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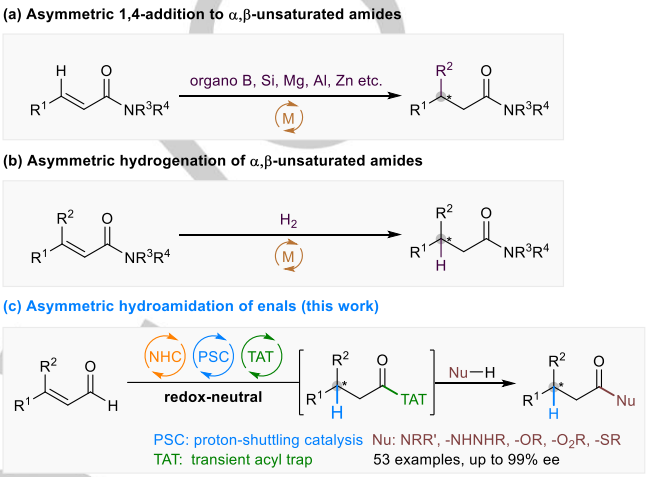
Enantioselective hydroamidation of enals by trapping of a transient acyl species

Pengfei Yuan,[a] Jiean Chen,*[a] Jing Zhao,*[b] Yong Huang*[a]

Dedicated to Professor David W. C. MacMillan on the occasion of his 50th birthday ((optional))

Abstract: An enantioselective synthesis of β-chiral amides by asymmetric and redox-neutral hydroamidation of enals is reported. In this reaction, a chiral *N*-heterocyclic carbene (NHC) catalyst reacts with enals to generate the homoenolate intermediate. Upon highly enantioselective β-protonation *via* proton-shuttle catalysis, the resulting azolium intermediate reacts with imidazole to yield the key β-chiral acyl species. This transient intermediate provides access to diversified β-chiral carbonyl derivatives, such as amides, hydrazides, acids, esters, and thioesters. In particular, β-chiral amides can be prepared in excellent yield and *ee* (40 chiral amides, up to 95% yield and 99% *ee*). This modular strategy overcomes the challenge of the disruption by basic amines of the high selective proton-shuttling process.

Amides are versatile synthetic intermediates that can be converted to various heterocylic scaffolds. They are also an essential functionality common in biomolecules and pharmaceutical agents.[1] Replacement of natural amino acid residues with a chiral amide often yields analogues with increased conformal rigidity, enhanced metabolic stability, and improved membrane permeability.[2] Chiral amides containing a β-stereogenic center comprise an important class of natural amino acid surrogates.[3] Consequently, tremendous efforts have been directed toward devising synthetic routes to β-chiral amides using enantioselective catalysis. So far, the two established general approaches to β-chiral amides require reductive environments. Asymmetric 1,4-conjugate addition of organometallic reagents, catalyzed by transition metals, allows convenient installation of a β-substituent to α,β-unsaturated amides with high enantioselectivity (Scheme 1a).[4] Alternatively, various β-disubstituted α,β-unsaturated amides can be hydrogenated to generate the desired β-chiral methine motif (Scheme 1b).[5] However, both the reductive nature of these transformations, and the involvement of coordinative transition metal species limit the reaction scope. Reactions involving substrates containing basic nitrogen atoms in general, and heterocycles in particular, are very challenging. In this paper, we report our findings of an organocatalytic and redox-neutral pathway to β-chiral amides *via* enantioselective hydroamidation of enals (Scheme 1c).



Scheme 1. Asymmetric synthesis of β-chiral amides.

From the perspective of redox economy, the oxidation state of enals is the same as that of amides, acids and esters and direct conversion of enals to amides is a redox-neutral process. Instead of hydride addition, an alternative process can be envisioned linking a direct protonation process with nucleophilic addition. Conversion of enals to homoenaloates, mediated by NHCs, is a well-established strategy with which to generate a nucleophilic β-carbon.[6] Upon β-protonation and tautomerization, the resulting acyl azolium intermediate can react with nucleophiles to yield β-chiral carboxylic acid derivatives. Recently, asymmetric β-protonation/esterification and β-protonation/thioesterification were reported by Scheidt and by our laboratory.[7] During our studies, we discovered that enantiomeric control of the β-protonation is very sensitive to the choice of the proton-shuttle. Bridgehead tertiary amines, DABCO and quinuclidine for example, exhibit unparalleled reaction efficiency and selectivity and, in contrast, simple tertiary amines and pyridine derivatives afford slow reactions and low enantioselectivity. The sensitivity to basic sites makes enantioselective hydroamidation far more challenging, as amine substrates will inevitably compete for protons and form non-selective proton shuttles. In addition, primary and secondary amines react with enals in several side pathways, such as imine/iminium formation and aza-Michael addition.[8] As a result, few reports are available of asymmetric hydroamidation of enals.

