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A General, Brønsted Acid-Catalyzed Hetero-Michael Addition of Nitrogen, Oxygen, and Sulfur Nucleophiles

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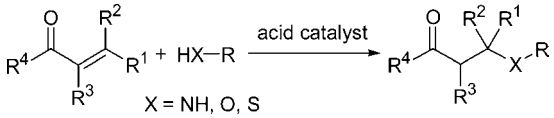
ABSTRACT

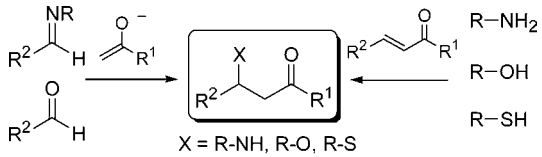


Strong Brønsted acids such as bis(trifluoromethanesulfon)imide catalyze the hetero-Michael addition of carbamates, alcohols, and thiols to α,β-unsaturated ketones, alkylidene malonates, and acrylimides. Scope, reaction rates, and yields are superior to comparable Lewis acid-catalyzed processes.

β-Amino and β-oxy carbonyl functionalities are ubiquitous motifs in natural products such as alkaloids and polyketides.[1] β-Amino carbonyl compounds are also important intermediates for the synthesis of amino alcohols, diamines, and β-amino acid derivatives, many of which serve as powerful antibiotics or other drugs.[2]

The reactions of enolates either with imines (Mannich reaction) or with carbonyl compounds (aldol reaction) are established methods for the synthesis of these moieties through carbon−carbon bond formation (Scheme 1).[3]

Scheme 1. Syntheses of β-Heteroatom Carbonyl Compounds



Alternatively, aza- or oxa-Michael additions can be used to create carbon−heteroatom bonds by reaction of α,β-unsaturated carbonyl compounds with amine or alcohol derivatives.[4] This pathway is particularly important for other heteronucleophiles such as thiols where Mannich- or aldol-analogous reactions do not exist.

The development of new synthetic strategies continues to attract attention as there are drawbacks to many of the existing methodologies. Mannich reactions often suffer from harsh conditions and long reaction times and aldol reactions generally call for stoichiometric amounts of base to form preactivated enolates. In contrast, hetero-Michael reactions normally only require catalytic amounts of a strong base or a Lewis acid to activate either the nucleophile or the acceptor

(1) Reviews: (a) Misra, M.; Luthra, R.; Singh, K. L.; Sushil, K. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Pergamon: Oxford, UK, 1999; Vol. 4, p 25. (b) Staunton, J.; Wilkinson, B. *Top. Curr. Chem.* **1998**, *195*, 49.

(2) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; John Wiley & Sons: New York, 1997. (c) Sewald, N. *Amino Acids* **1996**, *11*, 397. (d) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (e) Devine, P. N.; Heid, R. M., Jr.; Tschaen, D. M. *Tetrahedron* **1997**, *53*, 6739.

(3) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. (d) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 2. (e) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (f) Paterson, I.; Cowden, C. *Org. React.* **1997**, *51*, 1.

(4) (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, p 30. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (d) Berkessel, A. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995; Vol. E21e, p 4818.

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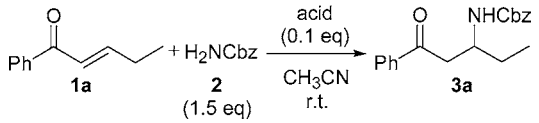
Table 1. Acid Catalysts in the Aza-Michael Addition of **1a** and **2**



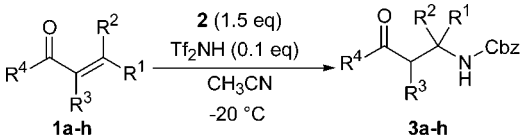
run	acid	time	yield/%
1	$(CF_3SO_2)_2NH$	10 min	98
2	CF_3SO_3H	10 min	91
3	$HBF_4{\cdot}OMe_2$	10 min	86
4	HBF_4 aq	2 h	92
5	p-TsOH	24 h	98
6	p-TsOH·H_2O	72 h	99
7	H_2SO_4	72 h	93
8	CH_3SO_3H	72 h	47
9	HCl	72 h	trace
10	CF_3CO_2H	72 h	trace
11	CH_3CO_2H	72 h	–

