Et$_3$B-mediated and palladium-catalyzed direct allylation of β-dicarbonyl compounds with Morita–Baylis–Hillman alcohols

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Abstract
A practical and efficient palladium-catalyzed direct allylation of β-dicarbonyl compounds with both cyclic and acyclic Morita–Baylis–Hillman (MBH) alcohols, using Et$_3$B as a Lewis acid promoter, is described herein. A wide range of the corresponding functionalized allylated derivatives have been obtained in good yields and with high selectivity.

Introduction
In nucleophilic allylic substitutions, π-allylpalladium complexes are useful intermediates for the construction of carbon–carbon and carbon–heteroatom bonds in organic synthesis [1]. Usually, palladium species are used as catalysts in the Tsuji–Trost reaction involving, as substrates, allyl carboxylates [2], carbonates [3], and phosphates [4]. Obviously, the direct nucleophilic allylic substitution of allyl alcohols is a more attractive process especially from an economical and environmental point of view [5], as water, generated by this reaction, is a non-toxic byproduct. However, the poor ability of the hydroxy moiety, as a leaving group, has limited the use of the allyl alcohols as substrates. Correlatively, some efforts have been made in this direction by the use of transition metals such as copper [6], nickel [7], ruthenium (I, II) [8], and palladium (0, II) [9,10] as the catalyst or by converting the allylic alcohols into esters of inorganic acids, e.g., As$_2$O$_3$ [11], B$_2$O$_3$ [12], CO$_2$ [13,14].

More recently the Lewis acids, such as, Ti(OiPr)$_4$ [15], BEt$_3$ [16-19], BPh$_3$ [20], SnCl$_2$ [21], and FeCl$_3$ [22], have also been reported to catalyze these reactions by coordination with the hydroxy moiety, thereby increasing its leaving group ability [23-28].

Recently, Tamaru and co-workers have intensively investigated the use of triethylborane as an additive with either Pd(PPh$_3$)$_4$ or Pd(OAc)$_2$ as catalysts for the allylation of a variety of active methylene compounds [29], aldehydes [30], ketones [31], and imines [32] with only common allylic alcohols.

As part of an ongoing program studying the behavior of MBH derivatives [33] towards β-dicarbonyl compounds, our research
group [34-37] has reported an interesting synthesis of bicyclic dienones in a one-pot process involving the reaction of 2-(acetoxymethyl)cyclohex-2-enone with 1,3-dicarbonyl compounds using K$_2$CO$_3$ as a weak base.

Later, Chamakh and Amri [38] have described a one-pot synthesis of (E)-4-alkylidene-2-cyclohexen-1-ones through a cross coupling of the MBH carboxylates with aliphatic 1,3-diketones in the presence of K$_2$CO$_3$. A drawback of these synthetic approaches is the need to first perform the acylation step of the corresponding allyl MBH alcohols. For this reason, we herein report an efficient direct method for the allylation of β-dicarbonyl compounds with MBH alcohols [39,40] 1a and 1b (Figure 1) considered as multi-functionalized starting materials bearing both allyl alcohol and Michael acceptor moieties.

Results and Discussion

We first investigated the allylation of diethyl malonate (2a) with the allylic alcohol 1a in DMF in the presence of Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%). Under these conditions, no reaction took place at 80 °C for 3 days (Table 1, entry 1).

On the other hand, the allylation slowly proceeded in the presence of NaH (0.5 equiv) but only a trace of the expected product 3a was obtained (Table 1, entry 2). Interestingly, the allylation reaction, carried out in DMF at 80 °C, gave a better result (30% yield in 12 h), using, in addition to NaH (0.5 equiv), 1 equiv of Et$_3$B (Table 1, entry 3). Moreover, a remarkable improvement in yield (60% in 6 h) was also observed for the allylation of diethyl malonate (2a) with the MBH alcohol 1a using an excess of Et$_3$B (3 equiv) and 1 equiv of NaH (Table 1, entry 4).

