery of a wide range of bond-forming methods, which can be exemplified by some of the most classical reactions, such as Pictet–Spengler reactions, Mannich reactions, and Alder-ene reactions.[1] Ketene iminium ions, a sub-class of highly functionalized iminium ions, however, received very little attention.[2] This lack of interest can be partly attributed to the synthetic availability of this class of compounds as well as their highly reactive nature.

The existing methods for the synthesis of ketene iminium ions are rather limited. Commonly, they can be generated as reactive intermediates through either dehydration of amide or dehydrohalogenation of α-haloenamines.[2] Relative harsh reaction conditions and low reaction yields were encountered in most cases. An alternative, however, less common approach for the generation of ketene iminium ions, is through the protonation of ynamine or ynamides.

Ynamides have recently attracted major attention from the synthetic organic community, leading to the discovery of a large number of novel methods for the synthesis of structurally diverse heterocycles, carbocycles, and an array of useful organic functional groups.[3,4,5] Generating followed by trapping the ketene iminium intermediates with nucleophiles represents a novel bond-forming process, and offers expedite approaches for the synthesis of highly functionalized organic building blocks. Among the wide range of nucleophiles, electron rich heterocycles, such as indoles and pyrroles are particularly appealing.[4a]

Development of efficient methodologies for regioselective functionalization of indoles and pyrroles are of great importance, since these ring systems can be found as structural motifs in numerous biologically active natural products and pharmaceuticals.[6] Among these heterocycles, their vinyl derivatives have attracted major attentions. Vinylpyrroles and vinylindoles are not only common structural features in natural products, but also are viable key building blocks that are frequently employed in the synthesis of alkaloids and other biologically important heterocycles.[7,8] In addition, vinylpyrroles have found extensive applications in material science as vinyl monomers, molecular switches, photo- and electroconducting materials.[8g] As a result, considerable amount of efforts has been devoted to the development of new methodologies for efficient synthesis of vinylpyrroles and vinylindoles.[9] Though significant progresses have been made in this field, there remain serious limitations among these methods, which are characterized by the necessity of introducing electron-withdrawing nitrogen protecting groups and/or other reactive functional groups such as halogen, acyl groups, phosphrances, or amines on to the heterocycles in order to facilitate the key vinylation step.[8g,9a] Thus, developing a general method, which can realize direct vinylation of unfunctionalized indoles or pyrroles, still holds great synthetic potential.

☆ Note: Contribution from the Department of Chemistry, University of Minnesota

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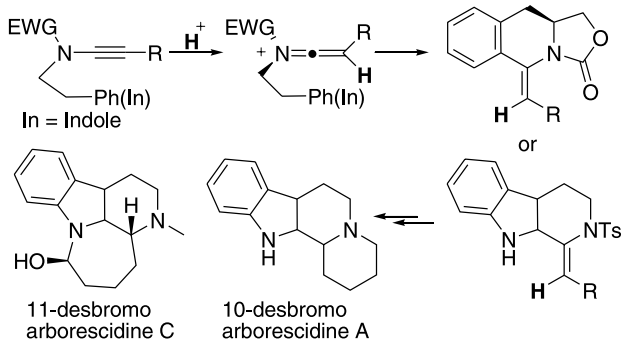
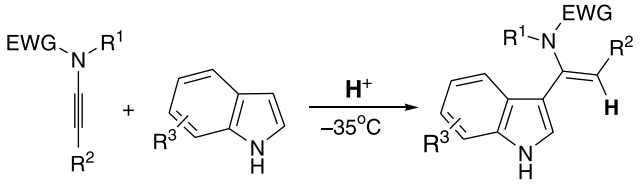
Early this year, we reported a Brønsted acid-catalyzed highly stereoselective intramolecular ynamide-arene cyclization by trapping the in situ generated active ketene iminium intermediates with internally tethered arenes. Both aromatic carbocycles and heterocyles are demonstrated to the efficient nucleophiles for the transformation, leading to the synthesis of isoquinoline and carboline derivatives, respectively. Furthermore, this novel ketene imminium Pictet–spengler cyclization process was successfully applied as the corner stone step in the total synthesis of β-carboline indole alkaloids desbromoarborescidine A and C (Scheme 1).[5a]



Scheme 1. Ketene iminium Pictet–Spengler cyclizations.

As an extension of this work, intermolecular trapping of the in situ generated ketene iminium intermediates with indoles was then investigated. Recently, we reported a Brønsted acid-catalyzed highly regio- and stereoselective cis-hydroarylation of ynamides. This process features nucleophilic attack on the in situ generated ketene iminium intermediates with indoles, and provides an efficient method for the direct construction of vinyl indoles (Scheme 2).[4a] These vinylindole derivatives are synthetic equivalents to masked dienamides, and react efficiently with dienylphiles such as DMAD in a [4+2] fashion to afford carbazole derivatives. Herein, we disclose the scope and limitation of this novel hydroarylation protocol in full account.



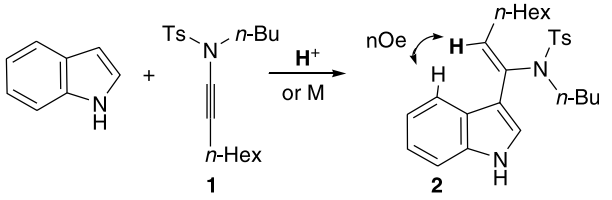
Scheme 2. cis-Hydroarylation of ynamides.

2. Results and discussions

2.1. Feasibility establishment

Given the lack of literature precedents, our initial effort was orientated toward the establishment of the feasibility of this new design. Employing the readily made ynamids **1** (1.0 equiv) and indole (1.4 equiv) as the model substrates, a series of transitional metal π-acids and Brønsted acids were investigated as summarized in Table 1.

Table 1. Catalyst screening

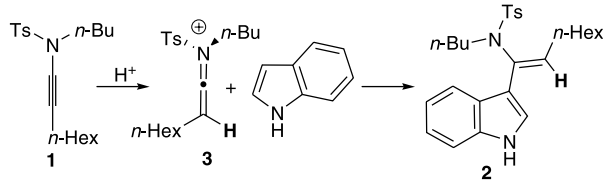


Entry	M^+ (mol%)	Solvent	Temperature (°C)	Yield (%)[a]
1	$PtCl_2$ (10)	Toluene	80	ND
2	$PtCl_4$ (10)	Toluene	80	ND
3	$Pd(Ac)_2$(10)	Toluene	80	ND
4	$PdCl_2$ (10)	Toluene	80	ND
5	PNBSA (10)[b]	Toluene	80	ND
6	Tf_2NH (5)	CH_2Cl_2	Room temperature	84[c]
7	Tf_2NH (10)	CH_2Cl_2	−35	81[d]
8	TfOH (10)	CH_2Cl_2	−35	ND

[a] Isolated yields.
[b] PNBSA, *p*-nitrobenzenesulfonicacid.
[c] *Z*/*E*=6:1 by ^{1}H NMR.
[d] *Z*/*E*>30:1 by ^{1}H NMR.

Initial screenings employing alkynophilic transition metal π-acids including platinum salts and palladium salts turned out to be very unsuccessful (entry 1–4). Though ynamide **1** was totally consumed in all these cases, very complex reaction mixtures were obtained, in which only trace amount of the desired products were observed by ^{1}H NMR analysis of the crude reaction mixtures. At this point, we turned our attention to Brønsted acid. Based on our previous experiences, *para*-nitrobenzenesulfonic acid (PNBSA) and trifluoromethanesulfone imide (Tf_2NH) were tested. Tf_2NH was proved to be the most active catalyst for this transformation (entries 5 and 6). At room temperature, with 5% loading of the catalyst, the desired vinylindole **2** was separated in 84% yield. This hydroarylation reaction is highly regioselective furnishing exclusively C-3 vinylation product **6** as expected.[6b] The fact that Tf_2NH is a better catalyst for this transformation is quite surprising, since PNBSA gave superior results in the intramolecular version of this transformation.[5a]

More interestingly, this reaction is moderately stereoselective when conducted at room temperature favoring the formation of (*Z*)-enamide as the major isomer with a *Z*/*E* ratio of 6:1, which was confirmed by NOE studies. This stereoselectivity outcome is not surprising, and can be explained by the rationale that indole nucleophile would prefer to approach the ketene iminium intermediate **3** from the less hinder side—the hydrogen side, in order to avoid to the unnecessary steric interaction with the hexyl group (Scheme 3). Based on this model, an improved selectivity



Scheme 3. Stereoselectivity rationale.

was expected when the reaction was conducted at relatively lower temperature. To our delight, when conducted at −35 °C with 10% catalyst loading, the reaction proceeded at a reasonable speed, leading to the formation of (*Z*)-enamide almost exclusively.

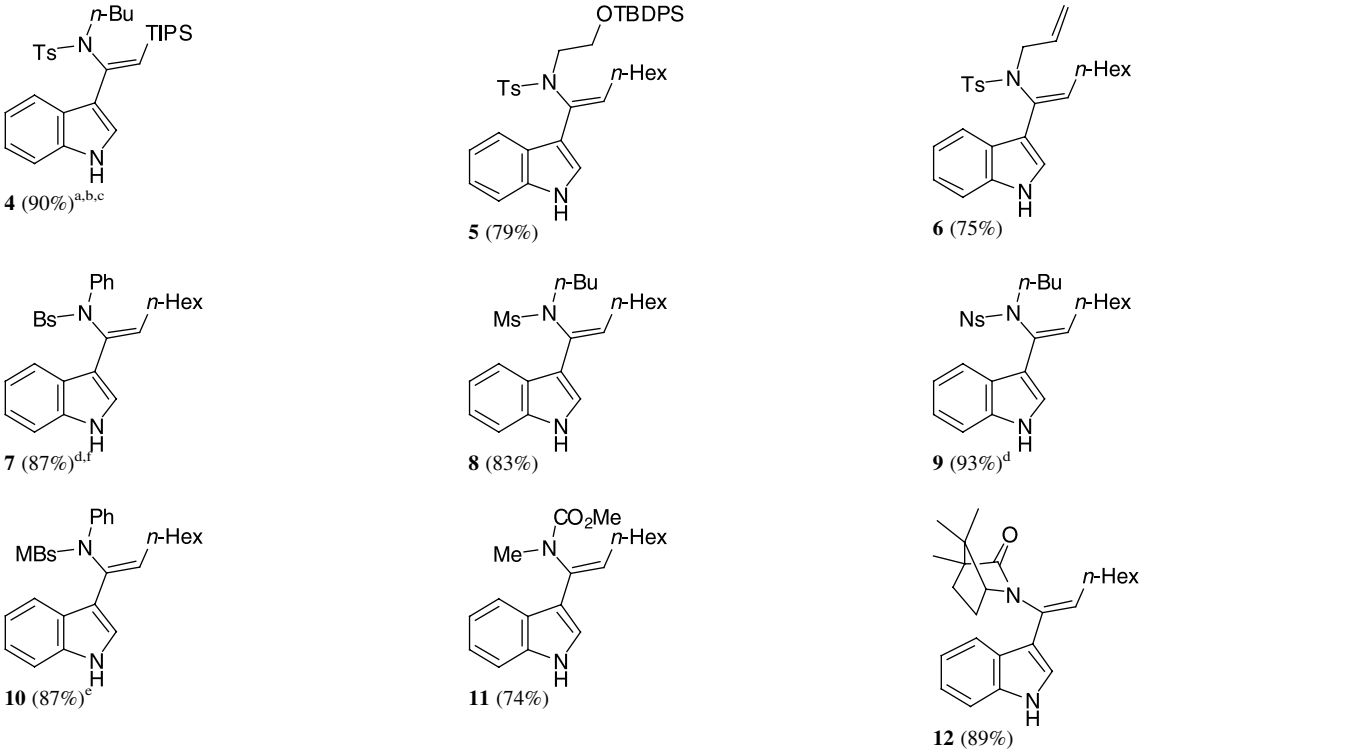
2.2. Reaction of indole with different ynamides

In order to establish the scope of this novel hydroarylation protocol, we first tested the reaction of indole with various types of ynamides under the optimized reaction conditions. This protocol is proved to be quite general with respect to variations on ynamides as summarized in Table 2. In addition to alkyl substituted alkynes, silyl substituted alkyne also survived the acidic reaction condition giving vinylindole **4** in excellent yield. Potentially useful functional groups such as silyl protected alcohol and allyl group were successfully introduced into the reaction system (**5** and **6**). Sulfonyl groups with different degree of electron withdrawing power, including Bs, Ms, Ns, and MBs, were all viable substrates for this transformation, furnishing the vinyl indole derivatives in comparable efficiency (**7**–**10**). For vinylindole **9** and **10**, however, the reactions were observed to be much slower, and resulted in a relatively larger amount of the (*E*)-isomers. This can be attributed to the relatively stronger electron withdrawing power of nitro and phenyl substituents, which resulted in the further delocalization of the lone pair electrons on the ynamide nitrogens. As a result, relatively higher energy was required to generate the ketene iminium intermediates from protonation of these two ynamide precursors. In addition to sulfonyl-substituted ynamides, carbamate-derived and aza-camphor-derived ynamides also underwent the desired transformation, giving the vinylindole derivatives in good yield (**11** and **12**).

2.3. Reaction of substituted indoles with ynamide 1

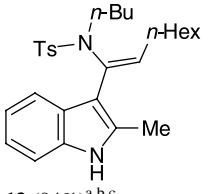
We then turned our attention to study the scope of this transformation toward various substituted indoles employing ynamide **1** as the model substrate (Table 3). Indoles with electronically neutral alkyl and aryl substitutions, including 2-methylindole, 2-phenylindole, 7-methyldindole, 2-methyl-7-isopropylindole, were investigated. The hydroarylation processes were very efficient for all these substrates affording the desired vinylindoles in good to excellent yields. It was also observed that sterically demanding C-2 substituted indoles are less reactive for the vinylation process (**13**, **14**, and **16**). Much higher reaction temperature (25 °C) had to be employed for the reaction to proceed at a reasonable speed. Interestingly, though conducted at room temperature, the desired (*Z*)-enamides were the exclusive product in these reactions, which can be attributed to the increased steric interaction between the C-2 substituents and the approaching ketene iminium intermediate **3**. Electron-donating methoxy group and weak electron-withdrawing groups, such as chloride and bromide,

Table 2. Coupling of indole with different ynamides

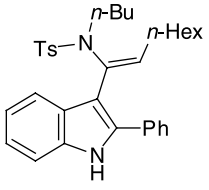


[a] All reactions were conducted at −35 °C, using ynamides and indole at the ratio of 1:1.4 with 10 mol% Tf_2NH in CH_2Cl_2 (0.1 M).
[b] Isolated yields for all entries.
[c] *Z*/*E*>25:1 by ^1H NMR unless otherwise indicated.
[d] *Z*/*E*=10:1 by ^1H NMR.
[e] *Z*/*E*=13:1 by ^1H NMR.
[f] Bs, Benzenesulfonyl; PMBs, *p*-methoxybenzenesulfonyl.

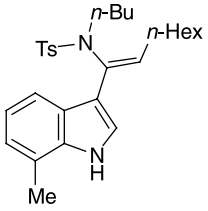
Table 3. Coupling of ynamide **1** with substituted indoles



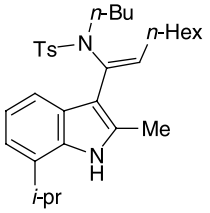
13 (94%)[a,b,c]



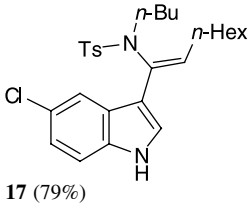
14 (91%)[a]



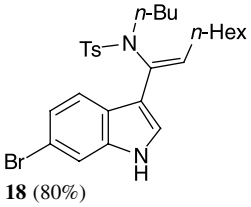
15 (88%)[d]



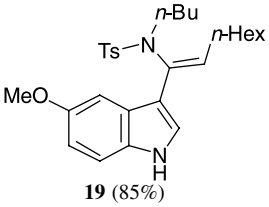
16 (84%)[a]



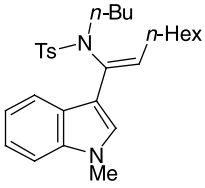
17 (79%)



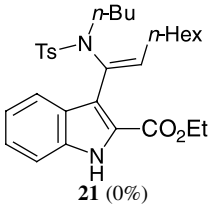
18 (80%)



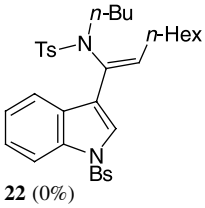
19 (85%)



20 (85%)



21 (0%)



22 (0%)

[a] Reactions were conducted at room temperature.
[b] Isolated yields for all entries.
[c] *Z*/*E*>25:1 by ^{1}HNMR.
[d] Reactions were conducted at −35 °C unless otherwise indicated.

can also be tolerated in this transformation (**17**, **18**, and **19**). *N*-Methyl indole should similar reactivity, affording vinylindole **20** in good yield. Strong electron-withdrawing substitutions, such as carbonyl and sulfonyl groups, had detrimental effect on this transformation (**21** and **22**). No desired vinylation products were observed even after prolonged reaction time at room temperature. Diminished electrophilicity of the substituted indoles caused by the electron-withdrawing groups are responsible for these results.