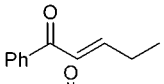
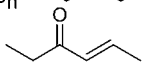
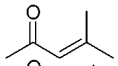
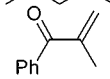
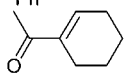
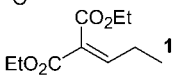
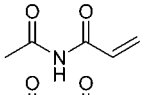
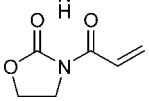
component. To the latter end, lanthanide triflates, $FeCl_3$, $InCl_3$, $CeCl_3$/NaI, $Bi(NO_3)_3$, platinum group metal complexes, and other Lewis acids have been used successfully in aza-Michael additions[5] and asymmetric variants involving chiral Lewis acids have been reported.[6] Similarly, numerous examples exist of base-mediated oxa-Michael additions and Lewis acid catalysis has been achieved with Pd or Zn salts.[7]

With most weak nucleophiles such as carbamates or alcohols, intramolecular hetero-Michael additions are far more prominent than intermolecular applications. Recently, this problem was addressed by Kobayashi et al. and our group when it was discovered that catalytic amounts of Pd-$(CH_3CN)_2Cl_2$,[8] $Cu(OTf)_2$,[9] or noble metal chlorides[10] such as $PtCl_4$, AuCl, $ReCl_5$, and $RhCl_3$ could be used in a mild, intermolecular aza-Michael reaction of carbamates and α,β-unsaturated ketones.

In our search toward an economical, environmentally friendly route to β-amino and β-oxy carbonyl compounds, we became intrigued by the idea of dispensing with metal catalysts or strong bases altogether and using catalytic amounts of cheap, readily available and nontoxic Brønsted acids instead. We reasoned that activation of Michael

Table 2. Aza-Michael Addition of **2** to α,β-Unsaturated Carbonyl Compounds



run	enone		time	yield/%
1[a]		**1a**	10 min	98
2[a]		**1b**	10 min	94
3		**1c**	12 h	97
4		**1d**	12 h	84
5		**1e**	12 h	77 *trans* 4 *cis*
6		**1f**	12 h	91
7		**1g**	72 h	84
8		**1h**	72 h	49

[a] Reaction at room temperature.

acceptors by protonation of the carbonyl group (pK_a ca. −5 for α,β-unsaturated ketones) should be feasible in the presence of weakly basic nucleophiles, with leveling effects limiting efficiency for more basic Michael donors. Although some acid mediated, mostly intramolecular aza- and oxa-Michael reactions have been described,[11] no universal method for acid-catalyzed hetero-Michael additions has been reported.

Initial studies were carried out using benzyl carbamate ($CbzNH_2$, **2**) and 1-phenyl-2-penten-1-one (**1a**) as a model system (Table 1). While carboxylic acids or hydrochloric acid were not effective (runs 9−11), catalysis could be achieved with strong acids such as bis(trifluoromethanesulfon)imide (Tf_2NH, run 1), triflic acid (TfOH, run 2), or tetrafluoroboric acid (run 3). Compared to reaction times observed with $Pd(CH_3CN)_2Cl_2$ (24 h) or $Cu(OTf)_2$ (3 h), the rate acceleration induced by these Brønsted acid catalysts was dramatic. Weaker sulfonic acids (runs 5−8) and aqueous or hydrated acids (runs 4, 6) could be used as well, but reaction rates were significantly reduced.

Rapid conversion was observed when the reaction was carried out in dichloromethane, acetonitrile, or nitromethane. Solvents with weakly basic oxygen functionalities such as

(5) For representative examples, see: (a) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827. (b) Pérez, M.; Pleixats, R. *Tetrahedron* **1995**, *51*, 8355. (c) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, P.; Tolomelli, A. *J. Org. Chem.* **2001**, *66*, 8657. (d) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2001**, *42*, 6719. (e) Loh, T.-P.; Wei, L.-L. *Synlett* **1998**, 975. (f) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052. (g) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960. (h) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109.

(6) (a) Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823. (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (c) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2001**, 1240. (d) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2002**, *43*, 829. (e) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615.

