An efficient and practical method for the enantioselective synthesis of tertiary trifluoromethyl carbinols.

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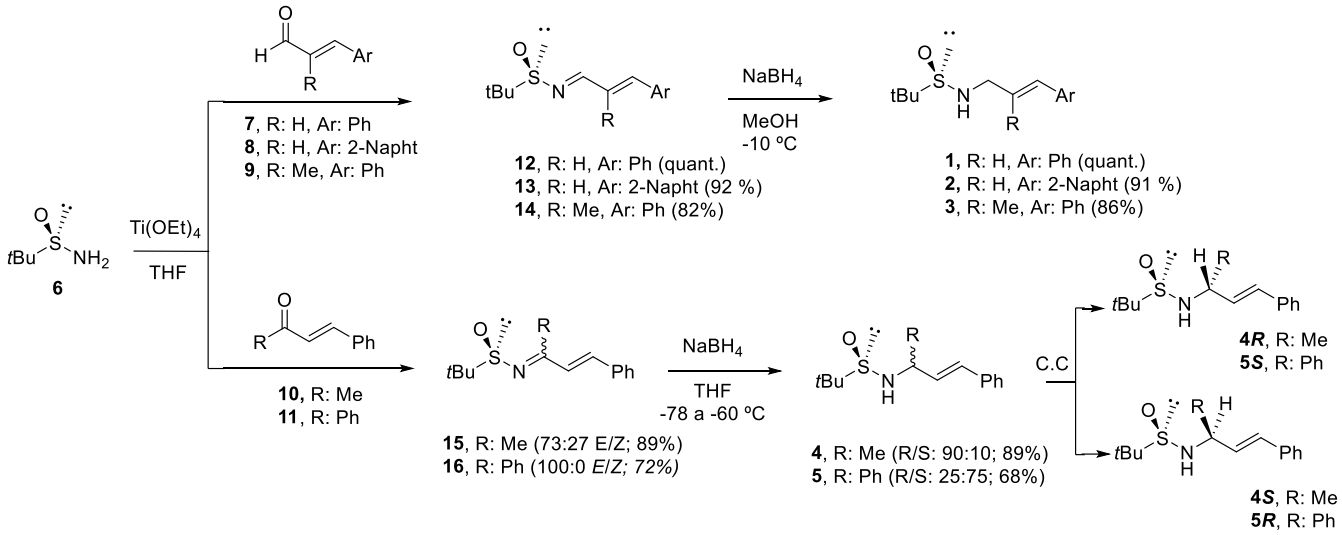
Abstract. An efficient sulfinamide/olefin based chiral ligand, *MetSulfolefin*, has been developed for the enantioselective rhodium-catalysed addition of aryl-boronic acids to trifluoromethyl ketones. This shelf-stable ligand is insensitive to air, oxygen and moisture, and it is obtained in only two high yielding steps from cheap commercially available (*R*)-*tert*-butanesulfinamide. The new ligand tolerates the use of hindered boronic acids and leads to the formation of a series of chiral trifluoromethyl-substituted tertiary carbinols in high yields and excellent enantioselectivities (up to >99% ee).

Keywords: Tertiary trifluoromethylcarbinols; Chiral sulfinamide-olefin; Enantioselective rhodium-catalysed arylation; Shelf-stable ligand; Cost effective synthetic approximation

The preparation of organofluorine compounds is an important goal in modern synthetic chemistry, consequence of their significance in important fields including pharmaceuticals, agrochemicals, material science and catalysis.[1] Particularly enantiomerically enriched trifluoromethyl-substituted alcohols having a tetrasubstitued chiral center are important compounds with remarkable biological activities.[2] Thus, the preparation of enantiomerically pure tertiary trifluoromethyl carbinols have been a standing area of interest in the last two decades. In this sense, numerous methods for the trifluoromethylation of carbonyl compounds have been attempted affording in general low enantioselectivities.[3] A significant alternative that has been lately carried out is the asymmetric rhodium-catalysed addition of arylboronic acids to trifluoromethyl ketones.[4] Boronic acids are attractive nucleophiles because of their wide availability, good stability and non-toxic nature apart from being compatible with a large range of functional groups.[5] In contrast to the Rh-catalysed addition of boronic acids to α,β-unsaturated carbonyl compounds and aldehydes,[6] the addition of carbon nucleophiles to trifluoromethyl ketones is still a challenging synthetic problem, as the methods developed so far, generally afford the fluorinated compounds with a tetrasubstitued chiral carbon with moderate yields and ee's.[7] In the few approaches developed for this transformation, the use of P-coordinating chiral ligands containing a phosphine,[4b] phosphite[4f] or phosphoradimite group[4a] prevails. Of these ligands, the best results have been obtained with the C_2-symmetric P-chiral ligands BIPOPs,[4b] developed initially in the laboratories of Boeringer Ingelheim,[8] whose synthesis require an arduous process of more than 10 steps of which one is a kinetic resolution.[9]

