

# Ligand-Free Suzuki Coupling of Arylboronic Acids with Methyl (*E*)-4-Bromobut-2-enoate: Synthesis of Unconventional Cores of HIV-1 Protease Inhibitors

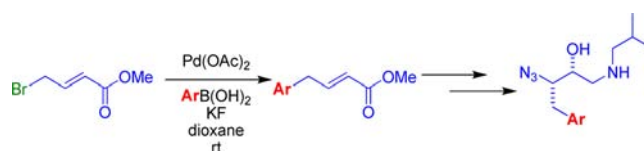
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## ABSTRACT



An effective ligand-free Suzuki coupling protocol to unite methyl (*E*)-4-bromobut-2-enoate with several arylboronic acids has been accomplished. Thus, a number of variously functionalized methyl 4-arylcrotonates have been achieved in high to excellent yields under mild conditions. This method enables the preparation of diverse aryl-substituted cores of HIV-1 protease inhibitors.

Metal-catalyzed cross-couplings are powerful tools for organic chemists to form new C–C bonds.<sup>1</sup> Among these cross-coupling processes, the Suzuki reaction<sup>2</sup> is one of the most attractive because of the ready availability of organoboron compounds, their high compatibility toward numerous functional groups, air-stability, and lower toxicity than other organometallic species. Over the past decade, impressive enhancements have been achieved through the potential to unite different electrophiles with organoboron reagents as the nucleophilic component. Palladium-catalyzed couplings of alkynyl, aryl, alkenyl, and alkyl electrophiles with boronic acids have been widely described in the literature. Nevertheless, protocols involving allylic halides have not been extensively explored,<sup>3</sup> although these are extremely useful for the concomitant formation of new C–C bonds and the introduction of allylic moieties to target compounds.

(1) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

(2) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723–6737.

(3) (a) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396–2397. (b) Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. *Org. Lett.* **2005**, *7*, 1829–1832. (c) Alacid, E.; Nájera, C. *J. Organomet. Chem.* **2009**, *694*, 1658–1665.

In our continuous pursuit of new HIV-1 protease inhibitors (PIs) bearing unconventional P1-ligands,<sup>4</sup> we have speculated a convenient synthetic route to introduce diversity into the common hydroxyethylamino core<sup>5</sup> present in several approved PIs (e.g., darunavir<sup>6</sup>) (Scheme 1). In a simple retrosynthetic approach, variously functionalized aromatic groups can be incorporated by Suzuki coupling between an activated C(sp<sup>3</sup>) bromide (allylic electrophile) and an array of arylboronic acids to furnish methyl 4-arylcrotonates (**2**).

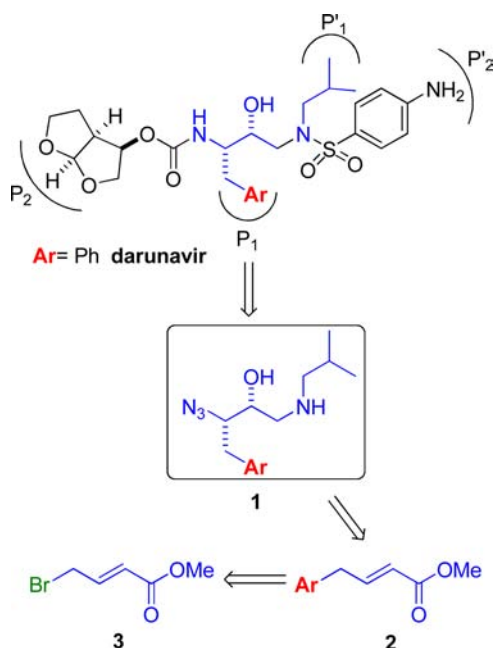
Some strategies to prepare (*E*)-4-arylbut-2-enoates in moderate to good yield imply a new C=C bond formation

(4) (a) Chiumminto, L.; Funicello, M.; Lupattelli, P.; Tramutola, F.; Campaner, P. *Tetrahedron* **2009**, *65*, 5984–5989. (b) Bonini, C.; Chiumminto, L.; De Bonis, M.; Di Blasio, N.; Funicello, M.; Lupattelli, P.; Pandolfo, R.; Tramutola, F.; Berti, F. *J. Med. Chem.* **2010**, *53*, 1451–1457. (c) Chiumminto, L.; Funicello, M.; Lupattelli, P.; Tramutola, F.; Berti, F.; Marino-Merlo, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2948–2950.

