Synthetic Methods

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Direct Catalytic Intermolecular α-Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis**

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The α-alkylation of carbonyl compounds is a fundamental carbon–carbon bond-forming reaction in organic synthesis.[1] The conventional α-alkylation of carbonyl compounds is performed by utilizing stoichiometric amounts of metal enolates for addition to alkyl halides. In this context, the catalytic direct α-alkylation of nonstabilized aldehydes and ketones is challenging due to competing side reactions, such as aldol condensations, Cannizzaro and Tishchenko reactions, and N- or O-alkylations.[2,3] Therefore, metal-catalyzed methods that rely on the stoichiometric use of preactivated aldehydes and ketones as their metal enolates,[4] silyl enol ethers,[5] enol carbonates,[6] or enamines[7] have been developed. There are a few methods for the catalytic intermolecular α-alkylation of nonactivated aldehydes and ketones. For example, Tamaru and co-workers reported that the α-allylic alkylation of aldehydes is possible in the presence of a catalytic amount of palladium and a slight excess of Et_3B.[8] Most recently, transition-metal catalysis was employed in the α-alkylation of ketone enolates with alcohols.[9]

Organocatalysis is a fast forward-moving research field.[10] In this area, phase-transfer catalysis is used in the α-alkylations of glycine derivatives.[11] In addition, palladium catalysis has been combined with chiral phase-transfer catalysis for the α-allylation of glycine imino esters.[11f–g] Moreover, Koga and co-workers have developed oligoamine-mediated α-benzylations of preformed cyclohexanone lithium enolates.[12] Most recently, List and Vignola reported an elegant amino acid catalyzed intramolecular aldehyde α-alkylation reaction.[13] Well-designed, two-component activation systems with Pd that combine metal catalysis and the employment of stoichiometric or catalytic amounts of an organic catalyst have also been successfully employed in allylic alkylation reactions.[14] Herein, we report the first direct intermolecular α-alkylation of aldehydes, which involves catalytic enamine intermediates. The novel catalytic reaction assembles the corresponding α-allylic alkylated

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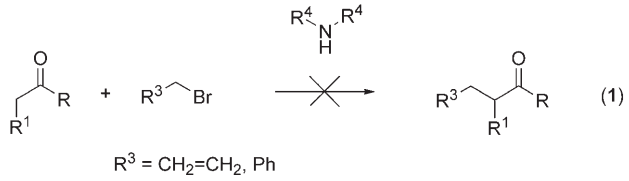
aldehydes and cyclic ketones in high yield and chemoselectivity by combining enamine- and transition-metal-catalysis in one pot.

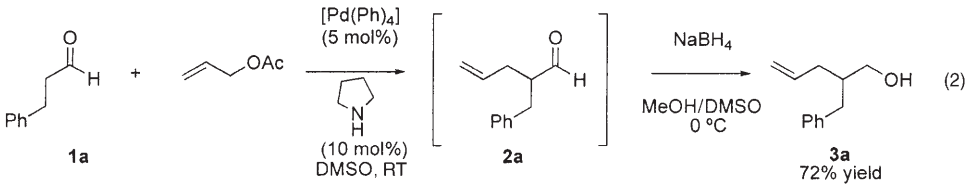
As part of our research program on amine catalysis,[15–16] we have made several attempts to alkylate catalytic enamine intermediates (generated in situ) with allyl or benzyl bromides [Eq. (1)]. However, our initial attempts into the intermolecular α-alkylation of aldehydes and cyclohexanone failed and the N-alkylation of the pyrrolidine and proline catalysts occurred.

Inspired by the work of Trost and Tsuji on allylic alkylations,[5] the use of



previously reported two-component catalyst systems with Pd,[14] and our experience from initial experiments, we decided to pursue a different highly challenging strategy for the α-alkylation of aldehydes and cyclic ketones: the one-pot combination of transition-metal and enamine catalysis (Scheme 1). Thus, the merging of two powerful catalytic cycles would enable both electrophilic and nucleophilic activation, which is not possible by one activation mechanism alone. For example, our reaction design would plausibly enable C–C bond formation by allowing catalytic enamine intermediates generated in situ to attack catalytically generated electrophilic palladium π-allyl complexes. Reductive elimination and subsequent hydrolysis of the iminium intermediate would regenerate the Pd^0 and amine catalysts, respectively, and yield the α-allylic alkylated aldehyde or ketone.