In order to address this issue, we proposed a strategy which uses a transient acyl trap (TAT).[9] Ideally, a TAT should be far less basic than quinuclidine, whose conjugate acid has p*K*a = 11, and protons in the reaction system, located exclusively at the bridgehead nitrogen. At the same time, the

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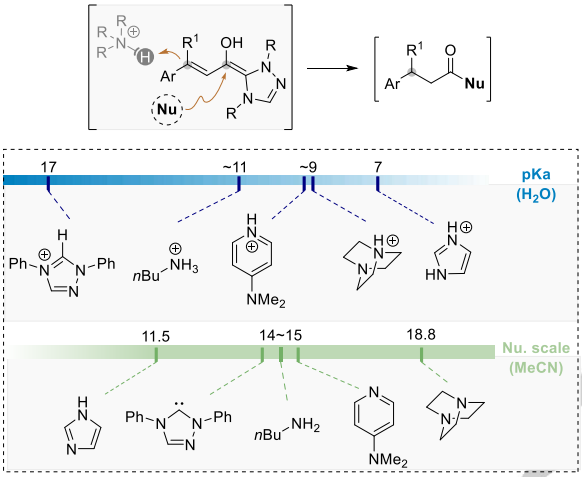
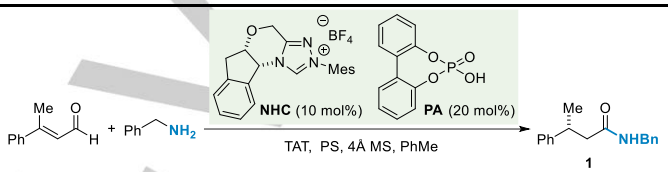
TAT needs to be sufficiently nucleophilic[10] toward the acyl azolium intermediate, in order to lead to effective NHC turnover. As shown in Scheme 2, although primary amines are nucleophiles competent for NHC turnover, they are indistinguishable from quinuclidine in terms of p*K*a. Similarities in basicity will lead to several active proton-shuttling species and compromise asymmetric induction. Azoles are several orders of magnitude less basic than amines and are known to react with acyl azolium species leading to NHC turnover.[1c,7c,7f,11] However, basicity and nucleophilicity vary largely depending on the nature of the heterocycle. We decided to search for an azole suitable as a TAT that can effectively promote the enantioselective hydroamidation reaction with good enantiomeric control.



Scheme 2. Balance of basicity and nucleophilicity for asymmetric hydroamidation of enals. [a] The pKa values were obtained from the ibond database (http://ibond.nankai.edu.cn) and the Nu values were obtained from Mayr's database (http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank)

β-Methyl cinnamaldehyde and benzylamine were chosen as standard substrates for an initial investigation of reaction conditions (Table 1). Biphenol-derived phosphoric acid (PA) in combination with DABCO, was used as the proton-shuttling catalyst (PSC). In the absence of a TAT, little hydroamidation product was observed (entry 1) and the major side product was identified by GC-MS analysis as the corresponding imine. We found that imidazole is an excellent TAT for hydroamidation, yielding the desired β-chiral amide (**1**) in 74% yield and 93% *ee* (entry 2). The weak basicity of imidazole probably results in exclusive residence of protons on DABCO. In the absence of PA, the reaction was significantly slower and less selective, indicating the essential role of the PSC (entry 3).[7f] Replacement of DABCO with other tertiary amines led to low conversion and *ee*, with the exception of quinuclidine, which also contains a bridgehead nitrogen (entries 4-6). Other TATs were also examined and we found that carboxylic acid activators, HOAT[12] and HOBT, were both good TAT agents, but the reactions proceeded in nearly a racemic manner (entries 7 and 8). The p*K*a values of HOAT and HOBT (3.3 and 4.6, respectively) are much lower than that of the conjugate acid of DABCO (p*K*a = 8.9), making non-selective proton transfer predominant. Low yield was observed using DMAP as a TAT. Although DMAP has been frequently employed as an acyl transfer catalyst for NHC turnover, the corresponding acetyl pyridinium species is quite unstable and decomposes before the addition of amine (entry 9). Pyrrole failed to promote the hydroamidation (entry 10) but high yield was observed using 1,2,3-triazole as the TAT. However, moderate *ee* was obtained. The relatively high acidity of 1,2,3-triazole (p*K*a = 9.4) likely interferes with the proton-shuttling process. In summary, a delicate balance of acidity and nucleophilicity is vital to secure the highly enantioselective β-protonation and the efficient acyl trapping process. Increasing the reaction temperature to 40 °C further improved the reaction yield to 92% (entry 12).

