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An Isothiourea-Catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides

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Supporting Information

ABSTRACT: Benzotetramisole promotes the catalytic asymmetric [2,3]-rearrangement of allylic quaternary ammonium salts (either isolated or prepared *in situ* from *p*-nitrophenyl bromoacetate and the corresponding allylic amine), generating *syn*-α-amino acid derivatives with excellent diastereo- and enantioselectivity (up to >95:5 dr; up to >99% ee).

The [2,3]-rearrangement[1] of glycine-derived allylic ammonium ylides is widely recognized as a versatile process for the synthesis of stereodefined unnatural α-amino acid derivatives containing multiple stereocenters.[2] Current limitations of this process include the difficulty associated with the generation and isolation of the reactive ammonium salts,[3] alongside the paucity of catalytic asymmetric methods for inducing enantiocontrol.[4] Recent work by Tambar and Sohelie has elegantly utilized Pd-catalyzed allylic substitution to facilitate tandem ammonium ylide generation and [2,3]-rearrangement, generating racemic *anti*-configured products **3** with high diastereoselectivity (Scheme 1, eq 1).[5] While asymmetric [2,3]-rearrangements of allylic ammonium ylides can be induced by chiral auxiliary control as demonstrated by Sweeney and co-workers,[4a] Somfai et al. have applied stoichiometric asymmetric Lewis acids to promote the enantioselective rearrangement of allylic amines **5** (Scheme 1, eq 2).[4b,6] Within the past 15 years, advances in asymmetric organocatalysis[7] have been applied to asymmetric [3,3]-sigmatropic rearrangements.[8] However, organocatalytic [2,3]-

Scheme 1. [2,3]-Rearrangements of Allylic Ammonium Ylides

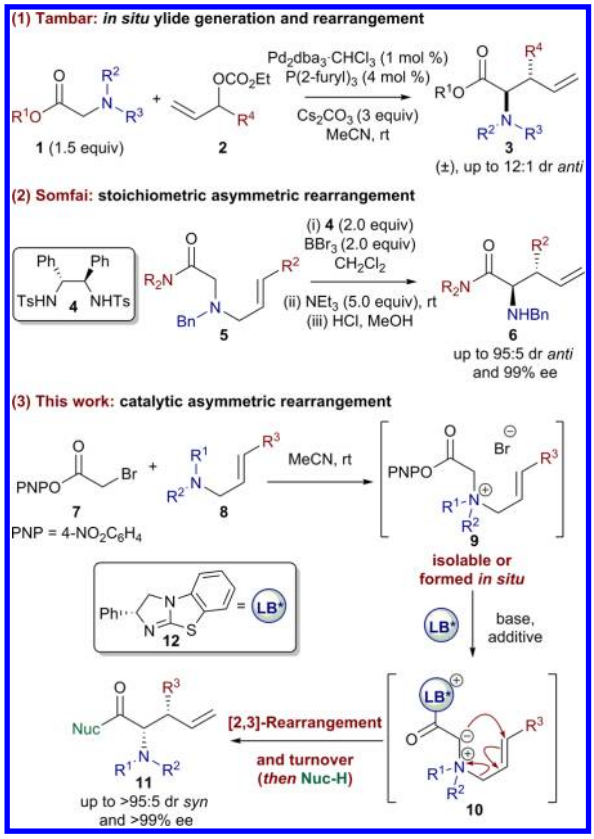
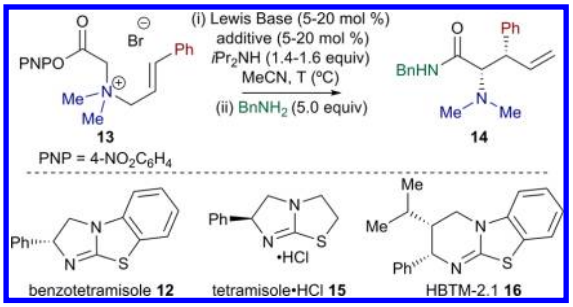


