Et_3B-Mediated Palladium-Catalyzed Direct Allylic Substitution Reactions of Morita-Baylis-Hillman Alcohols with Aromatic Amines

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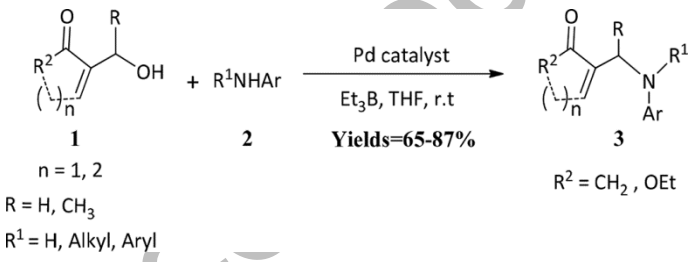
ABSTRACT

An efficient, direct allylic amination of both cyclic and acyclic Morita–Baylis–Hillman alcohols with aromatic amines, in THF at room temperature, under the catalysis of Pd(0)/Et_3B, is reported herein. The corresponding amines are obtained with a high α-regioselectivity in 65-87% yields.

GRAPHICAL ABSTRACT



KEYWORDS: Amination; allylic substitution; palladium; catalysis; organic synthesis

1. INTRODUCTION

Palladium-catalyzed C–N bond formation is an established and efficient method for the synthesis of nitrogen-containing natural compounds of biological interest.[1] Although

being the most straightforward and desirable from economical and ecological point of view, a few reports have dealt with the direct use of allylic alcohols as allylating agents in Pd-catalyzed amination reaction since the hydroxyl moiety is not a good leaving group.[2]

Some of these methods involve a transition metal catalyzed-Tsuji-Trost type allylation reaction of amines [3], among them, the catalytic allylic amination of primary and secondary amines with allylic alcohols reported by Muzart,[4] while other protocols required the presence of Bronsted[5] or Lewis acid[6] catalysts. In Kimura's study,[7] it was reported that a catalytic amount of Et_3B efficiently promoted Pd-catalyzed direct allylation of amines with allylic alcohols. The main substrates of these transformations are restricted to common allylic, benzylic, and propargylic alcohols.[8]

On the other hand, transition metal-catalyzed nucleophilic substitution of allylic Morita–Baylis–Hillman (MBH) adducts, as multi-functionalized substrates, has not been well investigated.[9] Over the last decades, the reaction of MBH acetates with various amines, in the presence of palladium(0) catalyst, has shown interesting reaction profiles under different conditions.[10] Recently, Wang and co-workers[11] reported a highly α-regioselective palladium-catalyzed allylic amination of MBH acetates with simple aromatic amines.

Unfortunately, all these catalytic nucleophilic substitutions are strictly limited to MBH acetates. We believe that the scope and utility of these types of reactions would be greatly expanded if an experimental protocol using efficient catalysts could be implemented for

the corresponding alcohols. Accordingly, Liu and co-workers [12] desribed a highly regioselective *N*-nucleophilic substitution of MBH alcohols with aromatic amines promoted by $In(OTf)_3$.

Based on these results and in continuation of our ongoing interest in the study of the nucleophilic substitution of cyclic MBH adducts with a large variety of nucleophiles,[13-17] we hypothesized that the MBH alcohols, bearing both an allyl alcohol and enone moieties, may also react with amines or other nucleophiles in the presence of suitable palladium catalysts through a similar pathway. This protocol would be therefore an efficient synthetic route for a wide range of β'-amino MBH derivatives. [12 and 18] Herein, we wish to report a highly α-regioselective amination of both cyclic and acyclic MBH alcohols with aromatic amines, promoted by Et_3B and catalyzed by Pd(0), under mild conditions (THF at room temperature).

2. RESULTS AND DISCUSSION

We have selected the MBH alcohol **1a**[16] and simple aniline **2a** as typical coupling partners during the optimization study. The alkylation of aniline (1.2 mmol) **2a** with alcohol **1a** (1.0 mmol) in THF was first examined in the presence of $Pd(OAc)_2$ (5 mol%), PPh_3(10 mol%), under nitrogen atmosphere. Under these conditions, no reaction took place in refluxing THF within 24 h (Table 1, entry 1). Interestingly, the reaction slowly proceeded when Et_3B (1 equiv) was used, as the Lewis acid, providing the allylamine **3a** in 50% isolated yield (Table 1, entry 2). Moreover, the use of an excess of Et_3B (2-3 equiv), under the same conditions, gave **3a** within a shorter reaction time (2-3h), in a

better yield (74-75%) (Table 1, entries 3 and 4) while the use of 2 equiv of Et_3B, in THF, at room temperature, yielded the allylamine **3a** in 76% yield, through a cleaner nucleophilic substitution in 24h (Table 1, entry 5).

