JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Amine-Catalyzed Asymmetric (3 + 3) Annulations of β′-Acetoxy Allenoates: Enantioselective Synthesis of 4*H*-Pyrans

Chunjie Ni and Xiaofeng Tong*

Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, 1 Gehu Road, Changzhou 213164, China

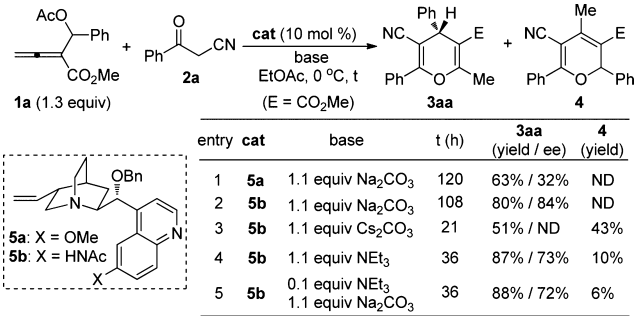
Supporting Information

ABSTRACT: The asymmetric (3 + 3) annulations of β′-acetoxy allenoates with either 3-oxo-nitriles or pyrazolones have been realized by using 6′-deoxy-6′-[(L)-*N*,*N*-(2,2′-oxidiethyl)-valine amido]quinine (**6h**) as the catalyst. The three functions of catalyst **6h**, including Lewis base (quinuclidine N), H-bond donor (amide NH), and Brønsted base (morpholine N), cooperatively take crucial roles on the chemo- and enantioselectivity, allowing for the construction of 4*H*-pyran and 4*H*-pyrano[2,3-*c*]pyrazole in high yields and enantioselectivity.

The cinchona alkaloids have been recognized as privileged chiral scaffolds in asymmetric catalysis.[1] In this context, due to the strong nucleophilicity of their quinuclidine nitrogen, cinchona alkaloids are extremely valuable tertiary amine catalysts[2] for a wide range of asymmetric reactions.[3] However, their potential toward the amine-catalyzed asymmetric annulation of allenoate remains largely underexplored. It was not until 2011 that the first asymmetric version of cinchona alkaloid-based amine-catalyzed (2 + 2) annulations of allenoates with imines was realized by Masson and Zhu.[4] Subsequently, similar asymmetric (2 + 4) annulations of allenoates with various oxo-dienes were developed by the groups of Tong, Bohan, Shi, Cheng, and Xu.[5] Nevertheless, the amine-catalyzed asymmetric annulations of allenoates are sporadically reported, in sharp contrast to the well-developed phosphine-catalyzed analogues.[6]

Here, we report the asymmetric (3 + 3) annulations of β′-acetoxy allenoates **1** with 3-oxo-nitriles **2** by using cinchona alkaloid-based tertiary amine as catalyst for enantioselective synthesis of 4*H*-pyran (Scheme 1). Due to the installment of the β′-acetoxy group, allenoates **1** are liable to form an inherently electrophilic 1,3-dien-2-aminium intermediate via the addition−elimination reaction with amie catalyst, thus accommodating a pronucleophile as the other reaction partner with the help of a base additive.[7] This route is completely different from the well-known nucleophilic zwitterion mechanism in the field of the Lewis base catalysis of allenoates.[8] However, this feature, in turn, would bring about a new challenge associated with the competitive addition−elimination reaction between allenoate **1** and nucleophilic substrate, especially in the case of the sterically congested chiral amine catalyst.[9] To overcome the intrinsic challenge and accomplish high enantioselectivity, a novel trifunctional cinchona alkaloid-based amine catalyst has been developed.[10] Thus, we saw an opportunity to demonstrate the utility of our (3 + 3) annulations toward the advancement of the amine-catalyzed asymmetric allenoate annulation and the biologically relevant 4*H*-pyran.[11]

Scheme 1. Preliminary Attempts at Asymmetric (3 + 3) Annulation of 1a and 2a



entry	cat	base	t (h)	3aa (yield / ee)	4 (yield)
1	**5a**	1.1 equiv Na_2CO_3	120	63% / 32%	ND
2	**5b**	1.1 equiv Na_2CO_3	108	80% / 84%	ND
3	**5b**	1.1 equiv Cs_2CO_3	21	51% / ND	43%
4	**5b**	1.1 equiv NEt_3	36	87% / 73%	10%
5	**5b**	0.1 equiv NEt_3 1.1 equiv Na_2CO_3	36	88% / 72%	6%

