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N-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Bromoenal and 1,3-Dicarbonyl Compounds

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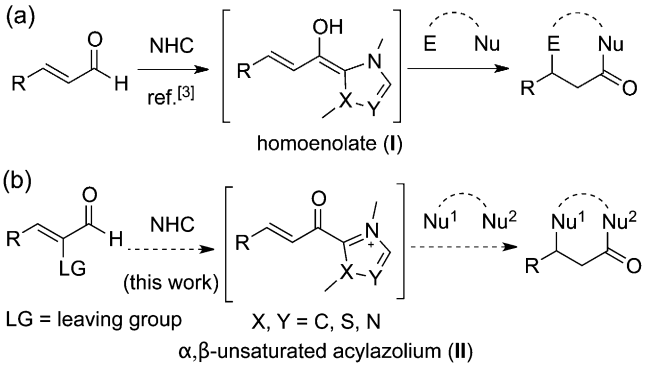
Abstract: Highly enantioselective [3+3] annulation reactions of bromoenals and 1,3-dicarbonyl compounds are reported. In addition, both enantiomers of the resultant dihydropyranone could be easily obtained by choosing N-heterocyclic carbenes (NHCs) with the same stereocenter but different substituents under the optimized reaction conditions.

Keywords: annulation reactions; asymmetric catalysis; bromoenals; dihydropyranones; N-heterocyclic carbenes



Scheme 1. NHC-catalyzed generation of homoenolate from enals [reaction (a)], and α,β-unsaturated acylazolium from enals with leaving group [reaction (b)].

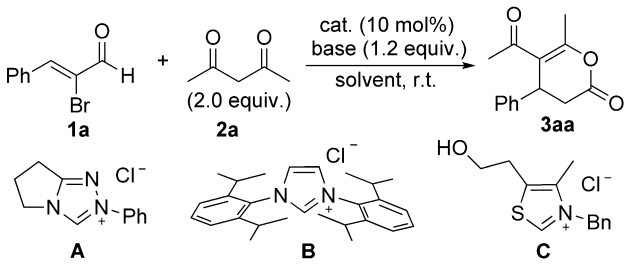
The N-heterocyclic carbene (NHC) catalysis can be traced back to 1943 when Ugai et al. reported the thiazolium salt-catalyzed benzoin reaction of aldehydes, and 1958 when Breslow proposed the mechanism with *in situ* generated carbene as the active catalyst.[1,2] In 2002, Bode et al. and Glorius et al. independently reported the pioneering NHC-catalyzed reaction of enals, involving the homoenolate intermediate (**I**) which may work as an analogue of a 1,3-dipole [Scheme 1, reaction (a)].[3] After that, the extended umpolung reactions of α-functionalized aldehydes catalyzed by NHC have received great attention and made tremendous progress. Beside enals,[4] many functionalized aldehydes, including ynals,[5] α-chloroaldehydes,[6] aryloxyacetaldehydes,[7] α-ring aldehydes,[8] and β-haloenals,[9] have been explored for NHC-catalyzed extended umpolung reaction.

We envision that α,β-unsaturated acylazolium intermediate (**II**) could be generated when enals with a leaving group were used, thus reversing the reactivity of the 1,3-dipole of homoenolate (**I**) to a 1,3-biselectrophile (**II**) [Scheme 1, reaction (b)]. Interestingly, the generation of 1,3-biselectrophile (**II**) has been reported from α,β-unsaturated acyl fluorides by Lupton et al.,[10] from ynals by Bode et al. and Xiao et al.[11] and from enals with an oxidant by Studer et al.[12] In this communication, we wish to report the generation of α,β-unsaturated acylazolium from bromoenal and the enantioselective reaction with 1,3-dicarbonyl compounds. During the preparation of this manuscript, You et al. and Xiao et al. reported the enantioselective reaction of α,β-unsaturated acylazolium generated *in situ* from enals and ynals, respectively.[13]

Firstly, the reaction of 2-bromocinnamaldehyde (**1a**) and acetoacetone (**2a**) catalyzed by achiral NHCs was investigated (Table 1). We are pleased to find that the corresponding annulation product **3aa** could be obtained in 80% yield in the presence of 10 mol% triazolium salt **A** and 1.2 equivalents of DIPEA (entry 1). The reaction also worked well using DABCO, Cs_2CO_3, or K_2CO_3 as the base (entries 2–4). Solvent screening revealed THF to be the best choice (entries 4–7). Imidazolium salt **B** led to better yields than thiazolium salt **C** (entry 8 *vs.* 9).

