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cis-Enals in *N*-heterocyclic carbene-catalyzed reactions: distinct stereoselectivity and reactivity†

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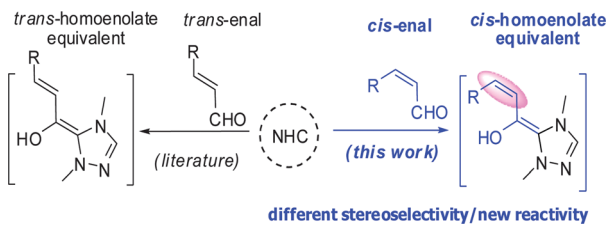
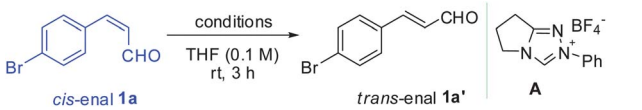
The first successful generation of *cis*-homoenolate equivalents from *cis*-enals under the catalysis of *N*-heterocyclic carbenes (NHCs) has been realized. The *cis*-homoenolate intermediates undergo effective reactions with α,β-unsaturated imines to afford chiral cyclic ketone products. Compared to the *trans*-enals, *cis*-enals show different stereoselectivities and new reactivity patterns.

Homoenolate has been an important intermediate in both mechanistic and synthetic studies since its first report in 1962.[1] Recently with *N*-heterocyclic carbene (NHC) catalysis,[2] the generation of homoenolate equivalents from *trans*-enals has been proven to be a powerful approach in synthetic transformations.[3] In principle, the formation of *cis*-homoenolate equivalents from the reaction of *cis*-enals with NHC catalysts is possible (eqn (1)). Thus, the use of *cis*-enals may allow the efficient access to diastereomers of reaction products that are otherwise challenging to obtain.[4,5] However, in addition to their problematic synthesis,[6] the facile isomerization of *cis*-enals or their intermediates to the *trans* isomers under catalytic conditions often precludes their use. Nevertheless, their potential utility in providing alternative stereochemical outcomes makes them attractive starting materials for the development of new catalytic reactions. In the attempted reactions using *cis*-enal substrates under NHC catalysis for homoenolate generation, only products identical to those derived from the corresponding *trans*-enals were obtained.[7,8] Here we report the first successful employment of *cis*-enals in NHC-mediated *cis*-homoenolate generation. We have shown that *cis*-enals can offer different stereoselectivities and somewhat surprisingly distinct reactivity patterns. This result is expected to encourage a re-evaluation of *cis*-enals in organic catalytic reactions involving enal substrates for both synthetic applications and mechanistic investigations.[9]



We first studied how each of the common components (base, counter anion, NHC catalyst, *etc.*) under typical NHC catalysis conditions affected the enal isomerizations. As can be seen from Table 1, the isomerization caused by base DBU alone was minimal, while the DBU–acid salts present in typical NHC catalytic conditions could isomerize the *cis*-enal (entries 2–3). The counter anions present under NHC catalysis conditions could dramatically affect the enal isomerizations (entries 2–4).[10] When BF_4^- was the counter anion, the isomerization could be significantly suppressed (entry 3). Additional studies indicated that the presence of NHC (**A**) did not lead to further enal isomerization, with most enal remaining as the *cis*-enal isomer (entry 5), which suggested that the stereo-integrity of *cis*-enals could be conserved when

Table 1 Suppression of *cis*-to-*trans* enal isomerization



Entry	Conditions	**1a** : **1a'**[a]
1	DBU (30 mol%)	>99 : 1
2	DBU·HCl (30 mol%)	12 : 88
3	DBU·HBF_4 (30 mol%)	77 : 23
4	DBU (30 mol%), HOAc (30 mol%)	24 : 76
5	**A** (20 mol%), DBU (30 mol%)	79 : 21
6	As entry 5, but for 7 h	62 : 38
7	As entry 5, but for 12 h	<5 : 95[b]

[a] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [b] ~10% enal left as *trans*/*cis*-enal mixture; ~90% of the enal was converted to acid and lactone as estimated by ^{1}H NMR analysis; see main text). DBU = 1,8-diazabicycloundec-7-ene.

