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Catalytic intermolecular C(sp³)—H amination with sulfamates for the asymmetric synthesis of amines

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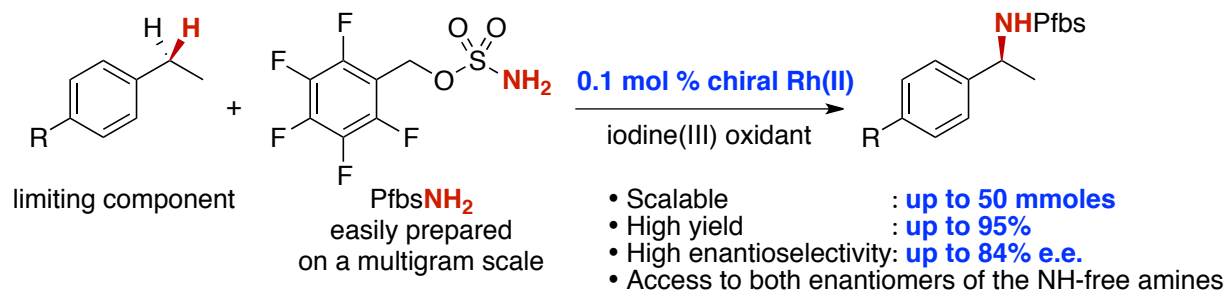
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Graphical Abstract



Abstract

This manuscript reports a practical catalytic asymmetric benzylic C(sp³)—H amination through the intermolecular insertion of a rhodium-bound nitrene species. The reaction of various substrates used as the limiting component, with a readily accessible sulfamate Pfb₃NH₂ and the chiral rhodium(II) catalyst Rh₂(*S*-tfptad)₄ in the presence PhI(OPiv)₂ can be performed on a multigram scale, affording the corresponding benzylic amines with high levels of efficiency and enantiocontrol. This process offers new opportunities for the asymmetric synthesis of amines.

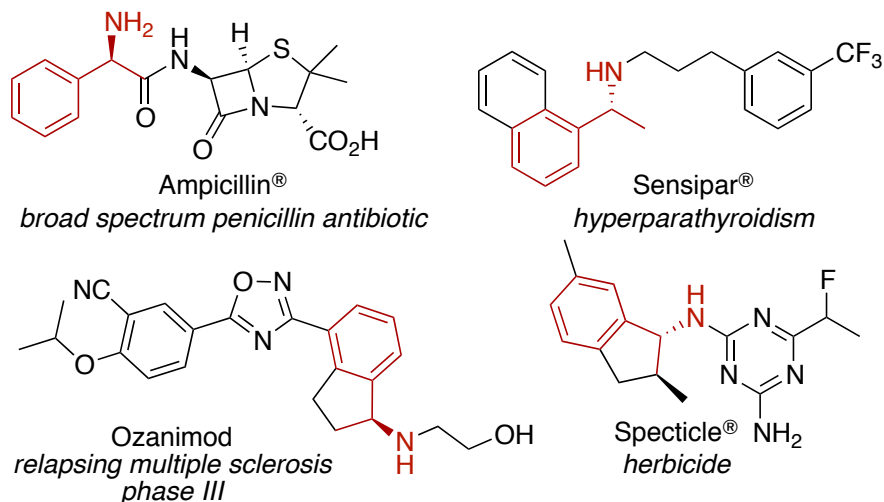
Keywords

carbon-nitrogen bond, C(sp³)—H functionalization, amination, catalysis, asymmetric, rhodium, hypervalent iodine.

Introduction

Nitrogen is a cornerstone atom in life sciences because it plays a crucial role on the properties of bioactive compounds. Several different nitrogen functional groups can be identified in a wide range of pharmaceuticals and agrochemicals, but also in a collection of small building blocks that have been designed to be part of recent leads developed by the pharmaceutical industry.^{1,2} Among these functionalities, α -branched benzylic amines are an important scaffold that is the component of many approved drugs or clinical candidates (Figure 1).

