

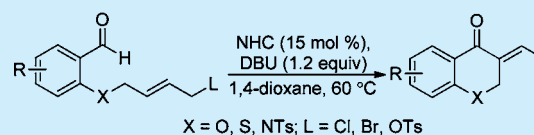
N-Heterocyclic Carbene Catalyzed Intramolecular Acylation of Allylic Electrophiles

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Supporting Information

ABSTRACT: The N-heterocyclic carbene (NHC) catalyzed addition reaction has been well documented recently; however, the NHC-catalyzed substitution reaction especially the S_N2' type reaction remains a challenge. As one of the most fundamental reaction types in organic chemistry, the S_N2' reaction catalyzed by NHC would be a powerful tool in organic synthesis. Therefore, the first NHC-catalyzed intramolecular S_N2' substitution reaction of aldehyde with allylic electrophiles has been developed. A variety of α,β -unsaturated chromanones were obtained under a domino S_N2' reaction and isomerization. Mechanistic experiments were conducted to confirm the nature of this S_N2' reaction.



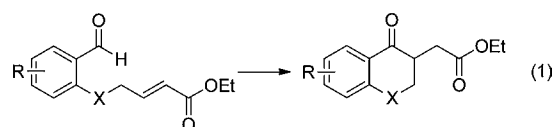
Umpolung reactivity is a valuable synthetic strategy in organic chemistry because it offers unconventional methods to traditional bond formations.¹ In recent years, important advances in NHC catalyzed addition reactions have been achieved in this field,² such as the benzoin condensation^{2,3} and the Stetter reaction.^{2,4} Various electrophiles have been explored in the NHC-catalyzed addition reactions.^{2–5} Besides the NHC-catalyzed addition of the acyl anion equivalent to the activated Michael acceptor (Scheme1, eq 1),⁴ the hydro-

substitution reaction.^{7d} It is important and increasingly challenging to develop new reaction partners, especially new reaction types to extend the application of the NHC catalysis. To the best of our knowledge, the NHC-catalyzed reaction of the acyl anion equivalent with any S_N2' electrophiles has not been reported.⁸ Here we wish to report the NHC-catalyzed intramolecular S_N2' acylation of allylic electrophiles, which leads to the formation of α,β -unsaturated chromanones after isomerization (Scheme1, eq 3).

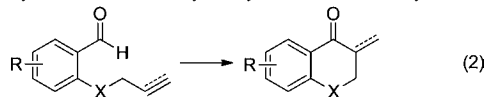
Scheme 1. NHC-Catalyzed Intramolecular Cyclizations

Previous work:

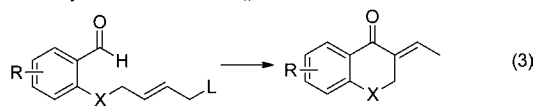
NHC-catalyzed intramolecular Stetter reaction



NHC-catalyzed intramolecular hydroacylation of alkenes/alkynes



This work:

NHC-catalyzed intramolecular S_N2' substitution reactions

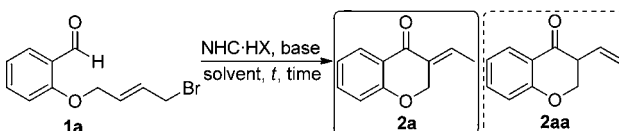
acylation of unactivated alkenes and alkynes has also been developed (Scheme1, eq 2).⁶ However, compared with the successfully developed NHC-catalyzed addition reactions, the utilization of NHCs for the nucleophilic substitution reactions is still lacking; only a few examples using activated alkyl or aryl halides have been explored.⁷ In some cases, even a stoichiometric amount of NHCs is used to realize the

Inspired by the NHC-catalyzed addition reactions, we envisage that the acyl anion equivalent could nucleophilically attack an allylic electrophile intramolecularly as an S_N2' substitution reaction, and the catalytic cycle would be closed if a base can deprotonate the addition intermediate to release an acid HL. The process is similar to the Stetter reaction, but the enolate protonation step via an intramolecular proton transfer in the Stetter reaction was replaced by an intermolecular deprotonation step in this designed reaction. Accordingly, a good leaving group is expected to be beneficial to this substitution reaction.

