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Metal free regio – and stereoselective semireduction of CF₃-substituted *N*-allenamides†

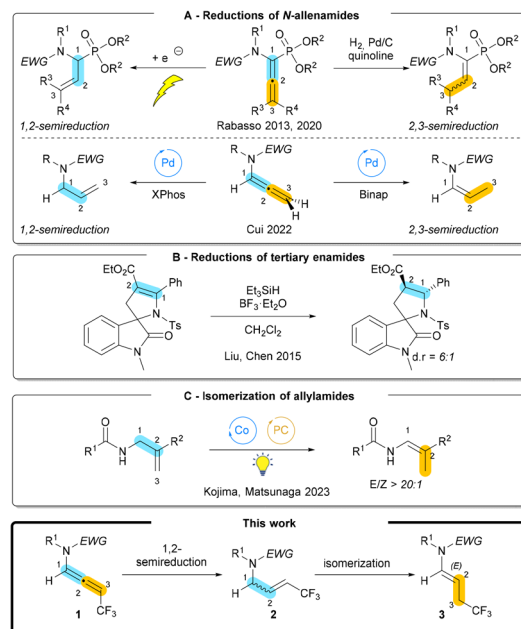Clément Gommenginger, [ID] ‡ Maxime Hourtoule, [ID] ‡ Marco Menghini [ID] and Laurence Miesch [ID] *

We developed a chemoselective metal-free access for the 1,2- and 2,3-semireduction of CF₃-*N*-allenamides. The enamide functionality of CF₃-substituted *N*-allenamides could be efficiently reduced by Et₃SiH/BF₃·OEt₂ in total regioselectivity and good stereoselectivity, whereas DBU promoted the isomerization of the resulting allyl amide leading exclusively to the *E*-configured enamide.

Introduction

Allenamides represent a privileged subclass of allenes and have become key substrates in myriad transformations,[1] including those leading to the construction of nitrogen-containing scaffolds.[2] Regioselective semireduction of *N*-allenamides paves the way for the synthesis of both enamides and allylic amides, two ubiquitous classes of synthetic intermediates critical for the synthesis of heterocyclic compounds. Enamides and allylic amides represent bioactive pharmacophores in drug molecules and have become more popular reagents for the incorporation of nitrogen-based functional groups.[3] In particular, unsaturated nitrogen containing fluorinated compounds are of ongoing interest in synthetic methodologies.[4] Nonetheless, the semireduction of allenes is confronted with significant challenges such as the control of chemo-, regio-, and stereo-selectivities. Both π-bonds can be reduced to the corresponding alkane, and the differentiation of 1,2- *vs.* 2,3-semireduction becomes complicated.[5] Furthermore, the stereocontrol of the formed alkene adds another challenge to the problematic semireduction of allenes. In the case of *N*-allenamides, the problems remain and in addition, these points have been less explored for those substrates. Specific semireduction has been examined by classical

methods and specific tools including electrochemical reduction. Notably, Rabasso *et al.* have reported the chemo- and stereoselective reduction of α-amino allenylphosphonates to α-amino vinylphosphonates by using H₂ and a poisoned palladium catalyst.[6] Recently, these authors developed an electrochemical process to reduce the tertiary enamide moiety of α-amino allenylphosphonates (Scheme 1A).[7] More recently, Cui *et al.* reported a ligand-controlled regiodivergent semireduction. XPhos and BINAP allowed a switch between the 1,2- and 2,3-semireduction reactions with the same palladium pre-catalyst (Scheme 1A).[8]

Documented examples of either the reduction of tertiary enamides or the isomerization of allylamides are rare. In this regard, spirocyclic oxindoles have been efficiently reduced by a combination of Et₃SiH and BF₃·OEt₂ (Scheme 1B).[9] A combi-

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Scheme 1 Synthetic routes to allylic amides and enamides.

nation of cobalt and photoredox catalysis was used to promote an isomerization by a hydrogen atom transfer to produce poly-substituted enamides (Scheme 1C).[10]

Results and discussion

Herein we report a formal metal-free 1,2- and 2,3-semireduction of CF$_3$-substituted N-allenamides. Given the unusual reactivity of N-allenamides and inspired by literature precedents, we first examined the possibility of discriminating one functional group in our substrate *i.e.*, either the enamide-substituted alkene or the trifluoromethyl-functionalized olefin. Importantly, delocalization of the nitrogen lone pair toward the allenic moiety confers a dual reactivity to these entities and dictates the addition of a nucleophile α or γ to the nitrogen atom.[11] Trifluoromethylated N-allenamides were obtained by treatment of terminal ynamides with trifluoromethylated diazomethane according to our previously developed strategy.[12]

