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Catalytic Synthesis of γ-Lactams via Direct Annulations of Enals and *N*-Sulfonylimines

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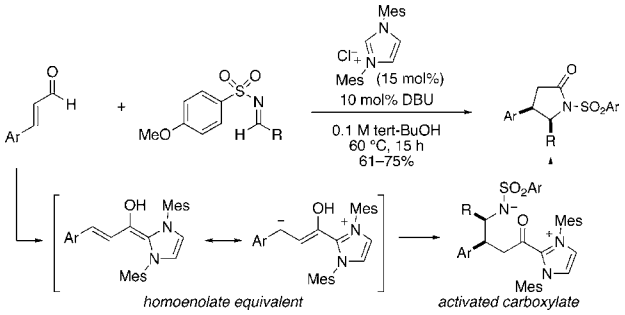
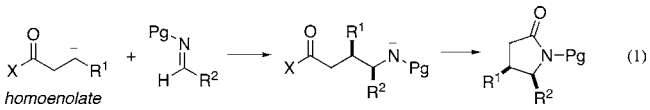
ABSTRACT



Cinnamaldehydes and *N*-sulfonylimines undergo direct annulations to cis-disubstituted γ-lactams via the intermediacy of catalytically generated homoenolates. Critical to the success of this process was overcoming inhibition of the N-heterocyclic carbene catalyst by the electrophilic imines. The overall process proceeds with good yields and diastereoselectivites and requires no stoichiometric reagents or additives.

γ-Lactams are widespread structural features of natural and designed biologically active molecules, including the core structure of the nootropics, or so-called "smart drugs".[1] Their utility in pharmaceutical development, however, is diminished by the need for multistep synthetic sequences for their preparation; even the few known direct methods require prior synthesis of complex reactants.[2,3] An attractive approach to γ-lactams would be the addition of a homoenolate equivalent to an appropriate imine, followed by cyclization (eq 1). While this strategy has been successfully applied to the synthesis of γ-lactones,[4] only scattered and limited reports of homoenolate additions to imines have appeared,[5] presumably due to incompatibilities of the imine substrates with the harsh or reductive conditions typically used for homoenolate formation.[6]



Recently, we[7] and Glorius[8] independently reported the nucleophile-catalyzed generation of homoenolates from α,β-unsaturated aldehydes and their reaction with an electrophilic

(1) Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180−222.
(2) (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (b) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C. *Org. Lett.* **2003**, *5*, 1761−1763.
(3) For an elegant and practical two-step approach to trans-disubstituted γ-lactams, see: Yee, N. K. *Tetrahedron Lett.* **1997**, *38*, 5091−5094.
(4) Fukuzawa, S.-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483.
(5) (a) Abbas, M.; Neuhaus, C.; Krebs, B. *Synlett* **2005**, 473−476. (b) DiMauro, E.; Fry, A. J. *Tetrahedron Lett.* **1999**, *40*, 7945−7949. (c) Okamoto, S.; Teng, X.; Fuji, S.; Takayama, Y. Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 3462−3471.
(6) (a) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B., Flemming, I., Eds; Pergamon: Oxford, 1991; Vol. 2, pp 441−454. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932−948.
(7) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371.
(8) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208.

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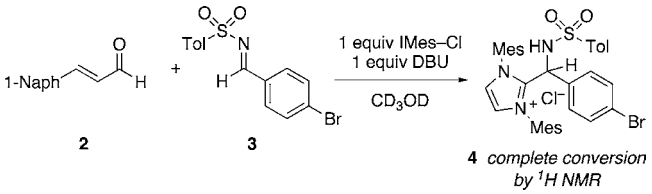
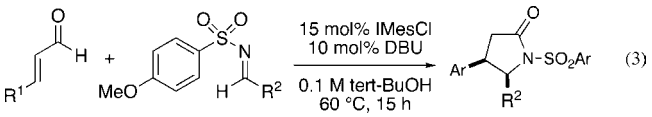
aldehyde, leading to a direct, stereoselective synthesis of γ-lactones. The nucleophilic catalyst derived from 1,3-bis(2,4,6-trimethylphenyl)-2-chloroimidazolium chloride (IMes-Cl) reacted reversibly with either aldehyde, but the use of a sterically demanding heterocyclic carbene permitted bond-forming reactions only from the umpolung of the α,β-unsaturated aldehyde.

