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An efficient and general synthesis of 3-substituted propionaldehydes using the Suzuki–Miyaura coupling

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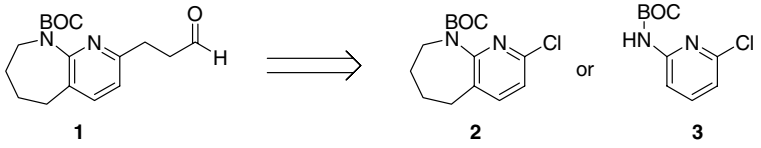
Abstract—An efficient method to prepare 3-substituted propionaldehyde derivatives using a Suzuki–Miyaura coupling is reported. The reaction has been demonstrated on a range of substrates including several where the Heck reaction with allyl alcohol failed to give the desired aldehyde product.

As part of a drug discovery program aimed at the preparation of $\alpha_v\beta_3$ integrin antagonists,[1] we required the synthesis of the propionaldehyde derivative **1**. We have recently reported the one-pot synthesis of chloropyrido[2,3-*b*]azepine **2** from the substituted pyridine **3**.[2] We therefore envisaged using compound **2** in the synthesis of **1** employing a Pd-mediated coupling to append the desired propionaldehyde moiety (Scheme 1).

Our initial plan was to use the Heck reaction of allyl alcohol with compound **2** to provide aldehyde **1** in a single step. Unfortunately, using standard Heck conditions[3] or Jeffery modifications[4] we observed none of the desired product. These procedures have been primarily used for the coupling of aryl iodides, which are considerably more reactive than pyridyl chlorides such as **2** and this may account for the observed lack of reactivity in our case.

Recently, there have been many advances in Pd-mediated coupling reactions and the utility of aryl chlorides in particular has been demonstrated. Improvements in the Heck reaction have resulted from the use of sterically hindered phosphine ligands,[5] palladacycles,[6] phosphite ligands,[7] heterocyclic carbene ligands,[8] various additives (Ph_4PCl[9] and *N*,*N*-dimethylglycine[9]), and others.[10] We pursued several of these avenues with chlorides **2** and **3** but found little success in their coupling with allyl alcohol. Notably, these improvements to the Heck reaction are rarely demonstrated using allyl alcohol as the olefin. The reaction can suffer from regioselectivity issues both in the coordination/insertion stage and in the reductive elimination step.



1 2 3

Scheme 1.

Keywords: Suzuki–Miyaura coupling; Chloropyrido[2,3-*b*]azepine; Propionaldehyde derivative.
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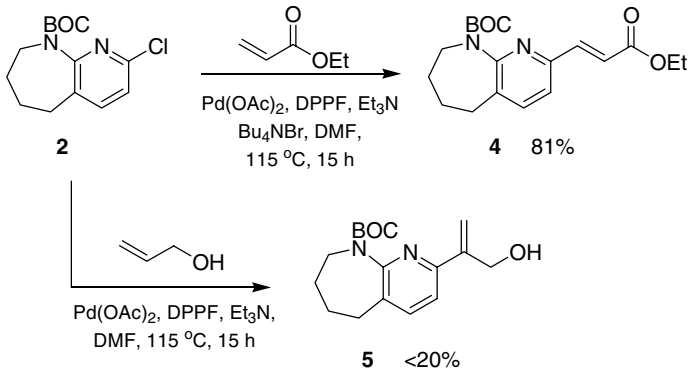


Scheme 2.

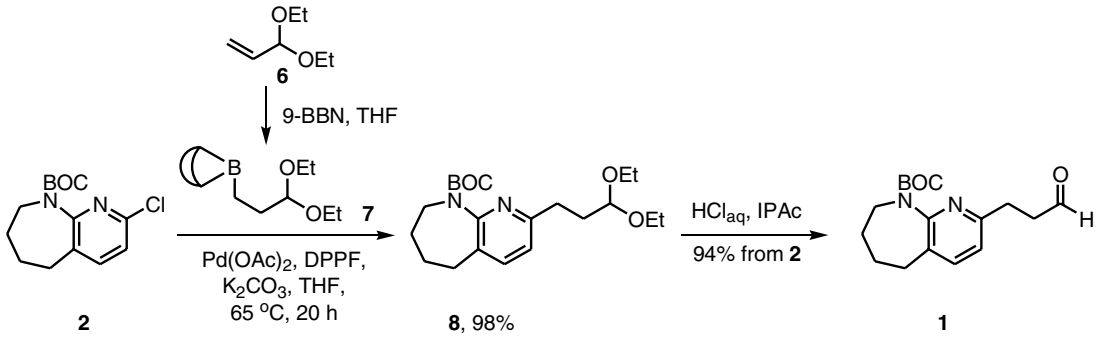
We initially presumed that the limiting step in the Heck reaction of compound **2** with allyl alcohol was the oxidative addition.[11] However, when changing from allyl alcohol to ethyl acrylate as the Heck acceptor, we obtained good yields of the expected adduct **4** (Scheme 2). Applying similar conditions to the reaction with allyl alcohol afforded low yields of the undesired alcohol **5** as the only identifiable product. This may not be surprising as others have noted that 1,1′-bis(diphenylphosphino)ferrocene (dppf) is a poor ligand for such couplings.[12]

