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A General, Simple Catalyst for Enantiospecific Cross Couplings of Benzylic Ammonium Triflates and Boronic Acids: No Phosphine Ligand Required

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Abstract

Highly improved conditions for the enantiospecific cross coupling of benzylic ammonium triflates with boronic acids are reported. This method relies on the use of Ni(cod)₂ without ancillary phosphine or *N*-heterocyclic carbene ligands as catalyst. These conditions enable the coupling of new classes of boronic acids and benzylic ammonium triflates. In particular, both heteroaromatic and vinyl boronic acids are well tolerated as coupling partners. In addition, these conditions enable the use of ammonium triflates with a variety of substituents at the benzylic stereocenter. Further, naphthyl-substitution is not required on the benzylic ammonium triflate; ammonium triflates with simple aromatic substituents also undergo this coupling. Good to high yields and levels of stereochemical fidelity are observed. This new catalyst system greatly expands the utility of enantiospecific cross couplings of these amine-derived substrates for the preparation of highly enantioenriched products.

Keywords

enantiospecific cross coupling; nickel catalysis; carbon–nitrogen bond activation; benzylic electrophiles

1. Introduction

Diarylalkanes and triarylalkanes constitute important compounds in organic synthesis and often possess exciting biological activities.¹ An efficient strategy for the preparation of these chiral compounds is a cross coupling of a benzylic electrophile with an organometallic

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Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/>

reagent.^{2,3} However, until recently, both enantioselective and enantiospecific cross couplings of benzylic electrophiles required the use of reactive, air-sensitive organometallic coupling partners, such as Grignard or organozinc reagents.^{4,5,6,7} This requirement limited the convenience and functional group tolerance of these reactions. To overcome this restriction, we developed an enantiospecific, nickel-catalyzed cross coupling of benzylic ammonium triflates with aryl boronic acids (Scheme 1A).⁸ This method not only allows the use of commercially available, functional group tolerant boronic acid coupling partners, but also enables the use of amine-derived substrates. In our view, amines are ideal starting materials for enantiospecific reactions due to their wide availability in excellent enantiopurity via a variety of methods.⁹ Simultaneously with the Jarvo lab,¹⁰ we have also developed an enantiospecific, nickel-catalyzed cross coupling of alcohol-derived substrates with organoborane coupling partners; our reaction enabled the coupling of benzylic pivalates with arylboroxines.¹¹ Notably, this coupling relied on a simple nickel catalyst, bis(cyclooctadiene)nickel [Ni(cod)₂], without the need for ancillary phosphine or *N*-heterocyclic carbene (NHC) ligands.

Although these new methods represent a significant advance by enabling the use of commercially available aryl boronic coupling partners, several limitations exist in the scope of substrates that can be used. In particular, our previous investigations of the cross couplings of benzylic ammonium triflates focused largely on the use of carbocyclic aryl boronic acids with only one example of a vinyl boronic acid.⁸ Our attempts to use heteroaromatic boronic acids resulted in modest yields and ee's. In addition, substituents other than methyl were not demonstrated at the benzylic stereocenter (R¹) in the enantiospecific cross couplings of ammonium triflates. Further, enantiospecific couplings of benzylic electrophiles were limited to those that possess an aromatic substituent with an extended π system, such as 2-naphthyl or biphenyl.^{12,5b, c, 6, 13} For example, under our previously reported conditions, the cross couplings of benzylic ammonium salts **1** with naphthyl substituents (Ar¹ = 2-Np) occurs with an average yield of 72%.⁸ However, the cross coupling of benzylic ammonium triflates with substituted phenyl substituents occurs with an average yield of only 45%. Given the importance of heteroaromatic and substituted phenyl groups in pharmaceutical agents and other biologically active compounds,¹⁴ we sought to develop conditions for the enantiospecific cross coupling of benzylic ammonium triflates that would overcome these limitations. We now report a general and simple catalyst system for the cross coupling of benzylic ammonium triflates with boronic acids (Scheme 1B). By using Ni(cod)₂ as catalyst without any ancillary phosphine or NHC ligands, we have achieved efficient cross couplings with heteroaromatic boronic acids. These conditions are also amenable to the use of vinyl boronic acids, as well as carbocyclic aryl boronic acids. In addition, these conditions are effective for ammonium triflates with a variety of substituents at the benzylic stereocenter (R¹). Finally, under these conditions, we have obtained promising results in the cross coupling of benzylic ammonium triflates substituted with non-naphthyl aromatic groups. This method greatly expands the utility of enantiospecific cross couplings of these amine-derived starting materials, which are available in exceptional enantiopurity.

2. Results and discussion

As stated above, our previous attempts to cross couple heteroaromatic boronic acids or ammonium triflates with non-naphthyl aryl substituents resulted in modest yields and/or levels of stereochemical fidelity. In an effort to overcome these limitations and identify a simpler, more convenient, and less expensive catalyst, we found that high yields and ee's were possible in the absence of an ancillary phosphine ligand. Simply using $\text{Ni}(\text{cod})_2$ as catalyst resulted in a highly efficient catalyst system. This new "phosphine-less" catalyst system facilitates the convenience of this method, lessens the cost of the catalyst, and simplifies purification of the products by eliminating potential contamination by a phosphine ligand. As described below, these conditions are amenable to the use of new classes of boronic acids and benzylic ammonium triflate substrates.

Using this newly optimized, simple catalyst system, high yields and levels of stereochemical fidelity were observed in the couplings of a number of heteroaromatic boronic acids. In all cases, the reactions gave inversion of the absolute stereochemistry of the benzylic stereocenter with high levels of stereochemical fidelity. Oxygen-containing heteroaromatic groups can be coupled to deliver dibenzofuran **2** and benzofuran **3** in high yields and excellent ee's (Table 1, entries 1 and 3). Although some heteroaromatic boronic acids coupled in similar yields with either phosphine-containing or phosphine-less catalysts,¹⁵ we observed dramatic differences in yield with dibenzofuranyl boronic acid. The use of $\text{Ni}(\text{cod})_2/\text{P}(\text{o-Tol})_3$ as catalyst resulted in only 15–27% yield of product **3** (entry 2). Under the phosphine-less reaction conditions, pyridyl boronic acids also underwent efficient coupling to give products **4** and **5** in 70 and 88% yield, respectively (entries 4 and 5). Although product **4** was formed in 75% ee (entry 4), pyridine **5** was formed in 95% ee (entry 5).¹⁶

