Organocatalysis

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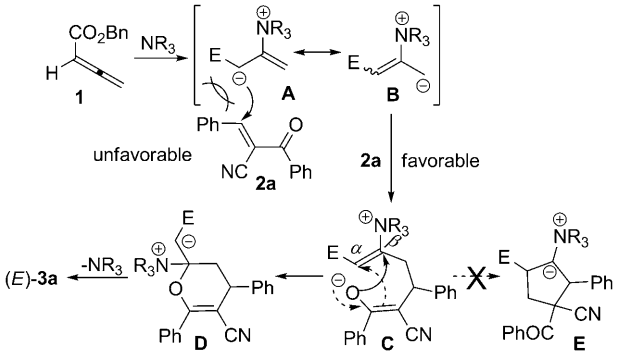
Enantioselective Amine-Catalyzed [4+2] Annulations of Allenoates and Oxo-dienes: An Asymmetric Synthesis of Dihydropyrans**

*Xiaojun Wang, Tong Fang, and Xiaofeng Tong**

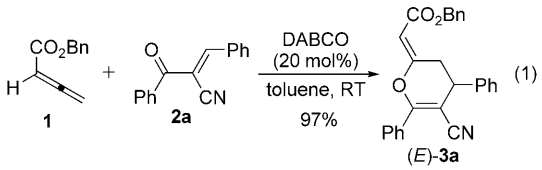
Substituted pyran rings are important structural units found in biologically active compounds and natural products.[1] Given their high importance, many excellent methods have been developed to synthesize substituted pyrans.[2] However, new reactions leading to functionalized pyrans with stereogenic center(s) are still in high demanding and remain challenging, especially in terms of asymmetric catalysis and atom economy.[3]

In the past decades, various Lewis bases have been extensively explored as nucleophilic catalysts for application in novel reaction protocols.[4] In this context, Lewis base catalyzed reactions of allenoates have attracted much attention as new synthetic methods for generating diversity and complexity.[5] In sharp contrast to the well-developed phosphine catalysis of allenoates,[6] the corresponding amine analogue is relatively rare and only a few examples, as far as we know, have been reported.[7–9] For all these cases of amine catalysis, the first mechanistic step is proposed as the addition of the amine catalyst to the allenoate to form zwitterionic intermediates **A** and **B** (Scheme 1), which are subsequently captured by various electrophiles such as aldehydes,[7] imines,[8] or activated alkenes.[9]



Scheme 1. Proposed mechanism. E = CO_2Bn, Bn = benzyl.

During our study of the phosphine-catalyzed [4+2] annulations, we found that readily available oxodiene **2a** worked well as a 1,4-amphiphilic reagent to react with phosphonium-containing zwitterions.[10] Thus, we envisioned that compound **2a** would also be capable of interacting with ammonium-containing zwitterions **A** and/or **B** (Scheme 1). Eventually, when a solution of allenote **1** and **2a** in toluene was treated with 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature, compound 3,4-dihydro-2*H*-pyran (*E*)-**3a** was isolated in 97% yield [Eq. (1)]. Therefore, the amine-



catalyzed [4+2] annulation of oxodiene **2a** and allenote **1** was realized, and it might serve as a complementary process to Diels–Alder reactions[11] of α,β-unsaturated carbonyl compounds with electron-rich alkenes.

The proposed catalytic cycle is shown in Scheme 1. Addition of DABCO to allenoate **1** delivers zwitterionic intermediate **A**, which coexisted with its resonance form **B**. Subsequently, oxodiene **2a** would preferentially interact with **B** over **A** owing to the steric hindrance between the ester group of **A** and the phenyl group of **2a**, thus generating enolate intermediate **C**. Then, intramolecular addition of an oxygen-containing nucleophile at the β position in enolate **C** forms intermediate **D**. Finally, elimination of the amine catalyst produces **3a** and regenerates the catalyst, thereby accomplishing [4+2] annulation. Notably, the intramolecular addition of a carbon-containing nucleophile at the α position in intermediate **C**—which should have produced intermediate **E**, an analogue to that involved in classical phosphine-catalyzed [3+2] cycloaddition—is less likely owing to the poorer ability of the ammonium ion to stabilize the corresponding ylide, thus demonstrating the different catalytic behavior between amine and phosphine Lewis bases.[9,12]

