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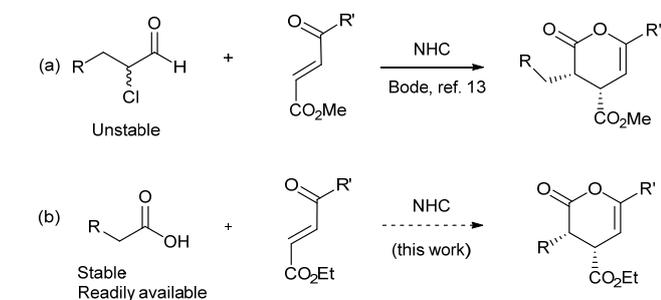
N-Heterocyclic Carbene-Catalyzed Cyclocondensation of 2-Aryl Carboxylic Acid and Enones: Highly Enantioselective Synthesis of δ -Lactones.

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The enantioselective N-heterocyclic carbene-catalyzed [4 + 2] cyclocondensation of 2-aryl carboxylic acids and enones was developed, affording the corresponding chiral δ -lactones in good yields with good diastereo- and high enantioselectivities.

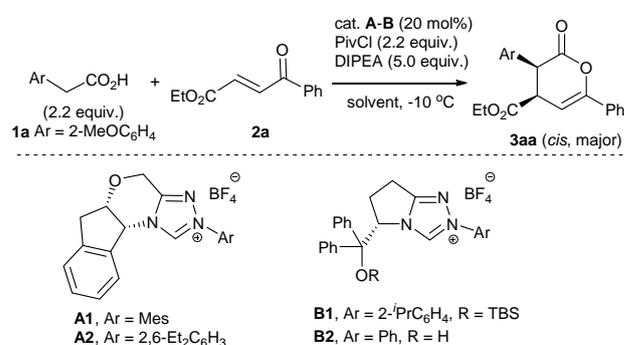
The N-heterocyclic carbenes (NHCs) have been demonstrated as efficient organocatalysts for various reactions.¹ Particularly, the NHC-catalyzed generation of azolium enolates from α -chloroaldehydes,² formylcyclopropanes,³ α -aryloxy aldehydes,⁴ enals,⁵ ketenes,⁶ and esters⁷ have been extremely successful. However, the usage of stable and readily available carboxylic acids as the substrate for the NHC-catalyzed reactions has received little attention.⁸ Recently, Scheidt *et al.* reported the NHC-catalyzed enantioselective annulations for dihydroquinolones by in situ generation of azolium enolates from carboxylic acid.⁹ Simultaneously, our group reported the NHC-catalyzed enantioselective [3 + 2] cyclocondensation of α,β -unsaturated carboxylic acids with α -amino ketones and [3+3] cyclocondensation with imines.¹⁰

Scheme 1 NHC-catalyzed synthesis of δ -lactones

δ -Lactones are widely found in numerous natural and unnatural bioactive compounds.¹¹ Thus, efficient construction of δ -lactones have been a continuing target for organic chemists.¹² In 2006, Bode *et al.* reported the pioneering NHC-catalyzed [4 + 2] cycloaddition of chloroaldehydes with enones to give δ -lactones (Scheme 1, reaction a).¹³ However, only the α -chloro- β,β -dihydroaldehydes were reported for the reaction, possible due to the sensitivity of α -chloroaldehydes to moisture and oxygen.¹⁴ Being readily available, stable and easy to manipulate, carboxylic acid would be useful alternative to chloroaldehyde for the NHC-catalyzed reaction. In this

communication, we report the NHC-catalyzed generation of azolium enolate from carboxylic acids and the following [4 + 2] cyclocondensation with enones to give δ -lactones (Scheme 1, reaction b).¹⁵

Table 1. Optimization of the reaction conditions.



