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Asymmetric N-Heterocyclic Carbene (NHC)-Catalyzed Annulation of Modified Enals with Enolizable Aldehydes

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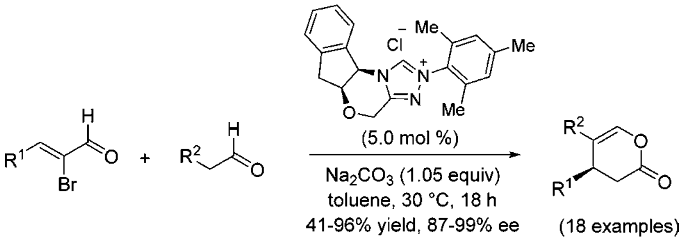
ABSTRACT



N-Heterocyclic carbene (NHC)-catalyzed highly enantioselective lactonization of modified enals with enolizable aldehydes, proceeding via the α,β-unsaturated acylazolium intermediates, is reported. The reaction results in the asymmetric synthesis of synthetically important 4,5-disubstituted dihydropyranones.

The benzoin reaction, the cyanide or N-heterocyclic carbene (NHC)-catalyzed union of two aromatic aldehydes, is a valuable strategy to construct new C–C bonds leading to the formation of α-functionalized carbonyl compounds (Scheme 1, eq 1).[1,2] The reaction proceeds through a unique umpolung strategy, generating the nucleophilic Breslow intermediate,[1d] and its mechanism has been extensively studied.[3] This umpolung notion was extended to the concept of conjugate umpolung (via homoenolate equivalents) in 2004 independently by the groups of Glorius[4] and Bode.[5] They intercepted the homoenolate equivalents generated from enals and NHCs with aldehydes, and the reaction lead to the formation of γ-butyrolactones (eq 2). Interestingly, however, the coupling of two different aldehydes under NHC-catalysis can always meet with various selectivity issues. For instance, the reaction of an enal with another aldehyde under NHC-catalysis can result in eight possible products (two γ-butyrolactones, four benzoin products, and two Stetter products). In many cases, the desired

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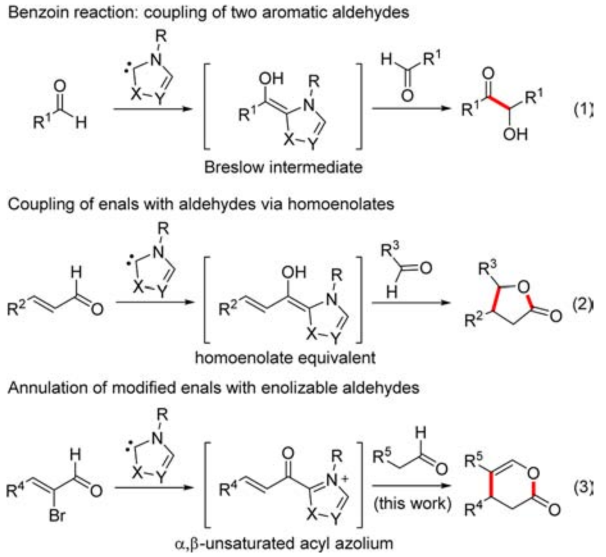
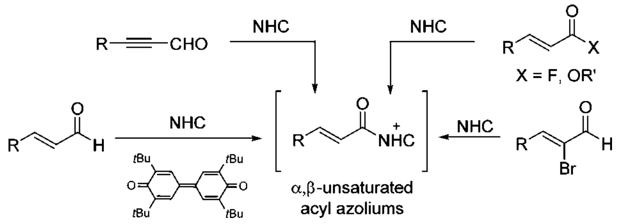
Scheme 1. NHC-Calatyzed Cross-Coulping of Aldehydes



product formation can be achieved by tuning the electronic and steric properties of the NHC-catalysts as well as the proper design of substrates.[6] Herein, we report the NHC-catalyzed highly enantioselective lactonization of modified enals with enolizable aldehydes, the formal [3 + 3] annulation reaction, and the reaction resulted in the synthesis of chiral 4,5-disubstituted dihydropyranone derivatives (eq 3). The reaction proceeds via the generation of chiral α,β-unsaturated acyl azolium intermediates,[7−11] without the use of external oxidants and works under mild reaction conditions. It may be noted in this context that the important methods for the generation of α,β-unsaturated acyl azoliums include the reaction of α,β-unsaturated esters or acyl fluorides with NHCs,[7,8] treatment of enals with NHCs followed by stoichiometric oxidation of the generated Breslow intermediate,[9] reaction of ynals with NHCs,[10] and the reaction of 2-bromoenals with NHCs (Scheme 2).[11]