(5) Although (2*S*,3*S*)-1,2-epoxy-3-(Boc-amino)-4-phenylbutane, a common key intermediate in the synthesis of several PIs, is commercially available, this is expensive and limited only to the incorporation of a phenyl as the P1 ligand.

(6) Ghosh, A. K.; Anderson, D. D.; Weber, I. T.; Mitsuya, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1778–1802.

**Scheme 1.** Retrosynthesis of PIs Bearing Disparate Ar Groups as P1 Ligands



by Wittig-like reaction,<sup>7</sup> modified Julia olefination,<sup>8</sup> or alkene cross-metathesis.<sup>9</sup> However, some limitations remain: (1) required starting materials are not readily accessible and (2) some functional groups are not tolerated. Furthermore, to date, only very few examples of cross-coupling based synthesis of (*E*)-4-arylbut-2-enoates have been described. Besides the Heck reaction, which in this case does not afford high regio- and sometimes stereoselectivity,<sup>10</sup> only one effective example has been accomplished: a low-valent iron complex catalyzed reaction of phenylmagnesium bromide with methyl 4-bromocrotonate.<sup>11</sup> A palladium-catalyzed Stille coupling of (*Z*)-vinylstannyl carboxylate with benzyl bromide has been reported as well, providing the product with *cis* stereochemistry.<sup>12</sup>

Considering the synthetic potential of the arylation of 4-bromocrotonates and the lack of systematic studies on these electrophiles, we have been motivated to investigate this specific process to accomplish a general high-yield Suzuki protocol that furnishes (*E*)-4-arylbut-2-enoates.<sup>13</sup>

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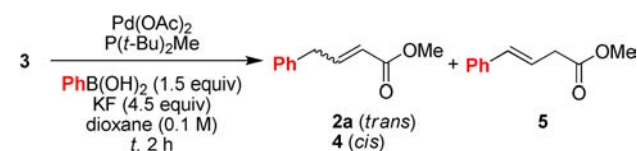
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(13) A first attempt of Suzuki reaction between ethyl 4-bromocrotonate and thiénylboronic acids has been described in: Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M.; Lupattelli, P.; Pandolfo, R. *Tetrahedron: Asymmetry* **2006**, *17*, 2919–2924.

**Table 1.** Effect of Various Reaction Parameters on the Efficiency of a Suzuki Cross-Coupling



entry	Pd(OAc) <sub>2</sub> (mol %)	P( <i>t</i> -Bu) <sub>2</sub> Me (mol %)	temp (°C)	ratio 2a:4:5 <sup>a</sup>	yield of 2a <sup>a</sup> (%)
1	5	20	70	74:23:3	74
2	5	15	70	74:23:3	74
3	5	10	70	74:23:3	74
4	5	5	70	95:5:0	95
5	5	–	70	95:5:0	95
6	5	–	50	97:3:0	97
7	5	–	rt	98:2:0	98
8	5	10	rt	–	–
9	2.5	–	rt	98:2:0	98 <sup>b</sup>
10	1	–	rt	98:2:0	75
11	–	–	rt	–	–
12 <sup>c</sup>	2.5	–	rt	98:2:0	80
13 <sup>d</sup>	2.5	–	rt	–	–

<sup>a</sup> Determined by GC analysis versus a calibrated internal standard (average of two experiments). <sup>b</sup> Isolated yield (average of two experiments). <sup>c</sup> 1.1 equiv of phenylboronic acid was employed. <sup>d</sup> No KF.

