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Direct Allylation of In Situ Generated
Aldehyde Acyl Anions by Synergistic NHC
and Palladium Catalysis

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The above article from *Angewandte Chemie International Edition*, published online on May 21, 2014 in Wiley Online Library (www.onlinelibrary.wiley.com, DOI: 10.1002/ange.201400623) and in print,^[1] has been retracted by agreement between the corresponding author, the journal Editor, Dr. Peter Göllitz, and Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. The retraction has been agreed upon because by performing additional characterization data analyses, the authors discovered that the structures of the products (table 1) were incorrectly assigned: A double-check of the data revealed that the major isolated products were allyl esters and not the expected allyl ketones. The authors acknowledge this severe mistake and its potential impact on the community.

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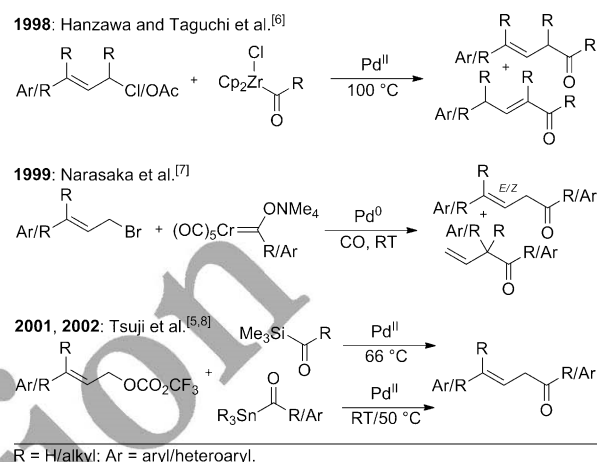
Direct Allylation of In Situ Generated Aldehyde Acyl Anions by Synergistic NHC and Palladium Catalysis**

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Abstract: The direct regioselective allylation of in situ generated aldehyde acyl anions has been achieved by synergistic NHC and Pd catalysis. It provides an efficient access to valuable β,γ -unsaturated ketones under mild reaction conditions starting from easily accessible allylic carbonates and aldehydes without any preactivation. The synergistic catalysis method demonstrated herein adds a new dimension to the area of metal-mediated C allylation.

The development of efficient organo-metal-catalyzed synthetic processes involving synergistic catalysis is much desired. However, this task is challenging because it requires the discovery of a perfect balance between the reactivity of the catalysts with the substrates, the compatibility of the catalysts, and the reaction kinetics.^[1] In continuation of our research interest in developing novel synthetic methodologies, we envisaged that such a multicatalytic system would be highly useful for the direct allylation of in situ generated aldehyde acyl anions. Seminal reports^[2] demonstrated organo-metal cooperative catalysis for allylation reactions, but the functionalities that can be directly introduced to the allylic system are still limited^[3] to phenols, amines, thiols, enolates, activated methylene groups, and benzoin.^[4] To the best of our knowledge, aldehydes have never been shown to react directly as nucleophiles with π -allylpalladium complexes under such conditions because of their electrophilic nature.^[5]

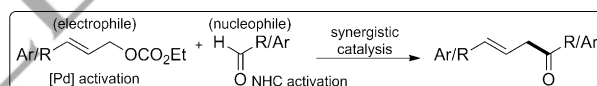
Pd-mediated allylations of acylzirconocene chloride,^[6] acylchromate complexes,^[7] acylsilanes^[5] and acylstannanes^[8] have been reported (Scheme 1), but they rely on the preactivation of the acyl species using stoichiometric amounts of the reagent in a separate step. Some of these reactions also suffer from low regioselectivity,^[7] requirement of heating (50–100 °C) of the reaction mixture,^[5,6,8] *cis/trans* isomerization^[7] of the double bond, and its prototropic rearrangement to the corresponding α,β -unsaturated ketone.^[6] The development of a straightforward, catalytic, and milder process would directly provide an efficient access to β,γ -unsaturated ketones, which are frequently observed in natural products and biologically active compounds.^[5,8,9] They have been used also for the



Scheme 1. Previously reported methods for the Pd-mediated allylation of acyl anions. Cp = cyclopentadienyl.

synthesis of fine chemicals and complex structures.^[5,8,10] In view of their importance and the contemporary interest, many methods for their synthesis have been reported recently, starting from various other substrates.^[9–11]

We envisioned (Scheme 2) that after umpolung, which is achieved in situ by a catalytic amount of an N-heterocyclic carbene (NHC), the aldehyde would react as a nucleophile



Scheme 2. Proposed synergistic NHC and Pd catalysis.

