

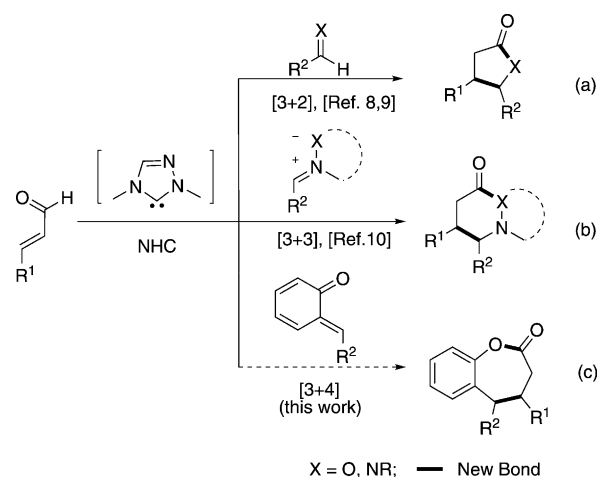
N-Heterocyclic Carbene Catalyzed [4+3] Annulation of Enals and *o*-Quinone Methides: Highly Enantioselective Synthesis of Benzo- ϵ -Lactones**

Hui Lv, Wen-Qiang Jia, Li-Hui Sun, and Song Ye*

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 1 a).^[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 1 b).^[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 1 c). Although the formation of



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

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]

Initially, a model reaction of the *o*-quinone methide **1a** with cinnamaldehyde (**2a**) was investigated under the catalysis of NHCs derived from L-pyrroglutamic 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–

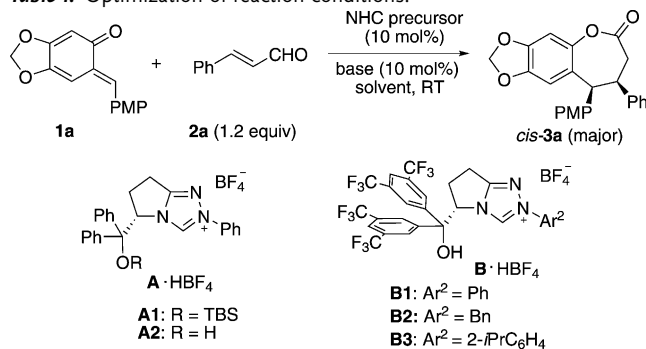
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Table 1: Optimization of reaction conditions.

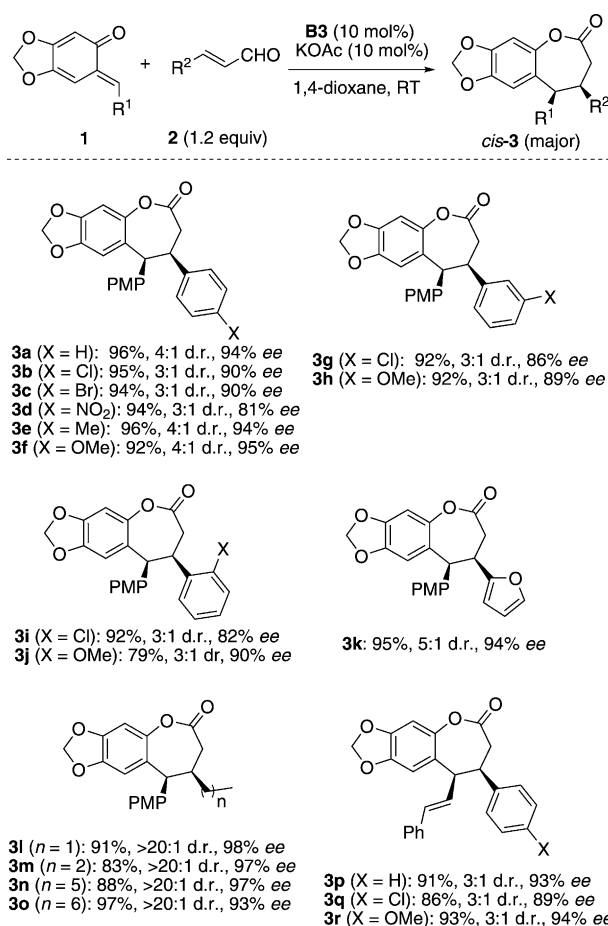


Entry	Cat.	Base, solvent	Yield [%] ^[a]	d.r. ^[b]	ee [%] ^[c]	<i>cis</i> - 3 a	<i>trans</i> - 3 a
1	A1	DBU, THF	trace	n.d.	n.d.	n.d.	
2	A2	DBU, THF	49	5:1	96	n.d.	
3	B1	DBU, THF	30	5:1	90	15	
4	B2	DBU, THF	63	2:1	88	23	
5	B3	DBU, THF	90	3:1	94	42	
6	B3	DBU, toluene	94	2:1	87	48	
7	B3	DBU, CH ₂ Cl ₂	88	3:1	92	43	
8	B3	DBU, Et ₂ O	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 ₃ CN	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 ₂ CO ₃ , 1,4-dioxane	38	3:1	94	25	
16	B3	Et ₃ N, 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 ¹H NMR spectroscopy. [b] Diastereoselectivity determined by ¹H NMR analysis of unpurified reaction mixture. [c] Enantiomeric excess of *cis*-**3 a** and *trans*-**3 a** determined by HPLC on a chiral column [d] Combined yield of isolated diastereomers. [e] 10 mol % of Mg(OTf)₂, LiClO₄ 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, LiClO₄, and Cu(OTf)₂ were used as additives (entries 12–14). Evaluation of the bases indicated that KOAc and Et₃N worked as well as DBU, whereas the usage of Cs₂CO₃ 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-MeOC₆H₄) 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 enantioselectivity (**3d**). Substrates with



Scheme 2. Substrate scope of enals and *o*-quinone methides. Reaction for **3 o** 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 (R² = ethyl, *n*-propyl) and long-chain alkyl groups (R² = *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

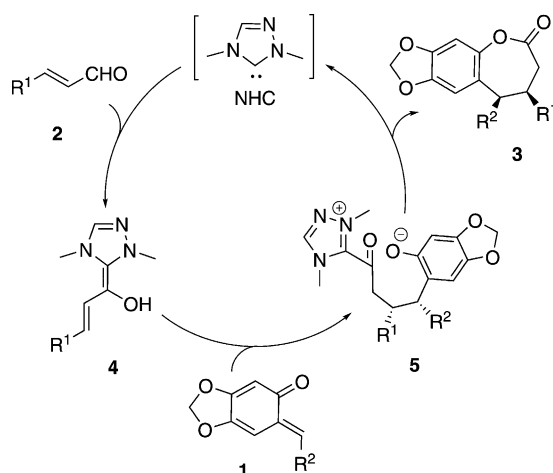


Figure 1. Proposed catalytic cycle.

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) diastereoselectivities. 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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