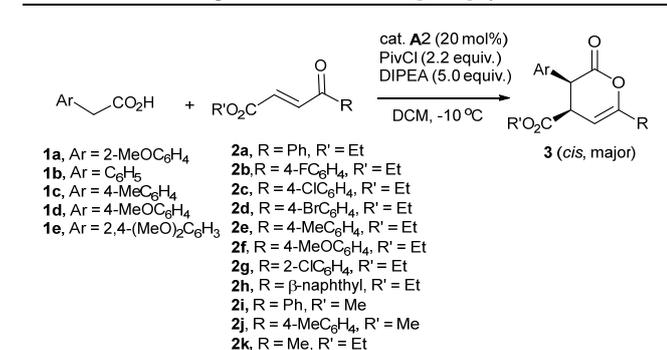
entry	cat.	solvent	yield ^a (%)	cis:trans ^b	ee ^c (%)
1	A1	DCM	18	2:1	99(70)
2	A2	DCM	77	10:1	99(79)
3	B1	DCM	trace	/	/
4	B2	DCM	trace	/	/
5	A2	THF	25	4:1	99(77)
6	A2	ether	41	3:1	99(71)
7	A2	CH ₃ CN	19	1:2	92(97)
8	A2	toluene	39	16:1	99(45)
9	A2	DCM (0 °C)	68	3:1	99(87)
10	A2	DCM (rt)	1:6	3:1	99(70)

⁴⁵ ^a Isolated yield of the mixture of two diastereoisomers. ^b Determined by ¹H NMR (300 MHz) spectroscopy of the unpurified reaction mixture. ^c Enantiomeric excess of *cis*-**3a** followed of *trans*-**3a** in parenthesis. PivCl = Pivaloyl chloride, Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran, TBS = *tert*-butyldimethylsilyl.

Initially, the reaction of 2-(2-methoxyphenyl)acetic acid **1a**, via the in situ generated anhydride with pivaloyl chloride, with enone **2a** was investigated under NHC catalysis (Table 1). We were encouraged to find that the desired δ -lactone **3a** was obtained in 18% yield with 2:1 dr and 99% ee for *cis*-isomer and 70% ee for *trans*-isomer in the presence of 20 mol% of *N*-mesityl tetracyclic NHC precursor **A1**¹⁶ (entry 1). The yield and diastereoselectivity was dramatically improved with *N*-2,6-diethylphenyl tetracyclic NHC precursor **A2**¹⁷ was employed as

the catalyst (entry 2). On the contrary, the reaction using the NHC precursor **B1** or **B2**, derived from *L*-pyroglutamic acid,¹⁸ gave only trace of desired cycloadduct (entries 3 and 4). Decreased yield and diastereoselectivity was resulted when the reaction was carried out in THF, ether or acetonitrile (entries 5-7). The reaction in toluene gave cycloadduct with improved diastereoselectivity but in low yield (entry 8). The diastereoselectivity was decreased when the reaction was carried out at 0 °C or rt, due to the partially epimerization of *cis*-**3a** to *trans*-**3a** (entries 9 and 10).

Table 2. Substrate scope for enantioselective [4 + 2] cyclocondensation.

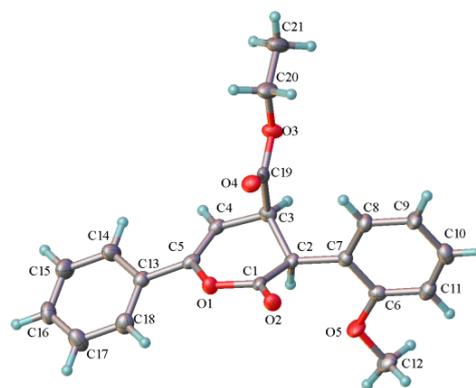


entry	1	2	3	yield ^a (%)	<i>cis</i> : <i>trans</i> ^b	ee (%) ^c
1	1a	2a	3aa	77	10:1	99
2	1a	2b	3ab	67	10:1	99
3	1a	2c	3ac	61	10:1	98
4	1a	2d	3ad	55	7:1	99
5	1a	2e	3ae	55	6:1	99
6	1a	2f	3af	80	10:1	99
7	1a	2g	3ag	63	6:1	98
8	1a	2h	3ah	33	3:1	99
9	1b	2a	3ba	88	1:1	ND
10	1c	2a	3ca	72	6:1	98
11	1d	2a	3da	58	3:1	99
12	1e	2a	3ea	54	6:1	99
13	1e	2e	3ee	66	20:1	99
14	1e	2f	3ef	50	>20:1	99
15	1a	2i	3ai	66	10:1	99
16	1a	2j	3aj	65	10:1	99
17	1a	2k	3ak	27	>20:1	97

^a Isolated yield of the mixture of two diastereoisomers. ^b Determined by ¹H NMR (300 MHz) spectroscopy of the unpurified reaction mixture. ^c Enantiomeric excess of *cis*-**3**. ND = not determined.

