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Enamines as Surrogates of Alkene Carbanions for the Reductive Alkenylation of Secondary Amides: An Approach to Allylamines

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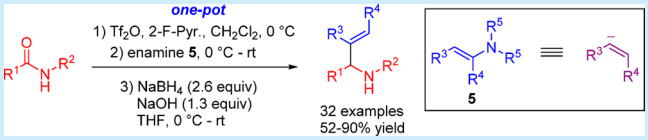
Supporting Information

ABSTRACT: A new strategy to construct allylamines through reductive alkenylation of secondary amides with enamines is reported. The method features the use of trifluoromethanesulfonic anhydride as an activation reagent of amides, and enamines as unconventional alkenylation reagents. In this manner, enamines serve as surrogates of alkene carbanions instead of the classical enolates equivalents. A possible mechanism involving a Hoffmann-like elimination of the amine−borane complex intermediate is proposed.



Amides are a class of readily available and stable compounds which are widespread in nature.[1] Compared with their utilization as synthetic modules, direct use of amides as versatile synthetic intermediates has been impeded by the low electrophilicity of amides. Until recently, considerable progress has been achieved for the direct conversion of amides into functional groups with lower oxidation states.[2−5]

As part of our long-term interest in developing amide based C−C bond-forming reactions,[5] our group has developed one-pot methods for the synthesis of secondary carbinamines by the reductive alkylation of amides using trifluoromethanesulfonic anhydride (Tf_2O) as the activation reagent[6] and organometallic reagents as nucleophiles. However, attempted extension of these methods to the synthesis of allylamines with less reactive vinylmetallic reagents was unsuccessful.[5a,b] More recently, we have disclosed an intermolecular alkenylation of secondary amides **1** with simple alkenes as C-nucleophiles for the preparation of α,β-unsaturated ketimines and α,β-enones **2** (Figure 1, eq 1).[5f] The method was extended to constructing 2-alkenylpyrrolidines and piperidines **3** (Figure 1, eq 2).[5g] However, only 1-aryl and 1,2-disubstituted alkenes could be used in these methods to introduce β-aryl or β,β-disubstituted alkenyl moieties. It is worth mentioning that the reaction with *N*-vinylacetamide resulted in the formation of saturated mono-*N*-acyl-1,3-diamine derivative **4** (Figure 1, eq 3). In addition, secondary amides should have an *N*-2,6-dimethylphenyl group to avoid possible side reactions. Therefore, development of a new method for the reductive alkenylation of amides with a wide substrate scope is desirable.

The seminal work of Stork in 1954 on the *C*-monomethylation of enamines (**5**)[7] inaugurated the use of enamines as stable and more reactive yet chemoselective surrogates of enols and enolates (Figure 2).[8]

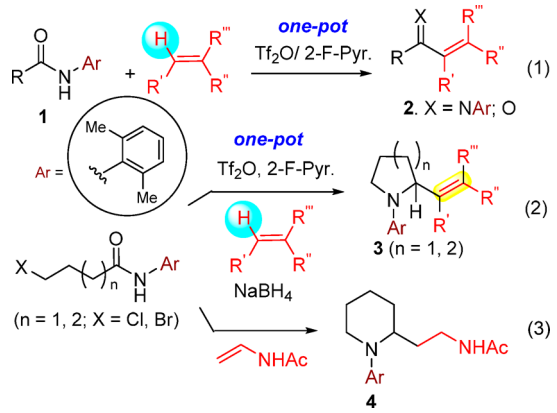


Figure 1. Transformations of secondary amides **1** via reductive alkenylation with alkenes.

More recently, enamines have been documented as key intermediates in several organocatalytic enantioselective reactions.[9] In all these reactions, enamines (**5**) serve as synthetic equivalents of enolates (**S-1**). We wish to report herein that enamines (**5**) can also be employed as surrogates of alkene carbanions (**S-2**) in the reaction with secondary amides.

Our work initiated with a serendipitous discovery: in reaction of Tf_2O activated benzamide **6a** with enamine **5a** followed by *in situ* reduction with 10.0 equiv of $NaBH_4$ in CH_3OH, the expected 1,3-diamine **7** was not isolated, but rather an allylic amine **8aa** was produced predominantly (Scheme 1).

