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Transition-Metal-Free Stereocomplementary Cross-Coupling of Diols with Boronic Acids as Nucleophiles

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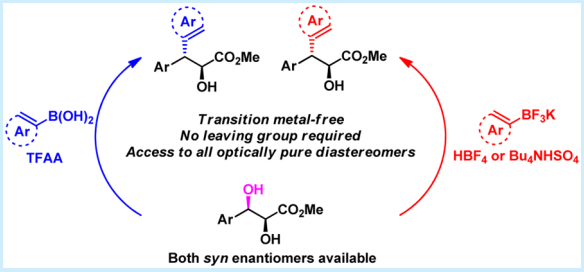
Supporting Information

ABSTRACT: The transition-metal-free diastereoselective C(sp^2)−C(sp^3) cross-coupling between unprotected diols and boronic acids or potassium organotrifluoroborates is reported. Depending on the reaction conditions, the *syn* or the *anti* reaction products are obtained in a stereocomplementary fashion. This type of coupling is developed with alkenyl-, heteroaryl- and arylboron compounds as carbon nucleophiles.

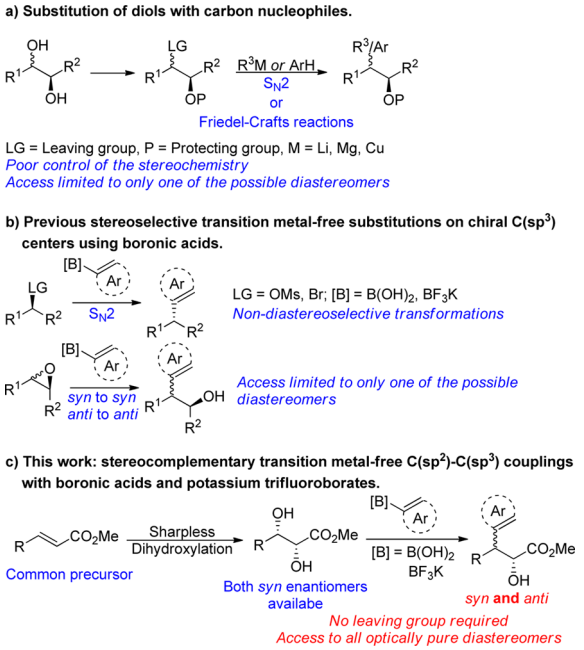


Chiral molecules that contain contiguous stereogenic centers are ubiquitous among natural and bioactive products.[1] It is frequent that the different diastereomers of a drug exhibit distinct pharmacological activities.[2] Consequently, there is a current tendency in drug discovery to study such chiral drugs in their pure diastereoisomeric and enantiomeric forms. This urges the organic synthesis community to develop versatile, stereoselective synthetic methods able to produce each of the optically pure diastereomers of a drug candidate to be tested individually.[3] Diastereoselective asymmetric reactions have been amply investigated in the literature, but most approaches are commonly limited to the synthesis of only one of the possible relative configurations.[4] The advancement in synthetic methods that allow the stereoselective synthesis of every diastereomer of a given compound from a common starting material is currently a challenging research topic.

We have focused our attention on the functionalization of chiral diols by substitution of one of the hydroxyl groups with a carbon nucleophile (Scheme 1). Both enantiomers of optically pure *syn* or *anti* diols are readily accessible from a common *cis* or *trans* alkene by the Sharpless asymmetric dihydroxylation reaction with the "AD-mix-α" or "AD-mix-β" reagents.[5] Nucleophilic substitutions on diols using conventional organometallics such as organolithiums, organomagnesiums, or cuprates are not frequent and require previous transformation of the reacting hydroxyl group into a good leaving group.[6] Some Friedel−Crafts-type reactions have also been used for the installation of aryl groups,[7] but their scope is limited to electron-rich aryls as nucleophiles, and their site-selectivity depends on the electronic demand of the substituents in the ring. Most importantly, either of these transformations affords, at best, only one of the possible diastereomers of the final product.

Instead, we have considered the use of alkenyl-, aryl-, and heteroarylboronic acids and potassium organotrifluoroborates as nucleophiles in the stereocontrolled transition metal-free C-(sp^2)−C(sp^3) cross-couplings with chiral secondary benzylic unprotected alcohols. Making use of enantiomerically pure *syn* diols as starting materials, the reaction leads to the stereodivergent synthesis of every diastereomer of β,β-disubstituted α-hydroxyesters.