Our investigation commenced with the screening of cinchona alkaloid-based catalysts for the model reaction of **1a** and **2a** (Scheme 1). After several attempts, we found that, with the help of Na_2CO_3 in EtOAc at 0 °C, catalyst **5a** was able to delivere product (*S*)-**3aa** in 63% yield and 32% ee (entry 1).[12] Catalyst **5b** gave much better results, affording **3aa** in 80% yield and 84% ee, albeit with a long reaction time (entry 2). Obviously, the improved performances were attributed to the additional amide NH of **5b** as an H-bond donor. It was a surprise that the use of stronger base Cs_2CO_3 produced 51% yield of **3aa** along with 43% yield of side product **4** (entry 3). The isolation of **4** arose from direct reaction of **1a** and **2a** without the involvement of amine catalyst.[13] The use of Et_3N was found to be beneficial, not only diminishing **4** to 10% but alo shortening the desired reation time to 36 h albeit only with 73% ee (entry 4). The fact that the reaction performances strongly depended on the base additive led us to realize that, likely due to the less catalytic activity of **5b**,[9] a proper rate of nucleophile generation would be requisite; slow rate further retarded the desired reaction, while fast one triggered the side reaction. Indeed, the combination of 0.1 equiv Et_3N and 1.1 equiv Na_2CO_3 further suppressed the side reaction and, more importantly, imposed no negative effect on the desired reaction (entry 5). In this case, Et_3N was regenerated via the reaction of $[Et_3NH]^+$ and Na_2CO_3, thus requiring only a catalytic amount of Et_3N with stoichiometric amount of Na_2CO_3. Unfortunately, further optimization of reaction conditions failed to improve the reaction efficiency and selectivity.[13]

Received: May 13, 2016
Published: June 16, 2016

DOI: 10.1021/jacs.6b04935
J. Am. Chem. Soc. 2016, 138, 7872−7875

Despite these aforementioned challenges, the preliminary results inspired us to focus on catalysts **6** (Figure 1), which was

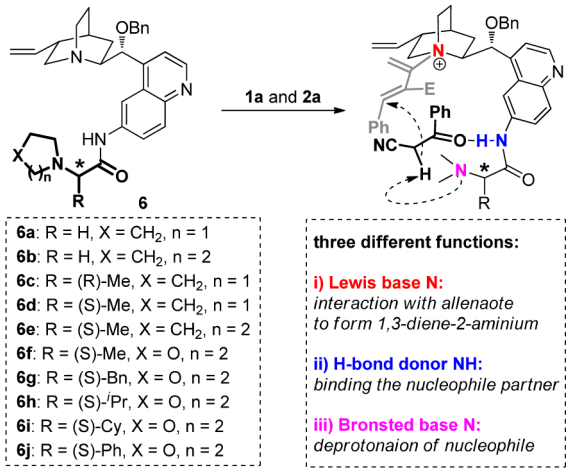
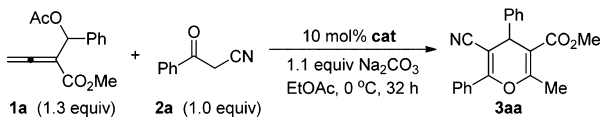


Figure 1. Structure of catalyst **6** and a postulated working model.

accessed from the incorporation of the scaffold of **5b** and a tertiary amino acid unit.[14] Compared with the individual functions of **5b** and Et_3N, we envisioned that the three different active centers of catalysts **6**, including Lewis base quinuclidine nitrogen, H-bond donor amide NH, and Brønsted base amine, might cooperatively take effect, thus not only enabling synchronous generation of the related 1,3-diene-2-aminium intermediate and nucleophile partner but also enforcing their reaction in a pseudo-intramolecular manner (Figure 1). The cooperative effect, if workable, would facilitate the desired reaction and make no redundant nucleophile available for the side reaction. Meanwhile, the newly introduced chiral scaffold of the amino acid unit was capable of subtly diversifying the stereodescriminating microenvironment along with the robust quinine parent skeleton. Moreover, struturally modificable catalysts **6** could be easily prepared via the Pd(0)-catalyzed coupling reaction of readily available 6′-OTf-quinine and the corresponding amino amides.[15]