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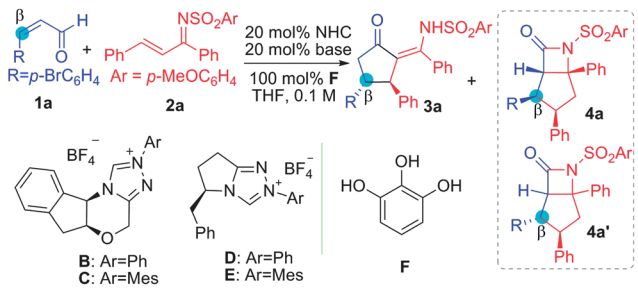
developing reactions based on the NHC-bound homoenolate intermediates of *cis*-enals. Over a longer reaction time (*e.g.*, 12 h) in the presence of NHC (**A**), the majority of the enal substrate (~90%) converted to acid, and a trace amount of the γ-lactone product, formed *via* addition of the homoenolate β-carbon derived from one enal molecule to the aldehyde moiety of another enal molecule, was obtained.[3c] The remaining ~10% enal was mostly *trans*-isomer (entry 7). Encouraged by this observation that enal isomerization could be suppressed over a reasonable period of time (entries 3 and 5), we evaluated the reaction between *cis*-enal **1a** and α,β-unsaturated imine **2a**, as summarized in Table 2. The corresponding *trans*-enal reactions with unsaturated imines[11] have previously been reported by Bode and co-workers under NHC catalysis to give bicyclic β-lactam **4a** (Table 2).[12]

We started by using **A** as the NHC pre-catalyst. We initially expected to generate *cis*-homoenolate from *cis*-enal **1a** and thus to obtain a bicyclic β-lactam adduct **4a′** as a diastereomer of the Bode reaction product **4a**. To our surprise, an unexpected ketone adduct (**3a**) was observed in 30% isolated yield (entry 1). The new adduct **3a** possesses opposite stereochemistry on the enal β-carbon, as compared to that of the *trans*-enal-derived lactam product **4a** (confirmed by X-ray structure of **3g**).[13] Mechanistically, our ketone product **3a** was formed presumably *via* an intramolecular Claisen-type addition of the enamide α-carbon to the NHC-bound ester intermediate **III** as a key step (Scheme 1). It should be noted that under NHC catalysis, the addition of carbon nucleophiles for the release of catalyst is relatively rare. Elegant examples include Nair *et al.*'s intramolecular addition of carbon nucleophiles using a dibenzylidene cyclopentanone substrate,[3l] and Smith *et al.*'s NHC-mediated rearrangement reactions involving intermolecular addition of enolates to acylazolium intermediates.[14]

