N-Heterocyclic Carbene Catalyzed Cross Coupling of Aromatic Aldehydes with Baylis–Hillman Bromides: An Easy Access to α-Arylidene-γ-keto Esters

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Abstract: N-Heterocyclic carbene catalyzed carbonyl umpolung reaction of aldehydes with Baylis–Hillman (BH) bromides as activated halides were realized for the first time. This intermolecular cross-coupling reaction features the easily available catalyst and mild reaction conditions to provide α-arylidene- γ-keto esters in excellent yields for a wide range of substrates. Thus, the present work opens up a new aspect of the synthetic utility of BH adducts via the reactivity umpolung of aldehydes.

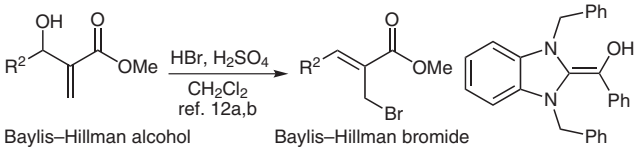
Key words: N-heterocyclic carbenes, umpolung, acyl anion, Baylis–Hillman bromides, α-arylidene- γ-keto esters

The generation of acyl anion by N-heterocyclic carbene (NHC), that is, reactivity umpolung is a crucial enterprise due to the broad utility of this concept in organic synthesis.[1,2] This approach generally includes the reaction of Breslow intermediate (Scheme 1) with various electrophilic reagents such as aromatic aldehydes, namely, benzoin reaction,[3] and Michael acceptors, namely, Stetter reaction.[4] Recently, several electrophilic reagents such as ketones,[5] enolethers,[6a] epoxides,[6b] aziridines,[7] nitroalkenes,[8] and imines[9] have been used as good acceptors for the acyl anion during the umpolung reaction.

In recent years, Morita–Baylis–Hillman chemistry has become one of the best methods to provide highly functionalized molecules and has been widely employed for the synthesis of various biologically active molecules and natural products.[10] Allylic structure present in Baylis–Hillman (BH) alcohols can be further utilized by converting the hydroxyl group into a suitable leaving group like acetate or bromide (Scheme 1) as nucleophilic acceptors in many useful synthetic transformations.[11] In many cases the bromo group present at allylic position of BH bromides[12] directs the attack of nucleophile.[11]

To date, only a few reports described the NHC-catalyzed carbon–carbon bond-formation reaction using activated halides such as *p*-nitrofluorobenzene[13] and heteroaryl chloride.[14] Very recently, Lin et al.[15] reported efficient NHC-mediated cross-coupling of aromatic aldehydes with benzyl halides. As intrigued by their findings and our continuous interest in Baylis–Hillman chemistry,[16] we envisioned the cross-coupling of Breslow intermediate with BH bromides under basic conditions and the development of an efficient method to obtain α-arylidene-γ-keto esters. BH bromides are activated allylic halides which are distinct from benzyl halides in structure and reactivity. Thus, it was unclear at the outset whether the NHC-catalyzed cross-coupling of aldehydes with BH bromides would be effective and whether it would follow the S_N2 or S_N2' pathway. Literature survey reveals that there are some reports on the nucleophilic substitution reactions (S_N2) of certain carbon,[17] oxygen,[18] nitrogen,[18b,19a] and sulfur[18b,19b] nucleophiles with BH bromides. However, nucleophilic substitution reaction of BH halides with carbon nucleophiles, such as acyl anions, has not been studied so far.

α-Arylidene-γ-keto esters, products of the present reaction, are important precursors for biologically and pharmaceutically relevant γ-butyrolactones,[20] pyrroles,[21] furans,[22] and cyclopentadienones,[23] thus, a variety of approaches have been developed for their synthesis,[24] but a general and practical methodology is still needed for chemists to construct α-arylidene-γ-keto ester skeleton from simple and readily available starting materials. To date, BH bromides have not been utilized for the synthesis of α-arylidene-γ-keto esters via cross-coupling reaction. In view of applicability of the reaction, our initial efforts were focused on the systematic examination of different readily available NHC-precursors **3a–f** to optimize the reaction conditions. We set up a series of experiments to check the performance of the reaction using benzaldehyde (**1a**) and (*Z*)–2-(bromomethyl)-3-phenylprop-2-enoate (**2a**) as model substrates. It was found that the reaction at room temperature gives satisfactory yield of product **4a** (Table 1).