Hence, we gauged the potential of catalyst **6** toward the chemo- and enantioselectivity issues (Table 1). Delightfully, catalyst **6a** bearing a pyrrolidine-modified glycine unit delivered **3aa** in 92% yield (entry 1). Side product **4** was not observed, demonstrating a crucial role of the attached Brønsted base amine on the chemoselevtivity. Catalyst **6b** with a piperidine-modified glycine unit gave somewhat lower ee (entry 2). Catalyst **6c**

Table 1. Identification of Catalysts 6[a]



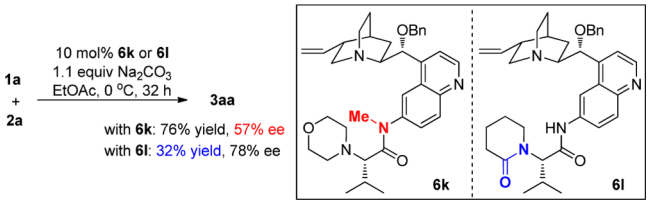
entry	cat	% yield[b]/% ee[c]	entry	cat	% yield/% ee
1	**6a**	92/70	6	**6f**	96/82
2	**6b**	96/65	7	**6g**	96/87
3	**6c**	85/68	8	**6h**	96/92
4	**6d**	94/75	9	**6i**	96/90
5	**6e**	96/67	10	**6j**	81/83

[a]For reaction conditions, see the SI. [b]Isolated yield. [c]Determined by HPLC analysis.

derived from D-alanine gave inferior enantioselectivity than that of L-alanine-derived **6d** (entries 3 and 4), indicating that the L-amino acid unit would be favorable for enantioselectivity. While catalyst **6e** bearing the piperidine-modified L-alanine unit was not a good choice, catalyst **6f** with the morpholine-modified one delivered **3aa** in 96% yield and 82% ee (entries 5 and 6). Then, on the basis of the substructure of morpholine Brønsted base, the amino acid moiety was further modulated, which finally disclosed that L-valine-derived catalyst **6h** worked best, delivering **3aa** in 96% yield and 92% ee (entries 7−10).

As comparison, catalyst **6k**, a derivative of **6h** via methylation of the amide NH group, was also tested for the reaction of **1a** and **2a**, which gave **3aa** only with 57% ee (Scheme 2). Moreover,

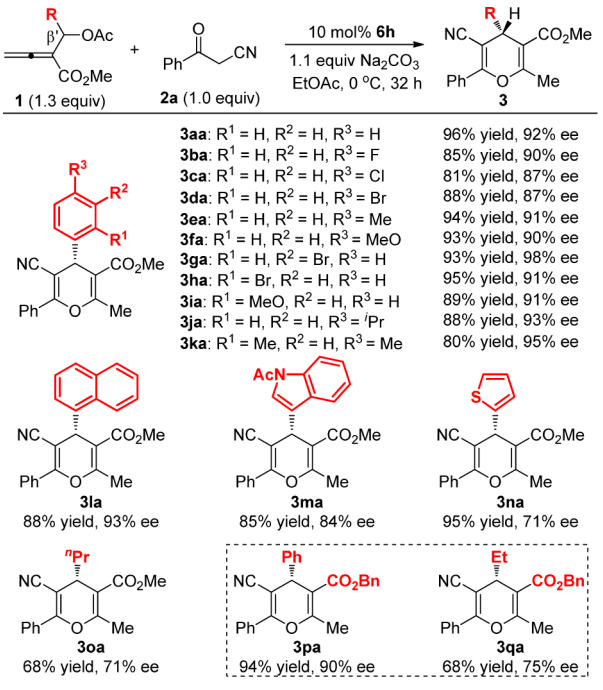
Scheme 2. 6k- or 6l-Catalyzed Reaction of 1a and 2a



catalyst **6l**, a variant of **6h** via replacing the tertiary amine with amide, gave **3aa** only in 32% yield. These results further demonstrated the crucial roles of the amide NH and tertiary amine in catalyst **6h** on the asymmetric induction and reaction efficiency, respectively.

