Asymmetric Synthesis of α-Branched Amines via Rh(III)-Catalyzed C–H Bond Functionalization

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Supporting Information

ABSTRACT: The first asymmetric intermolecular addition of non-acidic C–H bonds to imines is reported. The use of the activating N-perfluorobutanesulfonyl imine substituent is essential for achieving sufficient reactivity and provides outstanding diastereoselectivity (>98:2 dr). Straightforward removal of the sulfonyl group with HCl yields the highly enantiomerically enriched amine hydrochlorides.

Due to their prevalence in drugs and natural products, chiral α-branched amines are important synthetic targets, and the addition of organometallic reagents to imines serves as one of the principal approaches for their preparation.1–3 Recently, the transition-metal-catalyzed addition of non-acidic C–H bonds to imines has been developed and provides a powerful alternative because of the vast number of potential starting inputs, high functional group compatibility, and lack of waste byproducts.4–6 Herein, we report, to our knowledge, the first examples of the intermolecular asymmetric addition of non-acidic C–H bonds to imines by Rh(III)-catalyzed aromatic C–H bond addition to N-perfluorobutanesulfonyl imines (Scheme 1).7–10 These transformations proceed with >98:2 diastereoselectivity using both tertiary carboxamide and azo directing groups, with the azo group not having been reported previously for C–H bond additions to imines.11 Moreover, for both classes of products the sulfonyl group can be removed by straightforward acid treatment to provide amine hydrochlorides in excellent yields and with high enantiomeric purities.

While we and others have reported on the synthesis of α-branched amines by Rh(III)-catalyzed additions of sp² C–H bonds to N-Boc and N-sulfonyl imines, only racemic α-branched amines have so far been obtained.4 Because the diastereoselective addition of organometallic reagents to N-tert-butanesulfonyl imines is one of the most frequently used methods for the asymmetric synthesis of branched amines,3 we explored the Rh(III)-catalyzed addition of C–H bonds to N-tert-butanesulfonyl imines. However, we did not observe any reaction, a result that was also independently reported by Shi and co-workers.4f

We therefore focused on the more activating N-perfluorobutanesulfonyl group developed by Liu.10 Our initial investigations centered on the identification of a suitable catalyst and reaction conditions for coupling benzamide 1a and racemic imines (±)-2 (R = CF₃) to afford chiral branched amine (±)-3 (R = CF₃) (Table 1). A mixture of 5 mol % of the precatalyst [Cp*RhCl₂]₂ and 20 mol % of AgSbF₆ in DCE at 75 °C provided the desired product (±)-3 (R = CF₃) in 21% yield (entry 1). However, a byproduct resulting from cyclization, (±)-4, was also observed in 7% yield. Increasing the temperature to 90 °C did not improve the reaction conversion and resulted in a greater proportion of the undesired byproduct (±)-4 (entry 2). As a consequence the reaction was carried out at 50 °C to avoid generating (±)-4 (entry 3).

Attempts to carry out the reaction in coordinating solvents such as t-BuOH (entry 4) and THF (entry 5) led to lower conversion to (±)-3, consistent with previous findings for Rh(III)-catalyzed imine additions.4 Further optimization studies revealed that improved yields of (±)-3 can be achieved by increasing the catalyst loading (entry 6) and increasing the reaction concentration (entry 7). Performing the reaction at concentrations higher than 0.75 M was not pursued due to solubility issues. As compared to AgSbF₆, the completely non-coordinating halide abstractor AgB(C₆F₅)₄ resulted in an appreciable improvement in yield for addition to the sulfonyl imine (±)-2 (R = H), which lacks an electron-withdrawing substituent on the aromatic ring (entry 8 versus 9). On increasing the stoichiometry of benzamide 1a from 1.5 to 2 equiv relative to sulfonyl imine (±)-2 (R = H), a slight improvement in yield was observed (entry 10). Importantly, under all of the conditions examined, the reactions proceeded with exceedingly high asymmetric induction, with diasteromer 3 being observed with >99:1 dr as determined by ¹H and ¹³C NMR as well as HPLC analysis.12

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Scheme 1. Addition of C–H Bonds to Imines

Previous work

This work

[Diagram of the reaction scheme]

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Having established that the Rh(III)-catalyzed addition of benzamides \(1a\) to perfluorobutanesulfonyl imines \((\pm)-2\) proceeds with high diastereoselectivity, we coupled a series of pyrrolidinyl benzamides \(1\) and enantiomerically pure \(N\)-perfluorobutanesulfonyl imines \(2\) to explore the reaction scope (Table 2). Electron-neutral \((3a,e-\rangle\) and electron-rich pyrrolidinyl benzamides with meta \((3b)\) or para \((3c)\) substitution provided good yields of addition products, while a more electron-deficient pyrrolidinyl benzamide coupled in poor yield \((3d)\). For \(\text{Cp}^\ast\text{Rh}(\text{III})\) complexes, concerted metalation–deprotonation has been reported to proceed more slowly for electron-deficient substrates, and this is presumably the reason for the lower yield.\(^{13}\)

Various functional groups such as methoxy \((3c)\), chloro \((3e)\), nitro \((3g)\), trifluoromethyl \((3f)\), ester \((3h)\), methyl \((3i)\), and fluoro \((3k)\) functionality were well tolerated in the transformation. The use of aromatic imines with electron-withdrawing substituents at the para position provided the chiral branched amine products in good yields \((3e,3g,3h,3i)\), while an imine with an electron-donating para methyl group required that \(\text{Ag}_2\text{CO}_3\) be added for a comparable yield to be obtained \((3i)\). Sulfinyl imines with ortho \((3j)\) and meta \((3k)\) substitution patterns were also effective. Although alkyl imides did not provide addition products (data not shown), coupling occurred with an activated \(N\)-perfluorobutanesulfonyl imino ester to provide arylglycine \(3l\).