Scheme 1 Baylis–Hillman bromide and Breslow intermediate

Among the tested precatalysts, **3c** was found to be most efficient for the present umpolung reaction and afforded 70% yield of the desired product **4a** (Table 1, entry 3). When the amount of the precatalyst **3c** was decreased from 25 mol% to 20 mol% relative to substrate **1a**, the

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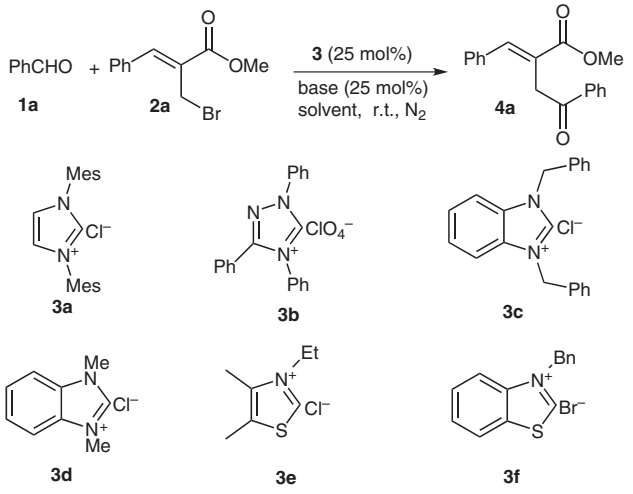
yield of the product **4a** significantly reduced (Table 1, entry 7), but the use of 30 mol% of **3c** did not affect the yield (Table 1, entry 8). Optimization of solvents for the cross-coupling of **1a** with **2a** was also undertaken, and it was found that among the tested solvents, THF was the best while others gave diminished yields (Table 1, entries 12 and 13). DBU was found to be the best base among the bases tested (Table 1, entries 3, 9–11).

Table 1 Optimization of Intermolecular Aldehyde–BH Bromide Cross-Coupling[a]



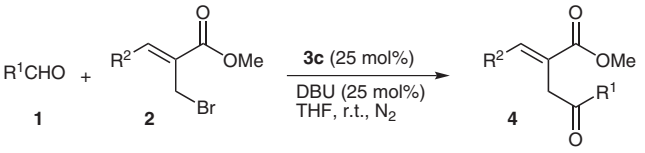
Entry	Precatalyst (mol%)	Solvent	Base	Time (h)[b]	Yield **4a** (%)[c]
1	**3a** (25)	THF	DBU	48	0
2	**3b** (25)	THF	DBU	48	0
3	**3c** (25)	THF	DBU	16	70
4	**3d** (25)	THF	DBU	48	25
5	**3e** (25)	THF	DBU	48	0
6	**3f** (25)	THF	DBU	48	0
7	**3c** (20)	THF	DBU	16	55
8	**3c** (30)	THF	DBU	16	70
9	**3c** (25)	THF	DABCO	48	10
10	**3c** (25)	THF	Et_3N	36	20
11	**3c** (25)	THF	Cs_2CO_3	30	40
12	**3c** (25)	MeCN	DBU	48	26
13	**3c** (25)	CH_2Cl_2	DBU	48	35

[a] For experimental procedure, see ref. 25.
[b] Stirring time at r.t.
[c] Yield of isolated and purified product **4a**.

With these optimized conditions (25 mol% of **3c**, 25 mol% of DBU, in THF at r.t. under positive pressure of nitrogen),[25] a variety of aromatic aldehydes and Baylis–Hillman bromides have been explored to examine the generality of the reaction. The results are listed in Table 2.