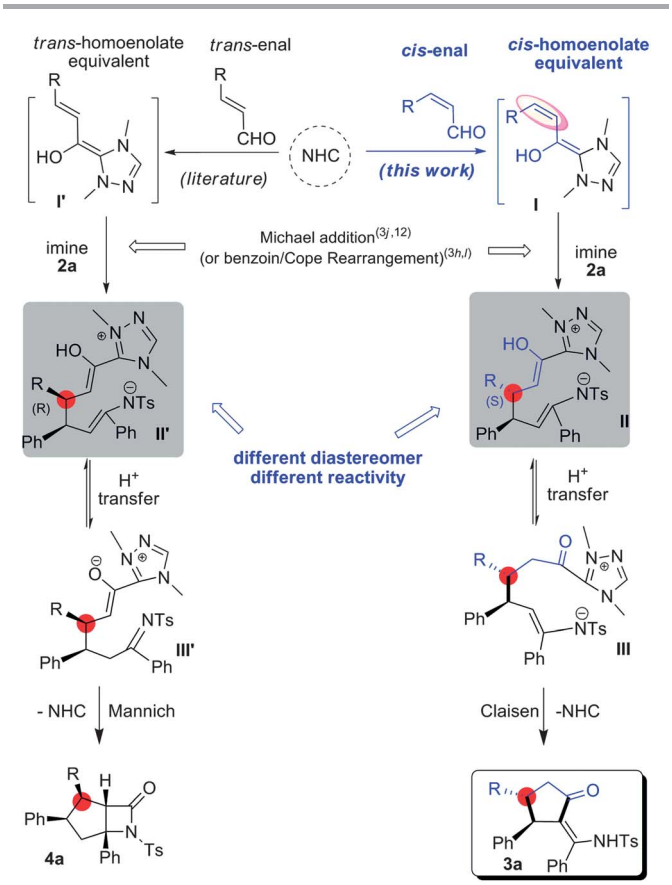
Postulated pathways for the comparison of the reactions of *cis*- and *trans*-enals are shown in Scheme 1. The reaction of the conjugated Breslow intermediate (**I** from *cis*-enal or **I′** from *trans*-enal) with unsaturated imine **2a** likely goes through a concerted benzoin/Cope rearrangement[3j,12] process or a direct Michael addition pathway.[3h,l] The resulting intermediates **II** and **II′** are diastereomers of each other. These two diastereomers then display distinct reactivity patterns. Specifically, the intermediate **II** from the *cis*-enal underwent likely reversible proton transfer to give intermediate **III** followed by Claisen-type reaction involving addition of the enamide carbon to the NHC-bound ester

Table 2 Screening of chiral NHC catalysts and bases[a]



Entry	NHC	Add.	Base	**3a** : **4a**[b]	Yield[c] (%)	ee[d] (%)
1	**A**	—	DBU	41 : 59	30	—
2	**A**	**F**	DBU	94 : 6	65	—
3	**A**	**F**	*t*-BuOK	95 : 5	53	—
4	**A**	**F**	KHMDS	95 : 5	61	—
5	**A**	**F**	DMAP	75 : 25	22	—
6	**B**	**F**	DBU	70 : 30	46	−77
7	**C**	**F**	DBU	72 : 28	41	−99
8	**D**	**F**	DBU	85 : 15	57	92
9	**E**	**F**	DBU	65 : 35	49	95
10[e]	**D**	**F**	TEA	99 : 1	52	92
11[e]	**D**	**F**	DIEA	99 : 1	61	92
12[e]	**D**	**F**	KHMDS	92 : 8	65	90
13[e]	**D**	**F**	*t*-BuOK	90 : 10	55	91
14[e,f]	**D**	**F**	DIEA	99 : 1	75	92
15[e,g]	**D**	**F**	DIEA	99 : 1	71	91
16[e,f]	**D**	—	DIEA	83 : 17	37	91
17[e,f]	**D** (10 mol%)[h]	**F**	DIEA	98 : 2	58	90

[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.1 mmol), rt, 12 h. [b] Determined *via* ^{1}H NMR analysis of unpurified reaction mixtures. [c] Isolated yield based on **2a**. [d] Enantiomeric excess of **3a**, determined *via* chiral-phase HPLC; absolute configuration was determined by X-ray (**3g**, see the ESI). [e] **1a** (0.3 mmol), **2a** (0.1 mmol), base (40 mol%), rt, 24 h. [f] 0.5 M. [g] 1.0 M. [h] 10 mol% **D**. Mes = 2,4,6-trimethylphenyl. TEA = triethylamine. DMAP = 4-(dimethylamino)pyridine. KHMDS = potassium bis(trimethylsilyl)amide. DIEA = *N*,*N*′-diisopropylethylamine.

