Asymmetric Catalysis

Enantioselective Suzuki Reactions: Catalytic Asymmetric Synthesis of Compounds Containing Quaternary Carbon Centers**

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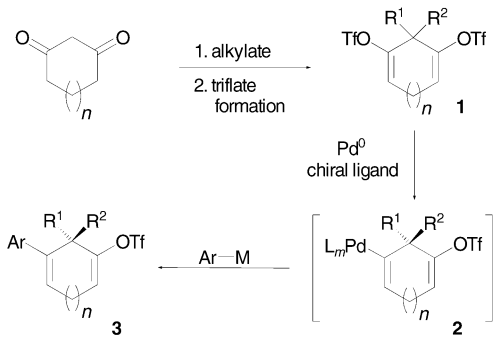
Palladium-catalyzed coupling reactions are some of the most widely used and reliable transformations available to organic chemists, and it is therefore not surprising that the efforts taken to adapt these key transformations to asymmetric processes are ongoing.[1] The use of enantiomerically pure palladium catalysts in inter- and intramolecular Heck reactions is well established and has been applied to a number of successful total syntheses.[2] The systems studied in Heck reactions generally involve carbon–carbon double bond transposition, thus resulting in the stereoselective formation of a new sp^3 center. The development of enantioselective cross-coupling reactions, such as Suzuki and Stille couplings, is more complex, in that generally the reactions result in the union of two sp^2 centers with no stereogenic sp^3 centers being produced. An elegant solution, reported recently by the research groups of both Buchwald and Cammidge, is to use Suzuki coupling reactions to produce axially chiral systems.[3–5] Hayashi et al. have developed a metal-catalyzed asymmetric biaryl synthesis; a desymmetrization approach was employed to allow palladium- and nickel-catalyzed enantioselective Kumada couplings to generate axially chiral systems with high selectivities.[6] A similar approach has also been employed to prepare systems containing planar chirality.[7] Herein, we utilize a desymmetrization strategy to detail the first report on the intermolecular enantioselective Suzuki couplings that produce compounds containing stereodefined sp^3 carbon centers.[8]

An important consideration with desymmetrization strategies is that the *meso*- or the achiral substrates are readily available and do not require laborious synthetic sequences.[9] For this reason we were drawn to the use of ditriflates **1**, derived from the corresponding cyclic 1,3-diketones, as attractive and readily available desymmetrization substrates (Scheme 1). We reasoned that the reaction of the triflates



Scheme 1. Desymmetrization-based enantioselective palladium couplings. Tf = trifluoromethanesulfonyl.

such as **1** with a chiral palladium catalyst should allow selective oxidative addition to produce enantiomerically enriched vinyl–palladium species **2**. Coupling of intermediate **2** with a nucleophilic partner should deliver the enantiomerically enriched desymmetrized products **3** containing a defined quaternary stereocenter. Intermediates similar to **2** are common in many cross-coupling processes and variation in the coupling partner should allow a range of enantioselective palladium-catalyzed coupling reactions to be developed. The wide availability, low toxicity, and good tolerance towards oxygen and water of boronic acids and esters prompted us to focus our initial study on the development of an enantioselective Suzuki reaction.[10]

We focused on the coupling of a five-membered ditriflate **1a** and boronic acid **4** as a platform to evaluate conditions for the proposed Suzuki couplings.[11,12] Experiments revealed that the optimal catalyst for this coupling was generated from MeO–MOP (MOP = (diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl) and $Pd(OAc)_2$ using dioxane as the reaction solvent (Scheme 2).[13] Under these conditions, the coupled product could be obtained with 77% *ee*.

With optimized conditions for the selective union of **1a** and **4** in hand, we further explored the tolerance of the process towards a range of boronic acids (Table 1).[15] Both the *para*- and the *meta*-substituted acetylbenzene boronic

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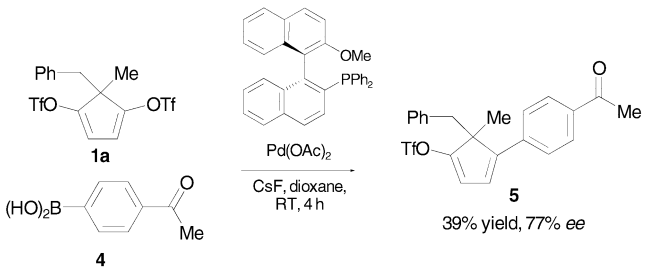
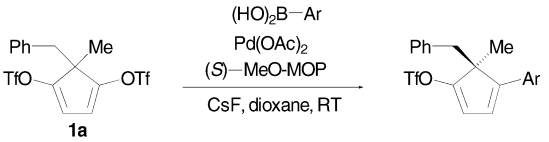


Scheme 2. Desymmetrization of the ditriflate **1a**.