Table 1. Optimization of Reaction Conditions



entry[a]	LB	additive	T (°C)	yield (%)[b,c]	dr[d]	ee[e]
1	**15**	–	rt	(83)[c]	89:11	81 (*ent*)
2	**15**	HOBt	rt	68	93:7	84 (*ent*)
3	**15**	HOBt	0 to rt	88	92:8	89 (*ent*)
4	**15**	HOBt	−20	65	91:9	93 (*ent*)
5	**12**	–	−20	61	92:8	95
6	**12**	**HOBt**	**−20**	**76**	**>95:5**	**99**
7	**16**	HOBt	−20	(33)[c]	62:38	ND[f]
8	**12**	HOAt	−20	49	90:10	98
9	**12**[g]	HOBt[g]	−20	62	88:12	96
10	**12**[h]	HOBt[h]	−20	41[i]	79:21	92

[a]Reactions performed on 0.24 mmol scale, 20 mol %, unless stated otherwise. [b]Isolated yield after chromatographic purification of >95:5 dr. [c]Yield in parentheses determined by ^{1}H NMR in comparison with internal standard (4-nitrotoluene). [d]Determined by ^{1}H NMR analysis of crude material. [e]Determined by chiral HPLC analysis. [f]ND = not determined. [g]10 mol %. [h]5 mol %. [i]84:16 mixture of diastereoisomers (isolated).

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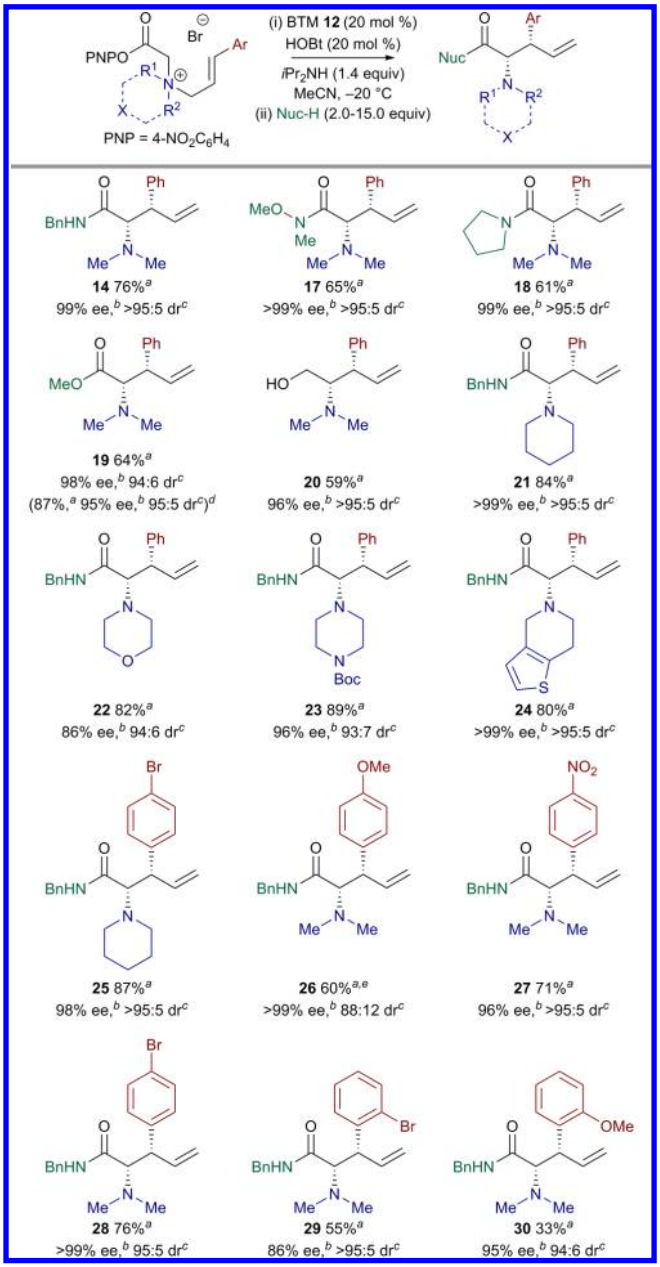
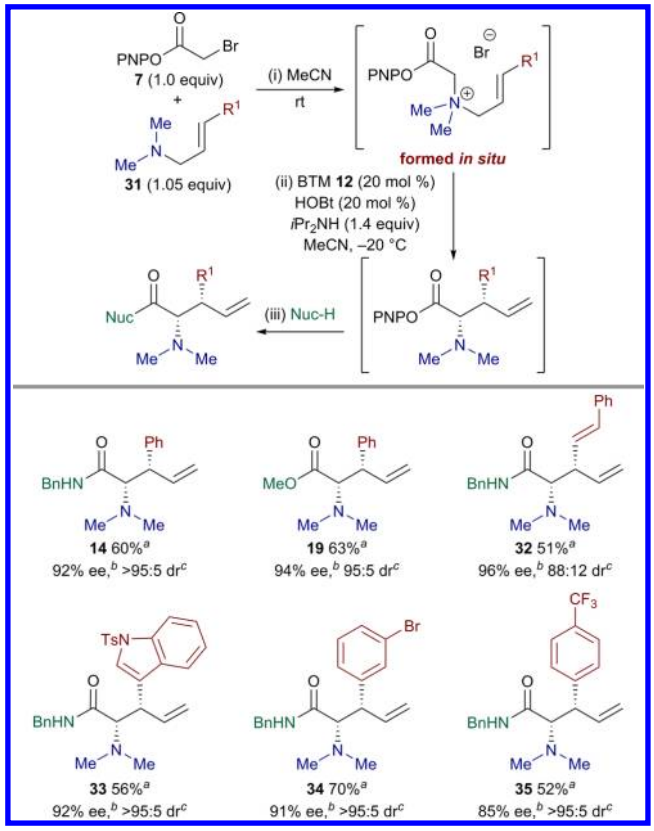
Table 2. Scope of Isolable Ammonium Salts