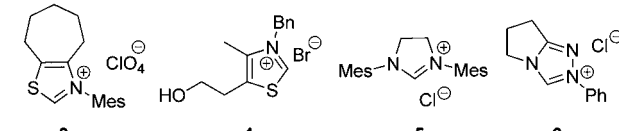
To test this hypothesis, an NHC-catalyzed S_N2' substitution cyclization of compound **1a** bearing an aldehyde group and an allylic bromide was examined. To our delight, the substitution cyclization product was obtained. Treatment of **1a** with thiazolium salt **3** in the presence of 2.0 equiv of K_2CO_3 in acetonitrile at 80 °C for 5 h resulted in the formation of α,β -unsaturated chromanone **2a** in 28% yield (Table 1, entry 1). Notably, the desired product **2aa** was not observed; the reason can be ascribed to the isomerization of the α -vinyl ketone moiety to the more stable α,β -unsaturated ketone with the *E*-configuration under the reaction conditions.⁹ Next we attempted to optimize the reaction by varying different parameters systematically. Various bases and solvents were

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Table 1. Optimization of the Reaction Conditions^a


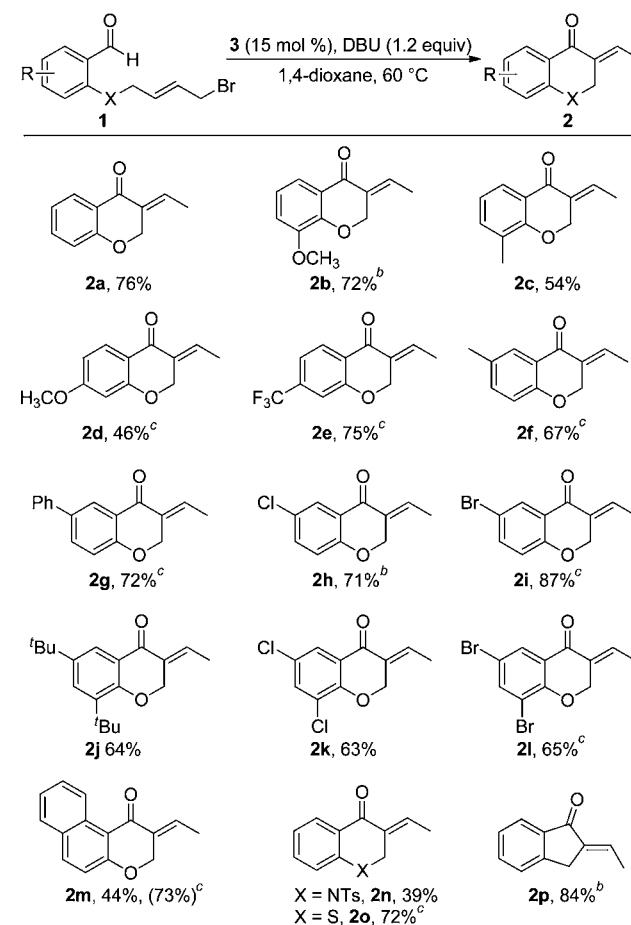
entry	NHC·HX (x mol %)	base (equiv)	solvent	t (°C)	time (h)	yield (%) ^b
1	3 (15)	K ₂ CO ₃ (2.0)	CH ₃ CN	80	5	28
2	3 (15)	K ₂ CO ₃ (2.0)	THF	70	5	5
3	3 (15)	K ₂ CO ₃ (1.2)	1,4-dioxane	60	2	16
4	3 (15)	Cs ₂ CO ₃ (1.2)	1,4-dioxane	60	2	15
5	3 (15)	DBU (1.2)	CH ₃ CN	60	2	63
6	3 (15)	DBU (1.2)	1,4-dioxane	60	1.5	76
7	3 (15)	DBU (1.2)	THF	60	2	65
8	3 (15)	DBU (1.2)	1,4-dioxane	25	3	43
9	3 (15)	DBU (0.3)	1,4-dioxane	60	2	14
10	3 (15)	DBU (2.0)	1,4-dioxane	60	2	<5
11	3 (10)	DBU (1.1)	1,4-dioxane	60	1.5	64
12	4 (15)	DBU (1.2)	1,4-dioxane	60	2	9
13	5 (15)	DBU (1.2)	1,4-dioxane	60	2	<5
14	6 (15)	DBU (1.2)	1,4-dioxane	60	2	6