In the field of asymmetric catalysis, ligand design has played a central role for the development of efficient metal and organo-catalysed processes.[10] However, modern asymmetric catalysis requires ligands that are not only highly enantioselective but also structurally simple, chemically stable, and that both enantiomers are easily accessible by practical, cost effective synthetic approximations. In this sense, sulfinyl-based ligands present indubitable advantages for their application in asymmetric catalysis.[11] They are air, oxygen, and moisture stable, and currently a number of highly efficient approaches allow the rapid synthesis of both enantiomers of sulfinyl-based ligands and to easily modulate their structure.[12] Moreover, and much like the synthetically challenging P-chiral phosphines, they are ideally suited for the construction of diverse metal-ligand complexes with a well-defined chiral environment due to the close proximity of the chiral sulfur atom to the coordination sphere of the metal. Within the chiral sulfinyl ligands developed recently, mixed sulfur/olefin ligands have shown excellent behaviour in Rh-catalysed asymmetric catalysis.[13]



Scheme 1: Synthesis of Sulfinamide-olefin derivatives 1 - 5.

In particular, simple *tert*-butylsulfinamide derivative **1** (Sulfolefin, figure 1), enclosing a chiral sulfur atom as the sole chiral center, proved to be efficient catalyst precursor for Rh-catalysed addition of arylboronic acids to activated ketones including trifluoromethyl ketones, albeit with moderate enantioselectivities.[14] Taking into account these results, and in order to enhance the enantioselectivity, so that the process is synthetic interest, in the present work differently substituted *tert*-butylsulfinamide-olefin ligands (**2** - **5**) were synthesized. The ligands were designed in order to assess the importance of the substituents at both olefinic carbons (compounds **2** and **3**, Figure 1), and at the allylic position (compounds **4** and **5**, Figure 1). We have also evaluated the influence of the stereochemistry of the chiral allylic carbon of this type of ligands on the stereochemical outcome of the rhodium-catalysed reaction (Figure1).

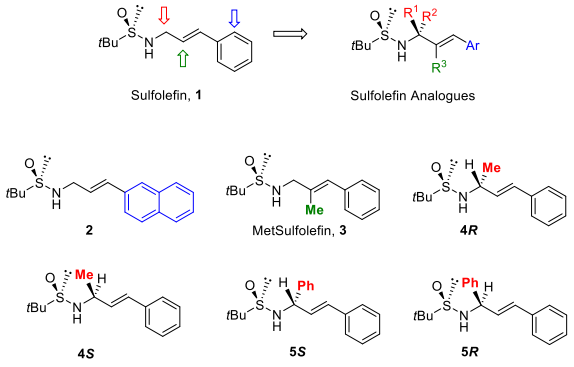


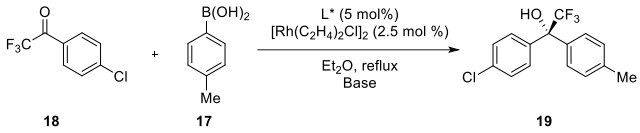
Figure 1. Sulfolefin type ligands used in this work

Ligands **1-5**[15] were obtained in excellent yields and in only 2 simple synthetic steps from commercially available (*R*)-*tert*-butanesulfinamide **6**,[16] Scheme 1, by condensation with the corresponding α,β-insaturated carbonyl compound **7-11,**[17] followed by the reduction of the obtained *tert*-butylsulfinyl imines, **12-16**.[18] The chemoselective reduction of the C=N double bond with sodium borohydride yielded the desired sulfinamide-olefins in high chemical yields. The methyl and phenyl allylic substituted derivatives **4**[15c] and **5**[15d] were obtained as a pair of diastereomers, epimers at the allylic position, and were resolved by column chromatography (Scheme 1). The obtained sulfinamide/olefin derivatives were then assayed as chiral ligands in the enantioselective rhodium-catalysed addition of *p*-tolylboronic acid **17** to trifluoromethyl *p*-chlorophenyl ketone **18**, as model reaction. The reaction was carried out using 5 mol% of the chiral ligand, in diethyl ether, under reflux during 3 hours, using KF or K_2CO_3 as the base, and the results are collected in table 1.