Based on the above proposed mechanism, we envisioned that the use of suitable chiral amine catalysts might induce an asymmetric Michael-type addition of **B** to **2a**, thus leading to the construction of a stereogenic center at the C4-position of **3a**. To our delight, simple cinchona alkaloids (CA; Scheme 2)[13] were found to be excellent candidates to achieve asymmetric catalysis (Table S1, in the Supporting Informa-

[*] X. Wang, T. Fang, Dr. X. Tong
Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology
Meilong Road No. 130, Shanghai, 200237 (China)
Fax: (+86) 21-6425-3881
E-mail: tongxf@ecust.edu.cn

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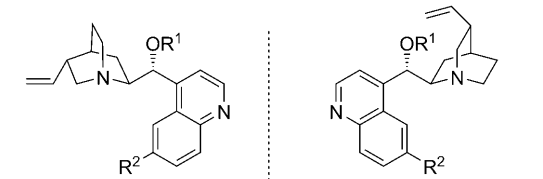
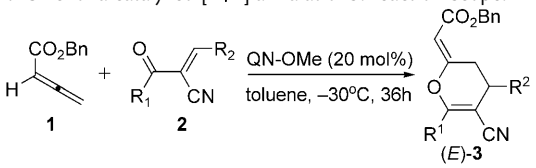


Scheme 2. Cinchona alkaloids (CA) employed in this study.

tion) and QN-OMe was identified as the best to give **3a** with 90% *ee* in 70% yield (Table S1, entry 5). Then, the scope of the asymmetric [4+2] annulation was investigated and the results are summarized in Table 1. In general, the reactions produce substituted 2*H*-pyrans **3** with high enantiomeric excess from a wide arrange of substrates **2** with substituted phenyl groups, heteroaromatic rings, alkyl or alkene groups (Table 1, entries 1–13). Moreover, some of the pyrans **3** can be obtained with excellent optical purity after just a single recrystallization (Table 1, entries 2–4 and 13). On the other hand, the opposite enantiomeric products are also readily obtained using quinidine (QD) as the catalyst in PhCl, albeit with somewhat lower *ee* values (Table 1, entries 14–16). Again, exclusive *E* selectivity of the *exo*-cyclic double bond was observed in all cases and the corresponding *Z* isomers were not detected at all.

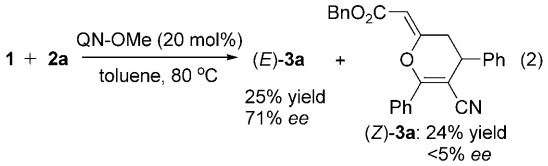
Table 1: Cinchona-catalyzed [4+2] annalations: reaction scope.[a]



Entry	R^1	R^2	**3**	Yield [%][b]	*ee* [%][c,d]
1	Ph	Ph	(+)-**3a**	70	90
2	Ph	4-$MeOC_6H_4$	(+)-**3b**	97	90 (99)
3	Ph	2-furan	(+)-**3c**	88	82 (99)
4	Ph	2-thiophene	(+)-**3d**	91	88 (98)
5	Ph	4-BrC_6H_4	(+)-**3e**	70	83
6	Ph	2-BrC_6H_5	(+)-**3f**	83	82
7	2-thiophene	Ph	(+)-**3g**	75	90
8	C_5H_{11}	Ph	(+)-**3h**	92	90
9	Ph	styryl	(+)-**3i**	94	84
10	Ph	3,4-$(MeO)_2C_6H_3$	(+)-**3j**	73	89
11	C_5H_{11}	4-$MeOC_6H_4$	(+)-**3k**	94	90
12	4-BrC_6H_4	4-$MeOC_6H_4$	(+)-**3l**	50	82
13	4-$MeOC_6H_4$	4-BrC_6H_4	(+)-**3m**	86	92 (99)
14[e]	Ph	Ph	(−)-**3a**	82	81
15[e]	Ph	2-thiophene	(−)-**3d**	85	71
16[e]	C_5H_{11}	Ph	(−)-**3h**	91	81

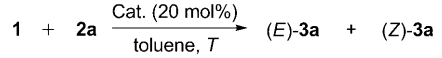
[a] Reaction conditions: to a solution of **2** (0.3 mmol) and catalyst (20.2 mg, 20 mol%) in toluene (4 mL) at −30°C was slowly added a solution of **1** (104.4 mg, 0.6 mmol, 2.0 equiv) in toluene (4 mL) over 20 min. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase using a Chiralcel AD-H column. [d] The data in parentheses was obtained after a single recrystallization. [e] With the use of QD (19.1 mg, 20 mol%) as the catalyst and PhCl as the solvent at −20°C.