^aReactions were carried out with compound **1a** (0.2 mmol), NHC·HX (x mol %), and base (equiv) in solvent (2 mL). ^bIsolated yield.

screened, and we eventually discovered that a DBU (1.2 equiv) in a 1,4-dioxane system at 60 °C for 1.5 h dramatically enhanced the yield to 76% (Table 1, entry 6). As expected, using a substoichiometric amount of DBU (0.3 equiv) gave the product in low yield (Table 1, entry 9). Surprisingly, excess DBU (2.0 equiv) resulted in only a trace amount of the product (Table 1, entry 10), which may be ascribed to the product being unstable under these basic reaction conditions.¹⁰ Attempts to decrease the catalytic loading to 10 mol % reduced the yield clearly (Table 1, entry 11 vs 6). We have also investigated other NHCs including compounds **4–6** (Table 1, entries 12–14), none of which was found to be as effective as **3**.¹¹

Having identified the optimized conditions, we examined this new method in a range of substrates with different substitution patterns of the aromatic ring (Scheme 2). Overall, a variety of α,β -unsaturated chromanones were successfully prepared, and various substituents on the aromatic ring were found to be tolerable in this process. Substrates with electron-rich substituents at the 3-position and electron-deficient substituents at the 4-position of the phenyl ring resulted in the desired chromanones with good yields (**2b**, **c**, **e**). However, the electron-rich 4-methoxyl substituted substrate **1d** returned a moderate yield (**2d**). The negative effects of the electron-rich substrate **1d** on the yield may be attributed to the low reactivity of the aldehyde with the NHC catalyst. Substrates with various substituents at the 5-position of the phenyl ring are all well tolerated (**2f–i**). The 1-naphthaldehyde substrate also returned a good yield (**2m**), and a higher yield was obtained by decreasing the reaction time (**2m**, 73%, 0.5 h vs 44%, 1.5 h). This phenomenon is similar to the case previously observed

Scheme 2. NHC-Catalyzed Acylation of Allylic Bromides: Variation of the Aromatic Ring^a

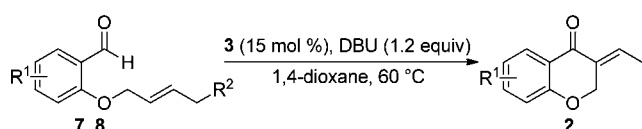
^aFor the standard reaction conditions, see Table 1, entry 6. Yields shown are for the isolated products. ^bReaction time is 1.0 h. ^cReaction time is 0.5 h.

during optimization of the reaction (Table 1, entry 10), indicating that this type product is unstable under basic reaction conditions.¹⁰ Additionally, disubstituted substrates with alkyl and halogen substituents worked well (**2j–l**). Furthermore, substrates with a nitrogen or sulfur tether also returned the desired acylation and isomerization products with moderate to good yields (**2n**, **o**). Satisfactorily, α,β -unsaturated indanone **2p** was obtained in 84% yield under the optimal conditions. Unfortunately, an aliphatic aldehyde substrate returned no desired product.¹²

Besides allylic bromide as an electrophile, other electrophiles such as allylic chloride and tosylate are all suitable for this NHC-catalyzed substitution cyclization reaction (Table 2). Under the optimal conditions, chloro-aldehyde **7** was examined; however, the desired product **2a** was obtained only in 6% yield (Table 2, entry 1). This may be ascribed to the leaving ability of chloride not being as good as that of bromide; then, the reaction temperature was raised to 80 °C, and the yield was increased to 29%. As a good leaving group, tosylate substrate **8a** here resulted in a comparable yield as bromide substrate **1a** (Table 2, entry 3). Similar results were observed when other tosylate substrates were employed in this reaction (Table 2, entries 4–6).