Because allylic amines[10−18] represent an important structural motif frequently found in natural products,[19] pharmaceuticals (e.g., the antifungal drug naftifine,[20] the calcium channel blocker

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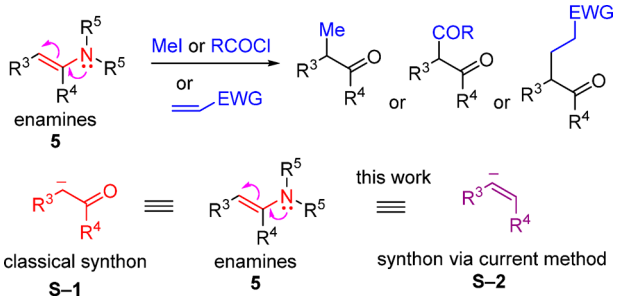
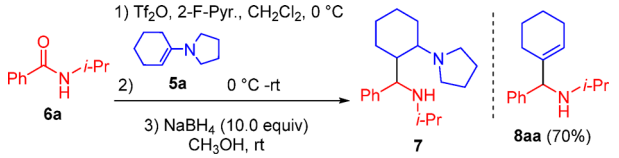


Figure 2. Enamines as synthetic equivalents of enolate (**S-1**) in the Stork enamine reactions and as the unconventional, mild, and regioselective surrogates of the alkene carbanions **S-2**.

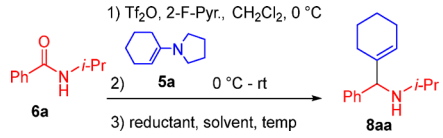
Scheme 1. Serendipitous Discovery from an Attempted Reduction of an Adduct of Benzamide 6a and Enamine 5a



flunarizine[21]), and biologically relevant compounds[22] and serve as versatile building blocks in organic synthesis, we decided to explore this reaction.

A variety of reductants were then screened (Table 1). When the reduction with $NaBH_4$ was performed in THF, 81% of allylamine **8aa** was produced (entry 2). Reduction with KBH_4, $LiBH_4$, and $NaBH_3CN$ also led to the formation of allylamine **8aa**, albeit with lower yields (entries 3–5). The reaction optimization (cf. SI for a complete table) showed the reduction with 8.0 equiv of $NaBH_4$ at 0 °C was optimal, which produced allylamine **8aa** in an isolated yield of 82% (entry 6). Further studies on the mechanism (Scheme 2) showed that the amount of $NaBH_4$ can be decreased to 2.6 equiv in the presence of 1.3 equiv of NaOH, which produced allylamine **8aa** in an isolated yield of 82% (entry 8). In this regard, $NaHCO_3$ was less efficient as a base (entry 7).

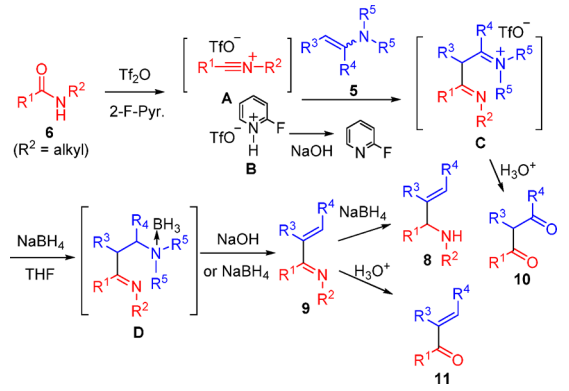
Table 1. Optimizations on Reductive Alkenylation of Secondary Amides with Enamines[a]



entry	reductant (equiv)	solvent	base (equiv)	8aa[b] (%)
1	$NaBH_4$(10.0)	CH_3OH		70 (70[c])
2	$NaBH_4$(10.0)	THF		81
3	KBH_4(10.0)	THF		62
4	$LiBH_4$(10.0)	THF		70
5	$NaBH_3CN$ (10.0)	HOAc		35
6	$NaBH_4$ (8.0)	THF		84 (82[c])
7	$NaBH_4$ (2.6)	THF	$NaHCO_3$(1.3)	47
8	$NaBH_4$ (2.6)	THF	NaOH (1.3)	82 (82[c])

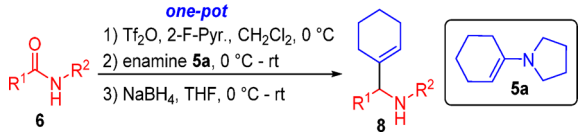
[a]Reaction conditions: Tf_2O (1.1 equiv), 2-F-Pyr. (1.2 equiv), CH_2Cl_2 (0.1 M), 0 °C, 20 min; then enamine (2.0 equiv), 0 °C to rt, 3 h; then reductant, 6 h; quenched by satd $NaHCO_3$. [b]Determined by ^1H NMR with Ph_3CH as internal standard. [c]Isolated yield.