Although the reaction mechanism depicted in Scheme 1 can account for the product formation, the following two issues still need to be further addressed: 1) the mechanism for the observed high *E* selectivity in **3** and 2) the origin of enantioselectivity. Our theoretical calculations at the b3Lyp/6-31G* level indicate that (*E*)-**3a** is about 14.2 kJ mol^{-1} lower in free energy than its isomer (*Z*)-**3a** (see the Supporting Information). In fact, (*Z*)-**3a** was isolated in 24% yield along with (*E*)-**3a** when the reaction of **1** and **2a** was run at 80°C [Eq. (2)]. Surprisingly, (*Z*)-**3a** was almost racemic while the corresponding (*E*)-**3a** had 71% *ee*.



We proposed that the quinoline moiety in QN-OMe would also be active enough at high temperature to promote [4+2] annulation and lead to racemic (*Z*)-**3a** owing to the large separation between its nitrogen center and the chiral environment.[14] Experimental evidence for this postulation was obtained by switching the catalyst to quinoline (Table 2).

Table 2: Control experiments.

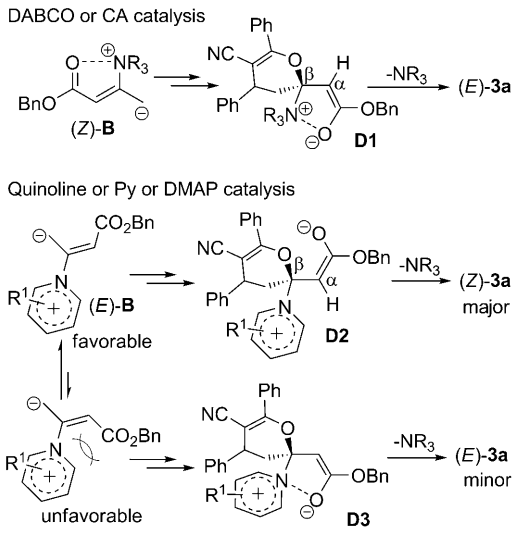


Entry	Catalyst	*T* [°C]	(*E*)-**3a** [%][a]	(*Z*)-**3a** [%][a]
1	quinoline	80	trace	21
2	quinoline	RT	n.r.	n.r.
3	pyridine	RT	23	34
4	DMAP	RT	17	37

[a] Yield of isolated product. DMAP = 4-dimethylaminopyridine, n.r. = no reaction.

The reaction of **1** and **2a** in the presence of 20 mol% of quinoline at 80°C exclusively produced (*Z*)-**3a** in 21% yield (Table 2, entry 1). When the reaction temperature was lowered to room temperature no reaction took place (Table 2, entry 2). Interestingly, when either pyridine or DMAP was employed as the catalyst, the reaction proceeded smoothly even at room temperature and gave a mixture of (*E*)-**3a** and (*Z*)-**3a** with the thermodynamically unfavorable *Z* isomer as the major product (Table 2, entries 3 and 4).

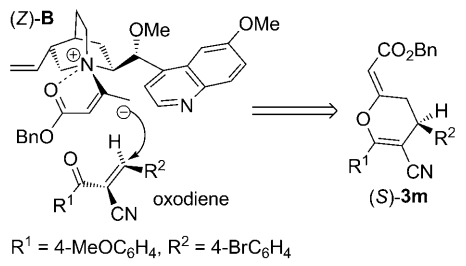
The above results imply that the environment around the catalytic nitrogen center may play a crucial role in the *E*/*Z* selectivity observed in **3a**. Namely, the tertiary amine exclusively gives *E* selectivity while the while the amine being incorporated into the pyridyl aromatic system favors *Z* selectivity.[15] Following this argument, the rationality for *E*/*Z* selectivity is shown in Scheme 3. For DABCO and CA catalysis, the electrostatic interaction[16] between the oxygen atom of the ester group and ammonium in intermediate **B** would help it to adopt the (*Z*)-**B** form exclusively. This



Scheme 3. Elucidation of *E*/*Z* selectivity in **3a**. Py = pyridine.