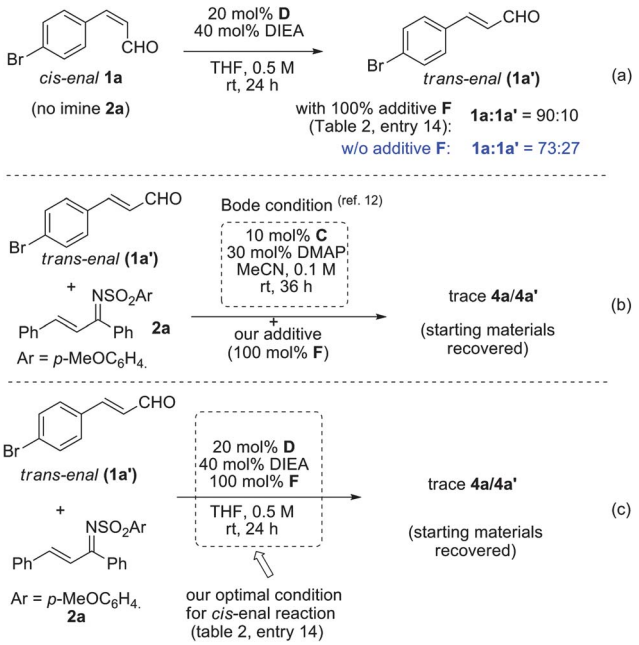


Scheme 1 Postulated reaction pathway of *cis*-enal **1** and unsaturated imine **2** (in comparison with the corresponding *trans*-enal reactions).

equivalent to afford ketone product **3a**. In contrast, intermediate **II′** derived from *trans*-enal underwent a Mannich-type reaction to eventually form previously reported lactam product **4a**.[12] The formation of different products (ketone **3a** *vs.* lactam **4a**) is a result of the different stereoconfigurations (different diastereomers) of the key intermediates **II** and **II′** generated from the *cis*- and *trans*-enals respectively. Notably, the observation of different products (4- *vs.* 5-membered lactones) has been reported in Bode's reaction of enals with α-hydroxy enones.[15] In Bode's work, the use of two different NHC catalysts led to different diastereomeric intermediates that cyclized in different manners (4- *vs.* 5-membered ring formation). In our reaction, the use of *cis*-enals led to a different stereoselectivity, and subsequently, an alternative reaction pattern was realized to form previously unobserved cyclic ketone products.

The lactam adduct **4a**, identical to that reported by Bode,[12] was also observed under most conditions with **A** as the NHC pre-catalyst (Table 2). The lactam **4a** likely came from direct reaction of the corresponding *trans*-enal **1a′** (resulting from isomerization of *cis*-enal **1a**) and imine **2a**. We then found that phenol-derived additives could significantly promote the desired *cis*-enal reactivity.[16] After additional studies, pyrogallol **F** was found to be an excellent additive to promote the desired *cis*-enal reactions to form **3a** with the undesired formation of **4a** suppressed for reasons that remain unclear at this moment (entry 2; for examples of other phenol additives, see ESI†). The diastereoselectivity of **3a** remained unaffected with the use of additive **F**. We then moved to develop enantioselective versions of the *cis*-enal reactions. Amino-indanol derived NHC pre-catalysts **B** (N-Ph) and **C** (N-Mes) were found to mediate the reaction with 41–46% yields and 77% and 99% ee respectively (entries 6–7). Amino acid-derived N-Ph substituted catalyst **D** and N-Mes substituted catalyst **E** (entries 8–9) were more effective than **B** and **C**. With **D** as the catalyst, **3a** was isolated in 57% yield with 92% ee (**3a** : **4a** = 85 : 15, entry 8). Finally, by using **D** as the NHC-precatalyst, DIEA as the base, and 100 mol% phenol derivative **F** in THF with 0.5 M concentration of **2a**, the reaction proceeded effectively to give ketone **3a** as a single diastereomer in 75% isolated yield and 92% ee, with only a trace amount of lactam **4a** observed (**3a** : **4a** >99 : 1, entry 14).