Figure 1. Examples of α -branched benzylic amines

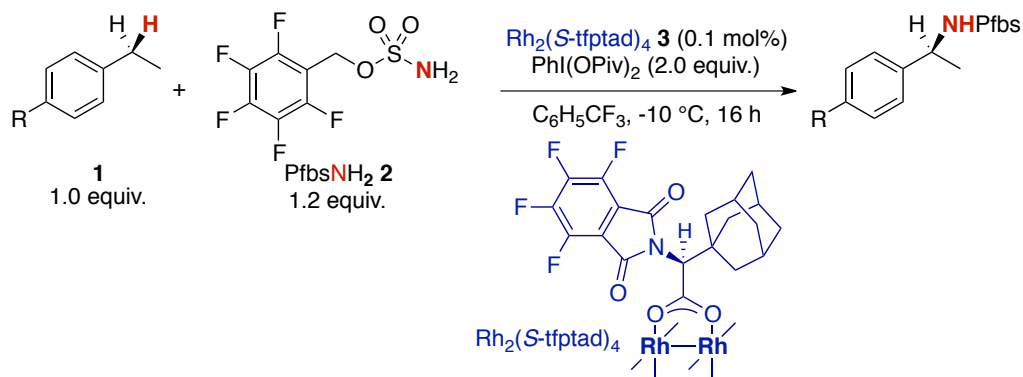


The paramount importance of nitrogen in life sciences has been the driving force for the discovery of new C—N bond forming reactions. Special attention has been recently paid to catalytic C—H amination that has emerged as a relevant alternative to catalytic C—N coupling in the last twenty years.³ Recent significant achievements have been reported with the advent of the transition metal-catalyzed nitrene transfer that relies on the combination of dirhodium(II) complexes and iodine(III) oxidants. It enables the direct amination of benzylic, allylic or tertiary C(sp³)—H bonds following nitrene insertion.⁴ The efficiency of the reaction and the practicability of the conditions are noteworthy, now making the reaction a useful tool in total synthesis.⁵

Early developments of the rhodium(II)-catalyzed C(sp³)-H amination have focused on the intramolecular reaction. The latter allows for modifying specific sites according to the nature of the tethered nitrene sources, with the sulfamates being the most efficient and versatile nitrene precursors.⁶ The careful design of chiral rhodium(II) complexes has led to develop an asymmetric version for the synthesis of enantiopure substituted amines.^{7,8} The intramolecular C(sp³)-H amination of sulfamates, interestingly, was applied to a scalable synthesis of a muscarinic antagonist but gram-scale reactions afforded the expected cyclic sulfamidate only in 50% yield.⁹

More recent studies have concentrated on the search for efficient conditions for the intermolecular C(sp³)-H amination reaction, as its applicability has been long limited by a low efficiency and a narrow scope. High yielding and stereoselective reactions have been reported in the presence of sulfonimidamides as chiral nitrene sources, however, these processes remain of limited application since they involve chiral auxiliaries in stoichiometric amounts.¹⁰ In parallel, Du Bois has designed new sulfamates for the chemoselective intermolecular C(sp³)-H amination of complex products.¹¹ These are efficient reactions that are run typically on a 0.3 mmole scale, however, a catalytic asymmetric version remains to be developed. In this context, we have recently reported the use of benzylic sulfamates in combination with a chiral rhodium(II) complex for the enantioselective benzylic C(sp³)-H amination (Scheme 1).¹² We, thus, wish to report in this communication our investigations on the practical features of the reaction.

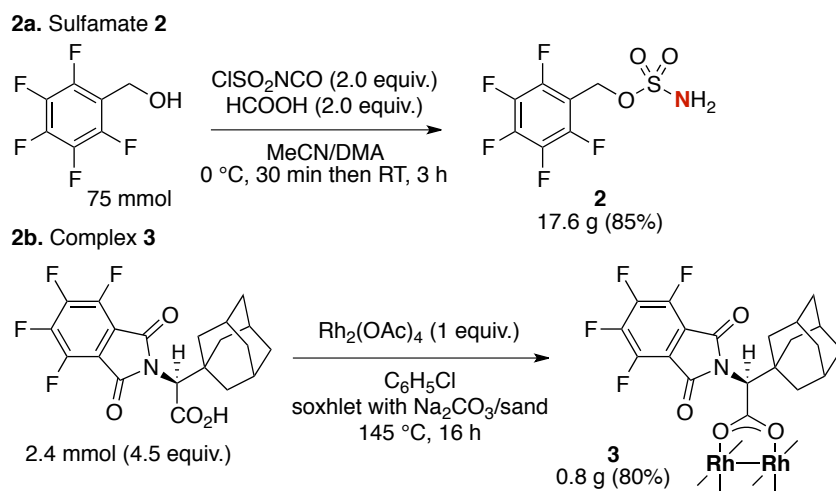
Scheme 1. Rhodium(II)-catalyzed asymmetric benzylic C(sp³)-H amination



