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Palladium-Catalyzed C-Allylation of Benzoins and an NHC-Catalyzed Three Component Coupling Derived Thereof: Compatibility of NHC- and Pd-Catalysts

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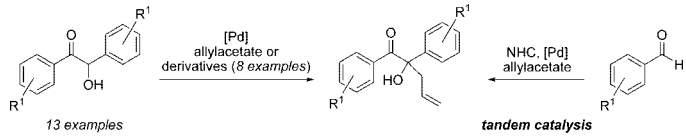
ABSTRACT



A large range of benzoins was successfully applied as C-nucleophiles in the palladium-catalyzed allylic alkylation with several allyl acetates, resulting in functionalized tertiary homoallylic alcohols. A number of unsymmetrical benzoins can be coupled with high levels of regio- and chemoselectivity. Finally, the challenging compatibility of free N-heterocyclic carbenes with a palladium catalyst has been utilized in a number of metal- and organocatalyzed three-component coupling reactions.

The benzoin condensation is one of the oldest reactions in organic chemistry, and early on,[1] it has been catalyzed by N-heterocyclic carbenes (NHCs). In the last couple of years, NHCs have become popular organocatalysts for a number of transformations.[2,3] Many attempts have been made to utilize benzoins as synthetic building blocks. Whereas O-allylation without epimerization can be realized using silver oxide as base,[4] no enantiomerically pure C-allylated product has been obtained directly from benzoin through desymmetrization of its prochiral enolate.[5] This is in stark contrast to the achievements and the versatility of the palladium-catalyzed asymmetric allylic alkylation.[6] Soft *C*-nucleophiles like malonates and ketoesters are especially suitable nucleophiles, and we reasoned that benzoins, which possess an acidic C−H bond, should exhibit similar properties.

Moreover, we envisaged that the combination of NHC-catalyzed umpolung[2,7] and palladium-catalyzed (asymmetric) allylic alkylation would allow a three component coupling and pave the way for new synthetic opportunities. In this process, two successive C−C bond formations would result in the formation of functionalized tertiary homoallylic alcohols from simple aldehydes and allylacetates. However, since NHCs also act as ligands and bind to metal complexes, which can result in the poisoning of both catalysts, the compatibility of a free NHC and a transition-metal catalyst and their parallel functioning is difficult to put into practice.

[§] These two authors have contributed equally to this work.

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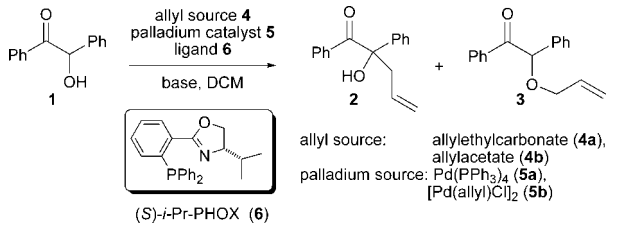
Thus, our study commenced with the palladium-catalyzed allylic alkylation of preformed benzoins.

Allylic Alkylation of Benzoins. The C-allylation of benzoins would provide an attractive alternative to the nucleophilic attack of an allylmetal species on the corresponding diones.[8] Interestingly, despite a report on the use of benzoin as an O-nucleophile in palladium-catalyzed allylic alkylation,[9] no corresponding C-allylated compounds with a free hydroxy group in α-position to a carbonyl function have been described.[10] Early on in our study on the allylation of benzoin, we realized that the nature of the base and the allyl source is critical for success (Table 1).[11] Use of allylethylcarbonate (**4a**) without base (ethoxide is generated) confirmed the reported tendency for *O*-allylation by using this electrophile (entries 1,2). The use of allylacetate (**4b**) results in the preferred formation of the C-allylated product **2**.[11] As the reaction rate was rather low with cesium carbonate (entry 4), we tested stronger bases such as hydride, and contrary to the use of NaH (entry 5), the desired isomer **2** was predominantly formed with KH (entries 6−9). At the outset of our study, benzoin was stirred with KH for 20 min to realize full deprotonation, and the resulting enolate was added to the other reactants. The reaction proceeded very quickly; however, the isolated yield of 59% (89:11 C/O ratio) was not optimal yet. Lowering the temperature (entry 7) was slightly beneficial, but the major advance was made by changing the catalyst system. Several ligands were screened and ^{i}Pr-PHOX (**6**) was found to be the optimal one, providing the product in very high selectivity of >95:5 (entry 8). Finally, addition of the base at a later stage significantly improved the yield (entry 9). The same reaction in THF and toluene[12] led to 78 and 54% isolated yield respectively, with excellent regioselectivity in both cases. Alternatively, DBU was found to be an efficient base and fair alternative to KH (Table 1, entry 10 and 11). However, the resulting reaction is slower and more limited to electron-poor benzoins (*vide infra*). Under these conditions, the formation of the *C*-allylated product through Claisen rearrangement from the *O*-allylated species can not be excluded.[13]

