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Diastereoselective synthesis of tetrahydroquinolines via a palladium-catalyzed Heck–Suzuki cascade reaction

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ABSTRACT

A method for the diastereoselective synthesis of tetrahydroquinolines via a palladium-catalyzed Suzuki terminated Heck reaction is described. The reaction provides access to tetrahydroquinolines containing both quaternary and tertiary stereocenters. Ligand effects, a rationale for the high level of diastereoselectivity, and a mechanistic hypothesis are discussed.

In the course of a recent medicinal chemistry program we became interested in the synthesis of tetrahydroquinolines (THQs) containing a quaternary stereocenter at C-4 and an aryl group at C-2. It was envisioned that these structures may be constructed from a palladium-catalyzed intramolecular insertion into a 2,2-disubstituted olefin in which the nascent alkyl-palladium(II) intermediate would be intercepted by transmetallation with an aryl boronic acid resulting in an alkyl-Suzuki coupling. Formally, this could be thought of as a Heck/Suzuki cascade (Scheme 1). Previously, this strategy has been applied to the synthesis of a variety of heterocycles and carbocycles.[1,2] However, diastereoselective variants and application of this transformation to the synthesis of THQs are limited. Herein, efforts toward this goal are described.

The reaction in Table 1 was investigated to test the feasibility of the strategy outlined above. Because $Pd_2(dba)_3$/P(*t*-Bu)$_3$ is known to be an excellent catalyst for both Heck[3] and Suzuki[4] couplings, the initial experiments were performed with this system in combination with K_3PO_4 as base. Gratifyingly, these conditions afforded the THQ in excellent yield and diastereoselectivity (Table 1, entry 1). The reaction also proceeds under anhydrous conditions, which may be of use when performing couplings with base labile protecting groups (Table 1, entry 2). A ligand is required for the coupling, but the success of the reaction is not dependent upon the use of P(*t*-Bu)$_3$ (Table 1, entry 3). Other ligands such as X-PHOS, PCy_3, BINAP, and PPh_3 are also effective, but in most cases deliver the THQ product with inferior levels of diastereoselectivity.[5] The diastereoselectivity appears to decline as the cone angle of the phosphine ligand decreases.[6] Finally, substrate modifications have a profound impact on the course of the reaction. Arylchlorides do not react under the optimized conditions (Table 1, entry 8). If a secondary amine (*N*-H instead of *N*-Bn) is used in the reaction, the direct Suzuki cross coupling product (product B) is obtained as the sole product (Table 1, entry 9).

With an effective set of conditions in hand, the scope of the reaction was investigated. A variety of aryl boronic acids were effective coupling partners. Both electron-rich (Table 2, entries 3, 4, and 6) and electron-poor (Table 2, entries 5, 10, and 12) boronic acids coupled smoothly to deliver the THQ products in excellent yield and diastereoselectivity. Moreover, heterocyclic boronic acids were effective coupling partners (Table 2, entries 2 and 6). Modifications, such as addition of a 6-fluoro- or 6-methyl-substituent, to the bromo-aniline were also tolerated (Table 2, entries 8, 10, and 11). Finally, substrates containing alternative nitrogen substituents such as *N*-PMB or *N*-Me are also effective coupling partners (Table 2, entries 9, 12, and 13).

In contrast to arylboronic acids, styrenylboronic acid did not provide the desired Heck/Suzuki coupling product under the optimized reaction conditions. Instead, the product from a direct Suzuki cross coupling was observed. This type of product was also observed with other very electron-rich boronic acids, such as 3-(*N*-Boc)indoleboronic acid (Scheme 2).[7]

These observations are consistent with the enhanced nucleophilicity of vinyl boronic acids and electron-rich heterocyclic boronic acids relative to aryl boronic acids. Interestingly, the direct cross coupling product was not observed in any appreciable amount in the case of any of the arylboronic acids shown in Table 2, with the exception of 3-thienylboronic acid (Table 2, entry 6).