With the optimized conditions in hand, the scope of the reaction substrates was briefly investigated (Table 2). It was found that both enones **2** with electron-withdrawing group (4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄) and those with electron-donating group (4-MeC₆H₄, 4-MeOC₆H₄) were suitable substrates, furnishing the corresponding δ-lactones in good yields and good diastereoselectivities and excellent enantioselectivities (entries 2-6). The reaction of enone **2g** with 2-chlorophenyl gave the cycloadduct **3ag** in 63% yield, 6:1 dr and 98% ee (entry 7), while the reaction of enone **2h** with β-naphthyl resulted in decreased yield and diastereoselectivity, but excellent enantioselectivity was kept (entry 8). Several 2-arylacetic acids were also tested for the reaction. It was found that the reaction of simple phenylacetic acid (**1b**) gave the δ-lactone **3ba** in high yield but with 1:1 dr (entry 9). 2-Arylacetic acids with 4-methylphenyl or 4-methoxyphenyl (**1c** and **1d**) worked well for the reaction

resulting in moderate diastereoselectivities but excellent enantioselectivities (entries 10 and 11). 2,4-Dimethoxyphenylacetic acid (**1e**) was also a workable substrate for the reaction with several enones (**2a**, **2e**, **2f**), giving the desired corresponding δ-lactones in good yield with good to high diastereoselectivities and excellent enantioselectivities (entries 12-14). The reaction of enones **2i** and **2j** with methyl esters instead of ethyl esters went also well (entries 15 and 16). The reaction of enone **2k** with alkyl instead of aryl substituent (R' = Et) gave the desired product **3ak** in low yield albeit with high diastereo- and enantioselectivity (entry 17).

Figure 1. X-Ray structure of **3aa**

The 3*S*, 4*R*-configuration of the cycloadduct **3aa** was determined by the X-ray analysis of its crystal. (Figure 1).¹⁹

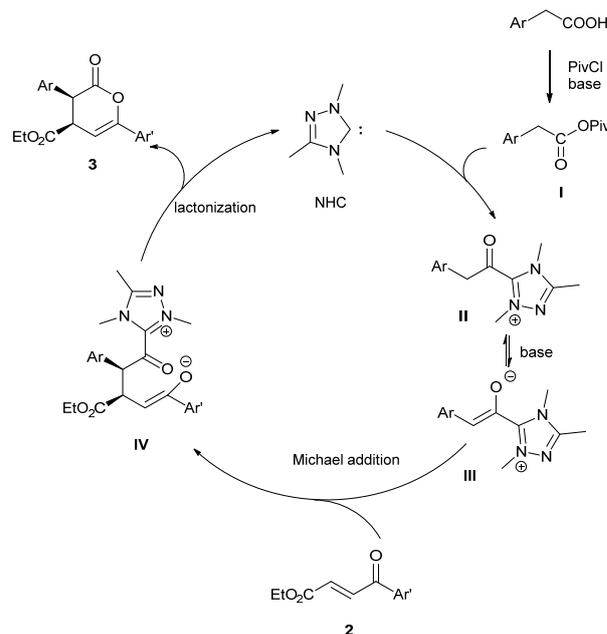


Figure 2. Plausible catalytic cycle.

A plausible catalytic cycle for the NHC-catalyzed [4 + 2] cyclocondensation of 2-arylacetic acid with enones is depicted in Figure 2. The addition of NHC to mixed anhydride **I**, which is formed in situ from the 2-arylacetic acid and pivaloyl chloride, gives acylazolium **II**. The Michael addition of enolate **III**, which is equivalent to the acylazolium **II** in the presence of base, affords adduct **IV**.²⁰ The intramolecular acylation of adduct **IV**

gives the final desired δ -lactone **3** and regenerates the NHC catalyst.

Conclusions

In summary, carboxylic acids were demonstrated as suitable substrates for the NHC-catalyzed reactions. The chiral NHC-catalyzed [4 + 2] cyclocondensation of carboxylic acid and enones gave the corresponding δ -lactones in good yields with good diastereo- and excellent enantioselectivities. The readily availability, easy to manipulate and mild reaction conditions make the NHC-catalyzed reaction of carboxylic acid potential useful for many related chemical transformations involving azolium enolates. Other related NHC-catalyzed reactions of carboxylic acids are underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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19. CCDC 1029598 (**3aa**) 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.
20. The concerted [4 + 2] cycloaddition of enolate and enones is less likely according to the moderate diastereoselectivities observed for most cases.