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Assembly of functionalized α-hydroxy carbonyl compounds via combination of N-heterocyclic carbene and Pd catalysts

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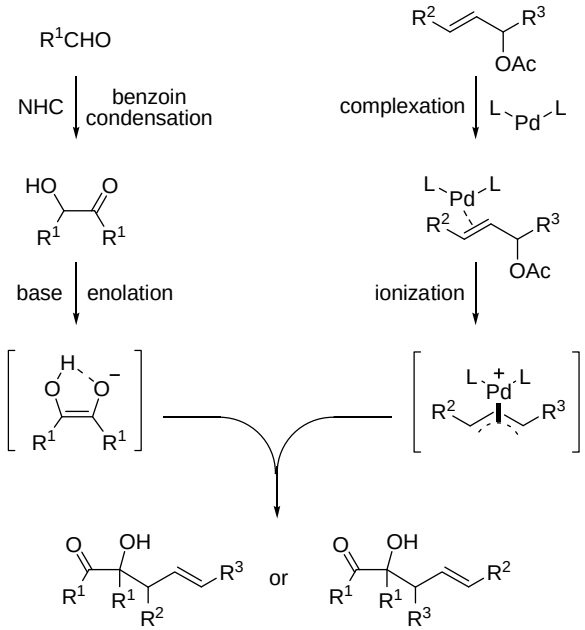
ABSTRACT

Functionalized α-hydroxy carbonyl compounds were prepared from various aldehydes and allylic acetates via a multicomponent reaction, which were catalyzed by N-heterocyclic carbene and Pd catalysts in one pot.

Carbon–carbon bond formation via new catalytic methods remains a formidable challenge. In this area, N-Heterocyclic carbenes (NHCs) have been known for a long time and successfully utilized in a variety of transformations.[1] They are effective catalysts in organocatalytic reactions[2] as well as powerful ligands in organometallic chemistry.[3] In the past decades, NHCs were attracted by their ability to catalyze the polarity reversal of carbonyl compounds, and have been employed effectively in a number of transformations, such as nucleophilic substitutions,[4] benzoin condensations,[5] Micheal–Stetter reactions,[6] homoenolate formations,[7] redox processes,[8] and Diels–Alder reactions.[9] In addition, the participation of NHCs in multicomponent reactions (MCRs) has attracted considerable attention. Several successful cases of NHCs-initiated MCRs were reported by Nair[10] and Ma,[11] respectively. In 2005, Zhai and co-workers reported a one-step assembly of functionalized γ-butyrolactones from benzaldehydes or benzoins via a NHCs-mediated tandem reaction.[12]

Allylic alkylation of carbon nucleophiles with π-allylpalladium species, known as the Tsuji–Trost reaction, is also a very fruitful and versatile method of carbon–carbon bond formation.[13] In 2006, Hamada and co-workers reported an efficient synthesis of 3-substituted 2,3-dihydroquinolin-4-ones using a one-pot sequential multi-catalytic process. In this transformation, Pd was employed to catalyze allylic amination, and thiazolium salt was employed to catalyze Stetter reaction.[14] Thereby, the development of diversity of allylic alkylation reaction will be of great significance.



Scheme 1. Assembly of α-carbonyl homoallylic alcohol from aldehydes and allylic acetates.

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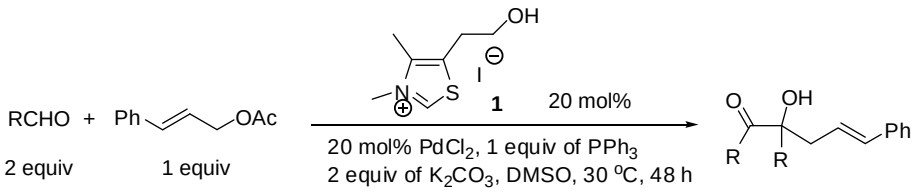
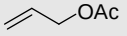
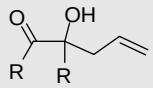
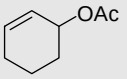
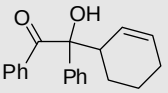
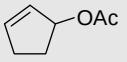
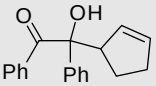
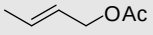
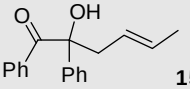
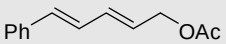
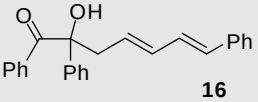
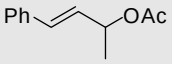
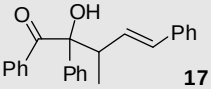
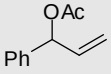
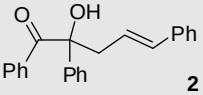
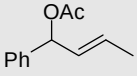
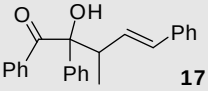
Table 1
Examination of scope of aldehydes in MCRs



