Organocatalysis

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N-Heterocyclic Carbene Catalyzed [4+3] Annulation of Enals and *o*-Quinone Methides: Highly Enantioselective Synthesis of Benzo-ε-Lactones**

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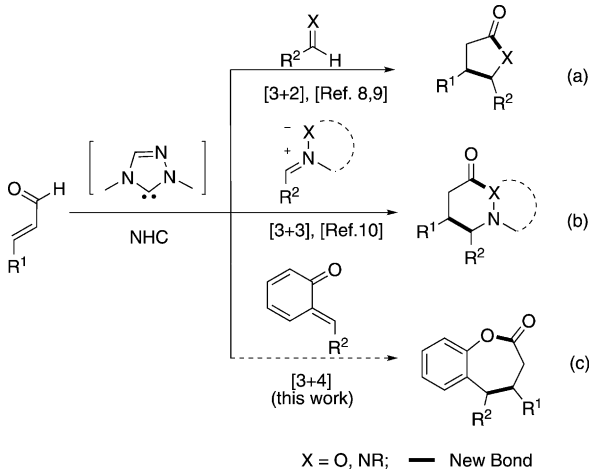
ε-Lactones are privileged motifs occurring in a wide variety of biologically active natural and unnatural products.[1] Therefore, the synthesis of ε-lactones has received considerable attention. The most applied approach to ε-lactones is the Bayer–Villiger oxidation of cyclohexanone.[2,3] In addition, several other interesting methodologies, including metal-catalyzed ring expansion of 3-(2-hydroxyphenyl)cyclobutanones,[4] metal-catalyzed carbonylation of 2-allylphenols,[5] and N-heterocyclic carbene catalyzed ring expansion of aldehydes[6] have been reported. However, most of these approaches are intramolecular reactions. The intermolecular reaction for the synthesis of ε-lactones has rarely been reported. More importantly, the catalytic enantioselective synthesis of ε-lactones has far less established.[3]

In the last decade, the N-heterocyclic carbene (NHC) catalyzed annulation reactions emerged as powerful methods for various heterocycles.[7] In 2004, Bode et al. and Glorius et al. independently reported the pioneering NHC-catalyzed [3+2] annulation of enals with aldehydes to give γ-butyrolactones (Scheme 1a).[8] Then, γ-lactams were synthesized by reaction with imines.[9] In 2007, Scheidt et al. developed the NHC-catalyzed [3+3] annulation of enals with azomethines or nitrones, thus giving the corresponding pyridazinones or 1,2-morpholinone (Scheme 1b).[10] In addition, the NHC-catalyzed annulations of enals with enones,[11,12] azadienes[13] or 1,3-diketones[14] were also developed.[15]

In the past several years, we established a series of NHC-catalyzed cycloaddition reactions of ketenes,[16] including the [2+4] cycloaddition of ketenes with *o*-quinone methides.[17,18] Herein we report the NHC-catalyzed [3+4] annulation of enals with *o*-quinone methides to give the corresponding benzo-ε-lactones (Scheme 1c). Although the formation of seven member lactones by an intermolecular reaction remains a challenge, and there are several potential competition reactions such as [3+2] and [4+2] annulations, we envision that the driving force of re-aromazation may make the desired [3+4] annulation feasible.[19]



Scheme 1. NHC-catalyzed [3+*n*] annulation of enals.

Initially, a model reaction of the *o*-quinone methide **1a** with cinnamaldehyde (**2a**) was investigated under the catalysis of NHCs derived from L-pyroglutamic acid (Table 1).[16,20] The precatalyst **A1**, previously found effective in cycloaddition of *o*-quinone methides and ketenes,[17] did not work for this reaction (Table 1, entry 1). Gratifyingly, the desired [3+4] annulation product **3a** could be obtained in 49% yield with 96% *ee* when the NHC **A2**, having a free hydroxy group, was employed (entry 2).[21] The possible hydrogen bonding between the hydroxy group and *o*-quinone methide could enhance the reactivity and improve the enantioselectivity. To further take the advantage of hydrogen bonding, the NHCs **B1**–**B3** with an α,α-bis(3,5-di(trifluoromethyl)phenyl) hydroxy substituent were tested. **B1** and **B2**, which worked well for the aza-benzoin reaction of enals with activated ketimines,[22] showed comparable results as **A2** (entries 3 and 4). Much better performance was observed (90% yield, 3:1 d.r. and 94% *ee*) when **B3**, having a bulky *N*-2-isopropylphenyl group, was utilized (entry 5). As reported,[8] the bulky substituent of **B3** could circumvent the possible C1 addition of the generated Breslow intermediate, and thus facilitate the C3 addition. Solvent screening revealed that reaction went smoothly in various solvents with a slightly better diastereoselectivity observed in diethyl ether or 1,4-dioxane (entries 6–

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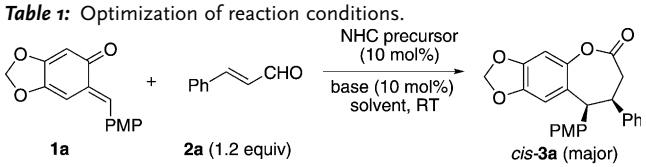
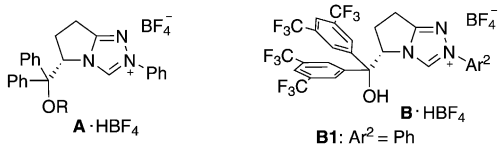
Table 1: Optimization of reaction conditions.