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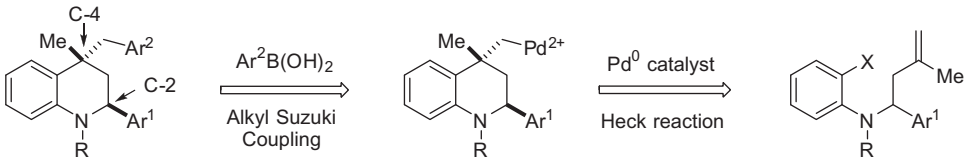
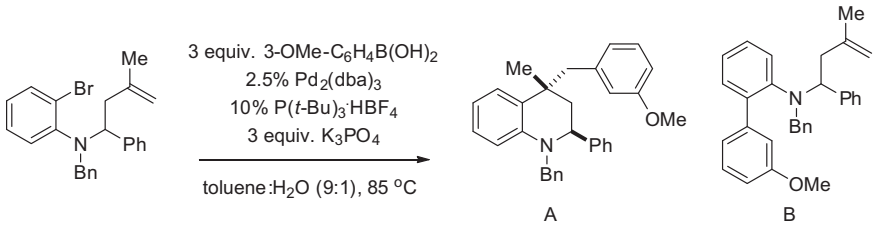


Scheme 1. Retrosythetic analysis for tetrahydroquinoline target compounds.

Table 1
Reaction optimization



Entry	Change from standard conditions	Conversion	Yield (%, product)	d.r.
1[a]	No change	100	93 (A)	>20:1
2[b]	No water	100	>99 (A)	>20:1
3[b]	No ligand	0	0	n.a.
4[b]	X-PHOS instead of P(*t*-Bu)$_3$	100	>99 (A)	>20:1
5[b]	P(Cy)$_3$ instead of P(*t*-Bu)$_3$	100	>99 (A)	10:1
6[b]	BINAP instead of P(*t*-Bu)$_3$	100	>99 (A)	6:1
7[b]	PPh$_3$ instead of P(*t*-Bu)$_3$	100	>99 (A)	3:1
8[b]	Cl instead of Br	0	0	
9[a]	N–H instead of N-Bn	100	95 (B)	

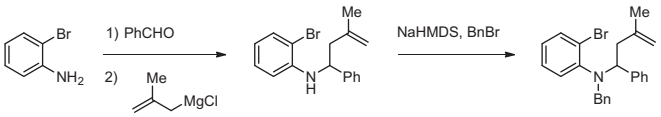
[a] Isolated yield. Diastereomeric ratio based from ^{1}H NMR analysis of crude reaction mixture.
[b] NMR yield calculated using internal standard of mesitylemne.

The reaction is believed to proceed through oxidative addition followed by the insertion into the olefin to yield the alkyl-palladium (II)-intermediate. This intermediate then undergoes transmetallation with boronic acid. Finally, reductive elimination affords tetrahydroisoquinoline and regenerates the catalyst, Pd(0)-P(*t*-Bu)$_3$ (Scheme 3).

A method for the synthesis of tetrahydroquinolines that employs a Heck–Suzuki cascade reaction has been described. The reaction tolerates a variety of coupling partners and provides THQs in good yield and with high levels of diastereoselectivity. A positive correlation between the cone angle of the phosphine ligand and the diastereoselectivity of the reaction was observed. Efforts are underway to apply this strategy to a variety of other highly-substituted heterocyclic systems.