Results and discussion

The reagent and the catalyst. The reported catalytic asymmetric reaction relies on the combination of the pentafluorobenzyl sulfamate **2** (Pfb₅NH₂) with the chiral complex tetrakis[(*S*)-(1-*N*-tetrafluorophthaloyl)-1-adamantylglycine] dirhodium(II) Rh₂(*S*-tfptad)₄ **3** in the presence of the commercially available hypervalent iodine reagent PhI(OPiv)₂.¹² On one hand, the sulfamate is easily accessible from the corresponding alcohol following reaction with sulfamoyl chloride generated *in situ* from chlorosulfonyl isocyanate in the presence of formic acid. The reaction performed on a 75 mmole scale allows for isolating compound **2** in 85% yield as a white solid (Scheme 2a). On the other hand, a simple ligand exchange with the adamantyl-derived ligand¹³ leads to the formation of the rhodium(II) complex **3** from the commercially available Rh₂(OAc)₄ on a gram-scale (Scheme 2b). It is noteworthy that the dirhodium(II) complexes do not require special handling as they are not air- and moisture-sensitive.

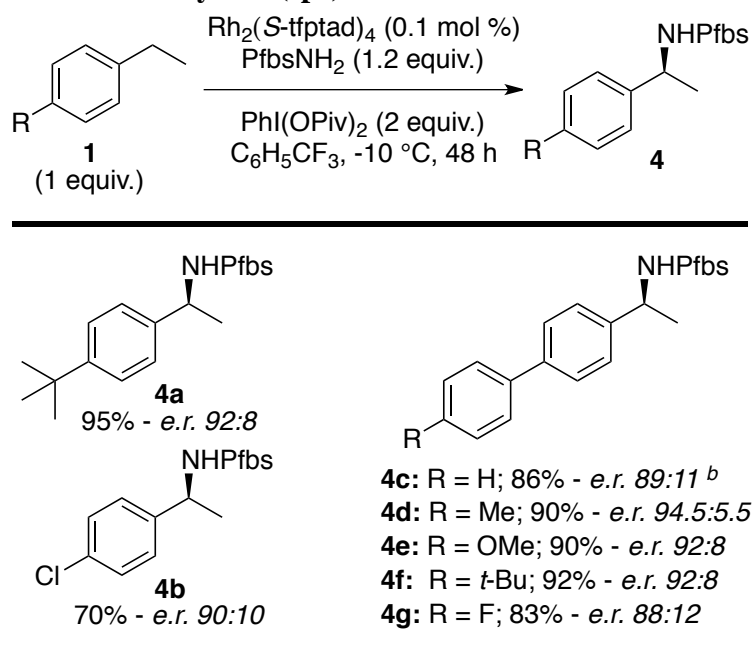
Scheme 2. Synthesis of sulfamate **2** and chiral rhodium(II) complex **3**



Scope and scale-up studies. The reaction of the sulfamate **2** and the complex **3** in the presence of PhI(OPiv)₂ proved to give excellent results under the optimal conditions, *i.e.* at -10 °C in trifluorotoluene that is a substitute solvent for reactions usually carried out in dichloromethane.¹⁴ Importantly, excellent conversions were obtained using the benzylic substrate as the limiting

component in the presence of only 0.1 mol% of the chiral rhodium catalyst **3**.^{12,15} The efficiency of this process, thus, led us to examine its applicability on a gram-scale (Table 1).