Table 1. Identification of a suitable TAT for asymmetric hydroamidation.[a]



entry	TAT	PS	T (°C)	yield (%)[b]	ee (%)[c]
1	—	DABCO	30	trace	-
2	imidazole	DABCO	30	74	93
3[d]	imidazole	DABCO	30	12	56
4	imidazole	Et_3N	30	60	59
5	imidazole	DIPEA	30	17	58
6	imidazole	quinuclidine	30	53	92
7	HOAT	DABCO	30	70	7
8	HOBT	DABCO	30	88	6
9	DMAP	DABCO	30	9	-
10	pyrrole	DABCO	30	6	48
11	1,2,3-triazole	DABCO	30	98	68
12	imidazole	DABCO	40	92[e]	95
13	imidazole	DABCO	50	21	86

[a] Reactions conditions: a solution of enal (0.1 mmol), TAT (0.1 mmol), PS (0.2 mmol), NHC precursor (0.01 mmol) and PA (0.01 mmol) in toluene was stirred at the indicated temperature overnight. The reaction was cooled to r.t. and benzylamine (0.12 mmol) was added. The mixture was stirred at r.t. for another 10 h. [b] Determined by GC analysis using biphenyl as internal standard. [c] Determined by chiral HPLC. [d] PA was omitted from the reaction. [e] Isolated yield.

With the optimized reaction conditions for the asymmetric hydroamidation in hand, we surveyed the scope of nitrogen nucleophiles (Table 2). Primary alkyl amines are well tolerated and the corresponding β-chiral amides are obtained in good to high yield and excellent *ee* (Products **1**-**8**). Enals with a sterically

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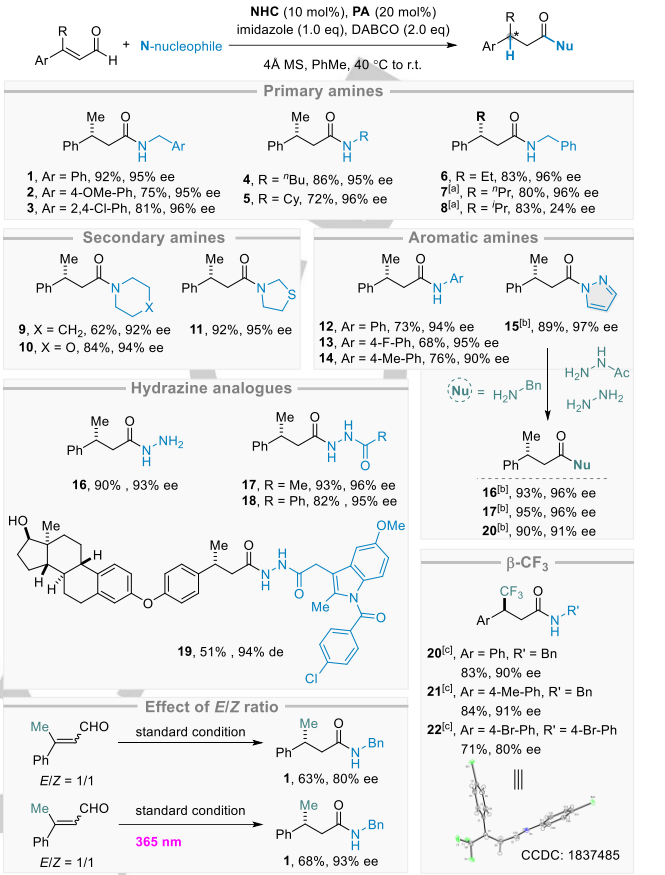
demanding β-alkyl group, such as isopropyl (product **8**), react with considerably lower enantioselectivity. The cyclic amines piperidine (**9**), morpholine (**10**) and thiazolidine (**11**) react, giving comparable yield and selectivity. The reactions involving acyclic secondary amines are very slow, for steric reasons. The transient acyl imidazole exhibits good reactivity towards weaker nitrogen nucleophiles, such as anilines and pyrazoles (products **12**-**15**). Pyrazole is also an effective TAT and the β-chiral acyl pyrazole (**15**) is an isolable acyl transfer reagent. It reacts with various amines, hydrazines and acyl hydrazines to deliver β-chiral amides and hydrazides (**16**, **17**, **20**). The reaction can be extended to complex drug scaffolds. A reaction employing both a structurally exotic enals and a hydrazide affords the estrone analogue (**19**) containing a β-chiral hydrazide functionality. Various functional groups, such as ketone, indole, ether and chlorine, are tolerated. By changing the PSC from DABCO to quinuclidine, products containing a β-trifluoromethyl group can be prepared in high yield and *ee*. (compounds **20**-**22**). *E*-enals lead to products with *R* configuration, except for β-CF_3, for which the olefin geometry is opposite. When a mixture of *E*/*Z* (1/1) isomers were subjected to the standard reaction conditions, the product was obtained in 63% yield and 80% ee. Control experiments show that the *Z*-isomer reacts considerably slower and isomerization from *Z* to *E* also occurs during the reaction. We found that this isomerization can be accelerated by UV light. Consequently, performing the reaction under a 365 nm UV lamp significantly improves the enantioselectivity for substrates with geometric isomers. This method represents a major advantage for starting materials that are difficult to prepare as pure *E*-isomers.