Scheme 2. NHC-Catalyzed Methods for the Generation of α,β-Unsaturated Acyl Azoliums



The present investigation was initiated by treating α-bromo cinnamaldehyde (**1a**) and 2-phenylacetaldehyde (**2a**) with the aminoindanol-derived triazolium salt **4**[12] and 1.05 equiv of Na_2CO_3. The reaction furnished the 4,5-diaryl dihydropyranone (**3a**) in 63% yield (based on ^1H NMR spectroscopy) and 98% ee (Table 1, entry 1).[13] It is noteworthy that, in this process, many selectivity issues arose, and the competing homoenolate annulation reactions as well as the benzoin and Stetter reaction pathways were largely suppressed under the present reaction conditions. As anticipated, the reaction did not work at all in the absence of the triazolium salt **4** (entry 2). An extensive base screening revealed that bases such as DABCO, DBU, DMAP, and Cs_2CO_3 furnished the desired product in either reduced yields or diminished selectivities (entries 3−6). The solvent optimization studies revealed that 1,4-dioxane returned comparable selectivity with improved yield (entry 7), whereas other solvents including THF and CH_2Cl_2 resulted in reduced selectivities (entries 8, 9). Finally, increasing the reaction time improved the isolated yield (75%) and the enantioselectivity was enhanced to 99% (entry 10).[14]

With the optimized reaction conditions in hand, we then evaluated the substrate scope of this interesting aldehyde coupling reaction. Initially, we examined various 2-bromoenals (Scheme 3). The unsubstituted parent

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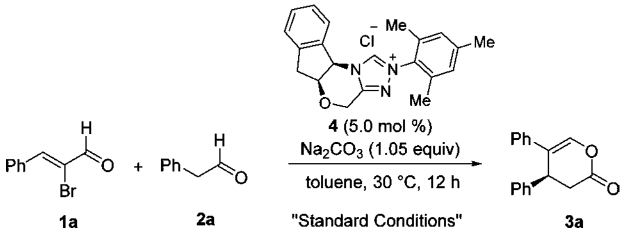
(14) See the Supporting Information for details.

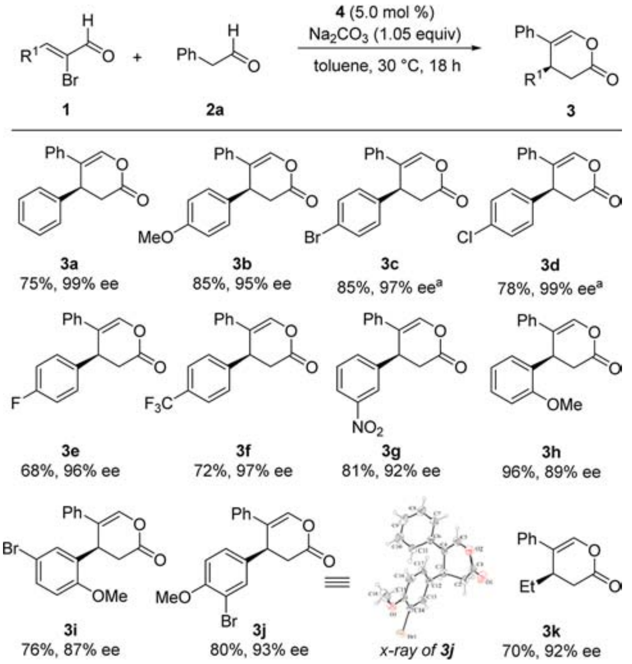
Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield **3a** (%)[b]	ee **3a** (%)[c]
1	none	63	98
2	reaction without **4**	<1	nd
3	DABCO instead of Na$_2$CO$_3$	27	98
4	DMAP instead of Na$_2$CO$_3$	82	93
5	DBU instead of Na$_2$CO$_3$	49	43
6	Cs$_2$CO$_3$ instead of Na$_2$CO$_3$	79	82
7	1,4-dioxane instead of toluene	70	95
8	THF instead of toluene	85	87
9	CH$_2$Cl$_2$ instead of toluene	44	89
10	*reaction time 18 h instead of 12 h*	*78 (75)*	*99*

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), **4** (5.0 mol %), Na$_2$CO$_3$ (1.05 equiv), toluene (1.0 mL), 30 °C, and 12 h. [b] The yields were determined by ^{1}H NMR analysis of crude products using CH$_2$Br$_2$ as the internal standard, isolated yield in parentheses. [c] Determined by HPLC analysis on a chiral column.