In addition to heteroaromatic boronic acid coupling partners, these reaction conditions are amenable to the use of vinyl boronic acids. Under our previous conditions, $\text{Ni}(\text{cod})_2/\text{P}(\text{o-Tol})_3$, we had found that (*E*)-2-phenylvinylboronic acid was an excellent coupling partner.⁸ We were pleased to observe that these new, simpler conditions also enable the use of vinyl boronic acids. The use of both electron-rich and electron-poor phenylvinylboronic acids results in high yields and exceptional levels of stereochemical fidelity (Table 1, entries 6, 8 and 9). Notably, an aryl chloride functional group is tolerated under these reaction conditions (entry 8). With vinyl boronic acids, the use of $\text{Ni}(\text{cod})_2/\text{P}(\text{o-Tol})_3$ as catalyst resulted in similar yields and ee's as the phosphine-less catalyst (entries 7 and 10). Thus, in this case, the main advantage of the phosphine-less catalyst system is the ease of purification of the products by eliminating potential contamination by a phosphine ligand. Notably, these cross couplings do not occur without the $\text{Ni}(\text{cod})_2$ catalyst (entry 11). The coupling of the more sterically demanding 1-phenylvinylboronic acid also proceeded with excellent stereochemical fidelity, albeit in reduced yield (entry 12). We also investigated the use of alkyl-substituted vinylboronic acids; however, their use resulted in complex product mixtures, likely due to olefin isomerization.

Having established a broadened scope with respect to the boronic acid coupling partner, we turned our attention to the ammonium triflate substrate. We were pleased to observe that our

new conditions provided high yields and exceptional levels of stereochemical fidelity with carbocyclic aryl boronic acids, such as *p*-tolyl boronic acid (Table 1, entry 13).⁸ The coupling was also successful with electron-poor aryl boronic acids, such as *p*-cyanophenylboronic acid, albeit in reduced yields (entry 14).¹⁷ In addition, the coupling of benzylic ammonium triflates with the bulkier *i*-propyl substituent also underwent coupling under these conditions to give diarylalkane **12** in 55% yield and 86% ee (entry 15). These conditions are also amenable to the formation of triarylmethane **13**, although in diminished ee (entry 16).

Emboldened by these results, we examined our new conditions for the coupling of simple, non-naphthyl-substituted benzylic ammonium triflates (Table 1, entries 17, 21 and 22). Although the stereochemical fidelity of these couplings is slightly diminished (80–92% ee), moderate to good yields are achieved with these highly challenging substrates.¹³ In particular, electron-poor substrates efficiently undergo coupling to give *p*-fluorophenyl and *m*-methoxyphenyl products **14** and **15** in 75 and 71% yield, respectively (entries 17 and 21). With these non-naphthyl-substituted electrophiles, the phosphine-less catalyst proved crucial. The addition of *t*-Bu-XantPhos or P(*o*-Tol)₃ to these reactions resulted in significantly lower yields of 29% and 39%, respectively (entries 18 and 19). In addition, control experiments demonstrated that this cross coupling does not occur to any appreciable extent in the absence of Ni(cod)₂ (entry 20). Even electron-rich *p*-methoxyphenyl product **16** could be formed under these conditions in 53% yield. To our knowledge, these are the highest yields achieved to date for benzylic electrophiles with simple phenyl substituents (not naphthyl or biphenyl) in enantiospecific couplings with an organoborane partner.

Although detailed mechanistic experiments are required to elucidate the nature of the active catalyst under our phosphine-less conditions, we hypothesize that this reaction occurs via oxidative addition of a nickel(0) species to the benzylic ammonium triflate, likely with inversion of configuration of the benzylic stereocenter, to form either an η^1 - or η^3 -bound nickel complex (**17**, Scheme 2).¹⁸ Subsequent transmetallation and reductive elimination, both with retention of configuration,¹⁹ then result in the observed diarylalkane product with net inversion of configuration at the benzylic stereocenter.

3. Conclusion

As described above, we have identified new, general conditions for the enantiospecific cross coupling of benzylic ammonium triflates with aryl and vinyl boronic acids. These conditions rely on the use of Ni(cod)₂ as catalyst without ancillary phosphine or *N*-heterocyclic carbene ligands. This simple catalyst system facilitates the convenience and lowers the cost of these cross couplings. Even more importantly, these conditions enable the efficient cross coupling of heteroaromatic and vinyl boronic acids, as well as benzylic ammonium triflates with various substituents at the benzylic stereocenter. Benzylic ammonium triflates with simple, non-naphthyl aryl substituents also underwent couplings under these conditions in good yields. We are now focused on understanding the nature of the active catalyst formed under these conditions, as well as the continued development of the scope of this enantiospecific conversion of widely available amine-derived substrates into valuable, highly enantioenriched di- and tri-arylalkanes and 1,3-diaryl allylic products.

4. Experimental Section

4.1 General

Reactions were performed either in a N₂-atmosphere glovebox in oven-dried 1-dram vials with Teflon-lined caps or in oven-dried round-bottomed flasks unless otherwise noted. Flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of N₂. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed on silica gel 60 (40-63 μ m, 60Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, or Cambridge Isotopes Laboratories and used as received with the following exceptions: toluene, CH₂Cl₂, dioxane, and Et₂O were dried by passing through drying columns.²⁰ Toluene and dioxane were then degassed by sparging with N₂ and stored over activated 4Å MS in a N₂-atmosphere glovebox. Anhydrous K₃PO₄ was purchased from Acros and stored in a N₂-atmosphere glovebox. MeOTf was purchased from TCI, America, and used as received. CDCl₃ was stored over oven-dried potassium carbonate. Proton nuclear magnetic resonance (¹H NMR), carbon nuclear magnetic resonance (¹³C NMR), and fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on 400 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl₃ = δ 7.28; (CD₃)₂CO = δ 2.07). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃ = δ 77.07; (CD₃)₂CO = δ 28.94). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, h = heptet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a NaCl plate. The mass spectral data were obtained at the University of Delaware mass spectrometry facility. Optical rotations were measured using a 2.5 mL cell with a 0.1 dm path length. Melting points were taken on a uni-melt Thomas Hoover capillary melting point apparatus.