Scheme 2. Possible Mechanism



Using $NaBH_4$ as the reductant, a wide array of secondary amides could undergo reductive alkenylation with enamines **5a** to produce the corresponding allylamines (Table 2). For benzamide derivatives, those bearing electron-donating groups on the phenyl ring (entries 2–5) gave higher yields than those having electron-withdrawing groups (entries 6–11). A variety of functional groups, such as halogen, nitro, cyano, and ester groups, are compatible under these reductive alkenylation conditions. It should be noted that the reaction could take place chemoselectively in the presence of an OAc group (entry

Table 2. Scope of Amides in Reductive Alkenylation of Secondary Amides with Enamines[a]



entry	R^1	R^2	product	yield[b] (%)
1	Ph	*i*-Pr	**8aa**	82 (82)[e]
2	*p*-MeC_6H_4	*i*-Pr	**8ba**	90 (89)[e]
3	*o*-MeC_6H_4	*i*-Pr	**8ca**	83
4	*p*-$AcOC_6H_4$	*i*-Pr	**8da**	87
5	*p*-$MeOC_6H_4$	*i*-Pr	**8ea**	85 (82)[e]
6	*p*-ClC_6H_4	*i*-Pr	**8fa**	58 (62)[e]
7	*o*-ClC_6H_4	*i*-Pr	**8ga**	60 (63)[e]
8	*p*-$O_2NC_6H_4$	*i*-Pr	**8ha**	54 (56)[e]
9	*p*-$MeO_2CC_6H_4$	*i*-Pr	**8ia**	70
10	*p*-NCC_6H_4	*i*-Pr	**8ja**	70 (72)[e]
11	*p*-$MeC(O)C_6H_4$	*i*-Pr	**8ka**	70[c]
12	2-Naphthyl	*i*-Pr	**8la**	82 (76)[e]
13	2-Thienyl	*i*-Pr	**8ma**	58
14	Ph	*c*-hex	**8na**	80
15	Ph	Et	**8oa**	81 (79)[e]
16	Ph	$(CH_2)_3OMe$	**8pa**	75
17	Ph	$(CH_2)_2CO_2Me$	**8qa**	81
18	Ph	$CH_2CH{=}CH_2$	**8ra**	60
19	Ph	Bn	**8sa**	63
20	*c*-hex	*i*-Pr	**8ta**	71
21	$MeO_2CCH_2CH_2CH_2$	*i*-Pr	**8ua**	65
22	Ph	2,6-diMePh	**8va**	–[d]
23	*t*-Bu	*i*-Pr	**8wa**	–[d]

[a]Reaction conditions: cf. Table 1, entry 6. [b]Isolated yield. [c]With concomitant reduction of the ketone group. [d]The reaction was complex with no desired product isolated. [e]Reaction conditions: cf. Table 1, entry 8.

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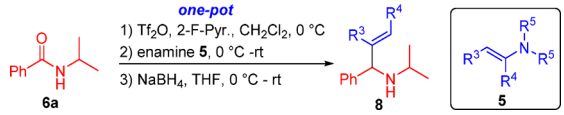
4), while concomitant reduction of the ketone carbonyl group was observed for keto amide (entry 11). The reductive alkenylation of sterically hindered 2-methylbenzamide **6c** and 2-chlorobenzamide **6g** also underwent smoothly to provide the desired products (entries 3 and 7). Other secondary aroyl amides, such as 2-naphthamide **6l** and thiophene-2-carboxamide **6m**, were also suitable substrates for the reaction. The *N*-substituents on the secondary aroyl amides could vary from alkyl substituents to benzyl or allyl group, and some functional groups such as ether and ester groups are tolerated (entries 14−19). The reductive alkenylation could also be extended to alkanamides (entries 20 and 21). High chemoselectivity was observed for ester amides **6u**, producing the corresponding ester amines **8ua** in 65% yield. However, *N*-(2,6-diMePh) amide and steric hindered pivalamide (entries 22 and 23) failed to give the desired allylamines.

