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Communication

"Sulfolefin": A Mixed Sulfinamido-Olefin Ligand in Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Trifluoromethyl Ketones.

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Performing catalytic enantioselective carbon-carbon bond forming reactions, especially for the synthesis of tertiary carbinols is one of the most challenging goals in modern asymmetric synthesis. Herein, we report an efficient enantioselective catalytic approach for the 1,2-addition of arylboronic acids to trifluoromethyl ketones affording tertiary trifluoromethyl-substituted alcohols with high yields and good enantioselectivities. The reported process uses as catalyst precursor the shelf stable sulfinamido-olefin ligand 1, "*sulfolefin*", obtained on a multigram scale and in one step from a sugar derived sulfinate ester.

Fluorinated compounds have found extensive application in the fields of materials, pharmaceuticals and agrochemistry.[1] Particularly, the syntheses of chiral tertiary trifluoromethyl-substituted alcohols have gained increasing interest due to their unique properties and unusual reactivities.[2] In this context, numerous methods for the trifluoromethylation of carbonyl compounds have been reported.[3] However, enantioselective trifluoromethylation is difficult to achieve and good enantiomeric excesses are rarely reached.[4]

An alternative strategy for the syntheses of trifluoromethyl substituted tertiary alcohols would be the addition of boronic acids to trifluoromethyl ketones, due to the ready availability, good stability, and non-toxic nature of various boronic acids as the starting materials.[5] However, the formation of tetrasubstituted carbons *via* the addition of carbon nucleophiles to ketones still constitutes a major challenge in synthetic chemistry.[6] Indeed, only three catalytic enantioselective arylations of fluorinated ketones have been reported,[7,8] affording trifluoromethylated carbinols with modest yields and ees in most cases.[8] The three methods employ P-coordinating ligands, either as a phosphine, phosphite, or phosphoramidite group. Despite their excellent coordinating behavior, P-based ligands which are generally obtained through multistep syntheses, suffer moreover from their poor stability toward oxygen, which imposes stringent experimental conditions. In sharp contrast sulfinyl-based ligands which have been scarcely used as catalyst precursors, present undeniable advantages for their applications in asymmetric catalysis.[9] In this sense, sulfinyl derivatives are air, oxygen and moisture stable, and are ideally suited for the construction of diverse metal-ligand complexes with a well-defined chiral environment as a result of the close proximity of the chiral sulfur atom to the coordination sphere of the metal.[10] Within our interest in the synthesis and applications of chiral sulfur derivatives in organic [11] and metal-promoted catalysis,[12] we have recently reported that C_2-symmetric bis-sulfoxides,[13] and C_1 mixed sulfinamido-olefin ligands are good catalyst precursors in Rh-promoted addition of boronic acids to activated alkene and ketones in organic solvent and in water.[14]

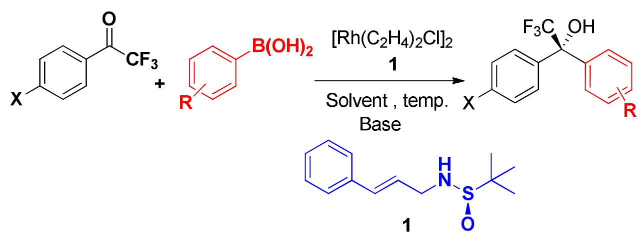


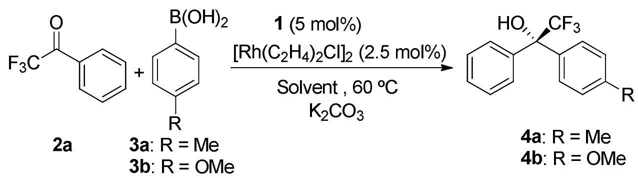
Figure 1: Rh-catalyzed addition of boronic acids to trifluoromethyl ketones using sulfolefin **1** as ligand.

Based on these premises, in the present work we report on the utilization of the simple cinnamylsulfinamide **1** ligand in the rhodium-catalyzed addition of arylboronic acids to trifluoromethylketones for the asymmetric synthesis of chiral trifluoromethylated tertiary alcohols, Figure 1.

The addition of *p*-tolylboronic acid **3a** to 2,2,2-trifluoroacetophenone **2a** was used as model reaction, and we were pleased to find that the reaction takes place and provides promising results (table 1, entries 1-4). Using $[Rh(C_2H_4)Cl]_2$ (2.5 mol%) as the catalyst precursor and "Sulfolefin" **1** (5 mol%) as the ligand, the addition proceeded at 60 ºC for 20 h to provide the desired product **4a** in an acceptable ee (66%), albeit in low yield in TBME described as the best solvent in the three catalytic enantioselective arylations of trifluoromethyl ketones reported to date (entry 1).[7,8] In attempt to ameliorate the yield and enantioselectivity of the process, we conducted a study using different ethereal solvents (table 1, entries 1-4). The use of dioxane (table 1, entry 2) afforded the product with identical ee

(66%), but in lower conversion (15% isolated yield), while the use of THF (table 1, entry 3) inhibits the reaction as no trace of the product **4a** was detected in the crude reaction mixture and the starting material was recovered unaltered. Gratifyingly, the use of diethyl ether (Et_2O) as the solvent did ameliorate not only the yield (73%) and the enantioselectivity (68 % *ee*) but also reduce the reaction time from 20 hours to only 3 hours (table 1, entry 4). The use of *p*-methoxyphenylboronic acid as nucleophile afforded the corresponding tertiary trifluoromethyl alcohol **4b** in good yield (65%) and good ee (70%), identifying Et_2O as the most suitable solvent in terms of activity and enantioselectivity for this reaction (table 1, entry 5).