Under the previous conditions, when the title reaction was carried out in toluene at reflux, the allylamine **3a** was obtained within 3h in 72% yield (Table 1, entry 6). Therefore, taking into account all our previous attempts (Table 1, entries 1-6), we decided to carry out all our further experiments in THF, at room temperature (RT), using $Pd(OAc)_2$ (5 mol%), PPh_3(10 mol%) and Et_3B (2 equiv) (Table 1, entry 5).

A plausible mechanism for Pd-Et_3B catalyzed allylic amination of alcohol **1a**, is presented in Scheme 2.[7] Triethylborane may coordinate to the hydroxyl group of **1a** to help it undergo oxidative addition to Pd(0),[19] generated *in situ*, affording a π-allylpalladium intermediate **I**. Subsequently, this intermediate is attacked directly by aromatic amine, as a soft nucleophile (pKa up to 25),[20] giving the intermediate **II** that undergoes a reductive elimination, releasing the *N*-allylamine **3a**, and closing the catalytic cycle (Scheme 1).

Next, when various anilines bearing electron-donating or withdrawing groups on the phenyl group, were allylated with the MBH alcohol **1a** in THF, we have also observed an excellent α-regioselectivity and the corresponding allyl amines **3b-d**[12] were prepared in 81-87 % yields (Table 2, entries 2-4).

Similarly, the reaction worked well with slightly hindered secondary amines **2e-g**, providing tertiary amines **3e-g**[12,18] in 66-77 % yields (Table 2, entries 5-7).

Next, we have shown that the amination of alcohol **1b**[17] that is slightly hindered at the β'-position, with primary and secondary amines **2a** and **2e**, was successful, affording the desired amines **3h** and **3i** [12, 18] in 65-66 % yields (Table 2, entries 8 and 9).

We have also investigated the allylation of primary and secondary amines **2a** and **2e** with the five-membered alcohol **1c**.[17, 21] This study revealed that the protocol still successful and the corresponding amines **3j** and **3k** [12, 18] were isolated in 70-74 % yields (Table 2, entries 10 and 11).

Under the catalysis of a combination of Pd(0) and Et_3B, we did not observe any γ-product along with the α-product **3a-j** using primary or secondary alcohols **1a-c**. We believe that this allylic substitution is under thermodynamic control, affording exclusively the α-product. [10a, 12]

Finally, In order to determine the scope of this direct amination protocol, we have investigated this time the allylation of aromatic amines with acyclic MBH adducts. The Literature survey revealed that Pd-mediated allylation of amines with acyclic MBH acetates, affording a mixture of α- and γ-products resulting from competitive S_N2 and S_N2' reactions (Scheme 2). On the other hand, the common amines reacted, at room temperature, with acyclic MBH alcohols in methanol, as the solvent, however, in a 1,4-

fashion as the hydroxyl moiety is not a good leaving group, providing the corresponding aminoalcohols (Scheme 2).

In our work, upon treatment of acyclic MBH alcohol **1d** [22] with aniline **2a** or *p*-anisidine **2b,** under the etablished condtions ($Pd(OAc)_2$ (5 mol%), PPh_3(10 mol%) and Et_3B (2 equiv)), in THF, at room temperature, the corresponding allylamines **3l** and **3m** [10a, 11 and 18c] were isolated in 78 and 72 % yields, respectively (Scheme 2, table 2, entries 12 and 13).

Because the allyl substrate **1d** is a primary alcohol, the α- and the γ-products, isolated in every case, are the same. We believe that they were obtained through a reaction mechanism similar to that of Scheme 2.

All these successful results clearly suggest that, under palladium catalysis, the straightforward allylation of aromatic amines worked well with both cyclic and acyclic MBH alcohols.

3. EXPERIMENTAL

3.1. Materials And Methods

General methods ^1H and ^{13}C NMR spectra were recorded on a Bruker-AV 300 spectrometer and chemical shifts reported in $CDCl_3$ with tetramethylsilane as an internal standard. All reactions were carried out in oven dried flasks. Common reagents were purchased from commercial sources and were used without further purification. The

Morita–Baylis–Hillman alcohols were prepared according to literature methods.[16, 17, 21 and 22] All the reactions were performed under nitrogen atmosphere.