Both electron-withdrawing and electron-donating substituents on the aromatic rings of aldehydes **1** and BH bromides **2** are tolerated to afford the corresponding product **4** in good to excellent yields (65–85%). However, under the present basic conditions aliphatic aldehydes did not give appreciable amount of the desired product **4** probably due to side reaction such as aldol reaction. The requisite BH bromides **2** were prepared employing the known method.[12a,b]

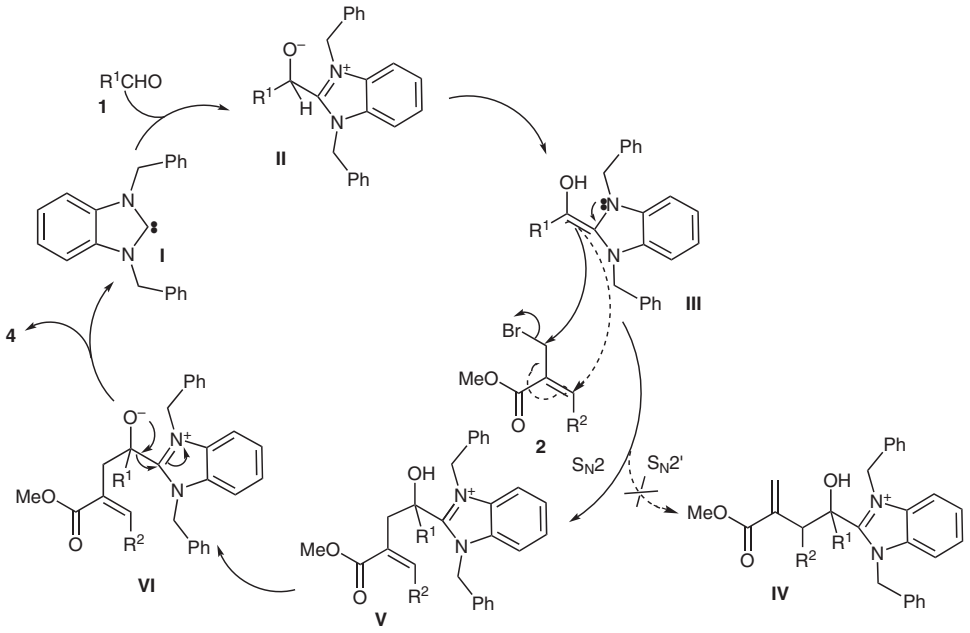
Table 2 Synthesis of α-Arylidene-γ-keto Esters **4** by Cross-Coupling of Aldehydes **1** with BH Bromides **2**[a]



Entry	R^1	R^2	Time (h)[b]	Product **4**	Yield (%)[c,d]
1	Ph	Ph	16	**4a**	70
2	4-ClC_6H_4	Ph	16	**4b**	72
3	4-MeC_6H_4	Ph	18	**4c**	65
4	4-$MeOC_6H_4$	Ph	16	**4d**	75
5	3-MeC_6H_4	Ph	18	**4e**	70
6	Ph	4-ClC_6H_4	14	**4f**	73
7	4-ClC_6H_4	4-ClC_6H_4	14	**4g**	75
8	4-MeC_6H_4	4-ClC_6H_4	18	**4h**	70
9	4-$MeOC_6H_4$	4-ClC_6H_4	14	**4i**	85
10	Ph	4-$MeOC_6H_4$	14	**4j**	74
11	4-ClC_6H_4	4-$MeOC_6H_4$	14	**4k**	75
12	4-MeC_6H_4	4-$MeOC_6H_4$	18	**4l**	77
13	2-ClC_6H_4	4-$MeOC_6H_4$	18	**4m**	72
14	4-$MeOC_6H_4$	4-$MeOC_6H_4$	12	**4n**	85

[a] Reaction conditions: **1/2**/DBU = 1:1:0.25 mmol, in THF (5 mL) at 25 °C. For experimental procedure, see ref. 25.
[b] Stirring time at r.t.
[c] Yield of isolated and purified products.
[d] All compounds gave C and H analyses within ±0.38% and satisfactory spectral (IR, ^1H NMR, ^{13}C NMR- and EI-MS) data.

On the basis of the above results, a tentative mechanism is depicted in Scheme 2. Carbene **I** is generated by deprotonation of benzimidazolium salt **3c** in the presence of DBU. Carbene **I** reacts with aldehyde **1** to give the Breslow intermediate **III** which undergoes S_N2 reaction at the bromine-bearing sp^3 carbon atom of BH bromide **2** in the S_N2 fashion. The intermediate **V** thus formed affords product **4** and regenerates carbene **I** to complete the catalytic cycle (Scheme 2). The formation of S_N2' reaction product through **IV** could not be observed at all under the present conditions. The absence of rearranged products



Scheme 2 Tentative mechanism for the formation of **4**

via **IV** is probably because the Breslow intermediate **III** does not attack the β-position due to steric effects as well as a stronger stabilization of the double bond by an extensive conjugation through the ester group and the aromatic ring. This is in conformity with the earlier observations where BH halides undergo S_N2 reaction with carbon, nitrogen, sulfur, and oxygen nucleophiles.[17–19]

In summary, we have developed for the first time an efficient NHC-catalyzed intermolecular cross-coupling of aromatic aldehydes with Baylis–Hillman bromides to provide a facile access to synthetically and pharmaceutically relevant α-arylidene-γ-keto esters.