Table 1. Catalytic C(sp³)-H amination on a 5 mmole scale ^a

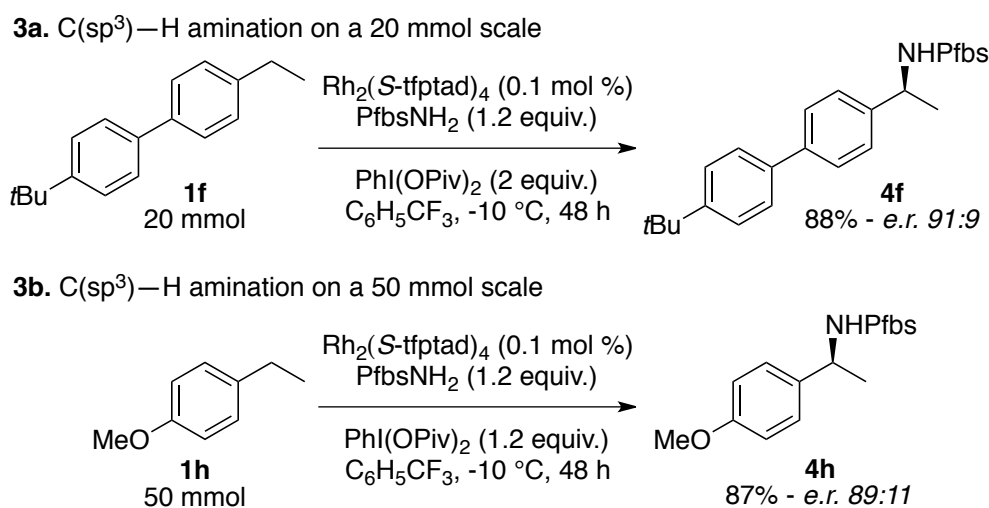


^a Reactions conditions: Substrate **1** (5 mmol), PfbsNH₂ **2** (6 mmol), Rh₂(S-tfptad) **3** (0.1 mol %), PhI(OPiv)₂ (10 mmol), trifluorotoluene (c = 0.4 M), -10 °C, 48 h. ^b Reaction on a 8 mmol scale.

In line with the previous reaction performed from compound **4d**,¹² we were pleased to find that upon scaling-up of the reaction to 5 mmoles, the enantioselectivity was maintained while the yields were found to slightly increase. For example, compound **4f** was isolated with an excellent yield of 92% whereas it was previously obtained with a yield of 82%.^{12,16} The same observation could be made for the reaction with compound **4c** carried out on 8 mmoles. The examples displayed in table 1 also highlight that the catalytic C(sp³)-H amination reaction applies to substrates with electron-donating or electron-withdrawing groups, though some withdrawing groups proved to be deleterious.¹⁷

Based on these results, reactions on larger scales were investigated (Scheme 3). Compound **1f**, thus, was engaged in a catalytic C(sp³)—H amination on a 20 mmole scale. The corresponding product **4f** was isolated with nearly equal efficiency and selectivity (Scheme 3a). However, the reaction revealed the need to reduce the amount of the hypervalent iodine reagent to make the process more sustainable. Test experiments were performed with compound **1a** using lower quantities of PhI(OPiv)₂; they demonstrated that the number of equivalents of the reagent could be reduced to 1.2 without decreasing significantly the yield while the enantioselectivity remains the same.¹⁸ These conditions were then applied to the reaction from the *p*-MeO-ethylbenzene **1h** on a 50 mmole scale. Pleasingly, the expected product **4h** was obtained with an excellent yield of 87% and an enantiomeric ratio of 89:11 (Scheme 3b). It is also noteworthy that the rhodium(II) complex can be recovered in 87% yield after purification by flash chromatography.

Scheme 3. Large scale C(sp³)—H amination reactions

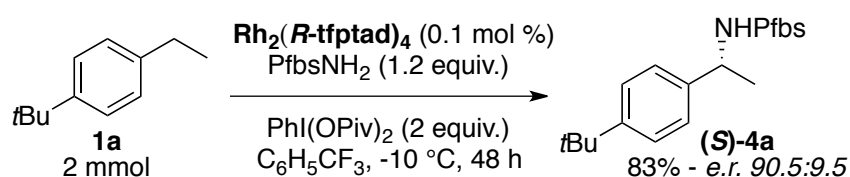


Synthetic application. The rhodium(II)-catalyzed asymmetric benzylic C(sp³)—H amination reaction offers several opportunities for the synthesis of nitrogen-containing molecules. First, the enantiomeric complex Rh₂(*R*-tfptad)₄, also accessible from 1-adamantanemethanol, gives access to the (*S*)-enantiomer of the benzylic amine **4a** with comparable levels of efficiency and enantiocontrol (Scheme 4a). The late-stage functionalization of complex products can also be