Mechanistic considerations

Scheme 1 illustrates the most probable catalytic cycle for the allylation of diethyl malonate (2a) with allylic alcohol 1a. We assume that there is first an activation of 1a through its conversion into I$_1$ using Et$_3$B [29], which further gives, in the presence of Pd(0), the π-allylpalladium complex I$_2$. This intermediate reacts then with the diethyl malonate carbanion I$_3$, in situ formed, to generate the promoter Et$_3$B of this nucleophilic allylic substitution and the desired allylated product 3a.

Next, under the previously optimized conditions (Table 1, entry 4), we examined the scope of the catalytic system, Et$_3$B/Pd(OAc)$_2$/PPh$_3$, for a wide range of 1,3-dicarbonyl compounds and related derivatives (pK$_a$ = 9–14) [29,31] using two typical MBH alcohols 1a and 1b. The results of this study are summarized in Table 2.

Like diethyl malonate (2a), the malonate derivative 2b (pK$_a$ = 13) [29] similarly reacted with the allylic alcohol 1a in
the presence of the catalytic system Pd(0)/Et₃B to exclusively
give the mono-allylated product 3a in 65% yield, whereas the
same reaction with ethyl 3-cyano-3-oxopropanoate (2c, pKₐ =
10.7) [43] whose acidity is relatively higher, led to a mixture of
the mono- and bis-alkylation products 3c and 4c in 45 and 23% 
yields, respectively (Table 2, entries 1–3).

Under the same conditions, the allylation of a variety of β-keto
esters and β-diketones (Table 2, entries 4–9), in DMF at 80 °C,
selectively gave the monoallylation products 3d–i in moderate
to good yields [44].

The analysis of 1H NMR spectra of the β-dicarbonyl derivati-
vatives 3a–i in CDCl₃ revealed that a keto–enol tautomerism
exists only for the acetylacetone derivative 3g and its enolic
form 5g in a 54:46 ratio, respectively (Table 2, entry 7), where-
as the other compounds 3a–f, 3h and 3i are exclusively in the
β-dicarbonyl form [45-47].
Moreover, the allylation of ethyl cyclopentanone-2-carboxylate (2j) [49] as a cyclic β-keto ester, with alcohol 1a, catalyzed by the same system, smoothly proceeded at 80 °C in DMF, providing, after 2 h, the mono-allylated product 3j in 12% yield, along with the tricyclic compound 6j, in good yield, which is resulting from the intramolecular conjugate addition of 3j carbanion on the enone moiety (Table 3, entry 2). Under the same conditions, the keto ester 2j reacted with alcohol 1a, in DMF at 80 °C for 6 h longer reaction time, to selectively afford the compound 6j in 76% yield (Table 3, entry 3).

| Entry | Nucleophile | T (°C)/Time (h) | Yield (%) |
|-------|-------------|-----------------|-----------|
| 1     | 2j          | 0 to rt/24      | N.R.      |
| 2     | 80/2        | 3j: 12% 6j: 75% |           |
| 3     | 80/6        | 6j: 76%         |           |

A plausible reaction mechanism for the formation of the tricyclic compound 6j from the MBH alcohol 1a is presented in Scheme 2. We believe that the treatment of the MBH alcohol 1a with Et₃B in the presence of Pd(OAc)₂ may generate a π-allyl-palladium intermediate I that further undergoes a nucleophilic substitution reaction with the β-keto ester carbanion derived from 2j, affording the monoallylated compound 3j. The conversion of the keto ester 3j into the tricyclic product 6j was further performed through an intramolecular conjugate addition of the β-keto ester carbanion onto the enone moiety (Scheme 2) [50,51].

The structure of the tricyclic compound 6j was elucidated on the basis of X-ray diffraction analysis (Figure 2).

In a previous report, Alexakis and co-workers have demonstrated that copper-catalyzed conjugate addition of Grignard reagents onto α-methyl cyclic enones, affording mainly the trans-2,3-disubstituted cyclohexanones as being the thermodynamic products [52]. Similarly, we believe that the intramolecular conjugate addition of carbanion 3j onto α-substituted enone moiety is under thermodynamic control, leading to the tricyclic compound 6j, in which the two hydrogens H₂ and H₃, are on a trans-ring junction whereas the second ring junction is cis (Figure 2).

