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N-Heterocyclic Carbene Catalyzed Reactions of α-Bromo-α,β-unsaturated Aldehydes/α,β-Dibromoaldehydes with 1,3-Dinucleophilic Reagents

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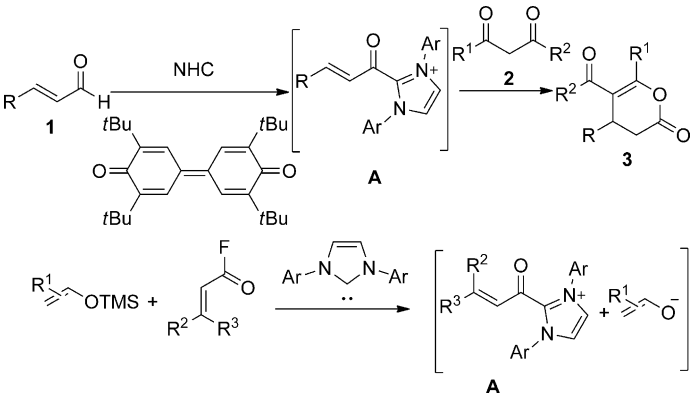
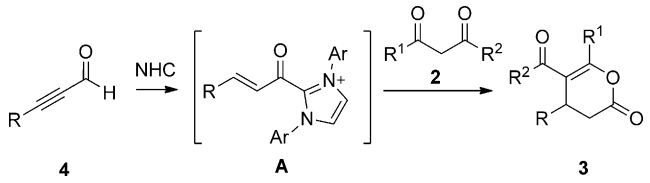
Over the past few years, N-heterocyclic carbene (NHC)-catalyzed umpolung reactions have drawn considerable attention from organic chemists due to their wide variety of applications in organic synthesis.[1] The classical umpolung reactions of aldehydes catalyzed by NHCs are the benzoin[1a,c,2] and Stetter reactions.[1a,c,3] Recent reports have revealed that NHCs could catalyze various redox-type transformations of functionalized aldehydes bearing reducible functionalities.[1a,c,4] The Michael reaction is a prominent way to construct C–C bonds.[5] Acylazolium ions **A**,[6] for use as Michael acceptors to conduct 1,4-addition reactions (or 1,2-addition reactions followed by Claisen rearrangements), can be obtained through oxidation or from α,β-unsaturated acid fluorides (Scheme 1).[6a,7] The NHC-catalyzed reactions of alkynyl aldehydes through intermediates of type **A** have also been documented (Scheme 2).[8] Since redox reactions catalyzed by NHCs provide an unconventional route to designed target molecules, more and more effort has recently been devoted to this area. Asymmetric NHCs have also been successfully applied to the redox reaction of 2-enal through acylazolium ion **A** as the Michael acceptor to conduct 1,4-addition reactions.[9,10] Inspired by this, we envisioned that Breslow intermediates **B**, generated by the reaction of 2-bromo-2-enal and an NHC, would readily give intermediates **A** through $a^3 \rightarrow d^3$ umpolung and debromination. This compound should then react with dinucleophiles without the need for external oxidants (Scheme 3). Herein, we report our preliminary results on the NHC-catalyzed reaction of 2-bromo-2-enal with dinucleophiles, such as 1,3-dicarbonyl compounds (*β*-keto enols), *β*-enamino ketones, and *β*-enamino esters (Scheme 4).

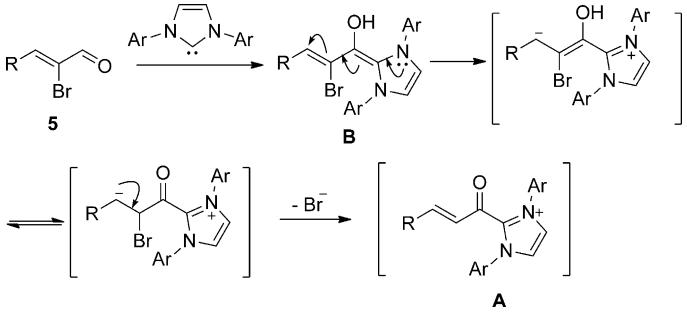
Firstly, *α*-bromocinnamic aldehyde (**5a**) and acetylacetone (**2a**) were used as model substrates to investigate the carbene catalyst precursors **8A**–**8E** (Table 1). Of these precatalysts, **8A**, **8D**, and **8E** were the less reactive compounds for



Scheme 1. The generation of acylazolium ions by oxidation or from α,β-unsaturated acid fluorides (TMS = trimethylsilyl).