We anticipated that the enamide moiety would be reduced by using a mixture of a hydride source with a Lewis acid similar to systems used with simple enamides.[9,13] Gratifyingly, as shown in Table 1, when CF$_3$-N-allenamide **1** was exposed to a mixture of Et$_3$SiH and BF$_3$·OEt$_2$, N-allyl amide **2** was exclusively obtained as a E/Z mixture (85:15) with 90% yield (Table 1, entry 1). Next, diverse Lewis acids were investigated (Table 1, entries 2–6).
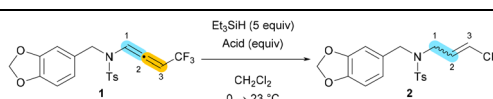
Whereas FeCl$_3$ only led to degradation of the starting material, InCl$_3$, TMSOTf, AgNTf$_2$ provided the desired 1,2-semireduction of the CF$_3$-N-allenamide **1**, although with lower

selectivities except for AgNTf$_2$ (Table 1, entry 6). Notably, the selectivity was inverted by employing AgOTf as Lewis acid (Table 1, entry 5). Even though the desired compound was obtained with triflic anhydride (Tf$_2$O), there was almost no selectivity in this case (Table 1, entry 7). Unfortunately, with AcOH instead of BF$_3$·OEt$_2$ the starting material was fully recovered (Table 1, entry 8). Replacing Et$_3$SiH by Hantzsch ester or lowering the amount of Et$_3$SiH was not effective (Table 1, entries 9 and 10). There was no significant erosion in selectivity when the loading of Lewis acid was lowered to 0.5 mol%, and a good yield (98%) was obtained in this case (Table 1, entry 11). Without any Lewis acid the reduction did not take place (Table 1, entry 12).

Using the determined optimal conditions, the scope of the reaction was examined (Table 2). Aryls (**2a–d**), hetero-aryls (**2m**), alkyls (**2e**), cycloalkyls (**2f–g**), as well as functionalized side-chains (**2h–l**) were accommodated in this transformation. The disubstituted N-allenamide **2n** underwent the 1,2-semireduction with 71% yield. Not only tosyl derivatives but also mesyl (**2o**), nosyl (**2q**), cyclopropyl (**2p**), thienyl (**2r**), as well as cyclic sulfonamides (**2s–t**) participated in this reduction. In this study, carbamates could not be investigated because we failed to obtain the corresponding CF$_3$-substituted N-allenamides.

Next, we wondered whether it would be possible to deprotonate the α-position of the nitrogen of the N-allyl-amide **2**. When the latter was treated with t-BuOK, enamide **3** was
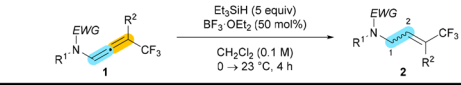
Table 1 Optimization of 1,2-semireduction of the CF$_3$-N-allenamide **1**

Entry[a]	Acid (equiv.)	Time (h)	Ratio E/Z[b]	Yield[c] (%)
1	BF$_3$·OEt$_2$ (5)	1	85:15	90
2	FeCl$_3$ (0.2)	1	—[d]	—[d]
3	InCl$_3$ (0.2)	6	75:25	89
4	TMSOTf (5)	1	60:40	34
5	AgOTf (0.2)	4	27:73	75
6	AgNTf$_2$ (0.2)	2	86:14	78
7	Tf$_2$O (5)	1	46:53	51
8	AcOH (5)	4	—[e]	—[e]
9[f]	BF$_3$·OEt$_2$ (5)	4	—[d]	—[d]
10[g]	BF$_3$·OEt$_2$ (1.2)	1	82:18	45
11	BF$_3$·OEt$_2$ (0.5)	4	82:18	98
12	—	18	—[e]	—[e]

[a] Reaction conditions: to a solution of **1** (0.15 mmol) in CH$_2$Cl$_2$ (1.5 mL), were added Et$_3$SiH (0.75 mmol) and the acid at 0 °C and then the mixture was stirred at 23 °C. [b] E/Z ratio was determined by ^{1}H-NMR-spectroscopy. [c] Isolated yields. [d] Only degradation of starting material was observed. [e] The starting material was fully recovered. [f] Hantzsch ester (5 equiv.) was used instead of Et$_3$SiH, and the reaction mixture was stirred at 40 °C. [g] 1.2 equiv. of Et$_3$SiH was used instead of 5 equiv.