3.2. Synthesis Of 3a As General Procedure For Allylic Amination Reaction

A solution of 5 mol% $Pd(OAc)_2$ catalyst and 10 mol% of PPh_3 in THF (1mL), was stirred at 25°C for 5 min, then a solution of alcohol **1a** (1 mmol), Et_3B (2 equiv.) and simple aniline **2a** (1.2 mmol) were added. The reaction mixture was stirred at 25°C and monitored by TLC until the starting material disappeared. The reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated to afford the crude product. Their further purification by flash column chromatography over silica gel (eluent: Petroleum ether–ether = 90:10) gave the pure allylic amine **3a** as a yellow oil (153 mg, 0.76 mmol, 76%): IR (FT-IR): 3398, 2921, 1661, 1600, 1504, 1385, 1247, 1170, 747, 691 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 7.17–7.12 (m, 2H), 6.9 (t, *J*= 4.5 Hz, 1H), 6.71– 6.66 (m, 1H), 6.57–6.54 (m, 2H), 4.07 (broad s, 1H), 3.93 (d, *J*=1.5 Hz, 2H), 2.44 (m, 2H), 2.37–2.32 (m, 2H), 2.02–1.93 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): 199.8, 147.8, 146.5, 136.0, 129.2, 117.5, 113.0, 43.3, 38.4, 25.7, 22.9; **MS (m/z):** 77 (63), 106 (53), 124 (40), 201 ($C_{13}H_{15}NO$, M^+, 100); HRMS (ESI+): m/z calcd for $[C_{13}H_{15}NO+H]^+$: 202.1233; found: 202.1232.

Compounds **3a-m** were fully characterized and their spectroscopic data were in agreement with those of previous work, see Ref. 10a, 11, 12 and 18.

CONCLUSION

In summary, we have developed a direct amination of cyclic and acyclic MBH alcohols with aromatic amines, under mild conditions, providing, in good to high yields, the desired monoallylamines **3**. The reaction proceeded in the presence of Et_3B as a promoter and Pd(0), as a catalyst, with exclusive α-regioselectivity. This protocol was found to be efficient and may open up a new area for various functionalizations of MBH alcohols.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra and Mass spectroscopy of synthesized materials can be found via the "Supplementary Content'' section of this article's webpage.

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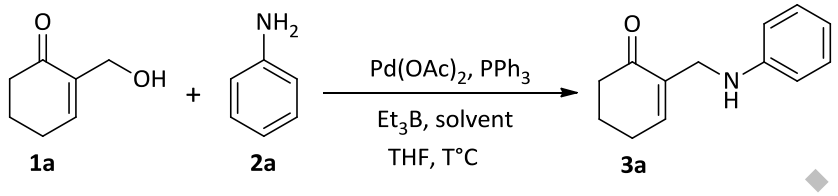
Table 1. Optimization of the reaction conditions for the amination of MBH alcohol **1a** with aniline **2a**[a]

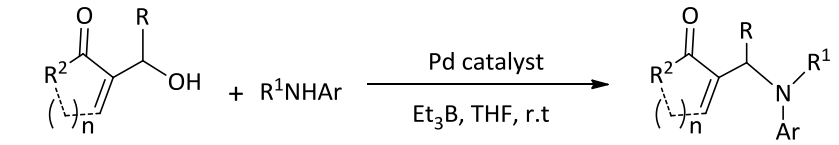


1a **2a** **3a**

Entry	Et_3B (equiv)	Solvent	T (°C), time (h)	Yield **3** (%)[a,b]
1	None	THF	Reflux/24	N.R
2	1	THF	Reflux/24	50
3	2	THF	Reflux/3	75
4	3	THF	Reflux/2	74
5	**2**	**THF**	**R.T/24**	**76**
6	2	Toluene	Reflux/3	72

[a]Reaction conditions: MBH alcohol (1.0 mmol), aniline (1.2 mmol), solvent (1mL) under nitrogen atmosphere. [b] Yields of isolated products.

Table 2. Pd.Et_3B-catalyzed amination of MBH alcohols **1a-d** with aromatic amines **2a-g**[a]



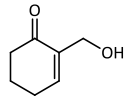
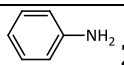
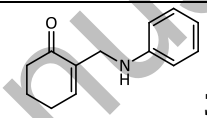
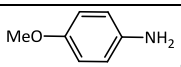
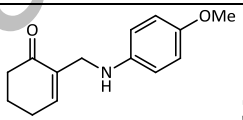
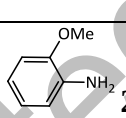
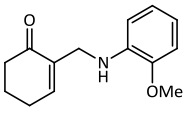
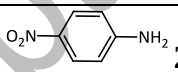
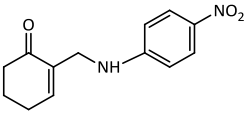
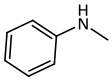
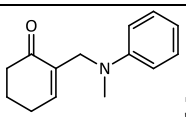
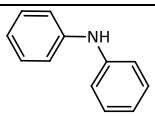
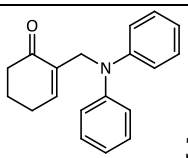
1 **2** **3**