With access to ester **4** secured, a circuitous route to aldehyde **1** could be envisaged. Unfortunately, this failed to meet our goal of a concise synthesis so we then examined an approach using the commercially available acrolein diethyl acetal (**6**) in a Suzuki–Miyaura coupling (Scheme 3).[13] If successful, this approach would overcome the regioselectivity problem of allyl alcohol in the Heck reaction as the regioselectivity would be determined in the hydroboration step. Brown has already reported a 98:2 ratio in favor of the desired **7** when using 9-BBN as the reagent.[14] This protocol would have the added advantage that the sensitive aldehyde would not be produced in the coupling reaction but rather unmasked under mild, acidic conditions in the reaction work-up. Alternatively, the aldehyde could remain protected as the acetal if desired.

This reaction has rarely been utilized although Suzuki had first demonstrated its use in a single coupling with a pyrone triflate several years ago.[15,16] With this precedent in mind, we pursued the reaction with aryl chloride **2** and were gratified to find that the coupling proceeded cleanly using $Pd(OAc)_2$ and dppf in THF at reflux to afford **8** in near quantitative yield following chromatography (98%). Alternatively, we could incorporate an acid treatment in the reaction work-up and obtain aldehyde **1** in a single pot (94% overall from **2**). It is interesting to note that the hydrolysis can be achieved under sufficiently mild conditions such that the Boc protecting group survives intact.

After studying this Suzuki–Miyaura reaction of chloride **2** with acetal **7**, a few points of interest were noted. Since the hydroboration is conducted in THF, this becomes the solvent of choice for the coupling reaction. The addition of polar solvents such as DMF did not hinder the reaction or provide any improvement. In order to achieve complete conversion of the starting aryl chloride, 1.5–2.0 equiv of borane adduct **7** were used. We thought this was due to the thermal instability of **7**; however, when the hydroboration mixture alone was heated at 65 °C for 24 h and then subjected to the coupling, no reduction in yield was noted. A slight excess of olefin **6** was charged to the hydroboration as residual 9-BBN led to reductive dechlorination of the starting material. Even though the Heck reaction of acrolein acetals has been reported,[17] excess olefin did not lead to by-products in our case.

Most of our work was conducted using the dppf ligand in conjunction with $Pd(OAc)_2$ and we frequently observed an induction period in initiation of the reaction. Premixing of the $Pd(OAc)_2$ and dppf failed to accelerate the reaction although others have noted that

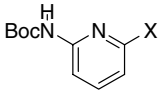
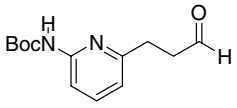
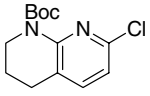
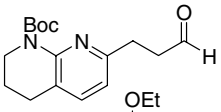
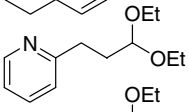
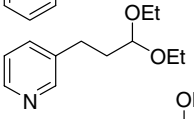
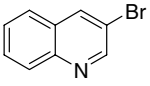
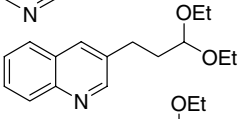
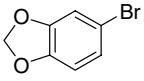
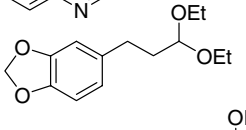
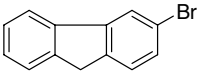
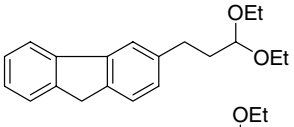
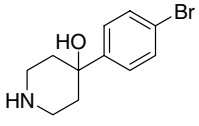
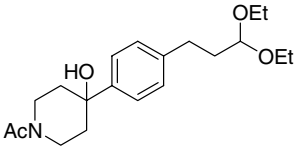
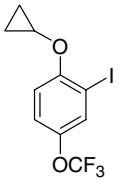
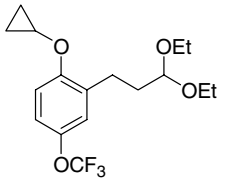
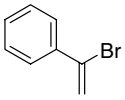
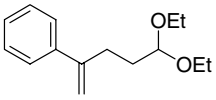


Scheme 3.

this can be beneficial.[18] More recently, we have had considerable success using the conditions highlighted by the Fu group.[19] Using $PCy_3/Pd(OAc)_2$ in conjunction with added water provided a significantly more active catalyst. These changes not only shortened the reaction times but also allowed a reduction in the palladium loading to 1% while maintaining high yields (>90%) of compound **1**.