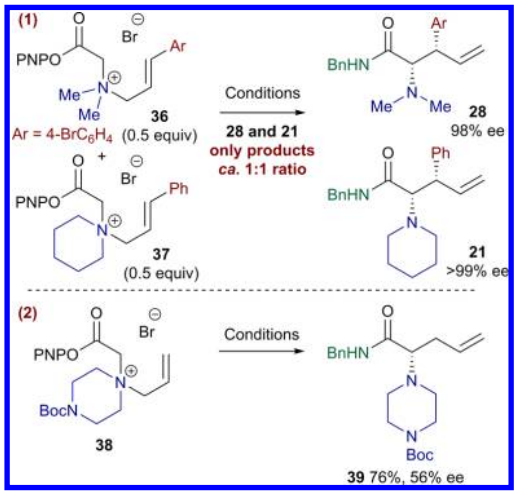
[a]Isolated yield after chromatographic purification of >95:5 dr. [b]Determined by chiral HPLC analysis. [c]Determined by ^{1}H NMR analysis of crude material. [d]Performed on 9.6 mmol scale. [e]Isolated in 93:7 dr.

Table 3. *In Situ* Generated Ammonium Salts



[a]Isolated yield after chromatographic purification of >95:5 dr. [b]Determined by chiral HPLC analysis. [c]Determined by ^{1}H NMR analysis of crude material.

Scheme 2. Mechanistically Significant Examples[a]



[a]Conditions: (i) **12** (20 mol %), HOBt (20 mol %), iPr$_2$NH (1.4 equiv), MeCN, −20 °C, 24 h; (ii) BnNH$_2$ (5.0 equiv), rt, 24 h.

sigmatropic rearrangements are an underexplored concept, with the secondary amine-catalyzed [2,3]-Wittig rearrangement developed by Gaunt et al. representing the current state-of-the-art within this area.[9] Given our interest in Lewis base promoted organocatalytic processes,[10] in this manuscript we show that sub-stoichiometric isothioureas[11] promote the asymmetric [2,3]-rearrangement of ylides **10** derived from isolable or *in situ* generated allylic ammonium salts **9**, forming stereodefined α-amino acid derivatives **11** with excellent *syn*-diastereo- and enantiocontrol (up to >95:5 dr and 99% ee) (Scheme 1, eq 3).