With the optimal catalyst **6h** in hand, we turned our attentions to explore the reaction scope. First, a range of allenoates **1** were examined by reacting with substrate **2a** (Scheme 3). Various aryl groups at β'C position of allenoates **1** [4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 2-$MeOC_6H_4$, 4-$^iPrC_6H_4$, 2,4-$(Me)_2C_6H_3$] were found to be tolerated, and the corresponding products **3ba**−**3ka** were isolated in 80%−95% yields and with 87%−99% ee. Allenoate

Scheme 3. Substrate Scope of Allenoate 1

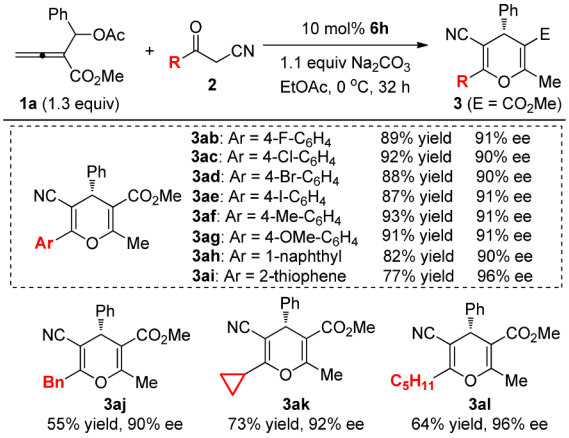


DOI: 10.1021/jacs.6b04935
J. Am. Chem. Soc. 2016, 138, 7872−7875

1l with a 1-naphthyl substituent was also a suitable substrate, delivering **3la** in 88% yield and 93% ee. Notably, *N*-acetyl-indole and thiophene were also compatible, giving the corresponding products **3ma** and **3na** in excellent yields and somewhat lower ee values. In contrast, the reaction of allenoate **1o** with an alkyl ^{n}Pr substituent gave product **3oa** only in moderate yield and enatioselectivity. In addition to methyl esters **1a**−**1o**, benzyl esters **1p** and **1q** were also examined, which exhibited very similar reactivity. For the reactions of allenoates **1n**, **1o**, and **1q**, the somewhat lower enantioselectivity would be due to their relatively sterically smaller β'-substituents (R group), which might result in the lower stereoselectivity of the newly formed C=C bond in the corresponding 1,3-diene-2-aminium intermediate.

Next, we moved on to investigate the substrate scope of **2** (Scheme 4). It was found that various β-aryl nitriles **2**, including

Scheme 4. Substrate Scope of 3-Oxo-nitrile 2

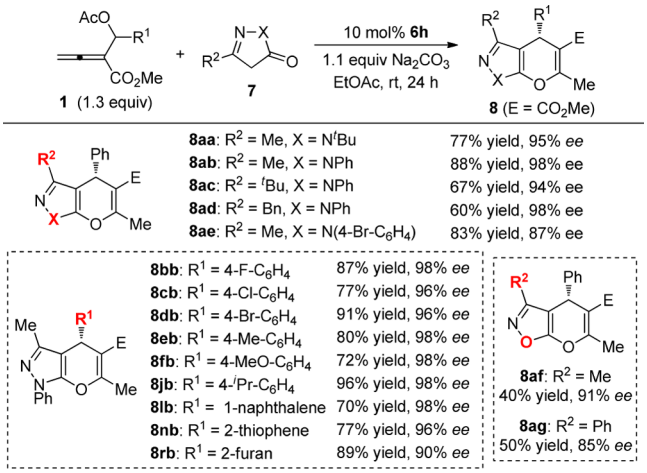


phenyl substituents with either electron-withdrawing (4-F, 4-Cl, 4-Br, and 4-I) or electron-donating groups (4-Me and 4-MeO), 1-naphthalene as well as 2-thiophene, were well tolerated, affording products **3ab**−**3ai** in good yields and excellent enantioselectivity. For the cases of β-alkyl nitriles **2j**-**2l**, high enantioselectivity was also obtained although the corresponding yields were moderate.