Table 1: Solvent effect on the enantioselective rhodium-catalyzed addition of the arylboronic acids **3a** and **3b** to the trifluoromethyl ketone **2a**.[a]

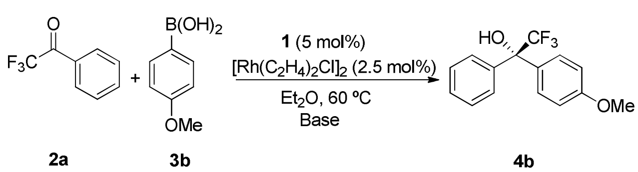


Entry	R	Solvent	Time (h)	Yield[b] (%)	*er* (%*ee*)[c]
1	Me	TBME	20	27	83: 17 (66%)
2	Me	dioxane	20	15	83: 17 (66%)
3	Me	THF	20	0	--
4	Me	Et_2O	3	73	84: 16 (68%)
5	OMe	Et_2O	3	63	85:15 (70%)

[a]All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$. [b]Isolated product. [c]Determined by chiral stationary phase HPLC using Chiralcel OJ-H® column

Next, and in order to unravel the effect of the base on the reaction, various inorganic and organic bases were screened on the addition reaction of 4-methoxyphenylboronic acid **3b** on trifluoroacetophenone **2a** (table 2). The use of potassium phosphate as base (table 2, entry 2) afforded the desired product **4b** with acceptable ee (64%) and modest yield (54%). Triethylamine afforded the product with enhanced ee (70%) but in very low yield (table 2, entry 3), while no product was formed when using potassium hydroxide as base (table 2, entry 4). Satisfyingly, the use of potassium fluoride gave the product in almost quantitative yield (99%) and with 72% ee (table 2, entry 5).

Table 2: Effect of the base on the enantioselective rhodium-catalyzed addition of arylboronic acid **3b** to trifluoromethyl ketone **2a**.[a]

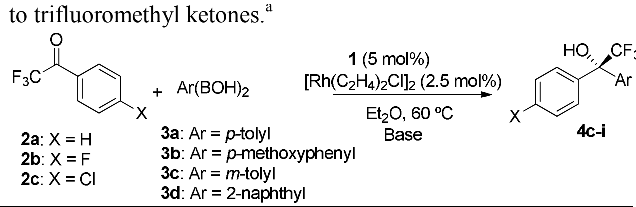


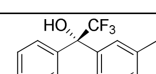
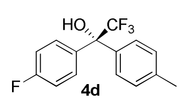
Entry	Base	Yield (%)[b]	*er* (%*ee*)[c]
5	K_2CO_3	63	85:15 (70%)
1	K_3PO_4	54	82: 18 (64%)
2	Et_3N	12	85: 15 (70%)
4	KOH	--	--
5	KF	99	85:15 (72%)

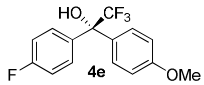
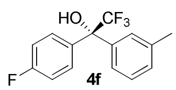
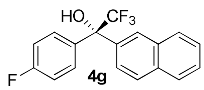
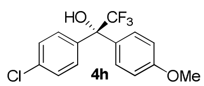
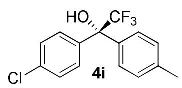
[a]All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$. [b]Isolated product. [c]Determined by chiral stationary phase HPLC using Chiralcel OJ-H® column

With these results in hand, the scope of the reaction was investigated using boronic acids with varied steric and electronic natures to different trifluoromethyl ketones. As similar enantioselectivities were obtained with potassium carbonate and with potassium fluoride, all condensations were conducted with both bases (table 3, entries 1-14). Lowering the temperature to 40ºC leads to the product in very low ee, so the reactions were conducted in Et_2O at 60ºC. The reaction is dependent on the electronic factors of both boronic acids and ketones. In this sense, boronic acids with electron donating substituents on the aryl group gave the products of addition with good yields (compare entries 1-14). While *para*-substituted aryls could be introduced with acceptable enantioselectivities and good yields (table 3, entries 3-6 and 11-14), *meta*-substituted aryls proceeded with lower ees and lower yield (table 3, entries 1-2 and 7-8). Ketone **2b** with a *para*-fluoro substituent (table 3, entries 3-10), gave the corresponding tertiary trifluoromethylated alcohols in slightly better yields and enantioselectivities than phenyl ketone **2a** and ketone **2c** with a *para*-chloro substituent (table 3, entries 11-14). In the addition of *para*-tolyl, *para*-methoxyphenyl groups to ketone **2b**, the corresponding tertiary alcohols **4d** and **4e**, were obtained with high yields and enantioselectivities of 78% and 76%, respectively (table 3, entries 3 and 5). Surprisingly, while in general potassium fluoride gave the final product in higher yield than potassium carbonate, a reversal effect was observed when using the 2-naphthyl boronic acid (table 3, entries 9 and 10). In this case, the corresponding tertiary alcohol **4g** was obtained with a significant decrease in the yield from 99%, obtained with potassium carbonate (table 3, entry 9) to 33% when potassium fluoride was used as base (table 3, entry 10).