**Table 2** Scope of the 1,2-semireduction of CF$_3$-N-allenamide **1**

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Table 3 Optimization of formal 2,3-semireduction of the CF$_3$-*N*-allenamide **1**

Entry[a]	Base (equiv.)	Yield[b] (%)
1	*t*-BuOK (5)	30
2	Cs$_2$CO$_3$ (5)	—[c]
3	TBAF (1M THF) (5)	48
4	TBAF (1M THF) (1.3)	57
5	Triton B (40% wt. CH$_3$OH) (5)	12
6	Triton B (40% wt. H$_2$O) (1.3)	66
7	Et$_3$N (5)	—[c]
8	TMG (1.3)	—[c]
9	DBU (1.3)	89
10	DBU (50 mol%)	78

[a] Reaction conditions: to a solution of **2** (0.10 mmol) in THF (1.0 mL), the base was added, and then the mixture was stirred at 23 °C for 18 h. [b] Isolated yields. [c] The starting material was fully recovered.

obtained, albeit with a moderate yield (Table 3, entry 1). The formation of an exclusive *E*-configured tertiary enamide **3** resulted formally in a 2,3-semireduction of CF$_3$-*N*-allenamide **1**. Whereas cesium carbonate was ineffective (Table 3, entry 2) for this reaction, tertiary ammonium salts showed acceptable yields of the target compound **3** (Table 3, entries 3–6). Although triethylamine (Et$_3$N) and tetramethyguanidine (TMG) were unproductive (Table 3, entries 7 and 8), 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) was well-suited for this transformation and provided the best yield for the formation of enamide **3** (Table 3, entry 9). Lowering the amount of DBU caused a decrease in the yield of the target compound (Table 3, entry 10).
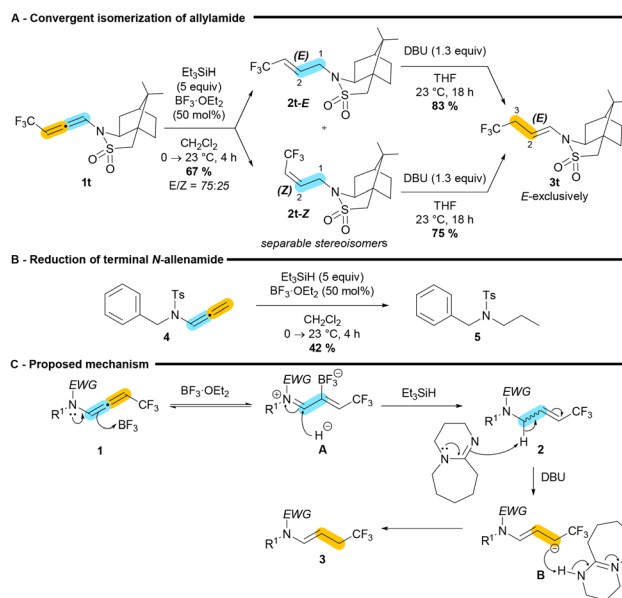
We then focused on the generality of this formal 2,3-semireduction. Various benzylamine derivatives were examined to react with DBU. As shown in Scheme 2, neutral (**3a**), different functional groups on the benzyl ring were tolerated (**3b–d**). Good yields were obtained as well with the disubstituted compound **3n**. X-Ray analyses of **3b** confirmed the structure of the *E*-configured enamide **3b** obtained (CCDC 2301994† contains the supplementary crystallographic data for the structure).[14] Linear alkyls (**3e**), cyclic alkyls (**3f–g**), as well as fluorinated side-chains (**3h**) on the nitrogen atom were compatible with this transformation. Moreover, the reaction proceeded smoothly in the presence of functionalized side-chains including unsaturated (**3i–j**), nitrile (**3k**), halogen (**3l**), disulfonamide (**3u**), pyridine (**3m**), as well as tetralone (**3v**) substituents. Enamides (**3u**, **3v**) were directly obtained in a sequential two step procedure from the corresponding *N*-allenamides because of the instability of allylamides **2u** and **2v**. Good yields were also obtained through modification of the electron-withdrawing group on the nitrogen atom (**3o–r**). Even the hindered cyclic sulfonamides exhibited good reactivity with the current protocol (**3s–t**).