Experimental procedures

Procedure for the Heck–Suzuki cascade reaction



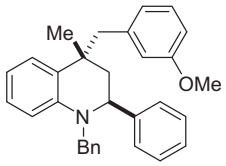
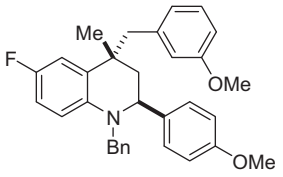
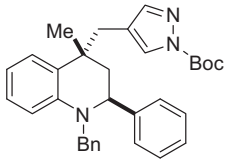
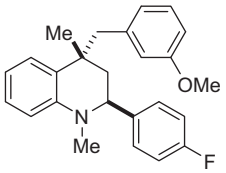
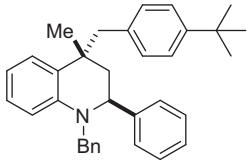
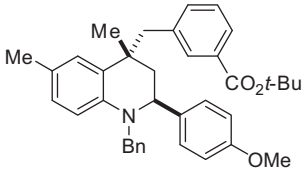
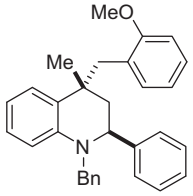
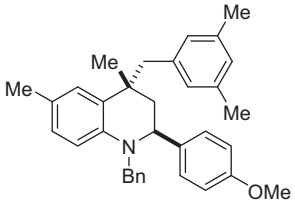
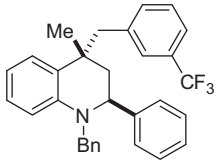
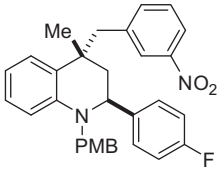
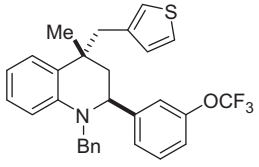
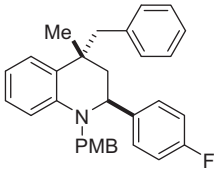
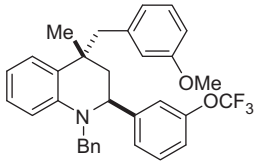
The arylbromide (122 mg, 0.3 mmol), 3-methoxy-phenylboronic acid (137 mg, 0.900 mmol), potassium phosphate (191 mg, 0.900 mmol), Pd$_2$(dba)$_3$ (6.87 mg, 0.008 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (8.70 mg, 0.030 mmol) were combined in a mixture of degassed toluene (0.81 ml) and water (0.09 ml) and heated to 90 °C for 14 h. At this time LC–MS showed a complete reaction. The reaction was cooled, diluted with ethyl acetate, and filtered through a small pad of silica gel eluting with ethyl acetate. The crude solution was concentrated and purified by silica gel chromatography (Biotage 25 g SNAP cartridge; 0–10% ethyl acetate in hexanes) to afford a clear viscous oil (121 mg, 93%). ^{1}H NMR (500 MHz) δ 7.35 (m, 1H), 7.30–7.15 (m, 10H), 7.12 (apparent t, J = 7.5 Hz, 1H), 6.89 (d, J = 9.3 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.79 (dd, J = 8 Hz, J = 2 Hz, 1H), 6.67 (apparent t, J = 7.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 6.32 (s, 1H), 4.75 (d, J = 16 Hz, 1H), 4.68 (dd, J = 11 Hz, J = 5 Hz, 1H), 4.06 (d, J = 16 Hz, 1H), 3.64 (s, 3H), 3.02 (d, J = 12.5 Hz, 1H), 2.82 (d, J = 12.5 Hz, 1H), 2.10 (dd, J = 14 Hz, J = 5 Hz, 1H), 1.98 (dd, J = 14 Hz, J = 12 Hz, 1H), 1.26 (s, 3H). LCMS calc. for $C_{31}H_{31}NO$ [M+1] 434.24, found 434.3.