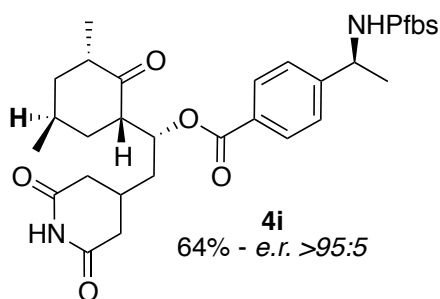
envisaged as highlighted by the aminated derivative of cycloheximide **4i** isolated as a single isomer (Scheme 4b). Finally, the pentafluorobenzylsulfamoyl group can be easily cleaved under mild conditions to afford the free amine **5** from compound **4f** in quantitative yield (scheme 4c). The deprotection was shown to occur without loss of the enantiomeric purity according to the HPLC analysis of the *N*-acetyl derivative of **5** (see supporting information).

Scheme 4. Synthetic application of the C(sp³)—H amination reaction

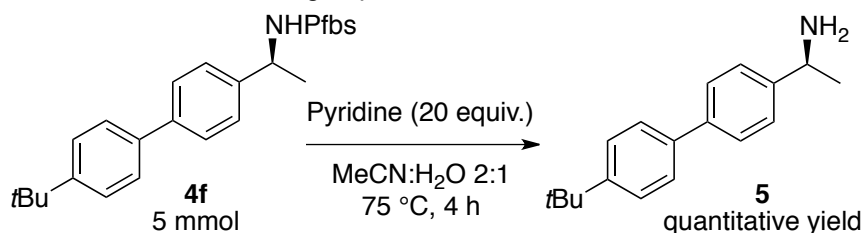
4a. C(sp³)—H amination with the (*R*)-rhodium(II) complex



4b. Late-stage C(sp³)—H amination



4c. Removal of the Pfb group



Conclusion

The design of reagents and chiral rhodium(II) complexes for nitrene transfers has led to develop an efficient catalytic C(sp³)—H amination reaction for the asymmetric synthesis of benzylic amines. The key features of the process, in addition to its efficiency and enantioselectivity, are the

readily access to the nitrogen source, the ease of handling of the rhodium complex and its low catalyst loading. Accordingly, the reaction can be performed on tens of mmoles scale without special equipment or loss of efficiency. Given the synthetic application provided by the reaction, we believe that it can be considered as a new robust C—N bond forming reaction of potential use in process chemistry.

Experimental Section

General Methods. Melting points were measured in capillary tubes on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP - C13, P31, F19 - probe or Dual C13 probe) and Avance 500 MHz (BB0 - ATM probe or BBI - ATM probe). Fluorine (^{19}F) NMR were recorded in the Bruker Avance II spectrometer. Carbon NMR (^{13}C) spectra were recorded at 125 or 75 MHz, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. NMR experiments were carried out in deuterated chloroform (CDCl_3), $\text{MeOH-}d_4$, or $\text{DMSO-}d_6$. Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane (TMS) or residual solvent peaks for ^1H and ^{13}C NMR spectra or trifluorotoluene for ^{19}F NMR spectra. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sept: septet, app.: apparent, m: multiplet, br.: broad. Coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained either with a LCT (Micromass) instrument using electrospray ionization (ES), or from a Time of Flight analyzer (ESI-MS) for the high resolution mass spectra (HRMS). Thin-layer chromatography was performed on silica gel 60 F254 on aluminium plates (Merck) and visualized under a UVP

Mineralight UVLS-28 lamp (254 nm) and by staining with solutions of either ninhydrin, basic KMnO_4 , phosphomolybdic acid, or acidic *p*-anisaldehyde in ethanol. Flash column chromatography was conducted on Merck silica gel 60 (40-63 μm) at medium pressure (300 mbar) or on puriFlash Spott II (Interchim). The enantiomeric excesses were determined by HPLC analysis on a Daicel Chiralpak IA-5 column or a Daicel Chiralpak IC-5 column. All reagents were obtained from commercial suppliers unless otherwise stated.

