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COMMUNICATION

"Sulfolefin": Highly modular mixed S/Olefin ligands for enantioselective Rh-catalyzed 1,4-addition†‡

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Reported is a single high yielding step approximation to mixed olefin/sulfinamide ligands enclosing a chiral sulfur atom as the sole chiral center. The synthetic design is validated by a rapid optimization of the substituent at the sulfinyl sulfur, and by the synthesis of an efficient, highly enantioselective catalyst for the Rh-catalyzed 1,4-addition of boronic acids to both, cyclic and acyclic olefins.

While chiral sulfinyl derivatives are known since the mid-sixties,[1] the last decade has witnessed a renewed interest toward their applications in asymmetric synthesis.[2] At the basis of this renaissance is the significant progress made in the synthesis of efficient chiral sulfinylating agents,[3] and the exceptional behaviour of sulfinamides as chiral intermediates for the production of enantiopure amines.[4] Chiral sulfinyl derivatives (sulfoxides,[5] and sulfinamides[6]), can indeed be considered as privileged chiral auxiliaries, as they have been used with success in a plethora of asymmetric chiral C–C and C–X bond formation. Surprisingly, despite their interesting metal-coordinating abilities,[7] the great efforts devoted to their applications in asymmetric catalysis have met with little success.[8] In all the catalytic processes where they were assayed, the reactivity and enantioselectivities obtained were far to compete with gold standard catalysts used in the literature.[9] An exception of this statute was reported in 2008 by Dorta's group, who found that C_2-symmetric atropoisomeric sulfoxides were among the best ligands for the Rh-catalyzed 1,4-addition of aryl boronic acids to cyclohexenones.[10] Beside bis-sulfoxides,[11] and in the course of this work, a second breakthrough was reported simultaneously by Knochel's,[12] Xu's,[13] and Du's[14] groups, who found that mixed sulfinyl-olefins are excellent catalyst precursors for the Rh-catalyzed 1,4-addition. However, in the case of the ligands with a *tert*-butyl sulfinyl group, the synthetic routes developed so far depend extremely on the utilization of *tert*-butane sulfinamide as a chiral source. Thus, besides limiting the modularity of the approximation, the synthesis of the ligands is not direct and includes a non-completely diastereoselective reduction/addition step. In a project directed toward the synthesis of chiral sulfinyl derivatives and their applications in stoichiometric asymmetric synthesis,[15a,b] as well as in organic[15c,d] and organometallic asymmetric catalysis,[9a] in the present work we report our preliminary results on the synthesis of modular sulfinamide/olefin mixed ligands and their application in highly enantioselective 1,4-addition of boronic acids to cyclic and acyclic α,β-unsaturated ketones. The designed "sulfolefin" ligands, Fig. 1, are derived from allylamines, contain a chiral sulfur atom as the sole chiral center, and can be easily obtained in a single step from a diastereomerically pure sulfinylating agent.

A large number of structurally different olefin-tethered amines are commercially available, so the modularity of the approximation depends greatly upon the capacity of the method used for the synthesis of the sulfinylating agents to create molecular and stereochemical diversity. The DAG-methodology,[16] developed in our laboratories is a general synthetic approximation for the synthesis of diastereomerically pure alkane and arene sulfinate esters. Additionally, using a single chiral auxiliary, both epimers at sulfur of the DAG-sulfinate esters are accessible in an enantiodivergent manner by a simple change of the tertiary amine used to catalyze the reaction.[17] Based on these premises, the synthesis of the sought "sulfolefin" ligands has been done by condensation of a lithium amide, obtained by treatment of the starting amine with butyllithium in THF at −78 °C, and a diastereomerically pure DAG-sulfinate esters, Scheme 1. In this preliminary work, DAG-sulfinate esters with *p*-tolyl, methyl, isopropyl, and *tert*-butyl substituents were used in order to assess the importance of the steric and electronic character of the substituent at the sulfinyl sulfur on the stereochemical outcome of the reaction.

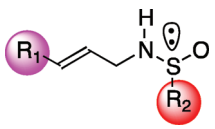

Fig. 1 Sulfolefin ligands.

