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

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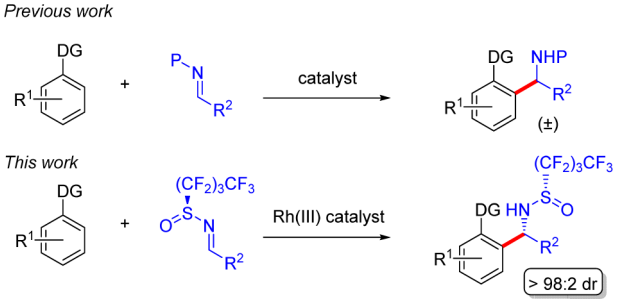
Supporting Information

ABSTRACT: The first asymmetric intermolecular addition of non-acidic C−H bonds to imines is reported. The use of the activating *N*-perfluorobutanesulfinyl imine substituent is essential for achieving sufficient reactivity and provides outstanding diastereoselectivity (>98:2 dr). Straightforward removal of the sulfinyl 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*-perfluorobutanesulfinyl 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 sulfinyl group can be removed by straightforward acid treatment to provide amine hydrochlorides in excellent yields and with high enantiomeric purities.

Scheme 1. Addition of C−H Bonds to Imines



While we and others have reported on the synthesis of α-branched amines by Rh(III)-catalyzed additions of sp^2 C−H bonds to *N*-Boc and *N*-sulfonyl imines, only racemic α-branched amines have so far been obtained.[4] Because the diasteroeselective addition of organometallic reagents to *N*-*tert*-butanesulfinyl 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*-butanesulfinyl 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*-perfluorobutanesulfinyl 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 = CF_3) to afford chiral branched amine (±)-**3** (R = CF_3) (Table 1). A mixture of 5 mol % of the precatalyst $[Cp^*RhCl_2]_2$ and 20 mol % of $AgSbF_6$ in DCE at 75 °C provided the desired product (±)-**3** (R = CF_3) 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 $AgSbF_6$ the completely non-coordinating halide abstractor $AgB(C_6F_5)_4$ resulted in an appreciable improvement in yield for addition to the sulfinyl 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 sulfinyl 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 diastereomer **3** being observed with >99:1 dr as determined by ^1H and ^{13}C NMR as well as HPLC analysis.[12]

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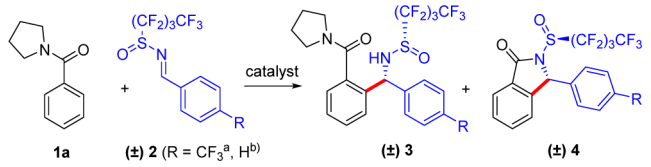
Table 1. Optimization of Reaction Conditions



entry	R	catalyst (mol%)	solv	temp (°C)	(±) 2 conc (M)	yield (%)[c] 3	yield (%)[c] 4
1	CF_3	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	DCE	75	0.50	21	7
2	CF_3	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	DCE	90	0.50	3	19
3	CF_3	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	DCE	50	0.50	28	
4	CF_3	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	*t*-BuOH	50	0.50	18	
5	CF_3	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	THF	50	0.50	26	
6	CF_3	$[Cp^*RhCl_2]_2$ (10)/$AgSbF_6$ (40)	DCE	50	0.50	45	
7	CF_3	$[Cp^*RhCl_2]_2$ (10)/$AgSbF_6$ (40)	DCE	50	0.75	49	
8	H	$[Cp^*RhCl_2]_2$ (10)/$AgSbF_6$ (40)	DCE	50	0.75	45	
9	H	$[Cp^*RhCl_2]_2$ (10)/$AgB(C_6F_5)_4$ (40)	DCE	50	0.75	59	
10	H	$[Cp^*RhCl_2]_2$ (10)/$AgB(C_6F_5)_4$ (40)	DCE	50	0.75	63[d]	

[a]Conditions: 1.5 equiv of **1** relative to (±)-**2** (R = CF_3) for 20 h. [b]Conditions: 1.5 equiv of **1** relative to (±)-**2** (R = H) for 48 h. [c]Determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as an external standard. [d]Conditions: 2 equiv of **1** relative to (±)-**2** (R = H) for 48 h.

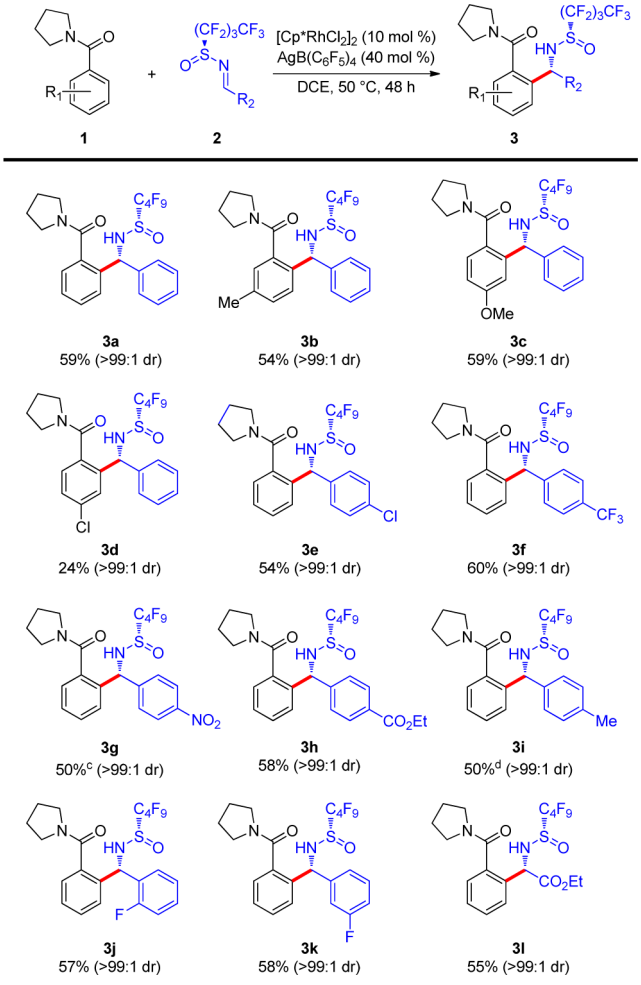
Having established that the Rh(III)-catalyzed addition of benzamides **1a** to perfluorobutanesulfinyl imines (±)-**2** proceeds with high disastereoselectivity, we coupled a series of pyrrolidinyl benzamides **1** and enantiomerically pure *N*-perfluorobutanesulfinyl imines **2** to explore the reaction scope (Table 2). Electron-neutral (**3a,e−j**) 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 Cp*Rh(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,f,g,h**), while an imine with an electron-donating para methyl group required that Ag_2CO_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 imines did not provide addition products (data not shown), coupling occurred with an activated *N*-perfluorobutanesulfinyl 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 C_4F_9 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