A1: R = TBS
A2: R = H

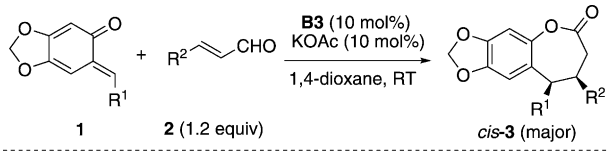
B1: Ar^2 = Ph
B2: Ar^2 = Bn
B3: Ar^2 = 2-*i*PrC$_6$H$_4$

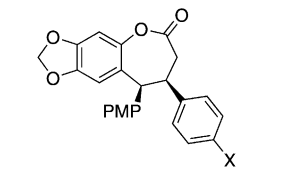
Entry	Cat.	Base, solvent	Yield [%][a]	d.r.[b]	*ee* [%][c]	
					cis-**3a**	*trans*-**3a**
1	**A1**	DBU, THF	trace	n.d.	n.d.	n.d.
2	**A2**	DBU, THF	49	5:1	96	n.d.
3	**B1**	DBU, THF	30	5:1	90	15
4	**B2**	DBU,THF	63	2:1	88	23
5	**B3**	DBU, THF	90	3:1	94	42
6	**B3**	DBU, tol	94	2:1	87	48
7	**B3**	DBU,CH_2Cl_2	88	3:1	92	43
8	**B3**	DBU, Et_2O	61	5:1	94	20
9	**B3**	DBU, DME	96	3:1	92	17
10	**B3**	DBU, 1,4-dioxane	97 (96)[d]	4:1	94	29
11	**B3**	DBU, CH_3CN	55	3:1	92	19
12[e]	**B3**	DBU, 1,4-dioxane	98	3:1	93	40
13[e]	**B3**	DBU, 1,4-dioxane	99	3:1	93	33
14[e]	**B3**	DBU, 1,4-dioxane	88	3:1	95	33
15	**B3**	Cs_2CO_3, 1,4-dioxane	38	3:1	94	25
16	**B3**	Et_3N, 1,4-dioxane	99	3:1	93	33
17	**B3**	KOAc, 1,4-dioxane	98 (96)[d]	4:1	94	40
18[f]	**B3**	KOAc, 1,4-dioxane	(84)[d]	4:1	92	n.d.

[a] Combined yield of the two diastereomers as determined by ^{1}H NMR spectroscopy. [b] Diastereoselectivity determined by ^{1}H NMR analysis of unpurified reaction mixture. [c] Enantiomeric excess of *cis*-**3a** and *trans*-**3a** determined by HPLC on a chiral column [d] Combined yield of isolated diastereomers. [e] 10 mol% of $Mg(OTf)_2$, $LiClO_4$ or $Cu(OTf)_2$ was used as the additive for the reaction in entries 12–14. [f] The reaction was carried out at 0°C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DME = 1,2-dimethoxyethane, n.d. = not determined, PMP = *p*-methoxyphenyl, THF = tetrahydrofuran.

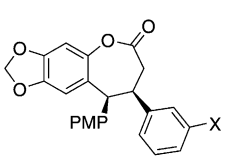
11). Further attempts to improve the diastereoselectivity was carried out by the addition of Lewis acids. However, no positive effect was identified when $Mg(OTf)_2$, $LiClO_4$, and $Cu(OTf)_2$ were used as additives (entries 12–14). Evaluation of the bases indicated that KOAc and Et_3N worked as well as DBU, whereas the usage of Cs_2CO_3 led to much lower yield (entries 10, 15–17). No improvement of yield and selectivity was observed for the reaction at 0°C (entry 18).

With the optimized reaction conditions in hand, the scope with respect to the *o*-quinone methides and enals was examined (Scheme 2). It was found that a broad range of enals could readily participate in this reaction. β-Aryl enals with moderate electron-withdrawing or electron-donating substituents (4-Cl, 4-Br, 4-Me, 4-MeOC$_6$H$_4$) worked well to give the desired ε-lactones in high yield with moderate diastereoselectivity and high enantioselectivity (**3b**,**c** and **3e**,**f**), whereas the enal with a *p*-nitrophenyl substituent showed decreased enantioselectvity (**3d**). Substrates with