For all substrate combinations examined, greater than 99:1 diastereoselectivity was observed, with the relative configuration for branched amine \(3a\) rigorously determined by X-ray structural analysis. A stereochemical model for the transformation is depicted in Scheme 2. Enantiomeric rhodacycles \(A\) and \(B\) are based upon the X-ray structures of corresponding cationic rhodacycles derived from 2-phenylpyridine, which have chiral, piano stool geometries.\(^{4b,c}\) We speculate that reaction occurs through \(C\) with the \(\text{C}_2\text{F}_5\) substituent pointing away from the reaction center. This model is consistent with prior detailed mechanistic studies on the addition of 2-phenylpyridine to \(N\)-sulfonyl and \(N\)-carbamoyl imines.\(^{14}\)

The substrate scope was further extended to include azobenzene, which incorporates a directing group that has

| entry | \(R\) | catalyst (mol\%) | solv | temp (°C) | \((\pm)\) 2 conc (M) | yield (%)\(^c\) |
|-------|------|-----------------|------|----------|----------------|----------------|
| 1     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(20)\) | DCE  | 75       | 0.50          | 21       | 7\|^e\) |
| 2     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(20)\) | DCE  | 90       | 0.50          | 3        | 19      |
| 3     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(20)\) | DCE  | 50       | 0.50          | 28       |
| 4     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(20)\) | i-\text{BuOH} | 50 | 0.50 | 18 |
| 5     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(20)\) | THF  | 50       | 0.50          | 26       |
| 6     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(40)\) | DCE  | 50       | 0.75          | 45       |
| 7     | \(\text{CF}_3\) | \(\text{[Cp}^\ast\text{RhCl}_2(5)/\text{AgSbF}_6(40)\) | DCE  | 50       | 0.75          | 49       |
| 8     | \(\text{H}\) | \(\text{[Cp}^\ast\text{RhCl}_2(10)/\text{AgB(C}_6\text{F}_5)_4(40)\) | DCE  | 50       | 0.75          | 45       |
| 9     | \(\text{H}\) | \(\text{[Cp}^\ast\text{RhCl}_2(10)/\text{AgB(C}_6\text{F}_5)_4(40)\) | DCE  | 50       | 0.75          | 59       |
| 10    | \(\text{H}\) | \(\text{[Cp}^\ast\text{RhCl}_2(10)/\text{AgB(C}_6\text{F}_5)_4(40)\) | DCE  | 50       | 0.75          | 63\(^d\) |

\(^a\)Conditions: 1.5 equiv of \(1\) relative to \((\pm)-2\) \((R = \text{CF}_3)\) for 20 h. \(^b\)Conditions: 1.5 equiv of \(1\) relative to \((\pm)-2\) \((R = \text{H})\) for 48 h. \(^c\)Determined by \(^1\text{H}\) NMR relative to 2,6-dimethoxytoluene as an external standard. \(^d\)Conditions: 2 equiv of \(1\) relative to \((\pm)-2\) \((R = \text{H})\) for 48 h.
not been previously utilized for this type of transformation (Table 3). Azobenzene as well as substituted azobenzenes added to N-perfluorobutanesulfonyl imino ester 2f under the optimized conditions to give arylglycines 6 in good yields and with outstanding diastereoselectivity. For unsymmetrical azobenzenes with 3,5-dimethyl substitution, complete regioselectivity for functionalization of the aromatic ring lacking the 3,5-dimethyl substituents was observed (6b,e). This result is consistent with our prior observations of the very strong steric bias exerted by meta substituents in additions of aromatic C–H bonds to polarized π-bonds.11b,d In a very preliminary study, the addition of 2-phenylquinoline to 4-trifluoromethylphenyl imine 2f was also evaluated (eq 1). The reaction proceeds in moderate yield and once again with very high diastereoselectivity.

The N-perfluorobutanesulfonyl group could readily be removed from the branched amine products by treatment with HCl as demonstrated for 3a and 6a (Scheme 3). Importantly, amine hydrochlorides 7a and 8a, respectively, were obtained in high yield and with high enantiomeric excess, indicating that no loss in stereochemical purity was observed during the synthesis sequence starting with perfluorobutanesulfanilamide of 99.25:0.75 (S,R) enantiomeric purity.

In summary, a cationic Rh(III) catalyst prepared from \([\text{Cp}^*\text{RhCl}_2]\_2\) and \(\text{AgB(C}_6\text{F}_5)_4\) was used for the directed addition of aromatic C–H bonds to N-perfluorobutanesulfonyl imines. The branched amine products were obtained with >98:2 dr for the pyrrolidinecarboxamide, azo, and quinolone directing groups. Straightforward removal of the sulfonyl group with HCl then provided the highly enantiomerically enriched amine hydrochlorides in very good yield. We are actively exploring different cationic Rh(III) and other metal catalysts for the addition of a broad range of non-acidic aromatic and alkenyl C–H bonds to N-perfluorobutanesulfonyl imines.

**ASSOCIATED CONTENT**

Supporting Information

Procedures, spectral data, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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