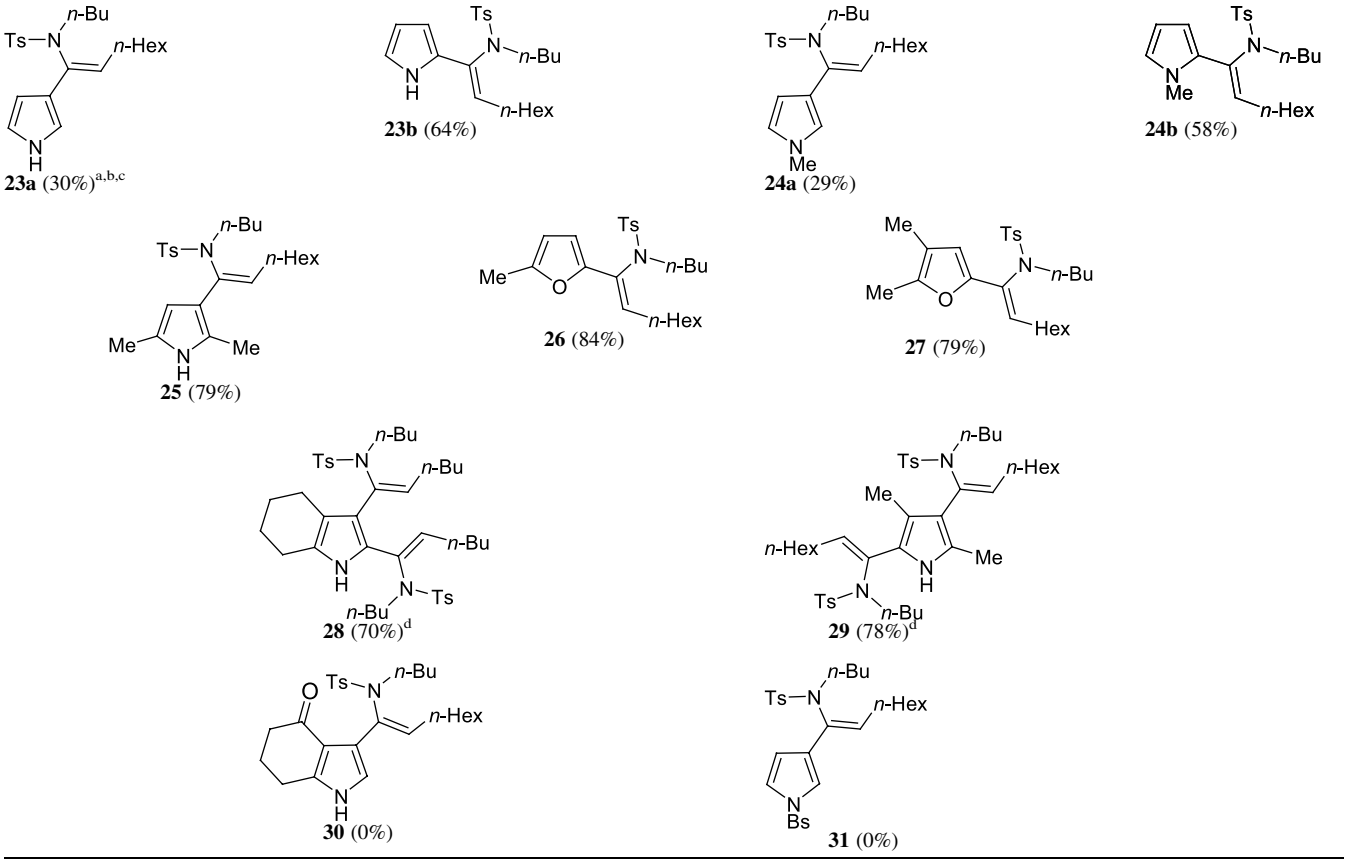
2.4. Couplings of pyrroles and furans with ynamide 1

Other nucleophilic heterocycles including furans and pyrroles were then investigated as summarized in Table 4. We were intrigued to discover that pyrroles also participated well in this vinylation process (**23**–**25**). Unfortunately, the hydroarylation involving pyrroles was only slightly regioselective affording C-3 and C-2 vinylation products in roughly 1/2 ratio. This result is somewhat unexpected, since C-2 carbon is generally believed to be the more nucleophilic site.[9d] Variation on the reaction temperature does not have significant affect on the ratio of C-2 and C-3 isomers.

When C-2 carbon was blocked, as with 2,3-dimethylpyrrole, C-3 vinylpyrrole **25** was produced as the only product in 79% yield. Vinylation of furans, on the other hand, showed excellent regioselectivity affording exclusively 2-vinylfurans in good yields (**26**,**27**). Following the lead that both the C-2 and C-3 positions of pyrroles can undergo the vinylation process, 2,3-divinylpyrrole, known to be excellent substrates for electrocyclic reactions, was prepared accordingly in good yields by simply employing an excess of the ynamides (**28**). Again, this vinylation protocol is not efficient for pyrroles with electron withdrawing substituents (**30**,**31**).

This new methodology has some distinct advantages over the existing methods: (1) There is no need to introduce protecting group on the indole nitrogen, (2) the hydroarylation employs unfunctionalized indoles, which circumvents the needs to introduce other functional groups, (3) the reaction is catalyzed by a Brønsted acid, which is more environmentally friendly than transition metals, and (4) more importantly, an enamide motif, which is otherwise difficult to introduce, is conveniently generated and can be employed for further transformations.

Table 4. Vinylation reactions involving pyrroles and furans

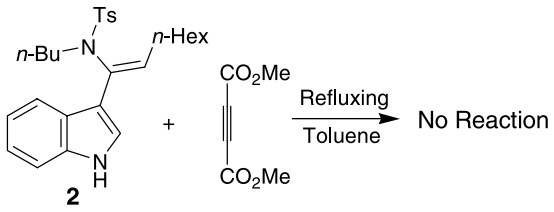


[a] All reactions were conducted at −35 °C, using ynamides and heteroarenes at the ratio of 1:2.5 with 10 mol% Tf_2NH in CH_2Cl_2 (0.1 M).
[b] Isolated yields for all entries.
[c] *Z*/*E*>20:1 by ^1H NMR unless otherwise indicated.
[d] Reactions were conducted at room temperature using ynamides and pyrroles at the ratio of 2:1.

2.5. Diels–Alder reaction of vinylindoles with DMAD

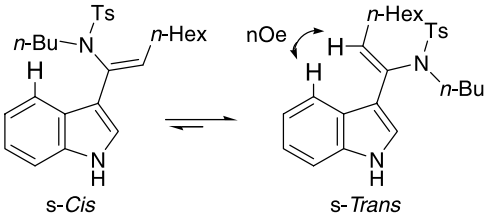
One of the most attractive features of this methodology is that the products can be considered synthetic equivalents to masked dienamides, which are excellent substrates for [4+2] cycloaddition reactions.[10,11,12,13,6b] In order to further demonstrate the synthetic utility of the new methodology, we investigated the Diels–Alder activity of these novel vinylindoles. Vinylindoles have been extensively studies for the Diels–Alder reactivations, which efficiently lead to the construction of polycyclic systems.[14]

Initial result was actually quite disappointing. No cycloaddition product was detected after refluxing a 0.1 M mixture of vinylindole **2** and DMAD in toluene for 24 h (Scheme 4).



Scheme 4. Attempted Diels–Alder reactions between vinylindole **2** and DMAD.

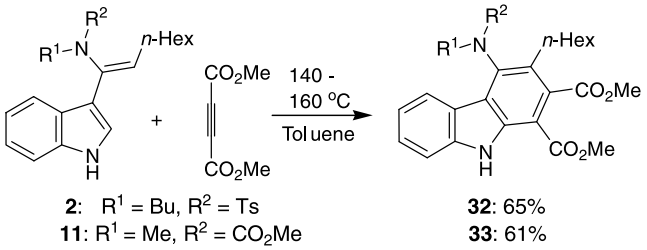
We attributed this unexpected lack of reactivity to the unfavorable configuration of the diene moiety.[14] The diene moiety of vinylindole **2** are expected to have two possible resonance stabilized configurations, *s*-cis and *s*-trans. Strong steric interaction between the butyl (or Ts) group on the nitrogen and the C-4 hydrogen seriously destabilizes the *s*-cis configuration, which is required for the Diels–Alder reaction. More importantly, the steric interaction between the bulky *N*-substituent and indole significant resist the rotation of the free diene single bond (Scheme 5).



Scheme 5. Configurations of vinylindole **2**.

Based on this rationale, we speculated that higher energy was required to access the *s*-cis configuration, and facilitate the intramolecular Diels–Alder reaction. To our delight, Diels–Alder reaction between vinylindole **2** and DMAD

proceeded smoothly in toluene at 160 °C, furnishing the oxidized cycloadduct carbazole **32** in good yield. Theoretically, reducing the steric bulkyness of the substitutions on the nitrogen would, to certain extend, favors the rotation of the diene single bond, and thus shift the resonance toward the *s*-cis configuration. This would in turn facilitate the cycloaddition reaction. As expected, vinylindole **11**, which has sterically less hindered substituents on the nitrogen, underwent Diels–Alder reaction at a lower temperature (140 °C) to afford carbazole **33** in 61% yield (Scheme 6).



Scheme 6. Diels–Alder reactions between vinylindoles and DMAD.

3. Conclusion

In conclusion, a Brønsted acid catalyzed hydroarylation of ynamide was developed, leading to the efficient construction of biologically and synthetically useful vinylpyrroles, vinylindoles, and vinylfurans with high regio- and stereocontrol. Diels–Alder reactivity of the vinylindole derivatives was probed and found to be efficient. Further applications of the methodology to the synthesis of alkaloids are currently under investigation.

4. Experimental

All reactions performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-300, VX-300, and VI-500 spectrometers using $CDCl_3$ or CD_2Cl_2 (except where noted) with TMS as standard. Melting points were determined using a Laboratory Devices MEL-TEMP. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses performed at University of Minnesota Department of Chemistry Mass Spectrometry Laboratory. All spectral data obtained for new compounds are reported here.

4.1. General procedure for the hydroarylation reactions: synthesis of vinylindole 2

A solution of ynamide **1** (168.0 mg, 0.5 mmol) and indole (82.0 mg, 0.7 mmol) in 5 mL of dry methylene chloride was cooled to −35 °C. To this stirring mixture, a solution of Tf_2NH (14.0 mg, 0.05 mmol) in 0.35 mL of CH_2Cl_2 was added slowly, leading to a bright yellow solution, which became darker as reaction proceeded. The reaction was kept at −35 °C for 1 h with the reaction process monitored by TLC analysis. Upon completion, the reaction mixture was warmed up to room temperature, and the stir was continued for another 30 min. Several drops of triethylamine were then added to the reaction mixture to neutralize the acid, resulting in a colorless solution. The solution was concentrated in vacuo, and the reside was purified by silica gel column flash chromatography [gradient eluent: 10–25% EtOAc in hexane] to give vinylindole **2** (183.0 mg, 81%) as a white solid.

4.1.1. Vinylindole 2. (183 mg, 81% yield) R_f=0.30 (20% EtOAc in hexane); mp 140–142 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.47 (br s, 1H), 7.82 (d, 1H, J=8.0 Hz), 7.77 (d, 2H, J=8.0 Hz), 7.39 (d, 1H, J=8.0 Hz), 7.33 (d, 2H, J=8.0 Hz), 7.22 (t, 1H, J=8.0 Hz), 7.19 (t, 1H, J=8.0 Hz), 6.86 (d, 1H, J=2.5 Hz), 6.16 (t, 1H, J=7.5 Hz), 3.50–3.38 (m, 2H), 2.48 (s, 3H), 2.32–2.05 (m, 2H), 1.59–1.42 (m, 4H), 1.42–1.21 (m, 8H), 0.96 (t, 3H, J=7.0 Hz), 0.86 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.9, 138.9, 137.2, 132.7, 130.7, 130.1, 128.0, 126.1, 124.7, 122.8, 120.8, 120.4, 115.5, 112.0, 49.5, 32.3, 31.6, 30.1, 29.9, 29.7, 23.2, 21.8, 20.6, 14.4, 14.0; IR (film) cm^{-1} 3385 (m), 2958 (s), 2927 (s), 1459 (w), 1338 (m), 1159 (s), 1089 (m); mass spectrum (ESI): *m/e* (% relative intensity) 475.4 (100) (M+Na)$^+$, 453.4 (16) (M+H)$^+$, 365.2 (27), 337.2 (23), 285.2 (15); *m/e* calcd for $C_{27}H_{36}N_2O_2SNa$ 475.2390, found 475.2398.

4.1.2. Vinylindole 4. (58 mg, 90% yield) R_f=0.33 (20% EtOAc in hexane); mp 160–162 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.17 (br s, 1H), 7.96–7.90 (m, 1H), 7.44 (d, 2H, J=8.1 Hz), 7.44–7.33 (m, 1H), 7.25–7.18 (m, 4H), 6.13 (s, 1H), 6.08 (d, 1H, J=2.7 Hz), 3.61 (t, 2H, J=7.8 Hz), 2.45 (s, 3H), 1.76–1.46 (m, 5H), 1.29 (d, 18H, J=7.5 Hz), 0.89 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 167.0, 161.4, 159.8, 152.9, 151.4, 150.6, 146.6, 146.1, 144.3, 143.6, 140.5, 135.0, 73.9, 54.4, 45.0, 44.0, 43.1, 37.3, 36.0; IR (film) cm^{-1} 3378 (m), 2942 (s), 2866 (s), 1596 (m), 1344 (m), 1156 (s), 773 (s); mass spectrum (ESI): *m/e* (% relative intensity) 547.3 (100) (M+Na)$^+$, 525.3 (23) (M+H)$^+$; *m/e* calcd for $C_{30}H_{44}N_2O_2SSiNa$ 547.2785, found 547.2784.

4.1.3. Vinylindole 5. (75 mg, 79% yield) R_f=0.36 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.34 (br s, 1H), 7.83 (d, 1H, J=7.2 Hz), 7.78 (d, 2H, J=8.4 Hz), 7.70–7.58 (m, 4H), 7.51–7.30 (m, 9H), 7.27 (dt, 1H, J=1.5, 7.2 Hz), 7.22 (dt, 1H, J=1.5, 7.2 Hz), 6.19 (t, 1H, J=7.5 Hz), 3.95–3.73 (m, 2H), 3.73–3.57 (m, 2H), 2.49 (s, 3H), 2.17–1.93 (m, 2H), 1.48–1.20 (m, 8H), 1.08 (s, 9H), 0.96 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 138.3, 137.3, 136.1, 136.0, 133.9, 132.0, 131.2, 130.1, 128.2, 128.1, 125.9, 125.0, 122.8, 120.8, 120.4, 115.2, 112.0, 62.6, 51.4, 32.3, 30.0, 29.9, 29.6, 27.1, 23.2, 21.8, 19.5, 14.5; IR (film) cm^{-1} 3391 (m), 2957 (m), 2930 (s), 2857 (m), 1428 (m), 1345 (m), 1161 (s), 1110 (s), 1090 (s); mass spectrum (ESI): *m/e* (% relative intensity) 701.8 (100) (M+Na)$^+$; *m/e* calcd for $C_{41}H_{50}N_2O_3SSiNa$ 701.3204, found 701.3218.

4.1.4. Vinylindole 6. (41 mg, 75% yield) R_f=0.28 (20% EtOAc in hexane); mp 131–132 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.36 (br s, 1H), 7.81 (d, 1H, J=8.0 Hz), 7.79 (d, 2H, J=8.0 Hz), 7.38 (d, 1H, J=8.0 Hz), 7.34 (d, 2H,

J=8.0 Hz), 7.22 (dt, 1H, J=1.0, 8.0 Hz), 7.17 (dt, 1H, J=1.0, 8.0 Hz), 6.95 (d, 1H, J=3.0 Hz), 6.15 (t, 1H, J=7.5 Hz), 6.88 (ddt, 1H, J=7.0, 10.5, 14.0 Hz), 5.05 (dd, 1H, J=1.5, 10.5 Hz), 5.03 (dd, 1H, J=1.5, 14.0 Hz), 4.18–4.00 (m, 2H), 2.47 (s, 3H), 2.16–1.96 (m, 2H), 1.50–1.25 (m, 8H), 0.95 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.0, 138.6, 137.3, 134.1, 132.4, 130.9, 130.1, 128.0, 125.9, 124.8, 122.8, 120.7, 120.4, 118.9, 112.0, 53.0, 32.3, 30.1, 29.9, 29.7, 23.2, 21.8, 14.5; IR (thin film) cm^{-1} 3393 (m), 2935 (w), 2926 (s), 1344 (s), 1159 (s); mass spectrum (ESI): *m/e* (% relative intensity) 459.6 (100) $(M+Na)^+$, 437.6 (22) $(M+H)^+$, 340.5 (55); HRMS (ESI) calcd for $C_{26}H_{32}N_2O_2SNa$ 459.2077, found 459.2075.

4.1.5. Vinylindole 7. (115 mg, 87% yield) R_f=0.23 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.48 (br s, 1H), 7.93 (d, 1H, J=7.8 Hz), 7.91 (d, 2H, J=7.8 Hz), 7.66–7.56 (m, 3H), 7.48 (t, 1H, J=7.8 Hz), 7.42–7.25 (m, 7H), 7.18 (d, 1H, J=2.4 Hz), 6.37 (t, 1H, J=7.2 Hz), 2.30 (q, 2H, J=7.5 Hz), 1.58–1.20 (m, 8H), 0.99 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 141.9, 141.2, 137.2, 133.4, 133.3, 132.3, 129.5, 129.3, 128.3, 125.9, 125.7, 125.3, 124.0, 122.9, 120.9, 120.3, 116.1, 112.2, 32.2, 29.8, 29.6, 29.5, 23.1, 14.5; IR (thin film) cm^{-1} 3402 (s), 2955 (m), 2926 (s), 1353 (m), 1165 (s), 1092 (m); mass spectrum (ESI): *m/e* (% relative intensity) 481.2 (100) $(M+Na)^+$, 459.3 (14) $(M+H)^+$, 235.1 (8); HRMS (ESI) calcd for $C_{28}H_{31}N_2O_2S$ 459.2101, found 459.2113.