Proof of concept studies focused upon asymmetric isothiourea-promoted [2,3]-rearrangement of pre-formed allylic ammonium salt **13** bearing an activated *p*-nitrophenyl ester (Table 1).[12,13] Treatment of ammonium salt **13** with tetramisole·HCl **15** (20 mol%) and iPr$_2$NH at room temperature (rt) led to [2,3]-rearrangement, with subsequent addition of benzylamine giving amide **14** in 89:11 dr and promising 81% ee (entry 1).[14] Further optimization showed that addition of HOBt (20 mol%) as a co-catalyst led to improved diastereo- and enantiocontrol (entry 2).[15] Alternative organic bases such as iPr$_2$NEt or NEt$_3$ could also be used without affecting

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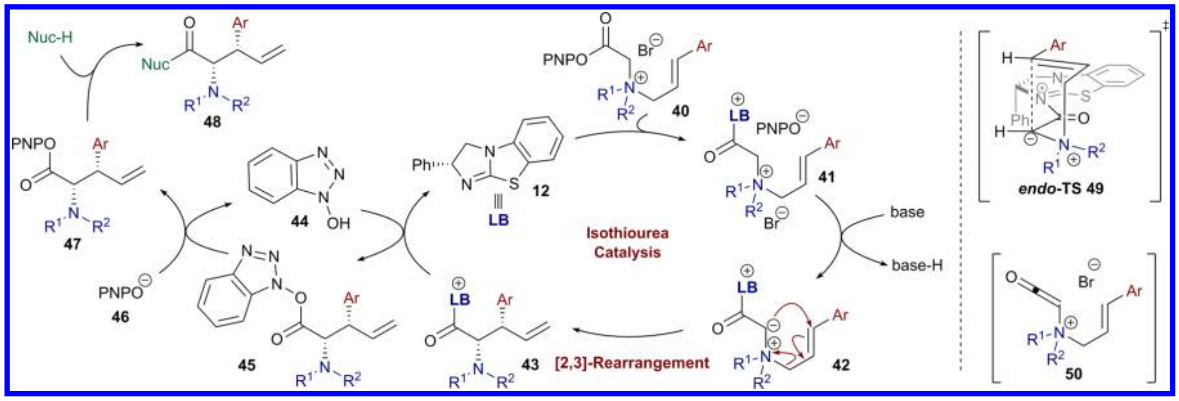
Scheme 3. Mechanistic and Stereochemical Proposal



stereocontrol, although *N*-methylmorpholine gave reduced diastereocontrol.[16] Lowering the reaction temperature to −20 °C gave increased product enantiomeric excess, while catalyst variation showed that benzotetramisole (BTM) was optimal, giving **14** in 76% yield, >95:5 dr, and 99% ee (entries 3−7). The additive HOBt is essential to achieve excellent stereocontrol when using BTM at −20 °C (entries 5 and 6), while reduced catalyst loadings gave lower, but still acceptable, asymmetric induction (entries 9 and 10).

With an optimized protocol identified, the scope of this process was initially examined through sequential variation of the nucleophile (Table 2). Using ammonium salt **13**, *N*,*O*-dimethylhydroxylamine, pyrrolidine, methoxide, or $LiAlH_4$ could be used to generate functionalized amino carbonyl and alcohol compounds **17**−**20** in good yields and high dr and ee. This process is readily scalable, with 1.95 g of amino ester **19** (86% yield, 95:5 dr, 95% ee) generated from 9.6 mmol of salt **13**. Various *N*-substituents encompassing simple and functionalized piperidines, morpholine and *N*-Boc-piperazine motifs are readily accommodated, giving functionalized amino amides (**21**−**25**) in excellent yield, dr, and ee (80−89%, >95:5 dr, and >99% ee). Variation of the allylic *C*(3)-aryl substituent within the salt showed that both electron-donating and -withdrawing 4-substituents are well tolerated (**26**−**28**). 2-Substitution of the aryl ring can also be incorporated, albeit in only modest isolated yields but high dr and ee (**29** and **30**).