To gain further insights into the reaction mechanism, we subjected *E*- and *Z*-configured allyl-amides **2t**-*E* and **2t**-*Z* to
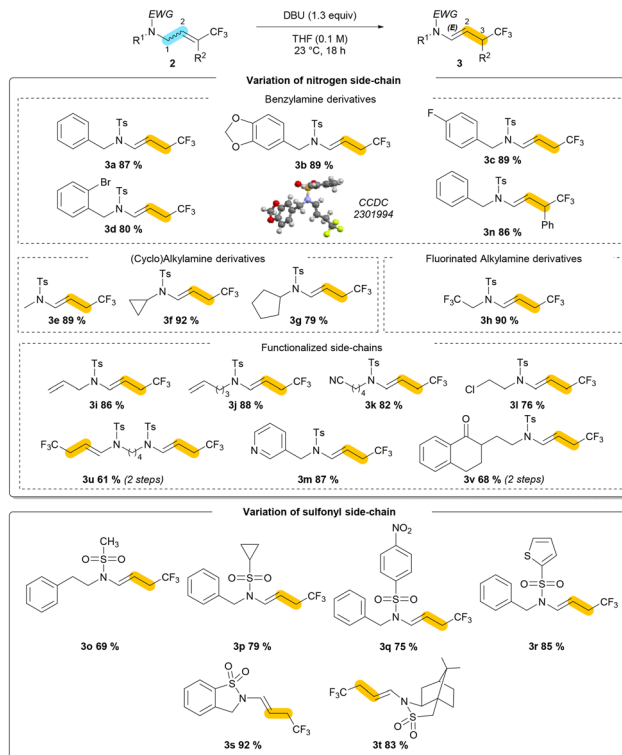
Scheme 2 Scope of the formal 2,3-semireduction of CF$_3$-*N*-allenamide **1**.

DBU. *E*-Enamide **3t** was the sole product formed in 83% and 75% yield, resepectively from the two isomeric starting materials (Scheme 3A), establishing that both stereoisomers **2t**-*E* and **2t**-*Z* react and form the same compound **3t**. Moreover, when terminal *N*-allenamide **4** was treated with

Scheme 3 Convergent isomerization, mechanical insight, and proposed mechanism.

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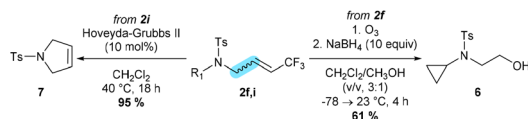
Scheme 4 Diversification of allylamides **2f** and **2i**.

Et$_3$SiH and BF$_3$·OEt$_2$, the totally reduced amide **5** was isolated in 42% yield, confirming that with unsubstituted *N*-allenamides **4**, a 1,4-addition of hydride takes place first, followed by reduction of the enamide formed (Scheme 3B).[11] Based on literature and on the experimental results, we propose the following mechanism (Scheme 3C). Activation of the CF$_3$-*N*-allenamide with BF$_3$·OEt$_2$ results in the formation of conjugated iminium ion **A**. Hydride addition occurs exclusively on the iminium ion, affording allylamides **2**.[13] No addition on the trifluoromethylated alkene has been observed. Accordingly, addition of Et$_3$SiH to CF$_3$-*N*-allenamide **1** (Table 1, entry 12) did not promote the addition of hydride on the trifluoromethyl-substituted alkene moiety. Deprotonation of **2** by DBU and subsequent delocalization of the carbanion α to the CF$_3$ moiety produces **B**. Protonation of the latter finally forms the thermodynamically more stable *E*-configured tertiary enamide **3**.

Unfortunately, when we tried to deprotect the nosyl group in **2q**, deprotection and isomerization took place simultaneously leading to an unstable enamine. We then carried out some additional transformations with allyl-amides as depicted in Scheme 4. Reductive ozonolysis of **2f** took place forming alcohol **6**, key building blocks for the construction of heterocyclic compounds in drug design.[15] Additionally, the requisite functionalized allyl-amide **2i** was transformed into unsaturated tosylsulfonamide **7** with good yields (Scheme 4).

Conclusions

In conclusion, we achieved a 1,2-semireduction of CF$_3$-substituted *N*-allenamides with Et$_3$SiH and BF$_3$·OEt$_2$. An isomerization of the formed allylamides in the presence of DBU resulted in a 2,3-semireduction of the CF$_3$-*N*-allenamide. We offer a metal-free facile and practical method for the regioselective access to various allylamides bearing a vinyl-CF$_3$ moiety as well as the formation of corresponding tertiary enamides. A wide variety of side chains could be adapted at the nitrogen atom including functional groups together with unique sulfonyl derivatives.

Author contributions

C. G. and M. H. contributed equally. L. M., C. G., and M. H. conceived and designed the experiments. L. M. directed the project. C. G., M. H., M. M. performed the experiments. L. M. wrote the paper. L. M., M. H., and

C. G. discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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