Thus, we first considered the Suzuki cross-coupling between methyl 4-bromocrotonate and phenylboronic acid, and the effect of different parameters was studied (Table 1). This reaction could, in principle, proceed toward the formation of three isomers: the desired coupling product **2a**, its *cis*-stereoisomer **4**, and its regioisomer **5** whereby the double bond rearranges to the styryl position.<sup>14</sup>

As shown in Table 1, this method was significantly sensitive to the relative amount of palladium source and ligand employed in the reaction.<sup>15</sup> On the basis of reported data on alkyl bromides,<sup>16</sup> we first began by using a 2- to 4-fold excess of P(*t*-Bu)<sub>2</sub>Me with respect to Pd source: the three isomers **2a**, **4**, and **5** were always generated in the same ratio (74:23:3, entries 1–3). In contrast, when the metal/ligand ratio was decreased to 1:1 or, even, in the absence of phosphine, this reaction afforded the desired *trans*-product **2a** with high selectivity (entries 4 and 5).

The latter result was delightfully interesting and rather unexpected. Indeed, although the acceleration observed in phosphine-free palladium-catalyzed Suzuki cross-couplings is well-known,<sup>17</sup> the positive effect on stereoselectivity

(14) Narahashi, H.; Shimizu, I.; Yamamoto, A. *J. Organomet. Chem.* **2008**, *693*, 283–296.

(15) For examples of cross-coupling reactions affected by the ratio of phosphine to palladium, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (b) Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y. *Org. Biomol. Chem.* **2008**, *6*, 3005–3013. (c) Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103–12105.

(16) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

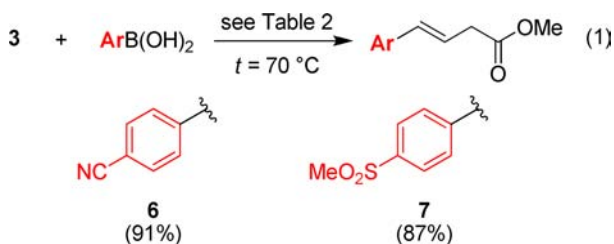
represents a novelty, particularly with allyl bromides as the electrophiles. The higher efficiency of such a ligand-free protocol was confirmed by the data obtained at lower temperatures (entries 6–8) and with lower catalyst loading, finally leading to the best conditions (entry 9).

For the Suzuki reaction illustrated in entry 9, different conditions were tested: (1) the use of toluene, DME, THF, and DMF rather than 1,4-dioxane as the solvent, resulted in formation of the product in somewhat diminished yield (75–90%); (2) on a gram scale, the reaction proceeded in 98% yield; (3) a first attempt of a ligandless nickel-catalyzed reaction by using NiI<sub>2</sub> (5 mol %) rather than the palladium source, essentially generated no coupling product.

Lower catalyst loading or amount of boronic acid resulted in identical selectivity but lower yield (entries 10 and 12). In the absence of either Pd catalyst or base (KF), essentially no product was observed (entries 11 and 13).

To explore the scope and limitation of this method, coupling reactions between a variety of arylboronic acids and methyl 4-bromocrotonate were investigated under the optimized conditions (Table 2). Gratifyingly, this protocol tolerated a variety of common functional groups such as alkyl, ether, thioether, hydroxyl, aryl, halogen, trifluoromethyl, nitro, and aldehyde, regardless of the *ortho*-, *meta*-, or *para*-position. The intrinsic reactivity of the employed nucleophile determined the ease of this cross-coupling. Particularly, electron-rich arylboronic acids (activated nucleophiles) displayed higher reactivity than electron-deficient ones (deactivated nucleophiles). Either activated or weakly deactivated nucleophiles were shown to react successfully with methyl 4-bromocrotonate under the standard conditions (entries 2–8). The use of hindered (entry 1) and electron-deficient (entries 9–11) arylboronic acids required longer reaction times.<sup>18</sup>

More challenging deactivated nucleophiles only reacted at higher temperature but afforded the styryl regioisomers (eq 1).