Table 1: Enantioselective Suzuki coupling of the ditriflate **1a** with representative boronic acids.[a]

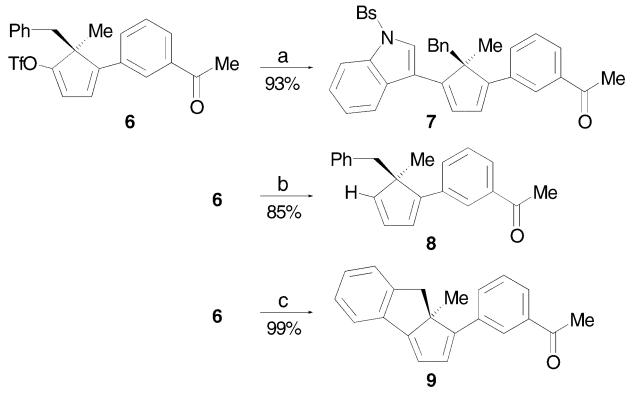


entry	Ar	Yield [%][b]	*ee* [%][c]
1	4-$C_6H_5C(O)Me$	46	77
2	3-$C_6H_5C(O)Me$	51	86
3	2-$C_6H_5C(O)Me$	< 5	–
4	4-C_6H_5CHO	47	73[d]
5	3-C_6H_5CHO	57	80[d]
6	2-C_6H_5CHO	41	82
7	4-C_6H_5-OH	43	74
8	3-furyl	53	72
9	3-*N*-Bs-indolyl[e]	66	85

[a] For all the reactions: 10 mol% Pd, 11 mol% ligand, 2.0 equiv base, 2.0 equiv boronic acid. [b] Yield of the isolated pure material. [c] Determined by chiral HPLC analysis using a Chiracel OD, OA, or OJ column. [d] *ee* values were determined (chiral HPLC) on a derivative, see Supporting Information for details. [e] Bs = benzenesulfonyl.

acids performed well, and provided the coupled products in 77 and 86% *ee*, respectively (entries 1 and 2). However, the corresponding *ortho*-substituted boronic acid displayed poor reactivity, presumably because of steric factors (entry 3). All the three positional isomers of formylbenzene boronic acid performed well (entries 4–6). The hydroxy functionality is compatible with the reaction conditions, thus allowing 4-hydroxybenzene boronic acid to deliver the product with 74% *ee* (entry 7). Finally, heterocyclic boronic acids are also tolerated well, with 3-furyl- and *N*-phenylsulfonyl-3-indole boronic acids providing the coupled products with enantioselectivities of 72 and 85%, respectively (entries 8 and 9). The enantiopurity of the products can be improved by simple recrystallization. For example, the enantioselectivity of the material obtained in entry 1 can be increased from 77 to 97% *ee* by a single recrystallization from a dichloromethane/hexane mixture (31% yield). The relatively close enantioselectivities obtained over a range of boronic acids are consistent with the oxidative addition being the enantiodetermining step; the variations observed are most likely as a consequence of differing reactivities between the boronic acids. The moderate to good yields obtained are a reflection on the catalyst's lifetime, with starting material (15%–25%) being recovered in all cases.

The enantioselective synthesis of quaternary carbon centers remains a considerable challenge;[16] the presence of such centers in the monocoupled products, obtained above, together with the remaining triflate group results in these compounds being useful synthetic intermediates. To demonstrate their utility we elaborated the remaining triflate functionality by a series of palladium-catalyzed reactions (Scheme 3). Monotriflate **6** was initially subjected to a second



Scheme 3. Functionalization of the monotriflate **6**. Reagents: a) KOH, *N*-phenylsulfonyl-3-indoleboronic acid, $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), THF, room temperature, 1 h; b) $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), NBu_3, HCO_2H, DMF, 60°C, 1 h; c) $Pd(OAc)_2$ (15 mol%), PPh_3 (30 mol%), NBu_3, DMF, 60°C, 1 h. Bs = benzenesulfonyl. Bn = benzyl

Suzuki coupling to provide bisaryl **7** in 93% yield. The triflate functionality present in **6** could also undergo palladium-catalyzed reduction (HCO_2H, NBu_3) to yield alkene **8** in 85% yield. Finally, the triflate functionality of **6** could be exploited in an intramolecular C–H coupling procedure to deliver tricylic **9** in quantitative yields.[17]

In conclusion, we have demonstrated that the use of a desymmetrization strategy allows highly enantioselective Suzuki coupling reactions that can deliver compounds containing stereodefined quaternary carbon centers. The process can tolerate a variety of functionalized boronic acids and also delivers products containing vinyl triflate units that can be functionalized by a range of palladium-catalyzed reactions. The enantioselectivities obtained are good and represent the highest that have been achieved for a Suzuki coupling in which stereogenic carbon centers are created.

Experimental Section

Dry degassed 1,4-dioxane (2 mL) was added to a mixture of ditriflate **1a** (93.20 mg, 0.20 mmol), the relevant boronic acid (0.40 mmol), $Pd(OAc)_2$ (4.50 mg, 0.02 mmol, 10 mol%), (*S*)-MeO–MOP (10.30 mg, 0.022 mmol, 10 mol%), and cesium fluoride (91.40 mg, 0.60 mmol). The reaction mixture was stirred for 6–10 h at room temperature. EtOAc (10 mL) and water (8 mL) were added and the aqueous layer was extracted using EtOAc (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 1–40% diethyl ether:hexane) to give the monotri-

flate products. See the Supporting Information for complete data for all novel compounds.

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