4.1.6. Vinylindole 8. (47 mg, 83% yield) R_f=0.12 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.61 (br s, 1H), 7.88 (d, 1H, J=7.8 Hz), 7.44 (d, 1H, J=7.8 Hz), 7.33 (d, 1H, J=2.7 Hz), 7.26 (dt, 1H, J=2.7, 7.8 Hz), 7.22 (dt, 1H, J=2.7, 7.8 Hz), 6.21 (t, 1H, J=7.5 Hz), 3.53–3.37 (m, 2H), 3.06 (s, 3H), 2.55–2.40 (m, 2H), 1.70–1.28 (m, 12H), 1.00 (t, 3H, J=6.9 Hz), 0.93 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 137.3, 132.7, 130.9, 126.1, 124.6, 122.8, 120.8, 120.3, 115.1, 112.1, 49.3, 40.7, 32.4, 31.6, 29.9, 29.6, 23.2, 20.7, 14.4, 14.1; IR (thin film) cm^{-1} 3381 (m), 2958 (m), 2929 (m), 1326 (s), 1150 (m); mass spectrum (ESI): *m/e* (% relative intensity) 399.2 (100) $(M+Na)^+$, 377.3 (10) $(M+H)^+$; HRMS (ESI) calcd for $C_{21}H_{32}N_2O_2SNa$ 399.2077, found 399.2064.

4.1.7. Vinylindole 9. (54 mg, 93% yield) R_f=0.36 (20% EtOAc in hexane); mp 122–124 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.38 (br s, 1H), 8.34 (d, 2H, J=9.3 Hz), 8.04 (d, 2H, J=9.3 Hz), 7.85 (dd, 1H, J=1.5, 7.5 Hz), 7.42 (d, 1H, J=1.5, 7.5 Hz), 7.25 (dt, 1H, J=1.5, 7.5 Hz), 7.24 (dt, 1H, J=1.5, 7.5 Hz), 6.83 (d, 1H, J=2.7 Hz), 6.25 (t, 1H, J=7.5 Hz), 3.52 (t, 2H, J=7.5 Hz), 2.23–2.04 (m, 2H), 1.70–1.20 (m, 12H), 0.98 (t, 3H, J=6.3 Hz), 0.91 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 150.3, 146.9, 137.1, 133.1, 130.3, 129.2, 125.9, 124.6, 124.3, 123.0, 121.0, 120.3, 115.2, 112.1, 50.4, 32.3, 31.7, 30.0, 29.9, 29.8, 23.2, 20.6, 14.4, 14.0; IR (thin film) cm^{-1} 3408 (m), 2958 (m), 2929 (m), 1532 (s), 1351 (s), 1161 (m); mass spectrum (ESI): *m/e* (% relative intensity) 506.3 (100) $(M+Na)^+$, 484.3 (3) $(M+H)^+$; HRMS (ESI) calcd for $C_{26}H_{33}N_3O_4SNa$ 506.2084, found 506.2089.

4.1.8. Vinylindole 10. (46 mg, 87% yield) R_f=0.22 (20% EtOAc in hexane); mp 102–103 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.39 (br s, 1H), 7.90–7.83 (m, 3H), 7.42 (d, 1H, J=6.9 Hz), 7.24 (t, 1H, J=6.9 Hz), 7.20 (t, 1H, J=6.9 Hz), 7.03 (d, 2H, J=8.7 Hz), 6.92 (d, 1H, J=2.7 Hz), 6.20 (t, 1H, J=7.5 Hz), 3.92 (s, 3H), 3.45–3.31 (m, 2H), 2.29–2.09 (m, 2H), 1.60–1.20 (m, 12H), 0.98 (t, 2H, J=6.6 Hz), 0.86 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.4, 137.2, 133.3, 132.7, 130.8, 130.1, 126.1, 124.7, 122.7, 120.7, 120.4, 115.4, 114.5, 112.0, 56.2, 49.4, 32.3, 31.6, 30.1, 30.0, 29.7, 23.2, 20.6, 14.4, 14.0; IR (thin film) cm^{-1} 3392 (m), 2957 (m), 2927 (m), 1596 (m), 1334 (m), 1260 (m), 1153 (s); mass spectrum (ESI): *m/e* (% relative intensity) 491.6 (100) $(M+Na)^+$, 469.6 (33) $(M+H)^+$; HRMS (ESI) calcd for $C_{27}H_{37}N_2O_3S$ 469.2519, found 469.2523.

4.1.9. Vinylindole 11. (14 mg, 74% yield) R_f=0.10 (20% EtOAc in hexane); colorless oil; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.50 (br s, 1H), 7.76 (d, 1H, J=8.0 Hz), 7.41 (d, 1H, J=8.0 Hz), 7.23 (t, 1H, J=7.5 Hz), 7.17 (t, 1H, J=7.5 Hz), 7.12 (d, 1H, J=3.0 Hz), 5.95 (t, 1H, J=7.5 Hz), 3.81 (s, J=3 Hz), 3.09 (s, 3H), 2.19 (q, 2H, J=7.5 Hz), 1.60–1.31 (m, 8H), 0.93 (t, 3H, J=7.0 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 157.1, 137.6, 134.9, 126.2, 125.7, 125.3, 123.4, 123.3, 122.8, 120.8, 120.5, 115.0, 112.1, 36.4, 32.3, 29.8, 29.7, 28.1, 28.0, 23.2, 14.4; IR (thin film) cm^{-1} 3311 (m), 2955 (m), 2927 (m), 1686 (s), 1458 (m), 1374 (w), 1163 (w); mass spectrum (ESI): *m/e* (% relative intensity) 337.2 (100) $(M+Na)^+$, 315.2 (24) $(M+H)^+$; HRMS (ESI) calcd for $C_{19}H_{26}N_2O_2Na$ 337.1886, found 337.1887.

4.1.10. Vinylindole 12. (49 mg, 89% yield) R_f=0.16 (25% EtOAc in hexane); colorless oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.26 (br s, 1H), 7.77 (d, 1H, J=8.1 Hz), 7.43 (d, 1H, J=8.1 Hz), 7.21 (dt, 1H, J=1.2, 7.2 Hz), 7.14 (dt, 1H, J=1.2, 7.2 Hz), 7.11 (d, 1H, J=2.7 Hz), 5.77 (dd, 1H, J=5.4, 8.7 Hz), 3.36 (s, 1H), 2.31–2.18 (m, 1H), 2.04–1.72 (m, 3H), 1.70–1.32 (m, 10H), 1.14 (s, 3H), 1.09 (s, 3H), 0.96 (t, 3H, J=6.9 Hz), 0.86 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 178.0, 137.0, 127.7, 127.5, 126.9, 123.9, 122.5, 120.3, 120.2, 115.0, 112.1, 68.4, 55.7, 49.8, 32.4, 31.2, 30.2, 29.9, 29.2, 27.3, 23.2, 19.7, 18.5, 14.5, 10.0; IR (thin film) cm^{-1} 3249 (m), 2959 (s), 2926 (s), 1686 (s), 1404 (w); mass spectrum (ESI): *m/e* (% relative intensity) 401.6 (100) $(M+Na)^+$, 379.5 (38) $(M+H)^+$, 318.5 (48); HRMS (ESI) calcd for $C_{25}H_{34}N_2ONa$ 401.2563, found 401.2563.

4.1.11. Vinylindole 13. (22 mg, 94% yield) R_f=0.35 (20% EtOAc in hexane); mp 89–90 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.16 (br s, 1H), 7.67 (d, 1H, J=7.8 Hz), 7.65 (d, 2H, J=8.1 Hz), 7.33 (d, 1H, J=7.8 Hz), 7.22 (d, 2H, J=8.1 Hz), 7.13 (dt, 1H, J=0.9, 7.2 Hz), 7.05 (dt, 1H, J=0.9, 7.2 Hz), 5.69 (t, 1H, J=7.2 Hz), 3.36 (t, 2H, J=7.8 Hz), 2.48 (s, 3H), 2.41 (s, 3H), 2.19 (q, 2H, J=7.2 Hz), 1.71–1.58 (m, 2H), 1.56–1.20 (m, 10H), 0.96 (t, 3H, J=6.9 Hz), 0.90 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.5, 138.6, 136.0, 135.4, 135.1, 130.0, 129.7, 128.6, 127.7, 121.7, 120.2, 119.8, 111.9, 110.7, 49.7, 32.2, 31.4, 30.0, 29.9, 29.8, 23.2, 21.7, 20.7, 14.4, 14.1, 13.2; IR (thin film) cm^{-1} 3385 (m), 2958 (s), 2928 (s), 1460 (m), 1334 (m), 1152 (s); mass spectrum (ESI): *m/e* (% relative intensity) 489.4 (100) $(M+Na)^+$, 467.4 (20) $(M+H)^+$; HRMS (ESI) calcd for $C_{28}H_{39}N_2O_2S$ 467.2727, found 467.2726.

4.1.12. Vinylindole 14. (24 mg, 91% yield) R_f=0.40 (20% EtOAc in hexane); mp 134–136 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.33 (br s, 1H), 7.86 (d, 1H, J=8.1 Hz), 7.65 (d, 2H, J=8.4 Hz), 7.50–7.38 (m, 4H), 7.33 (d, 2H, J=8.4 Hz), 7.24 (t, 1H, J=7.8 Hz), 7.15 (t, 1H, J=7.8 Hz), 7.03 (d, 2H, J=7.8 Hz), 6.00 (t, 1H, J=7.2 Hz), 2.93 (t, 2H, J=8.1 Hz), 2.39 (t, 2H, J=7.2 Hz), 2.34 (s, 3H), 1.60–1.20 (m, 10H), 0.97 (t, 3H, J=6.9 Hz), 0.93–0.80 (m, 2H), 0.74 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 142.5, 139.5, 137.5, 135.9, 135.0, 133.3, 129.4, 128.7, 128.5, 128.4, 128.1, 127.0, 122.3, 120.5, 120.0, 112.2, 110.3, 48.8, 31.6, 30.5, 29.2, 29.1, 28.8, 22.5, 20.9, 19.6, 13.7, 13.3; IR (thin film) cm^{-1} 3362 (m), 2958 (s), 2929 (s), 1456 (m), 1329 (m), 1152 (s); mass spectrum (ESI): *m/e* (% relative intensity) 551.4 (100) $(M+Na)^+$, 429.4 (26) $(M+H)^+$; HRMS (ESI) calcd for $C_{33}H_{40}N_2O_2SNa$ 551.2703, found 551.2722.

4.1.13. Vinylindole 15. (59 mg, 88%) R_f=0.88 (20% EtOAc in hexane); mp 100–102 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.35 (br s, 1H), 7.84 (d, 2H, J=8.4 Hz), 7.70 (d, 1H, J=7.5 Hz), 7.38 (d, 2H, J=8.4 Hz), 7.13 (t, 1H, J=7.5 Hz), 7.05 (d, 1H, J=7.5 Hz), 6.93 (d, 1H, J=2.4 Hz), 6.20 (t, 1H, J=7.2 Hz), 3.53–3.38 (m, 2H), 2.50 (s, 6H), 2.28–2.03 (m, 2H), 1.60–1.20 (m, 12H), 0.98 (t, 3H, J=6.6 Hz), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.9, 138.6, 136.7, 132.5, 130.9, 130.1, 128.0, 125.6, 124.5, 123.3, 121.3, 120.9, 118.0, 115.9, 49.5, 32.3, 31.6, 30.1, 29.9, 29.7, 23.2, 21.8, 20.6, 16.8, 14.5, 14.1; IR (thin film) cm^{-1} 3372 (m), 2958 (s), 2927 (s), 1439 (w), 1347 (m), 1159 (s); mass spectrum (ESI): *m/e* (% relative intensity) 489.3 (100) $(M+Na)^+$, 467.3 (15) $(M+H)^+$; HRMS (ESI) calcd for $C_{28}H_{38}N_2O_2SNa$ 489.2546, found 489.2552.

4.1.14. Vinylindole 16. (51 mg, 84% yield) R_f=0.45 (20% EtOAc in hexane); mp 107–109 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.12 (br s, 1H), 7.57 (d, 2H, J=8.4 Hz), 7.42 (quint, 1H, J=4.5 Hz), 7.15 (d, 2H, J=8.4 Hz), 6.97 (d, 2H, J=4.5 Hz), 5.64 (t, 1H, J=7.2 Hz), 3.33 (t, 2H, J=7.8 Hz), 3.20 (m, 1H, J=6.9 Hz), 2.46 (s, 3H), 2.34 (s, 3H), 2.16 (q, 2H, J=7.8 Hz), 1.70–1.56 (m, 2H), 1.52–1.18 (m, 10H), 1.38 (s, 3H), 1.35 (s, 3H), 0.93 (t, 3H, J=6.9 Hz), 0.88 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.4, 138.5, 136.1, 134.6, 133.4, 130.9, 130.3, 129.6, 128.6, 127.7, 120.5, 117.6, 117.4, 112.4, 49.9, 32.3, 31.4, 30.0, 29.9, 29.9, 29.5, 23.2, 23.2, 21.7, 20.7, 14.4, 14.2, 13.2; IR (film) cm^{-1} 3379 (m), 2959 (s), 2928 (s), 1457 (w), 1335 (w), 1152 (m), 1089 (w); mass spectrum (ESI): *m/e* (% relative intensity) 531.4 (100) $(M+Na)^+$, 509.4 (36) $(M+H)^+$, 393.2 (4), 282.2 (8); *m/e* calcd for $C_{31}H_{45}N_2O_2S$ 509.3202, found 509.3218.

4.1.15. Vinylindole 17. (46 mg, 79% yield) R_f=0.22 (20% EtOAc in hexane); mp 105–107 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.55 (br s, 1H), 7.78 (d, 2H, J=8.0 Hz), 7.77 (d, 1H, J=2.0 Hz), 7.35 (d, 2H, J=8.0 Hz), 7.30 (d, 1H, J=8.5 Hz), 7.15 (dd, 1H, J=2.0, 8.5 Hz), 7.01 (d, 1H, J=2.0 Hz), 6.07 (t, 1H, J=7.5 Hz), 3.38 (t, 2H, J=7.5 Hz), 2.46 (s, 3H), 2.17–1.98 (m, 2H), 1.56–1.21 (m, 12H), 0.94 (t, 3H, J=7.2 Hz), 0.83 (t, 3H, J=7.5 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.1, 138.3, 135.6, 132.8, 130.4, 130.1, 128.0, 127.1, 126.4, 126.2, 122.9, 119.8, 11.5, 113.2, 49.7, 32.3, 31.6, 30.0, 29.7, 23.2, 21.8, 20.6, 14.4, 14.0; IR (film) cm^{-1} 3374 (m), 2958 (s), 2928 (s), 1463 (m), 1344 (m), 1159 (s), 1090 (w); mass spectrum (ESI): *m/e* (% relative intensity) 509.3 (100) $(M+Na)^+$, 487.3 (6) $(M+H)^+$; *m/e* calcd for $C_{27}H_{35}ClN_2O_2SNa$ 509.2000, found 509.2010.

4.1.16. Vinylindole 18. (64 mg, 80% yield) R_f=0.31 (20% EtOAc in hexane); mp 141–143 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.64 (br s, 1H), 7.82 (d, 2H, J=8.1 Hz), 7.72 (d, 1H, J=8.7 Hz), 7.54 (d, 1H, J=2.5 Hz), 7.38 (d, 2H, J=8.1 Hz), 7.29 (dd, 1H, J=2.5, 8.7 Hz), 6.97 (d, 1H, J=2.7 Hz), 6.13 (t, 1H, J=7.0 Hz), 3.42 (t, 2H, J=7.5 Hz), 2.49 (s, 3H), 2.23–1.91 (m, 2H), 1.59–1.20 (m, 12H), 0.96 (t, 3H, J=6.9 Hz), 0.86 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.1, 138.3, 138.0, 132.9, 130.5, 130.1, 128.0, 125.4, 125.0, 123.8, 121.6, 116.0, 115.8, 115.0, 49.6, 32.3, 31.6, 30.0, 29.9, 29.6, 23.2, 21.8, 20.5, 14.4, 14.0; IR (film) cm^{-1} 3369 (m), 2959 (s), 2928 (s), 1455 (w), 1340 (m), 1158 (s), 1089 (w); mass spectrum (ESI): *m/e* (% relative intensity) 553.2 (100) $(M+Na)^+$, 531.2 (9) $(M+H)^+$, 376.2 (25); *m/e* calcd for $C_{27}H_{35}BrN_2O_2SNa$ 553.1495, found 553.1503.

4.1.17. Vinylindole 19. (41 mg, 85% yield) R_f=0.21 (20% EtOAc in hexane); mp 95–96 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.35 (br s, 1H), 7.81 (d, 2H, J=8.4 Hz), 7.37 (d, 2H, J=8.4 Hz), 7.31 (d, 1H, J=2.4 Hz), 7.30 (d, 1H, J=8.4 Hz), 6.89 (dd, 1H, J=2.4, 8.4 Hz), 6.86 (d, 1H, J=2.4 Hz), 6.12 (t, 1H, J=7.5 Hz), 3.90 (s, 3H), 3.48–3.32 (m, 2H), 2.49 (s, 3H), 2.28–2.04 (m, 2H), 1.59–1.20 (m, 12H), 0.96 (t, 3H, J=6.6 Hz), 0.86 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 154.5, 143.3, 137.9, 131.6, 130.1, 129.4, 127.4, 125.9, 124.8, 114.4, 111.9, 111.7, 102.0, 55.5, 48.7, 31.6, 30.9, 29.4, 29.2, 28.9, 22.5, 21.1, 19.8, 13.7, 13.3; IR (film) cm^{-1} 3387 (m), 2957 (m), 2929 (s), 1340 (m), 1158 (s); mass spectrum (ESI): *m/e* (% relative intensity) 505.3 (100) $(M+Na)^+$, 483.3 (45) $(M+H)^+$, 453.3 (6); *m/e* calcd for $C_{28}H_{39}N_2O_3S$ 483.2676, found 483.2687.

