Communication

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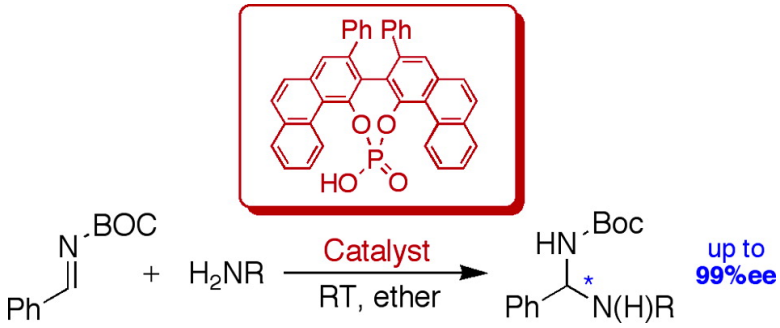

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Brønsted Acid-Catalyzed Imine Amidation

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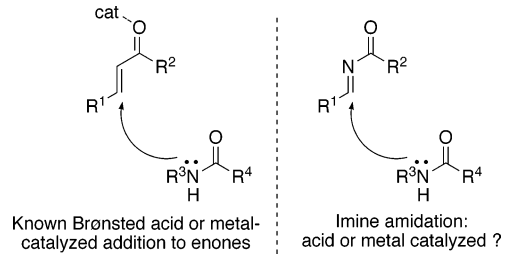
Stereoselective organocatalysis, the use of chiral organic small-molecules as activators for asymmetric reactions, has found much recent success.[1] Chiral Brønsted acids have recently been shown to be excellent organocatalysts in a number of interesting enantioselective transformations.[2] In light of these findings, new Brønsted acid-catalyzed reactions that produce centers of chirality represent potentially important processes that can be rendered stereoselective.[3] We would like to report our findings with regards to a new, efficient, high-yielding Brønsted acid-catalyzed asymmetric addition of amide nucleophiles to imines whereby chiral *N*,*N*-aminals are produced.

Catalytic asymmetric additions of carbon nucleophiles to imines have been a popular area of study for a number of research groups.[4] As a new approach to catalytic imine addition chemistry, we envisioned adding nitrogen nucleophiles to imine carbamates mediated by metals or by Brønsted acids to produce protected aminals. This approach was encouraging to us as it appeared to be somewhat analogous to recent catalytic conjugate additions of carbamates to enones (Scheme 1).[5]

Scheme 1. The Catalytic Amidation of Enones and Imines

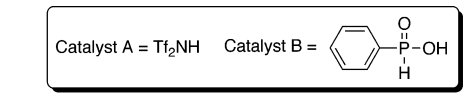


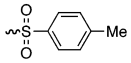
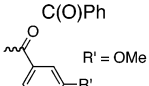
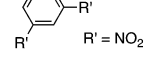
Previous work with regard to the addition of amide nucleophiles to imines has commonly required doubly activated imines, that is, those activated through the use of electron-withdrawing groups from the imine nitrogen and the imine carbon.[6] To the best of our knowledge, a general catalytic addition of amides to imines was previously not reported. Catalytic asymmetric variants of this type of addition were also previously unknown.

Protected aminals have been incorporated into peptide chains, and the resulting structures provide the so-called *retro-inverso* mimics.[7] These *retro-inverso* peptide mimics, first popularized by Goodman, have found applications as proteinase inhibitors, neurotensins, somatostatins, glycosidase inhibitors, amino acid based sweeteners, and in other applications.[8] Previous methods in the literature to synthesize aminal products of this type have normally been through Curtius or Hoffman-type rearrangements[7] of protected amino acid derivatives or by a benzotriazole-mediated approach by Katritzky.[9]

Our hypothesis (Scheme 1) was quickly validated through initial experiments. We first observed that aryl-substituted N-Boc imines[10] were not susceptible to the addition of acrylamide in ether at ambient temperatures. However, when we added catalytic amounts of organic Brønsted acids to the reaction, we found that the amide would readily add to the imine to provide high yields of aminal addition product **3e** (Table 1).[11]

Table 1. Brønsted Acid-Catalyzed Imine Amidation



Entry[a]	Ar	R	mol% Acid	Time	Isolated Yield **3**
1	Ph		0.5 mol% A	20 min	**3a = 99%**
2	Ph		5 mol% B	20 h	**3b = 91%**
3	Ph	CO_2Et	0.5 mol% A	20 min	**3c = 97%**
4	Ph	CO_2Bn	5 mol% B	13 h	**3d = 81%**
5	Ph	$C(O)CH{=}CH_2$	0.5 mol% A	20 min	**3e = 97%**
6	Ph	C(O)H	0.5 mol% A	20 min	**3f = 87%**
7	Ph	C(O)Me	10 mol% B	19 h	**3g = 91%**
8	Ph	C(O)Ph	0.5 mol% A	20 min	**3h = 91%**
9	Ph		5 mol% B	25 h	**3i = 84%**
10	Ph		5 mol% B	46 h	**3j = 49%**
11	2-MeC_6H_4	$C(O)CH{=}CH_2$	10 mol% B	24 h	**3k = 98%**
12	4-BrC_6H_4	$C(O)CH{=}CH_2$	10 mol% B	2.5 h	**3l = 94%**
13	4-$MeOC_6H_4$	$C(O)CH{=}CH_2$	5 mol% B	14 h	**3m = 91%**
14	2-thienyl	$C(O)CH{=}CH_2$	10 mol% B	10 h	**3n = 91%**
15	2-furyl	$C(O)CH{=}CH_2$	10 mol% B	11 h	**3o = 99%**

[a] General conditions: 2 molar equiv of the imine and 1 molar equiv of the amide.