Encouraged by these successful results on the allylation of β-dicarbonyl compounds with the alcohol 1a in the presence of Pd/Et₃B, we attempted to extend this methodology to the acyclic MBH alcohol 1b (Table 4). We initially reacted this substrate with ethyl acetoacetate (2e, 1.1 equiv) in the presence of the catalyst Pd(OAc)₂ without any additive. After stirring the reaction mixture for 24 h, either at room temperature or in refluxing THF, the starting alcohol 1b was recovered (Table 4,
Encouraged by these results and those of cyclic MBH alcohol 1a, we selected the acyclic alcohol 1b to react with stabilized carbanions derived from the β-keto esters 2e–f and β-diketones 2g–i in anhydrous THF using 1 equiv of NaH and 2 equiv of Et3B. Under these conditions, all these reactions worked well in refluxing THF, affording in 2 h the corresponding monoallylation products 7e–i [41,44] in 60–70% yields (Table 5, entries 1–4).

**Conclusion**

In summary, we have developed a mild and direct process for the C–C bond formation from the reaction of the MBH alcohols 1a and 1b with β-dicarbonyl compounds 2 in the presence of a palladium catalyst and Et3B (promoter) with the formation of only water as a side product. This method provides a straight-
Table 5: Palladium-catalyzed allylation of a variety of β-dicarbonyl compounds with the MBH alcohol 1b.

| Entry | β-Dicarbonyl compound 2 | Time (h) | Compound 7 | Yield 7 (%) |
|-------|------------------------|----------|------------|-------------|
| 1     | MeCOCH₂CO₂Et, 2e       | 2        | 7e [41,44] | 60          |
| 2     | Ph COCH₂CO₂Et, 2f      | 2        | 7f [41,44] | 68          |
| 3     | MeCOCH₂COMe, 2g        | 2        | 7g [41,44] | 65<sup>a</sup> |
| 4     | Ph COCH₂COMe, 2i       | 2        | 7i [41,44] | 70          |

<sup>a</sup>Containing 30% of the enolic form 8g.

forward and practical route to a range of allylated compounds. Further work is in progress in our laboratory to investigate the Pd catalysis of the reaction of the MBH adducts with various pronucleophiles including nitroalkanes, amines and thiols.

**Experimental General**

IR spectra were recorded on a Bruker IFS 66v/S spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded either on a Bruker AC-300 spectrometer (300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C) in CDCl<sub>3</sub>, using TMS as an internal standard (chemical shifts in δ values, J in Hz). Mass spectra (EI) were recorded on an Hewlett-Packard (70 eV) apparatus. Analytical thin-layer chromatography (TLC) was performed using Fluka Kieselgel 60 F254 precoated silica gel plates. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using Merck silica gel 60 and a gradient solvent system (petroleum ether/ether as eluents).

**General procedure for the allylation of β-dicarbonyl compounds with the MBH alcohols 1a and 1b**

Into a nitrogen-purged two-necked flask, equipped with a reflux condenser, containing 5 mL of DMF or THF, Pd(OAc)<sub>2</sub> (10 mol %), and PPh<sub>3</sub> (20 mol %) were added successively the 1,3-dicarbonyl compound 2 (1.1 mmol), NaH (1 mmol) and an Et<sub>3</sub>B solution 1.0 M (2 to 3 mmol) in THF. The mixture was stirred for 5 to 10 min at room temperature, then the MBH allylic alcohol 1a or 1b (1 mmol) was added. The mixture was stirred and heated at 80 °C for 3 to 6 h during which the mixture was colored black. When the reaction, followed by TLC, was finished, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with 2 M HCl, sat. NaHCO<sub>3</sub> and then brine. The organic extracts were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residual oil was subjected to column chromatography over silica gel (gradient: petroleum ether/ether = 4:1) to give the pure allylated products 3–8 in moderate to good yields.

**Supporting Information**

**Supporting Information File 1**

Experimental procedures, characterization and spectral data for synthesized compounds and X-ray data for compound 6j.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-234-S1.pdf](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-234-S1.pdf)

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