

Cite this: *Chem. Commun.*, 2011, **47**, 8670–8672

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COMMUNICATION

Chiral *N*-heterocyclic carbene catalyzed annulation of α,β -unsaturated aldehydes with 1,3-dicarbonyls†Zhi-Qiang Zhu,^a Xing-Liang Zheng,^b Ning-Fei Jiang,^b Xiaolong Wan^a and Ji-Chang Xiao*^a

Received 11th May 2011, Accepted 3rd June 2011

DOI: 10.1039/c1cc12778k

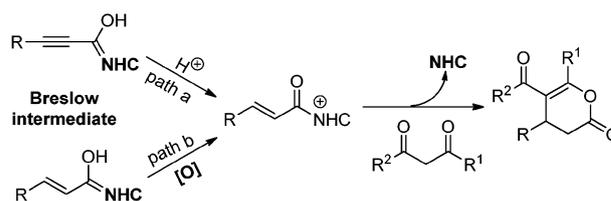
Chiral *N*-heterocyclic carbene catalyzed annulations of ynals and enals with 1,3-dicarbonyls have been described. The two reactions provided direct and efficient methods for enantioselective synthesis of functionalized dihydropyranones. Comparatively, the reactions starting from ynals were atom-economical; furthermore the reactions of enals demonstrated broader substrate compatibility.

The past decade has witnessed a growing interest in the area of *N*-heterocyclic carbenes (NHCs) owing to their versatility in organocatalytic transformations. A great variety of NHC-catalyzed reactions have been disclosed.¹ Those reactions involving aldehydes are generally thought to proceed *via* the nucleophilic Breslow intermediate.² The Breslow intermediate generated from α,β -unsaturated ynals undergoes protonation (Scheme 1, path a) to yield electrophilic α,β -unsaturated acyl azolium,^{3–5} which could be also produced by the oxidation (path b) of the Breslow intermediate derived from α,β -unsaturated enals.⁶ Subsequent annulation of α,β -unsaturated acyl azolium with 1,3-dicarbonyls led to the formation of 3,4-dihydropyranones.^{4,5,6b,7}

Dihydropyranones are very important intermediates in organic synthesis. They were widely employed in the synthesis of γ -lactones, substituted benzenoids, pyridones, *etc.*⁸ However, efficient methods for their enantioselective syntheses are still lacking.⁹ Recently, Bode *et al.* have developed a chiral NHC-catalyzed Claisen rearrangement starting from ynals and kojic acid derivatives.^{4a} Nevertheless, the desired annulated dihydropyranones were not stable enough to be isolated. Although chiral *N*-heterocyclic carbenes have recently achieved great progress, highly enantioselective annulations catalyzed by chiral NHC seems to be challenging. A suitable chiral NHC catalyst system might be the key to the successful relay of the stereochemical information of the above acyl azolium. Therefore, we explored chiral NHC-catalyzed annulation of α,β -unsaturated ynals or enals with 1,3-dicarbonyls.

Our investigation started with the reaction of 3-phenylpropionaldehyde **1a** with ethyl 3-oxobutanoate **2a** in the presence of chiral NHC precursors **A–C** (Table 1). We found that most of the selected carbene catalysts exhibited poor activity under conditions similar to our previous work (entry 1).⁵ A careful screening of chiral NHC catalysts revealed that the annulated product **3a** could be obtained in 29% yield and moderate selectivity when **C3** was used with the addition of catalytic amount of NaOAc (67% *ee*, entry 2).

We have noticed that in Bode's reports, the NHC-catalyzed reactions could occur smoothly in the absence of added base.^{4a,10} Inspired by this, we re-investigated the above annulation under conditions without added base. It was found that the reaction proceeded similarly to give 3,4-dihydropyranone **3a** in nearly the same yield but significantly increased enantioselectivity (31% yield and 87% *ee*, entry 3). However, cinnamic acid was isolated in 30% yield as a byproduct. The formation of cinnamic acid could be reasonably attributed to the hydrolysis of the intermediate α,β -unsaturated acyl azolium.^{3–7} We thought that the addition of desiccant might inhibit this side reaction. To our delight, the addition of 4 Å MS improved the reaction greatly, giving **3a** in 73% yield and 95% *ee* (entry 4). Extensive studies showed that MgSO₄ and silica are not suitable desiccants for the reaction (entries 5, 6). Simply increasing the reaction time or the amount of catalyst has limited influence on the reaction performance (entries 7, 8). However, reducing the catalyst loading to 5 mol% decreased the enantiomeric excess dramatically (entry 9). It was found that the reaction proceeded equally well at room temperature to afford the desired product in almost the same yield and enantioselectivity (entries 8 and 10). Longer reaction time was necessary for completion at room temperature. Further decrease of the temperature to 0 °C resulted in no reaction (entry 11). Increasing the ratio of ynal **1a** to 1,3-dicarbonyl **2a** further improved the efficiency of the annulation, giving **3a** in