Scheme 2. The generation of acylazolium ions from alkynyl aldehydes.



Scheme 3. An envisioned pathway for generating acylazolium ions from 2-bromo-2-enal.

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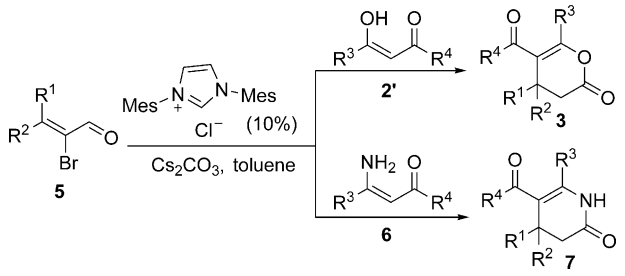
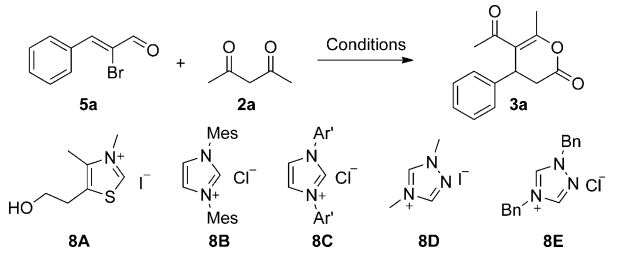


Scheme 4. The reactions presented in this work.

Table 1. Optimization of the reaction conditions.[a]



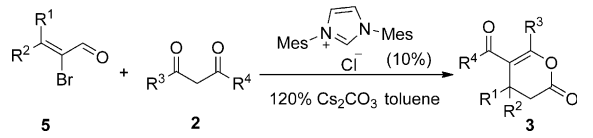
Entry	Precatalyst ([mol%])	Solvent	Base ([mol%])	T [°C]	t [h]	Yield [%][b]
1	**8A** (20)	THF	*t*BuOK (150)	25	10	n.r.
2	**8B** (20)	THF	*t*BuOK (150)	25	3	72
3	**8C** (20)	THF	*t*BuOK (150)	25	3	68
4	**8D** (20)	THF	*t*BuOK (150)	25	10	n.r.
5	**8E** (20)	THF	*t*BuOK (150)	25	10	n.r.
6	**8B** (20)	CH_2Cl_2	*t*BuOK (150)	25	3	26
7	**8B** (20)	$CHCl_3$	*t*BuOK (150)	25	3	18
8	**8B** (20)	toluene	*t*BuOK (150)	25	3	83
9	**8B** (20)	toluene	DBU (150)	25	3.5	72
10	**8B** (20)	toluene	Cs_2CO_3 (150)	25	2.5	90
11	**8B** (5)	toluene	Cs_2CO_3 (150)	25	3.5	80
12	**8B** (10)	toluene	Cs_2CO_3 (150)	25	2.5	94
13	**8B** (15)	toluene	Cs_2CO_3 (150)	25	2.5	92
14	**8B** (10)	toluene	Cs_2CO_3 (110)	25	2.5	91
15	**8B** (10)	toluene	Cs_2CO_3 (120)	25	2.5	94
16	**8B** (10)	toluene	Cs_2CO_3 (130)	25	2.5	94
17	**8B** (10)	toluene	Cs_2CO_3 (120)	15	4.5	86
18	**8B** (10)	toluene	Cs_2CO_3 (120)	20	3.5	88
19	**8B** (10)	toluene	Cs_2CO_3 (120)	30	2.5	90

[a] Mes = 2,4,6-$(CH_3)_3C_6H_2$; Ar′ = 2,6-$(CH_3CHCH_3)_2C_6H_3$; Bn = benzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Isolated yield; n.r. = no reaction.

this reaction. With precatalyst **8B** (20 mol%) and *t*BuOK (150 mol%) in THF, product **3a** was formed in a slightly higher yield than with **8C**. Thus, in the presence of **8B** (20 mol%), solvent and base screening was performed and showed that toluene and Cs_2CO_3 were preferable. The subsequent optimization study showed that the reaction proceeded better at 25 °C in the presence of 10 mol% **8B** and 120 mol% Cs_2CO_3.

To expand the scope of this NHC-catalyzed addition reaction, various dinucleophiles were tested (Table 2). The results revealed that symmetrical 1,3-diketones bearing aliphatic and aromatic substituents gave the desired products **3a** and **3e** in good yields. If an asymmetrical 1,3-diketone

Table 2. Substrate scope.



