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The first DMAP-mediated palladium-free Tsuji–Trost-type reaction of cyclic and acyclic Baylis–Hillman alcohols with active methylene compounds

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ABSTRACT

Direct allylic substitution of cyclic Baylis–Hillman alcohols with active methylene compounds under modified Taber's conditions (DMAP, toluene, reflux, 4 Å molecular sieves), with no Pd catalysts/activating agents, as is usually required for the process, affords the C-allylation products in moderate to good yields.

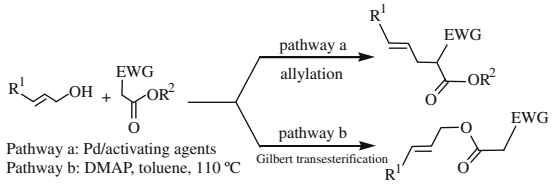
The type of compound obtained from the reaction of allylic alcohols with 3-oxoesters, is strongly dependent on the experimental conditions. Indeed, the Tsuji–Trost reaction[1] is a powerful tool in organic synthesis for the construction of carbon–carbon bonds, and involves Pd-catalyzed allylation of 1,3-dicarbonyl compounds with allyl substrates bearing various types of leaving group.

The direct allylation of 1,3-dicarbonyl compounds with allylic alcohols, instead of their corresponding allylic derivatives (i.e., halides, acetates, triflates, phosphates, etc.) is a very attractive approach because of the ready availability of alcohols, the atom-economy and the formation of water as the only side product. Since the hydroxy group is not a good leaving group, all previous allylation methods for accomplishing this task, need catalysts. Recently, using Pd catalysts/activating agents, several research groups have reported the direct allylic substitution of allyl alcohols by pronucleophiles in water,[2] toluene[3,4] or under neat conditions[5] (Scheme 1, pathway a).

Moreover, Lewis or Bronsted acids such as $BF_3{\cdot}OEt_2$,[6] $InCl_3$,[7] $FeCl_3$,[8] *p*-TsOH,[9] iodine[10] and H-Montmorillonite[11] have been reported to mediate the allylation of 1,3-dicarbonyl compounds. Recent reports have demonstrated that gold, silver,[12] certain metal triflates[13] as well as rare earth metals[14] could also be used as efficient catalysts for the allylation of 1,3-dicarbonyl compounds.

On the other hand, in a modified transesterification using Taber's methodology,[15] Gilbert[16] reported that treatment of allylic alcohols in refluxing toluene with 3-oxoesters and a catalytic amount of 4-dimethylaminopyridine (DMAP), afforded the corresponding allylic esters, as useful starting materials for Carroll rearrangements[17] (Scheme 1, pathway b).

It is notable that none of the previous allylating methods has described Lewis bases such as DMAP as efficient catalysts for the direct allylation of active methylene compounds with allylic alcohols.

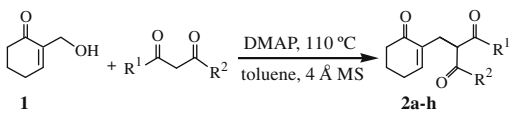


Scheme 1.

In connection with our previous study on the behaviour of Baylis–Hillman (BH) derivatives towards various nucleophiles,[18] we report in this Letter a straightforward procedure for the allylation of active methylene compounds (i.e., 1,3-dicarbonyl compounds and nitroalkanes) with cyclic and acyclic BH alcohols using DMAP as an efficient Lewis-base catalyst.

Thus, BH alcohol **1** reacted with ethyl benzoylacetate on treatment with DMAP (1.2 equiv) and 4 Å molecular sieves in refluxing toluene, with no formation of the expected transesterification product[15,16] nor the corresponding Carroll rearrangement product,[19] to generate exclusively, the β-dicarbonyl monoallyl derivative **2a**[20] in 80% yield (Scheme 2, Table 1, entry 1).

Mechanistically, we believe that the reaction starts with conjugate addition of DMAP to Michael acceptor **1**, followed by the elimination of the hydroxy moiety to afford intermediate **I**. Similarly, further conjugate addition of ethyl benzoylacetate enolate to **I**, then elimination of DMAP, provides compound **2a** (Scheme 3).



Scheme 2.