Scheme 3. Substrate Scope for the Asymmetric Synthesis of Dihydropyranones: Variation of the 2-Bromoenal Moiety



General reaction conditions: **1** (0.50 mmol), **2a** (0.50 mmol), **4** (5.0 mol %), Na2CO3 (1.05 equiv.), toluene (2.0 mL) at 30 °C for 18 h. The ee values were determined by HPLC analysis on a chiral column. [a]Reaction was run on 0.25 mmol scale.

system worked well, and electron-donating and -withdrawing groups at the 4-position of the aromatic ring underwent a smooth annulation reaction, leading to 4,5-disubstituted dihydropyranones in good yields and with excellent ee values over 95% in all cases (**3a**–**3f**). Moreover, substitution at the 3-position and 2-position of the β-aryl ring were well tolerated and furnished the desired product (**3g, 3h**) in good yield and high enantioselectivity. Additionally disubstituted substrates also afforded the expected product in good yield and selectivity (**3i, 3j**). In the case of **3j**, the structure and stereochemistry were unequivocally confirmed by single-crystal X-ray analysis.[15] Furthermore, challenging aliphatic aldehydes such as (*Z*)-2-bromopent-2-enal also afforded good yield and high enantioselectivity of the target product, further expanding the scope of this annulation reaction (**3k**).

Next, we examined the scope of the reaction with various enolizable aldehydes (Scheme 4). Phenyl acetaldehyde derivatives with electron-releasing and -withdrawing groups at the 4-position of the aromatic ring underwent a smooth annulation reaction affording the dihydropyranones in good yields and excellent selectivities (**3l**–**3n**). Moreover, the naphthyl acetaldehyde furnished the desired product in 94% ee (**3o**). Interestingly, the heterocyclic acetaldehyde derivatives resulted in moderate yield and high ee of the annulated product further expanding the scope of this reaction (**3p, 3q**). Additionally, this reaction is not limited to aromatic acetaldehyde derivatives. Gratifyingly, (*E*)-4-phenylbut-3-enal can also be used as a coupling partner affording the 5-styryl 4-phenyl dihydropyranone **3r** in moderate yield and 94% ee.[16]

A tentative mechanism for this NHC-catalyzed lactonization is shown in Scheme 5. The initially generated nucleophilic Breslow intermediate (**I**)[1d] by the addition of NHC to 2-bromoenal is converted into the key α,β-unsaturated acyl azolium intermediate **III** by the rapid debromination of the homoenolate equivalent **II**.[12] Nucleophilic addition of **2a** to **III** can proceed in a 1,4-fashion[9b,j] or in a 1,2-pathway.[9c–g] The 1,4-addition can directly generate the enol intermediate **IV**. Alternatively, the 1,2-addition of **2a** to **III** can form the hemiacetal intermediate **V**, which can undergo [3,3] sigmatropic rearrangement to furnish **IV**.[17]

We have carried out additional experiments to show the usefulness of generating α,β-unsaturated acylazoliums

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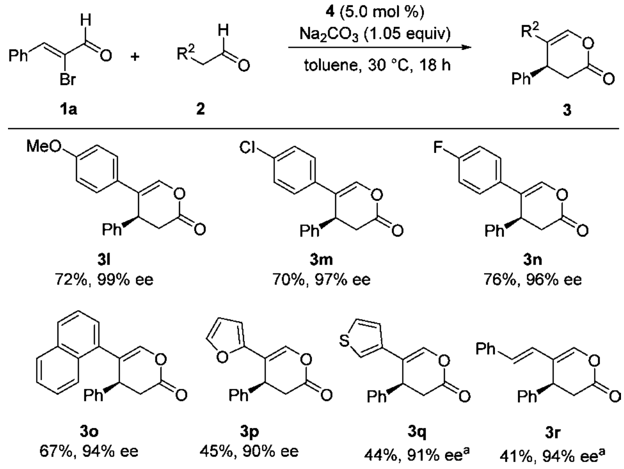
(15) CCDC-943669 (**3j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) It may be noted that linear aliphatic aldehydes such as *n*-heptanal and less enolizable aldehydes such as 3-phenylpropanal did not show any reactivity with α,β-unsaturated acylazoliums under the optimized conditions.