Further studies into the scope of the reaction were limited by the difficulty in the formation and isolation of certain ammonium salts. This was circumvented through the development of a one-pot protocol composed of *in situ* formation of the ammonium salt, followed by direct [2,3]-rearrangement under isothiourea catalysis (Table 3). Treatment of *p*-nitrophenyl bromoacetate **7** with excess amine **31** (R^1 = phenyl) followed by rearrangement and addition of benzylamine or NaOMe, gave both **14** and **19** respectively in comparable yield, ee and dr to rearrangement with of the isolated ammonium salt **13**. Pleasingly, this one-pot process allows the incorporation of styryl, heteroaryl and alternative aryl functional groups (**32**−**35**), for which isolation of the corresponding ammonium salts proved difficult in our hands.

Crossover studies with **36** and **37** (Scheme 2, eq 1) indicate that the allylic transfer process is intramolecular, consistent with the expected [2,3]-sigmatropic rearrangement.[16] Further mechanistic investigations showed that epimerization or racemization is not observed upon retreatment of the major diastereoisomer to the reaction conditions. Probing of the substrate scope showed that reduced enantioselectivity (56% ee) is observed with an *N*-allyl rather than a *N*-cinnamyl unit (**39**, Scheme 2, eq 2), indicating an aryl or vinyl unit may be a structural requirement for high enantioselectivity in this process.[17]

While a Brønsted base-catalyzed mechanism cannot be ruled out at present, the following mechanistic possibilities and catalytic cycle for this transformation are proposed (Scheme 3). Dicationic acyl ammonium ion **41**[18] can be formed through direct *N*-acylation of BTM (**12**) with **40**, with deprotonation of **41** with a suitable base forming ylide **42**. Alternatively, **42** may arise from the addition of **12** to ketene **50**, formed by formal elimination of *p*-nitrophenol from **40**.[19] [2,3]-Rearrangement of **42** gives acyl isothiouronium **43** that can either be intercepted by *p*-nitrophenoxide (**46**),[20] or alternatively with HOBt (**44**) as a nucleophilic co-catalyst followed by **46**, to give **47** in a second catalytic cycle as previously described by Rovis et al.[15] The observed *syn*-diastereoselectivity[21] may arise from the rearrangement occurring preferentially through an *endo*-type pre-transition-state assembly **49**. In this array, the carbonyl oxygen preferentially lies *syn* to the S atom within the isothiouronium ion, allowing a stabilizing electrostatic or n_o to σ^*_{C-S} interaction.[22] The stereodirecting phenyl unit adopts a pseudoaxial position to minimize 1,2-steric interactions, with rearrangement occurring *anti* to this substituent. A π-cation interaction between the allylic *C*(3)-aryl or styryl substituent and the acyl isothiouronium ion, previously suggested in other asymmetric isothiourea-catalyzed processes,[22d,23] is proposed as a necessary requirement for high stereocontrol.

In summary, we have developed the first catalytic asymmetric [2,3]-rearrangement of allylic ammonium ylides. Isothiourea BTM **12** promotes the rearrangement of *p*-nitrophenyl ester ammonium salts, producing *syn*-configured α-amino acid derivatives with excellent stereocontrol (up to >95:5 dr and >99% ee). Further investigations into this process are currently being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, X-ray structural data for **29**, and spectral and HPLC data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Stevens, T. S.; Creigton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193−3197. (b) Millard, B. J.; Stevens, T. S. *J. Chem. Soc.* **1963**, 3397−3403. (c) Jemison, R. W.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1969**, 294−295. (f) Marko, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 913−974. (d) Bruckner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 6, pp 873−908. (e) *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, UK, 2002.

(2) (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (b) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236−238. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027−1038.