As a comparison, under otherwise identical conditions without using additive **F**, the reaction gave a lower 37% yield of **3a** along with minor product **4a** in a 83 : 17 ratio (entry 16; compared with entry 14). We also evaluated the *cis*-enal isomerization under the optimal conditions with chiral catalyst **D** (Table 2, entry 14; in the absence of imine substrate **2a**). Similar to our observations in Table 1, the extent of *cis*-enal isomerization was relatively small (Scheme 2a). The corresponding reaction using *trans*-enal substrate (*e.g.*, **1a′**) and imine **2a** was also examined. Under Bode's optimal conditions,[12] plus our additive (100 mol% **F**), nearly none of products (**3a**, **4a**/**4a′**) were detected (Scheme 2b). It appears that the additive **F** completely suppresses this NHC-catalyzed reaction. Under our optimal conditions for *cis*-enal **1a**, with both achiral and chiral NHC catalysts (Table 2, entries 2 and 14), the corresponding reactions using *trans*-enal substrate **1a′** led to low conversion (<10%, most starting material recovered) with the previously observed Bode



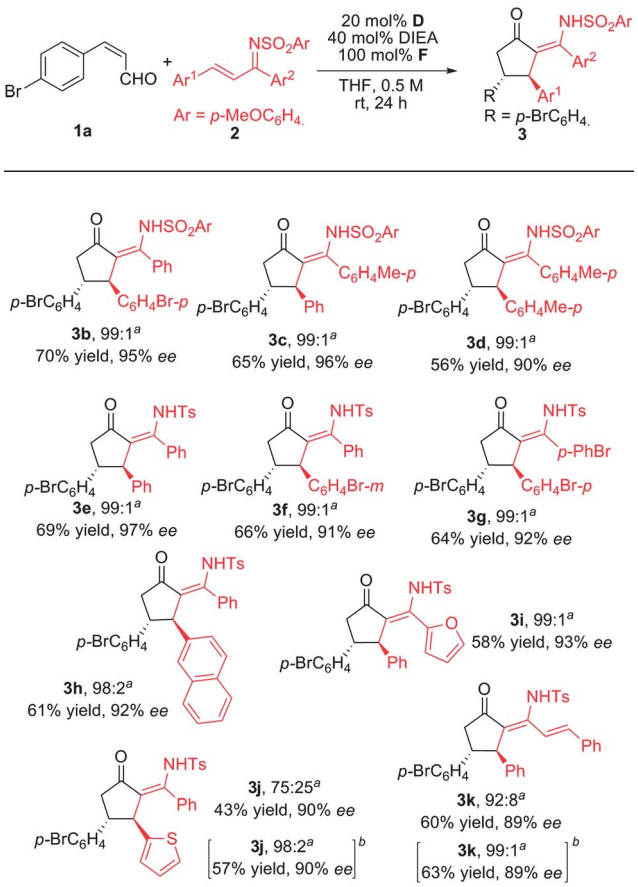
Scheme 2 Control experiments to understand the reactivity of *cis*-enal (in comparison with *trans*-enal).

product **4a** as the major product (Scheme 2c).[17] These results clearly indicated the generation of *cis*-homoenolate equivalent from *cis*-enals; and the *cis*-homoenolate intermediate led to the formation of product **3a**. The phenol additive (*e.g.*, **F**) was observed to facilitate the reactions of *cis*-enals with α,β-unsaturated imines, although the exact mode of action remained unclear.

Having established the optimal conditions, we examined the scope of the α,β-unsaturated imines **2** in the reaction with *cis*-enal **1a** (Scheme 3). Imines (**2**) with Ar^1 and Ar^2 substituted with electron-donating and -withdrawing functionalities on the phenyl rings all gave the desired ketone products in good yields and excellent enantioselectivities (**3b–d**). The reactions proceeded readily with imines having other *N*-protecting groups (*e.g.*, Ts) as well. Interestingly, heteroaryl imines were also found to be good substrates (**3i** and **3j**). Switching Ar^1 to a thiophenyl group or Ar^2 to a vinyl group (**3j** and **3k**) led to lower product selectivities (**3** : **4**) under the typical conditions used for other substrates; in these cases a switch of base from DIEA to TEA afforded better product selectivities and yields (**3j** and **3k**).

We next evaluated the effect of the *cis*-enal substrate in reactions with imine **2** (Scheme 4). Substituents on the β-phenyl ring of the *cis*-enal **1** did not influence the reaction outcome much, giving the ketone products in acceptable yields, excellent product selectivities (**3** : **4**) and enantioselectivities (**3a** and **3l–m**). Enals with heteroaryl or aliphatic substituents on the β-position also worked well (**3o** and **3p**).