Entry	R^1	R^2	R^3	R^4	Product	Yield [%][a]
1	Ph	H	Me	Me	**3a**	94
2	Ph	H	Me	OEt	**3b**	92
3	Ph	H	Me	OMe	**3c**	93
4	Ph	H	Me	Ph	**3d**	90
5	Ph	H	Ph	Ph	**3e**	93
6	Ph	H	Ph	OEt	**3f**	91
7	3-Br-4-MeOPh	H	Me	OEt	**3g**	88
8	3-Br-4-MeOPh	H	Me	OMe	**3h**	84
9	2-NO_2Ph	H	Me	Me	**3i**	88
10	4-MeOPh	H	Me	Me	**3j**	90
11	Me	H	Me	Me	**3k**	83
12	Me	Me	Me	Me	**3l**	76

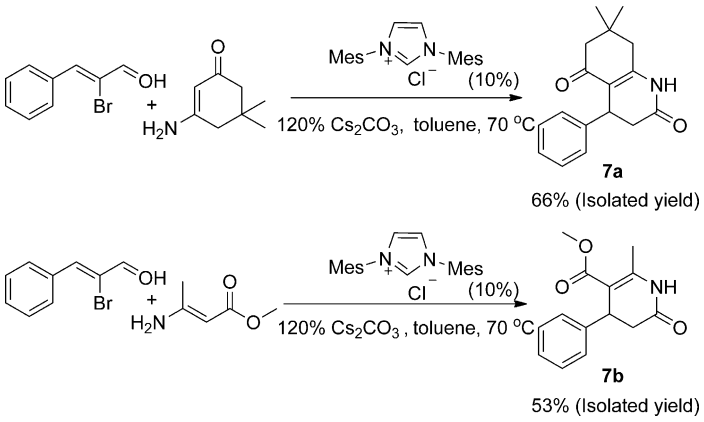
[a] Isolated yield.

(**2d**) was employed, product **3d** was obtained regiospecifically. The reaction also worked well for 1,3-keto esters, such as methyl 3-oxobutanoate (**2c**).

Furthermore, the results also indicated that both electron-donating (such as the methoxyl group, Table 2, entry 10) and electron-withdrawing groups (such as the nitro group, Table 2, entry 9) on compounds **5** were well tolerated in this protocol. More importantly, an α-bromo-β-disubstituted 2-enal could also participate in the reaction and gave the desired product **3l** efficiently, which highlights the fact that our strategy can be used to construct quaternary carbon centers (Table 2, entry 12).

To further explore the versatility of this protocol, other dinucleophiles, such as a β-enamino ketone and a β-enamino ester were used instead of the 1,3-dicarbonyl compounds. These reactions provided the desired dihydropyridine derivatives smoothly at 70 °C (Scheme 5).

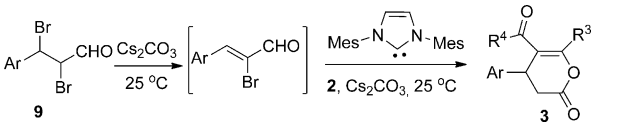
Inspired by reports concerning the reaction of α-chloroaldehydes and α-dichloroaldehydes catalyzed by NHCs, we utilized α,β-dibromoaldehydes in place of the 2-bromo-2-



Scheme 5. The use of β-enamino ketones and β-enamino esters as the dinucleophiles.

enal in this reaction.[11] The results show that 2-bromo-2-enals generated in situ by the reaction of α,β-dibromoaldehydes and Cs_2CO_3 efficiently give the final products **3** (Table 3, for details, see the Supporting Information).