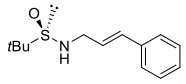
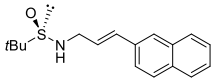
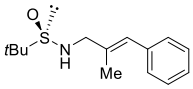
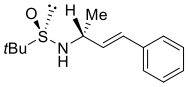
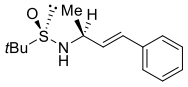
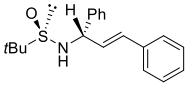
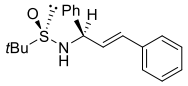
As can be seen from Table 1, the assayed ligands **1-4** were active catalyst precursors for the addition reaction, as the final trifluoromethylcarbinol**19** was obtained in good chemical yield (entries 1-10, table 1). A significant decrease in the chemical yields of the additions was observed in the case of both diastereomers of the phenyl derivatives **5*S*** and **5*R*** (entries 11 and 12, table 1), indicating the lower catalytic activity of these ligands. Neither potassium fluoride nor potassium carbonate, used as bases significantly influences the chemical yield nor the stereoselectivity of the process (entries 1-10, table 1). Comparison of the results obtained with the different ligands clearly illustrates the lack of influence of the nature of the substituent at the allylic position or its stereochemistry, *R* or *S*, on the enantioselectivity of the process. In the case of both diastereomeric methyl derivatives, **4*R*** and **4*S***, the ee's were similar to that previously obtained with the non-substituted sulfolefin **1** (compare entries 7 and 9 *vs* 1, Table 1), but a small decrease in the enantioselectivity was observed in the case of the phenyl substituted ligands **5*S*** and **5*R*** (entries 11

and 12, table 1), indicating the lower inductive capacity of both of them.

Table 1. Enantioselective Rh-catalysed addition of *p*-tolylboronic acid to the trifluoromethyl *p*-cholorophenyl ketone using sulfinamide/olefins **1** - **5** as chiral ligands.[a]



18 **17** **19**

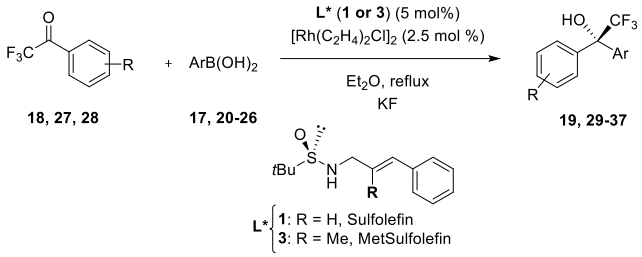
Entry	Ligand	L*	Base	Yield (%)	ee (%)
1		**1**	KF	90	74
2			K_2CO_3	81	76
3		**2**	KF	86	78
4			K_2CO_3	74	78
5		**3**	KF	99	94
6			K_2CO_3	77	96
7		**4*R***	KF	93	74
8			K_2CO_3	84	72
9		**4*S***	KF	81	72
10			K_2CO_3	80	70
11		**5*S***	KF	51[d]	60
12		**5*R***	KF	33[d]	68

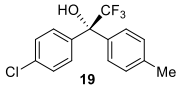
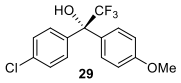
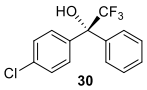
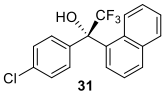
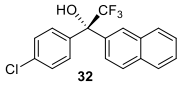
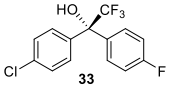
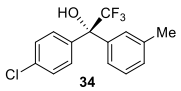
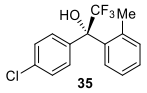
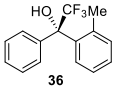
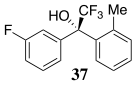
[a]All reaction were conducted using 0.67 mmol of ketone **18**, 1.34 mmol of boronic acid **17**, 2.01 mmol of base (KF or K_2CO_3), 5 mol % of ligand **1-5**, and 2.5 mol % of $[Rh(C_2H_4)_2Cl]_2$ under reflux in diethyl ether for 3 hours.[b]Isolated product. [c]Determined by chiral stationary phase HPLC using Chiralcel OJ-H® column [d]The starting ketone **18** was not consumed despite prolonging the reaction time overnight.