Table 2. Scope of nitrogen nucleophiles.



[a] The reaction was performed at 20 °C. [b] Pyrazole was used as TAT instead of imidazole. [c] Quinuclidine was used as PSC instead of DABCO, the reaction was conducted at 0 °C.

We next examined the scope of the enals. Compounds containing heterocyclic moieties are challenging substrates, due to catalyst deactivation by coordination, for both transition metal-catalyzed hydrogenation and Michael addition reactions. Accordingly, we paid special attention to enals with a β-heteroaryl substituent (Table 3). The presence of additional basic sites appears not to affect the highly selective protonation process. Moderate to good yields and high *ee* are obtained for enals with various substituted β-pyridyl groups (compounds **23**-**27**). Other β-heteroaryl systems, including benzofuryl, furyl, thienyl and benzothienyl, are well tolerated (compounds **28**-**34**). Remarkably, the use of propargyl amine leads to a product with a terminal alkyne moiety (**33**), a functional group incompatible with previous transition metal-catalyzed processes.

Table 3. Scope of enals containing a heterocyclic moiety.

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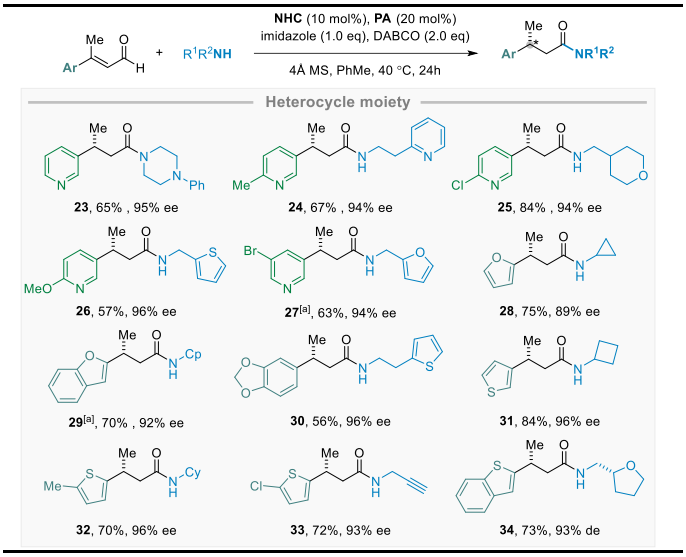
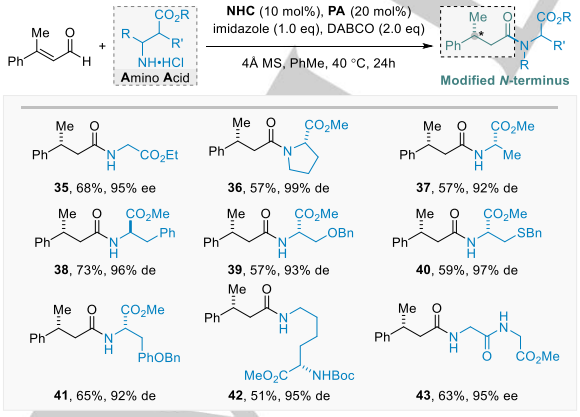