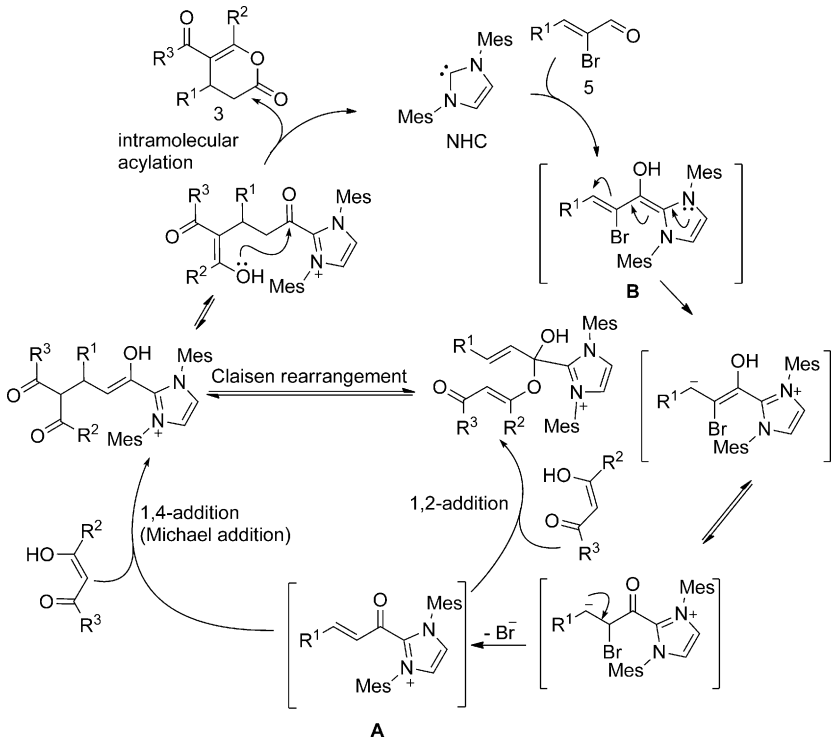
Table 3. The N-heterocyclic carbene catalyzed reaction of α,β-dibromoaldehyde with 1,3-dinucleophiles.



Entry	Ar	R^3	R^4	Product	Yield [%][a]
1	Ph	Me	Me	**3a**	92
2	Ph	Me	OEt	**3b**	72
3	Ph	Me	OMe	**3c**	81
4	Ph	Me	Ph	**3d**	87
5	Ph	Ph	Ph	**3e**	80
6	Ph	Ph	OEt	**3f**	79
7	3-Br-4-MeOPh	Me	OEt	**3g**	74
8	3-Br-4-MeOPh	Me	OMe	**3h**	78
9	2-NO_2Ph	Me	Me	**3i**	83

[a] Isolated yield.

The postulated catalytic cycle for this annulation reaction is shown in Scheme 6. Breslow intermediate **B**, generated by the reaction of α-bromocinnamic aldehyde with the NHC, is transformed into acylazolium ion **A** through $a^3 \rightarrow d^3$ umpolung and debromination. This is followed by reaction of the dinucleophile, such as a 1,3-dicarbonyl compound, with **A** through 1,4-addition and intramolecular acylation to deliver the final dihydropyranone product and regenerate the NHC catalyst.[6a,7a] However, the 1,2-addition of **A** and the dinucleophile, followed by a Claisen rearrangement and intramolecular acylation, could also liberate the NHC catalyst and give the ultimate product.[7b,8b] A detailed mechanistic study is currently underway in our laboratory.



Scheme 6. A proposed mechanism for these reactions.

In summary, we have discovered an NHC-catalyzed reaction of 2-bromo-2-enal/α,β-dibromoaldehyde with 1,3-dinucleophilic reagents, such as 1,3-dicarbonyl compounds (*β*-keto enols), *β*-enamino ketones, and *β*-enamino esters, to form highly functionalized 3,4-dihydropyranones or 3,4-dihydropyridin-2(1*H*)-ones from simple substrates. The ready availability of the starting materials, avoidance of external oxidants and the usefulness of the products all make this strategy quite attractive. More importantly, these studies not only provide a new method of forming two kinds of highly functionalized six-membered heterocyclic compound, but also expand on the applications of NHC-catalyzed reactions.

Experimental Section

Typical procedure for the NHC-catalyzed reaction of 2-bromo-2-enal/α,β-dibromoaldehyde with 1,3-dinucleophilic reagents: Catalyst **8B** (34 mg) and Cs_2CO_3 (391 mg or 716 mg for reactions with α,β-dibromoaldehydes) were weighed into an oven-dried vial (25 mL) and toluene (5 mL) was added to the reaction mixture. The resulting mixture was stirred at room temperature for 5 min. A solution of 2-bromo-2-enal (or α,β-dibromoaldehyde; 1.0 mmol) and the 1,3-dinucleophilic reagent (1.0 mmol) in toluene (5 mL) was then added. The mixture was stirred at room temperature (or, for the *β*-enamino ketone and *β*-enamino ester reagents as the dinucleophile, at 70 °C) until completion (monitored by TLC). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, mixtures of ethyl acetate/petroleum ether, 1:5 v/v).

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