Fortunately, the modification of the nature of the substituents at the vinylic position gave better results. Thus, a slight but not very significant increase in the enantiomeric excess was obtained when the phenyl group in ligand **1** was substituted by the napthyl group in **2** (entry 3 vs 1, table 1). However, the excellent result obtained with the ligand **3**, with a methyl substituent at the double bond, highlights the importance of the substituent at the non-terminal position of the olefin in this type of ligands. Thus, we were pleased to find that with this ligand the reaction affords the desired carbinol **19** with an interesting 90-96% ee (entries 5 and 6, table 1). This represents a significant improvement of the result obtained with the Sulfolefin ligand **1**, in terms of enantioselectivity of the rhodium catalysed arylboronic addition of **17** to the trifluoromethyl ketone **18** (compare entries 5 and 6 vs 1 and 2, table 1). Encouraged by the good result obtained with this sulfinamide-olefin **3**, which we have denominated *MetSulfolefin*, we decided to determine the scope of the reaction with this ligand using boronic acids with varied steric and electronic nature and different trifluoromethyl ketones. Taking into account that, as previously indicated in table 1, similar enantioselectivities were obtained using potassium carbonate or potassium fluoride as base, all the new additions were conducted with KF, and the results are collected in table 2.

The reaction is not dependent on the electronic factors of both boronic acids and ketones. In this sense, boronic acids with electron donor (**17**, **20**, **25** and **26**) or acceptor substituents (**24**) on the aryl group gave the products of addition with very high yields (compare entries 1-12, table 2). One of the first conclusions to be drawn from the data collected in the table is the superiority of the methyl-substituted ligand **3** compared to Sulfolefin **1** in terms of stereoselectivity (entries 1-4, table 1). The enantioselectivities obtained in the additions of aryl boronic acids **17** and **20** to the ketone **18** are significantly higher in the case of Metsulfolefin **3** as ligand, with 96% and 94% ee respectively (entries 1 and 3, table 2), compared to the ee's obtained with the Sulfolefin **1** that are under 65% (entries 2 and 4, table 2). It should be noted that with ligand **3** not only the *para*-substituted aryls could be introduced with very high enantioselectivities and good yields (entries 1, 3 and 8, table 2), but also the *meta*- and *ortho*-substituted aryls (entries 6, 7, 9 and 10, table 2). Thus, the addition of 3-methylboronic acid **25** to the trifluoromethyl ketone **19** gives the corresponding trifluoromethylcarbinol**34**, as a single enantiomer (entries 9 table 2) in very high chemical yields (91%). Interestingly the addition of the more challenging hindered boronic acids, which are less reactive and less enantioselective with the catalysts developed to date, affords the desired products with good yields and practically perfect enantioselectivities. In this sense, addition of 1-naphtylboronic acid **22** and 2-methylboronic acid **26** to the trifluoromethyl ketone **18** gives the corresponding trifluoromethyl carbinols **32** and **35** in high chemical yields and in 96 and >99% ee respectively (entries 6 and 10).

Table 2: Reaction scope of the enantioselective rhodium catalysed addition of arylboronic acids to trifluoromethyl ketones with MetSulfolefin **3** as chiral ligand.[a]



Entry.	Boronic acid (Ar)	Ketone (R)	Product	L*	yield (%)[b]	ee (%)[c]
1	**17** (4-Me-C_6H_4)	*18* (4-Cl)	 **19**	**3**	99	96
2				**1**	99	64
3	**20** (4-MeO-C_6H_4)	**18** (4-Cl)	 **29**	**3**	81	94
4				**1**	90	62
5	**21** (C_6H_4)	**18** (4-Cl)	 **30**	**3**	94	90
6	**22** (1-Napht)	**18** (4-Cl)	 **31**	**3**	71	96
7	**23** (2-Napht)	**18** (4-Cl)	 **32**	**3**	86	90
8	**24** (4-F-C_6H_4)	**18** (4-Cl)	 **33**	**3**	83	94
9	**25** (3-Me-C_6H_4)	**18** (4-Cl)	 **34**	**3**	91	>99
10	**26** (2-Me-C_6H_4)	**18** (4-Cl)	 **35**	**3**	83	>99
11[a]	**26** (2-Me-C_6H_4)	**27** (H)	 **36**	**3**	94	94
12[a]	**26** (2-Me-C_6H_4)	**28** (3-F)	 **37**	**3**	92	>99

[a]All reactions were conducted using 0.67 mmol of the ketone, 1.34 mmol of the arylboronic acid, 2.01 mmol of KF, 5 mol % of ligand **1** or **3**, and 2.5 mol % of $[Rh(C_2H_4)_2Cl]_2$ under reflux in diethyl ether for 3 h.[b]Isolated product. [c]Determined by chiral stationary phase HPLC using Chiralcel OJ-H® column