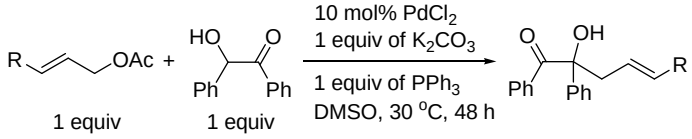
Entry[a]	R	Product	Yield[b] (%)
1	Ph	**2**	94
2	2-Cl–Ph	**3**	68
3	2-Br–Ph	**4**	53
4	4-Cl–Ph	**5**	86
5	4-Br–Ph	**6**	91
6	4-Me–Ph	**7**	53
7	2-fury l	**8**	87
8	4-MeO–Ph	—	—
9	4-NO_2–Ph	—	—

[a] All reactions were performed on a 1 mmol scale at 0.2 M.
[b] Isolated yields.

Table 2
Synthesis of α-carbonyl homoallylic alcohols via various allylic acetates

Entry[a]	RCHO	Allylic acetate	Product	Yield[b] (%)
1	PhCHO		 R = Ph **9**; 4-Cl-Ph **10**; 4-Br-Ph **11**; 2-fury **12**	85
2	4-Cl–PhCHO			69
3	4-Br–PhCHO			78
4	2-Furyl–CHO			82
5	PhCHO		 **13**	57
6	PhCHO		 **14**	73
7	PhCHO		 **15**	77
8	PhCHO		 **16**	43
9	PhCHO		 **17**	59
10	PhCHO		 **2**	86
11	PhCHO		 **17**	72

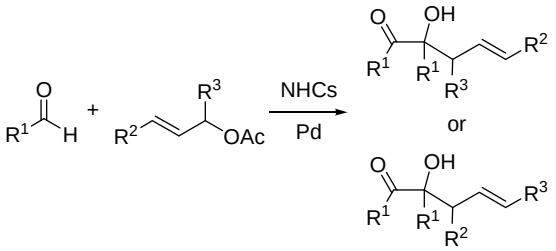
[a] All reactions were performed on a 1 mmol scale at 0. 2 M.
[b] Isolated yields. The diastereoselectivity of products 13, 14, and 17 was unable to be determined.



Entry	R	Product	Yield (%)
1	Ph	**2**	96
2	H	**9**	90

Scheme 2. Direct allylation of benzoin product.

Highly functionalized α-hydroxy carbonyl compounds are useful intermediates in synthesis.[15] Inspired by the attractive characteristics of NHCs and π-allylpalladium species, we decided to synthesize highly functionalized α-hydroxy carbonyl compounds utilizing NHCs and Pd catalysts in a one pot. Herein, we reported assembly of α-carbonyl homoallylic alcohols from aromatic aldehydes and allylic acetates via combination of NHCs and Pd catalysts in one pot; in this process, NHCs performed as organocatalyst rather than as ligand (Eq. 1).



(1)

As depicted in Scheme 1, when NHCs and Pd catalysts were coexisted in one pot, the product of the benzoin condensation was formed firstly, which was catalyzed by NHCs generated in situ from thiazolium salts in the presence of a weak base. Under the suitable basic conditions, the benzoin product was enolated, and then allylated by π-allylpalladium species. Finally, α-carbonyl homoallylic alcohol was effectively synthesized. In this two-component catalyst system, the NHCs have no interference with Pd catalyst, and the necessity of basic conditions was compatible between benzoin condensation and Tsuji–Trost reaction. It is worthy of mention that further functionalization of benzoin products was rarely reported, especially direct allylation, and we were glad to exhibit our work in this context.