The reaction mechanism may follow our proposal that involves an S_N2' reaction and isomerization. On the other hand,

Table 2. NHC-Catalyzed Acylation of Allylic Electrophiles: Variation of the Leaving Groups^a

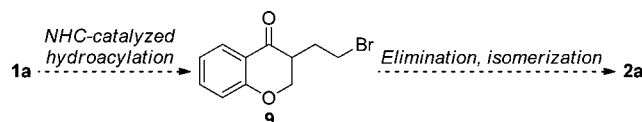


entry	substrate	R ¹	R ²	product	yield (%) ^b
1	7	H	Cl	2a	6
2	7	H	Cl	2a	29 ^c
3	8a	H	OTs	2a	70
4	8b	S-Me	OTs	2f	71
5	8c	S-Br	OTs	2i	81
6	8d	3,5-Br ₂	OTs	2l	83

^aFor the standard reaction conditions, see Table 1, entry 6. ^bYields shown are for the isolated products. ^cThe reaction temperature is 80 °C.

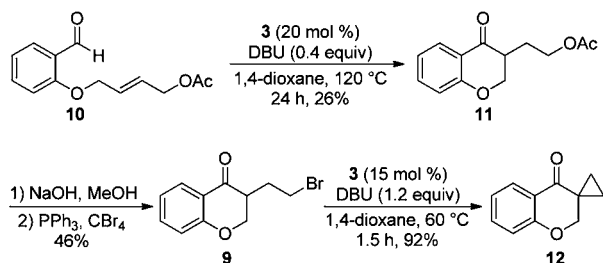
this reaction may follow the other possible pathway: first, the NHC-catalyzed hydroacylation of alkene to yield a bromo-intermediate,⁶ and, second, elimination of HBr under the basic conditions followed by isomerization to produce the desired product **2** (Scheme 3). However, the proposed bromo-intermediate **9** was not detected during the reaction even when the reaction was conducted at rt (Table 1, entry 8).¹³

Scheme 3. Possible Pathway to **2a**



To further probe the mechanism, the corresponding bromo-intermediate **9** was synthesized in three steps from compound **10** (Scheme 4). NHC-catalyzed hydroacylation of **10** according

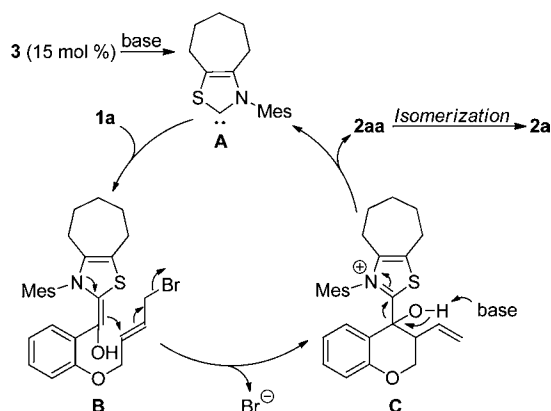
Scheme 4. Synthesis of Compound **9** and **12**



to the Glorius method gave ketone **11** quickly in 26% yield (none optimized).^{6a} Then, saponification and bromination of **11** yielded **9** (46%) in two steps. Treatment of **9** under the above-mentioned optimal conditions gave no **2a**, but compound **12** in 92% yield, as a result of an intramolecular substitution reaction. Thus, the addition–elimination–isomerization mechanism is ruled out, and the reaction mechanism should follow our proposal that involves an S_N2' substitution reaction and isomerization.

The proposed catalytic cycle is shown in Scheme 5. First, addition of carbene catalyst **A** to aldehyde **1a** forms Breslow intermediate **B**.¹⁴ Next intramolecular nucleophilic attack of the allylic bromide by the enaminol group via S_N2' type reaction gives intermediate **C**. Further deprotonation of hydroxyl group

Scheme 5. Proposed Catalytic Cycle



of **C** and liberation of NHC complete the catalytic cycle resulting in the formation of compound **2aa**. Finally, isomerization of **2aa** yields more stable α,β-unsaturated chromanone **2a**.

In summary, we have developed the first NHC-catalyzed intramolecular S_N2' substitution reaction of aldehyde with allylic electrophiles. Mechanistic studies revealed that this reaction does not follow the addition–elimination mechanism, but the S_N2' type reaction. The reaction features good yields and excellent functional-group tolerance, making it applicable to structurally complex compounds and drug discovery.¹⁵ A variety of α,β-unsaturated chromanones were obtained through a domino S_N2' reaction and isomerization. Further investigations on other NHC-catalyzed substitution reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds; and copies of ¹H, ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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- (12) For details, see the Supporting Information.
- (13) Monitored by crude H^1 NMR; column chromatography also gave no **9**.
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