Dimethyl benzyl amines were prepared either from the benzyl amines using Eschweiler-Clarke conditions²¹ or via reductive amination of benzaldehyde or acetophenone derivatives.²² It has been reported that epimerization does not occur under the Eschweiler-Clarke conditions.²³ The amine precursors for salts **1b** and **1c** were prepared via Grignard addition to *N-tert*butanesulfinyl aldimines, isolated as single diastereomers as determined by ¹H NMR analysis, and therefore assumed to be >95% ee.²⁴ Precursors for racemic ammonium triflates were synthesized via reductive amination of the corresponding acetophenone derivatives. Ammonium triflates **1a**, **1d**, and **1e** were prepared as previously described.⁸

4.2 General procedure for enantiospecific cross coupling

In a N₂-atmosphere glovebox, Ni(cod)₂ (either 1.6 mg, 0.006 mmol, 3 mol % or 5.5 mg, 0.020 mmol, 10 mol %) and K₃PO₄ (64.0 mg, 0.30 mmol, 1.5 equiv) were weighed into a 1-dram vial. Benzyl ammonium triflate **1** (0.20 mmol, 1.0 equiv) and boronic acid (0.30 mmol,

1.5 equiv) were added, followed by dioxane (0.6 mL, 0.33 M). The vial was capped with a Teflon-lined cap and removed from the glovebox. The mixture was stirred for 6 h at 80 °C. After cooling to room temperature, the reaction mixture was then diluted with Et₂O (1.5 mL) and filtered through a short plug of silica gel, which was rinsed with Et₂O (10 mL). The filtrate was concentrated and purified by silica gel chromatography to give the cross-coupled product.

4.2.1 (R)-4-(1-(naphthalen-2-yl)ethyl)dibenzo[b,d]furan (2)—General procedure was followed using 3 mol % Ni(cod)₂ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **2** (51 mg, 80%) as a white solid (mp 98–101 °C). The enantiomeric excess was determined to be 99% ee by chiral HPLC analysis (CHIRALPAK IB, 1.0 mL/min, 0.2% *i*-PrOH/hexane, λ=254 nm); *t*_R(major)=7.996 min, *t*_R(minor)=10.60 min. [α]_D²⁴ = +124.5° (c 1.11, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.85 – 7.71 (m, 5H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.38 (m, 4H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 4.5 Hz, 1H), 5.01 (q, *J* = 7.2 Hz, 1H), 1.90 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.1, 154.3, 142.7, 133.6, 132.3, 130.5, 128.0, 127.9, 127.7, 127.1, 127.0, 126.0, 125.7, 125.6, 125.5, 124.6, 124.2, 123.0, 122.7, 120.8, 118.7, 111.9, 39.0, 20.9; FTIR (NaCl/thin film) 3054, 2968, 1451, 1421, 1184, 751 cm⁻¹; HRMS (EI+) [M]⁺ calculated for C₂₄H₁₈O: 322.1358, found: 322.1342.

4.2.2 (R)-2-(1-(naphthalen-2-yl)ethyl)benzofuran (3)—General procedure was followed using 3 mol % Ni(cod)₂ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **3** (45.0 mg, 83%) as a white solid (mp 97–100 °C). The enantiomeric excess was determined to be 98% ee by chiral HPLC analysis (CHIRALPAK IC, 1.0 mL/min, 0.2% *i*-PrOH/hexane, λ=254 nm); *t*_R(minor)=6.26 min, *t*_R(major)=6.84 min. [α]_D²⁴ = –38.3° (c 1.46, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.91 (m, 3H), 7.86 (s, 1H), 7.67 – 7.46 (m, 5H), 7.38 – 7.25 (m, 2H), 6.61 (s, 1H), 4.55 (q, *J* = 7.2 Hz, 1H), 1.91 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 162.1, 155.0, 140.8, 133.7, 132.6, 128.8, 128.4, 127.9, 127.8, 126.2, 126.1, 126.0, 125.8, 123.6, 122.6, 120.6, 111.1, 102.4, 39.9, 20.4; FTIR (NaCl/thin film) 3053, 2973, 1455, 1255 cm⁻¹; HRMS (EI+) [M]⁺ calculated for C₂₀H₁₆O: 272.1201, found: 272.1186.

4.2.3 (R)-2-fluoro-3-methyl-5-(1-(naphthalen-2-yl)ethyl)pyridine (4)—General procedure was followed using 3 mol % Ni(cod)₂ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (5% EtOAc/1% Et₃N/hexanes) to give compound **4** (37 mg, 70%) as a pale yellow oil. The enantiomeric excess was determined to be 75% ee by chiral HPLC analysis (CHIRALPAK IB, 1.0 mL/min, 5.0% *i*-PrOH/hexane, λ=254 nm); *t*_R(minor)=5.99 min, *t*_R(major)=7.18 min. [α]_D²⁴ = –89.6° (c 0.73, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.11 (m, 1H), 7.86 – 7.70 (m, 3H), 7.61 – 7.51 (m, 1H), 7.52 – 7.37 (m, 2H), 7.33 – 7.22 (m, 1H), 6.79 – 6.67 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 1H), 2.21 (s, 3H), 1.74 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 162.7 (d, *J*_{C-F} = 238.4 Hz), 151.8 (d, *J*_{C-F} = 8.1 Hz), 145.7 (d, *J*_{C-F} = 15.15 Hz), 142.3, 136.9 (d, *J*_{C-F} = 5.1 Hz), 133.6, 132.2, 128.5, 127.7 (d, *J*_{C-F} = 4.0 Hz),

126.3, 125.8, 125.6, 110.7, 110.4, 39.6, 22.0, 19.8 (d, $J_{C-F} = 3.0$ Hz); ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{CO}$) δ 162.6 (d, $J_{C-F} = 232.3$ Hz), 151.9 (d, $J_{C-F} = 8.1$ Hz), 145.6 (d, $J_{C-F} = 16.2$ Hz), 142.6, 137.4 (d, $J_{C-F} = 4.0$ Hz), 133.7, 132.3, 128.2, 127.7, 127.5, 126.4, 126.1, 125.6, 125.5, 109.9 (d, $J_{C-F} = 19.2$ Hz), 39.0, 21.2, 18.6 (d, $J_{C-F} = 3.0$ Hz); FTIR (NaCl/thin film) 3053, 2968, 1608, 1485, 1373, 962 cm^{-1} ; HRMS (EI+) $[\text{M}]^+$ calculated for $\text{C}_{18}\text{H}_{16}\text{FN}$: 265.1267, found: 265.1252. Please note: Although two ^{13}C NMR peaks are coincident when CDCl_3 is used as solvent, all 18 ^{13}C NMR peaks are seen when $(\text{CD}_3)_2\text{CO}$ is used as solvent.