Synthesis of the pentafluorobenzyl sulfamate (2). In a flask under argon was added chlorosulfonyl isocyanate (13.0 mL, 150 mmol). The flask was cooled to 0 °C, and HCO_2H (5.70 mL, 150 mmol) was added slowly with vigorous stirring, while intense gas evolution was observed. The mixture solidified within 5 minutes. Anhydrous MeCN (6 mL) was added and the resulting solution was stirred for 30 minutes before the ice bath was removed. After 3 h, the mixture was cooled again to 0 °C, then a solution of pentafluorobenzyl alcohol (15.0 g, 75.0 mmol) in anhydrous DMA (10 mL) was added slowly over 10 minutes. The mixture was stirred at 0 °C for 30 minutes then the ice bath was removed. After 3 h at room temperature, 15 ml of water were added. The solution was extracted 3 times with AcOEt and the combined organic phases were washed with water, dried over Na_2SO_4 , filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt: 7/3) to afford the expected product as a white solid (17.6 g, 85%). m.p. = 84–85.5 °C. ^1H NMR (500 MHz, CDCl_3): δ 5.31 (s, 2H), 4.85 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 59.0. The peaks of the perfluoroarene ring are not listed. ^{19}F NMR (282 MHz, CDCl_3) δ -142.0 – -142.3 (m, 2F), -150.9 – -151.3 (m, 1F), -161.4 – -161.8 (m, 2F). IR (neat) 3350, 3259, 1659, 1520, 1505, 1365, 1313, 1167, 1133, 1048, 965, 928, 837, 680 cm^{-1} . HRMS = $[\text{M}-\text{H}]^-$ calculated for $[\text{C}_7\text{H}_3\text{F}_5\text{NO}_3\text{S}]^-$ = 275.9759, found 275.9737.

Synthesis of the rhodium(II) complex Rh₂(*S*-tfptad)₄ (3**).** To a mixture of (*S*)-tfptad (1.00 g, 2.43 mmol) and Rh₂(OAc)₄ (241 mg, 0.540 mmol) was added chlorobenzene (20.0 mL). The flask was adapted with a Soxhlet extractor containing a cartridge filled with a mixture of Na₂CO₃ and sand (3:1). The solution was heated to reflux for 16 h. The reaction mixture was then cooled down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/EtOAc: 98/2) to provide the title product as a green solid (798 mg, 80%). ¹H NMR (500 MHz, CDCl₃): δ 4.53 (s, 1H), 1.96 (s, 3H), 1.85 (d, *J* = 12.3 Hz, 3H), 1.73 – 1.57 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 185.6, 162.3 (2C), 147.1 (app. d, *J* = 281 Hz, 2C), 145.5 (app. d, *J* = 281 Hz, 2C), 113.7 (d, *J* = 10 Hz, 2C), 63.1, 39.6 (3C), 37.6, 36.8 (3C), 28.7 (3C). ¹⁹F NMR (282 MHz, CDCl₃) δ -136.5 – -137.1 (m, 2F), -142.7 – -144.5 (m, 2F). IR (neat) 2902, 2851, 1785, 1723, 1511, 1495, 1397, 1361, 1346, 1312, 1159, 1090, 950, 777, 756, 731 cm⁻¹.

Synthesis of compound 4h (50 mmol Scale). A flask containing 1-methoxy-4-ethylbenzene (6.80 g, 50.0 mmol) was charged with Rh₂(*S*-tfptad)₄ **3** (92 mg, 50.0 μmol) and **2** (16.6 g, 1.20 mmol). 80 ml of anhydrous PhCF₃ were added and the resulting mixture was cooled to -10 °C. PhI(OPiv)₂ (24.4 g, 60.0 mmol) was then added in one portion and the mixture was stirred at -10 °C for 48 h. DCM was then added followed by a saturated aqueous solution of thiourea. The color changed to dark brown and the mixture was stirred for 15 minutes. The content was transferred into a separatory funnel, and the organic layer was collected. The aqueous layer was extracted twice with DCM. The combined organic extracts were washed with saturated NaHCO₃, dried over Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt: 8/2) to afford the expected product **4h** as a