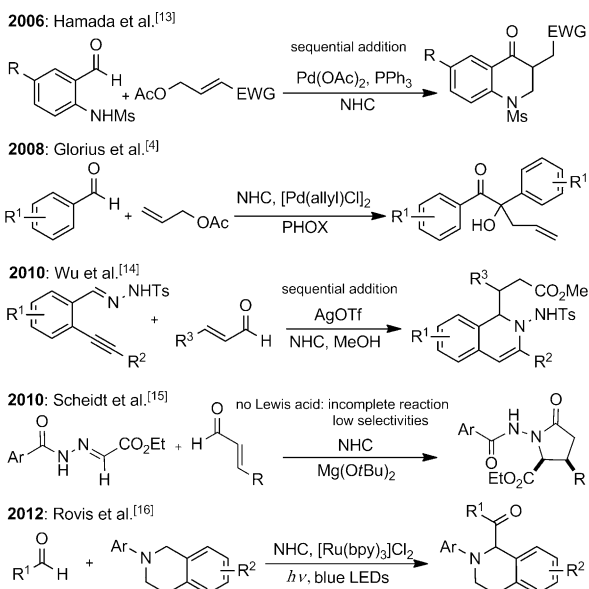
with the electrophilic π -allylpalladium complex to furnish the desired C-allylated product, the β,γ -unsaturated ketone. However, as a result of the high affinity of NHCs toward metal catalysts, their parallel functioning is challenging to put into practice,^[1,4,12] hence very few examples that demonstrate their compatibility were reported (Scheme 3).^[4,13–16] Only Scheidt and co-workers^[15] (Scheme 3) reported an example of NHC–Mg (Lewis acid) cooperative catalysis, which was further explored for other transformations.^[14] Interestingly, an example of NHC–transition metal synergistic catalysis, in which two catalytic species synergistically work together in the same elemental step to form a new C–C bond, particularly between two substrates that completely lack reactivity in the absence of either catalyst, has not been reported to date.

Based on all the above considerations, we endeavored to find suitable conditions for the proposed transformation

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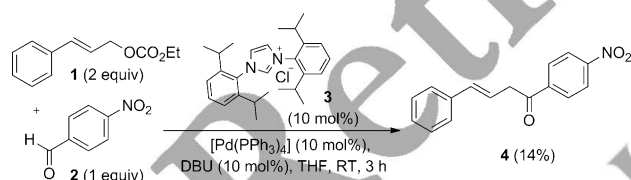
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Scheme 3. Early examples of NHC and metal catalyst compatibility. EWG = electron-withdrawing group, Ms = methanesulfonyl, PHOX = 2-[2-(diphenylphosphino)phenyl]-4-isopropyl-4,5-dihydrooxazole, Tf = trifluoromethanesulfonyl, Ts = toluene-*p*-sulfonyl, bpy = 2,2'-bipyridyl.

(Scheme 2). The first attempt to validate the proof-of-principle was the reaction of allyl carbonate **1** and aldehyde **2** using NHC precatalyst **3** and $[\text{Pd}(\text{PPh}_3)_4]$ in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in THF at room temperature. The reaction was vigorous and resulted in a complex mixture of products. The desired product **4** was obtained in 14% yield (Scheme 4).



Scheme 4. The first reaction attempted.

Encouraged by this result we began to optimize the reaction conditions. To overcome all the drawbacks associated with the development of this synergistic catalysis and to develop a general methodology, we undertook an extensive screening of suitable substrates, Pd catalysts, NHCs, organic/inorganic bases, additives, their molar ratios, the ideal temperature, the addition sequence, reaction solvents, and solvent combinations. Initially, we focused our attention on the search for an appropriate allyl source and thus screened five different allyl compounds (Figure 1). The reaction did not work at all with cinnamyl acetate (**5**). Cinnamyl bromide (**6**) and cinnamyl chloride (**7**) provided the expected product in very poor yields. With cinnamyl phenyl carbonate (**8**), a complex mixture of products along with a phenoxide-allylated side product was formed. The leaving functionality of allyl substrates seems to have an important role, indicating the need for a more reactive ethyl carbonate leaving group.