Although we had hoped this uniquely mild (neutral, organocatalytic, protic solvent, rt) process would unlock the long-sought addition of homoenolates to imines, these reactions were initially limited to a narrow range of aldehyde electrophiles. *N*-Alkyl and *N*-aryl imines were unreactive, leading to lactone dimers of the starting enal as the only product. More electrophilic imines such as *N*-tosyl and *N*-phosphinoyl reacted directly with the nucleophilic catalyst, leading to stable adducts that effectively inhibited any catalytic reactions. NMR experiments revealed an explanation for this disparate reactivity. The nucleophilic catalyst reacted preferentially with the *N*-sulfonylimines, thus effectively inhibiting the reaction of the catalyst with the aldehyde (Scheme 1).[9]

Scheme 1. Electrophilic Inhibition of Nucleophilic Catalysis



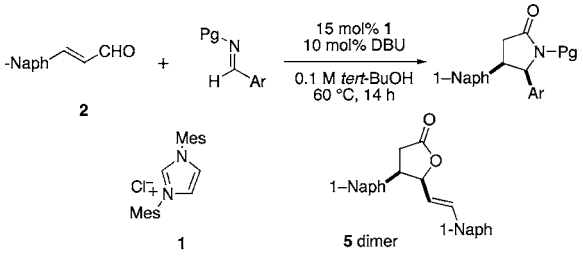
We reasoned that an efficient, catalytic process could be achieved if the initial addition of the catalyst to the imine was rendered reversible. To accomplish this, we synthesized and screened a variety of electron-rich *N*-sulfonyl imines for reaction with cinnamaldehyde derivative **2** (eq 2, Table 1). These studies led to the successful realization that *N*-4-methoxybenzenesulfonyl imines are ideally suited to catalytic annulations of imines and cinnamaldehydes (eq 3).[10] Significantly, NMR investigations revealed that while addition of the in situ-generated N-heterocyclic carbene to the imine is still the preferred reaction pathway, this addition is reversible over the time scale of the reaction and the catalyst reacts with the cinnamaldehyde, leading to product formation.[11]



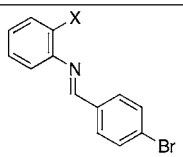
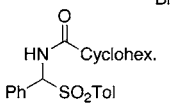
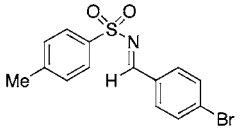
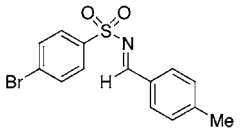
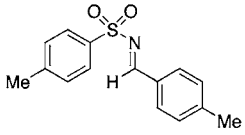
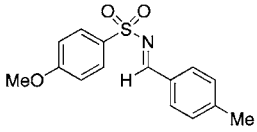
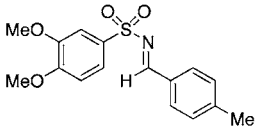
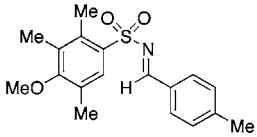
(3)

A variety of functionalized α,β-unsaturated aldehydes and *N*-4-methoxybenzenesulfonylimines give disubstituted γ-lactams in good yields under these catalytic conditions (Table 2).[12] The lactam products are formed with good to moderate

Table 1. Effect of Imine Protecting Groups



(2)