As far as we know these are the best enantioselectivities obtained in these types of transformations to date. In the case of the nonsubstituted ketophenone **27** the corresponding adduct **36** was obtained with a high 94% ee and 94% chemical yields (entry 11, table 2). The enantioselectivity was higher in the case of the *meta*-fluoro substituted ketone **28** allowing the formation of the corresponding carbinol **37** in >99% ee and 92% chemical yield (entry 12, table 2). Clearly, the presence of the "flag methyl" group[19] in the olefinic position of ligand **3** has improved significantly the enantioselectivity in the rhodium-catalysed additions of arylboronic acids to trifluoromethyl ketones, highlighting subtle effects in the steric and electronic reorganizations of the coordinated transition states, figure 2. In this sense, although the sulfolefin-type ligands can coordinate the rhodium in different ways, NMR and RX studies have shown that they generally act as bidentate ligands capable of coordinating the metal through the sulfur and the double bond.[13d, 14]

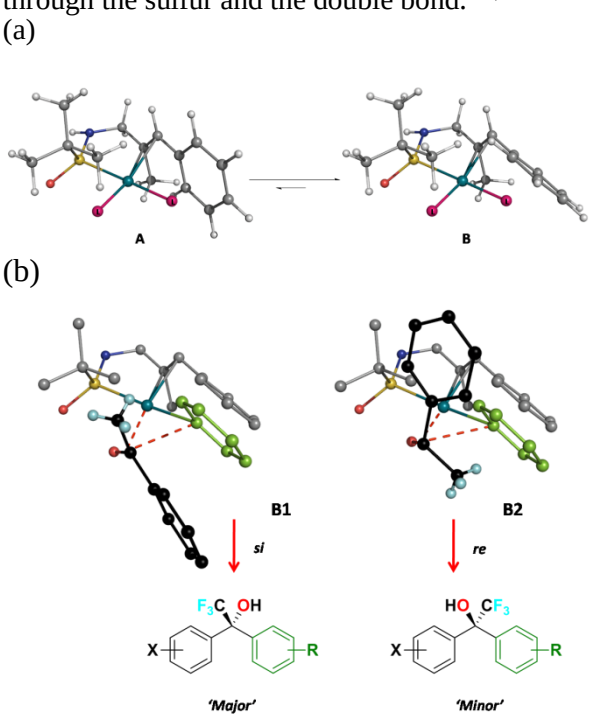


Figure 2.(a) Conformations, A(minor) and B(major), proposed for the square planar complex intermediate [3-RhL_2]. (b) Structure of the transition states, B1 and B2, proposed for the attack of the aryl group to the *si* and *re* face of the trifluoromethyl ketone.

In the square planar complex intermediate, figure 2, and due to an unfavourable steric interaction with the *cis* vinylic methyl group of ligand **3**, the phenyl group cannot be coplanar with the double bond, figure **2(a),** and rotates slightly out of this plane to give a new conformation, figure **2(b),** in order

minimize this interaction. In the new conformation, the phenyl ring points to the same side than the *tert*-butyl group, key element in the observed enantioselectivity, thus enhancing the whole stereochemical outcome of the process. In this sense, of the two possible intermediates **B1** and **B2**, formed through substrate coordination to the aryl rhodium intermediate in the proposed catalytic cycle of the Rh-catalysed addition of boronic acid to activated ketone, intermediate **B1** is much more favorable than intermediate **B2** with ligand **3.** Thus, insertion of the aromatic ring to the carbonyl group in intermediate **B1** (*si*face attack), followed by transmetallation explains the formation of the observed major isomer, figure 2.

In conclusion, we have developed an efficient sulfinamide/olefin based chiral ligand, *MetSulfolefin*, for the enantioselective rhodium-catalysed addition of aryl-boronic acids to trifluoromethyl ketones. This shelf stable ligand is insensitive to air, oxygen and moisture, and it is obtained in only two high yielding steps from cheap commercially available (*R*)-*tert*-butanesulfinamide. The new ligand leads to the formation of a series of chiral trifluoromethyl-substituted tertiary carbinols in high yields and excellent enantioselectivities (up to 100% ee). To the best of our knowledge "MetSulfolefin" can be considered as one of the best chiral ligands developed for this rhodium-catalysed process, up to now. The presence of a methyl group at the non-terminal vinylic position of this new chiral ligand seems to be the key to its success. Applications of this ligand in other rhodium-catalysed processes are currently under investigation and the results will be reported in due course

Experimental Section

(*R,E*)-*N*-2-Methyl-3-phenylprop-2-en-2-yl *tert*-butylsulfinamide, *Metsulfolefin* 3.