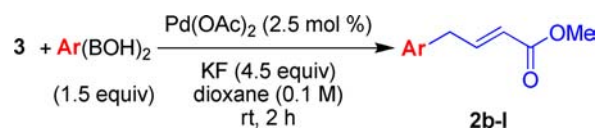


Other organoboron compounds can be utilized in this cross-coupling as well; indeed, the reaction with a boronate ester or a potassium trifluoroborate provided the coupling

(17) (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034–5037. (b) See reference 3a. (c) Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podestà, J. C. *Eur. J. Org. Chem.* **2009**, 3964–3972.

(18) Coupling products bearing electron-deficient aryl groups are more prone to isomerize to the corresponding styrene-like compounds. In this regard, reaction time was of paramount importance. Indeed, when these cross-couplings were conducted for longer than the necessary reaction time or at higher temperature, total conversion of allylbenzene products to styryl compounds occurred.

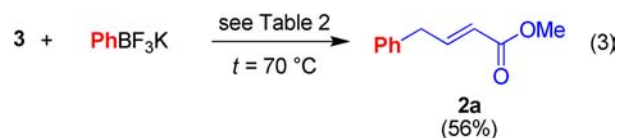
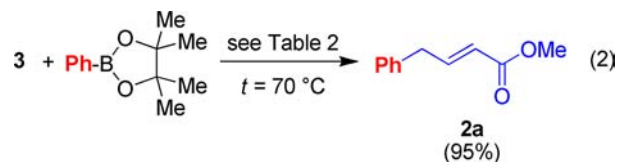
**Table 2.** Cross-Coupling of Methyl 4-Bromocrotonate with Arylboronic Acids



entry	ArB(OH) <sub>2</sub>	yield of 2 (%) <sup>a</sup>
1 <sup>b</sup>		<b>2b</b> , 96%
2		<b>2c</b> , 96%
3		<b>2d</b> , 97%
4		<b>2e</b> , 95%
5		<b>2f</b> , 94%
6		<b>2g</b> , 95%
7		<b>2h</b> , 96%
8		<b>2i</b> , 95%
9 <sup>b</sup>		<b>2j</b> , 94%
10 <sup>c</sup>		<b>2k</b> , 86%
11 <sup>b</sup>		<b>2l</b> , 84%

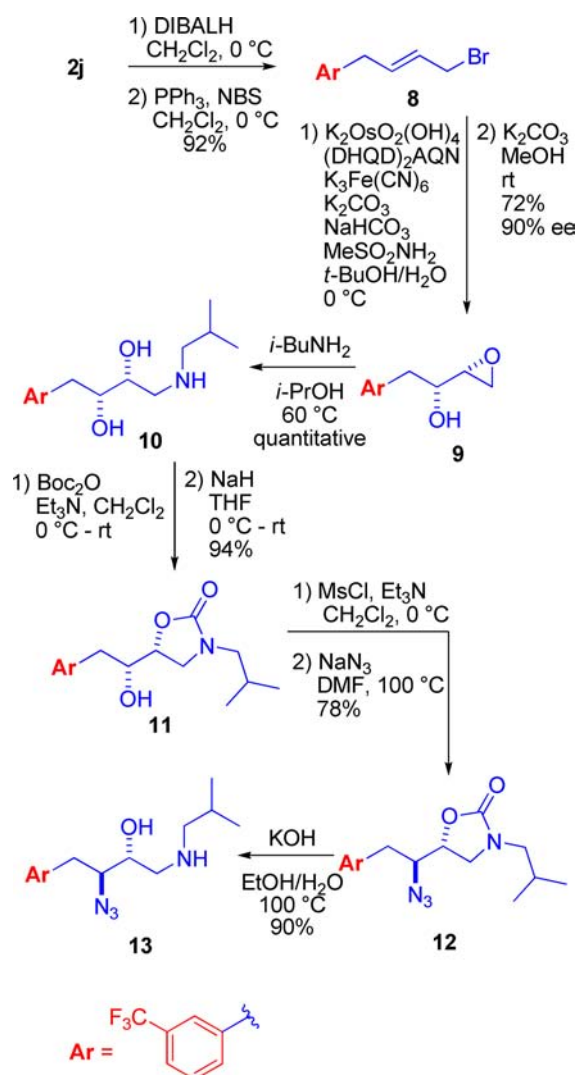
<sup>a</sup> Isolated yield (average of two experiments). <sup>b</sup> Run for 6 h. <sup>c</sup> Run for 10 h.

product in excellent or somewhat good yield, respectively (eqs 2 and 3).