4.1.18. Vinylindole 20. (59 mg, 85% yield) R_f=0.48 (20% EtOAc in hexane); mp 109–110 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.82 (d, 1H, J=7.5 Hz), 7.78 (d, 2H, J=8.1 Hz), 7.35 (d, 2H, J=8.1 Hz), 7.32 (d, 1H, J=7.5 Hz), 7.27 (t, 1H, J=7.5 Hz), 7.19 (t, 1H, J=7.5 Hz), 6.57 (s, 1H), 6.15 (t, 1H, J=7.2 Hz), 3.65 (s, 3H), 3.58–3.33 (m, 2H), 2.48 (s, 3H), 2.32–2.04 (m, 2H), 1.59–1.20 (m, 12H), 0.96 (t, 3H, J=7.5 Hz), 0.86 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.8, 138.3, 137.8, 132.3, 130.7, 130.0, 129.3, 128.1, 126.7, 122.4, 120.5, 120.4, 113.6, 110.1, 49.6, 33.2, 32.4, 31.7, 30.1, 30.0, 23.3, 21.8, 20.6, 14.5, 14.1; IR (film) cm^{-1} 2957 (s), 2927 (s), 1349 (m), 1160 (s); mass spectrum (ESI): *m/e* (% relative intensity) 489.3 (100) $(M+Na)^+$, 467.3 (15) $(M+H)^+$, 242.3 (5); *m/e* calcd for $C_{28}H_{38}N_2O_2SNa$ 489.2546, found 489.2552.

4.1.19. Vinylpyrrole 23a. (12 mg, 30% yield) R_f=0.28 (20% EtOAc in hexane); yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.23 (br s, 1H), 7.76 (d, 2H, J=8.7 Hz), 7.34 (d, 2H, J=8.7 Hz), 6.68 (dd, 1H, J=2.7, 4.8 Hz), 6.45 (dd, 1H, J=1.8, 4.5 Hz), 6.14 (ddd, 1H, J=1.8, 2.7, 4.5 Hz), 5.94 (t, 1H, J=7.5 Hz), 3.52–3.26 (m, 2H), 2.47 (s, 3H), 2.20–1.86

(m, 2H), 1.59–1.44 (m, 2H), 1.44–1.20 (m, 10H), 0.96 (t, 3H, J=6.6 Hz), 0.88 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.7, 138.8, 131.8, 129.9, 129.5, 128.0, 123.5, 118.8, 117.0, 106.9, 49.7, 32.3, 31.7, 29.9, 29.8, 29.3, 23.2, 21.8, 20.6, 14.4, 14.1; IR (film) cm^{-1} 3399 (m), 2959 (s), 2928 (s), 1340 (m), 1276 (s), 1261 (s); mass spectrum (ESI): *m/e* (% relative intensity) 425.3 (100) (M+Na)$^+$, 403.3 (17) (M+H)$^+$, 393.3 (7), 349.2 (5); *m/e* calcd for $C_{23}H_{34}N_2O_2SNa$ 425.2233, found 425.2223.

4.1.20. Vinylpyrrole 23b. (26 mg, 64% yield) R_f=0.57 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.81 (br s, 1H), 7.80 (d, 2H, J=8.4 Hz), 7.38 (d, 2H, J=8.4 Hz), 6.80–6.74 (m, 1H), 6.15–6.06 (m, 2H), 5.93 (t, 1H, J=7.5 Hz), 3.37 (t, 2H, J=7.5 Hz), 2.49 (s, 3H), 2.00–1.81 (m, 1H), 1.80–1.58 (m, 1H), 1.58–1.40 (m, 2H), 1.40–1.16 (m, 10H), 0.93 (t, 3H, J=7.2 Hz), 0.86 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.3, 137.6, 131.0, 130.8, 130.2, 129.4, 128.2, 118.6, 109.5, 107.8, 50.1, 32.2, 31.6, 29.8, 29.5, 28.9, 23.2, 21.8, 20.4, 14.4, 14.0; IR (film) cm^{-1} 3389 (m), 2957 (s), 2927 (s), 1343 (m), 1276 (s), 1261 (s), 1159 (s); mass spectrum (ESI): *m/e* (% relative intensity) 425.3 (100) (M+Na)$^+$, 403.3 (39) (M+H)$^+$, 393.3 (8), 349.2 (6); *m/e* calcd for $C_{23}H_{34}N_2O_2SNa$ 425.2233, found 425.2222.

4.1.21. Vinylpyrrole 24a. (12 mg, 29% yield) R_f=0.29 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.71 (d, 2H, J=8.5 Hz), 7.31 (d, 2H, J=8.5 Hz), 6.44 (t, 1H, J=2.5 Hz), 6.14 (t, 1H, J=2.0 Hz), 5.98 (t, 1H, J=2.5 Hz), 5.86 (t, 1H, J=7.0 Hz), 3.49 (s, 3H), 3.48–3.37 (m, 1H), 3.37–3.27 (m, 1H), 2.45 (s, 3H), 2.14–2.05 (m, 1H), 2.05–1.90 (m, 1H), 1.57–1.42 (m, 2H), 1.42–1.20 (m, 10H), 0.92 (t, 3H, J=7.0 Hz), 0.87 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.6, 138.9, 131.8, 129.9, 128.8, 128.0, 122.5, 120.9, 106.8, 49.7, 36.5, 32.3, 31.8, 29.9, 29.3, 23.2, 21.8, 20.6, 14.4, 14.1; IR (film) cm^{-1} 2957 (m), 2928 (m), 1345 (m), 1276 (s), 1261 (m), 1158 (m); mass spectrum (ESI): *m/e* (% relative intensity) 439.3 (100) (M+Na)$^+$, 417.3 (78) (M+H)$^+$; *m/e* calcd for $C_{24}H_{36}N_2O_2SNa$ 439.2390, found 439.2384.

4.1.22. Vinylpyrrole 24b. (24 mg, 58% yield) R_f=0.63 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.59 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=8.4 Hz), 6.34 (t, 1H, J=2.1 Hz), 5.97 (dd, 1H, J=2.7, 3.6 Hz), 5.68 (t, 1H, J=7.2 Hz), 5.67–5.63 (m, 1H), 3.70 (s, 3H), 3.30 (t, 2H, J=7.2 Hz), 2.46 (s, 3H), 2.31 (q, 2H, J=7.2 Hz), 1.64–1.24 (m, 12H), 0.96 (t, 3H, J=6.6 Hz), 0.92 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.7, 138.2, 136.9, 130.8, 129.9, 127.9, 123.9, 109.7, 107.5, 49.0, 35.5, 32.3, 31.4, 29.9, 29.8, 23.2, 21.8, 20.6, 14.4, 14.1; IR (film) cm^{-1} 2957 (m), 2928 (m), 1467 (w), 1346 (m), 1159 (m); mass spectrum (ESI): *m/e* (% relative intensity) 439.3 (100) (M+Na)$^+$, 417.3 (35) (M+H)$^+$; *m/e* calcd for $C_{24}H_{36}N_2O_2SNa$ 439.2390, found 439.2402.

4.1.23. Vinylpyrrole 25. (51 mg, 79% yield) R_f=0.35 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.71 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=8.4 Hz), 5.51 (t, 1H, J=7.2 Hz), 5.14 (br s, 1H), 3.55–3.05 (m, 2H), 2.47 (s, 3H), 2.27 (s, 3H), 2.27–2.10 (m, 2H), 2.08 (s, 3H), 1.56–1.24 (m, 12H), 0.95 (t, 3H, J=6.6 Hz), 0.88 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.5, 138.8, 132.8, 131.3, 129.8, 128.0, 125.4, 125.2, 118.4, 106.2, 48.8, 32.3, 31.4, 30.1, 29.9, 29.7, 23.2, 21.7, 20.5, 14.4, 14.1, 12.9, 12.8; IR (film) cm^{-1} 3378 (m), 2957 (m), 2926 (m), 1337 (m), 1154 (m); mass spectrum (ESI): *m/e* (% relative intensity) 453.3 (100) (M+Na)$^+$, 431.3 (42) (M+H)$^+$; *m/e* calcd for $C_{25}H_{39}N_2O_2S$ 431.2727, found 431.2706.

4.1.24. Vinylfuran 26. (35 mg, 84% yield) R_f=0.64 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.70 (d, 2H, J=8.5 Hz), 7.30 (d, 2H, J=8.5 Hz), 6.20 (t, 1H, J=7.5 Hz), 5.86 (d, 1H, J=3.5 Hz), 5.72 (d, 1H, J=3.5 Hz), 3.52–3.42 (m, 1H), 3.38–3.26 (m, 1H), 2.45 (s, 3H), 2.19 (s, 3H), 2.25–2.05 (m, 2H), 1.60–1.24 (m, 12H), 0.92 (t, 3H, J=7.0 Hz), 0.89 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 152.3, 150.6, 143.9, 138.3, 132.1, 129.9, 128.1, 128.0, 108.7, 107.6, 50.0, 32.3, 31.7, 29.9, 29.6, 29.0, 23.2, 21.8, 20.6, 14.4, 14.1, 13.8; IR (film) cm^{-1} 2958 (s), 2928 (s), 1350 (m), 1162 (m); mass spectrum (ESI): *m/e* (% relative intensity) 440.3 (100) (M+Na)$^+$, 418.3 (28) (M+H)$^+$, 376.2 (18); *m/e* calcd for $C_{24}H_{35}NO_3SNa$ 440.2230, found 440.2241.

4.1.25. Vinylfuran 27. (41 mg, 79% yield) R_f=0.68 (20% EtOAc in hexane); light yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.72 (d, 2H, J=8.4 Hz), 7.33 (d, 2H, J=8.4 Hz), 6.18 (t, 1H, J=7.5 Hz), 5.60 (s, 1H), 3.55–3.24 (m, 2H), 2.46 (s, 3H), 2.28–2.00 (m, 2H), 2.12 (s, 3H), 1.84 (s, 3H), 1.60–1.24 (m, 12H), 0.96 (t, 3H, J=6.6 Hz), 0.91 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.1, 147.5, 143.8, 138.3, 131.4, 129.9, 128.1, 127.9, 116.2, 111.3, 50.0, 32.3, 31.7, 29.9, 29.6, 29.0, 23.2, 21.7, 20.6, 14.4, 14.1, 11.6, 10.0; IR (film) cm^{-1} 2958 (s), 2927 (s), 1352 (m), 1162 (s); mass spectrum (ESI): *m/e* (% relative intensity) 454.3 (100) (M+Na)$^+$, 432.3 (40) (M+H)$^+$; *m/e* calcd for $C_{25}H_{37}N_2O_3SNa$ 454.2386, found 454.2395.

4.1.26. Divinylpyrrole 28. (38 mg, 70% yield) R_f=0.55 (20% EtOAc in hexane); yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.55 (br s, 1H), 7.83 (d, 2H, J=8.1 Hz), 7.55 (d, 2H, J=8.1 Hz), 7.40 (d, 2H, J=8.1 Hz), 7.23 (d, 2H, J=8.1 Hz), 6.33 (t, 1H, J=7.2 Hz), 5.62 (t, 1H, J=7.2 Hz), 3.43–3.23 (m, 4H), 2.49 (s, 3H), 2.55–2.48 (m, 2H), 2.42 (s, 3H), 2.40–2.18 (m, 4H), 1.80–1.09 (m, 22H), 1.09–0.81 (m, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.6, 143.2, 138.7, 137.7, 136.0, 134.1, 131.8, 130.3, 129.5, 128.3, 127.9, 126.8, 126.2, 119.4, 51.0, 50.5, 32.1, 32.0, 31.9, 31.6, 29.8, 29.1, 24.2, 23.5, 23.3, 23.1, 21.8, 21.7, 20.8, 20.5, 14.4, 14.2, 14.1, 14.0; IR (film) cm^{-1} 3360 (w), 2957 (m), 2930 (m), 1339 (m), 1157 (m); mass spectrum (ESI): *m/e* (% relative intensity) 758.4 (100) (M+Na)$^+$, 736.4 (39) (M+H)$^+$, 580.4 (28); *m/e* calcd for $C_{42}H_{61}N_3O_4S_2Na$ 758.3996, found 758.4005.

4.1.27. Divinylpyrrole 29. (57 mg, 78% yield) R_f=0.56 (20% EtOAc in hexane); yellow oil; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.22 (br s, 1H), 7.84 (d, 2H, J=8.1 Hz), 7.56 (d, 2H, J=8.1 Hz), 7.44 (d, 2H, J=8.1 Hz), 7.29 (d, 2H, J=8.1 Hz), 5.48 (t, 2H, J=7.5 Hz), 5.42 (t, 1H, J=7.5 Hz), 3.56–3.00 (m, 4H), 2.51 (s, 3H), 2.44 (s, 3H), 2.28–2.16 (m, 2H), 2.11 (s, 3H), 1.94 (s, 3H), 1.80–1.09 (m, 26H),

1.02–0.80 (m, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.6, 143.2, 139.1, 137.8, 135.9, 135.3, 131.4, 130.4, 129.6, 128.3, 127.7, 127.4, 127.2, 124.1, 119.5, 119.1, 50.0, 49.3, 32.2, 32.1, 31.5, 31.3, 30.0, 29.9, 29.8, 29.8, 29.1, 23.2, 23.2, 21.8, 21.7, 20.7, 20.4, 14.4, 14.1, 14.0, 12.6, 12.4; IR (film) cm^{-1} 3435 (w), 2958 (s), 2928 (s), 1341 (s), 1157 (s); mass spectrum (ESI): *m/e* (% relative intensity) 788.6 (100) $(M+Na)^+$; *m/e* calcd for $C_{44}H_{67}N_3O_4S_2Na$ 788.4465, found 788.4480.

4.1.28. Carbazole 32. A solution of vinylindole **2** (21.0 mg, 0.044 mmol) and DMAD (13.0 mg, 0.09 mmol) in toluene (0.45 mL) was heated at 160 °C in a seal tube. The reaction was monitored by TLC analysis. Upon completion, the solution was cooled to room temperature with stirring. White precipitation formed at this point, which was filtered and washed with cold toluene. The white powder was dried under vacuo to afford carbazole **32** (17.1 mg, 65% yield). R_f=0.44 (33% EtOAc in hexane); mp 258–260 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.28 (d, 1H, J=8.0 Hz), 7.27 (d, 2H, J=8.0 Hz), 7.42 (t, 1H, J=7.5 Hz), 7.40–7.29 (m, 3H, J=7.5 Hz), 4.22–4.01 (m, 1H), 4.05 (s, 3H), 3.94 (s, 3H), 3.55–3.44 (m, 1H), 2.45 (s, 3H), 2.44–2.32 (m, 1H), 2.13–1.98 (m, 1H), 1.82–1.66 (m, 1H), 1.66–1.39 (m, 2H), 1.39–1.03 (m, 9H), 0.89 (t, 3H, J=7.0 Hz), 0.81 (t, 3H, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 166.4, 143.8, 140.5, 139.0, 137.9, 136.2, 134.4, 131.5, 130.0, 127.7, 127.5, 126.6, 124.1, 121.0, 120.3, 110.9, 110.0, 52.9, 52.6, 51.5, 31.2, 30.6, 30.5, 30.2, 28.8, 22.8, 21.7, 20.4, 14.2, 13.8; IR (film) cm^{-1} 3409 (m), 2956 (m), 1731 (s), 1722 (s), 1341 (m), 1210 (m), 1161 (m); mass spectrum (ESI): *m/e* (% relative intensity) 615.1 (70) $(M+Na)^+$, 561.1 (100); *m/e* calcd for $C_{33}H_{40}N_2O_6SNa$ 615.2500, found 615.2524.

4.1.29. Carbazole 33. A solution of vinylindole **11** (15.0 mg, 0.048 mmol) and DMAD (14.0 mg, 0.10 mmol) in toluene (0.5 mL) was heated at 140 °C in a seal tube. The reaction was monitored by TLC analysis. Upon completion, the solution was cooled to room temperature. Evaporation of the solvent under reduced pressure afforded a residue, which was purified by silica gel flash chromatograph to afford carbazole **33** as a light yellow solid (13.2 mg, 61% yield). R_f=0.56 (33% EtOAc in hexane); mp 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (br s, 1H), 7.87 (d, 1H, J=8.1 Hz), 7.60–7.50 (m, 2H), 7.36–7.30 (m, 1H), 4.06 (s, 3H), 4.02 (s, 3H), 3.58 (s, 3H), 3.40 (s, 3H), 2.78–2.58 (m, 2H), 1.64–1.26 (m, 8H), 0.94 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 166.4, 156.6, 140.4, 139.9, 139.5, 134.5, 129.1, 127.6, 122.7, 122.0, 121.2, 120.5, 111.4, 108.6, 53.3, 52.9, 52.7, 36.5, 31.7, 31.3, 30.2, 29.2, 22.7, 14.3; IR (film) cm^{-1} 3346 (w), 2953 (m), 1696 (br s), 1210 (m); mass spectrum (ESI): *m/e* (% relative intensity) 477.2 (100) $(M+Na)^+$; *m/e* calcd for $C_{25}H_{30}N_2O_6Na$ 477.1996, found 477.1994.

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Synthesis of chiral allenes from ynamides through a highly stereoselective Saucy–Marbet rearrangement

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Abstract—A highly stereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols is described here. This rearrangement can be catalyzed by *para*-nitrobenzenesulfonic acid and leads to high diastereoselectivities for a range of different chiral propargyl alcohols and ynamides in a stereochemically intriguing matched, mismatched or indifferent manner. The stereoselective Saucy–Marbet rearrangement of ynamides provides an excellent entry to highly substituted chiral homo allenyl alcohols.