(3) (a) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2951−2952. (b) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2817−2821. (c) Gawley, R. E.; Moon, K. *Org. Lett.* **2007**, *9*, 3093−3096.

(4) (a) Workman, J. A.; Garrido, N. P.; Sancon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066−1067. (b) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352−9353.

(5) (a) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 12956−12959. (b) Nash, A.; Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 4770−4773. (c) Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 5138−5141.

(6) (a) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043−3049. (b) Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294−1300.

(7) MacMillan, D. W. C. *Nature* **2008**, *455*, 304−308.

(8) Moyano, A.; El-Hamdouni, N.; Atlamsani, A. *Chem.—Eur. J.* **2010**, *16*, 5260−5273.

(9) McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2116−2119.

(10) (a) Yeh, P.-P.; Daniels, D. S. B.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 964−967. (b) Stark, D. G.; Morrill, L. C.; Yeh, P.-P.; Slawin, A. M. Z.; O'Riordan, T. J. C.; Smith, A. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 11642−11646. (c) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146−4155. (d) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653−3657. (e) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714−2720.

(11) For a review of isothioureas in catalysis, see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109−2121. For seminal reports, see: (b) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351−1354. (c) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536−6537. (d) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347−4350.

(12) Chi and co-workers have used *p*-nitrophenyl esters in conjunction with N-heterocyclic carbenes (NHCs) as acyl azolium precursors, see: (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154−2157. (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956−4959. (c) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028−5031. (d) Chen, S.; Hao, L.; Zhang, Y.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5822−5825.

(13) The *tert*-butyl ester analogue of **13** was found to be inactive under the catalytic reaction conditions.

(14) The rearranged *p*-nitrophenyl ester could be isolated, albeit in modest yield; see Supporting Information for details.

(15) Rovis has previously demonstrated the use of nucleophilic co-catalysts to facilitate the turnover of NHC catalysts, see: (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796−13797. (b) Wheeler, P.; Vora, H. U.; Rovis, T. *Chem. Sci.* **2013**, *4*, 1674−1679.

(16) See Supporting Information for full details.

(17) Further investigation showed that the (*Z*)-cinnamyl isomer of **13** gave preferentially the *syn*-diastereoisomer but in reduced ee (dr 87:13, 64% ee).[16] This methodology is currently limited to aryl or styryl substituents at the vinylic position of the substrates.

(18) Dicationic amidines are well characterized, see: Corr, M. J.; Gibson, K. F.; Kennedy, A. R.; Murphy, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 9174−9175.

(19) *p*-Nitrophenoxide has been shown to rebound in related NHC-catalyzed processes, see: Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028−18029.

(20) Ketenes can be generated from *p*-nitrophenyl esters under basic conditions, see: (a) Tidwell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2006; pp 76−81. (b) Cho, B. R.; Kim, Y. K.; Yoon, C.-O. M. *J. Am. Chem. Soc.* **1997**, *119*, 691−697. (c) Cho, B. R.; Jeong, H. C.; Seung, Y. J.; Pyun, S. Y. *J. Org. Chem.* **2002**, *67*, 5232−5238. For examples of cationic ketenes, see: (d) Potts, K. T.; Murphy, P. M.; Kuehnling, W. R. *J. Org. Chem.* **1988**, *53*, 2889−2898. (e) Rudowska, M.; Wieczorek, R.; Kluczyk, A.; Stefanowicz, P.; Szewczuk, Z. *J. Am. Soc. Mass Spectrom.* **2013**, *24*, 846−856.

(21) Relative configuration of the products determined by derivatization to known ethyl ester **SI-55**.[16] Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094-5102. Absolute configuration determined by X-ray analysis of **29**. CCDC 981436 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(22) (a) Minkin, V. I.; Minyaev, R. M. *Chem. Rev.* **2001**, *101*, 1247−1266. (b) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A. *J. Am. Chem. Soc.* **1998**, *120*, 3104−3110. (c) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. *J. Chem. Inf. Model.* **2008**, *48*, 1−24. (d) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288−3291.

(23) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9638−9642.