Due to the marked benefit of this coupling compared to the Heck reaction with allyl alcohol, we examined its utility with a variety of substrates (Table 1). Yields in most cases are given for both dppf and PCy_3 conditions. The reaction of Boc-protected pyridine **3** afforded the expected aldehyde **10** in reasonable yield using the dppf ligand after incorporating the hydrolysis step into the work-up (entry 1). As we had found with compound **2**, in our hands, substrate **3** also failed in the Heck reaction with allyl alcohol. In this system, there is little advantage to using the analogous bromide **9** as a similar yield was achieved (76% yield, entry 2). However, resorting to the PCy_3 ligand with chloride **3**, the yield was considerably better (90%). It appears likely that the benefit of the PCy_3 catalyst system is most evident when coupling aryl chlorides (see entries 1, 3, and 4). The lower yields for entries 4 and 5 may be due, in part, to difficulties in the

Table 1. Suzuki coupling of borane **7** with representative aryl and vinyl halides

Entry	Aryl or vinyl halide	Product	Yield %[a] (dppf)	Yield %[a] (PCy_3)
				
1	**3**, X = Cl	**10**	75[b]	90[b]
2	**9**, X = Br		76[b]	—[d]
3			96[b]	97[b]
4			73	80
5			68	74
6			82	93
7			86	81
8			94	89
9			90[c]	82[c]
10			81	88
11			62	—[d]

[a] Reactions were performed using 10 mol% $Pd(OAc)_2$ with either 10 mol% dppf or 20 mol% PCy_3.
[b] Yield includes hydrolysis of the crude acetal coupling product with 2 M HCl.
[c] Yield of the isolated acetyl derivative obtained by Ac_2O/pyr treatment of the crude coupling mixture.
[d] Reaction not performed.

isolation and subsequent purification of the adducts. Typical aryl bromides gave good yields of the acetal products (entries 6–8). For ease of isolating the polar piperidine adduct (entry 9), the crude coupling mixture was acetylated affording the acetyl derivative in high yield. Not surprisingly, aryl iodides can also be used successfully in this reaction (entry 10). We chose this particular substrate[20] as in previous work on unrelated Pd-mediated Heck reactions this iodide had led to cyclopropyl ring opening as the major reaction pathway. Finally, reaction of α-bromostyrene afforded the desired acetal product in moderate yield (entry 11).[21]

In summary, we have demonstrated the use of borane derivative **7** in the Suzuki–Miyaura coupling with a range of aryl and vinyl halides. This coupling offers several advantages over the allyl alcohol Heck reaction, which has been used for the same transformation. The new protocol typically occurs under milder conditions and sensitive aldehydes are not produced in high temperature reaction mixtures where decomposition may occur. It is successful with relatively unreactive substrates like chloropyridines and, unlike the Heck reaction, there is little optimization of phosphine ligand or additives required. Finally, the issue of poor regioselectivity that is inherent to the Heck reaction of allyl alcohol is circumvented in this case.

Acknowledgements

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21. The reaction in entry 1 is typical: acrolein diethyl acetal (**6**) (2.08 g, 16 mmol) was added to a THF solution of 9-BBN (30 mL of 0.5 M, 15 mmol) and the reaction stirred at 20 °C for 12 h. The resulting solution of borane adduct **7** was added to a slurry of **3** (1.71 g, 7.50 mmol), $Pd(OAc)_2$ (0.17 g, 0.75 mmol), PCy_3 (0.42 g, 1.5 mmol), K_2CO_3 (2.1 g, 15 mmol), and water (270 μL, 15 mmol) in THF (17 mL) and the mixture heated at reflux for 13 h under a nitrogen atmosphere. Water (30 mL) was then added to the reaction mixture and the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine (30 mL) and concentrated in vacuo to afford the crude acetal. This material was dissolved in isopropyl acetate (30 mL) and treated with 2 M HCl (18 mL, 36 mmol) at 0 °C for 2.5 h. The organic layer was then separated and extracted with water (3 × 15 mL). The combined aqueous extracts were basified using 10% K_2CO_3 and extracted with EtOAc (4 × 30 mL). The combined EtOAc layers were washed with brine (30 mL) dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude oil by silica gel chromatography (hexanes–EtOAc, 75:25) afforded aldehyde **10** as a white solid (1.68 g, 90%): mp 70.5–72.5 °C; IR (Nujol mull): 1706, 3323 cm^{-1}; ^1H NMR (250 MHz, d_2-CH_2Cl_2): δ 9.73 (t, $J = 1.3$ Hz, 1H), 7.66 (t, $J = 7.9$ Hz, 1H), 7.48 (t, $J = 7.9$ Hz, 1H), 7.22 (s, br, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 2.91 (t, $J = 6.9$ Hz, 2H), 2.72 (m, $J = 6.9$ and 1.3 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (62.5 MHz, d_2-CH_2Cl_2): δ 202.1, 158.8, 152.5, 151.8, 138.8, 117.7, 109.6, 81.1, 42.6, 30.2, 28.3; Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.10; H, 7.27; N, 10.97.