4.2.4 (R)-2-methoxy-3-(1-(naphthalen-2-yl)ethyl)pyridine (5)—General procedure was followed using 3 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (5% EtOAc/1% EtN₃/hexanes) to give compound **5** (47 mg, 88%) as an oil. The enantiomeric excess was determined to be 95% ee by chiral SFC analysis (OJ-H, 3.0 mL/min, 40% *i*-PrOH(0.1% DEA)/CO₂, λ =254 and 220nm); t_{R} (major)=2.46 min, t_{R} (minor)=3.07 min. $[\alpha]_{\text{D}}^{24} = +58.4^\circ$ (c 1.73, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.09 – 8.02 (m, 1H), 7.85 – 7.74 (m, 3H), 7.73 – 7.67 (m, 1H), 7.52 – 7.31 (m, 4H), 6.88 – 6.78 (m, 1H), 4.61 (q, $J = 7.1, 6.0$ Hz, 1H), 3.95 (s, 3H), 1.68 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 161.6, 144.4, 142.7, 136.1, 133.6, 132.2, 129.1, 127.9, 127.8, 127.7, 127.1, 126.0, 125.6, 125.5, 116.9, 53.5, 37.9, 20.5; FTIR (NaCl/thin film) 3055, 2969, 2948, 1589, 1507, 1463, 1409, 1321, 1253, 1020 cm^{-1} ; HRMS (EI+) $[\text{M}]^+$ calculated for $\text{C}_{18}\text{H}_{17}\text{NO}$: 263.1310, found: 263.1297.

4.2.5 (S,E)-2-(4-(4-(trifluoromethyl)phenyl)but-3-en-2-yl)naphthalene (6)—General procedure was followed using 3 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **6** (53.0 mg, 81%) as a white solid (mp 70–73 °C). The enantiomeric excess was determined to be 98% ee by chiral HPLC analysis (CHIRALPAK IB, 0.8 mL/min, 100% hexane, λ =254 nm); t_{R} (major)=24.21 min, t_{R} (minor)=30.68 min. $[\alpha]_{\text{D}}^{24} = -30.5^\circ$ (c 1.18, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.90 – 7.76 (m, 3H), 7.76 – 7.64 (m, 1H), 7.54 (d, $J = 8.2$ Hz, 2H), 7.51 – 7.37 (m, 5H), 6.63 – 6.43 (m, 2H), 3.99 – 3.69 (m, 1H), 1.58 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.5, 141.13, 141.11, 138.0, 133.8, 132.4, 129.0 (q, $J_{C-F} = 32.3$ Hz), 128.3, 127.78, 127.76, 126.4, 126.3, 126.2, 125.64, 125.57 (q, $J_{C-F} = 4.0$ Hz), 125.5, 124.4 (q, $J_{C-F} = 272.7$ Hz), 42.8, 21.1; FTIR (NaCl/thin film) 3053, 2967, 1615, 1325, 1164, 1121, 1067 cm^{-1} ; HRMS (EI+) $[\text{M}]^+$ calculated for $\text{C}_{21}\text{H}_{17}\text{F}_3$: 326.1282, found: 326.1284.

4.2.6 (S,E)-2-(4-(4-chlorophenyl)but-3-en-2-yl)naphthalene (7)—General procedure was followed using 3 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give **7** (44.0 mg, 76%) as a white solid (mp 68–71 °C). The enantiomeric excess was determined to be 99% ee by chiral HPLC analysis (CHIRALPAK IB, 1.0 mL/min, 100% hexane, λ =254 nm); t_{R} (major)=22.47 min, t_{R} (minor)=28.85 min. $[\alpha]_{\text{D}}^{24} = -40.8^\circ$ (c 1.42, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.98 – 7.82 (m, 3H), 7.77 (s, 1H), 7.63 – 7.43 (m, 3H), 7.43 – 7.25 (m, 4H), 6.59 – 6.38 (m, 2H), 3.98 – 3.80 (m, 1H), 1.63 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.4, 141.0, 141.0, 137.9, 133.7,

132.3, 128.2, 127.69, 127.66, 126.3, 126.2, 126.1, 125.6, 125.4, 42.7, 21.0; ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{CO}$) δ 143.8, 137.2, 136.8, 134.5, 133.1, 132.7, 129.2, 128.7, 128.4, 128.3, 128.2, 128.1, 126.9, 126.6, 126.1, 125.8, 43.4, 21.4; FTIR (NaCl/thin film) 3052, 2965, 1490, 1091, 966 cm^{-1} ; HRMS (EI+) $[M]^+$ calculated for $\text{C}_{20}\text{H}_{17}\text{Cl}$: 292.1019, found: 292.0993. Please note: Although two ^{13}C NMR peaks are coincident when CDCl_3 is used as solvent, all 18 ^{13}C NMR peaks are seen when $(\text{CD}_3)_2\text{CO}$ is used as solvent.

4.2.7 (S,E)-2-(4-(4-methoxyphenyl)but-3-en-2-yl)naphthalene (8)—General procedure was followed using 3 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **8** (53.0 mg, 91%) as a white solid (mp 78–80 °C). The enantiomeric excess was determined to be 99% ee by chiral HPLC analysis (CHIRALPAK IA, 0.6 mL/min, 1% EtOAc/hexane, $\lambda=254$ nm); $t_R(\text{major})=27.88$ min, $t_R(\text{minor})=30.19$ min. $[\alpha]_D^{24} = -35.7^\circ$ (c 1.43, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.86 – 7.77 (m, 3H), 7.72 – 7.68 (m, 1H), 7.50 – 7.38 (m, 3H), 7.34 – 7.28 (m, 2H), 6.90 – 6.80 (m, 2H), 6.48 – 6.26 (m, 2H), 3.81–3.78 (m, 4H), 1.55 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.9, 143.4, 133.7, 133.1, 132.3, 130.4, 128.3, 128.1, 127.8, 127.7, 127.4, 126.5, 126.0, 125.4, 125.3, 114.0, 55.4, 42.7, 21.4; FTIR (NaCl/thin film) 2962, 1607, 1511, 1250, 1175, 1034 cm^{-1} ; HRMS (EI+) $[M]^+$ calculated for $\text{C}_{21}\text{H}_{20}\text{O}$: 288.1514, found: 288.1517.