To a solution of α-methylcinnamaldehyde (1.05 mL, 7.50 mmol, 100 mol%) and (*R*)-*tert*-butanesulfinamide **6** (1.0 g, 8.25 mmol, 110 mol%) in dry THF (25 mL), at room temperature under argon atmosphere, $Ti(OEt)_4$ (1.73 mL, 8.25 mmol, 110 mol%) was added. Once the starting material was consumed (24 h), the reaction mixture was hydrolysed with a saturated NaCl aqueous solution (25 mL). The resulting suspension was filtered through a pad of Celite. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (EtOAc:hexane, 1:10) to give 1.53 g of **(*R,E,E*)-*N*-2-Methyl-3-phenyl-prop-2-en-1-ylidene *tert*-butylsulfinamide, 14.** **14** (6.13 mmol, 82% yield) as yellow liquid. $[\alpha]_D^{20}$: -401.4 (*c*1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.46-7.45 (m, 2H), 7.42-7.39 (m, 2H), 7.35-7.31 (m, 1H), 7.10 (bs, 1H), 2.20 (d, *J* = 1.2 Hz, 3H), 1.24 (s, 9H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.2, 144.2, 136.0, 135.3, 128.8, 128.6, 57.5, 27.6, 13.2 ppm. HRMS: Calc. for $C_{14}H_{19}NOS$ $[M+H]^+$: 250.1260; found 250.1255 (-2.2111 ppm).

To a solution of the *N*-*tert*-butylsulfinylimine **14** (750 mg, 3 mmol, 100 mol%) in dry MeOH (20 mL), under argon atmosphere, at 0°C, $NaBH_4$ (113.8 mg, 6 mmol, 200 mol%) was added. Once the starting material was consumed, a saturated NH_4Cl aqueous solution was added. The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (EtOAc/hexane 1:3) to give 651.5 mg of **3** (2.59 mmol, 86% yield) as a white solid. M.p.: 72-73°. $[\alpha]_D^{20}$: -47.9 (*c* 1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.27-7.26 (m, 2H), 7.24-7.21 (m, 1H), 6.50 (bs, 1H), 3.82 (AB fragment of an ABX system, Δν = 58.7 ppm, *J* = 7.5, 5.1 and 14.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 1H), 1.91 (d, *J* = 0.8 Hz, 3H), 1.26 (s, 9H) ppm.^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.5, 135.5, 129.0, 128.3, 127.7, 126.8, 56.0, 54.2, 22.8, 16.4 ppm. HRMS: Calc. for $C_{14}H_{21}NOS$ $[M+H]^+$: 274.1236; found 274.1231 (-1.9480 ppm).

Rhodium-catalysed 1,2-addition of boronic acids to trifluoromethyl ketones. Typical Procedure.

To a mixture of the arylboronic acid (1.34 mmol), KF (2.01 mmol), the chiral ligand **3** (8.42 mg, 0.03 mmol, 5 mol %) and $[Rh(C_2H_4)_2Cl]_2$ (0.015 mmol, 2.5 mol %) was added the trifluoromethyl ketone (0.67 mmol) and Et_2O (10 mL). After stirring the mixture at reflux for 3 hours, the reaction mixture was directly purified by flash chromatography on silica gel (Hexane/$CH_2Cl_2$4:1) to afford the desired trifluoromethyl carbinol. The enantioselectivity was determined by chiral HPLC.

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References

[1] (a) J. Wang, M. Sánchez Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506; (b) I. Ojima, J. R. McCarthy, J. T. Welch, In *Biomedical Frontiers of Fluorine Chemistry;* ACS Editions: Washington DC, 1996; (c) T. Hiyama, In *Organofluorine compounds. Chemistry and Applications*; Yamamoto, H., Eds.; Springer: New York, 2000.

[2] (a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763-2793; (b) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873-888; (c) P. Tian, H.-Q. Dong, G.-Q. Lin, *ACS Catal.* **2012**, *2*, 95-119; (d) B. Jiang, Y.-G. Si, *Angew. Chem, Int. Ed.* **2004**, *43*, 216-218; (e) M. L. P. Price, W. J. Jorgensen, *J. Am. Chem. Soc.* **2000**, *122*, 9455-9466; (f) L. Tan, C.-Y. Chen. R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem. Int. Ed.* **1999**, *38*, 711-713; (g) F. Xu, R. A. Reamer, R. Tyllier, J. M. Cummins, E. J. J. Grabowski, P. J. Reider, D. B. Collum, J. C. Huffman, *J. Am. Chem. Soc.* **2000**, *122*, 11212-11218.