1. Introduction

The chemistry of electron deficient ynamines (Type I–V) and ynamides (Types VI–VIII) has blossomed in the past 10 years (Fig. 1).[1–11] Our own earlier efforts had focused on the use of chiral ynamides in the stereoselective Claisen rearrangement.[12,13] Specifically, we were able to establish a Brønsted acid catalyzed stereoselective Ficini–Eschenmoser–Claisen rearrangement (**1**→**2a**+**2b** in Fig. 2),[14,15] and communicated the stereospecificity in the Saucy–Marbet rearrangement[16,17] (**3**→**5a**–**d**) using chiral propargyl alcohols.[18] This latter rearrangement can provide an even greater synthetic implication because it leads to preparations of chiral allenes. Despite this potential and that Saucy and Marbet[16a] first reported this rearrangement in 1958, to our surprise, there have been very few studies concerning the stereoselectivity issues of the Saucy–Marbet

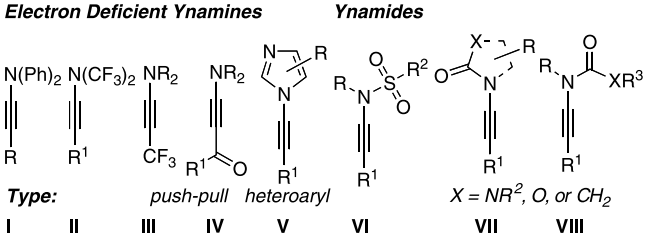

Figure 1.

Keywords: Ynamides; Saucy–Marbet rearrangement; Chiral allenes; Sibi and Evans' auxiliaries; Axial chirality.
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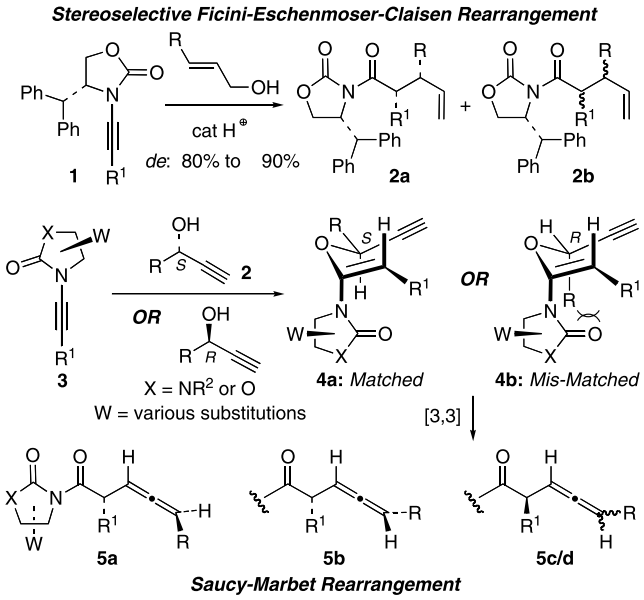


Figure 2.

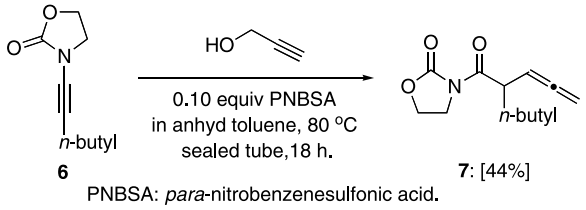
rearrangement.[19,20] We report here, our studies on stereoselective Saucy–Marbet rearrangements.

2. Results and discussions

2.1. The feasibility question

Although Ficini had reported the use of ynamines in related rearrangements,[21] it was not apparent as to how ynamides would behave in this case. Thus, reaction of achiral ynamide

6 with 2-propyn-1-ol was first examined. In the presence of 0.10 equiv of *para*-nitrobenzenesulfonic acid (PNBSA) at 80 °C in toluene, the rearrangement took place and afforded allene **7** in 44% yield (Scheme 1).

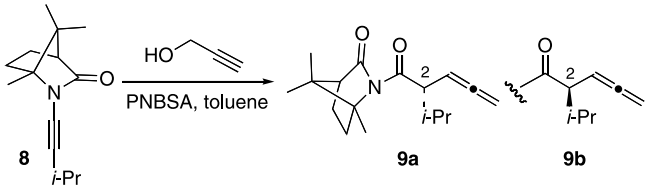


Scheme 1.

2.2. Stereoselectivity issues

Having established the feasibility of this arrangement, Boeckman's chiral lactam[22]-substituted ynamide **8** was chosen to explore conditions that could lead to high stereoselectivity at C2, because **8** represents one of the more reactive chiral ynamides and its rearrangement could proceed at lower temperatures than 80 °C.[15] As summarized in Table 1, attempts to run the reaction of **8** with 2-propyn-1-ol at temperatures below 45 °C failed to give the desired allene **9** (entries 1–4). When the reaction was carried out at 60 °C, **9** was isolated in 60% yield. However, the diastereomeric ratio was only 1.2:1, and the same ratio was observed at rt when a trace of amount product was found in ^{1}H NMR (entry 5 vs 2).

Table 1.



Entry	Temperature (°C)	PNBSA (equiv)	Yield (%)[a]	Ratio **a**:**b**[b]
1	0	0.10	NR[c]	ND[d]
2	rt	0.10	Trace	1:1
3	rt	0.20	NR[e]	ND
4	45	0.10	NR	ND
5	60	0.10	60	1.2:1
6	60	0.15	80	1:1
7	60	0.05	40	1:1
8	80	0.10	65	1:1

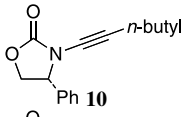
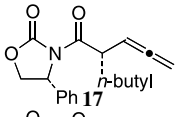
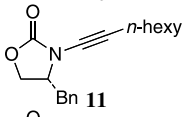
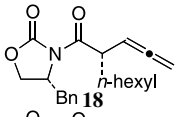
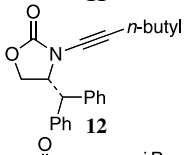
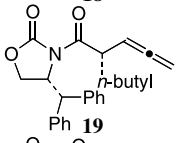
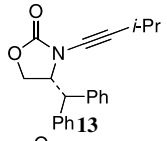
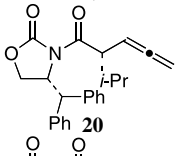
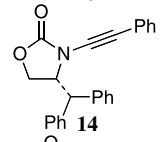
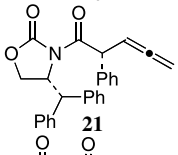
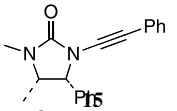
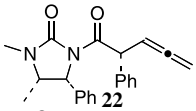
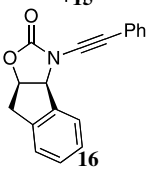
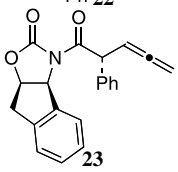
[a] Isolated yields.
[b] Ratios determined using ^{1}H NMR. Stereochemistry unassigned.
[c] NR: no reaction.
[d] ND: not determined.
[e] Hydrolysis of ynamide occurred.

Varying the amount of PNSBA did not affect the selectivity (entries 6 and 7) and the yield dropped when 0.05 equiv of PNSBA was used (entry 7). Reaction at 80 °C yielded results comparable to those at 60 °C (entry 5 vs 8).

2.3. The effect of chiral auxiliaries

Speculating that the chiral auxiliary of ynamides might play a role in the stereochemical outcome, we examined various chiral ynamides. As summarized in Table 2, ynamides **10**–**11** (entries 1 and 2) substituted with Evans' auxiliary,[23] and ynamides **12**–**14** (entries 3–5) substituted with Sibi's auxiliary[24] gave improved diastereoselectivity with **12** providing the best ratio (entry 3). However, selectivities here appeared to have reached the maximum as ynamides **13** and **14** with an *i*-Pr and Ph substituents, respectively, provided relatively lower selectivities as well as yields than **12** (entries 4 and 5 vs 3).

Table 2

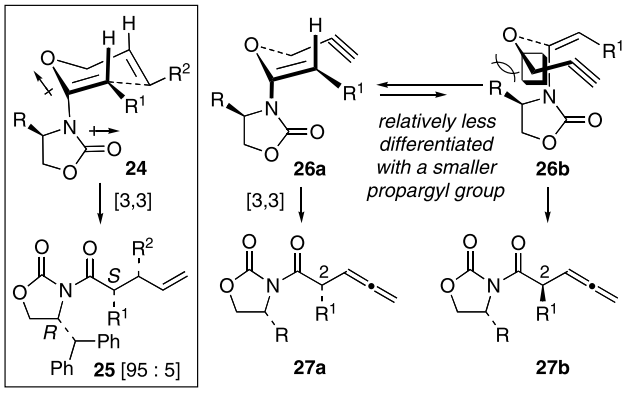
Entry	Ynamides[a]	Rearrangement products	Yield (%)[b]	Ratio[c]
1	 **10**	 **17**	60	67:33[d]
2	 **11**	 **18**	78	70:30
3	 **12**	 **19**	70	85:15
4	 **13**	 **20**	40	60:40
5	 **14**	 **21**	40	80:20
6	 **15**	 **22**	37[e]	78:22
7	 **16**	 **23**	70	63:37

[a] Reactions were carried out in toluene in the presence of 0.10 equiv of PNBSA and heated at 80–85 °C in a sealed tube for 12–18 h.
[b] Isolated yields.
[c] Ratios were determined by using ^{1}H NMR.
[d] Stereochemistry of the major isomer was assigned based on Claisen rearrangements using allyl alcohols. See Ref. 15.
[e] Extensive hydrolysis occurred.

Other auxiliaries were also screened, but none provided better ratios (entries 6–7). Ynamide **15** substituted with Close's auxiliary[25] provided a comparable ratio to that of **12**, although in lower yield in addition to hydrolysis of the ynamides (entry 6), whereas ynamide **16** substituted with chiral 1-amino-2-indanol derived auxiliary also led to a low diastereoselectivity (entry 7).

2.4. A proposed mechanistic model

Perplexed by the lack of diastereoselectivity, we examined the mechanistic model that was proposed in our previous Ficini–Claisen rearrangements using allyl alcohols.[15] As shown in Scheme 2, the rearrangement likely goes through a chair transition state shown in the *O*-allyl ketene aminal **24** (inside the left box). The ketene aminal **24** would assume a conformation similar to the Evans' model for asymmetric aldol reactions using chiral oxazolidinones,[23] minimizing the dipole interaction between the urethane C=O and vinyl C–O bond (worth ~2.6 Kcal mol^{-1}).[23] This would provide two sterically differentiated π-faces of the ketene aminal with the allylic substituent preferring the back face leading favorably to the major stereoisomer **25** after the (3,3)-sigmatropic rearrangement.

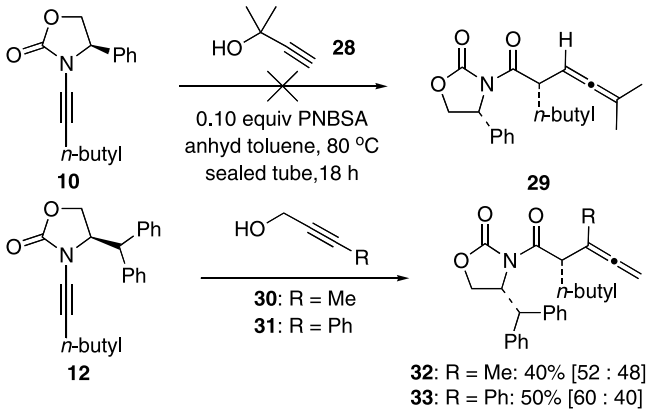


Scheme 2.

Based on this model, *O*-propargyl ketene aminals **26a** and **26b** would be responsible for the observed stereochemical outcome at C2 in which the more favored intermediate **26a** could lead to the moderately favored major isomer **27a**.[26] Larger *R* substituents such as a diphenyl methyl group in the Sibi's auxiliary should provide more differentiation to the two π-faces of the ketene aminal, thereby leading to enhanced diastereoselectivity.

However, the level of selectivity is much lower overall compared to those obtained using allyl alcohols.[15] This is likely due to the fact that the propargyl substituent is smaller than an allyl group, and thus, the π-facial differentiation of the ketene aminal is reduced with the steric interaction between the propargyl and R substituents shown in **26b** being less severe than an allyl group.

With this assessment in hand, we explored more bulky propargyl alcohols. We reacted 1,1-dimethyl-2-propyn-1-ol **28** with ynamide **10**, but it failed to produce the desired rearrangement product **29** with hydrolysis of **10** being the dominant event (Scheme 3). Because propargyl alcohol **28** is likely too bulky, thereby shutting down the formation of the ketene aminal, we turned to propargyl alcohols **30** and **31** with substituents at the terminal alkyne carbon. Reactions of **12** with propargyl alcohols **30** and **31** led to allenes **32** and **33** in 40 and 50% yields, respectively, but unfortunately with lower diastereoselectivities.

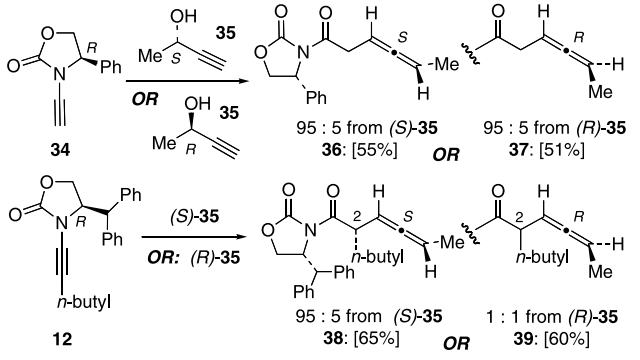


Scheme 3.

Therefore, these results were not informative. To further assess this mechanistic model, there remains one other possibility that would then involve chiral propargyl alcohols that are more bulky but with only one substituent at the propargyl carbon. However, by using chiral propargyl alcohols, we anticipated that we would run into potential match and mismatch situations (see Fig. 2), which could lead to a completely different endeavor, but one that would remain challenging stereochemically. However, this endeavor could also provide an excellent opportunity for constructing chiral allenes.

2.5. Chiral propargyl alcohols: match and mismatch

We quickly established the feasibility of Saucy–Marbet rearrangement using chiral ynamides (Scheme 4). Reactions of ynamide **34** with (*S*)-**35** and (*R*)-**35** using PNBSA at 100 °C gave allenes **36** and **37** in 55 and 51% yield, respectively, as single diastereomers, suggesting excellent chirality transfer from chiral alcohols to the allenic axial center.[16d,19a] Because **34** is unsubstituted at the terminal alkyne carbon, match and mismatch was not an issue.



Scheme 4. Conditions: 0.10–0.20 equiv PNBSA: *para*-nitrobenzenesulfonic acid. **34** or **12** in anhyd. toluene [0.025 M], 1.0–2.0 equiv alcohol, sealed tube.

However, while reactions of **12** led to **38** as a single diastereomer using (*S*)-**35**, allene **39** was isolated with 1:1 isomeric ratio when using (*R*)-**35**. Stereochemical assignment (see below) of **39** suggests that it is 1:1 at C2, thereby implying that potential mismatched intermediates were

involved. Stereochemistry of **38** was assigned by correlation with allene **40**[27] whose X-ray structure is shown in Figure 3.

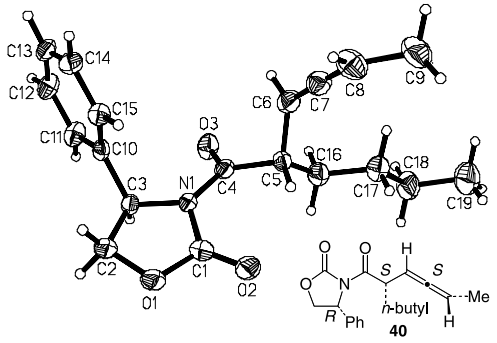
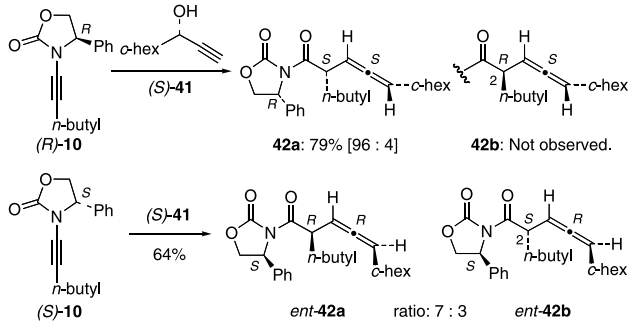


Figure 3.

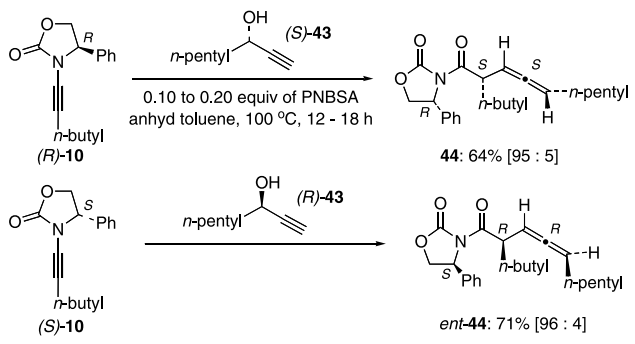
This case of match/mismatch is further confirmed via another set of experiments employing the same chiral propargyl alcohol (*S*)-**41** but changing the chirality of the ynamide. As shown in Scheme 5, reaction of (*R*)-**10** with (*S*)-**41** led to **42a** as a single diastereomer and no **42b** was observed by NMR, while the mismatched reaction of (*S*)-**10** with (*S*)-**41** gave both *ent*-**42a** and *ent*-**42b** in 64% yield but as a 7:3 mixture, again with respect to the C2 stereochemistry. It was intriguing that the ratio was not 1:1 (see below for more discussion).



Scheme 5.