Table 3: Reaction scope of "Sulfolefin"-catalyzed enantioselective rhodium-catalyzed addition of arylboronic acids to trifluoromethyl ketones.[a]



Entry	Product	Base	Yield[b] (%)	*er* (%*ee*)[c,d]
1	 **4c**	K_2CO_3	35	78:22 (56%)
2		KF	99	74:26 (48%)
3	 **4d**	K_2CO_3	86	89:11 (78%)
4		KF	64	82:18 (64%)

5		K_2CO_3	90	88:12 (76%)
6		KF	93	86:14 (72%)
7		K_2CO_3	29	83:17 (66%)
8		KF	40	84:16 (68%)
9		K_2CO_3	99	72:28 (44%)
10		KF	33	75:25 (50%)
11		K_2CO_3	58	83:17 (66%)
12		KF	90	81:19 (62%)
13		K_2CO_3	61	87:13 (74%)
14		KF	99	82:18 (64%)

[a]All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$. [b]Isolated product. [c]Determined by chiral stationary phase HPLC using Chiralcel OJ-H® column. [d]Absolute configurations were determined based on specific rotations.[8]

With regard to the stereochemical outcome of the reaction, one must take into account that ligand **1** can coordinate to the rhodium in different manners, due to the presence of an alkene function together with various heteroatoms, namely nitrogen, sulfur, and oxygen. Nevertheless, previous NMR studies have shown that sulfolefins act as bidentate ligands, coordinating to the rhodium atom through the olefin and the sulfinyl sulfur.[14a] Thus, through substrate coordination to the aryl rhodium intermediate in the proposed catalytic cycle of the Rh-catalyzed addition of boronic acid to activated ketone,[15] two possible intermediates **A** and **B** can be formed, figure 2. While more mechanistic studies are needed, we propose at this stage that owing to the major steric interaction between the aromatic ring of the trifluoromethyl ketone and *tert*-butyl group of the ligand, intermediate **A** is more favored than **B**. Consequently, insertion of the aromatic ring in the intermediate **A** (*Si* face attack), followed by transmetallation explains the formation of the observed major isomer, figure 2.

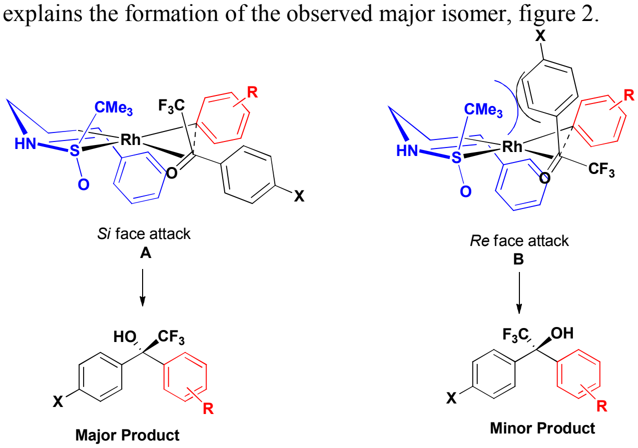


Figure 2. Proposed model for the stereochemical outcome of the reaction.

In summary, the extremely challenging catalytic asymmetric synthesis of trifluoromethyl substituted tertiary alcohols has been realized with good enantioselectivities (up to 79%) and high isolated yields (up to 99%) employing a rhodium/"sulfolefin catalyst. We are currently directing our efforts towards enhancing the enantioselectivity of this methodology and its applications for the syntheses of biologically active molecules.

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Notes and references

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[b]*Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/ Profesor García González, 2, 41012 Sevilla, Spain. Fax: +34954556737; Tel: +34954555993; E-mail: inmaff@us.es*

† Electronic Supplementary Information (ESI) available: Experimental procedures for the sulfolefin-Rh-catalyzed 1,2 addition of boronic acids to trifluoromethyl ketones, ^{1}H and ^{13}C spectra and HPLC chromatograms of the adducts **4a-4i** are given. See DOI: 10.1039/b000000x/

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Graphical Abstract

Trifluoromethyl-substituted tertiary alcohols were obtained with good yields and enantioselectivities using the shelf stable sulfolefin-**1** as catalyst precursor.