[3] (a) Chang, Y.; Cai, C. *Tetrahedron Lett.* **2005**, *46*, 3161-3164; (b) S. Roussel, T. Billard, B. R. Langlois, *Chem. Eur. J.* **2005**, *11*, 939-944; (c) G. K. S. Prakash, J. Hu, J. A. Olah, *J. Org. Chem.* **2003**, *68*, 4457-4463; (d) B. R. Langlois, T. Billard, *Synthesis* **2003**, *2*, 185-194 (e) J. Joubert, S. Roussel, C. Christophe, T. Billard, B. T. Langlois, T. Vidal, *Angew. Chem. Int. Ed.* **2003**, *42*, 3133-3136; (f) G. K. S. Prakash, J. Hu, G. A. Olah, *Org. Lett.* **2003**, *5*, 3253-3256; (g) S. Roussel, T. Billard, B. R. Langlois, *Synlett*, **2004**, 2119-2122; (h) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707-3710; (i) H. Kawai, K. Tachi, E. Tokunaga, M. Shiro, N. Shibata, *Org. Lett.* **2010**, *12*, 5104-5107; (j) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1-PR43.

[4] (a) S. L. X. Martina, B. C. J. Richard, J. G. de Vries, F. L. Feringa, A. J. Minnard, *Chem. Commun.* **2006**, 4093-4095; (b) R. Luo, K. Li, Y. Hu, W. Tang, *Adv. Synth. Catal.* **2013**, *355*, 1297-1302; (c) L. S. Dobson, G. Pattison, *Chem. Commun.* **2016**, *52*, 11116-11119; (d) V. Valdivia, I. Fernández, N. Khiar, *Org. Biomol. Chem.* **2014**, *12*, 1211-1214; (e) J. R. White, G. J. Price, P. K. Plucinsky, C. G. Frost, *Tetrahedron Lett.* **2009**, *50*, 7365-7368; (f) V. R. Jumde, S. Faccheti, A. Iuliano, *Tetrahedron: Asymmetry* **2010**, *21*, 2775-2781.

[5] (a) D. G. Hall, In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine.* Wiley-VCH: Weinheim, **2005**; (b) R. Shintai, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 3353-3356; (c) H. F. Duan, J.-H. Xie, X.-C. Qiao, L. X. Wang, Q.-L. Zhou, *Angew. Chem., Int. Ed.* **2008**, *47*, 4351-4353.

[6] (a) G. Berthon, T. Hayashi, In *Catalytic Asymmetric Conjugate Reactions*. Córdova, A., Eds.; Wiley-VCH: Weinheim, **2010**, chap. 1; (b) K. Yoshida, T. Hayashi, In *Modern Rhodium-Catalysed Organic Reactions*. P. A. Evans, Eds,; Wiley-VCH: Weinheim, **2005**, chap. 3; (c) H. J. Edwards, J. D. Hargrave, S. D. Penrose, C. G. Frost, *Chem. Soc. Rev.* **2010**, *39*, 2093-2105; (d) C. Defieber, H. Grútzmacher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4482-4502; (e) J. B. Johnson, T. Rovis, *Angew. Chem. Int. Ed.* **2008**, *47*, 840-871.

[7] (a) V. L. Steven, In *Quaternary Stereocenters. Challenges and Solutions for Organic Synthesis*. J. Christoffers, A. Baro, Eds.; Wiley-VCH: Weinheim, **2005**; (b) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 389-401; (c) J. Christoffers, A. Baro, *Adv. Synth.Catal.* **2005**, *247*, 1473-1482; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, *3*, 369-396.

[8] W. Tang, B. Qu, A. G. Capacci, S. Rodriguez, X. Wei, N. Haddad, B. Narayanan, S. Ma, N. Grinberg, N. K. Yee, D. Krishnamurthy, C. Senanayake, *Org. Lett.* **2010**, *12*, 176-179.

[9] G. Li, X.-J. Wang, Y. Zhang, Z. Tan, P. DeCroos, J. C. Lorenz, X. Wei, N. Grinberg, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2017**, *82*, 5456-5460.

[10] (a) Nelson, J. H. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; J. Seyden-Penne, Ed.; Wiley-Interscience: New York, **1995**; (b) D. A. Evans, J. S. Johnson, In *Comprehensive Asymmetric Catalysis*, Vol. I-III,; E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.; Springer: Berlin, **1999**; (c) C. S. Kramer, S. Bräse, In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*. P. Dalko, Ed. Wiley-VCH: Weinheim, **2013**; (d) W. Zhang, Y. Shi, X. Zhang, *Acc. Chem. Res.* **2007**, *40*, 1278-1290; (e) A. Pfaltz, W.J. Drury, *PNAS* **2004**, *101*, 5723-5726.

[11] I. Fernández, N. Khiar, In *Organosulfur Chemistry in Asymmetric Synthesis*; T. Toru, C. Bolm, Eds.; Wiley-VCH-Verlag:Weinheim, **2008**, pp. 265; (b) B. M. Trost, M. Rao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5026-5043;(c) G. Sipos, E. M. Drinkel, R. Dorta, *Chem. Soc. Rev*. **2015**, *44*, 3834-3860.