Scheme 1. Stereocomplementary C(sp^2)−C(sp^3) Cross-Coupling



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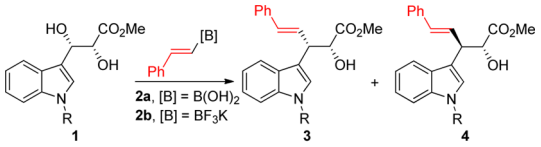
Boronic acids and potassium organotrifluoroborates are readily available reagents for organic synthesis.[8] In contrast to other organometallic carbon nucleophiles such as organolithiums, organomagnesiums, or cuprates, they are bench-stable reagents that can be used without the need for protection from humidity and are compatible with functional groups such as alcohols, which normally have to be protected when working with conventional organometallics. Because of the low nucleophilicity of alkenyl/arylboronic acids and organotrifluoroborates,[9] most of the reactions in which they participate have been traditionally catalyzed by transition metals. Even so, they are nucleophilic enough to take part in some transition metal-free additions to trigonal C(sp^2) centers, such as Mannich reactions, conjugate additions, or reactions with oxonium cations.[10] Extending the scope of synthetically useful reactions using boronic acids and their derivatives under transition-metal-free conditions is a matter of current interest. The nucleophilic ability of C(sp^2)−B compounds toward chiral C(sp^3) centers has been little considered,[11] and to the best of our knowledge, there are no precedents of diastereoselective transformations as the one reported herein. Also, there is no metal-catalyzed counterpart of this kind of stereoselective process.

We began our research by considering the stereodivergent synthesis of tryptophols.[12] These are indoles which bear a hydroxyethyl side chain attached at position C-3, which may be α- or β-substituted. Tryptophol and its derivatives have been isolated from various natural sources, and some of these compounds exhibit important biological activities. Thus, enantiopure *syn* diols **1**[13] were made to react with (*E*)-2-phenylvinylboronic acid (**2a**) or the corresponding potassium trifluoroborate (**2b**) under various conditions (Table 1).

Table 1. Metal-Free Cross-Coupling between Chiral Indolediols 1 and (*E*)-2-Phenylvinylboronic acid (2a) or Potassium (*E*)-2-Phenylvinylboronate (2b)



1a, R = CO_2Me
1b, R = Boc
1c, R = Bn

3a, **4a**, R = CO_2Me
3b, **4b**, R = H
3c, **4c**, R = Bn

entry	1	reaction conditions	3/4 (ratio)[a]	yield[b] (%)
1	**1a**	**2a**, TFAA, CH_2Cl_2[c]	**3a**/**4a** (66:34)	30
2	**1b**	**2a**, TFAA, CH_2Cl_2[c]	**3b**/**4b** (81:19)	34
3	**1c**	**2a**, TFAA, CH_2Cl_2[c]	**3c**/**4c** (98:02)	84
4	**1c**	**2b**, HBF_4, CH_3CN[d]	**3c**/**4c** (17:83)	95
5	**1b**	**2b**, HBF_4, CH_3CN[d]	**3b**/**4b** (10:90)	81
6	**1c**	**2b**, Bu_4NHSO_4, CH_2Cl_2[e]	**3c**/**4c** (06:94)	73

[a]Determined by ^{1}H NMR (300 MHz). [b]Combined isolated yields. [c]TFAA (0.5 equiv), rt, 15 min. [d]HBF_4·OEt_2 (1.5 equiv), −10 °C, 15 min. [e]Bu_4NHSO_4 (0.3 equiv), rt, 24−48 h.