With these conditions in hand, we screened a variety of benzoins (Table 2). Excellent regioselectivities and good yields were obtained when electron withdrawing groups are present and with five-membered heteroaromatics. Somewhat more *O*-allylated products were observed in case of electronrich substituents and *ortho* substitution. The pyridine derivative **7m** was not found to provide any product.

Gratifyingly, more highly substituted allylacetates can also be employed under similar conditions (Table 3). Reactions are generally slower and in some cases do not occur at all at

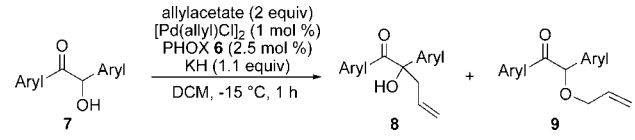
Table 1. Optimization of Reaction Conditions for the Allylation of Benzoin (**1**)[a]



entry	cat.	base	4	*t* (°C), time	GC-MS **1/2/3**	yield[b] **2/3**
1	**5a**[c]	no base	**4a**	rt, 16 h	34:0:66	n.d.
2	**5a**[c]	Cs_2CO_3	**4a**	rt, 16 h	4:5:91	n.d.
3	**5a**[c]	K_3PO_4	**4b**	rt, 40 h	33:77:0	n.d.
4	**5a**[c]	Cs_2CO_3	**4b**	rt, 40 h	20:80:0	n.d.
5	**5a**[c]	NaH	**4b**	rt, 24 h	10:31:59	n.d.
6	**5a**	KH[d]	**4b**	rt, 0.5 h	13:77:10	59% (89:11)
7	**5a**	KH[d]	**4b**	−78 to rt, 4 h	n.d.	69%[e] (83:17)
8	**5b**+**6**	KH[d]	**4b**	−78 to rt, 4 h	n.d.	81% (>95:5)
9	**5b**+**6**	KH[f]	**4b**[g]	−15, 1 h	n.d.	88% (>95:5)
10	**5b**+**6**	DBU	**4b**[g]	rt, 16 h	n.d.	70% (>95:5)
11[h]	**5b**+**6**	DBU	**4b**[g]	rt, 16 h	n.d.	89% (>95:5)

[a] Reaction conditions: benzoin (0.5 mmol), catalyst (1 mol %), ligand (2.5 mol %), base (1.1 equiv), allyl source (1.1 equiv), DCM (0.1 M). [b] Isolated yield. [c] Five mol %. [d] KH and benzoin were premixed for 20 min and added to the reaction mixture. [e] 17% of benzil was isolated. [f] KH was added last. [g] Two equiv. [h] *t*-AmylOH as solvent (0.5 M).

Table 2. Allylation of Differently Substituted Benzoins



entry	substrate	yield (%) **8**/**9**[a]	entry	substrate	yield (%) **8**/**9**[a]
1	**7**	88 (>95:5)[b]	8	**7g**	86 (94:6)
2	**7a**	93 (>95:5)	9	**7h**	81 (>95:5)
3	**7b**	77 (>95:5)	10	**7i**	43 (>95:5)[c]
4	**7c**	81 (>95:5)	11	**7j**	68 (>95:5)[d]
5	**7d**	82 (93:7)	12	**7k**	90 (>95:5)
6	**7e**	75 (89:11)	13.	**7l**	92 (>95:5)
7	**7f**	82 (>95:5)	14	**7m**	0

[a] Generally, ratios of *C*- and *O*-allylated in the isolated fraction are the same as in crude NMR, the products being inseparable. [b] Plus 4% bisallylated product. [c] Ratio of **8**/**9** before purification: 77:23 (based on NMR). [d] Plus 11% bisallylated product.