2.6. Synthesis of chiral allenes

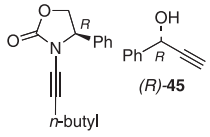
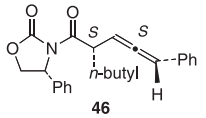
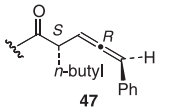
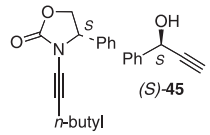
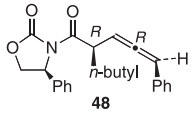
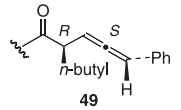
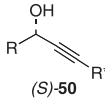
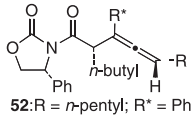
These results allowed us to construct a range of chiral allenes. For example, an appropriate matching of ynamides **10** with (*S*)-**43** and (*R*)-**43** led to **44** and *ent*-**44**, respectively, in high selectivities (Scheme 6).



Scheme 6.

In addition, we found that these rearrangements do not all experience either matching or mismatching. As shown in Table 3, reactions of both (*R*)-**10** and (*S*)-**10** with (*R*)-**45** and (*S*)-**45** gave rearranged products **46–49**, respectively, with high diastereoselectivities, although the matched cases (entries 1 and 3) are still higher overall than cases that would be presumed to be mismatched (entries 2 and 4). This finding provides the synthesis of all four possible diastereomeric homo allenyl amides.

Table 3

Entry	Ynamides and alkynols[a]	Rearrangement products	Yield[b]	Ratio[c]
1		 **46**	80	96 : 4
2	(*R*)-**10** (*S*)-**45**	 **47**	78	90 : 10
3		 **48**	77	96 : 4
4	(*S*)-**10** (*R*)-**45**	 **49**	75	89 : 11
5	(*R*)-**10**  (*S*)-**50**	 **52**:R = *n*-pentyl; R* = Ph	77	96 : 4
6	(*R*)-**10**	(*S*)-**51** **53**:R = *c*-hex; R* = *n*-butyl	71	96 : 4

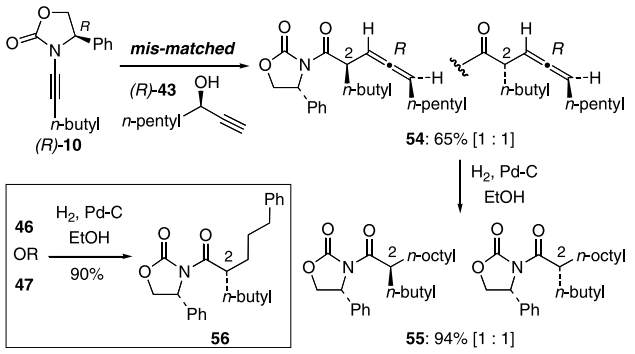
[a] Reactions were carried out in anhyd toluene in the presence of 0.10 to 0.20 equiv of PNBSA and heated at 100°C in a sealed tube for 12-18h.
[b] All are Isolated yields.
[c] Ratios were determined by using ^{1}H and/or ^{13}C NMR.

Finally, tri-substituted chiral homo allenyl amides **52** and **53** could also be obtained in high selectivities using (*S*)-**50** and (*S*)-**51**,[28] respectively (entries 5 and 6).

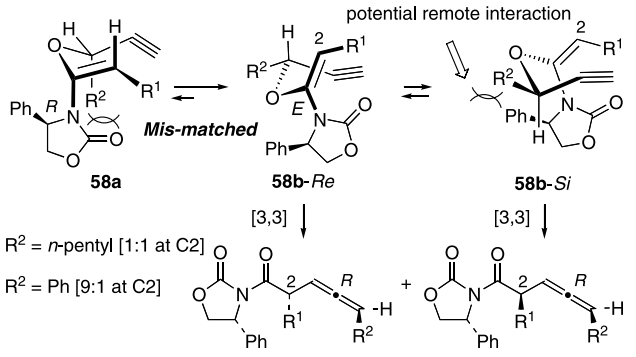
2.7. High axial stereoselectivity in the mismatch cases

To unambiguously establish all stereochemical issues, we further confirmed that (1) in the mismatched cases, stereoselectivity was very high for the allenic axial chirality, and (2) mismatching led to an isomeric mixture at the C2 stereocenter.

Toward this goal, the isomeric mixture **54** obtained with a 1:1 ratio from reaction of (*R*)-**10** with (*R*)-**43** was hydrogenated to give **55**, which remained as a 1:1 mixture (Scheme 7). This finding implies that the diastereoselectivity suffered only at C2 in mismatched cases, whereas the allene stereochemistry was transferred in high degrees of integrity from the chiral propargyl alcohol. On the other hand, hydrogenation of both **46** and **47** led to the same amide **56**, implying that stereoselectivity at C2 was the same when it was indifferent to match or mismatch.



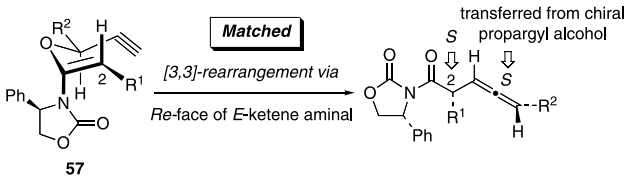
Scheme 7.



Scheme 9.

2.8. Mechanistic issues

Mechanistically, for the matched cases, that is, reactions of ynamide (*R*)-**10** (R^1=*n*-butyl) with chiral propargyl alcohols (*S*)-**41** (R^2=*c*-hex), (*S*)-**43** (R^2=*n*-pentyl), or (*R*)-**45** (R^2=Ph), (3,3)-sigmatropic rearrangement would likely proceed through the *E*-ketene aminal intermediate **57** in which the C2 stereochemistry is dictated by the preference of the rearrangement occurring at the *Re*-face of **57** (Scheme 8).[15] The allene stereochemistry is transferred directly from the chiral propargyl alcohol, and that should be true for both matched and mismatched cases.



Scheme 8.

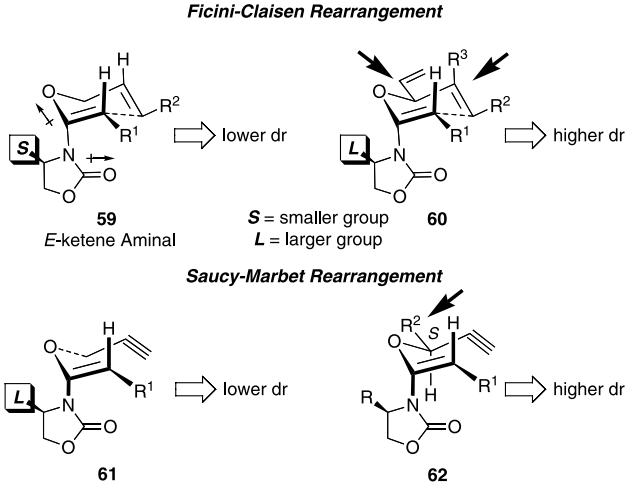
For mismatched and indifferent (for propargyl alcohols (*R*)-**45** or (*S*)-**45** with R^2=Ph in Table 3) cases, to address the C2 stereochemistry, we propose that the rearrangement could go through the same type of *E*-ketene aminal that is now mismatched as shown in **58a** owing to pseudo 1,3-diaxial interactions between the R^2 and the auxiliary groups (Scheme 9). Thus, it may be proposed that ketene aminal **58b** is the active conformation for the rearrangement with the R_2 group being equatorial. Because of this conformational preference, in the mismatched or indifferent cases, the (3,3)-sigmatropic rearrangement could occur at either or both *Re*- and *Si*-faces of **58b**, thereby providing some explanation for the observed stereochemical outcome at C2.[29]

When it is completely mismatched, that is, R^2=*n*-pentyl in the reaction of (*R*)-**43** with ynamide (*R*)-**10** to produce allene **54** (shown in Scheme 7 above), rearrangement could be proposed to proceed through both the *Re*- and *Si*-face of **58b**, and PM3 calculations using Spartan Model™ only showed a small energetic difference of ~0.6 Kcal mol^{-1}.[30] The ensuing (3,3)-rearrangement at both *Re*- and *Si*-faces of **58b** would then lead to a 1:1 isomeric ratio at C2 as observed for allene **54**[15] (Scheme 7).

On the other hand, for indifferent cases, when R^2=Ph as in (*R*)-**45** or (*S*)-**45**, the ensuing rearrangement may prefer to go through the *Re*-face of **58b** because PM3 calculations provide $\Delta E = 1.0$ Kcal mol^{-1} in favor of **58b**-*Re*.[30] This preference could be proposed as a result of the unfavorable remote interaction between the R^2 group, when it is more bulky (i.e., Ph vs *n*-pentyl in **43** or Me in **35**), with the auxiliary shown in **58b**-*Si*. This preference could then result in a 9:1 isomeric ratio at C2 in as shown in Table 3 for **46/48** versus **47/49**.

Although we remain uncertain if this remote interaction is the actual reason for the energetic preference for **58b**-*Re* over **58b**-*Si*, this phenomenon is at least consistent with the result shown in both Schemes 5 and 7. Firstly in Scheme 7, an expected 1:1 ratio was observed for allene **54** from the completely mismatched reaction of (*R*)-**10** with chiral propargyl alcohol (*R*)-**43** (R^2=*n*-pentyl). In contrast, as shown in Scheme 5, when the chiral propargyl alcohol (*S*)-**41**, where R^2=*c*-hex, was reacted with (*S*)-**10** also in a potential mismatch, instead of the expected 1:1 ratio, the corresponding allene **42** was obtained with an improved ratio of 7:3.[30] This can be attributed to the fact that the R^2 group (*c*-hex) in chiral propargyl alcohol (*S*)-**41** is larger than that (*n*-pentyl) in (*R*)-**43**

Finally, the mechanistic picture becomes even more clear and consistent when we examine the entire scope of Claisen rearrangements using ynamides. As shown in Scheme 10, the very same elements that dictate the level of



Scheme 10.

diastereoselectivity in the Ficini–Claisen rearrangement[14,15] also control the stereochemical outcome in these current Saucy–Marbet rearrangements. That is both rearrangements likely proceeds through the same chair-like transition-state shown in all four intermediates **59**–**62**, which are also all *E*-ketene aminals[15] with an orientation that are again consistent with the Evans' dipole argument.[23]

With this unified model in place, the critical element that can lead to high diastereomeric selectivity becomes the π-facial differentiation in these *E*-ketene aminals. The greater the differentiation would imply a greater selectivity. To achieve a greater π-facial differentiation, relevant factors could be deduced to the size of the chiral auxiliary (see the box in **59** and **60**) as well as the size of the allylic strand both at the allylic carbon (with a vinyl group, specifically shown in **60**[15]), and at the vinyl fragment (see black arrows in **60**) for the Ficini–Claisen rearrangement. We observed exactly these phenomena in our previous work,[15] and likewise for the Saucy–Marbet rearrangement, the relevant factors are also the size of the chiral auxiliary (see the box in **61**), and even more significantly, the size of the propargylic carbon (see the black arrow in **62**). In pursuing of this latter factor, we observed various interesting matched and mismatched scenarios that led to a greater mechanistic understanding of these pericyclic rearrangements.

Finally, one of the reviewers made an excellent suggestion. That is what would the outcome be from the reaction of an achiral ynamide with both antipodes of chiral propargyl alcohols. This suggested experiment should further provide interesting mechanistic insights. However, unfortunately, these reactions, specifically using ynamide **6** and chiral propargyl alcohols (*R*)-**45** and (*S*)-**45**, gave poor yields. Thus, we were unable to meaningfully determine their respective diastereomeric ratios.

3. Conclusion

We have described here a highly stereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols. This rearrangement provides an approach for synthesis of highly substituted chiral allenes.

4. Experimental

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separationd were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VXR-300, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and vanillin or $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses were performed at University of Minnesota Department of Chemistry Mass Spectrometry Laboratory. X-ray analyses were performed at University of Minnesota Department of Chemistry X-ray facility. All spectral data obtained for new compounds are reported here.

4.1. General procedure for propargyl alcohol addition/Saucy–Marbet rearrangement

Ynamide (0.2 mmol), anhyd *p*-nitrobenzenesulfonic acid (0.2 equiv), propargyl alcohol (1–2 equiv), and anhyd toluene (4 mL) were combined in a flame-dried 25 mL sealed tube under nitrogen atmosphere. The tube was sealed and the reaction mixture was heated at 100 °C for 24–48 h. The reaction was followed with TLC and/or LCMS analysis. Once completed by TLC analysis, the reaction was cooled to room temperature, filtered through Celite™, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (gradient: 0–25% EtOAc in hexanes) to provide the rearranged products in yields indicated in the text.

4.1.1. Allene 7. R_f=0.19 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87–0.97 (m, 3H), 1.29–1.38 (m, 4H), 1.56–1.62 (m, 1H), 1.78–1.84 (m, 1H), 4.03 (t, 2H, J=8.0 Hz), 4.33 (tq, 1H, J=1.5, 8.0 Hz), 4.39–4.43 (m, 1H), 4.41 (t, 1H, J=8.0 Hz), 4.79 (dd, 2H, J=2.0, 6.5 Hz), 5.31 (q, 1H, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 29.2, 31.6, 42.7, 61.8, 88.9, 153.0, 174.0, 208.4 (missing 2 signals due to overlap); IR (thin film) cm^{-1} 2957 (m), 2930 (m), 2862 (w), 1957 (w), 1780 (s), 1698 (s); mass spectrum (APCI): *m/e* (% relative intensity) 224 (13) $(M+H)^+$, 198 (50), 196 (66), 137 (59), 109 (40), 88 (100); HRMS-ESI *m/e* calcd for $C_{12}H_{17}NO_3Na$ 246.1101, found 246.1110.

4.1.2. Allene 9. R_f=0.52 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.86–1.02 (m, 9H), 1.45 (s, 3H), 1.58–1.64 (m, 3H), 1.81–1.86 (m, 2H), 1.95–2.06 (m, 2H), 2.07 (m, 1H), 2.35 (t, 1H, J=5.0 Hz), 4.08 (tt, 1H, J=1.5, 7.5 Hz), 4.67–4.75 (m, 2H), 5.16 (dt, 1H, J=7.0, 9.0 Hz); minor isomer: δ 0.86–1.02 (m, 9H), 1.45 (s, 3H), 1.58–1.64 (m, 3H), 1.81–1.86 (m, 2H), 1.95–2.06 (m, 2H), 2.07 (m, 1H), 2.35 (t, 1H, J=5.0 Hz), 4.14 (tt, 1H, J=1.5, 7.5 Hz), 4.67–4.75 (m, 2H), 5.28 (dt, 1H, J=7.0, 9.0 Hz); IR (thin film) cm^{-1} 2960 (m), 1955 (w), 1743 (s), 1692 (s); mass spectrum (APCI): *m/e* (% relative intensity) 276 (100) $(M+H)^+$, 252 (8), 220 (6), 154 (13); HRMS-ESI *m/e* calcd for $C_{17}H_{25}NO_2Na$ 298.1778, found 298.1777.

4.1.3. Allene 17. R_f=0.38 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.89 (t, 3H, J=7.5 Hz), 1.14–1.36 (m, 4H), 1.47–1.58 (m, 1H), 1.70–1.82 (m, 1H), 4.26–4.33 (m, 2H), 4.59 (dd, 1H, J=1.5, 6.5 Hz), 4.67–4.72 (m, 1H), 4.78 (dd, 1H, J=1.5, 12.0 Hz), 5.24 (q, 1H, J=9.0 Hz), 5.45 (dd, 1H, J=4.0, 9.0 Hz), 7.27–7.39 (m, 5H); minor isomer: δ 0.82 (t, 3H, J=7.5 Hz), 1.14–1.36 (m, 4H), 1.47–1.58 (m, 1H), 1.70–1.82 (m, 1H), 4.26–4.33 (m, 2H), 4.57 (dd, 1H, J=1.5, 6.5 Hz), 4.67–4.72 (m, 2H), 5.27 (q, 1H, J=9.0 Hz), 5.44 (dd, 1H, J=4.0,

9.0 Hz), 7.27–7.39 (m, 5H); IR (thin film) cm^{-1} 2957 (m), 2931 (m), 2861 (w), 1956 (w), 1781 (s), 1705 (s); mass spectrum (APCI): *m/e* (% relative intensity) 300 (48) $(M+H)^+$, 272 (21), 164 (100), 137 (41), 120 (47), 109 (26); HRMS-ESI *m/e* calcd for $C_{18}H_{21}NO_3Na$ 322.1414, found 322.1419.

4.1.4. Allene 18. $R_f=0.42$ (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.88 (t, 3H, $J=7.0$ Hz), 1.28–1.39 (m, 8H), 1.58–1.64 (m, 1H), 1.81–1.85 (m, 1H), 2.72–2.80 (m, 1H), 3.29 (dd, 1H, $J=3.0$, 8.5 Hz), 4.15–4.23 (m, 2H), 4.27–4.37 (m, 1H), 4.66–4.72 (m, 1H), 4.79 (dd, 1H, $J=2.0$, 6.5 Hz), 4.82–4.86 (m, 1H), 5.38 (dt, 1H, $J=6.5$, 8.0 Hz), 7.21–7.35 (m, 5H); minor isomer: δ 0.89 (t, 3H, $J=7.0$ Hz), 1.28–1.39 (m, 8H), 1.58–1.64 (m, 1H), 1.81–1.85 (m, 1H), 2.72–2.80 (m, 1H), 3.30 (dd, 1H, $J=3.0$, 8.5 Hz), 4.15–4.23 (m, 2H), 4.27–4.37 (m, 1H), 4.66–4.72 (m, 2H), 4.82–4.86 (m, 1H), 5.32 (dt, 1H, $J=6.5$, 8.0 Hz), 7.21–7.35 (m, 5H); IR (thin film) cm^{-1} 2954 (m), 2926 (m), 2856 (w), 1956 (w), 1781 (s), 1698 (s); mass spectrum (APCI): *m/e* (% relative intensity) 342 (100) $(M+H)^+$, 314 (41), 178 (73), 165 (54), 117 (46); HRMS-ESI *m/e* calcd for $C_2^1H_{27}NO_3Na$ 364.1883, found 364.1889.

