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NHC-catalyzed activation of α,β -unsaturated *N*-acyltriazoles: an easy access to dihydropyranones†

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An *N*-heterocyclic carbene catalyzed activation of α,β -unsaturated *N*-acyltriazoles is described. The *in situ* generated α,β -unsaturated acylazolium intermediates allowed an enantioselective formal [3+3] cycloaddition with 1,3-dicarbonyl compounds. The resulting dihydropyranones are formed in good to excellent yields and with high enantioselectivities.

The rapid development of asymmetric organocatalysis has provided a powerful and elegant strategy for the stereoselective formation of C–C and C–heteroatom bonds.¹ In this regard, *N*-heterocyclic carbenes (NHCs) proved to be efficient organocatalysts with significant contributions to synthetic chemistry enabling unique umpolung strategies.² Beside the classic NHC-catalyzed umpolung of aldehydes,³ the conjugate umpolung of enals⁴ and the extended generation of azolium enolates⁵ have also been well-documented. All the three NHC-activated intermediates involved react in a nucleophilic way.

Recently, much attention has been paid to the NHC-catalyzed generation of 1,3-bis-electrophilic α,β -unsaturated acylazolium intermediates, which can be used as Michael acceptors and cyclization protocols. To date, the NHC-catalyzed α,β -unsaturated acylazolium formation is achieved from enals,⁶ α -bromoaldehydes,⁷ ynals,⁸ α,β -unsaturated acyl fluorides,⁹ and α,β -unsaturated esters.¹⁰ A recent report on α,β -unsaturated carboxylic acid substrates *via in situ* formed mixed anhydrides was presented by Ye's group.¹¹ However, there remains much room for the exploration of α,β -unsaturated ester surrogates in NHC catalysis (Scheme 1). Recent advances revealed the ability of *in situ* generated α,β -unsaturated acyl ammonium species prepared from α,β -unsaturated anhydrides¹² and acyl chlorides.¹³ However, the catalytic asymmetric Michael addition of nucleophiles to α,β -unsaturated amides still remains a challenge, due to their lower reactivity.¹⁴

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Scheme 1 Formation of NHC-derived α,β -unsaturated acylazolium intermediates.

The facile generation of the NHC–enolate intermediate from the *in situ* formed acyl imidazole was achieved by Scheidt *et al.* (Scheme 2, eqn (1)).¹⁵ Subsequently, they directly employed the acyl imidazole as precursor and successfully conducted a formal [4+2] annulation for the synthesis of dihydrocoumarins (Scheme 2, eqn (2)).¹⁶ We envisioned that α,β -unsaturated *N*-acyltriazole amide substrates may offer an alternate entry for the generation of α,β -unsaturated acylazoliums for the [3+3] cycloaddition with 1,3-diketones (Scheme 2, eqn (3)).

Scheme 2 NHC activation of amides for the generation of azolium enolates and α,β -unsaturated acylazolium intermediates. CDI = 1,1'-carbonyldiimidazole.

To test our hypothesis, the NHC-catalyzed [3+3] cyclization of ethyl benzoylacetate (**1a**) and the cinnamic *N*-acyltriazole **2a** was chosen as a model reaction. We started our studies using K_2CO_3 as the base in toluene at room temperature without the addition of the NHC-precatalyst. As we had hoped, no product was obtained, which meant that the base did not catalyze this process (Table 1, entry 1). We were pleased to find that the reaction worked well only in the presence of the NHC catalyst and that it afforded the desired product **3a** in 62% yield employing the achiral precatalyst **A** (Table 1, entry 2). To achieve the enantioselective transformation, we turned our attention towards chiral triazolium precatalysts and found that the (*S*)-pyroglutamic acid-derived triazolium salt **D**¹⁷ resulted in a good yield of 71% and an enantiomeric excess of 82% (Table 1, entry 5). Further base screening revealed that bases, such as CS_2CO_3 , Li_2CO_3 , K_3PO_4 , KOAc, NEt_3 and DBU, resulted in either reduced yields or diminished enantioselectivities (Table 1, entries 9–14). Solvent optimization showed that the reaction in mesitylene,

Table 1 Optimization of the reaction conditions^a

A

B

C

F

G

C R = TBS, Ar = Mes
D R = TBDPS, Ar = Mes
E R = TBDPS, Ar = C₆F₅

Entry	NHC	Base	Solvent	Yield ^b (%)	ee ^c (%)
1	—	K_2CO_3	Toluene	—	—
2	A	K_2CO_3	Toluene	62	—
3	B	K_2CO_3	Toluene	34	46
4	C	K_2CO_3	Toluene	65	76
5	D	K_2CO_3	Toluene	71	82
6	E	K_2CO_3	Toluene	Trace	—
7	F	K_2CO_3	Toluene	78	66
8	G	K_2CO_3	Toluene	68	–73
9	D	CS_2CO_3	Toluene	74	72
10	D	Li_2CO_3	Toluene	Trace	—
11	D	K_3PO_4	Toluene	71	77
12	D	KOAc	Toluene	66	82
13	D	NEt_3	Toluene	36	81
14	D	DBU	Toluene	74	75
15	D	K_2CO_3	Mesitylene	62	82
16	D	K_2CO_3	DCM	6	71
17	D	K_2CO_3	PhCl	53	75
18 ^d	D	K_2CO_3	Toluene	65	83
19 ^{d,e}	D	K_2CO_3	Toluene	72	89
20 ^{d,f}	D	K_2CO_3	Toluene	43	90