Table 2. Substrate Scope for Benzamide Addition[a,b]



[a]Conditions: **1** (0.30 mmol) and **2** (0.15 mmol) in DCE (0.75 M) for 48 h. [b]Isolated yield after purification by silica gel chromatography. [c]Reaction performed at lower concentration (0.50 M DCE) due to solubility. [d]Reaction performed in 1,4-dioxane with Ag_2CO_3 (40 mol %).

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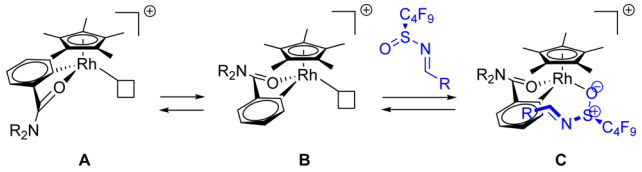
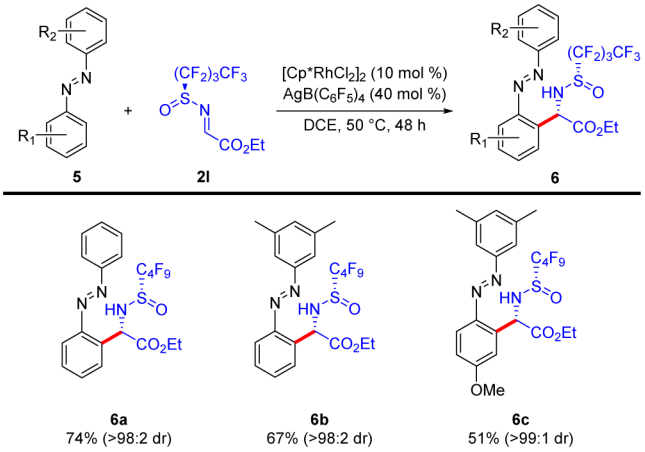
Scheme 2. Stereochemical Model



not been previously utilized for this type of transformation (Table 3).[11] Azobenzene as well as substituted azobenzenes

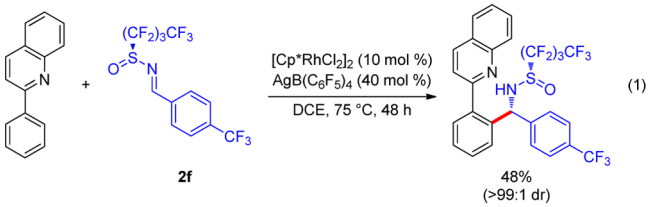
Table 3. Azobenzenes as New Directing Group[a,b]



[a]Conditions: **1** (0.225 mmol) and **2** (0.15 mmol) in DCE (0.75 M) for 48 h. [b]Isolated yield after purification by silica gel chromatography.

added to *N*-perfluorobutanesulfinyl imino ester **2l** 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**,**c**). 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.

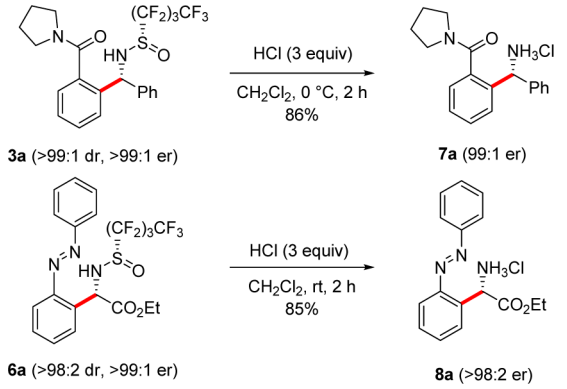


(1)

The *N*-perfluorobutanesulfinyl 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 perfluorobutanesulfinamide of 99.25:0.75 (*S*:*R*) enantiomeric purity.

In summary, a cationic Rh(III) catalyst prepared from $[Cp^*RhCl_2]_2$ and $AgB(C_6F_5)_4$ was used for the directed

Scheme 3. Preparation of Amine Hydrochlorides



addition of aromatic C−H bonds to *N*-perfluorobutanesulfinyl imines. The branched amine products were obtained with >98:2 dr for the pyrrolidinecarboxamide, azo, and quinolone directing groups. Straightforward removal of the sulfinyl 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*-perfluorobutanesulfinyl 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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(14) X-ray structures have been determined for seven-membered rhodacycles obtained upon addition of 2-phenylpyridine to *N*-carbamoyl and *N*-sulfonyl imines. For each class of imine, the nitrogen and an oxygen of the nitrogen substituent were both observed to be coordinated to the cationic rhodium center. See refs 4b,c.