Substrate preparation

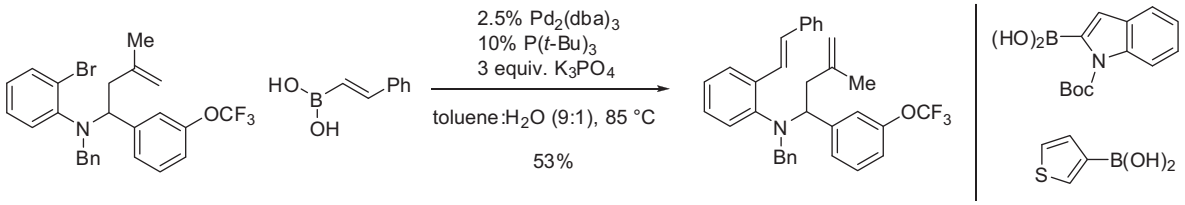
2-Bromoaniline (2.18 g, 12.67 mmol) and benzaldehyde (1.287 ml, 12.67 mmol) are combined in DCE (10 ml) with MgSO$_4$ and heated to 65 °C until the reaction is judged to be complete by NMR. The MgSO$_4$ is removed by filtration and the crude material is concentrated and dissolved in THF. The solution is cooled to 0 °C and treated with 2-methyl-allylmagnesium chloride (27.9 ml, 13.94 mmol). The mixture is stirred until the reaction is judged to be complete by NMR. The reaction is quenched with saturated ammonium chloride and the product is extracted with ethyl acetate. The extracts are dried over Na$_2$SO$_4$, filtered, and concentrated. The crude material is purified by silica gel chromatography (Biotage 100 g SNAP cartridge; 0–10% ethyl acetate in hexanes) to afford 2-bromo-*N*-(3-methyl-1-phenylbut-3-en-1-yl)aniline as yellow oil (3.75 g, 94%).

Sodium bis(trimethylsilyl)amide (3.83 ml, 3.83 mmol) was added to a solution of 2-bromo-*N*-(3-methyl-1-phenylbut-3-en-1-

Table 2
Additional examples of tetrahydroquinolines prepared via the diastereoselective Heck–Suzuki cascade

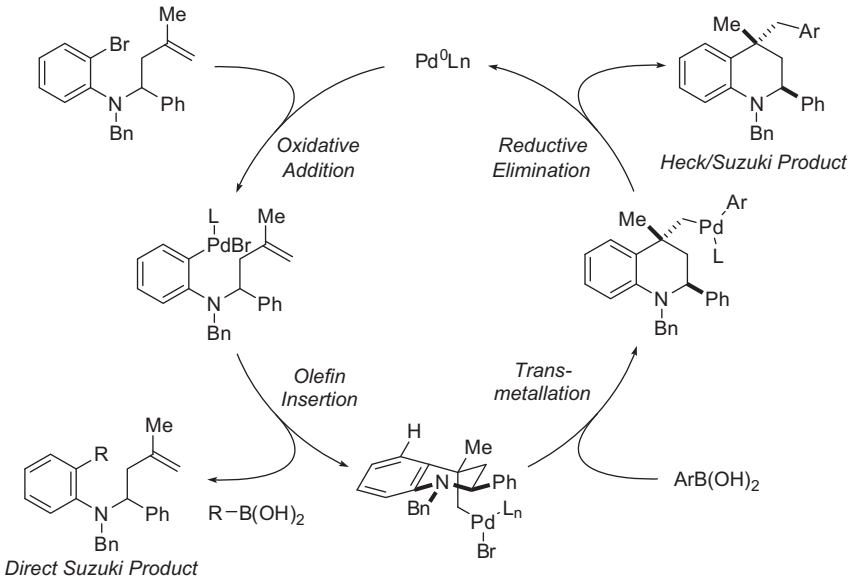
Entry	Product	Yield (%), d.r.[b]	Entry	Product	Yield (%), d.r.[b]
1		93, >20:1	8		95, >20:1
2		95, >20:1	9		93, >20:1
3		88, >20:1	10		97, >20:1
4		72, >20:1	11		90, >20:1
5		58, >20:1	12		99, >20:1
6[a]		63, >20:1	13		95, >20:1
7		95, >20:1			

[a] Isolated with the direct cross coupling product (as in Table 1, product B) in a ratio of 2:1 as an inseparable mixture of compounds. Yield is based on ^{1}H NMR.
[b] Diastereomeric ratio is for the crude reaction mixture.