brown oil (17.9 g, 88%, 89:11 e.r.). The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IC-5 column: 90:10 heptane/IPA, flow rate 1 mL/min, $\lambda = 266$ nm: T_R Major = 12.2 min, T_R Minor = 14.6 min. ^1H NMR (300 MHz, CDCl_3) δ 7.21 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.13 – 5.00 (m, 2H), 4.75 (d, $J = 6.6$ Hz, 1H), 4.58 (app. quint., $J = 6.8$ Hz, 1H), 3.80 (s, 3H), 1.55 (d, $J = 6.8$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 159.5, 133.7, 127.5 (2C), 114.2 (2C), 58.2, 55.4, 54.4, 22.9 ppm. The peaks of the perfluoroarene ring are not listed. ^{19}F NMR (282 MHz, CDCl_3) δ -141.9 – -142.1 (m, 2F), -151.8 – -152.0 (m, 1F), -161.9 – -162.2 (m, 2F) ppm. IR (neat) $\nu = 3276, 2972, 1659, 1526, 1499, 1460, 1436, 1359, 1308, 1296, 1259, 1169, 1135, 1046, 983, 942, 929, 878, 820, 777$ cm^{-1} . HRMS = $[\text{M}-\text{H}]^-$ calculated for $[\text{C}_{16}\text{H}_{13}\text{F}_5\text{NO}_2\text{S}] = 410.0490$, found 410.0524.

Deprotection of compound 4f. To a solution of **4f** (2.60 g, 5.00 mmol, 1.00 eq.) in acetonitrile-water (2:1, 40 mL) was added pyridine (1.61 mL, 100 mmol, 20.0 eq.). The mixture was stirred at 75 °C for 4 h before being concentrated under reduced pressure. The residue was transferred into a separatory funnel using AcOEt, then the organic layer was washed with HCl (6M). The acidic aqueous layer was extracted twice with AcOEt and the combined organic layers were concentrated under reduced pressure. Subsequent addition of heptane and concentration was repeated until complete removal of the remaining pyridine. The desired product was obtained sufficiently pure as a white solid (1.26 g, 99%). m.p. = 82–84 °C. ^1H NMR (300 MHz, DMSO) δ 7.64 (d, $J = 8.1$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 2H), 7.51 – 7.46 (m, 4H), 4.59 – 4.52 (m, 1H), 1.60 (d, $J = 6.8$ Hz, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, MeOD) δ 151.0, 142.0, 138.2, 137.8, 127.9 (2C), 127.5 (2C), 126.7 (2C), 126.0 (2C), 57.0, 34.5, 30.9 (3C), 19.6 ppm. IR (neat) $\nu = 3029, 2925, 2448, 1727, 1501, 1382, 1289, 1256, 1167, 1056, 1029, 1003, 850, 810$ cm^{-1} . HRMS = $[\text{M}-\text{NH}_3]^+$ calculated for $[\text{C}_{18}\text{H}_{21}] = 237.1643$, found 237.1637.

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Supporting Information.

General procedures. Characterization, ^1H , ^{13}C NMR, and ^{19}F NMR spectra of Pfb₃NH₂ **2**, the rhodium complex **3**, and compounds **4a-i** and the *N*-Ac derivative of **5**. HPLC of compounds **4** and the *N*-Ac derivative of **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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- (16) Recrystallization of compound **4f** allows for increasing the enantiomeric ratio up to 96:4. See reference 12.
- (17) For some examples of unsuccessful substrates: starting from methyl 4-ethylbenzoate, the catalytic C(sp³)—H amination reaction affords the corresponding product with a low conversion of 35%, whereas no reaction takes place from *p*-cyano ethylbenzene.

(18) Reactions of **1a** with PfbS-NH_2 and $\text{Rh}_2(\text{S-tfptad})_4$ in the presence of either 1.6, 1.4, or 1.2 equivalents of $\text{PhI}(\text{OPiv})_2$ led to isolate product **4a** in 85% yield and with an e.r. of 90:10.