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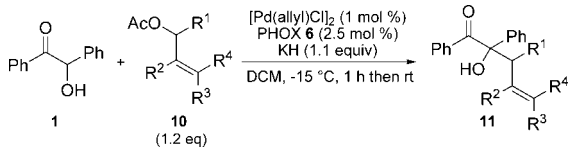
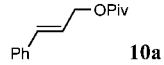
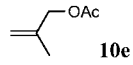
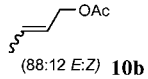
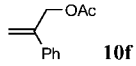
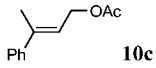
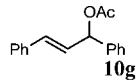
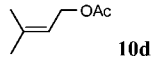
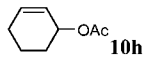
Table 3. Allylation of Benzoin using Substituted Allylacetates



entry	10	yield (%)	entry	10	yield (%)
1	 **10a**	85	5	 **10e**	64
2	 (88:12 *E:Z*) **10b**	79	6	 **10f**	57[a]
3	 **10c**	52	7	 **10g**	81[b]
4	 **10d**	31	8	 **10h**	18[c]

[a] Ratio of 85:15 C/O-allylation. [b] With substrate **7k**, dr = 60:40; ee = 8% and 11%; with substrate **1**: 64% yield, dr = 57:43, ee not determined. [c] Plus 41% mixture of other isomers.

−15 °C (TLC control). Therefore, the standard protocol began at −15 °C but also included stirring at ambient temperature overnight. Products were obtained in modest to good yields.

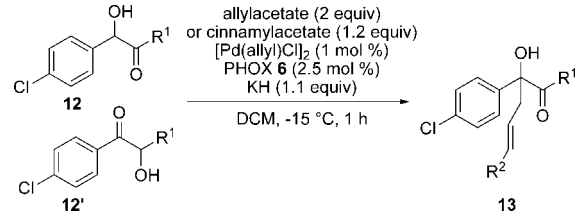
Thus far, the enantioselectivities obtained for the products of Tables 2 and 3 were quite low and did not exceed 26% using the enantiomerically pure ^{i}Pr-PHOX ligand. BINAP, bisoxazolines and Trost's ligand gave even lower yields and enantioselectivities.

To get access to a larger variety of products, we next investigated the use of unsymmetrical benzoin substrates, which could lead to four possible isomers (Table 4). These benzoins are readily available through published cross benzoin condensations[14] and exist as tautomeric mixtures **12**/**12′** as indicated in Table 4. The efficiency of the reaction depends on the substituents. Whereas α-hydroxyacetophenone **12a** and the α-hydroxyvinylketone **12f** led to complete degradation, the other alkyl−aryl hydroxyketones offer the product regio- and chemoselectively in moderate yield. This constitutes a more direct route to these interesting allyl hydroxyketones.[15]

Having shown the feasibility of these benzoin α-allylations, we turned our attention to the tandem benzoin formation/allylation catalysis.

Tandem Catalytic System. Althought tandem catalysis allows reaching molecular complexity from simple substrates in a one pot procedure, few examples are described in the literature due to the problem of compatibility of many catalytic systems. This is particularly true for the use of free N-heterocyclic carbenes as organocatalysts in the presence of another transition-metal based catalyst, since NHCs can readily act as ligands for the metal and lead to the formation

Table 4. Allylation of Aryl-Alkyl Hydroxyketones



entry	12/12′	R^1	R^2	product	yield (%)
1	0/100	H	H	**13a**	0
2	78/22	Me	H	**13b**	55
3	78/22	Me	Ph	**13c**	43[a]
4	72/28	*i*-Pr	H	**13d**	58
5	72/28	*i*-Pr	Ph	**13e**	52
6	100/0	$CHCH_2$	H	**13f**	0

[a] Mixture of 83:17 of *C*-allylated regioisomers.

of stable complexes.[3] So far, only one NHC acting as an organocatalyst has been shown to be compatible with a transition metal, in an allylation/Stetter tandem reaction.[16] Other catalysts involving allylpalladium species have been used together with chiral phosphoric acids,[17a] secondary amines[17b,c] for enamine formation from aldehydes, rhodium for activation of α-ketonitrile,[17d] chiral phase transfer catalyst for iminoester,[17e] stoichiometric amount of phosphines for activation of enones,[17f] and boron for alcohol transfer.[17g]