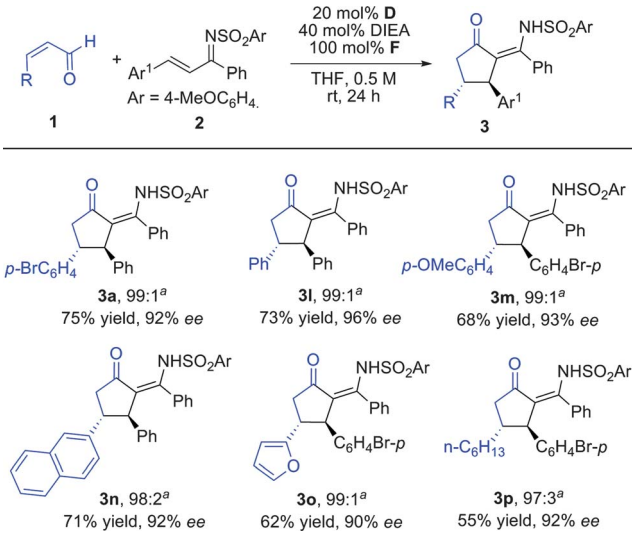
The chiral cyclic ketone products **3** are amenable to further transformations to potentially useful molecules (Scheme 5). For example, under oxidative cleavage with ozone, **3a** gave 2-hydroxy cyclopentenone **5** in good yield. 2-Hydroxy cyclopentenone is a core structure found in many bioactive natural products such as



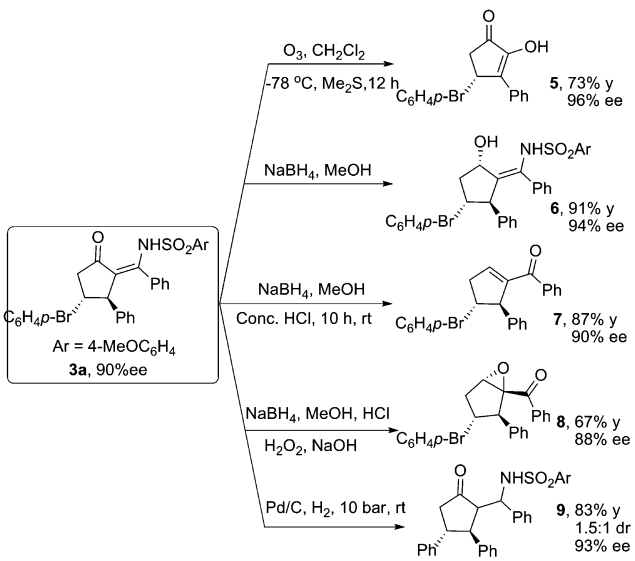
Scheme 3 Scope of α,β-unsaturated imines. Reactions were performed under conditions identical to those for Table 2, entry 14. The ketone products (**3**) were formed essentially as a single diastereomer (determined *via* ^{1}H NMR analysis of unpurified reaction mixtures). Reported yields are the isolated yields based on **2**. [a] Ratio of ketone product **3** to lactam adduct **4**. [b] TEA as base.

flavaglines and terpestacin.[18] Reduction of **3a** by $NaBH_4$ gave cyclic alcohol **6** as essentially a single diastereomer in 94% ee. This alcohol adduct (**6**) could undergo dehydration to give optically enriched α,β-unsaturated ketone **7** in excellent yield. A one-pot oxidative treatment of the reduction mixture of **3a** could lead to epoxide product **8** as a single diastereomer with 67% overall yield and 88% ee. A Pd/C-catalyzed hydrogenation of **3a** could also been achieved to give debrominated β-amino ketone **9** in 83% yield and 93% ee, albeit in low diastereoselectivity.