For the reactions with (*E*)-2-phenylvinylboronic acid (**2a**), we chose conditions which in our hands had already proven of use in conjugate addition reactions and in ring-opening of epoxides or cyclopropanes.[11] These consisted of the promotion of the nucleophilic addition by using trifluoroacetic anhydride (TFAA) in CH_2Cl_2. When the reaction was carried out using a methyl carbamate as protecting group of the indole nitrogen atom (**1a**), we observed replacement of the benzylic hydroxyl group by (*E*)-phenylvinyl with poor diastereoselectivity and low yield (entry 1). Replacement of the methyl carbamate protecting group with Boc (**1b**) gave rise to an increase in diastereoselectivity and yield (entry 2), but the coupling products (**3b** and **4b**) were obtained N-deprotected. When Bn was used as protecting group (**1c**), compound **3c** was formed in good yield and high diastereoselectivity (entry 3) with retention of the configuration at the reacting carbon.[14] In search for a switch in stereoselectivity, we carried out the reaction of indole **1c** with potassium (*E*)-2-phenylvinyltrifluoroborate (**2b**) under HBF_4 promotion (entry 4). This gave rise to the desired reversal of the diastereoselectivity, and compound **4c** was formed exclusively and in good yield with inversion of the configuration at the reacting center.[14] When these conditions were applied to indole **1b**, the coupling reaction took place again together with N-deprotection (entry 5). Finally, high diastereoselectivity in favor of **4c** was observed when the reaction of **1c** with **2b** was promoted by Bu_4NHSO_4, although the yield was slightly lower (entry 6). Under the optimized conditions, the reaction of **2a** (entry 3) and **2b** (entry 6) with the enantiomer of **1c**[15] led to the enantiomers of **3c** or **4c**. Therefore, as exemplified for **1c**, the overall procedure permits the synthesis of all four diastereomers of the final tryptophols in a stereocomplementary approach.

Next, we looked into the scope of this metal-free cross-coupling reaction with regard to the boronic acid component (Figure 1). A

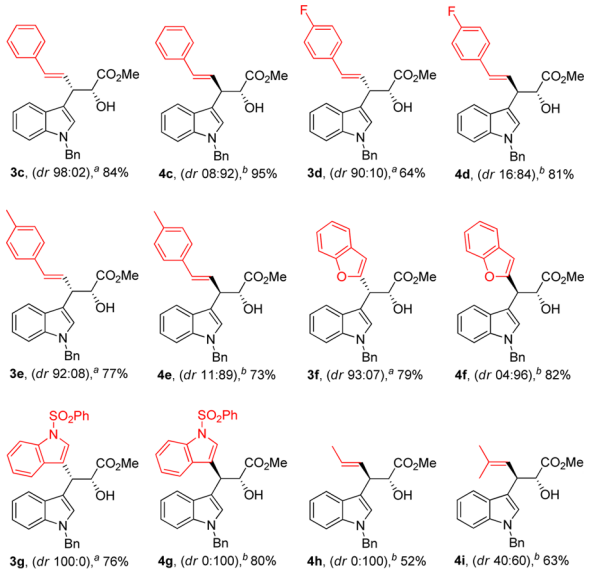


Figure 1. Cross-coupling between **1c** and alkenyl/hetarylboronic acids or potassium trifluoroborates. The diastereomeric ratios were determined by ^{1}H NMR (300 MHz). Combined isolated yields are given. Key: (a) $RB(OH)_2$ (1.25 equiv), TFAA (0.5 equiv), rt, 15 min; (b) RBF_3K (1.5 equiv), Bu_4NHSO_4 (0.3 equiv), rt, 24−48 h.

variety of tryptophols were synthesized in moderate to good yields upon reaction of **1c** with styryl- and hetarylboronic acids or potassium trifluoroborates. Compounds **3c−g** were obtained as the major products upon reaction with boronic acids in the presence of TFAA, whereas compounds **4c−g** were obtained as the major reaction products upon reaction with potassium trifluoroborates in the presence of Bu_4NHSO_4. We found better stereoselectivity in the reactions with boronic acids (formation of isomers **3**) in comparison to the reactions where trifluoroborates were involved (formation of isomers **4**), although it is worth mentioning that separation of the minor diastereomers could be carried out in most cases by column chromatography, which is

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important from a preparative standpoint. However, simple alkenylboronic acids failed to afford the cross-coupling products **3h** and **3i** by promotion with TFAA. On the other hand, the corresponding trifluoroborates reacted smoothly under Bu_4NHSO_4 promotion to give the corresponding isomers **4h** and **4i**, albeit in lower yields than the styryl counterparts.