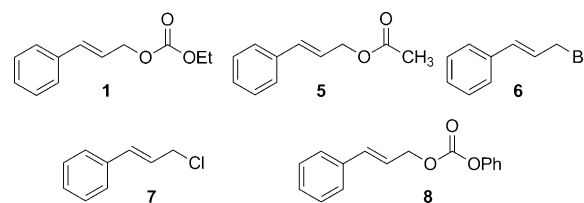


Figure 1. Screening of various allyl substrates.

Hence, our initial choice, cinnamyl ethyl carbonate (**1**), proved to be appropriate.

In our search for an appropriate base, we screened organic and inorganic bases such as DBU, DABCO, TMEDA, DMAP, DIPEA, Et_3N , pyridine, 1,1,3,3-tetramethyl guanidine, pyrrolidine, diisopropylamine, NaHMDs, NaNH_2 , NaOAc, *t*BuOK, K_3PO_4 , K_2CO_3 , Cs_2CO_3 , and Ag_2CO_3 , and their combinations at different molar ratios. Though K_2CO_3 , TMEDA, and DABCO worked well, the substrate scope was very limited. For example, K_2CO_3 provided good to moderate yields when carbonate **1** was treated with an aromatic aldehyde that bears electron-withdrawing groups, but there was no reaction with an aromatic aldehyde bearing electron-donating groups. Finally, a random selection through trial and error resulted in 1-methylpiperazine as the optimal base. 1-methylpiperazine worked well with all types of substrates substituted either on the allyl carbonate or aldehyde, plausibly because of its optimal basicity under homogenous conditions.

The effect of various NHCs and their molar ratios on the yield was also studied. Four different types of NHC precatalysts were screened (Figure 2). The Glorius NHC precatalyst **10**^[17] provided better yields with minimum side reactions under mild reaction conditions. This result could be due to the effective tolerance between Pd^0 and NHC **10**.^[4]

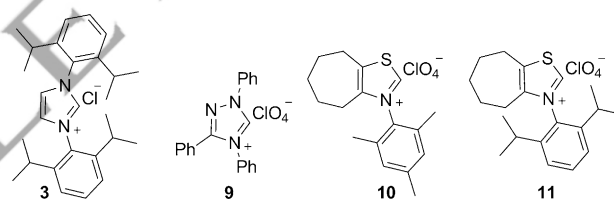


Figure 2. Assessment of various N-heterocyclic carbene precatalysts.

Pd catalysts such as $[\text{Pd}(\text{PPh}_3)_4]$, $[\text{Pd}(\text{dba})_2]$, $[\text{PdCl}_2(\text{PPh}_3)_2]$, $[\text{Pd}_2(\text{dba})_3]$, $[\text{Pd}(\text{dppf})\text{Cl}_2]\cdot\text{CH}_2\text{Cl}_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{OAc})_2\cdot t\text{BuXPhos}$, $\text{Pd}(\text{OAc})_2\cdot\text{BINAP}$, and $\text{PdCl}_2\cdot t\text{BuXPhos}$ were also screened. Out of these nine Pd catalysts evaluated, $[\text{Pd}(\text{PPh}_3)_4]$ was identified as the best for the present transformation. The molar ratio 1:3 of Pd catalyst to NHC provides better yields compared to the molar ratio 1:1. The effect of various additives, such as FeCl_3 , LiCl, AcOH, neocuproine, MeOH, phenol, and *t*BuOH was also studied. We did not observe significant improvement in the yield with any of these additives. The effect of the solvent was equally prominent as that of the base. We screened various solvents, such as MeCN, THF, 1,4-dioxane, DMF, NMP, CH_2Cl_2 , DME, toluene, *t*BuOH, and DCE, and several combinations of them (v/v).

MeCN stood out as the most suitable solvent. All the above parameters were tested at various molar ratios, different addition sequences, and temperatures ranging from 0 °C to 60 °C. Decomposition of the formed product was observed at higher temperatures.

Optimized conditions for the developed reaction included the addition of a solution of the aldehyde (1 equiv) and the base 1-methylpiperazine (20 mol %) in acetonitrile to the reaction mixture containing the allyl carbonate (2 equiv), the NHC (**10**, 15 mol %), [Pd(PPh₃)₄] (5 mol %), and MgSO₄ in acetonitrile at 0 °C over a period of 10–15 minutes. The reaction mixture was gradually allowed to warm up to room temperature and stirring was continued until completion of the reaction (by TLC). Purification by column chromatography furnished the desired β,γ-unsaturated ketone and the excess of unreacted allyl carbonate could also be recovered. It

is important to note that the careful choice of the allyl substrate, the NHC/Pd catalyst, the base, and their molar ratios and the solvent drastically changed the mode of reaction from a tandem benzoin formation/α-allylation^[4] to novel aldehyde acyl anion allylation.