Finally, we could exploit the ability to obtain an array of 4-arylcrotonates in our synthesis of the core of PIs. As an

**Scheme 2.** Synthesis of the Hydroxyethylamino Core of PIs Starting from 4-Arylcrotonate **2j**



example, we report in Scheme 2 this approach starting from cross-coupling product **2j**.

Thus  $\alpha,\beta$ -unsaturated ester **2j** was reduced by DIBALH in  $CH_2Cl_2$  to the corresponding allyl alcohol, which was subsequently transformed to allyl bromide **8** by using  $PPh_3$

(19) For an alternative synthesis of allyl bromides via cross-metathesis, see: Blanco, O. M.; Castedo, L. *Synlett* **1999**, 5, 557–558.

(20) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, 35, 448–451.

(21) The preparation of a chiral hydroxy epoxide similar to compound **9** was previously reported in: Fernandes, R. A. *Tetrahedron: Asymmetry* **2008**, 19, 15–18. However, therein,  $(DHQD)_2PHAL$  was used as the chiral ligand in the AD. In our case, those conditions afforded the desired product in only 54% yield and 80% ee.

and NBS in  $CH_2Cl_2$  in 92% yield over the two steps.<sup>19</sup> At this stage, we introduced the two stereocenters by Sharpless asymmetric dihydroxylation of compound **8**, using  $(DHQD)_2AQN$  under reported conditions,<sup>20</sup> to furnish the corresponding *syn*-bromo diol. The latter intermediate was cyclized with  $K_2CO_3$  in MeOH to chiral hydroxy epoxide **9** in 72% yield and 90% ee.<sup>21</sup> Next, the oxiranyl ring-opening reaction on **9** with *i*-BuNH<sub>2</sub> in *i*-PrOH at reflux afforded product **10** in quantitative yield. The resulting amino diol was first protected at the amino function with  $Boc_2O$ ,  $Et_3N$  in  $CH_2Cl_2$  and then, without any purification, was cyclized with NaH in THF to render the respective oxazolidin-2-one **11** in 94% yield.<sup>22</sup> It is noteworthy that the process of cyclization only affords the five-membered ring rather than the six-membered one, which indicates that the formation of the oxazolidin-2-one ring is highly preferred.<sup>23</sup> Therefore, we had the regioselective protection of the vicinal amino alcohol, whereas the adjacent free hydroxy group was prone to be activated by  $MsCl$ ,  $Et_3N$  in  $CH_2Cl_2$  and then displaced by  $NaN_3$  in DMF to furnish product **12** in 78% yield over the two steps. The latter compound represents a very attractive, highly functionalized synthon which can be used as a versatile building block. At last, deprotection of the amino alcohol moiety mediated by basic hydrolysis furnished the desired compound **13** in 90% yield.<sup>24</sup>

In conclusion, we have described effective, ligand-free, palladium-catalyzed Suzuki cross-couplings of methyl 4-bromocrotonate with arylboronic acids. It is noteworthy that this protocol is not air-sensitive and does not require special handling. Studies on the potential to drive this reaction toward the stereoselective formation of *cis*-products are ongoing in our laboratory.

Furthermore, we have shown how this reaction can be efficiently used as the first step in a high-yield enantioselective synthesis of the core of PIs incorporating diverse aromatic groups as unconventional P1-ligands.

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**Supporting Information Available.** Experimental procedures and characterization data. This material is available free of charge via Internet at <http://pubs.acs.org>

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The authors declare no competing financial interest.