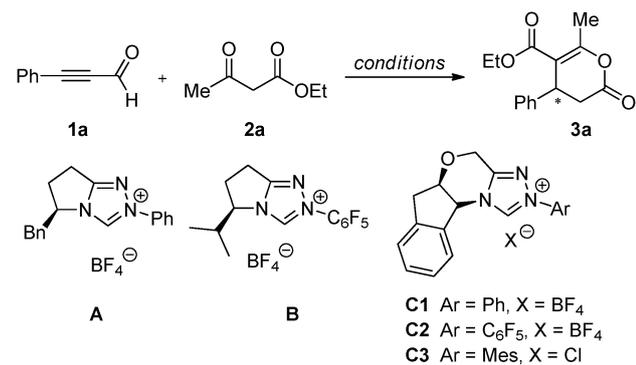
Scheme 1 NHC-catalyzed annulations to dihydropyranones.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc12778k

Table 1 Optimization of reaction conditions^a

Entry	Cat. (mol%)	Additive	T/t, °C/h	Yield ^b (%)	Ee ^c (%)
1 ^d	A-C3 (10)	<i>t</i> -BuOK	rt/2	—	—
2 ^d	C3 (10)	NaOAc	rt/24	29	67
3	C3 (10)	—	40/24	31	87
4	C3 (10)	4 Å MS	40/8	73	95
5	C3 (10)	MgSO ₄	40/24	33	88
6	C3 (10)	Silica	40/24	—	—
7	C3 (10)	4 Å MS	40/24	65	96
8	C3 (15)	4 Å MS	40/8	71	95
9	C3 (5)	4 Å MS	40/24	62	58
10	C3 (10)	4 Å MS	40/48	71	95
11	C3 (10)	4 Å MS	0/24	—	—
12 ^e	C3 (10)	4 Å MS	40/8	75	96
13 ^f	C3 (10)	4 Å MS	40/8	81	98
14 ^f	C3 (10)	—	40/8	31	85

^a Performed on a 0.2 mmol scale with 1 equiv. of **1a**, 1.2 equiv. of **2a**, 200 mg of additives and indicated amounts of catalyst in 0.1 M in toluene. ^b Isolated yield. ^c Determined by HPLC analysis on a chiral column. ^d Performed in THF with 10 mol% of additive. ^e 1.2 equiv. of **1a** and 1 equiv. of **2a** were used. ^f 1.5 equiv. of **1a** and 1 equiv. of **2a** were used.

81% yield and 98% ee (entries 12, 13). Even with a high ratio of **1a** to **2a**, the addition of 4 Å MS was still necessary for the success in achieving good yield and enantioselectivity (entry 14).

With the optimised conditions in hand, the scope of the substrate was investigated (Table 2). High enantioselectivity was obtained for other aryl-substituted ynals, regardless of the position and electronic nature of the substituent on the aryl ring (entries 2–11). However, the yield of the dihydropyranones was somewhat influenced by the electronic properties of the substituents. Introduction of electron-withdrawing groups such as Cl and Br on the aromatic ring decreased the yield greatly (entries 8, 9). With 3-(4-nitrophenyl)propionaldehyde, only a complex mixture was afforded (not shown). However, fluorine substituents seemed to have no remarkable effect on the reactivity (entries 6, 7). In the case of aliphatic substituted ynals, the enantioselectivity was slightly decreased even at room temperature (entries 12, 13; 85% ee). Other 1,3-dicarbonyl derivatives such as methyl 3-oxobutanoate and 1,3-diketones were also applicable to this annulation, giving the desired product in excellent enantioselectivities (entries 14–16, 95–96% ee). It should be mentioned that all the above dihydropyranones **3a-p** are rather stable, which is much different from those obtained from the reaction of ynals with kojic acid derivatives.^{4a}

Considering that the same acyl azolium intermediate was involved in NHC-catalyzed reaction of ynals and enals,⁴⁻⁶

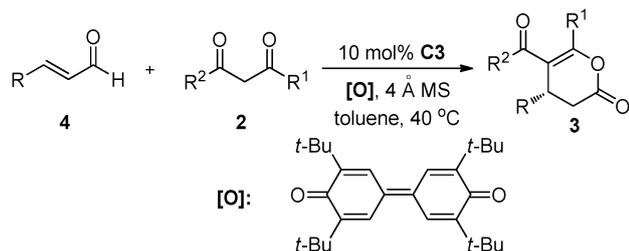
Table 2 NHC-catalyzed enantioselective annulation of ynals with 1,3-dicarbonyls^a

Entry	R	R ¹ , R ²	Yield ^b (%)	Ee ^c (%)
1	Ph	Me, OEt	81 (3a)	98 ^d
2	4-OMeC ₆ H ₄	Me, OEt	67 (3b)	92
3	4-MeC ₆ H ₄	Me, OEt	82 (3c)	97
4	3-MeC ₆ H ₄	Me, OEt	87 (3d)	95
5	2-MeC ₆ H ₄	Me, OEt	77 (3e)	96
6	4-FC ₆ H ₄	Me, OEt	66 (3f)	96
7 ^e	2-FC ₆ H ₄	Me, OEt	74 (3g)	92
8	4-ClC ₆ H ₄	Me, OEt	49 (3h)	94
9	4-BrC ₆ H ₄	Me, OEt	34 (3i)	96
10	1-Naphthyl	Me, OEt	81 (3j)	92
11	2-Thienyl	Me, OEt	71 (3k)	94
12 ^f	1-Butyl	Me, OEt	68 (3l)	85
13 ^f	1- <i>c</i> -C ₆ H ₁₁	Me, OEt	52 (3m)	85
14	Ph	Me, OMe	71 (3n)	95
15	Ph	Me, Me	46 (3o)	95
16 ^f	Ph	Me, Ph	60 (3p)	96

