Enantioselective rhodium-catalyzed addition of arylboronic acids to trifluoromethyl ketones†

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The catalytic asymmetric 1,2-addition of a series of arylboronic acids to 2,2,2-trifluoroacetophenones is described with high isolated yields (up to 96%) and good enantioselectivities (up to 83% ee) using a rhodium(I)/phosphoramidite catalyst.

Due to their unique properties and unusual reactivities, fluorinated compounds have found extensive application in the fields of materials, pharmaceuticals, and agrochemistry.[1] As a consequence, the annual number of publications and patents concerning fluorinated products has steadily increased over the last three decades.[2] Fluorinated compounds bearing a trifluoromethyl substituent represent an interesting sub-class of this type of structures, often providing unique biological activities.[1,3] In this context, numerous methods for the trifluoromethylation of carbonyl compounds have been reported.[4] However, enantioselective trifluoromethylation is difficult to achieve and enantiomeric excesses exceeding 50% are rarely reached, except when the substrate is very hindered.[5]

An alternative strategy for the synthesis of trifluoromethyl substituted tertiary alcohols (Fig. 1) would be the addition of carbon nucleophiles to trifluoromethyl ketones. However, the formation of quaternary carbons *via* the addition of carbon nucleophiles to ketones still constitutes a major challenge in synthetic chemistry.[6] So far, the use of trifluoromethyl ketones as substrates in enantioselective organometallic addition reactions has been limited.[7] To the best of our knowledge no catalytic enantioselective arylation of fluorinated ketones has been reported so far.

Most of the enantioselective transformations described for the construction of tertiary alcohols from ketones involve the addition of alkyl, alkenyl and arylzinc reagents.[8] The lack of readily available zinc reagents severely limits these methods. We envisioned that, for activated ketones, the introduction of aryl moieties by asymmetric rhodium-catalyzed addition of arylboron reagents would be a more convenient method.[9] Arylboronic acids have received increasing attention as arylation reagents because they are shelf-stable, readily available, and compatible with a large variety of functional groups.[10] Rhodium-catalyzed addition of sp^2-hybridized carbon nucleophiles has made considerable progress during the last decade.[11] Our group has demonstrated that phosphoramidites are excellent ligands for the highly enantioselective rhodium-catalyzed conjugate addition of arylboronic acids to enones.[12] Phosphoramidites[13] comprise a low-cost class of ligands that are easily tunable and therefore highly suitable for ligand variation.[14] Recently, a ligand library approach led to the identification of phosphoramidite ligands that provide high enantioselectivity in the rhodium-catalyzed addition of arylboronic acid to imines[15] and good enantioselectivities in their addition to aldehydes.[16] A recent publication of Hayashi describing the asymmetric arylation of isatins with a Rh/MeO-MOP catalyst[17] prompted us to divulge our own results in this area.[18] Herein we report the first rhodium-catalyzed addition of arylboronic acids to 2,2,2-trifluoroacetophenones with enantioselectivities up to 83%.

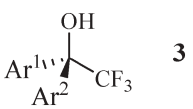

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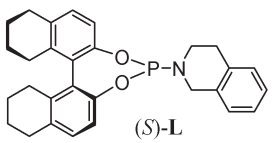
Fig. 1 Trifluoromethyl substituted diarylmethanols.

Initial experiments were performed with 2,2,2-trifluoroacetophenone (**1a**) and 3 equivalents of *para*-methoxyphenylboronic acid (**2a**). Variation of solvents identified methyl *tert*-butyl ether (MTBE) as the most suitable solvent for this reaction in terms of activity and enantioselectivity, although virtually identical results were obtained in acetone. An array of binol-based phosphoramidite ligands was screened, leading to the identification of phosphoramidite ligand **L** (Fig. 2) as an efficient ligand for this reaction.

A catalyst was generated *in situ* from 5 mol% of $[(C_2H_4)_2$-Rh(acac)] and 12.5 mol% of phosphoramidite **L**. According to ^{19}F NMR, 60% conversion was obtained after 16 h in refluxing MTBE. Column chromatography afforded the pure product **3a** in 50% yield with a promising enantioselectivity of 68% (Table 1, entry 1). As already observed for the addition of arylboronic acids to aldehydes,[16,19] the reaction is rather sensitive to electronic effects both in substrate and arylboronic acid. Addition of the less nucleophilic *para*-chlorophenylboronic acid **2b** gave the corresponding tertiary alcohol **3b** in even lower yield, but with a slightly



(*S*)-**L**

Fig. 2 Phosphoramidite (*S*)-**L**.