We next applied the newly developed “synergistic catalysis” protocol to the synthesis of diverse β,γ-unsaturated ketones. The substrate scope of the developed method was studied on several different allyl carbonates and aldehyde substrates to establish the generality of the process (Table 1). Cinnamyl ethyl carbonate (**1**) was treated with differently substituted aromatic and aliphatic aldehydes to investigate the effect of electronic factors (Table 1, entries 1–5). Electron-donating and electron-withdrawing substituents on the aromatic aldehyde were tolerated at various positions. The process was also compatible with an additional reactive

Table 1: Substrate scope.^[a]

R = H/alkyl; Ar = aryl/heteroaryl; R' = -OCO₂Et

Entry	Carbonate	Aldehyde	Product (t, Yield ^[b])	Entry	Carbonate	Aldehyde	Product (t, Yield ^[b])
1	Ph-CH=CH-CH ₂ -R'		 (5 h, 65%)	10	Ar-CH=CH-CH ₂ -R' Ar = 3,4-(OCH ₂ O)-C ₆ H ₃		 (18 h, 57%)
2 ^[c]	Ph-CH=CH-CH ₂ -R'		 (24 h, 56%)	11	Ar-CH=CH-CH ₂ -R' Ar = 3,4-(OCH ₂ O)-C ₆ H ₃		 (12 h, 47%)
3	Ph-CH=CH-CH ₂ -R'		 (12 h, 65%)	12	Ar-CH=CH-CH ₂ -R' Ar = 3,4-(OCH ₂ O)-C ₆ H ₃		 (12 h, 72%)
4	Ph-CH=CH-CH ₂ -R'		 (18 h, 41%)	13	Ar-CH=CH-CH ₂ -R' Ar = 1-naphthyl		 (18 h, 47%)
5	Ph-CH=CH-CH ₂ -R'		 (18 h, 23%)	14	Ar-CH=CH-CH ₂ -R' Ar = 2-furyl		 (12 h, 73%)
6	Ar-CH=CH-CH ₂ -R' Ar = <i>p</i> -NO ₂ -C ₆ H ₄		 (10 h, 72%)	15	Ph-CH=CH-CH ₂ -R'		 (12 h, 50%)
7	Ar-CH=CH-CH ₂ -R' Ar = <i>p</i> -Cl-C ₆ H ₄		 (10 h, 60%)	16	Ar-CH=CH-CH ₂ -R' Ar = <i>p</i> -F-C ₆ H ₄		 (18 h, 45%)
8	Ar-CH=CH-CH ₂ -R' Ar = <i>p</i> -Me-C ₆ H ₄		 (10 h, 75%)	17			 (5 h, 95%)
9	Ar-CH=CH-CH ₂ -R' Ar = 3,4-(OCH ₂ O)-C ₆ H ₃		 (18 h, 66%)				

[a] Reaction conditions: allyl carbonate (2 equiv), aldehyde (1 equiv), NHC **10** (15 mol %), [Pd(PPh₃)₄] (5 mol %), and 1-methylpiperazine (20 mol %).

[b] Yields of isolated products. [c] The reaction was quenched before it reached room temperature to avoid side reactions.

aldehyde functionality (Table 1, entry 2). An aliphatic aldehyde also provided the expected product, but in low yield, and interestingly, the α -allylated product^[2b] was not observed (Table 1, entry 5). The effect of an electron-withdrawing substituent (Table 1, entry 6), halides (Table 1, entries 7, 16), an alkyl substituent (Table 1, entry 8), and electron-donating substituents (Table 1, entries 9–12) at various positions of the aromatic ring of the allyl carbonates, as well as bicyclic aromatic (Table 1, entry 13) and heteroaromatic (Table 1, entry 14) ethyl carbonates were studied, and all of these substrates reacted well.