4.2.8 (R)-2-(3-phenylbut-3-en-2-yl)naphthalene (9)—General procedure was followed using 3 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexane) to give compound **9** (26 mg, 50%) as a white solid (mp 64–65 °C). The enantiomeric excess was determined to be 96% ee by chiral HPLC analysis (CHIRALCEL OD-H, 0.8 mL/min, 1% *i*-PrOH/hexane, $\lambda = 254$ nm); $t_R(\text{minor})=6.33$ min, $t_R(\text{major})=6.73$ min. $[\alpha]_D^{24} = -64.0^\circ$ (c 0.64, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.88 – 7.76 (m, 3H), 7.76 – 7.70 (m, 1H), 7.53 – 7.42 (m, 3H), 7.42 – 7.33 (m, 2H), 7.33 – 7.16 (m, 3H), 5.53 (s, 1H), 5.27 (t, $J = 1.3$ Hz, 1H), 4.24 (q, $J = 7.0$ Hz, 1H), 1.60 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5, 142.7, 142.2, 133.7, 132.3, 128.2, 128.2, 127.8, 127.7, 127.3, 126.8, 126.6, 125.9, 125.4, 113.5, 44.4, 21.8; ^{13}C NMR (101 MHz, $(\text{CD}_3)_2\text{CO}$) δ 152.6, 142.8, 142.1, 133.7, 132.2, 128.0, 127.9, 127.53, 127.46, 127.2, 126.6, 126.4, 125.82, 125.79, 125.3, 112.5, 43.7, 21.2; FTIR (NaCl/thin film) 3053, 2967, 2930, 2361, 2337, 1624, 1599, 1506 cm^{-1} ; HRMS (EI+) $[M]^+$ calculated for $\text{C}_{20}\text{H}_{18}$: 258.1409, found: 258.1422. Please note: Although two ^{13}C NMR peaks are coincident when CDCl_3 is used as solvent, all 18 ^{13}C NMR peaks are seen when $(\text{CD}_3)_2\text{CO}$ is used as solvent.

4.2.9 (S)-2-(1-p-tolylethyl)naphthalene (10)—General procedure was followed using 10 mol % $\text{Ni}(\text{cod})_2$ and benzylic ammonium triflate **1a** prepared in 99.6% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **10** (40 mg, 82%) as a white solid. The enantiomeric excess was determined to be >99% ee by chiral HPLC analysis (CHIRALPAK IB, 0.4 mL/min, 100% hexane, $\lambda=254$ nm); $t_R(\text{major})=21.65$; ^1H NMR (400 MHz, CDCl_3) δ 7.86 – 7.66 (m, 4H), 7.52 – 7.36 (m, 2H), 7.31 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.21 – 7.06 (m, 4H), 4.29 (q, $J = 7.2$ Hz, 1H), 2.32 (s, 3H), 1.72 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 144.0, 143.3, 135.6, 133.5, 132.1,

129.1, 128.0, 127.8, 127.7, 127.6, 126.9, 126.0, 125.4, 125.3, 44.5, 21.9, 21.1. The spectral data for this compound matches that reported in the literature.⁸ Comparison of the HPLC spectrum of this product to that previously obtained in our laboratory confirmed that the absolute configuration of this product is *S*.⁸

4.2.10 (S)-2-(2-methyl-1-p-tolylpropyl)naphthalene (12)—General procedure was followed using 10 mol % Ni(cod)₂ and benzylic ammonium triflate **1b** prepared in >95% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **12** (30 mg, 55%) as a white solid (mp 77–78 °C). The enantiomeric excess was determined to be 86% ee by chiral HPLC analysis (CHIRALPAK IB, 0.8 mL/min, 100% hexane, λ = 254 nm); *t*_R(major)=8.24 min, *t*_R(minor)=8.93 min. [α]_D²⁴ = –33.5° (c 0.864, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.61 (m, 4H), 7.49 – 7.31 (m, 3H), 7.31 – 7.16 (m, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 3.53 (d, *J* = 10.8 Hz, 1H), 2.67 – 2.47 (m, 1H), 2.25 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 142.7, 141.7, 135.5, 133.6, 132.1, 129.1, 128.0, 127.9, 127.6, 127.5, 126.5, 126.2, 125.8, 125.1, 60.5, 31.6, 22.0, 21.9, 21.0; FTIR (NaCl/thin film) 3053, 3019, 2955, 2922, 2868, 1508, 1457, 1385, 813, 760, 741 cm^{–1}; HRMS (EI+) [M]⁺ calculated for C₂₁H₂₂: 274.1722, found: 274.1724.

4.2.11 (S)-2-(phenyl(p-tolyl)methyl)naphthalene (13)—General procedure was followed using 10 mol % Ni(cod)₂ and benzylic ammonium triflate **1c** prepared in >95% ee. The crude material was purified by silica gel chromatography (100% hexanes) to give compound **13** (36 mg, 58%) as an oil. The enantiomeric excess was determined to be 52% ee by chiral HPLC analysis (CHIRALCEL OD-H, 0.3 mL/min, 0.2% *i*-PrOH/pentane, λ = 254 nm); *t*_R(major)=38.59 min, *t*_R(minor)=40.72 min. [α]_D²⁴ = +37.6° (c 1.88, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.71 (m, 3H), 7.54 (s, 1H), 7.49 (dt, *J* = 6.1, 3.5 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.33 – 7.26 (m, 1H), 7.26 – 7.20 (m, 2H), 7.20 – 7.09 (m, 4H), 5.74 (s, 1H), 2.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 143.9, 141.7, 140.7, 135.9, 133.4, 132.1, 129.5, 129.4, 129.1, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 126.3, 125.9, 125.6, 56.5, 21.1. The spectral data for this compound matches that reported in the literature.^{5c}

4.2.12 (R)-2-(1-(4-fluorophenyl)ethyl)naphthalene (14)—General procedure was followed using 10 mol % Ni(cod)₂ and benzylic ammonium triflate **1d** prepared in 99% ee. The crude material was purified by silica gel chromatography (100% petroleum ether) to give compound **14** (38 mg, 75%) as an oil. The enantiomeric excess was determined to be 92% ee by chiral HPLC analysis (CHIRALCEL OD-H, 0.8 mL/min, 100% hexane, λ = 254 nm); *t*_R(minor)=24.62 min, *t*_R(major)=31.78 min; ¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.76 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.49 – 7.37 (m, 2H), 7.29 – 7.23 (m, 1H), 7.23 – 7.16 (m, 2H), 7.01 – 6.91 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 1H), 1.70 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 161.3 (d, *J*_{C–F} = 245.4 Hz), 143.6, 141.9 (d, *J*_{C–F} = 4.0 Hz), 133.5, 132.1, 129.1 (d, *J*_{C–F} = 7.1 Hz), 128.1, 127.7, 127.6, 126.7, 126.1, 125.5, 125.3, 115.1 (d, *J*_{C–F} = 21.2 Hz), 44.1, 21.9. The spectral data for this compound matches that reported in the literature.⁸ Comparison of the HPLC spectrum of this product to that

previously obtained in our laboratory confirmed that the absolute configuration of this product is *R*.⁸