4.1.5. Allene 19. $R_f=0.47$ (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.88 (t, 3H, $J=7.5$ Hz), 1.24–1.34 (m, 4H), 1.54–1.59 (m, 1H), 1.74–1.77 (m, 1H), 4.22–4.24 (m, 1H), 4.37–4.49 (m, 2H), 4.73 (d, 1H, $J=5.5$ Hz), 4.81–4.83 (m, 2H), 5.16 (dt, 1H, $J=7.0$, 8.0 Hz), 5.34 (ddd, 1H, $J=3.5$, 5.5, 8.0 Hz), 7.11–7.20 (m, 4H), 7.24–7.34 (m, 6H); minor isomer: δ 0.88 (t, 3H, $J=7.5$ Hz), 1.24–1.34 (m, 4H), 1.54–1.59 (m, 1H), 1.74–1.77 (m, 1H), 4.22–4.24 (m, 1H), 4.37–4.49 (m, 2H), 4.70 (d, 1H, $J=5.5$ Hz), 4.81–4.83 (m, 2H), 5.24 (dt, 1H, $J=7.0$, 8.0 Hz), 5.34 (ddd, 1H, $J=3.5$, 5.5, 8.0 Hz), 7.11–7.20 (m, 4H), 7.24–7.34 (m, 6H); IR (thin film) cm^{-1} 2955 (m), 2929 (m), 2859 (w), 1955 (w), 1782 (s), 1698 (s); mass spectrum (APCI): *m/e* (% relative intensity) 390 (96) $(M+H)^+$, 364 (52), 266 (43), 254 (100), 193 (41), 137 (54); HRMS-ESI *m/e* calcd for $C_{25}H_{27}NO_3Na$ 412.1883, found 412.1893.

4.1.6. Allene 20. $R_f=0.46$ (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.85 (d, 3H, $J=7.0$ Hz), 0.95 (d, 3H, $J=7.0$ Hz), 1.97 (septet, 1H, $J=7.0$ Hz), 4.18 (t, 1H, $J=9.0$ Hz), 4.34–4.38 (m, 1H), 4.39–4.46 (m, 1H), 4.72 (d, 1H, $J=7.0$ Hz), 4.74 (d, 1H, $J=5.0$ Hz), 4.79 (d, 1H, $J=6.0$ Hz), 5.12 (dt, 1H, $J=7.0$, 9.0 Hz), 5.33–5.37 (m, 1H), 7.10–7.34 (m, 10H); minor isomer: δ 0.79 (d, 3H, $J=7.0$ Hz), 0.93 (d, 3H, $J=7.0$ Hz), 2.06 (septet, 1H, $J=7.0$ Hz), 4.06 (t, 1H, $J=9.0$ Hz), 4.34–4.38 (m, 1H), 4.39–4.46 (m, 1H), 4.68 (d, 1H, $J=7.0$ Hz), 4.71 (d, 1H, $J=5.0$ Hz), 4.86 (d, 1H, $J=6.0$ Hz), 5.24 (dt, 1H, $J=7.0$, 9.0 Hz), 5.33–5.37 (m, 1H), 7.10–7.34 (m, 10H); IR (thin film) cm^{-1} 2965 (m), 2872 (w), 1958 (w), 1782 (s), 1696 (s); mass spectrum (APCI): *m/e* (% relative intensity) 375 (33) $(M)^+$, 350 (100), 332 (27), 254 (46), 123 (13); HRMS-ESI *m/e* calcd for $C_{24}H_{25}NO_3Na$ 398.1727, found 398.1714.

4.1.7. Allene 21. $R_f=0.37$ (25% EtOAc in hexane); orange oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (d, 1H, $J=9.9$ Hz), 4.03 (dd, 1H, $J=8.1$, 9.0 Hz), 4.30 (dd, 1H, $J=8.2$, 9.0 Hz), 4.34–4.46 (m, 2H), 4.65 (d, 1H, $J=5.7$ Hz), 4.98 (dt, 1H, $J=8.4$, 9.9 Hz), 5.28–5.36 (m, 1H), 6.88–7.44 (m, 15H); IR (thin film) cm^{-1} 3060 (w), 3028 (w), 1954 (w), 1770 (s), 1368 (m), 1185 (m); mass spectrum (APCI): *m/e* (% relative intensity) 410 (100) $(M+H)^+$, 254 (15); HRMS-ESI *m/e* calcd for $C_{27}H_{23}NO_3Na$ 432.1570, found 432.1582.

4.1.8. Allene 22. $R_f=0.23$ (25% EtOAc in hexane); white solid, mp 76–77 °C; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.78 (d, $J=7.0$ Hz, 3H), 2.81 (s, 3H), 3.83 (dq, $J=7.0$, 8.5 Hz, 1H), 4.60–4.80 (m, 2H), 5.24 (d, $J=8.5$ Hz, 1H), 5.56 (ddd, $J=6.5$, 6.5, 8.5 Hz, 1H), 6.03 (ddd, $J=1.5$, 1.5, 8.5 Hz, 1H), 7.10–7.45 (m, 10H); minor isomer: 0.74 (d, $J=7.0$ Hz, 3H), 2.80 (s, 3H), 3.89 (dq, $J=7.0$, 8.5 Hz, 1H), 4.65–4.80 (m, 2H), 5.37 (d, $J=8.5$ Hz, 1H), 5.63 (ddd, $J=6.5$, 6.5, 8.5 Hz, 1H), 5.94 (ddd, $J=1.5$, 1.5, 8.5 Hz, 1H), 6.80–6.90 (m, 2H), 7.10–7.45 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer only δ 14.9, 28.2, 48.6, 53.5, 59.8, 76.8, 90.7, 127.0, 127.1, 128.1, 128.3, 128.5, 128.8, 136.5, 138.8, 155.2, 171.2, 208.3 (missing 4 signals due to overlap); IR (thin film) cm^{-1} 3030w, 2925w, 1956w, 1729s, 1681m, 1372m; mass spectrum (LCMS-APCI): *m/e* (% relative intensity) 347 (100) $(M+H)^+$, 191 (25); HRMS-ESI *m/e* calcd for $C_{22}H_{22}N_2O_2Na$ 369.1573, found 369.1583.

4.1.9. Allene 23. $R_f=0.40$ (25% EtOAc in hexane); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) major isomer: δ 3.34 (d, 1H, $J=2.4$ Hz), 3.37 (d, 1H, $J=2.7$ Hz), 4.67 (ddd, 1H, $J=1.6$, 6.0, 11.1 Hz), 4.76 (ddd, 1H, $J=1.4$, 6.2, 13.8 Hz), 4.83 (d, 1H, $J=5.1$ Hz), 5.26–5.33 (ddd, 1H, $J=2.0$, 5.1, 7.2 Hz), 5.63–5.76 (m, 1H), 6.01 (d, 1H, $J=7.2$ Hz), 7.16–7.54 (m, 9H); minor isomer: δ 3.34 (d, 1H, $J=2.4$ Hz), 3.37 (d, 1H, $J=2.7$ Hz), 4.67 (ddd, 1H, $J=1.6$, 6.0, 11.1 Hz), 4.76 (ddd, 1H, $J=1.4$, 6.2, 13.8 Hz), 4.81 (d, 1H, $J=4.5$ Hz), 5.16–5.22 (ddd, 1H, $J=3.1$, 4.1, 6.9 Hz), 5.63–5.76 (m, 1H), 5.90 (d, 1H, $J=6.9$ Hz), 7.16–7.54 (m, 9H); IR (thin film) cm^{-1} 3064 (w), 3031 (w), 1956 (m), 1778 (s), 1696 (s), 1365 (s), 1191 (s), 856 (m); mass spectrum (APCI): *m/e* (% relative intensity) 331 (100) $(M)^+$, 306 (34), 289 (25), 176 (86), 157 (40); HRMS-ESI HRMS-ESI *m/e* calcd for $C_{21}H_{17}NO_3Na$ 354.1101, found 354.1116.

4.1.10. Allene 32. $R_f=0.44$ (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.88 (t, 3H, $J=6.5$ Hz), 1.21–1.33 (m, 4H), 1.64 (t, 3H, $J=3.0$ Hz), 1.60–1.68 (m, 1H), 1.70–1.78 (m, 1H), 4.29 (t, 1H, $J=6.5$ Hz), 4.40 (d, 2H, $J=6.0$ Hz), 4.72 (m, 3H), 5.34 (q, 1H, $J=5.0$ Hz), 7.11–7.15 (m, 4H), 7.24–7.34 (m, 6H); IR (thin film) cm^{-1} 3062 (m), 3027 (m), 2926 (w), 1715 (s), 1604 (m); mass spectrum (APCI): *m/e* (% relative intensity) 404 (43) $(M+H)^+$, 378 (20), 254 (23), 151 (100), 123 (21); HRMS-ESI *m/e* calcd for $C_{26}H_{29}NO_3Na$ 426.2040, found 426.2036.

4.1.11. Allene 33. $R_f=0.42$ (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer δ 0.88 (t, 3H, $J=7.5$ Hz), 1.30–1.43 (m, 4H), 1.76–1.87 (m, 2H), 4.44 (d, 2H, $J=6.0$ Hz), 4.69 (d, 1H, $J=4.0$ Hz), 5.08 (tt, 1H, $J=1.5$, 7.5 Hz), 5.24 (dd, 2H, $J=1.5$, 7.5 Hz), 5.27–5.30 (m, 1H), 6.88 (d, 2H, $J=7.5$ Hz), 7.02 (d, 2H, $J=7.5$ Hz), 7.16–7.51 (m, 11H); IR (thin film) cm^{-1} 2954 (m), 2923 (m), 2857 (w), 1776 (s), 1701 (s); mass spectrum (APCI): *m/e* (% relative intensity) 466 (16) $(M+H)^+$, 440 (11), 254 (6), 213

(100), 185 (7); HRMS-ESI *m/e* calcd for $C_{31}H_{32}NO_3$ 466.2377, found 466.2378.

4.2. Employing chiral propargyl alcohols

4.2.1. Allene 36. R_f=0.38 (25% EtOAc in hexanes); clear oil; $[\alpha]_D^{23}$ −68.2 (*c* 0.51, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.62 (dd, 3H, *J*=3.0, 7.0 Hz), 3.66 (ddq, 2H, *J*=2.5, 7.0, 18.0 Hz), 4.31 (dd, 1H, *J*=3.5, 9.0 Hz), 4.71 (t, 1H, *J*=9.0 Hz), 5.09–5.16 (m, 1H), 5.21 (dddd, 1H, *J*=2.5, 3.0, 7.0, 7.0 Hz), 5.44 (dd, 1H, *J*=3.5, 9.0 Hz), 7.27–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 36.1, 57.5, 70.0, 82.5, 86.7, 125.9, 128.6, 129.0, 138.7, 153.2, 170.4, 205.9; IR (thin film) cm^{-1} 2970 (m), 2961 (m), 2925 (m), 2870 (w), 1776 (s), 1705 (s); mass spectrum (APCI): *m/e* (% relative intensity) 258 (23) $(M+H)^+$, 164 (28), 146 (26), 120 (100), 95 (92), 87 (21); HRMS-EI *m/e* calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1045.

4.2.2. Allene 37. R_f=0.38 (25% EtOAc in hexanes); clear oil; $[\alpha]_D^{23}$ −51.6 (*c* 0.60, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.62 (dd, 3H, *J*=3.0, 7.0 Hz), 3.66 (ddq, 2H, *J*=2.5, 7.0, 18.0 Hz), 4.31 (dd, 1H, *J*=3.5, 9.0 Hz), 4.71 (t, 1H, *J*=9.0 Hz), 5.09–5.16 (m, 1H), 5.21 (dddd, 1H, *J*=2.5, 3.0, 7.0, 7.0 Hz), 5.44 (dd, 1H, *J*=3.5, 9.0 Hz), 7.27–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 36.1, 57.5, 70.0, 82.5, 86.7, 125.9, 128.6, 129.0, 138.7, 153.2, 170.4, 205.9; IR (thin film) cm^{-1} 2970 (m), 2961 (m), 2925 (m), 2870 (w), 1776 (s), 1705 (s); mass spectrum (APCI): *m/e* (% relative intensity) 258 (23) $(M+H)^+$, 164 (28), 146 (26), 120 (100), 95 (92), 87 (21); HRMS-EI *m/e* calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1050.

4.2.3. Allene 38. R_f=0.42 (25% EtOAc in hexanes); mp 92–94 °C; $[\alpha]_D^{23}$ −122.0 (*c* 0.91, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.86–0.89 (m, 3H), 1.25–1.32 (m, 4H), 1.49–1.56 (m, 1H), 1.70 (dd, 3H, *J*=3.0, 7.0 Hz), 1.71–1.77 (m, 1H), 4.23 (dq, 1H, *J*=1.0, 7.5 Hz), 4.41 (dd, 1H, *J*=3.0, 9.0 Hz), 4.44 (t, 1H, *J*=9.0 Hz), 4.72 (d, 1H, *J*=5.5 Hz), 5.05 (ddt, 1H, *J*=3.5, 7.5, 11.5 Hz), 5.22 (ddq, 1H, *J*=2.0, 7.5, 7.5 Hz), 5.34 (ddd, 1H, *J*=3.5, 5.5, 8.5 Hz), 7.10–7.15 (m, 4H), 7.25–7.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.2, 29.1, 31.0, 43.3, 50.4, 56.2, 64.5, 87.3, 89.0, 126.9, 127.7, 128.2, 128.6, 128.7, 129.4, 137.8, 139.4, 152.8, 174.1, 205.4 (missing 1 signal due to overlap of the terminal allene carbons); IR (thin film) cm^{-1} 2956 (m), 2922 (m), 2854 (w), 1781 (s), 1691 (s); mass spectrum (APCI): *m/e* (% relative intensity) 404 (75) $(M+H)^+$, 378 (21), 360 (20), 254 (33), 193 (18), 151 (100); HRMS-EI *m/e* calcd for $C_{26}H_{29}NO_3$ 403.2147, found 403.2137.

4.2.4. Allene 39. R_f=0.42 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.86–0.89 (m, 3H), 1.24–1.32 (m, 4H), 1.51–1.59 (m, 1H), 1.70 (dd, 3H, *J*=3.0, 7.0 Hz), 1.71–1.78 (m, 1H), 4.15 (dq, 1H, *J*=1.0, 7.5 Hz), 4.36–4.46 (m, 2H), 4.74 (d, 1H, *J*=5.0 Hz), 5.08–5.14 (m, 1H), 5.20 (ddq, 1H, *J*=2.0, 7.5, 7.5 Hz), 5.30–5.34 (m, 1H), 7.10–7.15 (m, 4H), 7.25–7.33 (m, 6H); minor isomer: δ 0.86–0.89 (m, 3H), 1.24–1.32 (m, 4H), 1.51–1.59 (m, 1H), 1.63 (dd, 3H, *J*=3.0, 7.0 Hz), 1.71–1.78 (m, 1H), 4.10 (dq, 1H, *J*=1.0, 7.5 Hz), 4.36–4.46 (m, 2H), 4.69 (d, 1H, *J*=5.0 Hz), 5.08–5.14 (m, 1H), 5.20 (ddq, 1H, *J*=2.0, 7.5, 7.5 Hz), 5.30–5.34 (m, 1H), 7.10–7.15 (m, 4H), 7.25–7.33 (m, 6H); IR (thin film) cm^{-1} 2956 (m), 2922 (m), 2854 (w), 1781 (s), 1691 (s); mass spectrum (APCI): *m/e* (% relative intensity) 404 (75) $(M+H)^+$, 378 (21), 360 (20), 254 (33), 193 (18), 151 (100); HRMS-EI *m/e* calcd for $C_{26}H_{29}NO_3$ 403.2147, found 403.2140.

4.2.5. Allene 40. R_f=0.41 (25% EtOAc in hexanes); mp 74–75 °C; $[\alpha]_D^{23}$ −16.7 (*c* 1.26, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.25–1.27 (m, 4H), 1.51 (dd, 3H, *J*=3.5, 7.0 Hz), 1.53–1.57 (m, 1H), 1.73–1.80 (m, 1H), 4.26 (dd, 1H, *J*=4.5, 9.0 Hz), 4.26–4.30 (m, 1H), 4.69 (t, 1H, *J*=9.0 Hz), 5.11–5.17 (m, 2H), 5.45 (dd, 1H, *J*=4.5, 9.0 Hz), 7.29–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 29.2, 30.9, 43.2, 57.7, 69.7, 87.7, 88.6, 125.8, 128.5, 129 .0, 138.8, 153.1, 173.4, 205.3 (missing 1 signal due to overlap of the terminal allene carbons); IR (thin film) cm^{-1} 2960 (m), 2927 (m), 2859 (w), 1780 (s), 1704 (s); mass spectrum (APCI): *m/e* (% relative intensity) 314 (33) $(M+H)^+$, 270 (15), 164 (20), 151 (100), 123 (36), 120 (46); HRMS-EI *m/e* calcd for $C_{19}H_{23}NO_3$ 313.1677, found 313.1676.

4.2.6. Allene 42a. R_f=0.43 (25% EtOAc in hexanes); mp 95–97 °C; $[\alpha]_D^{23}$ −8.7 (*c* 0.60, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.86–1.02 (m, 5H), 1.06–1.20 (m, 2H), 1.24–1.36 (m, 4H), 1.49–1.63 (m, 6H), 1.70–1.88 (m, 3H), 4.25 (dd, 1H, *J*=4.0, 9.0 Hz), 4.27 (dq, 1H, *J*=2.0, 6.5 Hz), 4.69 (t, 1H, *J*=9.0 Hz), 5.20 (dt, 1H, *J*=4.0, 6.0 Hz), 5.23 (dt, 1H, *J*=4.0, 6.0 Hz), 5.45 (dd, 1H, *J*=4.0, 9.0 Hz), 7.26–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 26.0, 26.1, 29.4, 30.5, 32.8, 32.9, 37.0, 37.2, 43.2, 57.7, 69.8, 90.0, 99.5, 125.9, 128.6, 129.1, 138.9, 153.4, 173.5, 203.7; IR (thin film) cm^{-1} 2924 (m), 2859 (w), 1785 (s), 1707 (s), 1457 (m), 1379 (m); mass spectrum (APCI): *m/e* (% relative intensity) 382 (66) $(M+H)^+$, 219 (100), 191 (6), 164 (8), 120 (9); HRMS-EI *m/e* calcd for $C_{24}H_{31}NO_3$ 381.2304, found 381.2300.