A variety of aromatic aldehydes with electron-donating/withdrawing, alkyl, halide, and alkyl halide substituents (Table 1, entries 1–12, 14–17), and benzaldehyde (Table 1, entry 13) were reacted smoothly under the developed protocol. Though we did not notice any particular reactivity pattern, it appears that aromatic allyl carbonates and aldehydes with electron-withdrawing substituents are better substrates. In addition to the above-mentioned variations in carbonate, we were interested in the effect of the substituent at the alkene carbon atom of the allyl carbonate. Accordingly, we selected two allyl carbonates (Table 1, entry 15 and 16) with a methyl substituent on alkene carbon atom, and their reactivity was comparable to those of the unsubstituted ones. In all the above-mentioned cases, only aromatic allyl carbonates without any substituent at the α -carbon atom to the alkene were used, hence we next studied the reactivity of an aliphatic allyl carbonate with a substituent at the α -carbon atom to the alkene. Cyclohexenyl ethyl carbonate (Table 1, entry 17) was selected for this purpose and we were delighted to find that it reacted quite fast with *p*-nitrobenzaldehyde (**2**) to cleanly provide the expected product in excellent yield. We did not observe the formation of the regioisomer, the double bond *cis*-isomer, α,β -unsaturated ketone, or the tandem benzoin formation/ α -allylation^[4] product in any example (Table 1) under these reaction conditions. Overall, a variety of functional groups were tolerated on both the substrates to furnish the corresponding β,γ -unsaturated ketones in moderate to excellent yields (Table 1). All the entries mentioned in Table 1 were performed on a scale of 0.1–0.3 mmol of the corresponding aldehydes. The robustness of the developed protocol was also studied at a higher scale on representative examples. The reactions in entries 1, 4, 5, and 17 were repeated on a 10 mmol scale to obtain the products in 60 %, 43 %, 21 %, and 92 % yield, respectively, which are comparable with the yields obtained at the smaller scale. The time required for the reactions was reduced substantially at a higher scale, indicating further scope to reduce the amount of catalysts.

Several control experiments were performed to investigate the mechanistic aspects of the newly developed catalytic transformation. In the absence of either NHC or Pd catalyst, the reaction did not work at all. Moreover, when the NHC precatalyst, base, and Pd catalyst were stirred together in acetonitrile for 30 minutes followed by the addition of the substrates, the expected product was formed with a lower yield, probably indicating that the ligation of the in situ formed NHC with the Pd catalyst might be facile in the absence of both substrates. This outcome perhaps also

excludes the possibility of a Pd–NHC complex being an actual catalyst for this transformation, however, a thorough investigation is necessary. A plausible reaction mechanism for the synergistic catalysis protocol developed herein is depicted in Figure 3. We believe that two catalytic cycles operate

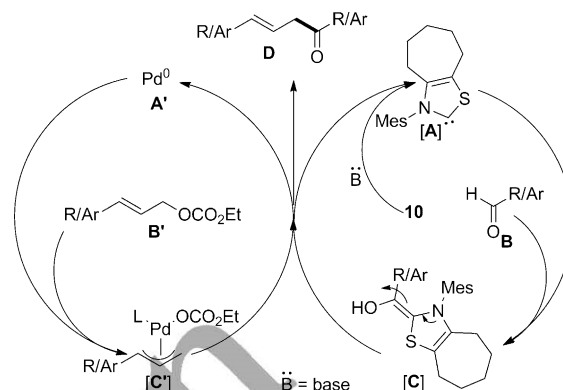


Figure 3. A plausible reaction mechanism for the developed protocol.

simultaneously, wherein one cycle involves the deprotonation of thiazolium precatalyst **10** by the base 1-methylpiperazine to generate NHC (**A**), which reacts with aldehyde **B** to form a Breslow intermediate (**C**). The other catalytic cycle comprises the reaction of Pd catalyst **A'** with allyl carbonate **B'** to form palladium allyl complex (**C'**). Both active intermediates react with each other and the catalytic cycles work synergistically to form a new C–C bond to provide product **D**. Finally, the NHC (**A**) and the Pd⁰ species (**A'**) are regenerated for further catalytic cycles.

In conclusion, we developed an efficient catalytic system for the C allylation involving NHC and Pd⁰ catalysts, which work synergistically to provide value-added β,γ -unsaturated ketones from allylic carbonates and aldehydes as readily available starting materials. A straightforward experimental procedure, mild reaction conditions, high regioselectivity, high functional-group tolerance, and moderate to excellent yields without the requirement of aldehyde preactivation are some of the important features of this organo–metal-catalyzed C(sp²)–C(sp³) bond-forming methodology. Currently, we are exploring its potential to develop an enantioselective direct allylation of aldehyde acyl anions by investigating appropriate combinations of ligands and chiral NHC or transition-metal catalysts to access enantiomerically pure products with variable regioselectivity.

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