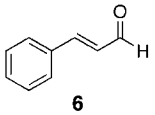
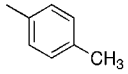
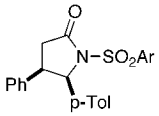
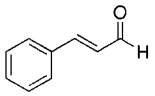
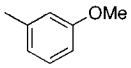
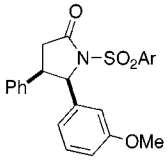
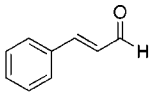
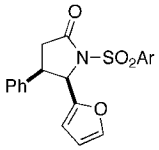
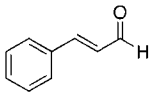
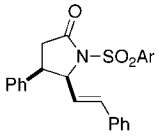
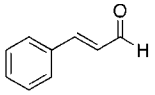
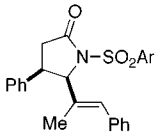
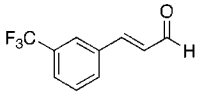
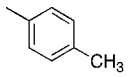
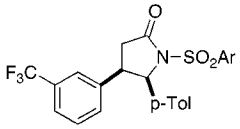
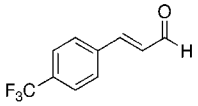
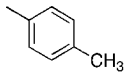
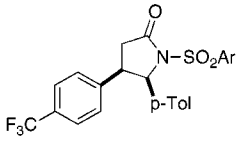
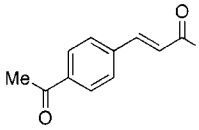
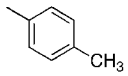
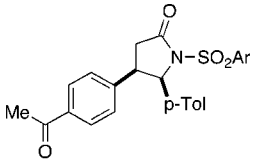
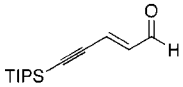
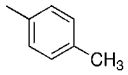
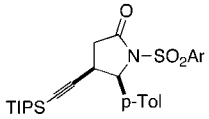
Entry	Imine		Conv.[b](%). (% dimer)[d]	Yield[c]/% (dr)
1		X=H	0 (15)	–
2		X=F	0 (91)	–
3		X=OMe	0 (69)	–
4[e]			>20 (trace)	–
5			38 (5)	11
6			14 (2)	–
7			93 (4)	64 (>10:1)
8			96 (4)	75 (>10:1)
9			73 (2)	Nd
10			0 (39)	–

[a] All reactions were performed with 1 equiv of **2**, 1 equiv of imine, 15 mol % IMes-Cl, and 10 mol % DBU at 0.1 M in *tert*-BuOH at 60 °C. [b] Ratio of remaining enal to lactam and/or lactone products as measured by ^{1}H NMR analysis of unpurified reaction mixtures. [c] Isolated yield following silica gel chromatography. [d] Lactone homodimer. [e] Performed with 10 equiv of NEt_3.

(9) For the irreversible reaction of N-heterocyclic carbenes with strong electrophiles, see: (a) Nair, V.; Bindu, V.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *116*, 5240−5245. (b) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289−4291.

(10) Only a few reports on the use of 4-methoxybenzenesulfonyl imines as electrophiles have appeared. In both cases, these provided few or no advantages over the *N*-tosyl imines. See: (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (b) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456−457.

Table 2. Catalytic Annulations of Enals and Imines via Catalytically Generated Homoenolates

entry	cinnamaldehyde	imine (R =)	Product	No.	yield[b]/ %	dr
1	 **6**	 **7**		**8**	70	4:1
2	 **6**	 **9**		**10**	69	3:1
3[c]	 **6**	 **11**		**12**	73	1.7:1
4[d]	 **6**	 **13**		**14**	61	8:1
5	 **6**	 **15**		**16**	62	5:1
6	 **17**	 **7**		**18**	70	3:2
7	 **19**	 **7**		**20**	70	3.5:1
8	 **21**	 **7**		**22**	65	3.5:1
9[e]	 **23**	 **7**		**24**	51	10:1

[a] Unless otherwise indicated, all reactions were performed with 1 equiv of enal, 1 equiv of imine, 15 mol % IMes-Cl, and 10 mol % DBU at 0.1 M in *tert*-BuOH at 60 °C for 14 h. Ar = 4-MeOC$_6$H$_4$. [b] Combined yield of lactam diastereoisomers after silica gel chromatography. [c] Conditions: 2 equiv of **11**, 75 °C, 63 h. [d] Reaction at room temperature. [e] Performed with addition of 1 equiv of **23** to 3 equiv of **7** over 3 h.