^a Performed on a 0.2 mmol scale with 1.5 equiv. of **1**, 1 equiv. of **2**, 10 mol% of **C3**, and 200 mg of 4 Å MS in 0.1 M in toluene at 40 °C for 8 h. ^b Isolated yield after chromatography. ^c Determined by HPLC analysis on a chiral column. ^d Absolute configuration determined by conversion to (*R*)-methyl 5-oxo-3-phenylhexanoate. ^e 1 equiv. of aldehyde and 1.5 equiv. of 3-oxobutanoate were used. ^f At room temperature for 48 h.

we extended the above investigation to α,β -unsaturated enals. After simple screening of the catalyst and optimization of reaction conditions, it was found that the above conditions were still the best (see ESI[†]). The only modification was the addition of quinone oxidant (Table 3). Under this optimal condition, the reaction could accommodate a variety of enals and 1,3-dicarbonyls. Both electron-rich and electron-poor aryl or heteroaryl-substituted enals reacted well with 1,3-dicarbonyls, giving the desired annulated dihydropyranones in moderate to good yields (37–90%) and high enantioselectivities (generally $\geq 90\%$) (entries 1–15, 17–22). The electronic properties of the substituents on the aryl ring had no obvious effect on the reactivity, which is different from the above reaction with ynals. In the case of aliphatic-substituted aldehyde, (*E*)-but-2-enal (entry 16), the enantioselectivity decreased slightly as compared with the aryl-substituted ones, which is similar to the reaction with ynals (Table 2, entries 12, 13).

In summary, we developed two chiral *N*-heterocyclic carbene catalyzed annulations of ynals and enals, respectively with 1,3-dicarbonyls, which provide direct and efficient methods for stereoselective synthesis of functionalized dihydropyranones from simple starting materials. The molecular sieves played a crucial role in the yield and selectivity. The mild conditions and high enantioselectivities make this approach quite attractive. The reactions starting from ynals are atom-economical. Furthermore the reactions of enals demonstrated broader substrate compatibility. Efforts aimed at further investigation of the chiral NHC-catalyzed reactions of α,β -unsaturated aldehydes are currently underway.

Table 3 NHC-catalyzed enantioselective annulation of enals with 1,3-dicarbonyls^a

Entry	R	R ¹ , R ²	t/h	Yield ^b (%)	Ee ^c (%)
1	Ph	Me, OEt	10	83 (3a)	98
2 ^{d,e}	4-OMeC ₆ H ₄	Me, OEt	66	73 (3b)	91
3	4-MeC ₆ H ₄	Me, OEt	24	77 (3c)	92
4	3-MeC ₆ H ₄	Me, OEt	16	87 (3d)	97
5	2-MeC ₆ H ₄	Me, OEt	18	81 (3e)	97
6 ^e	4-FC ₆ H ₄	Me, OEt	48	74 (3f)	92
7	2-FC ₆ H ₄	Me, OEt	12	85 (3g)	97
8	4-ClC ₆ H ₄	Me, OEt	12	73 (3h)	95
9	4-BrC ₆ H ₄	Me, OEt	12	77 (3i)	97
10	4-CNC ₆ H ₄	Me, OEt	12	37 (3q)	96
11	4-CF ₃ C ₆ H ₄	Me, OEt	12	42 (3r)	93
12	4-CO ₂ MeC ₆ H ₄	Me, OEt	12	67 (3s)	98
13	4-COCH ₃ C ₆ H ₄	Me, OEt	12	72 (3t)	96
14	3-NO ₂ C ₆ H ₄	Me, OEt	24	56 (3u)	97
15	2-Thienyl	Me, OEt	16	84 (3k)	97
16 ^e	Me	Me, OEt	66	81 (3v)	83
17	Ph	Me, OMe	12	81 (3n)	94
18	Ph	Et, OEt	22	72 (3w)	95
19	Ph	Ph, OEt	24	66 (3y)	92
20	Ph	Me, Me	22	58 (3o)	95
21	Ph	Me, Ph	24	60 (3p)	90
22	Ph	Ph, Ph	24	90 (3y)	90

^a Performed on a 0.3 mmol scale with 1.5 equiv. of **4**, 1 equiv. of **2**, 1 equiv. of **[O]**, 10 mol% of **C3**, and 300 mg of 4 Å MS in 0.1 M in toluene at 40 °C. ^b Isolated yield after chromatography. ^c Determined by HPLC analysis on a chiral column. ^d 1 equiv. of aldehyde and 1.5 equiv. of 3-oxobutanoate were used. ^e At room temperature.

We thank the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Natural Science Foundation (20972179, 21032006) for financial support.

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