After establishing the feasibility of the reaction catalyzed by achiral NHCs, the enantioselective reaction

Table 1. Reaction catalyzed by achiral NHCs.



Entry	Catalyst	Base	Solvent	Yield [%][a]
1	**A**	DIPEA	THF	80
2	**A**	DABCO	THF	74
3	**A**	Cs_2CO_3	THF	79
4	**A**	K_2CO_3	THF	85
5	**A**	K_2CO_3	Et_2O	17
6	**A**	K_2CO_3	toluene	52
7	**A**	K_2CO_3	DCM	48
8	**B**	K_2CO_3	THF	98
9	**C**	K_2CO_3	THF	49

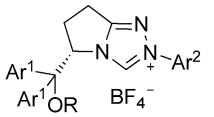
[a] Isolated yield.

was then investigated (Table 2). A series of chiral NHC precursors **D**, easily prepared from L-pyroglutamic acid, was screened. After some optimization, we are pleased to find that the reaction with 10 mol% of pre-NHC **D1** gave the desired adduct (−)-**3aa** in 72% yield with 93% *ee* (entry 1). It is interesting that the enantioselectivity could be reversed when the proper NHCs and conditions are employed (entry 2). Experiments revealed that both the structure of the NHCs and the property of the base play roles in the reversal of the selectivity. NHCs with a free hydroxy group showed reversed but varied selectivity (entries 2 and 3). In contrast with the nucleophilic but relatively weak base (DBACO and DMAP), a non-nucelophilic but strong base (DIPEA and K_2CO_3) resulted in low enantioselectivities (entries 2, 4–6). The reaction also worked in toluene or dichloromethane, albeit with decreased selectivity (entries 7 and 8). Lowering the temperature to 0 °C benefits the enantioselectivity (−92% *ee*) (entry 2 *vs.* 9)

With two optimized reaction conditions A (Cat. **D1**, K_2CO_3,) and conditions B (Cat. **D2**, DABCO) for (−)-**3** and (+)-**3**, respectively, in hand, the reaction scope was briefly investigated (Table 3). Reactions of the bromoenal with a *para*-chlorophenyl group (**1b**) gave the desired dihydropyranones (−) and (+)-**3ba**, respectively, in good yield with high enantioselectivity (entry 2). The bromoenal with a strong electron-withdrawing group (**1c**, R^1=4-$NO_2C_6H_4$) gave (−)-**3ca** in 74% yield with 84% *ee* (conditions A), and (+)-**3ca** in 82% yield with 87% *ee* (conditions B) (entry 3). The bromoenal with a strong electron-donating group (**1d**, R^1=4-$MeOC_6H_4$) resulted in decreased yield and enantioselectivity of (−)-**3da** under conditions A, while high eanantioselectivity was kept to give (+)-**3da** in 76% yield with 92% *ee* under conditions B (entry 4). Bromoenals with *meta*- or *ortho*- substituted aryl groups (R^1=3-Cl-, 2-Cl-, 2-NO_2-C_6H_4) all worked well under conditions A and B to give (−)-**3** and (+)-**3**, respectively, in good yield with high enantioselectivity (entries 5–7). It is noteworthy that bromoenal **1h** with an alkyl chain (R^1=*n*-Pr) also gave the desired annulation product with good enantioselectivity [72% *ee* for (−)-**3ha**, 93% *ee* for (+)-**3ha**] albeit with quite low yields under our current conditions (entry 8).

Several 1,3-dicarbonyl compounds were also tested for the reaction (entires 9–12). Alkyl acetoacetates (**2b** and **2c**) gave comparable results as acetoacetone (entries 9 and 10). The reaction of butyryl acetate

Table 2. Reaction of **1a** and **2a** catalyzed by chiral NHCs.

