Communication

Amine-Catalyzed Asymmetric (3+3) Annulations of #'-Acetoxy Allenoates: Enantioselective Synthesis of 4H-Pyrans

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

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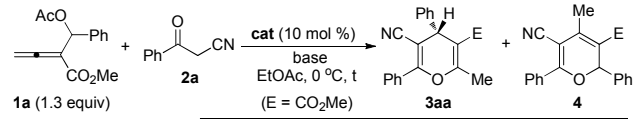
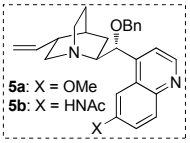
Supporting Information Placeholder

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'-oxydiethyl)-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 enantio-selectivity, 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].





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%

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

Our investigation commenced from 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). Obviuosly, the improved performances were attributed to the additional amide NH of **5b** as an H-bond donor. It was 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 shortening the desired reation time to 36 hours 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]

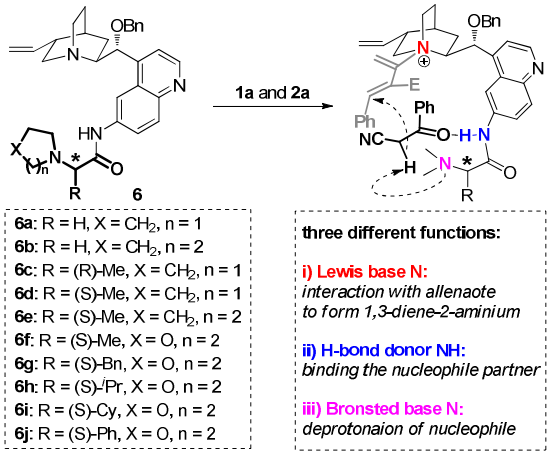
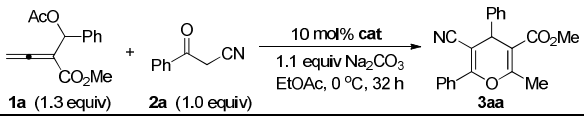


Figure 1. The structure of catalyst 6 and a postulated working model

Despite these aforementioned challenges, the preliminary results inspired us to focus on catalysts **6** (Figure 1), which was 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 psuedo-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 micro-enviroment 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 enantio-selectivity issues (Table 1). Delightfully, catalyst **6a** bearing a pyrrolidine-modified glycine unit delivered **3aa** in 92% yield (entry 1). Side product **4** wasn't 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** 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 delivred **3aa** in 96% yield and 82% ee (entries 5 and 6). Then, on the basis of

Table 1. Identification of Catalysts 6[a]

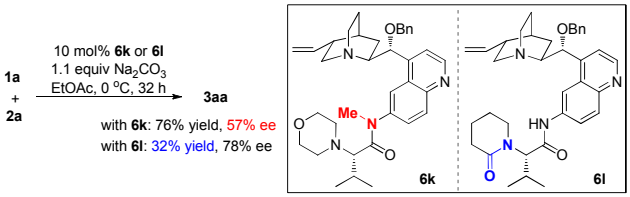


entry	cat	%yield[b]/%ee[c]	entry	cat	%yield/%ee
1	**6a**	92 / 70	6	**6f**	96/ 82
2	**6b**	96 / 65	7	**6g**	96 / 87
3	**6c**	85 / 68	8	**6h**	96 / 92
4	**6d**	94 / 75	9	**6i**	96 / 90
5	**6e**	96 / 67	10	**6j**	81 / 83

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

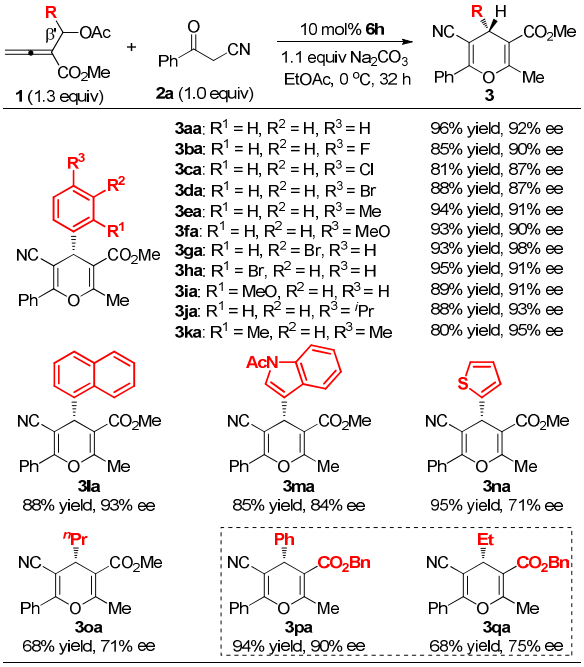
the substructure of morpholine Brønsted base, the amino acid moiety was further modulated, which finally disclosed that L-valine-derived catalyst **6h** worked best, delivering **3aa** in 96% yield and 92% ee (entries 7-10).

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, 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.