Thiazolium salts **1** as classical NHCs organocatalyst were utilized. The multicomponent reaction of cinnamyl acetate with various aldehydes was examined.[16] As revealed in Table 1, a variety of substituted aldehydes underwent this reaction. Benzaldehyde, 4-Cl-,and 4-Br-substituted benzaldehyde gave desired α-carbonyl homoallylic alcohols in excellent yields (entries 1, 4, and 5). Benzaldehydes with substituents of 2-Cl, 2-Br, and 4-Me afforded the desired products in moderate yields (entries 2, 3, and 6). While benzaldehydes with either strong electron-withdrawing or electron-donating groups, such as 4-MeO and 4-NO_2, were subjected to this reaction, the desired products were not obtained (entries 8 and 9). The satisfactory result was also obtained with furfural and cinnamyl acetates (entry 7).

The influence of various allylic acetates on this reaction has been examined, and the representative results are summarized in Table 2. When aliphatic allylic acetates participated in this reaction, the desired products were obtained in moderate to good yields (entries 1–7). The conjugated homoallylic alcohol **16** was obtained in 43% yield when conjugated cinnamyl acetate was subjected to this reaction (entry 8). Benzaldehyde with α-substituted cinnamyl acetate provided the corresponding product **17** in moderate yield (entry 9). When 1-phenylallyl acetate was employed, the linear product **2** was obtained in satisfactory yield (entry 10), and none of the branched products was detected. Similarly, 1-phenylbut-2-enyl acetate underwent this reaction and gave product **17** in good yield (entry 11).

To confirm the more precise course of this one-pot reaction, benzoin product and allylic acetate were utilized directly under similar reaction conditions, but in the absence of thiazolium salt **1** (Scheme 2). As we expected, the desired α-carbonyl homoallylic alcohols **2** and **9** were obtained in excellent yields, which further proved that the above transformations from aldehydes and allylic acetates to the products were in the sequence of initial benzoin condensation followed by the Tsuji–Trost reaction.

In summary, we have developed a simple method of an assembly of functionalized α-hydroxy carbonyl compounds from various aldehydes and allylic acetates. The multicomponent reaction was mediated by an unprecedented combination of NHCs and palladium catalysts, which furnish α-carbonyl homoallylic alcohols in moderate to excellent yields. Further investigations into the development of various multicomponent reactions catalyzed by NHCs and transition-metal, as well as catalytic asymmetric allylic alkylation reactions by employing chiral NHCs and/or chiral ligands, are currently underway in our laboratory.

Acknowledgments

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16. *General procedure for synthesis of α-carbonyl homoallylic alcohol*: A round-bottomed flask equipped with a magnetic stirring bar was charged with thiazolium salt **1** (0.2 mmol), $PdCl_2$ (0.2 mmol), PPh_3 (1 mmol), and K_2CO_3 (2 mmol) in 5 ml DMSO. This was followed by the addition of aldehyde (2 mmol) and allylic acetate (1 mmol), and the resulting solution was stirred for 48 h at 30 °C under argon atmosphere. After cooling to room temperature, 40 ml of ethyl acetate was added and washed with brine (3 × 5 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, elution with 30:1 petroleum ether/EtOAc) afforded the desired product α-carbonyl homoallylic alcohol. *Product* **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 6.9 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.49–7.47 (m, 3H), 7.44–7.21 (m, 8H), 6.35 (d, J = 15.9 Hz, 1H), 6.23–6.13 (m, 1H), 4.35 (s, 1H), 3.34 (dd, J = 13.8, 7.2 Hz, 1H), 3.15 (dd, J = 13.8, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 141.7, 136.8, 135.1, 134.5, 132.7, 130.1, 128.8, 128.4, 128.0, 127.4, 126.2, 125.5, 123.5, 81.7, 43.2; mp: 127–128 °C; HRMS (ESI) Calcd. for $C_{23}H_{24}NO_2$ $[M+NH_4]^+$ 346.1802, found 346.1810. *Product* **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.34–7.23 (m, 9H), 7.13 (d, J = 7.5 Hz, 1H), 6.99–6.95 (m, 1H), 6.51 (d, J = 15.6 Hz, 1H), 6.24–6.14 (m, 1H), 3.94 (s, 1H), 3.37 (dd, J = 14.5, 6.9 Hz, 1H), 3.21 (dd, J = 14.5, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 138.2, 136.8, 135.3, 135.1, 133.0, 132.4, 131.5, 131.0, 129.5, 129.2, 128.6, 128.5, 127.5, 127.0, 126.3, 125.6, 123.3, 81.6, 40.6; mp: 112–115 °C.