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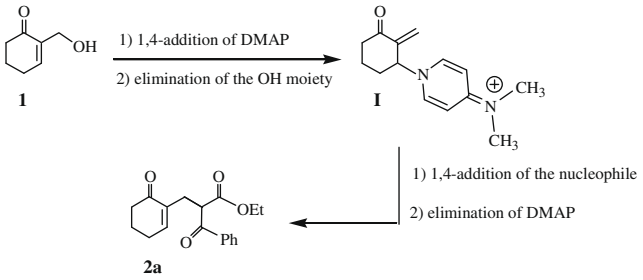
Table 1
DMAP-mediated allylation of β-dicarbonyl compounds with cyclic Baylis–Hillman alcohol **1**

Entry	Product	R^1	R^2	**2** (yield %)
1	**2a**	Ph	OEt	80
2	**2b**	Me	OEt	58
3	**2c**	Me	OMe	42
4	**2d**	Me	OBz	44
5	**2e**	Me	Ph	60
6	**2f**	Ph	Ph	80
7	**2g**	Me	Me	64
8	**2h**	Et	Et	40



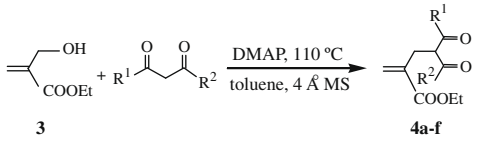
Scheme 3.

The overall reaction can be described as a palladium-free Tsuji–Trost-type process. This particular behaviour of allylic alcohol **1** towards ethyl benzoylacetate, affording the monoallylation product **2a** instead of the expected transesterification product, is likely due to the presence of an electron-withdrawing group on the activated alkene, which would appear to be essential for this transformation.

In order to investigate the scope and limitations of this simple monoallylation method, we investigated the behaviour of acyclic BH alcohol **3**[22] towards 3-oxoesters (Scheme 4, Table 2, entries 1–3) and β-diketones (Scheme 4, Table 2, entries 4–6). We found that under the above-mentioned conditions (DMAP, toluene, reflux, 4 Å molecular sieves), the reaction gave the allylation products **4a–f**[23] in a 68–95% yield.

This protocol was successfully extended to the reaction of allyl alcohol **1** and other 3-oxoesters (Table 1, entries 2–4) as well as β-diketones (Table 1, entries 5–8), leading to allylation products **2b–h**[21] in moderate to good yields.

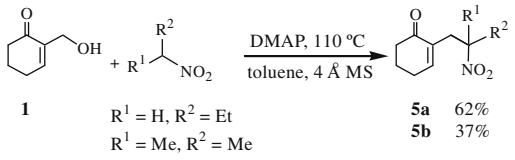
Finally, we demonstrated that other carbon pronucleophiles, that is, 1-nitro- and 2-nitropropanes, reacted with alcohol **1**, under the same conditions, to give nitro derivatives **5a–b** in 37–62% yields (Scheme 5).



Scheme 4.

Table 2
DMAP-mediated allylation of β-dicarbonyl compounds with acyclic BH alcohol **3**

Entry	Product	R^1	R^2	**4** (yield %)
1	**4a**	Ph	OEt	95
2	**4b**	Me	OEt	78
3	**4c**	Me	OBz	68
4	**4d**	Me	Ph	87
5	**4e**	Ph	Ph	88
6	**4f**	Me	Me	75



Scheme 5.

In summary, we have described a simple and direct allylic substitution of primary BH alcohols **1** and **3** with a variety of pronucleophiles under modified Taber's conditions. Work is in progress in our laboratory to investigate the generality of this direct substitution of BH alcohols by various soft nucleophiles (i.e., amines and thiols), and to establish suitable experimental conditions to enable transesterification of the BH alcohols with 3-oxoesters.

Acknowledgement

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20. General procedure for the allylation of carbon pronucleophiles with cyclic BH alcohols. Preparation of compound **2a**: a mixture of allyl alcohol **1** (5 mmol, 0.63 g), ethyl benzoylacetate (10 mmol, 1.92 g) and DMAP (6 mmol, 0.372 g) was dissolved in toluene (50 mL), containing 10 g of oven-dried 4 Å molecular sieves. The mixture was then heated under reflux for 20 h. The reaction mixture was washed with brine and dried. The toluene was removed and the residue was purified by column chromatography to furnish pure **2a** (1.2 g, 80%). Viscous yellow oil; IR ($CHCl_3$): 1737, 1699, 1600, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04–8.03 (m, 2H), 7.58–7.44 (m, 3H), 6.88 (t, J = 4.0 Hz, 1H), 4.75–4.70 (m, 1H), 4.13 (q, J = 6.9 Hz, 2H), 2.85–2.81 (m, 2H), 2.41–2.26 (m, 4H), 1.92–1.86 (m, 2H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 195.5, 172.2, 149.4, 136.1, 135.7, 133.5, 128.7, 128.6, 61.1, 52.5, 38.3, 30.6, 26.0, 22.8, 14.0; MS (*m/z*): 300 (M^+, 2), 282 (45), 255 (15), 254 (22), 226 (5), 195 (14), 149 (22), 121 (5), 105 (100), 77 (33).
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