conformation might be further consolidated with the formation of enolate **D1** (short distance between the α hydrogen and the β oxygen) (Scheme 3), whose stereochemical arrangement enables **3a** to be produced with *E* selectivity via elimination of amine catalyst. In the cases of pyridine and quinoline, however, the positive charge of ammonium in **B** might be weakened by the delocalization effects of its attached aromatic ring, so is the oxygen–ammonium electrostatic interaction mentioned above. Thus, the steric hindrance between the pyridyl ring and the ester group in **B** might become the dominating factor, which mainly leads to the (*E*)-**B** form (long distance between the α hydrogen and the β oxygen; Scheme 3). Consequently, enolate **D2** would be formed, which is responsible for the formation of (*Z*)-**3a**.[17]

After establishing the mechanism for the observed *E*/*Z* selectivity in **3a**, we then focused on the enantioselectivity. The absolute configuration of **3m** was determined to be *S* by X-ray crystal structure analysis (see the Supporting Information).[18] The observed enantioselectivity can be explained by the proposed reaction model shown in Scheme 4.[19] In the process of CA catalysis, we believe that the quinoline moiety in the catalyst might play a dual steric role in the asymmetric induction. One is to push the ester group of (*Z*)-**B** to its opposite side, thus rendering intermediate (*Z*)-**B** to adopt the arrangement as depicted in Scheme 4. The other is to shield the upper face of (*Z*)-**B**, thus guiding the attack of oxodiene **2** from bottom face. To avoid the steric hindrance between the R^2 group of oxodiene and (*Z*)-**B** (not shown), oxodiene would approach the *re* face. As a result, product **3m** is forced to adopt the *S* configuration. According to this plausible reaction model, the same sense of asymmetric induction is believed to be in operation for **3a**–**3l**. Although the mechanistic hypothesis of the interaction between the oxygen atom of the ester group and ammonium in intermediate **B** is not solid evidence, it does account for the observed stereochemical outcome, including *E*/*Z* selectivity and enantioselectivity. The exact catalytic mechanism still needs more investigations.



Scheme 4. Plausible reaction model.

In summary, we have reported the asymmetric [4+2] annulations of allenoate with oxodienes using commercially available cinchona catalysts. This reaction protocol provides a facile entry to substituted 2*H*-pyrans **3** with good to excellent enantiomeric excess. Notably, both enantiomeric products can be readily obtained simply through switching the catalyst and reaction solvent. One limitation of the method, however, is the prerequisite cyano substituent in oxodiene **2**. This substituent acts as a strong electron-withdrawing group to match the reactivity of zwitterionic intermediate **B**. Presumably, the interaction of the ester group and the aminium in zwitterions **B** is essential for the desired stereochemical outcome. Further investigations of the reaction mechanism and synthetic transformation are currently underway.

Experimental Section

General procedure: A mixture of oxodiene **2a** (0.3 mmol) and QN-OMe (20.2 mg, 20 mol%) was introduced into a Schlenk tube (25 mL) containing toluene (4 mL) and stirred at −30°C. To this reaction mixture, a solution of allenoate **1** (0.6 mmol, 2.0 equiv) in toluene (4 mL) was slowly added over 20 min. After 36 h, the mixture was warmed to RT and then directly subjected to column chromatography on silica gel (petroleum ether/EtOAc 10:1→5:1 gradient) to give the product **3a** as slight yellow solid (86.4 mg, 70% yield, m.p 105–108°C). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.88$ (d, $J = 6.8$ Hz, 2H), 7.55–7.47 (m, 3H),7.39–7.26 (m, 10H), 5.89 (s, 1H), 5.14 (d, $J =$ 12.8 Hz, 1H), 5.09 (d, $J = 12.8$ Hz, 1H), 3.96 (t, $J = 6.0$ Hz, 1H), 3.86 (dd, $J = 15.6$ Hz, $J = 6.0$ Hz, 1H), 3.31 ppm (dd, $J = 15.6$ Hz, $J =$ 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.9$, 163.2, 161.3, 139.4, 135.8, 131.4, 131.1, 129.0, 128.6, 128.5, 128.2, 128.0, 127.9, 127.2, 118.2, 102.7, 89.9, 66.0, 38.5, 29.5 ppm. HRMS (EI) calcd for $C_{27}H_{21}NO_3$ 407.1521, found 407.1525. $[\alpha]_D^{26} = +103.3$ deg cm^3 g^{-1} dm^{A1} ($c = 2.21$ g cm^{-3} in $CHCl_3$); 90% *ee* (HPLC on a chiral stationary phase using a Chiralcel AD-H column, *n*-hexane/isopropanol = 90:10, 0.9 mL min^{-1}, λ_{max} 254 nm, $t_R = 15.8$ min and 26.7 min).

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