(17) Based on detailed kinetic and theoretical studies, Studer et al. and Bode et al. proposed the mechanism of the addition of nucleophiles to α,β-unsaturated acylazoliums. Studer et al. proposed the conjugate addition mechanism. Depending on the nucleophile and the structure of the α,β-unsaturated acylazolium ion, Bode et al. invoked the initial 1,2-addition followed by [3,3]-sigmatropic rearrangement.

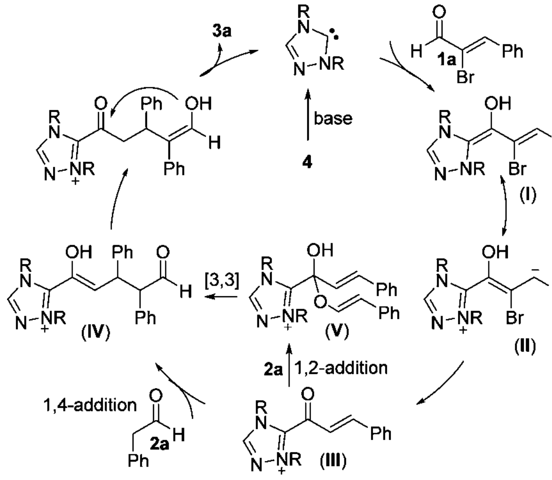
(18) We thank the reviewer for suggesting these experiments.

Scheme 4. Variation of the enolizable aldehyde moiety



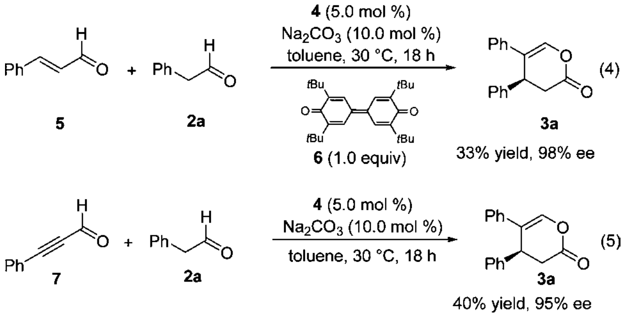
General reaction conditions: **1a** (0.50 mmol), **2** (0.50 mmol), **4** (5.0 mol %), Na_2CO_3 (1.05 equiv), toluene (2.0 mL) at 30 °C for 18 h. The ee values were determined by HPLC analysis on a chiral column. [a]Reaction was run on 0.25 mmol scale.

Scheme 5. Tentative Mechanism of the NHC-Catalyzed Annulation of 2-Bromoenals



from 2-bromoenals in the context of the present reaction. Treatment of cinnamaldehyde **5** with **2a** under the reaction conditions using oxidant **6** afforded the desired product **3a** in 33% yield and 98% ee (Scheme 6, eq 4).

Scheme 6. Reactions Using Enal (under oxidative conditions) and Ynal



Moreover, the reaction of 3-phenylpropiolaldehyde **7** with **2a** in the presence of carbene precursor **4** and Na_2CO_3 furnished **3a** in 40% yield and 95% ee (eq 5). Although the enantioselectivity is comparable, the reactivity is lower in both cases compared to reaction with 2-bromoenals. These experiments tend to indicate that the generation of α,β-unsaturated acylazoliums from 2-bromoenals affords the dihydropyranones in better yields compared to the generation of the same intermediate from either enal or ynal.[18]

In conclusion, we have developed a highly enantioselective NHC-organocatalyzed lactonization of 2-bromoenals with enolizable aldehydes proceeding via the chiral α,β-unsaturated acylazolium intermediates. Mild reaction conditions, relatively low catalyst loadings, and high ee of the products are the noteworthy features of this reaction.

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Supporting Information Available. Detailed experimental procedures, single crystal X-ray data of **3j**, and characterization and HPLC data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.