In contrast to our previous observations with alkenyl and hetarylboronic acids and/or trifluoroborates, arylboronic acids did not afford any substitution products under TFAA or Bu_4NHSO_4 promotion, and only the transformation of indoles **1** into **5** was detected.[16] This behavior of the aryl derivatives was not completely surprising, as it is frequently the case that arylboronic compounds react much slower than the alkenyl and heteraryl counterparts in other types of metal-free couplings as well.[10] Based on observations carried out in the monitoring of the reaction between **1c** and **2c** with TFAA,[14] we devised an alternative protocol to encourage the metal-free cross-coupling reactions between diols **1** and arylboronic acids. This consisted of the previous formation of a transient cyclic boronate ester **6** between the arylboronic acids and diols **1** (Figure 2). In this way,

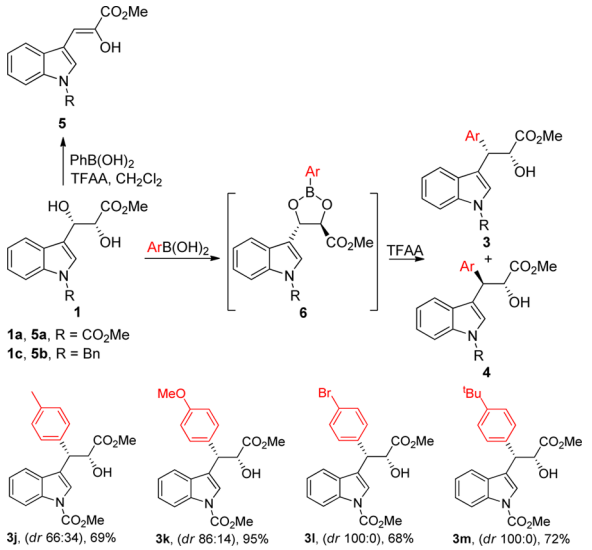


Figure 2. Cross-coupling between **1a** and arylboronic acids. The diastereomeric ratios have been determined by ^{1}H NMR (300 MHz). Combined isolated yields are given. Conditions: (1) **1a** (1.0 equiv), $ArB(OH)_2$ (1.0 equiv), 15 min, rt; (2) TFAA (0.5 equiv), rt, 15 min.

the decomposition of **1** into **5** was prevented, and intramolecular transfer of the aryl moiety was possible upon treatment with TFAA to give compounds **3j**−**m**. Best results were obtained using diol **1a** as starting material, which is substituted with an electron-withdrawing group on the indole nitrogen.

In addition, we have looked into the scope of this metal-free cross-coupling reaction with regard to the diol component. As shown in Figure 3, the reaction was also useful for the stereocomplementary synthesis of α-hydroxyesters other than tryptophols, provided the starting diol is endowed with an electron-rich (hetero)aromatic ring.

Besides their pharmacological significance, tryptophols are also versatile platforms for further chemical elaborations (Scheme 2).[17] As an example of synthetic application, we have developed the transformation of **4f** into the β,β-diaryl-α-aminoester **10**. This type of β,β-diarylalanine derivatives constitute synthetically challenging structural motifs, which are important as pharmacophores and as intermediates in the synthesis of natural products.[18]

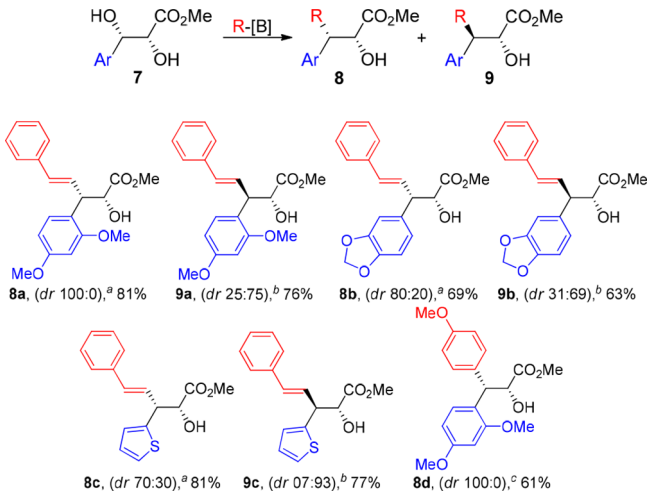
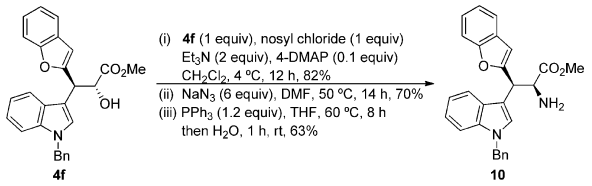