(7) (a) Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403. (b) Hosokawa, T.; Sinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001. (c) Dheilly, L.; Lievre, C.; Frechou, C.; Demailly, G. *Tetrahedron Lett.* **1993**, *34*, 5895.

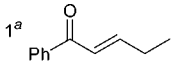
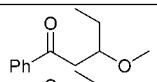
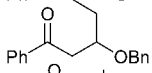
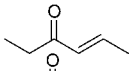
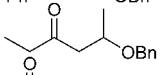
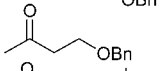
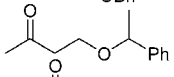
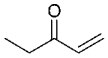
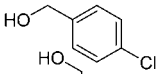
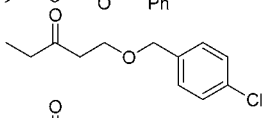
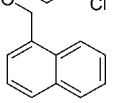
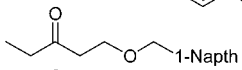
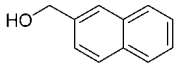
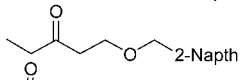
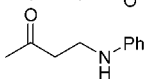
(8) Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25.

(9) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891.

(10) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319.

(11) (a) Darvesh, S.; Grant, A. S.; MaGee, D. I.; Valenta, Z. *Can. J. Chem.* **1989**, *67*, 2237. (b) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953. (c) McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849. (d) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. (e) Newman, M. S.; Waltcher, I.; Ginsberg, H. F. *J. Org. Chem.* **1952**, *17*, 962 (intermolecular). (f) Hoffman, A. *J. Am. Chem. Soc.* **1927**, *49*, 530 (intermolecular).

Table 3. Hetero-Michael Addition of α,β-Unsaturated Ketones with Alcohols and Aniline

run	enone	nucleophile	adduct	time/h	yield/%
1[a]	 **1a**	CH_3OH **4**	 **11**	48	84
2	"	 **5**	 **12a**	48	72
3[b]	 **1b**	"	 **12b**	12	86
4	 **1i**	"	 **12c**	1	85
5[c]	"	 **6**	 **13**	24	79
6	 **1j**	 **7**	 **14**	12	73
7	"	 **8**	 **15**	12	85
8	"	 **9**	 **16**	12	89
9	 **1i**	H_2N—Ph **10**	 **17**	4	98

[a] CH_3OH as solvent. [b] 8 equiv of **5**. [c] HBF_4·OMe_2 as catalyst, see ref 16.

THF, ether, or acetone interfered with protonation equilibria and gave little or no conversion. Poor solubility limited the use of less polar solvents such as toluene. Tf_2NH was chosen as a standard catalyst, as it is one of the strongest known acids[12] and has been shown to be a superior catalyst in condensation reactions, alkyne hydrations, Friedel−Crafts acylations, conjugated allylations, and polymerization reactions under mild conditions.[13]

Having established the remarkable catalytic activity of Tf_2NH in the conjugate addition of **2** to β-monosubstituted enones **1a** and **1b** (Table 2), we focused our investigations on substrates that had reacted only sluggishly in the presence of metal catalysts. Enones bearing additional α- or β-substituents such as **1c**, **1d**, and **1e** could be converted readily with use of acid catalysts, and a good, thermodynamically controlled diastereoselectivity was obtained for the addition to **1e**.[14] It was also possible to extend the scope of the reaction to acceptors other than α,β-unsaturated ketones. Good yields were obtained when the alkylidene malonate **1f** and the acrylimides **1g** and **1h** were used.[15] This pathway offers a possible route to β-amino acid derivatives, e.g. via malonate decarboxylation or selective imide hydrolysis.

Although benzyl carbamate protected amine moieties are known to be sensitive to cleavage in acidic media, low H^+ concentrations and the use of nonaqueous solvents completely suppressed this pathway and decomposition products could not be detected in any case.