Concentrating initially on reactivity, we screened over 25 anhydrous acids for catalytic activity and found that trifluoromethanesulfonimide (A) and phenyl phosphinic acid (B) were excellent catalysts for the reaction. However, it should be noted that many of the organic acids screened could catalyze this process. Typically, a very low catalyst loading was required when Tf_2NH was employed. In our variation of the amide nucleophile, we were pleased to find good substrate generality. Sulfonamides (entries 1 and 2) and carbamates (entries 3 and 4) were found to add efficiently in good yields. Acrylamide, formamide, acetamide, benzamide, and substituted benzamides (entries 5−10) were readily added to imine **1** using the Brønsted acid-catalyzed conditions (Table 1).

Our preliminary investigation into imine generality showed that a variation of the aryl substituent on the imine carbon resulted in no detrimental effects with regard to reactivity (Table 1, above). For example, the reaction of acrylamide with 2-methyl-, 4-bromo-, and 4-methoxyphenyl-substituted imines (entries 11−13) all pro-

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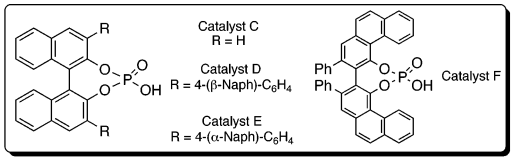
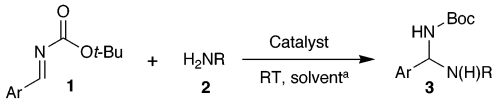
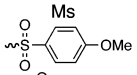
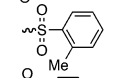
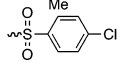
Table 2. Catalytic Asymmetric Imine Amidation





Entry[a]	Ar	R	mol% Acid[b]	Time	Yield and ee **3**
1	Ph	Ts	5 mol% C	16 h	**3a** = 95%, **<5% ee**
2	Ph	Ts	4 mol% D	20 h	**3a** = 96%, **60% ee**
3	Ph	Ts	5 mol% E	24 h	**3a** = 99%, **71% ee**
4	Ph	Ts	5 mol% F	1 h	**3a** = 95%, **94% ee**
5	Ph	Ms	5 mol% F	1 h	**3b** = 86%, **93% ee**
6	Ph		5 mol% F[c]	1 h	**3p** = 89%, **91% ee**
7	Ph		20 mol% F[c]	50 h	**3q** = 80%, **73% ee**
8	Ph		20 mol% F[d]	15 h	**3r** = 98%, **95% ee**
9	4-ClC_6H_4	Ts	10 mol% F	17 h	**3s** = 88%, **94% ee**
10	4-BrC_6H_4	Ts	10 mol% F[d]	13 h	**3t** = 96%, **92% ee**
11	4-$CF_3C_6H_4$	Ts	10 mol% F[d]	20 h	**3u** = 99%, **99% ee**
12	4-$MeOC_6H_4$	Ts	10 mol% F[d]	17 h	**3v** = 92%, **90% ee**
13	2-thienyl	Ts	10 mol% F[d]	17 h	**3w** = 94%, **87% ee**

[a] General conditions: 2 molar equiv of the imine and 1 molar equiv of the amide with diethyl ether as the solvent. Enantiomers were separated by chiral HPLC and compared to racemic material in all cases. [b] Catalysts were derived from S-BINOL and S-VAPOL. [c] Catalyst derived from R-VAPOL. [d] Toluene was used as the solvent.

vided high yield of the respective aminal product. The use of two heteroaromatic substituted imines (2-thienyl and 2-furyl) as substrates also provided high yields of the aminal product (entries 14 and 15 from Table 1).

Our initial exploration of the viability of a catalytic asymmetric variant showed that sulfonamides could, in fact, be added to imine **1** in high enantioselectivity when particularly hindered Brønsted acids were used (Table 2). Use of chiral BINOL derived phosphoric acid catalysts provided moderate enantiomeric excess when bulky substituents (catalysts D and E) were in the 3,3′ positions (entries 2 and 3). This was a similar effect observed in previous chiral Brønsted acid-catalyzed reactions.[2b,d] It was found that the hindered VAPOL[12] (vaulted biphenanthrol) derived phosphoric acid (F) could provide excellent enantioselectivities for the addition of *p*-toluenesulfonamide (entry 4), methanesulfonamide (entry 5), 4-methoxybenzenesulfonamide (entry 6), and 4-chlorobenzenesulfonamide (entry 8) to imine **1**.[13] In the case of *o*-toluenesulfonamide, a moderate enantioselectivity was found for the addition (entry 7). The longer reaction time and lower enantioselectivity in this case is presumably due to steric factors. The use of *para*-substituted benzaldehyde derived imines (entries 9−12) in the reaction gave the respective addition products in excellent enantioselectivity.[14] A heteroaromatic imine substrate (2-thienyl) was also shown to provide a highly enantioselective *N*,*N*-aminal product (entry 13). The chiral products formed have been found to be quite stable. Decomposition and/or racemization were not observed in solution over several days.

In our initial work, we have found that amide substrates provide lower enantioselectivities with the above catalysts. For example, the addition of acrylamide or acetamide to imine **1** mediated by catalyst (F) provided a low enantioselectivity (14 and 12% ee, respectively). Benzylcarbamate addition to **1** under the same conditions resulted in only moderate enantioselectivity (50% ee).

The scope (catalyst, imine, and nucleophile), reaction mechanism, and utility of this new catalytic process are currently being investigated in our laboratory and will be reported in due course.

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Supporting Information Available: Characterization, chiral HPLC conditions, experimental preparations (18 pages, print/PDF), and spectra (23 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Note: For highly reproducible ee's, exhaustively dried catalyst, imine, and sulfonamide are required. See Supporting Information for requisite details.

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