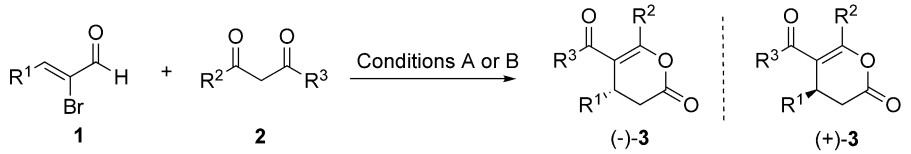


D (Ar^1, R, Ar^2)
D1 (Ph, TMS, C_6F_5)
D2 [(3,5-CF_3)$_2C_6H_3$, H, Bn]
D3 (Ph, H, Ph)

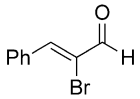
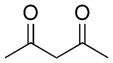
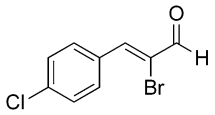
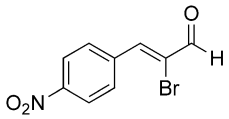
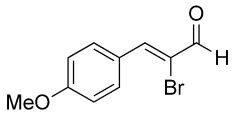
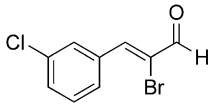
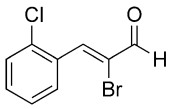
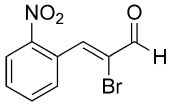
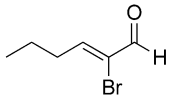
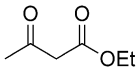
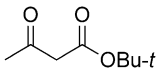
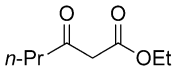
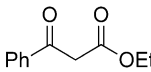
Entry	Catalyst	Base	Solvent	*T* [°C]	Yield [%][a]	*ee* [%][b]
1	**D1**	K_2CO_3	toluene	−20	72	93
2	**D2**	DABCO	THF	r.t.	93	−89
3	**D3**	DABCO	THF	r.t.	44	−45
4	**D2**	DMAP	THF	r.t.	81	−88
5	**D2**	DIPEA	THF	r.t.	45	4
6	**D2**	K_2CO_3	THF	r.t.	93	35
7	**D2**	DABCO	toluene	r.t.	52	−35
8	**D2**	DABCO	CH_2Cl_2	r.t.	61	−74
9	**D2**	DABCO	THF	0	82	−92

[a] Isolated yield.
[b] Determined by chiral HPLC.

Table 3. Enantioselective synthesis of (+)- and (−)-**3** catalyzed by NHC **D1** or **D2**.



Conditions A: Cat **D1** (10 mol%), K_2CO_3 (1.2 equiv.), toluene, -20 °C
Conditions B: Cat **D2** (10 mol%), DABCO (1.2 equiv.), THF, 0 °C

Entry	**1**		**2**		Conditions A			Conditions B		
					(−)-**3**	Yield [%][a]	*ee* [%][b]	(+)-**3**	Yield [%][a]	*ee* [%][b]
1		**1a**		**2a**	(−)-**3aa**	72	93	(+)-**3aa**	82	92
2		**1b**		**2a**	(−)-**3ba**	96	92	(+)-**3ba**	87	93
3		**1c**		**2a**	(−)-**3ca**	74	84	(+)-**3ca**	82	87
4		**1d**		**2a**	(−)-**3da**	57	78	(+)-**3da**	76	92
5		**1e**		**2a**	(−)-**3ea**	94	91	(+)-**3ea**	88	90
6		**1f**		**2a**	(−)-**3fa**	88	95	(+)-**3fa**	95	83
7		**1g**		**2a**	(−)-**3ga**	81	94	(+)-**3ga**	82	87
8		**1h**		**2a**	(−)-**3ha**	37[c]	72	(+)-**3ha**	25[c]	93
9		**1a**		**2b**	(−)-**3ab**	82	89	(+)-**3ab**	90	88
10		**1a**		**2c**	(−)-**3ac**	78	93	(+)-**3ac**	90	90
11		**1a**		**2d**	(−)-**3ad**	63	93	(+)-**3ad**	81	72
12		**1a**		**2e**	(−)-**3ae**	83	92	(+)-**3ae**	59[d]	47[d]

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] Most bromoenal **1h** was recovered.
[d] Reaction carried out at room temperature.

(**2d**) afforded (−)-**3ad** in 63% yield with 93% *ee* under conditions A, and (+)-**3ad** in 81% yield with decreased selectivity (72% *ee*) (entry 11). The reaction of benzoyl acetate (**2e**) worked well under the catalyst **D1** (conditions A) to give (−)-**3ad**, but required room temperature to give (+)-**3ae** in moderate yield with moderate enantioselectivity under catalyst **D2** (conditions B) (entry 12).

The possible catalytic cycle is depicted in Figure 1. The addition of NHC to bromoaldehyde gives Breslow intermediate **A**, which is tautomerized to bromoketone **B.** The leaving of the bromide generates key intermediate **C**,[15] which is a potential 1,3-biselectrophile. The Michael addition of 1,3-carbonyl compounds gives adduct **D**, followed by ring-closure to furnish the annulation product and regenerate the NHC.