4.2.7. Allene *ent*-42a/*ent*-42b. R_f=0.43 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer **a**: δ 0.86–1.02 (m, 5H), 1.06–1.20 (m, 2H), 1.24–1.36 (m, 4H), 1.49–1.63 (m, 6H), 1.70–1.88 (m, 3H), 4.28 (dd, 1H, *J*=4.0, 9.0 Hz), 4.34 (dq, 1H, *J*=2.0, 6.5 Hz), 4.67 (t, 1H, *J*=9.0 Hz), 5.20 (dt, 1H, *J*=2.0, 6.0 Hz), 5.26–5.31 (m, 1H), 5.43 (dd, 1H, *J*=4.0, 9.0 Hz), 7.26–7.40 (m, 5H); minor isomer **b**: δ 0.86–1.02 (m, 5H), 1.06–1.20 (m, 2H), 1.24–1.36 (m, 4H), 1.49–1.63 (m, 6H), 1.70–1.88 (m, 3H), 4.26 (dd, 1H, *J*=4.0, 9.0 Hz), 4.34 (dq, 1H, *J*=2.0, 6.5 Hz), 4.67 (t, 1H, *J*=9.0 Hz), 4.96 (dt, 1H, *J*=2.0, 6.5 Hz), 5.23–5.26 (m, 1H), 5.45 (dd, 1H, *J*=4.0, 9.0 Hz), 7.26–7.40 (m, 5H); IR (thin film) cm^{-1} 2924 (m), 2859 (w), 1785 (s), 1707 (s), 1457 (m), 1379 (m); mass spectrum (APCI): *m/e* (% relative intensity) 382 (66) $(M+H)^+$, 219 (100), 191 (6), 164 (8), 120 (9); HRMS-EI *m/e* calcd for $C_{24}H_{31}NO_3$ 381.2304, found 381.2310.

4.2.8. Allene 44. R_f=0.39 (25% EtOAc in hexanes); mp 50–51 °C; $[\alpha]_D^{23}$ −18.4 (*c* 0.38, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*=7.0 Hz), 0.90 (t, 3H, *J*=7.0 Hz), 1.22–1.25 (m, 4H), 1.26–1.36 (m, 6H), 1.52–1.56 (m, 1H), 1.74–1.79 (m, 1H), 1.84–1.89 (m, 2H), 4.25 (dd, 1H, *J*=4.0, 9.0 Hz), 4.29 (dq, 1H, *J*=2.5, 8.0 Hz), 4.69

(t, 1H, J=9.0 Hz), 5.14–5.19 (m, 2H), 5.45 (dd, 1H, J=4.0, 9.0 Hz), 7.14–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 13.9, 22.3, 22.4, 28.4, 28.6, 29.2, 30.8, 31.1, 43.3, 57.6, 69.6, 89.1, 93.1, 125.7, 128.4, 128.9, 138.7, 153.1, 173.4, 204.5; IR (thin film) cm^{-1} 2965 (m), 2930 (m), 2925 (m), 2860 (w), 1777 (s), 1702 (s); mass spectrum (APCI): *m/e* (% relative intensity) 370 (40) $(M+H)^+$, 326 (7), 207 (100), 164 (6), 120 (12); HRMS-EI *m/e* calcd for $C_{23}H_{31}NO_3$ 369.2304, found 369.2296.

4.2.9. Allene *ent*-44. R_f=0.39 (25% EtOAc in hexanes); mp 52–53 °C; $[\alpha]_D^{23}$ +13.0 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, J=7.0 Hz), 0.90 (t, 3H, J=7.0 Hz), 1.22–1.25 (m, 4H), 1.26–1.36 (m, 6H), 1.52–1.56 (m, 1H), 1.74–1.79 (m, 1H), 1.84–1.89 (m, 2H), 4.25 (dd, 1H, J=4.0, 9.0 Hz), 4.29 (dq, 1H, J=2.5, 8.0 Hz), 4.69 (t, 1H, J=9.0 Hz), 5.14–5.19 (m, 2H), 5.45 (dd, 1H, J=4.0, 9.0 Hz), 7.14–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 13.9, 22.3, 22.4, 28.4, 28.6, 29.2, 30.8, 31.1, 43.3, 57.6, 69.6, 89.1, 93.1, 125.7, 128.4, 128.9, 138.7, 153.1, 173.4, 204.5; IR (thin film) cm^{-1} 2965 (m), 2930 (m), 2925 (m), 2860 (w), 1777 (s), 1702 (s); mass spectrum (APCI): *m/e* (% relative intensity) 370 (40) $(M+H)^+$, 326 (7), 207 (100), 164 (6), 120 (12); HRMS-EI *m/e* calcd for $C_{23}H_{31}NO_3$ 369.2304, found 369.2299.

4.2.10. Allene 46. R_f=0.25 (25% EtOAc in hexanes); mp 84–86 °C; $[\alpha]_D^{23}$ +98.7 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz), 1.29–1.40 (m, 4H), 1.61–1.64 (m, 1H), 1.83–1.85 (m, 1H), 4.25 (dd, 1H, J=4.0, 9.0 Hz), 4.45 (dq, 1H, J=2.0, 7.0 Hz), 4.70 (t, 1H, J=9.0 Hz), 5.45 (dd, 1H, J=4.0, 9.0 Hz), 5.70 (t, 1H, J=7.0 Hz), 6.19 (dd, 1H, J=2.0, 7.0 Hz), 7.13–7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 29.6, 30.8, 43.5, 57.9, 69.9, 93.7, 97.0, 126.0, 126.7, 126.9, 128.6, 128.7, 129.1, 134.0, 140.2, 153.4, 173.2, 205.6; IR (thin film) cm^{-1} 2964 (m), 2933 (m), 2865 (w), 1781 (s), 1707 (m); mass spectrum (APCI): *m/e* (% relative intensity) 376 (20) $(M+H)^+$, 332 (8), 213 (100), 185 (16), 120 (7); HRMS-EI *m/e* calcd for $C_{24}H_{25}NO_3$ 375.1834, found 375.1838.

4.2.11. Allene 47. R_f=0.25 (25% EtOAc in hexanes); mp 95–97 °C; $[\alpha]_D^{23}$ −150.8 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz), 1.26–1.40 (m, 4H), 1.58–1.65 (m, 1H), 1.83–1.89 (m, 1H), 4.29 (dd, 1H, J=4.0, 9.0 Hz), 4.42 (dq, 1H, J=2.0, 7.0 Hz), 4.70 (t, 1H, J=9.0 Hz), 5.47 (dd, 1H, J=4.0, 8.5 Hz), 5.73 (t, 1H, J=7.0 Hz), 6.00 (dd, 1H, J=2.0, 7.0 Hz), 7.15–7.56 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 29.5, 31.3, 43.5, 57.7, 69.8, 93.6, 96.8, 126.0, 126.6, 126.8, 128.6, 128.7, 129.2, 133.8, 138.8, 153.3, 172.8, 205.5; IR (thin film) cm^{-1} 2964 (m), 2933 (m), 1781 (s), 1707 (m), 1385 (m); mass spectrum (APCI): *m/e* (% relative intensity) 376 (20) $(M+H)^+$, 332 (8), 213 (100), 185 (16), 120 (7); HRMS-EI *m/e* calcd for $C_{24}H_{25}NO_3$ 375.1834, found 375.1830.

4.2.12. Allene 48. R_f=0.25 (25% EtOAc in hexanes); mp 86–87 °C; $[\alpha]_D^{23}$ −99.1 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz), 1.29–1.40 (m, 4H), 1.61–1.64 (m, 1H), 1.83–1.85 (m, 1H), 4.25 (dd, 1H, J=4.0, 9.0 Hz), 4.45 (dq, 1H, J=2.0, 7.0 Hz), 4.70 (t, 1H, J=9.0 Hz), 5.45 (dd, 1H, J=4.0, 9.0 Hz), 5.70 (t, 1H, J=7.0 Hz), 6.19 (dd, 1H, J=2.0, 7.0 Hz), 7.13–7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 29.6, 30.8, 43.5, 57.9, 69.9, 93.7, 97.0, 126.0, 126.7, 126.9, 128.6, 128.7, 129.1, 134.0, 140.2, 153.4, 173.2, 205.6; IR (thin film) cm^{-1} 2964 (m), 2933 (m), 2865 (w), 1781 (s), 1385 (m); mass spectrum (APCI): *m/e* (% relative intensity) 376 (20) $(M+H)^+$, 332 (8), 213 (100), 185 (16), 120 (7); HRMS-EI *m/e* calcd for $C_{24}H_{25}NO_3$ 375.1834, found 375.1833.

4.2.13. Allene 49. R_f=0.25 (25% EtOAc in hexanes); mp 81–83 °C; $[\alpha]_D^{23}$ +126.5 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz), 1.26–1.40 (m, 4H), 1.58–1.65 (m, 1H), 1.83–1.89 (m, 1H), 4.29 (dd, 1H, J=4.0, 9.0 Hz), 4.42 (dq, 1H, J=2.0, 7.0 Hz), 4.70 (t, 1H, J=9.0 Hz), 5.47 (dd, 1H, J=4.0, 8.5 Hz), 5.73 (t, 1H, J=7.0 Hz), 6.00 (dd, 1H, J=2.0, 7.0 Hz), 7.15–7.56 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 29.5, 31.3, 43.5, 57.7, 69.8, 93.6, 96.8, 126.0, 126.6, 126.8, 128.6, 128.7, 129.2, 133.8, 138.8, 153.3, 172.8, 205.5; IR (thin film) cm^{-1} 2964 (m), 2933 (m), 2865 (w), 1781 (s); mass spectrum (APCI): *m/e* (% relative intensity) 376 (20) $(M+H)^+$, 332 (8), 213 (100), 185 (16), 120 (7); HRMS-EI *m/e* calcd for $C_{24}H_{25}NO_3$ 375.1834, found 375.1827.

4.2.14. Allene 52. R_f=0.50 (25% EtOAc in hexanes); clear oil; $[\alpha]_D^{23}$ −94.0 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, J=7.0 Hz), 0.92 (t, 3H, J=7.0 Hz), 1.24–1.28 (m, 2H), 1.32–1.42 (m, 6H), 1.52–1.55 (m, 2H), 1.71–1.92 (m, 4H), 4.18 (dd, 1H, J=4.5, 9.0 Hz), 4.65 (t, 1H, J=9.0 Hz), 5.05 (dt, 1H, J=2.0, 7.0 Hz), 5.44 (dd, 1H, J=4.5, 9.0 Hz), 5.53 (dt, 1H, J=2.0, 7.0 Hz), 7.18–7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.3, 22.6, 28.4, 29.0, 29.8, 31.3, 31.6, 43.5, 57.8, 65.5, 69.5, 90.1, 96.5, 125.7, 126.3, 128.1, 128.2, 128.8, 131.5, 136.5, 138.4, 153.4, 173.3, 204.5; IR (thin film) cm^{-1} 2960 (m), 2932 (m), 2862 (w), 1784 (s), 1702 (s); mass spectrum (APCI): *m/e* (% relative intensity) 446 (8) $(M+H)^+$, 284 (22), 283 (100); HRMS-EI *m/e* calcd for $C_{29}H_{35}NO_3$ 445.2617, found 445.2615.

4.2.15. Allene 53. R_f=0.48 (25% EtOAc in hexanes); clear oil; $[\alpha]_D^{23}$ −47.5 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, 3H, J=7.0 Hz), 0.92 (t, 3H, J=7.0 Hz), 0.94–0.97 (m, 2H), 1.07–1.32 (m, 12H), 1.55–1.80 (m, 9H), 4.24 (dd, 1H, J=4.5, 8.5 Hz), 4.41 (t, 1H, J=7.0 Hz), 4.67 (t, 1H, J=8.5 Hz), 5.16–5.18 (m, 1H), 5.46 (dd, 1H, J=4.5, 8.5 Hz), 7.28–7.36 (m, 5H);^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.2, 22.2, 22.5, 25.8, 26.0, 27.9, 29.5, 29.6, 30.2, 30.7, 33.0, 37.5, 44.2, 46.2, 57.7, 67.3, 100.1, 103.1, 125.9, 128.4, 128.8, 138.8, 153.3, 173.6, 200.9; IR (thin film) cm^{-1} 2958 (m), 2940 (m), 2856 (w), 1784 (s), 1701 (s); mass spectrum (APCI): *m/e* (% relative intensity) 438 (73) $(M+H)^+$, 394 (7), 340 (10), 275 (100), 177 (17); HRMS-EI *m/e* calcd for $C_{28}H_{39}NO_3$ 437.2930, found 437.2920.

4.2.16. Allene 54. R_f=0.39 (25% EtOAc in hexanes); clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.81–0.91 (m, 6H), 1.21–1.57 (m, 11H), 1.70–2.01 (m, 3H), 4.26 (dd, 1H, J=4.2, 9.0 Hz), 4.31–4.36 (m, 1H), 4.68 (t, 1H, J=9.0 Hz), 5.19–5.25 (m, 2H), 5.45 (t, 1H, J=9.0 Hz), 7.27–7.40 (m, 5H); minor isomer: δ 0.81–0.91 (m, 6H), 1.21–1.57

(m, 11H), 1.70–2.01 (m, 3H), 4.28 (dd, 1H, J=4.2, 9.0 Hz), 4.31–4.36 (m, 1H), 4.70 (t, 1H, J=9.0 Hz), 4.98 (dq, 1H, J=1.8, 6.6 Hz), 5.20–5.25 (m, 1H), 5.44 (t, 1H, J=9.0 Hz), 7.27–7.40 (m, 5H); IR (thin film) cm^{-1} 2965 (m), 2930 (m), 2925 (m), 2860 (w), 1777 (s), 1702 (s); mass spectrum (APCI): *m/e* (% relative intensity) 370 (46) $(M+H)^+$, 326 (9), 207 (100), 120 (26), 87 (12); HRMS-EI *m/e* calcd for $C_{23}H_{31}NO_3$ 369.2304, found 369.2300.

4.2.17. Hydrogenated product 55. R_f=0.39 (25% EtOAc in hexanes); clear oil; ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 0.77 (t, 3H, J=6.9 Hz), 0.85–0.91 (m, 3H), 0.88 (t, 3H, J=6.9 Hz), 0.98–1.08 (m, 4H), 1.14–1.29 (m, 8H), 1.36–1.46 (m, 3H), 1.51–1.67 (m, 2H), 3.77–3.86 (m, 1H), 4.26 (dd, 1H, J=3.9, 9.0 Hz), 4.68 (t, 1H, J=9.0 Hz), 5.46 (dd, 1H, J=3.9, 9.0 Hz), 7.27–7.40 (m, 5H); minor isomer: δ 0.77 (t, 3H, J=6.9 Hz), 0.85–0.91 (m, 3H), 0.88 (t, 3H, J=6.9 Hz), 0.98–1.08 (m, 4H), 1.14–1.29 (m, 8H), 1.36–1.46 (m, 3H), 1.51–1.67 (m, 2H), 3.77–3.86 (m, 1H), 4.27 (dd, 1H, J=3.9, 9.0 Hz), 4.68 (t, 1H, J=9.0 Hz), 5.46 (dd, 1H, J=3.9, 9.0 Hz), 7.27–7.40 (m, 5H); IR (thin film) cm^{-1} 2955 (m), 2942 (m), 2862 (w), 1782 (s), 1703 (s); mass spectrum (APCI): *m/e* (% relative intensity) 374 (100) $(M+H)^+$, 282 (22), 211 (22), 183 (75), 164 (82), 120 (23); HRMS-EI *m/e* calcd for $C_{23}H_{35}NO_3$ 373.2617, found 373.2612.

4.2.18. Hydrogenated product 56. R_f=0.25 (25% EtOAc in hexanes); clear oil; $[\alpha]_D^{23}$ −32.9 (*c* 0.42, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=6.9 Hz), 1.24–1.28 (m, 4H), 1.33–1.52 (m, 4H), 1.54–1.70 (m, 2H), 2.48 (t, 2H, J=7.5 Hz), 3.89 (dddd, 1H, J=5.1, 7.8, 10.5, 13.2 Hz), 4.27 (dd, 1H, J=6.9, 9.0 Hz), 4.69 (t, 1H, J=9.0 Hz), 5.46 (dd, 1H, J=6.9, 9.0 Hz), 7.03–7.05 (m, 2H), 7.18–7.37 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.8, 28.5, 29.5, 31.5, 32.4, 35.8, 42.5, 57.8, 69.6, 125.6, 126.0, 128.2, 128.3, 128.7, 129.1, 139.2, 142.1, 153.4, 176.4; IR (thin film) cm^{-1} 2955 (m), 2942 (m), 2862 (w), 1782 (s), 1703 (s); mass spectrum (APCI): *m/e* (% relative intensity) 380 (100) $(M+H)^+$, 217 (22), 189 (73), 164 (49), 87 (41); HRMS-EI *m/e* calcd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2155.

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30. These calculations were carried out with some constraints. Specifically, the terminal alkyne carbon and C2 in **58b**-*Re* and **58b**-*Si* were placed within proximity (2.31 Å) of bond formation in transition states. PM3 calculations showed an energetic difference of 1.3 Kcal mol^{-1} in favor of **58b**-*Re* when R^2=*c*-hex.