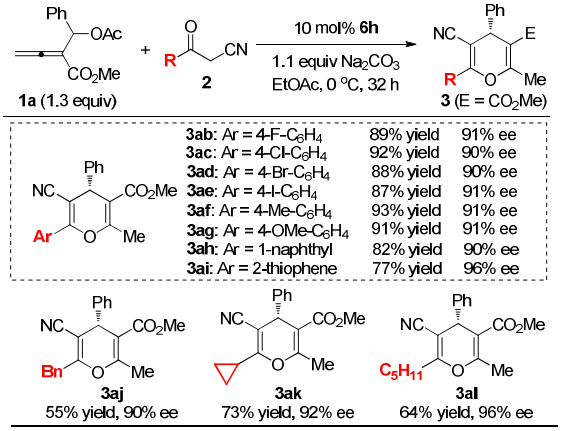
Scheme 2. 6k or 6l-Catalyzed Reaction of 1a and 2a

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 **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.



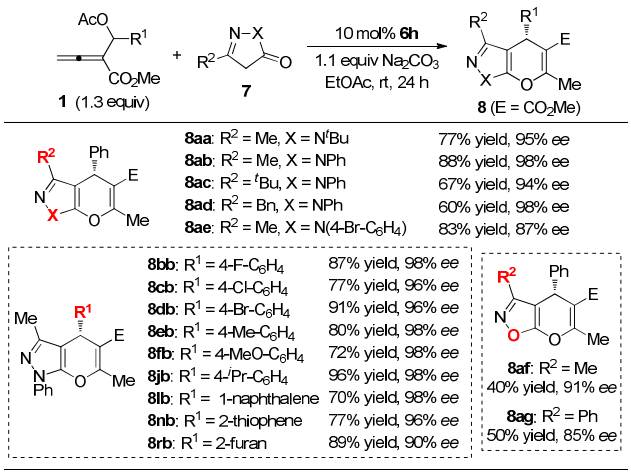
Scheme 3. Substrate Scope of Allenoate 1

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



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

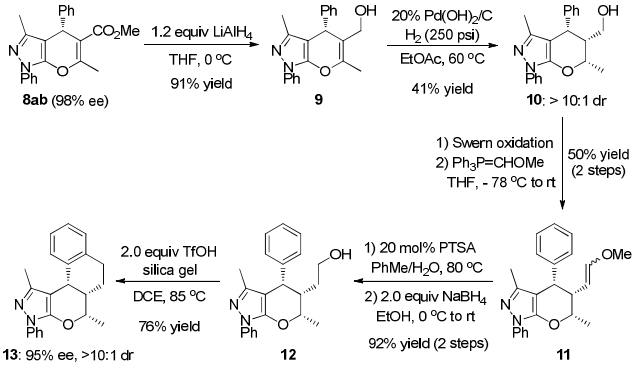
In considering other possible pronucleophile partners for (3+3) annulations with allenaotes **1**, we elected to pursue the use of pyrazolones **7**, which would result in the biologically interesting pyrano[2,3-c]pyrazoles[16] (Scheme 5). Delightedly, the reactions of allenoates **1** and pyrazolones **7** smoothly occured, 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,



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

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 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'-oxydiethyl)-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

Detailed experimental procedures, characterization of new compounds, crystallographic data (**3aa** and **8ae**). 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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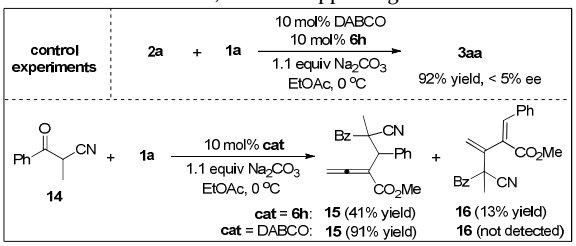
(9) Due to their sterically congested scaffold, catalysts **5** and **6** are less active than DABCO. The reduced catalytic activity would largely retard the following two steps: i) their addition to allenoate **1a**; ii) the attack of **2a** to 1,3-dien-2-aminium intermediate, which was supported by the results of the following two control experiments. For the detailed discussions, see the Supporting Information.



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(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 Supporting Information.

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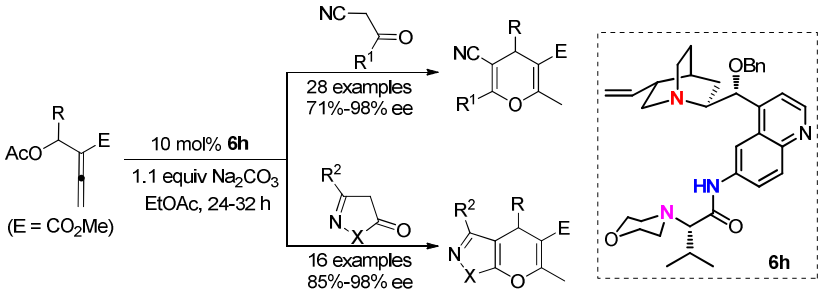
NC
O
R1
28 examples
71%-98% ee
R
E
NC
R1
O
AcO
R
E
(E = CO2Me)
10 mol% 6h
1.1 equiv Na2CO3
EtOAc, 24-32 h
R2
N
X
O
16 examples
85%-98% ee
R2
R
E
N
X
O
OBn
N
N
HN
N
O
O
6h