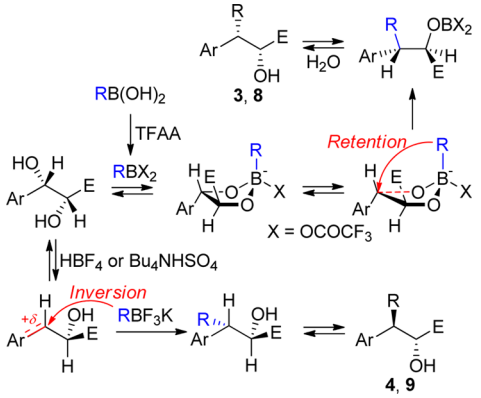
Figure 3. Cross-coupling between chiral diols **7** and boronic acids or potassium trifluoroborates. The diastereomeric ratios have been determined by ^{1}H NMR (300 MHz). Combined isolated yields are given. Key: (a) $RB(OH)_2$ (1.25 equiv), TFAA (0.5 equiv), rt, 15 min; (b) RBF_3K (1.5 equiv), Bu_4NHSO_4 (0.3 equiv), rt, 24−48 h; (c) (1) **1a** (1.0 equiv), $ArB(OH)_2$ (1.0 equiv), 15 min, rt; (2) TFAA (0.5 equiv), rt, 15 min.

Scheme 2. Transformation of Tryptophol 4f into the β,β-Diaryl-α-aminoester 10



On the basis of the above preliminary results and observations, the proposed mechanism is illustrated in Scheme 3. Interaction of

Scheme 3. Plausible Reaction Course[a]



[a]Ar = electron-rich (hetero)aromatic ring, E = ester group, X = OH, $OCOCF_3$.

a boronic acid with TFAA can give a Lewis acidic mono- or diacylboronate (RBX_2, X = OH, $OCOCF_3$),[19] which can coordinate the diol moiety to give a reactive boronate species (X = $COCF_3$). Assisted by the electron-rich (het)aryl group, incipient carbocation formation would trigger the operation of an S_Ni-type mechanism, which would lead to the $C(sp^2)-C(sp^3)$

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coupling product with retention of the original configuration at the benzylic carbon.

On the other hand, the presence of acid (HBF_4 or Bu_4NHSO_4) would give rise to the formation of a benzylic carbocation intermediate.[11] Direct addition of a potassium organotrifluoroborate from the least hindered face (*Re* face)[20,21] would explain the major formation of the diastereomer with inversion of the original configuration at the benzylic carbon.[22]

In conclusion, we have developed for the first time the transition metal-free, $C(sp^2)-C(sp^3)$, diastereoselective cross coupling between unprotected *syn* diols and alkenyl-, hetaryl-, and arylboronic acids or potassium organotrifluoroborates. By using boronic acids in the presence of TFAA, the reaction takes place with retention of configuration, whereas the use of potassium organotrifluoroborates and HBF_4 favors formation of the reaction products with inversion of configuration at the benzylic carbon. Given that the starting *syn* diols are easily obtained in either optically pure form by the Sharpless dihydroxylation of alkenes, the method provides all four diastereomers of the coupling products in a stereocomplementary approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03192.

Full experimental details, synthesis of the starting materials, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(21) Trifluoroborates are nucleophilic enough to transfer their organic backbone to electrophilic centers directly without the need of coordination. See, for example: Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438. See also ref 11.

(22) Although oxonium stabilization of the benzylic carbocation intermediate is possible, we have previously demonstrated (ref 11a) that epoxides react with organotrifluoroboronic acids under TFAA promotion via formation of a B-unsaturated RBF_2 species, following a borderline S_Ni mechanism with inversion of the configuration. Reaction via the epoxide would require coordination of an unsaturated boron species to the oxygen of the epoxide. This is unlikely to happen under the present reaction conditions (RBF_3K, HBF_4, or Bu_4NHSO_4).

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