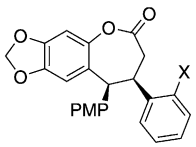




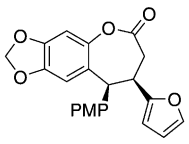
3a (X = H): 96%, 4:1 d.r., 94% *ee*
3b (X = Cl): 95%, 3:1 d.r., 90% *ee*
3c (X = Br): 94%, 3:1 d.r., 90% *ee*
3d (X = NO_2): 94%, 3:1 d.r., 81% *ee*
3e (X = Me): 96%, 4:1 d.r., 94% *ee*
3f (X = OMe): 92%, 4:1 d.r., 95% *ee*



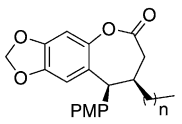
3g (X = Cl): 92%, 3:1 d.r., 86% *ee*
3h (X = OMe): 92%, 3:1 d.r., 89% *ee*



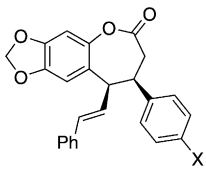
3i (X = Cl): 92%, 3:1 d.r., 82% *ee*
3j (X = OMe): 79%, 3:1 dr, 90% *ee*



3k: 95%, 5:1 d.r., 94% *ee*



3l (*n* = 1): 91%, >20:1 d.r., 98% *ee*
3m (*n* = 2): 83%, >20:1 d.r., 97% *ee*
3n (*n* = 5): 88%, >20:1 d.r., 97% *ee*
3o (*n* = 6): 97%, >20:1 d.r., 93% *ee*



3p (X = H): 91%, 3:1 d.r., 93% *ee*
3q (X = Cl): 86%, 3:1 d.r., 89% *ee*
3r (X = OMe): 93%, 3:1 d.r., 94% *ee*

Scheme 2. Substrate scope of enals and *o*-quinone methides. Reaction for **3o** run at 60°C.

meta and *ortho* substituents were also suitable for the reaction without an apparent change in yield, albeit with a somewhat decreased enantioselectivity (**3g**–**3j**). β-2-Furyl enal worked well to give the ε-lactone **3k** in 95% yield with 5:1 d.r. and 94% *ee*. Notably, β-alkyl enals worked even better than β-aryl enals in terms of diastereo- and enantioselectivities. All the examined β-alkyl enals, having both short-chain alkyl groups (R^2 = ethyl, *n*-propyl) and long-chain alkyl groups (R^2 = *n*-hexyl or *n*-heptyl), gave the desired products (**3l**–**3o**) in high yields with remarkably improved diastereoselectivities (d.r. > 20:1) and excellent diastereoselectivities (93–98% *ee*). It should be noted that the reaction of dec-2-enal went slowly at room temperature, but went smoothly at 60°C. In addition, *o*-quinone methides having a cinnamyl substituent also worked well for the reaction, thus affording the desired ε-lactones **3p**–**3r** in very good yields with moderate diastereoselectivity and excellent enantioselectivity.

The seven-membered ring structure of the benzo-ε-lactone **3l** was unambiguously established by X-ray analysis of its crystal structure (see Figure S1 in the Supporting Information).[23,24]

The proposed catalytic cycle is depicted in Figure 1. The addition of NHC to an enal gives the vinyl Breslow intermediate **4**, which reacts with the *o*-quinone methides **1** by Michael addition to give the adduct **5**. Intramolecular

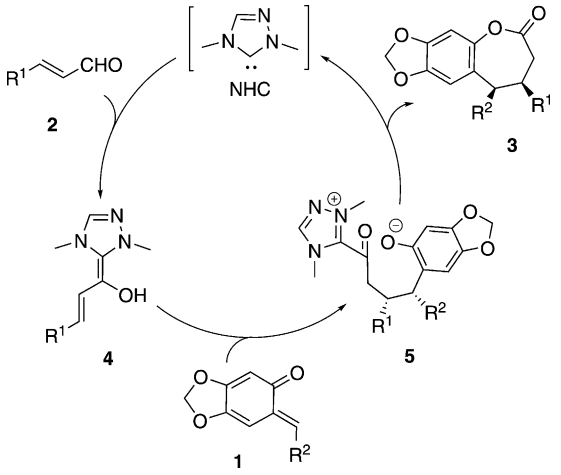


Figure 1. Proposed catalytic cycle.

lactonization of **5** furnishes the final [4+3] annulation product **3** and regenerates the NHC.[15a–c,25] Another mechanism proceeding through the in situ generated unsaturated acyl azolium and phenol is disfavored as confirmed by control experiments.[26]

In summary, an unprecedented NHC-catalyzed [4+3] annulation of enals with *o*-quinone methides has been established.[27] The reaction worked well for both β-aryl and β-alkyl enals, thus giving the corresponding benzo-ε-lactones in high yields with moderate (for β-aryl enals) to excellent (for β-alkyl enals) diastereoselectivties. High to excellent enantioselectivities (81–98% *ee*) were achieved by using a chiral triazolium NHC with a free hydroxy group. Further investigation on the reaction scope and related other NHC-catalyzed annulation reactions are underway in our laboratory.

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[27] We have become aware of a related study by Scheidt and co-workers involving the formal [4+3] annulation of NHC-homoenolates and *o*-quinone methides generated in situ. K. Scheidt, personal communication.