The reaction features the easily available catalyst and mild reaction conditions. The present work opens up a new aspect of the synthetic utility of Baylis–Hillman adducts via the reactivity umpolung of aldehydes.

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(25) **General Procedure for the Synthesis of α-Arylidene-γ-keto Esters 4**

A flame-dried round-bottom flask was charged with benzimidazolium salt **3c** (0.25 mmol), aldehyde **1** (1.0 mmol), and THF (5 mL) under positive pressure of nitrogen followed by addition of DBU (0.25 mmol) with a syringe. After stirring for 10 min at r.t., BH bromide **2** (1.0 mmol) was added. The reaction mixture was stirred at r.t. for 12–18 h (Table 2). After completion of the reaction (the disappearance of **2**, monitored by TLC), the reaction mixture was concentrated under reduce pressure. The residue was purified by flash column chromatography using hexane–EtOAc as eluent to afford product **4** in 65–85% yield.

Characterization Data of Representative Compounds 4

Compound **4a**: IR (film) : ν_{max} = 1714, 1642 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OMe), 5.20 (s, 2 H, CH_2), 7.57–7.25 (m, 8 H_{arom}, Ph), 7.88–7.80 (m, 2 H_{arom}, Ph), 8.02 (s, 1 H, C = CH). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 40.6, 52.5, 126.1, 127.2, 128.1, 128.9, 129.7, 130.6, 133.4, 135.6, 137.2, 138.5, 166.5, 193.4. MS (EI): *m/z* = 280 [M^+]. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: 77.44; H, 5.96.

Compound **4c**: IR (film): ν_{max} = 1712, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, Me), 3.86 (s, 3 H, OMe), 5.14 (s, 2 H, CH_2), 7.50–7.19 (m, 5 H_{arom}, Ph), 7.90–7.77 (m, 4 H_{arom}, 4-MePh), 7.96 (s, 1 H, C = CH). ^{13}C NMR

(100 MHz, $CDCl_3$/TMS): δ = 25.4, 41.5, 53.1, 126.2, 127.1, 127.9, 128.7, 129.4, 130.2, 134.34, 135.41, 138.2, 143.3, 167.3, 193.2.MS (EI): *m/z* = 294 [M^+]. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.86; H, 6.54.
Compound **4d**: IR (film): ν_{max} = 1709, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 5.20 (s, 2 H, CH_2), 7.55–7.22 (m, 5 H_{arom}, Ph), 7.38–7.28 (m, 2 H_{arom}, 4-MeOPh), 7.86–7.82 (m, 2 H_{arom}, 4-MeOPh), 7.98 (s, 1 H, C = CH). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 40.3, 52.8, 55.1, 114.2, 126.5, 127.5, 128.1, 129.1, 129.8, 130.7, 134.9, 137.6, 165.8, 167.3, 191.2. MS (EI): *m/z* = 310 [M^+]. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.52; H, 5.85. Found: C, 73.18; H, 5.50.
Compound **4k**: IR (film): ν_{max} = 1711, 1636 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 5.15 (s, 2 H, CH_2), 7.32–7.22 (m, 4 H_{arom}, 4-ClPh), 7.37–7.30 (m, 2 H_{arom}, 4-MeOPh), 7.85–7.80 (m, 2 H_{arom}, 4-MeOPh), 7.98 (s, 1 H, C = CH). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 47.3, 52.4, 55.1, 113.8, 127.5, 128.3, 129.1, 129.9, 130.6, 133.1, 134.1, 137.9, 165.9, 167.6, 192.2. MS (EI): *m/z* = 344 [M^+]. Anal. Calcd for $C_{19}H_{17}ClO_4$: C, 66.19; H, 4.97. Found: C, 66.50; H, 4.79.