Scheme 2. Boronic acid substrates that yield direct Suzuki coupling products.

yl)aniline (1.01 g, 3.19 mmol) in THF (12 ml) cooled to 0 °C. The reaction was stirred for 1 h at 0 °C and then benzylbromide (0.399 ml, 3.35 mmol) was added. The reaction was allowed to warm to rt and stirred overnight. The reaction was quenched with saturated ammonium chloride solution and the product was extracted with ethyl acetate. The combined extracts were dried over



Scheme 3. Proposed mechanism of the diastereoselective tetrahydroquinoline synthesis.

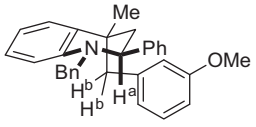
Na_2SO_4, filtered, and concentrated. The material was recrystallized from DCM/hexanes (1:9) to afford *N*-benzyl-2-bromo-*N*-(3-methyl-1-phenylbut-3-en-1-yl)aniline as a cream colored solid (365 mg, 28%). ^{1}H NMR (500 MHz) δ 7.59 (apparent d, J = 8 Hz, 1H), 7.36–7.29 (m, 5H), 7.21–7.16 (m, 4H), 7.12 (m, 1H), 7.06 (apparent t, J = 8 Hz, 1H), 6.88 (m, 1H), 6.76 (apparent d, J = 8 Hz, 1H), 4.67 (broad s, 1H), 4.61 (dd, J = 10 Hz, J = 5 Hz, 1H), 4.59 (broad s, 1H), 4.29 (d, J = 15 Hz, 1H), 3.90 (d, J = 15 Hz, 1H), 2.84–2.82 (m, 2H), 1.63 (s, 3H). LCMS calc. for $C_{31}H_{31}NO$ [M+1] 406.11, found 406.1.

Acknowledgements

The author would like to thank Mikhail Reibarkh for helpful NOE studies and Petr Vachal, Harry Chobanian, and Christopher Plummer for helpful discussions.

References and notes

1. A similar Heck/Suzuki cascade has been used for the synthesis of a variety of heterocyclic systems including one example of THQ, see: (a) Lu, Z.; Hu, C.; Guo, J.; Li, J.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 480; For a diastereoselective synthesis of methylenetetrahydrofurans employing this strategy see: (b) Braun, M.; Richrath, B. *Synlett* **2009**, 968.
2. For the use of this strategy for the synthesis of other carbocyclic and heterocyclic systems, see: (a) Oh, C. H.; Sung, H. R.; Park, S. J.; Ahn, K. H. *J. Org. Chem.* **2002**, *67*, 7155; (b) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511; (c) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741; (d) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972; (e) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 3882; (f) Arthius, M.; Pontikis, R.; Florent, J.-C. *Tetrahedron Lett.* **2007**, *48*, 6397; (g) Marchal, E.; Cupif, J.-F.; Uriac, P.; van de Weghe, P. *Tetrahedron Lett.* **2008**, *49*, 3713; (h) Guo, L.-N.; Duan, X.-H.; Hu, J.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Eur. J. Org. Chem.* **2008**, 1418; (i) Arthius, M.; Pontikis, R.; Florent, J.-C. *J. Org. Chem.* **2009**, *74*, 2234.
3. (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989; (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
4. (a) Lou, S.; Fu, G. C. *Adv. Synth. Catalysis* **2010**, *352*, 2081; (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
5. The cone angles for PPh_3, PCy_3, and P*t*-Bu_3 are 145°, 170°, and 182°. These values were taken from: (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313; The cone angle for BINAP is 189° which does not fit the hypothesis that has been put forward. However, BINAP is bidentate and other factors may be involved. The cone angle for BINAP was taken from: (b) Niksch, T.; Gorling, H.; Weigand, W. *Eur. J. Inorg. Chem.* **2010**, 95.
6. The relative stereochemistry was determined by performing a ^{1}H–^{1}H 2D NOE (NOESY) experiment on product A of Table 1. There was a strong NOE between H^a and H^b and no NOE observed between H^a and the protons of the methyl group. This indicates that the benzyl group and H^a are on the same face of the molecule and that both reside in pseudoaxial positions.



7. This side product is observed in a related method for the synthesis of methylenetetrahydrofurans, see Ref. 1b.