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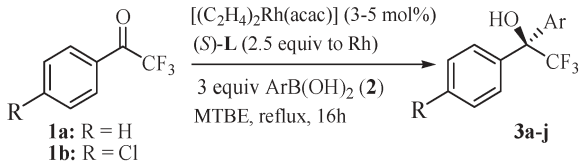
Table 1 Enantioselective rhodium/phosphoramidite-catalyzed asymmetric arylation of **1**[a]



1a: R = H
1b: R = Cl

3a-j

Boronic Acids:

2a: Ar = *p*-methoxyphenyl
2b: Ar = *p*-chlorophenyl
2c: Ar = *p*-tolyl
2d: Ar = phenyl
2e: Ar = *m*-methoxyphenyl
2f: Ar = *m*-tolyl
2g: Ar = *m*-chlorophenyl
2h: Ar = *o*-tolyl
2i: Ar = 2-naphthyl

Entry	Substrate	R	Boronic acid	Product	Yield[b] (%)	ee[c,d]
1	**1a**	H	**2a**	**3a**	50	68
2	**1a**	H	**2b**	**3b**	28	72
3[e]	**1b**	Cl	**2a**	**3c**	96	68
4[e]	**1b**	Cl	**2c**	**3d**	91	83
5	**1b**	Cl	**2d**	**3b**	90	79
6	**1b**	Cl	**2e**	**3e**	94	71
7	**1b**	Cl	**2f**	**3f**	91	76
8	**1b**	Cl	**2g**	**3g**	52	83
9	**1b**	Cl	**2h**	**3h**	40	50
10	**1b**	Cl	**2i**	**3i**	69	76

[a] Reactions were performed on 0.178 mmol scale in 2.5 mL of MTBE at reflux for 16 h with 3.0 equiv of arylboronic acid (**2**) with a catalyst generated *in situ* from 5 mol% $[(C_2H_4)_2Rh(acac)]$ and 12.5 mol% (*S*)-**L**. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] The absolute configuration of the products is unknown. [e] Conditions could be optimized to 3 mol% of catalyst and 2 equiv of arylboronic acid without affecting the outcome of the reaction.

higher selectivity of 72% ee (entry 2). To our delight, the activated *para*-chloro-substituted substrate **1b** and arylboronic acid **2a** could be converted into the corresponding tertiary alcohol with 96% yield and 68% ee (entry 3).

With these results in hand, the scope of the reaction was investigated. Also the addition of phenylboronic acid (**2d**) proceeded to full conversion and the alcohol **3b** could be obtained in 90% yield with 79% ee (entry 5). Electron donating substituents on the aryl-group of the boronic acid **2** increased the rate of the reaction, whereas the presence of electron-withdrawing substituents has a retarding effect (compare entries 1–8). Both *para*- and *meta*-substituted aryls could be introduced with good enantioselectivities and high yields (entries 3, 4, 6, 7, and 8). Addition of *ortho*-substituted aryls did not proceed to full conversion and results in a considerable drop in enantioselectivity (entry 9). Although a good enantioselectivity of 76% was obtained in the addition of the sterically hindered 2-naphthylboronic acid to **1b**, the reaction did not proceed to full conversion and the product **3i** was obtained in 69% yield (entry 10).

In the addition of *para*-methoxyphenyl and *meta*-methoxyphenyl groups, high yields were obtained with enantioselectivities of 68 and 71%, respectively (entries 3 and 6). *meta*-Tolyl substituted alcohol **3f** was obtained in high yield with 76% ee (entry 7). The best results were achieved with the addition of a *para*-tolyl group. Tertiary alcohol **3d** was obtained in 91% yield with an enantioselectivity of 83% (entry 4). The conditions could be optimized to 3 mol% of catalyst and 2 equivalents of arylboronic acid without affecting the outcome of the reaction (entries 3 and 4).

In summary, catalytic asymmetric synthesis of trifluoromethyl substituted tertiary alcohols has been realized with good enantioselectivities (up to 83%) and high isolated yields (up to 96%) employing a rhodium/phosphoramidite-catalyst. We are currently directing our efforts towards enhancing the scope and enantioselectivity of this methodology.

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