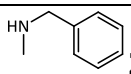
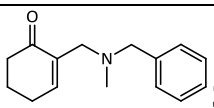
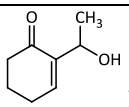
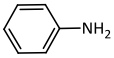
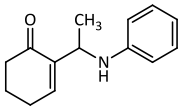
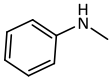
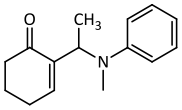
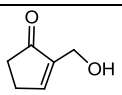
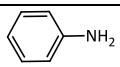
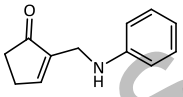
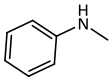
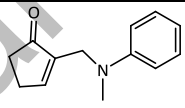
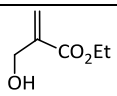
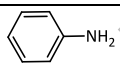
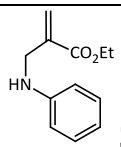
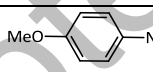
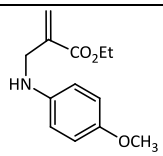
n = 1, 2

R = H, CH_3

R^1 = H, Alkyl, Aryl

R^2 = CH_2 , OEt

Entry	Alcohol **1**	Amine **2**	Time (h)	Compound **3**	Yield **3** (%)[a]
1	 **1a**	 **2a**	**24**	 **3a**	**76**[c]
2	**1a**	 **2b**	**20**	 **3b**	**84**[c]
3	**1a**	 **2c**	**20**	 **3c**	**87**[c]
4	**1a**	 **2d**	**24**	 **3d**	**81**[b,c]
5	**1a**	 **2e**	**12**	 **3e**	**77**[c]
6	**1a**	 **2f**	**24**	 **3f**	**72**[c]

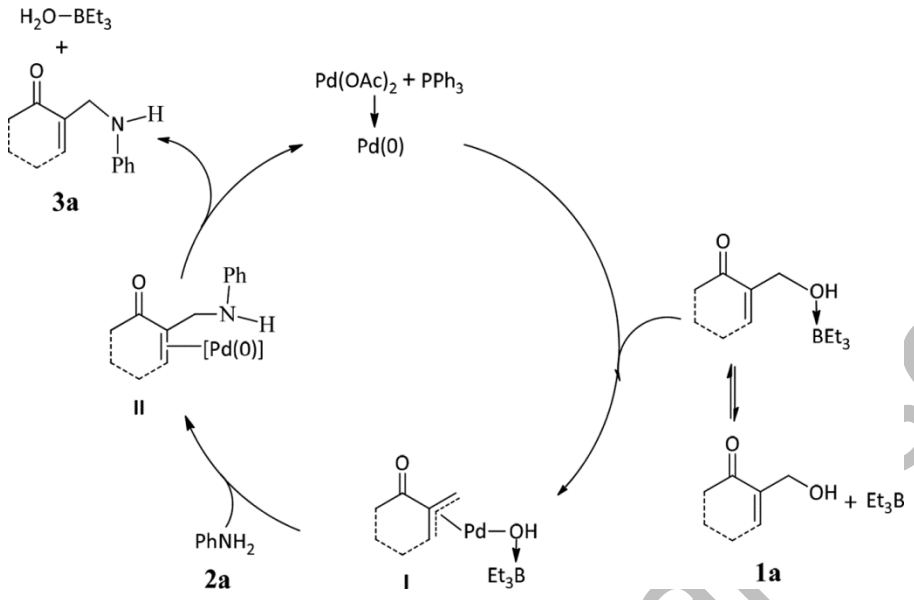
7	**1a**	 **2g**	**22**	 **3g**	**66[c]**
8	 **1b**	 **2a**	**24**	 **3h**	**65[c]**
9	**1b**	 **2e**	**20**	 **3i**	**66[c]**
10	 **1c**	 **2a**	**24**	 **3j**	**70[c]**
11	**1c**	 **2e**	**24**	 **3k**	**74[c]**
12	 **1d**	 **2a**	**2**	 **3l**	**78[d]**
13	**1d**	 **2b**	**24**	 **3m**	**72[d]**

[a]Reaction conditions: $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol %), Et_3B(2 equiv), MBH alcohol (1.0 mmol), aniline (1.2 equiv), THF (1mL), under nitrogen atmosphere at r.t [b] using 1 equiv of aniline.

[c] Analogous as described in [12,18].

[d] Analogous as described in [10a,11]

Scheme 1. Plausible reaction mechanism for Pd·Et_3B catalyzed allylic alkylation of aniline **2a** with MBH alcohol **1a**



Scheme 2. Reactions of acyclic MBH adducts with amines under different conditions