[12] (a) E. Wojaczynska, J. Wojaczynkski, *Chem. Rev.* **2010**, *110*, 4303-4356; (b) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129-6144; (c) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han, I. Gallou, *Aldrich. Chim. Acta* **2005**, *38*, 93-104; (d) I. Fernández, N. Khiar, *Chem. Rev*. **2003**, *103*, 3651-3705.

[13] (a) R. Mariz, X. J. Luan, M. Gatti, A. Linden, R. Dorta, *J. Am. Chem. Soc*. **2008**, *130*, 2172-2173; (b) J. J. Burgi, R. Mariz, M. Gati, E. Drinkel, X. J. Luan, S. Blummenrit, A. Linden, R. Dorta, *Angew. Chem. Int. Ed.* **2009**, *48*, 2768-2771; (c) T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Maer, P. Knochel, *Org. Lett.* **2011**, *13*, 3182-3185; (d) X. Feng, Y. Wang, B. Wei, J. Yang, H. Du, *Org. Lett.* **2011**, *13*, 3300-3303; (e) G. Chen, J. Gui, L. Li, J. Liao, *Angew. Chem.* **2011**, *123*, 7823-7827; *Angew. Chem. Int. Ed.* **2011,** *50*, 7681-7685; (f) X. Feng, B. Wei, J. Yang, H. Du, *Org. Biomol. Chem*. **2011**, *9*, 5927-5929; (g) F. Xue, X.-C. Li, B.-S. Wan, *J. Org. Chem.* **2011**, *76*, 7256-7262; (h) Y. Wang, X. Feng, H. Du, *Org. Lett*. **2011**, *13*, 4954-4957.

[14] (a) V. Valdivia, N. Bilbao, J. F. Moya, C. Rosales-Barrios, A. Salvador, R. Recio, I. Fernández, N. Khiar, *RSC Adv*. **2016**, *6*, 3041-3047; (b) N. Khiar, A. Salvador, V. Valdivia, A. Chelouan, A. Alcudia, E. Álvarez, I. Fernández, *J. Org. Chem*. **2013**, *78*, 6510-6521; (c) N. Khiar, V. Valdivia, A. Salvador, A. Chelouan, A. Alcudia, I. Fernández,

Adv. Synth. Catal. **2013**, *355*, 1303-1307; (d) N. Khiar, A. Salvador, A. Chelouan, A. Alcudia, I. Fernández, *Org. Biomol. Chem.* **2012**, *10*, 2366-2368.

[15] (a) T.-S. Zhu, S.-S. Jin, M.-H. Xu, *Angew. Chem. Int. Ed*. **2012**, *51*, 780 –783; (b) S.-S. Jin, H. Wang, T.-S. Zhu, M.-H. Xu, *Org. Biomol. Chem.* **2012**, *10*, 1764-1768; (c) A. Adamkiewicz, J. Mlynarski, *Eur. J. Org. Chem.* **2016**, *5*, 1060-1065; (d) Z.-J. Liu, J.-T. Liu, *Chem. Comm.* **2008**, *41*, 5233-5235.

[16] M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev*. 2**010**, *110*, 3600–3740.

[17] (a) A. Nordqvist, C. Björkelid, M. Andaloussi, A.M. Jansson, S. L. Mowbray, A. Karlén, M. Larhed, *J. Org. Chem*. **2011**, *76*, 8986–8998. (b) N. Solin, L. Han, S. Che, O. Terasaki, *Catal. Commun.* **2009**, *10*, 1386–1389.

[18] (a) J.L. García-Ruano, I. Fernández, M. del Prado, A. Alcudia, *Tetrahedron: Asymmetry* **1996,** *7*, 3407-3414. (b) G. K. Surya-Prakash, M. Mandal, G. A. Olah, *Org. Lett*. **2001**, *3*, 2847-2850. (c) J. P. McMahon, J. A. Ellman, *Org. Lett*. **2005,** *7*, 5393-5396.

[19] The term "flag methyl" was introduced by the Ciba Geygi group in the development of Imatinib [R. Capdeville, E. Buchdunger, J. Zimmermann, A. Matter, *Nat. Rev. Drug Discov*. **2002**, *1*, 493-502]. Thus, the improved activity and selectivity of the rhodium catalysed addition of arylboronic acids to trifluoromethyl ketones with ligand **3**, the methylated analogue of sulfolefin **1**, could be considered similar to the well known effect of methylation of substrates in medicinal chemistry, favouring a conformation suitable for the ligand-enzyme interaction.

An efficient and practical method for the enantioselective synthesis of tertiary trifluoromethyl carbinols

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