4.2.13 (S)-1-methoxy-3-(1-p-tolylolethyl)benzene (15)—General procedure was followed using 10 mol % Ni(cod)₂ and benzylic ammonium triflate **1e** prepared in >99% ee. The crude material was purified by silica gel chromatography (0–1% Et₂O/hexanes) to give compound **15** (32 mg, 71%) as an oil. The enantiomeric excess was determined to be 83% ee by chiral HPLC analysis (CHIRALPAK IA, 10.8 mL/min, 1% *i*-PrOH/hexane, λ=254 nm); *t*_R(minor)=5.55 min, *t*_R(major)=5.81 min; ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.21 (m, 1H), 7.20 – 7.08 (m, 4H), 6.92 – 6.82 (m, 2H), 6.77 (ddt, *J*= 8.1, 2.4, 1.4 Hz, 1H), 4.14 (q, *J*= 7.1 Hz, 1H), 3.82 (s, 3H), 2.36 (s, 3H), 1.66 (d, *J*= 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.7, 148.4, 143.3, 135.6, 129.4, 129.2, 127.5, 120.2, 113.8, 110.9, 55.2, 44.5, 22.0, 21.1. The spectral data for this compound matches that reported in the literature.⁸ Comparison of the HPLC spectrum of this product to that previously obtained in our laboratory confirmed that the absolute configuration of this product is *S*.⁸

4.2.14 (S)-1-methoxy-4-(1-p-tolylolethyl)benzene (16)—General procedure was followed using 10 mol % Ni(cod)₂ and benzylic ammonium triflate **1f** prepared in 99.5% ee. The crude material was purified by silica gel chromatography (0–1% Et₂O/Hexane) to give compound **16** (24 mg, 53%) as an oil. The enantiomeric excess was determined to be 81% ee by chiral HPLC analysis (CHIRALCEL OJ-H, 0.8 mL/min, 100% hexane, λ=254 nm); *t*_R(major)=45.54 min, *t*_R(minor)=55.21 min. [α]_D²⁴ = –23.0° (c 1.02, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.07 (m, 6H), 6.90 – 6.79 (m, 2H), 4.09 (q, *J*= 7.2 Hz, 1H), 3.79 (s, 3H), 2.33 (s, 3H), 1.62 (d, *J*= 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.9, 143.9, 138.9, 135.5, 129.2, 128.6, 127.5, 113.8, 55.4, 43.6, 22.3, 21.1. The spectral data for this compound matches that reported in the literature.²⁵

4.3 Procedure for benzyl ammonium triflates

4.3.1 (S)-N,N,N,2-tetramethyl-1-(naphthalen-2-yl)propan-1-aminiumtrifluoromethane sulfonate (1b)—The dimethylbenzylamine (179 mg, 0.79 mmol, 1.0 equiv) was dissolved in Et₂O (0.17 mL, 4.0 M). MeOTf (0.17 mL, 1.0 mmol, 1.3 equiv) was added dropwise at 0 °C. The formation of two layers was observed. After complete addition the reaction mixture was stirred for an additional 15 minutes at 0 °C. The top layer was decanted off. The bottom layer was then washed with Et₂O (5 mL × 3) and then hexanes (5 mL × 3). Residual solvent was removed from the resulting oil *in vacuo* to give **1b** (298 mg, 97%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 7.96 – 7.86 (m, 2H), 7.86 – 7.80 (m, 1H), 7.58 – 7.44 (m, 3H), 4.61 (d, *J*= 5.2 Hz, 1H), 3.20 (s, 9H), 2.89 – 2.70 (m, 1H), 1.15 – 0.99 (m, 6H); ¹⁹F NMR (565 MHz, CDCl₃) δ –78.4; FTIR (NaCl/thin film) 2975, 1490, 1278, 1166, 1030, 828, 638 cm^{–1}; LRMS (ESI) [M–OTf]⁺ calculated for [C₁₇H₂₄N]⁺ : 242.2, found: 242. The ¹³C NMR spectrum of **1b** was complex due to the presence of rotamers. Please see the spectrum in the Supplementary Data.

4.3.2 (S)-N,N,N-trimethyl-1-(naphthalen-2-yl)-1-phenylmethanaminiumtrifluoromethane (1c)—The dimethylbenzylamine (245 mg, 0.94 mmol, 1.0 equiv) was dissolved in Et₂O (0.24 mL, 4.0 M). MeOTf (0.13 mL, 1.2

mmol, 1.3 equiv) was added dropwise at 0 °C. The formation of two layers was observed. After complete addition the reaction mixture was stirred for an additional 15 minutes at 0 °C. The top layer was decanted off. The bottom layer was washed with Et₂O (5 mL × 3) and then hexanes (5 mL × 3). Residual solvent was removed from the resulting oil *in vacuo* to give salt **1c** (225 mg, 57%) as a white fluffy solid (mp 61–63 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.98 – 7.76 (m, 6H), 7.58 – 7.39 (m, 5H), 6.12 (s, 1H), 3.25 (s, 9H); FTIR (NaCl/thin film) 3042, 1489, 1262, 1225, 1158, 1030, 735 cm⁻¹; ¹⁹F NMR (565 MHz, CDCl₃) δ –78.3; LRMS (ESI) [M–OTf]⁺ calculated for [C₂₀H₂₂N]⁺ : 276.2, found: 276. The ¹³C NMR spectrum of **1b** was complex due to the presence of rotamers. Please see the spectrum in the Supplementary Data.

4.3.3 (S)-1-(4-methoxyphenyl)-N,N,N-trimethylethanaminium

trifluoromethanesulfonate (1f)—The dimethylbenzylamine (426 mg, 2.4 mmol, 1.0 equiv) was dissolved in Et₂O (0.6 mL, 4.0 M). MeOTf (0.30 mL, 3.1 mmol, 1.3 equiv) was added dropwise at 0 °C. White precipitate formed immediately. After complete addition the reaction mixture was stirred for an additional 15 minutes at 0 °C. The precipitate was isolated by filtration and washed with Et₂O (2 x 5 mL). The resulting solid was dried under vacuum to give salt **1f** (783 mg, 73%) as a white solid (mp 94–95 °C): ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.36 (m, 2H), 7.06 – 6.81 (m, 2H), 4.79 (q, *J* = 13.7, 6.8 Hz, 1H), 3.81 (s, 3H), 3.09 (s, 9H), 1.77 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 161.3, 131.8, 124.0, 120.7 (q, *J*_{C–F} = 321.2 Hz), 114.6, 73.8, 55.5, 50.8, 15.0; ¹⁹F NMR (565 MHz, CDCl₃) δ –78.5; FTIR (NaCl/thin film) 2967, 1611, 1518, 1258, 1157, 1029, 838 cm⁻¹; LRMS (ESI) [M–OTf]⁺ calculated for [C₁₂H₃₀NO]⁺ : 194.2, found: 194.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