In an initial experiment, we treated 3-phenylpropionaldehyde (**1a**; 1.5 mmol) with allyl acetate[17] (0.5 mmol) in the presence of a catalytic amount of $[Pd(PPh_3)_4]$[18] (5 mol%) and pyrrolidine (10 mol%) in dimethyl sulfoxide (DMSO; 2 mL) at room temperature [Eq. (2)]. To our delight, the reaction was highly chemoselective, and we were able to



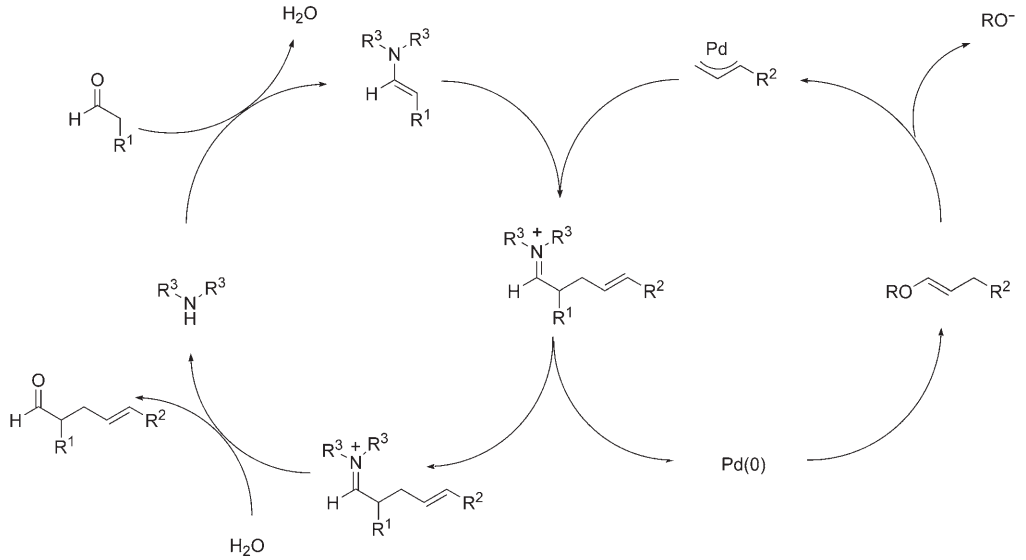
isolate the corresponding α-benzylic alcohol **3a** in 72% yield after 16 h by reduction of the α-allylic alkylated aldehyde **2a** in situ with excess $NaBH_4$.

In addition, we found that other cyclic and acyclic secondary amines catalyzed the direct allylic alkylation reactions between aldehyde **1a** and allyl acetate but with lower efficiency than pyrrolidine (Table 1).

Encouraged by these initial results, we decided to investigate the combined transition-metal- and amine-catalyzed direct allylic alkylation reactions for a set of simple aldehydes **1** (Table 2).

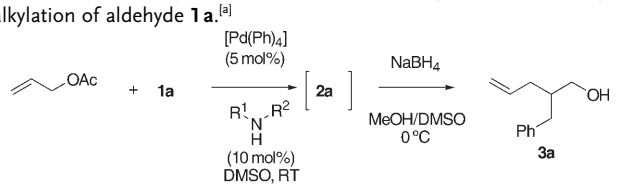
The reactions proceeded smoothly to give the corresponding α-allylic alkylated alcohols **3a–d** after reduction in situ of **2a–d**, respectively, in high yield with high chemoselectivity. In addition, the combined palladium- and amine-catalyzed reactions furnished quaternary carbon centers. For example, the α-allylic alkylated cyclohexanone carboxaldehyde **2e** was isolated in 65% yield. The direct allylic alkylation of cyclic ketones was also investigated (Table 3).

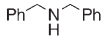
The direct catalytic allylic alkylation reactions were efficient, and the corresponding α-allylic alkylated ketones **5** were isolated in high yield: for example, **5a** was recovered in 95% yield. Thus, the one-pot combination of transition-metal



Scheme 1. Combined transition-metal and enamine catalysis.

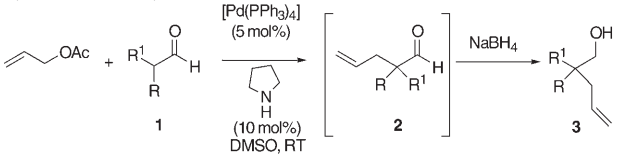
Table 1: Combined palladium- and amine-catalyzed direct α-allylic alkylation of aldehyde **1a**.[a]

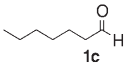
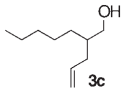
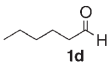
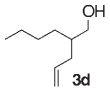


Entry	Amine catalyst	**3a**	
		t [h]	Yield [%][b]
1		16	72
2		16	45
3		16	20
4		16	37

[a] See the Experimental Section for the reaction conditions. [b] Yield of the isolated product after column chromatography on silica gel.

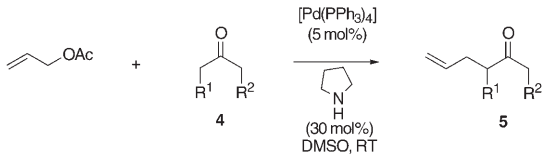
Table 2: Combined palladium- and amine-catalyzed direct α-allylic alkylation of aldehydes **1**.[a]

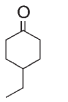
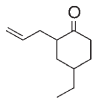
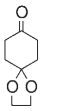
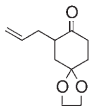
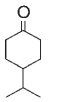
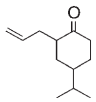
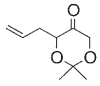