The scope of the enamines was then investigated (Table 3). Besides pyrrolidine enamine of cyclohexanone **5a**, enamines

Table 3. Scope of Enamines in Reductive Alkenylation of Secondary Amides with Enamines[a]



enamine	product[b](%)	enamine	product[b](%)
5a	**8aa**, 82	**5h** E/Z > 50:1	(*E*)-**8ah**,[d] 63
5b / **5c**	**8ab** 38[c] from **5b**, 55 from **5c**	**5i**	(*Z*)-**8ai**,[d] 67[c]
5d	**8ad**, 58	**5j**	**8aj**, 70
5e	**8ae**, 70, dr = 1:1	**5k**	**8ak**, 52[c]
5f E/Z > 50:1	(*E*)-**8af**,[d] 63	**5l**	**8al**, 73[c]
5g	**8ag**, 52	**5m**	**8am**, trace

[a]Reaction conditions: cf. Table 1, entry 8. [b]Isolated yield. [c]Reaction conditions: cf. Table 1, entry 6. [d]*E*/*Z* stereochemistry determined by NMR (cf. the SI for the NOESY results).

derived from other cyclic ketones such as cycloheptanone and cyclopentanone could also react smoothly with Tf_2O activated amide **6a** to afford the corresponding allylamines products **8ab**−**ad**, albeit with lower yields. Enamines from aromatic ketones such as acetophenone and propiophenone could also be used to produce the allylic amine products **8af**−**ah**. When the enamine of ethyl acetoacetate was used, *β*-enamino ester **8ai** was obtained, which may have resulted from the isomerization of the corresponding allylamine product.

The introduction of vinyl groups containing a halogen or ester group indicated the functional group tolerance and advantage of enamines over organometallic reagents. Furthermore, enamines derived from aldehydes (**5j**−**l**) could serve as useful alkenylation reagents as well. It seemed that the steric hindrance of enamines had much influence on the reaction. Only a trace amount of the corresponding allylamine product was obtained for sterically hindered enamine derived from 3,3-dimethylbutyraldehyde (**5m**).

A possible mechanism was then proposed (Scheme 2). As reported previously[3b] and proved in our recent research,[5f] activation of amide **6** with Tf_2O in the presence of 2-fluoropyridine would result in the formation of nitrilium ion intermediate **A** along with 2-fluoropyridinium salt **B**. Trapping of intermediate **A** by enamine **5** would give iminium ion **C**.

The reduction of **C** with $NaBH_4$ would give an amine-borane complex **D**.[23a] The amine−borane complex **D** might undergo a Hoffmann-like *β*-elimination reaction[23b] to yield the *α*,*β*-unsaturated imine (enamine) **9**, which was further reduced with $NaBH_4$ to give allylamine product **8**. The chemoselective 1,2-reduction of enimines with $NaBH_4$ has been demonstrated previously.[5g] We envisioned that the excess $NaBH_4$ in our reaction could serve as the base to facilitate such elimination and the introduction of additional base into the reduction system would help to decrease the amount of $NaBH_4$. Moreover, 2-fluoropyridinium salt **B** can consume some $NaBH_4$ that could also be prevented by deprotonation with a base. Indeed, in the presence of 1.3 equiv of NaOH, the amount of $NaBH_4$ can be decreased to 2.6 equiv without much influence on the yields of the products (Table 2, entries 1, 2, 5−8, 10, 12, and 15; see the SI for more examples of NaOH addition). Moreover, under the optimized conditions, the reaction of **6a** with **5c** produced **8ab** in an improved 55% yield (Table 3, entry 2). The steric hindrance on the *β*-positon of enamine and the R^1 group of the amide apparently has a distinct influence on the reactivity of elimination and reduction, respectively, which is consistent with our previous observations (enamines **5j** versus **5m**, Table 3; entry 23, Table 2).

In conclusion, stemming from a serendipitous discovery, we have developed a new strategy to construct allylamines. This work illustrates a new example of how reaction optimization guided by mechanistic considerations can lead to a practical synthetic method. Through this work, the synthetic utility of enamines was extended from serving as enolates equivalents in Stork's reactions to function as unconventional, mild, and regioselective surrogates of the alkene carbanions **S-2**. Moreover, this work provides a new, direct transformation of secondary amides with C−C bond formation under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03943.

Experimental procedure, product characterization data, $^1H/^{13}C$ NMR spectra of new compounds, and NOESY spectra of compounds **8af**, **8ah**, and **8ai** (PDF)

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§C.-C.Y. and T.-T.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to the memory of the late Professor Gilbert Stork.

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