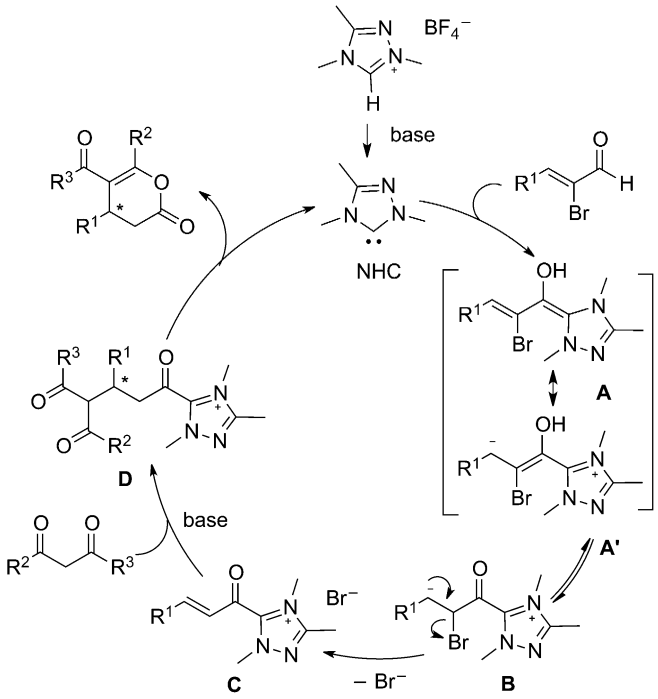


Figure 1. Possible catalytic cycle.

Based on the stereochemical outcome and the crucial effect of the hydroxy group of the catalyst, two possible favored transition states **A** and **B** are proposed for the reaction catalyzed by NHC **D1** and **D2**, respectively (Figure 2). In **TS A**, the enolate attacks from the less hindered face of the unsaturated acylazolium generated from NHC **D1**. In **TS B**, there is a H-bonding between NHC **D2** and enolate, which thus reverses the selectivity. Strong bases, such as K_2CO_3 and DIPEA, may deprotonate the free hydroxy group of the NHC and thus inhibit the possilbe H-bonding between catalyst and substrate and disfavor the reversal of the enantioselectivity (Table 2, entries 2, 4–6).[14]

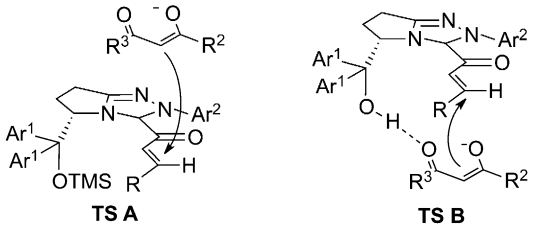


Figure 2. Possible transition states.

In conclusion, a highly enantioselective [3+3] annulation reaction of bromoenals and 1,3-dicarbonyl compounds has been reported. The α,β-unsaturated acylazolium salt is believed to be the key intermediate generated from the addition of an N-heterocyclic carbene to bromoenals. In addition, both enantiomers of the resultant dihydropyranone could be easily obtained by choosing NHCs with same stereocenter but different substituents under optimized reaction condition.

Experimental Section

Typical Procedure

An oven-dried 50-mL Schlenk tube equipped with a stir bar was charged with triazolium salt [conditions A: **D1** (7.6 mg, 0.0284 mmol); condition B: **D2** (18.6 mg, 0.0284 mmol)] and 2-bromocinnamaldehyde (60 mg, 0.284 mmol). The tube was closed with a septum, evacuated, and back-filled with nitrogen. To this mixture was added solvent [conditions A: toluene (0.56 mL); conditions B: THF (2.8 mL)] and acetoacetone (56.9 mg, 0.569 mmol), then the mixture was cooled to the given temperature (conditions A: −20 °C; conditions B: 0 °C). The base [conditions A: K_2CO_3 (47.1 mg, 0.341 mmol); conditions B: DABCO (41.6 mg, 0.341 mmol)] was added to the tube. The mixture was further stirred overnight, then diluted with ethyl acetate and passed through a short silica pad. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether) to give the desired product (−)-**3** (conditions A) or (+)-**3** (conditions B).

Acknowledgements

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