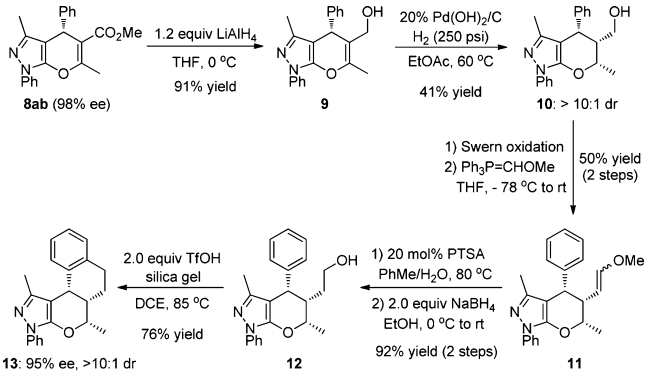
In considering other possible pronucleophile partners for (3 + 3) annulations with allenaotes **1**, we elected to pursue the use of pyrazolones **7**, which would result in the biologically interesting pyrano[2,3-*c*]pyrazoles[16] (Scheme 5). Delightedly, the reactions of allenoates **1** and pyrazolones **7** smoothly occurred, delivering pyrano[2,3-*c*]pyrazoles **8** in good yields and with high enantioselectivity even at room temperature. Isoxazolones **7f** and **7g** were also good nucleophile partners, which reacted well with **1a** to give the corresponding 4*H*-pyrano[3,2-*d*]isoxazoles **8af** and **8ag** with high enenatioselectivity abeit in relatively lower yields.

To demonstrate the synthetic potential of this (3 + 3) annulation, an enantioselective synthesis of pyranopyrazole **13** was studied (Scheme 6). This class of compound is known to have fungicide activity.[17] As illustrated in Scheme 6, upon treatments of $LiAlH_4$ reduction and catalytic hydrogenation, the conversion of **8ab** into *cis*-**10** was achieved with good diastereoselectivity albeit in low overall yield. Using classic manipulations of one-carbon elongation and Friedel−Crafts reaction,[18] compound **13** was finally obtained with high level of enantioselectivity and diastereoselectivity.

Scheme 5. 6h-Catalyzed (3 + 3) Annulations of 1 and 7



Scheme 6. Synthesis of Compound 13



In summary, we have realized the asymmetric (3 + 3) annulations of β'-acetoxy allenoates **1** with either 3-oxo-nitriles **2** or pyrazolones **7** by using 6′-deoxy-6′ [(L)-*N*,*N*-(2,2′-oxidiethyl)-valine amido]quinine **6h** as the catalyst. Although the precise working model is not clear at this stage, the three functions of catalyst **6h**, including Lewis base (quinuclidine nitrogen), H-bond donor (amide N−H) as well as Brønsted base (morpholine nitrogen), are believed to cooperatively take effect to enhance enantioselectivity and overcome the side reaction, allowing for the isolation of 4*H*-pyrans **3** and pyrano[2,3-*c*]pyrazoles **8** in high chemical yields and enantioselectivity. Further study of the application of catalysts **6** is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04935.

Experimental details and data (PDF)
Crystallographic data for **3aa** (CIF)
Crystallographic data for **8ae** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*txf@cczu.edu.cn

Notes

The authors declare no competing financial interest.

DOI: 10.1021/jacs.6b04935
J. Am. Chem. Soc. 2016, 138, 7872−7875

■ ACKNOWLEDGMENTS

This work is supported by NSFC (No. 21272066 and 21472042). We are grateful to Changzhou University for experimental assistance and financial support.

■ REFERENCES

(1) (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011.

(2) For a review, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(3) For selected reviews, see: (a) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (d) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (e) Stegbauer, L.; Sladojevich, F.; Dixon, D. J. *Chem. Sci.* **2012**, *3*, 942. (f) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (g) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *2010*, 1229.

(4) (a) Denis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5356. (b) Zhao, Q.-Y.; Huang, L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2012**, *354*, 1926. (c) Takizawa, S.; Arteaga, F. A.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Org. Lett.* **2013**, *15*, 4142.