Our study commenced with an investigation of different types of NHCs (Figure 1). The goal was to find an NHC

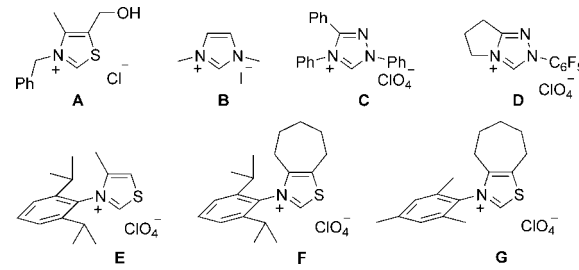


Figure 1. NHCs tested for tandem benzoin/allylation reactions.

that is catalytically active and that does not irreversibly bind to the palladium catalyst, thereby poisoining both catalysts. For this screening, we used a tertiary alcohol as solvent and DBU, a standard base for carbene formation, since under these conditions the allylation step was shown to work (Table 1, entry 11). We were pleased to find that thiazolidinylidenes

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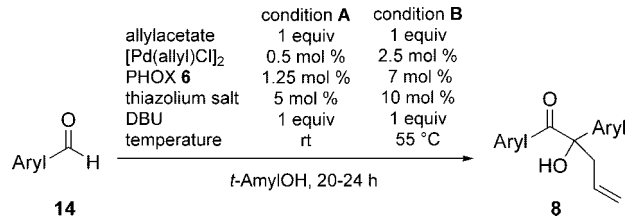
are tolerant of the metal catalyst and proved to be the most efficient (see Supporting Information). Recently, we have introduced the thiazolium salt **E** for the diastereoselective synthesis of trifluoromethylated γ-butyrolactones conjugate umpolung.[7a] In our study, the two new derivatives thereof **F** and **G** were found to be the most efficient organocatalysts, being tolerant of the palladium cocatalyst.

Two optimal sets of conditions were identified by this initial study. Electron-poor as well as electron-rich benzaldehyde derivatives could be reacted in this three component coupling catalyzed in parallel by an NHC as organocatalyst and a palladium complex (Table 5). In addition, heterocyclic aldehydes like *2*-furfuraldehyde and *2*-thiophenecarbaldehyde led to the products in good yield. In the case of electronrich aromatics somewhat more forcing conditions like a higher reaction temperature of 55 °C were required (condition B). In all cases, only the *C*-allylation could be observed. This compatibility of an NHC and a transition-metal catalyst represents a major advance and should be useful for related processes.

In conclusion, we have demonstrated the potential of palladium-catalyzed allylic alkylation of benzoins and related compounds. Remarkably high regio- and chemoselectivities were obtained in many cases, whereas the enantioselectivity of this reaction is still troublesome. Moreover, the rare compatibility of NHC catalysts with a transition-metal catalyst has been demonstrated in a multicomponent coupling. The investigation of other dually catalyzed reactions using NHCs is ongoing in our laboratory.

Table 5. Tandem Benzoin/Allylation Reaction



entry	aryl	condition	NHC's salt	8	isolated yield
1	C_6H_5-	A	**G**	**2**	56%
2	*p*-F-C_6H_4-	A	**F**	**8a**	76%
3	*p*-Cl-C_6H_4-	A	**F**	**8b**	73%
4	2-furyl-	A	**G**	**8k**	83%
5	2-thiophenyl-	A	**G**	**8l**	89%
6	*m*-Me-C_6H_4-	B	**G**	**8n**	69%
7	*p*-Me-C_6H_4-	B	**G**	**8c**	64%
8	*m*-CH_3O-C_6H_4-	B	**G**	**8h**	76%
9	*p*-CH_3O-C_6H_4-	B	**G**	**8d**	32%

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Supporting Information Available: Experimental details, products characterization, and spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It is stated in ref 9 that the *O*-allylated product **3** decomposes partially under GC conditions. Although this problem has to be considered, we initially based our optimization on the results of GC-MS analysis (entries 1−6 of Table 1).

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