In summary, we have successfully employed *cis*-enals in NHC catalyzed transformations. The catalytically generated *cis*-homoenolate intermediates allow opposite diastereoselectivities and even new reaction patterns to be realized. Mechanistically, the use of *cis*-enals sheds insightful light on NHC-mediated enal activations and the reactivities of the enal-derived intermediates. The current NHC catalysis (as well as enal iminium catalysis) is mainly developed for *trans*-enals. Our present study indicates that these catalysts and/or conditions are at least not optimal for *cis*-enals with respect to reaction selectivity and/or efficiency. We expect that further studies on the *cis*-enal and related catalytic processes will lead to new or significantly improved catalysts, richer product diversities, and deeper mechanistic understanding.



Scheme 4 Scope of *cis*-enals. Reactions were performed under conditions identical to those for Table 2, entry 14. Ketone products (**3**) were formed essentially as a single diastereomer (determined *via* ^{1}H NMR analysis of unpurified reaction mixtures). Reported yields are the isolated yields based on **2**. [a] Ratio of ketone product **3** to lactam adduct **4**.



Scheme 5 Synthetic transformations of ketone product **3a**.

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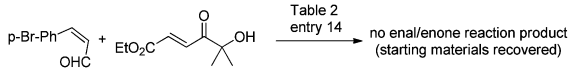
14 (*a*) J. E. Thomson, K. Rix and A. D. Smith, *Org. Lett.*, 2006, **8**, 3785; (*b*) J. E. Thomson, C. D. Campbell, C. Concellón, N. Duguet, K. Rix, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2008, **73**, 2784; (*c*) C. D. Campbell, C. J. Collett, J. E. Thomson, A. M. Z. Slawin and A. D. Smith, *Org. Biomol. Chem.*, 2011, **9**, 4205.

15 J. Kaeobamrung and J. W. Bode, *Org. Lett.*, 2009, **11**, 677. Following one referee's suggestion, we tried Bode's α-hydroxy enone substrate to react with *cis*-enal under our conditions. No product between enal and enone was observed. Instead, enone was recovered; most enal was recovered as a mixture of *cis*/*trans*-isomers; the enal was partly converted to acids.



16 Phenol derivatives have been used as H-bonding additives in enamine catalysis, for an example, see: (*a*) T. J. Peelen, Y. Chi and S. H. Gellman, *J. Am. Chem. Soc.*, 2005, **127**, 11598. For examples of using phenol or its derivatives in NHC-mediated reactions, see: (*b*) C. Concellón, N. Duguet and A. D. Smith, *Adv. Synth. Catal.*, 2009, **351**, 3001; (*c*) J. A. Cowan, J. A. C. Clyburne, M. G. Davidson, R. L. W. Harris, J. A. K. Howard, P. Küpper, M. A. Leech and S. P. Richards, *Angew. Chem., Int. Ed.*, 2002, **41**, 1432; (*d*) C. M. Filloux, S. P. Lathrop and T. Rovis, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20666; (*e*) D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2011, **133**, 10402; (*f*) X. Fang, X. Chen and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2011, **50**, 11782.

17 Under our optimal conditions for *cis*-enal **1a** with both achiral and chiral NHC catalysts (Table 2, entries 2 and 14), the corresponding reactions using *trans*-enal substrate **1a′** in several conditions (solvents such as THF, EtOAc, CH_2Cl_2, toluene, CH_3CN, and bases such as TEA, DMAP, DBU and KHMDS) led to only low conversion (<10%; starting materials recovered) with the previously observed Bode's lactam **4a** as the major product.

18 (*a*) A. G. Myers, M. Siu and F. Ren, *J. Am. Chem. Soc.*, 2002, **124**, 4230; (*b*) B. M. Trost, G. Dong and J. A. Vance, *J. Am. Chem. Soc.*, 2007, **129**, 4540; (*c*) F. Thuaud, Y. Bernard, G. Turkeri, R. Dirr, G. Aubert, T. Cresteil, A. Baguet, C. Tomasetto, Y. Svitkin, N. Sonenberg, C. G. Nebigil and L. Desaubry, *J. Med. Chem.*, 2009, **52**, 5176.