1. a Cheltsov AV, Aoyagi M, Aleshin A, Yu EC-W, Gilliland T, Zhai D, Bobkov AA, Reed JC, Liddington RC, Abagyan R. *J. Med. Chem.* 2010; 53:3899. [PubMed: 20441222] b Huang Z, Ducharme Y, Macdonald D, Robichaud A. *Curr. Opin. Chem. Biol.* 2001; 5:432. [PubMed: 11470607] c Alami, M.; Messauoudi, S.; Hamze, A.; Provot, O.; Brion, J-D.; Liu, J-M.; Bignon, J.; Bakala, J. Dihydro-Iso-Ca-4 and Analogues: Potent Cytotoxics, Inhibitors of Tubulin Polymerization p. 2009WO2009/147217d Messauoudi S, Hamze A, Provot O, Tréguier B, Rodrigo De Losada J, Bignon J, Liu J-M, Wdzieczak-Bakala J, Thoret S, Dubois J, Brion J-D, Alami M. *ChemMedChem.* 2011; 6:488. [PubMed: 21360820] e Moree WJ, Li B-F, Jovic F, Coon T, Yu J, Gross RS, Tucci F, Marinkovic D, Zamani-Kord S, Malany S, Bradbury MJ, Hernandez LM, O'Brien Z, Wen J, Wang H, Hoare SRJ, Petroski RE, Sacca A, Madan A, Crowe PD, Beaton G. *J. Med. Chem.* 2009; 52:5307. [PubMed: 19663387] f Beaton, G.; Moree, WJ.; Jovic, F.; Coon, T.; Yu, J. Sleep Inducing Compound and Methods Relating Thereto p. 2006US2006/14797

2. For other methods, see: Zhang J, Bellomo A, Creamer AD, Dreher SD, Walsh PJ. *J. Am. Chem. Soc.* 2012; 134:13765. [PubMed: 22816972] Luan Y, Schaus SE. *J. Am. Chem. Soc.* 2012; 134:19965. [PubMed: 23206197] Fessard TC, Andrews SP, Motoyoshi H, Carreira EM. *Angew. Chem., Int. Ed.* 2007; 46:9331. Lewis CA, Chiu A, Kubryk M, Balsells J, Pollard D, Esser CK, Murry J, Reamer RA, Hansen KB, Miller SJ. *J. Am. Chem. Soc.* 2006; 128:16454. [PubMed: 17177366] Pathak TP, Gligorich KM, Welm BE, Sigman MS. *J. Am. Chem. Soc.* 2010; 132:7870. [PubMed: 20486685] Nave S, Sonawane RP, Elford TG, Aggarwal VK. *J. Am. Chem. Soc.* 2010; 132:17096. [PubMed: 21080646] Roesner S, Casatejada JM, Elford TG, Sonawane RP, Aggarwal VK. *Org. Lett.* 2011; 13:5740. [PubMed: 21995597] Bolshan Y, Chen C, Chilenski JR, Gosselin F, Mathre DJ, O'Shea PD, Roy A, Tillyer RD. *Org. Lett.* 2004; 6:111. [PubMed: 14703363]
3. For examples of the opposite approach (enantiospecific couplings of alkyl nucleophiles with aryl halides), see: Imao D, Glasspoole BW, Laberge VS, Crudden CM. *J. Am. Chem. Soc.* 2009; 131:5024. [PubMed: 19301820] Ohmura T, Awano T, Sugimoto M. *J. Am. Chem. Soc.* 2010; 132:13191. [PubMed: 20822146] Awano T, Ohmura T, Sugimoto M. *J. Am. Chem. Soc.* 2011; 133:20738. [PubMed: 22129167] Sandrock DL, Jean-Gérard L, Chen C.-y. Dreher SD, Molander GA. *J. Am. Chem. Soc.* 2010; 132:17108. [PubMed: 21077687] Lee JCH, McDonald R, Hall DG. *Nat. Chem.* 2011; 3:894. [PubMed: 22024887] Li L, Wang C-Y, Huang R, Biscoe MR. *Nat. Chem.* 2013; 5:607. [PubMed: 23787752]
4. For enantioselective couplings of benzylic electrophiles with organozinc reagents, see: Arp FO, Fu GC. *J. Am. Chem. Soc.* 2005; 127:10482. [PubMed: 16045323] Binder JT, Cordier CJ, Fu GC. *J. Am. Chem. Soc.* 2012; 134:17003. [PubMed: 23039358] Do H-Q, Chandrashekar ERR, Fu GC. *J. Am. Chem. Soc.* 2013; 135:16288. [PubMed: 24164502]
5. For enantiospecific cross couplings of with Grignard reagents, see: López-Pérez A, Adrio J, Carretero JC. *Org. Lett.* 2009; 11:5514. [PubMed: 19943702] Greene MAM, Yonova IMI, Williams FJF, Jarvo ERE. *Org. Lett.* 2012; 14:4293. [PubMed: 22568515] Taylor BLH, Harris MR, Jarvo ER. *Angew. Chem., Int. Ed.* 2012; 51:7790. Taylor BLH, Swift EC, Waetzig JD, Jarvo ER. *J. Am. Chem. Soc.* 2011; 133:389. [PubMed: 21155567] Li M-B, Tang X-L, Tian S-K. *Adv. Synth. Catal.* 2011; 353:1980.
6. For enantiospecific cross couplings with organozinc reagents, see: Wisniewska HM, Swift EC, Jarvo ER. *J. Am. Chem. Soc.* 2013; 135:9083. [PubMed: 23751004]
7. For an enantiospecific coupling of an α -cyanohydrin meslate with a boronic acid, see: He A, Falck JR. *J. Am. Chem. Soc.* 2010; 132:2524. [PubMed: 20121273]
8. Maity P, Shacklady-McAtee DM, Yap GPA, Sirianni ER, Watson MP. *J. Am. Chem. Soc.* 2013; 135:280. [PubMed: 23268734]
9. a Nugent, TC. *Chiral Amine Synthesis*. Wiley-VCH Verlag GmbH & Co. KGaA; Weinheim: 2010. b Mereyala HB, Pola P. *Tetrahedron Asym.* 2003; 14:2683. c Savile CK, Janey JM, Mundorff EC, Moore JC, Tam S, Jarvis WR, Colbeck JC, Krebber A, Fleitz FJ, Brands J, Devine PN, Huisman GW, Hughes G. *J. Science.* 2010; 329:305. d Vries T, Wynberg H, van Echten E, Koek J, ten Hoeve W, Kellogg RM, Broxterman QB, Minnaard A, Kaptein B, van der Sluis S, Hulshof L, Kooistra J. *Angew. Chem., Int. Ed.* 1998; 37:2349.
10. Harris MR, Hanna LE, Greene MA, Moore C, Jarvo ER. *J. Am. Chem. Soc.* 2013; 135:3303. [PubMed: 23414579]
11. Zhou Q, Srinivas HD, Dasgupta S, Watson MP. *J. Am. Chem. Soc.* 2013; 135:3307. [PubMed: 23425080]
12. Biphenyl-substituted benzylic electrophiles are coupled in high yields only under Jarvo's conditions using a Ni/NHC catalyst system to deliver triarylmethanes. See ref 10.
13. For examples of the use of chelating groups to accelerate reactions of phenyl-substituted systems, see: Correa A, Leon T, Martin R. *J. Am. Chem. Soc.* 2014; 136:1062. [PubMed: 24377699] Srogl J, Liu W, Marshall D, Liebeskind LS. *J. Am. Chem. Soc.* 1999; 121:9449. ^c Refs 5b, 5c, 6, 10.
14. a Ghose A, Viswanadhan V, Wendoloski J. *J. Comb. Chem.* 1999; 1:55. [PubMed: 10746014] b Xu J, Stevenson J. *J. Chem. Inform. Comput. Sci.* 2000; 40:1177.
15. Benzofuran 2 was formed in 87% yield, as determined by ¹H NMR analysis, when Ni(cod)₂/P(o-Tol)₃ was used as catalyst [Conditions: 10 mol % Ni(cod)₂, 22 mol % P(o-Tol)₃, benzofuranyl boronic acid (1.2 equiv), K₃PO₄ (1.3 equiv), dioxane, 80 °C, 6 h].