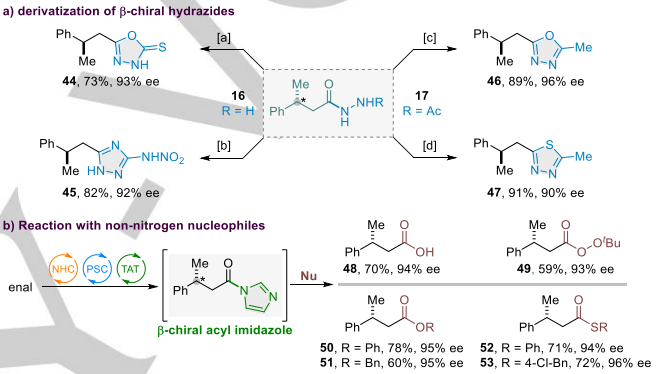
[a] 5.0 equiv. DABCO was used.

We applied this transformation to the synthesis of novel peptide mimetics by replacing one natural amino acid with a β-chiral amide (Table 4). Despite their attenuated nucleophilicity, a series of amino acid esters, as the hydrochlorides, react smoothly with the transient β-chiral acyl imidazole, affording the desired peptidomimetics in moderate yield and excellent stereoselectivity. Amino acids with either L- or D-configuration show little or no discrepancy in reactivity or selectivity. Serine, cysteine, tyrosine and lysine were protected before the ligation. A tripeptide mimetic (**43**) was prepared using Gyl-Gyl-OMe, in 63% yield and 95% *ee*. Multiple hydrogen-bond donors and acceptors present in the substrate do not interfere with the delicate proton-shuttling process. It is perceivable that this new ligation method might be applied to longer peptides and offer a unique strategy for the modification of the *N*-terminus of biologically relevent peptides and peptidomimetics.

Table 4. Ligation with amino acids and peptides.



To further demonstrate the synthetic utility of this reaction, we converted the β-chiral hydrazide products into several pharmacologically relevant heteroarenes (Scheme **3a**).[13] Products **16** and **17** were transformed to the corresponding analogues of 1,3,4-oxadiazole-2(3*H*)-thione (**44**), 1,2,4-triazole (**45**), 1,3,4-oxadiazole (**46**) and 1,3,4-thiadiazole (**47**). The transient β-chiral acyl imidazole species can also be intercepted by non-nitrogen nucleophiles. This maneuver leads to a streamlined synthesis of various β-chiral carboxylic acid derivatives. Basic workup affords the carboxylic acid **48**. Treatment with *t*-butyl hydroperoxide gives the perester **49**. The corresponding esters and thioesters are obtained using alcohols, phenols and thiols, respectively (compounds **50**-**53**). All derivatization reactions proceed with little loss of optical purity.



Scheme 3. Derivatization of β-chiral hydrazides and the transient acyl imidazole species. [a] CS_2, KOH, EtOH, reflux. [b] *N*-methyl-*N*-nitroso-*N'*-nitroguanidine, H_2O; KOH, H_2O, reflux; acidified with 68% HNO_3. [c] $POCl_3$, reflux. [d] Lawesson's reagent, DCM, reflux.

In summary, we have developed a new approach to asymmetric hydroamidation of enals by tethering NHC catalysis, proton-shuttling catalysis and a transient-acyl-trapping strategy. The use of a TAT overcomes the longstanding problem of basic amines disrupting the enantioselective protonation step. The combination of an NHC, a bridgehead nitrogen base (PSC) and an azole (TAT) constitutes a robust system for asymmetric β-protonation of various enals. The transient acyl azole species can be converted to a wide range of chiral carboxylic acid derivatives with high enantioselectivity. Synthetic applications demonstrate that this method can be used for the modification of peptides and synthesis of chiral heteroarenes. Exploration of this strategy using biomolecules with more complex molecular structures is currently in progress.

Acknowledgements

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Competing financial interests

The authors declare no competing financial interests.

Keywords: proton-shuttling catalysis • asymmetric hydroamidation • chiral amide • enantioselective protonation • *N*-heterocyclic carbene

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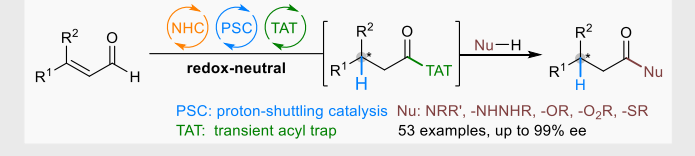

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Enantioselective hydroamidation of enals by trapping of a transient acyl species