In contrast to our transition metal catalysts, Tf_2NH also efficiently mediates oxa-Michael additions (Table 3). Simple alcohols such as methanol were suitable nucleophiles (run 1) and good yields were obtained with the synthetically more useful benzyl alcohols **5**−**7** (runs 2−6).[16] Both 1- and 2-naphthylmethanol were similarly effective (runs 7−8), which allows the introduction of the NAP protecting group.[17] Alcohols are considerably less reactive than carbamates, hence only poor yields were obtained with acceptors other than terminal or β-monosubstituted enones. Aryl alcohols could not be employed due to the competitive interference of Friedel−Crafts-type reactions, but aniline, the more nucleophilic nitrogen analogue, furnished the addition product in excellent yield (run 9).

Further experiments revealed that the same concept could be applied successfully to thiols, which constitute another class of weakly basic nucleophiles and are normally activated by deprotonation.[18,19] In addition, thiols are notoriously difficult to use in the presence of Lewis acidic metals due to their strong tendency to poison these catalysts, although recent advances have been made.[20]

Both benzenethiol (**18**) and benzyl mercaptan (**19**) were effective in this reaction (Table 4). Benzyl sulfides, which

(12) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N.; Volkonskii, A. Y.; Vlasov, V.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047.

(13) (a) Isihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 1045. (b) Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* **2000**, 1777. (c) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45. (d) Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215. (e) Desmurs, J.-R.; Ghosez, L.; Martins, J.; Deforth, T.; Mignani, G. *J. Organomet. Chem.* **2002**, *646*, 171.

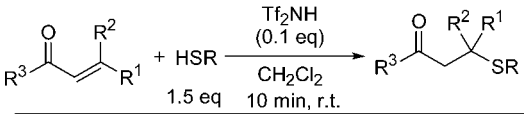
(14) All aza- and oxa-Michael additions studied were reversible at room temperature and −20 °C.

(15) High conversions were also observed with alkylidene derivatives of Meldrum's acid at −20 °C in CD_3CN, but products rapidly reverted to the starting materials via retro-Michael addition at room temperature, even in the absence of a catalyst.

(16) In run 5, lower yields and diether formation of **6** were observed with Tf_2NH as a catalyst.

(17) Gaunt, M. J.; Boschetti, C. E.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **1999**, *40*, 1803.

Table 4. Hetero-Michael Addition with Sulfur Nucleophiles



run	enone	thiol	adduct	yield/%
1[a]	**1i**	HS−Ph **18**	**20**	66
2	**1j**	HS, Ph **19**	**21a**	91
3	**1b**	"	**21b**	93
4	**1c**	"	**21c**	98

[a] Reaction in CH_3CN, 60 min.

are standard functionalities in organic synthesis for the protection of thiols,[21] could be synthesized by reaction of **19** with terminal, disubstituted and trisubstituted enones in excellent yields and reaction times (runs 2−4).

These examples demonstrate that Brønsted acid catalysis can be superior to metal ion catalysis when weakly basic nucleophiles are used in the hetero-Michael reaction. In addition, Brønsted acids are not only advantageous in terms of reactivity, but also regarding waste disposal and cost. The procedure described herein complements our previous research on the catalytic aza-Michael addition as mild transition metal catalysts such as $Pd(CH_3CN)_2Cl_2$ gave better results when reactive, but highly acid-labile substrates such as 2-cyclohexenone were used.

In summary, the first general, Brønsted acid-catalyzed hetero-Michael addition has been developed. This easy and economical process can be used for the construction of Cbz-, naphthylmethyl-, or benzyl-protected β-amino, β-oxy, or β-thio carbonyl compounds. Further refinements and applications of this procedure are now in progress and will be reported shortly.

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Supporting Information Available: Experimental procedure and characterization data of all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Review: Mikolajczyk, M.; Drabowicz, J.; Kielbasinsksi, P. In *Houben-Weyl*: *Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995; Vol. E21e, p 5017. For more recent examples, including enantioselective syntheses, see: (a) Sundarajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389. (b) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974. (c) Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1995**, *60*, 6188. (d) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141. (e) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (f) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **1997**, *53*, 2421.

(19) It has been noted more than 50 years ago that HCl accelerates the addition of dodecanethiol to mesityl oxide: (a) Stephens, J. R.; Hydock, J. J.; Kleinholz, M. P. *J. Am. Chem. Soc.* **1951**, *73*, 4050. (b) Posner, T. *Chem. Ber.* **1902**, *35*, 799.

(20) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(21) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1999; p 457.