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), NHC (20 mol%), base (40 mol%), solvent (1 mL), rt, 18 h. ^b Yields of isolated **3a** after flash column chromatography. ^c The ee value was determined by HPLC on a chiral stationary phase. ^d Addition of 3 Å MS. ^e Performed at –5 °C for 48 h. ^f Performed at –10 °C for 48 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

DCM or PhCl gave inferior results (Table 1, entries 15–17). The addition of 3 Å MS slightly improved the enantioselectivity (Table 1, entry 18). Finally, we performed the reaction at –5 °C with prolonged reaction time and fortunately, the product was obtained with good yield and high enantioselectivity (Table 1, entry 19). Further lowering of the reaction temperature to –10 °C led to a dramatic loss of yield (Table 1, entry 20).

With the optimized reaction conditions in hand, we then investigated the effect of different cinnamic *N*-acyl heterocycles (Scheme 3). To some extent, the reactivity of this process depended on the leaving group ability of the *N*-acyl heterocycles. Surprisingly, all other cinnamic *N*-acyl heterocycles tested gave no products or afforded only trace amount of **3a**.

The next step was to evaluate the substrate scope of the 1,3-dicarbonyl compounds **1**. As shown in Table 2, the use of ethyl benzoylacetate **1a** provided the desired dihydropyranone in 66% yield and 86% ee (Table 2, **3a**). Electron-donating substituents such as 4-OMe on the aromatic ring gave comparable results (Table 2, **3b**), while electron-withdrawing groups such as 4-Cl and 4-NO₂ decreased the enantioselectivities, albeit with higher reactivities (Table 2, **3c,d**). Moreover, 1,3-diketones were tolerated well and afforded the desired dihydropyranones **3e–h** in good yields and ee-values. Additionally, aliphatic β-ketone esters were also suitable substrates, thus giving the adducts **3i–k** in good yields with good to high ee-values. With regard to the α,β-unsaturated *N*-acyltriazoles for the reaction with **1a** in this protocol, the electron-donating and electron-withdrawing substituents in the *para*- and *ortho*-position of the aromatic ring (R³) allowed smooth [3+3] cycloadditions and afforded the corresponding products **3l–o** in good yields and ee values.

The absolute configuration of **3m** bearing a chlorine atom was unambiguously determined to be (*S*) by X-ray crystal-structure analysis (Fig. 1).¹⁸

A plausible reaction mechanism for the NHC-catalyzed [3+3] cycloaddition is shown in Scheme 4. Initially, nucleophilic 1,2-addition/elimination of the NHC with the α,β-unsaturated *N*-acyltriazole **2** generates the α,β-unsaturated acylazolium key intermediate **I**. The base-mediated deprotonation of the

Scheme 3 Variation of the cinnamic *N*-acyl heterocycles.

Table 2 Substrate scope^a

3	R ¹	R ²	R ³	Yield ^b (%)	ee ^c (%)
a	Ph	OEt	Ph	66	86
b	4-MeOC ₆ H ₄	OEt	Ph	71	82
c	4-ClC ₆ H ₄	OEt	Ph	94	76
d	4-NO ₂ C ₆ H ₄	OEt	Ph	96	62
e	Ph	CO ₂ Et	Ph	77	79
f	Ph	Me	Ph	75	81
g	Ph	Ph	Ph	65	82
h	Me	Me	Ph	68	80
i	Me	OEt	Ph	81	85
j	Me	OBn	Ph	62	83
k	Et	OMe	Ph	88	83
l	Ph	OEt	4-MeC ₆ H ₄	65	77
m	Ph	OEt	4-ClC ₆ H ₄	67	79
n	Ph	OEt	4-BrC ₆ H ₄	78	76
o	Ph	OEt	2-BrC ₆ H ₄	74	79

^a Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **D** (0.1 mmol), K₂CO₃ (0.2 mmol), toluene (5 mL), 3 Å MS, -5 °C, 48 h. ^b Yield of isolated **3** after flash column chromatography. ^c The ee value was determined by HPLC on a chiral stationary phase.

Fig. 1 Absolute configuration [X-ray, $\chi_{\text{abs}} = 0.067$ (10)] of **3m**.

Scheme 4 Proposed catalytic cycle.

1,3-dicarbonyl compound forms enolate **1'**, which undergoes a Michael addition with intermediate **I**. Proton transfer of **II** generates the adduct **III**, which in turn undergoes an intramolecular lactonization to furnish the target cycloadduct **3** and to release the NHC catalyst.

In conclusion, we have developed an enantioselective NHC-organocatalytic net [3+3] cycloaddition of 1,3-dicarbonyl compounds with α,β -unsaturated *N*-acyltriazoles generating the desired dihydropyranones in good to excellent yields and high enantioselectivities. This protocol provides a novel NHC activation mode for the generation of α,β -unsaturated acylazolium intermediates. Further applications of α,β -unsaturated *N*-acyltriazoles are ongoing in our laboratory.

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