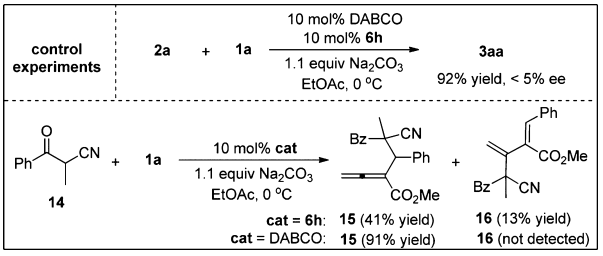
(5) (a) Wang, X.; Fang, T.; Tong, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5361. (b) Ashtekar, K. D.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 5732. (c) Pei, C.-K.; Jiang, Y.; Wei, Y.; Shi, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11328. (d) Pei, C.-K.; Jiang, Y.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 4355. (e) Wang, F.; Luo, C.; Shen, Y.-Y.; Wang, Z.-D.; Li, X.; Cheng, J.-P. *Org. Lett.* **2015**, *17*, 338. (f) Zhang, S.; Luo, Y.-C.; Hu, X.-Q.; Wang, Z.-Y.; Liang, Y.-M.; Xu, P.-F. *J. Org. Chem.* **2015**, *80*, 7288.

(6) For reviews, see: (a) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089. (b) Pei, C.-K.; Shi, M. *Chem. - Eur. J.* **2012**, *18*, 6712.

(7) (a) Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828. (b) Li, K.; Hu, J.; Liu, H.; Tong, X. *Chem. Commun.* **2012**, *48*, 2900. (c) Hu, J.; Tian, B.; Wu, X.; Tong, X. *Org. Lett.* **2012**, *14*, 5074. (d) Ni, C.; Wang, M.; Tong, X. *Org. Lett.* **2016**, *18*, 2240. For the phosphine-catalyzed analogues: (e) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (f) Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400. (g) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (h) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183. (i) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803.

(8) For selected reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Wei, Y.; Shi, M. *Chem. - Asian J.* **2014**, *9*, 2720. (c) Xie, P.; Huang, Y. *Org. Biomol. Chem.* **2015**, *13*, 8578. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (g) Voituriez, A.; Marinetti, A.; Gicquel, M. *Synlett* **2015**, *26*, 142. (h) Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, *2011*, 2766. (i) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (j) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

(9) Due to their sterically congested scaffold, catalysts **5** and **6** are less active than DABCO. The reduced catalytic activity would largely retard the following two steps: (i) their addition to allenoate **1a**; (ii) the attack of **2a** to 1,3-dien-2-aminium intermediate, which was supported by the results of the following two control experiments. For the detailed discussions, see the SI.



(10) For selected reviews on multifunctional catalysts, see: (a) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (b) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20678. (c) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117. (d) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (g) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.

(11) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (b) Liu, R. H.; Zhang, W. D.; Gu, Z. B.; Zhang, C.; Su, J.; Xu, X. K. *Nat. Prod. Res.* **2006**, *20*, 866. (c) Gunatilaka, A. A. L. *J. Nat. Prod.* **2006**, *69*, 509.

(12) The absolute configurations of **3aa** (CCDC 1044357) and **8ae** (CCDC 1436273) were established to be (*S*) through the X-ray crystal structure analysis. Other products were assinged by analogy.

(13) For the detail, see the SI.

(14) For reviews, see: (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (b) Chen, Y.-C. *Synlett* **2008**, *2008*, 1919. (c) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (d) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (e) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *2008*, 1759.

(15) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(16) (a) Kuo, S. C.; Huang, L. J.; Nakamura, H. *J. Med. Chem.* **1984**, *27*, 539. (b) Foloppe, N.; Fischer, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor, A. E. *Bioorg. Med. Chem.* **2006**, *14*, 4792. (c) Catarzi, D.; Cecchi, L.; Colotta, V.; Filacchioni, G.; Martini, C.; Tacchi, P.; Lucacchini, A. *J. Med. Chem.* **1995**, *38*, 1330.

(17) (a) Hartmut, S.; Wilhelm, B. PatentDE3243714, May 30, 1984. (b) Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett.* **2015**, *17*, 1417. (c) Enders, D.; Grossmann, A.; Gieraths, B.; Duzdemir, M.; Merkens, C. *Org. Lett.* **2012**, *14*, 4254. (d) Bakthadoss, M.; Kannana, D.; Selvakumar, R. *Chem. Commun.* **2013**, *49*, 10947.

(18) Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, W. F.; Jones, J. E.; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146.

DOI: 10.1021/jacs.6b04935
J. Am. Chem. Soc. 2016, 138, 7872−7875