selectivity, with preference for the cis diastereomer.[13] Overall, an unusual reactivity pattern emerges: more electron-deficient aldehydes make for better nucleophiles, while more electron-rich imines are the preferred electrophiles. No stoichometric reagents were used in the annulations; side reactions arising from benzoin, Stetter, and aza-benzoin reactions were not observed, and only traces of the undesired lactone dimer of the enal were detected.[14] The annulations are tolerant of air and moisture, and do not require aqueous workup. This leads to an operationally simple, truly catalytic process: simply warming a *t*-BuOH solution of 1.0 equiv of enal and 1.0 equiv of imine in the presence of sub-

(11) For experiments and spectral data, see Supporting Information. Further studies on the mechanism and kinetics of the reversible addition of the catalyst to the imine are in progress.

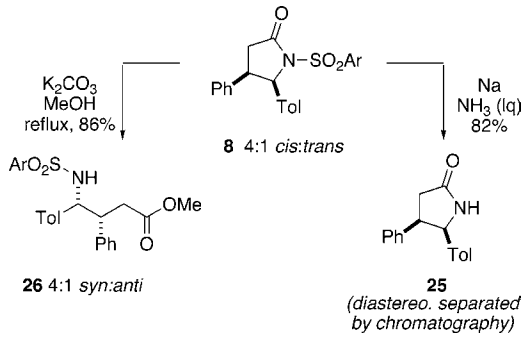
(12) **Typical Procedure for Catalytic Annulations.** Cinnamaldehyde (0.90 g, 6.8 mmol, 1.0 equiv), imine **13** (2.05 g, 6.8 mmol, 1.0 equiv), and IMes-Cl (0.35 g, 1.0 mmol, 15 mol %) were weighed into an oven-dried flask. The flask was sealed with a septum, evacuated, and back-filled with argon. To this mixture was added 68 mL of *tert*-BuOH followed by DBU (0.10 mL, 0.68 mmol, 10 mol %), and the resulting solution was stirred for 14 h at 25 °C. The reaction was concentrated under reduced pressure and purified by flash chromatography (4:1 hexane/EtoAc) to afford the lactam products as a white solid (1.8 g, 61% yield, 8/1 cis:trans).

stoichiometric amounts of commercially available IMesCl and DBU leads directly to the γ-lactam products.

Remarkably, optimal conditions mandate the use of protic reaction solvents; no lactam products are observed when the annulations are performed in THF, toluene, or CH_2Cl_2. Interestingly, these results starkly contrast our recent discovery that homoenolates catalytically generated from triazolium salts can be protonated under mild conditions, leading to catalytically generated activated carboxylates suitable for esterifications.[15]

The lactam products are synthetically useful structures for the synthesis of natural products and pharmaceutical precursors. The *N*-sulfonyl protecting group is easily removed under a variety of reductive conditions (Scheme 2).[16] Alternatively, this moiety activates the lactam toward nucleophilic ring opening by alkoxides and other nucleophiles, leading to γ-amino acid derivatives.

Scheme 2. Deprotection and Ring-Opening of Catalytically Prepared *N*-Sulfonyl Lactams



In summary, we have identified *N*-4-methoxybenzenesulfonyl imines as a solution to electrophilic inhibition of nucleophilic catalysis in the N-heterocyclic carbene-catalyzed addition of enals to imines. This unique process affords disubstituted γ-lactam products through the synthetically challenging addition of homoenolate equivalents to imines. Furthermore, it complements ongoing efforts in direct, organocatalytic methods for carbon−carbon bond formation and invites further mechanistic investigations on the unique chemistry of catalytically generated reactive species.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR studies of catalyst inhibition. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Imine decomposition and unreacted enal constitute the mass balance.

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