16. The reason for the difference in stereochemical fidelity in the formation of 4 and 5 is currently unclear and the subject of active investigation.
17. With $\text{Ni}(\text{cod})_2/\text{P}(\text{o-Tol})_3$ as catalyst, product 11 was formed in 76% yield and 95% ee. See ref 8.
18. Both the η^1 and η^3 forms of benzyl nickel(II) intermediates have been observed. See: Matsubara R, Gutierrez AC, Jamison TF. J. Am. Chem. Soc. 2011; 133:19020. [PubMed: 22066899]
19. Retention of configuration is well preceded in reductive elimination. See: Stille JK. Hartley FR, Patai S. Oxidative Addition and Reductive Elimination. The Chemistry of the Metal–Carbon Bond. 1985; 2:625. John Wiley & Sons, Ltd. New York Netherton MR, Fu GC. Angew. Chem., Int. Ed. 2002; 41:3910.
20. Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. Organometallics. 1996; 15:1518.
21. Icke RN, Wisegarver BB, Alles GA. Org. Synth. Coll. Vol. 1955; 3:723.
22. Reductive aminations were carried out according to literature procedure, except that Me_2NH was formed in situ from $\text{Me}_2\text{NH}\cdot\text{HCl}$ and Et_3N . See: Bhattacharyya S. Synth. Commun. 2000; 30:2001.
23. Sunman CJ, Farkas EJ. Org. Chem. 1985; 50:1110.
24. a Procopiou G, Lewis W, Harbottle G, Stockman RA. Org. Lett. 2013; 15:2030. [PubMed: 23556427] b Aggarwal VK, Barbero N, McGarrigle EM, Mickle G, Navas R, Suarez R, Unthank MG, Yar M. Tetrahedron Lett. 2009; 50:3482.
25. Teranishi S, Kurahashi T, Matsubara S. Synlett. 2013; 24:2148.

A. Prior Art **B. This Work** **Scheme 1.**

Prior art and our advances in enantiospecific cross couplings of benzylic ammonium triflates

Scheme 2.
Proposed Reaction Mechanism

Table 1

Scope of boronic acids and ammonium triflates^a

$ \begin{array}{c} \text{R}^2\text{-B(OH)}_2 \text{ (1.5 equiv)} \\ \text{Ni(cod)}_2 \\ \text{K}_3\text{PO}_4 \text{ (1.5 equiv)} \\ \text{dioxane (0.33 M)} \\ 80^\circ\text{C, 6 h} \end{array} \xrightarrow{\hspace{1cm}} \begin{array}{c} \text{R}^1 \\ \\ \text{Ar}^1\text{-CH-CH-R}^2 \\ \\ \text{NMe}_3\text{OTf} \\ \text{1} \end{array} $				
entry	product	mol % Ni(cod) ²	yield (%) ^b	ee (%) ^c
1		3	80	99
2 ^d		3	(15–27)	97
3		3	83	98
4		3	70	75
5		3	88	95 ^e
6		3	81	98
7 ^d		3	(79)	>99
8		3	76	99
9		3	91	99
10 ^d		3	(92)	96
11		0	0	n.d. ^f
12		3	50	96

$ \begin{array}{c} \text{R}^1 \\ \\ \text{Ar}^1-\text{C}-\text{NMe}_3\text{OTf} \\ \mathbf{1} \end{array} \xrightarrow[\text{K}_3\text{PO}_4 \text{ (1.5 equiv), dioxane (0.33 M), 80 }^\circ\text{C, 6 h}]{\text{R}^2-\text{B(OH)}_2 \text{ (1.5 equiv), Ni(cod)}_2} \begin{array}{c} \text{R}^1 \\ \\ \text{Ar}^1-\text{C}-\text{R}^2 \end{array} $				
entry	product	mol % Ni(cod) ²	yield (%) ^b	ee (%) ^c
13	10	10	82	>99
14	11	3	(49)	>99
15 ^g	12	10	55	86
16 ^g	13	5	58	52
17	14	10	75	92
18 ^h		10	(29)	92
19 ⁱ		10	(39)	88
20		0	(0.3)	n.d. ^f
21	15	10	71	83
22	16	10	53	80

^a Conditions: ammonium triflate **1** (0.20 mmol, 1.0 equiv), boronic acid (0.3 mmol, 1.5 equiv), Ni(cod)₂, K₃PO₄ (1.5 equiv), dioxane (0.33 M), 80 °C, 6 h. Starting materials were 99% ee, unless noted otherwise.

^b Isolated yields. Yields in parentheses determined by ¹H NMR analysis using an internal standard.

^c Determined by HPLC analysis using a chiral stationary phase, unless noted otherwise.

^d P(*o*-Tol)₃ (7 mol %) was added to this reaction.

^e Determined by SFC analysis using a chiral stationary phase.

^f_{n.d.} = not determined.

^g Amino precursor prepared via Grignard addition to *N-tert*-butanesulfinyl aldimine as a single diastereomer. Starting material assumed to be >95% ee.

^h *t*-Bu-XantPhos (12 mol %) was added to this reaction.

ⁱ P(*o*-Tol)₃ (22 mol %) was added to this reaction.