Entry	Aldehyde	Product	*t* [h]	Yield [%][b]
1	 **1a**	 **3a**	16	72
2	 **1b**	 **3b**	16	70
3	 **1c**	 **3c**	17	76
4	 **1d**	 **3d**	17	80
5	 **1e**	 **2e**	15	65[c]

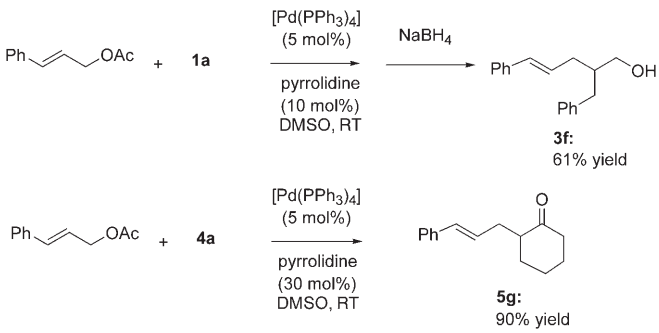
[a] See the Experimental Section for the reaction conditions. [b] Yield of the isolated product of the corresponding alcohol **3** after column chromatography on silica gel. [c] The yield of the isolated product of aldehyde **2e**.

Table 3: Combined palladium- and amine-catalyzed direct allylic α-alkylation of ketones **4**.[a]



Entry	Ketone	Product	*t* [h]	d.r.[b]	Yield [%][c]
1	 **4a**	 **5a**	16		95
2	 **4b**	 **5b**	16	1:1	90
3	 **4c**	 **5c**	16	1:1	85
4	 **4d**	 **5d**	16		82
5	 **4e**	 **5e**	15	2:1	70
6	 **4f**	 **5f**	14		65

[a] See the Experimental Section for the reaction conditions. [b] Determined by NMR spectroscopic analysis. [c] Yield of the isolated product after column chromatography on silica gel.



Scheme 2. Regioselective catalytic α-allylic alkylation of aldehydes and ketones.

and enamine catalysis is applicable to the synthesis of functional α-allylic alkylated cyclohexanones. Notably, the combined palladium- and amine-catalyzed reactions proceed with excellent regioselectivity when a substituted allylic acetate or carbonate is used as the electrophile. For example, the treatment of aldehyde **1a** or ketone **4a** with cinnamyl acetate furnished α-alkylated alcohol **3f** in 61% yield and ketone **5g** in 90% yield, respectively, as single regioisomers (Scheme 2). Thus, the combined palladium and amine-catalyzed allylic alkylation reaction exhibited excellent regioselectivity with respect to the electrophile.

We also investigated a catalytic asymmetric version of the allylic alkylation reaction. In preliminary studies, inexpensive optically active pyrrolidine derivatives or (*S*)-proline provides α-allylic alkylated alcohol **3a** and ketone **4a** with high

enantioselectivity but in moderate yields (see the Supporting Information).

In summary, we have developed a simple method for the direct catalytic allylic alkylation of aldehydes and cyclic ketones. The direct catalytic highly chemo- and regioselective intermolecular α-allylic alkylation reaction is mediated by an unprecedented combination of palladium and enamine catalysis which furnishes α-allylic alkylated aldehydes and cyclic ketones in high yield. Thus, transition-metal and amine catalysis can be efficiently merged for the development of selective reactions. We are currently focusing on the following topics: 1) expansion of the concept of one-pot combinations of transition-metal and enamine catalysis to other metals and electrophiles; 2) the development of catalytic asymmetric allylic alkylation (AAA) reactions by employing simple and inexpensive optically active amine catalysts and/or chiral metal ligands. The initial results will be reported in due course.

Experimental Section

Typical experimental procedure (Table 1, entry 1): A mixture of allyl acetate (0.5 mmol) and $[Pd(PPh_3)_4]$ (5 mol%) in DMSO (2 mL) was stirred for 5 min. Aldehyde **1a** (1.5 mmol, 3 equiv) and amine (10 mol%) were added to the reaction mixture, which was stirred at room temperature for 15–16 h. The reaction was quenched by reduction of aldehyde **2a** in situ with excess $NaBH_4$ to yield the corresponding alcohol **3a**. Aqueous work up and purification by column chromatography (toluene/EtOAc, 3:1) furnished alcohol **3a** in 72% yield as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$–7.15 (m, 5H), 5.82 (m, 1H), 5.22 (m, 2H), 3.59–3.52 (m, 2H), 2.69–2.63 (m, 2H), 2.15 (t, $J = 6.8$ Hz, 2H), 1.97–1.90 ppm (m, 1H); ^{13}C NMR: $\delta =$ 35.7, 37.5, 42.6, 64.9, 116.8, 126.2,128.6, 129.4, 137.1, 140.7 ppm.

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[17] Allyl carbonates could also be used as electrophiles.

[18] The initial palladium complexes were $[Pd(PPh_3)_4]$ generated in situ, commercially available $[Pd(PPh_3)_4]$, or $[Pd(dppa)_2]$ (dppa = 1,2-bis(diphenylphosphanyl)acetylene).