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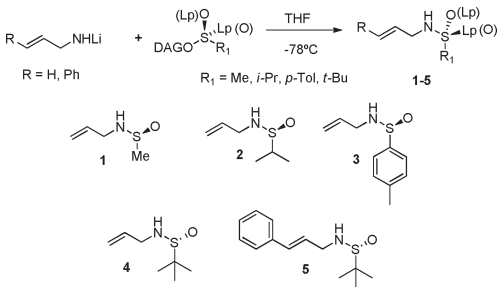
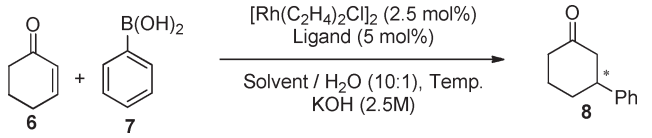
†Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of ligands **1**–**5**, and of the 1,4 addition, ^{1}H, and ^{13}C spectra of the ligands and of the adducts **8**, **12**–**15**, structural studies of the Rh-complexes derived from ligands **1** and **5**, and HPLC chromatograms of racemic and enantiopure ligands and adducts are given. See DOI: 10.1039/c2ob07132k

‡Dedicated to the memories of Prof. Rafael Suau and Prof. Mohamed Soufiaoui



Scheme 1 Synthesis of sulfolefin ligands.

Table 1 Enantioselective Rh-catalyzed 1,4-addition using sulfolefins **1–5**[a]



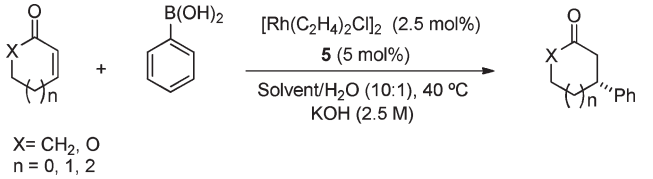
Entry	Ligand[a]	*T*/°C	Solvent	Yield (%)[b]	ee[c] (Config.)
1	**1**	40	Toluene	89	34 (*S*)
2	**2**	40	Toluene	87	12 (30)[d] (*S*)
3	**3**	40	Toluene	89	38 (*S*)
4	**4**	40	Toluene	92	84 (*R*)
5	**4**	r.t.	Toluene	80	80 (*R*)
6	**4**	60	Toluene	89	50 (*R*)
7	**5**	40	Toluene	98	90 (*R*)
8	**5**	r.t.	1,4-Dioxane	93	99 (*R*)
9	**5**	r.t.	Methanol	95	99 (*R*)

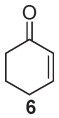
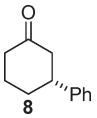
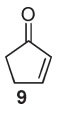
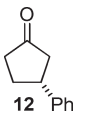
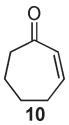
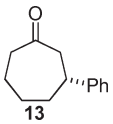
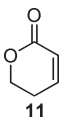
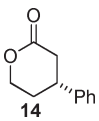
[a] All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$. [b] Isolated product. [c] Determined by chiral stationary phase HPLC using Chiralcel OD-H column. [d] Reaction conducted in methanol at room temperature.

Ligands **1–5**, Scheme 1, were obtained in excellent yields and were then assayed in the model reaction pioneered by Hayashi and Miyaura, namely the Rh-catalyzed 1,4-addition of aryl boronic acids to electron-deficient olefins.[18] Using 5 mol% of the ligand, the reaction of 2-cyclohexanone **6** and phenyl boronic acid **7** in toluene at 40 °C is clean and affords compound **8** with full conversion in less than two hours in all cases. The results obtained in this study are collected in Table 1.

We were delighted to find that all the assayed ligands were active catalyst precursors for the reaction as the final adduct **8** was always obtained in good chemical yield. Comparison of the results obtained with the ligands derived from allylamine **1–4** (Table 1, entries 1–4) illustrates clearly the dependence of the enantioselectivity of the process on the nature of the substituent at the sulfinyl sulfur. Ligand **1** with a simple methylsulfinyl group affords the desired product with 89% yield and with an interesting 34% ee (Table 1, entry 1). On the other hand, although the result obtained with ligand **3** was expected, the behavior of ligand **2** was disappointing (Table 1, entry 2), especially if compared with the good result obtained with ligand **4** (Table 1, entry 4). In contrast to this, we have recently shown that the isopropylsulfinyl group confers higher chemical reactivity and better enantiomeric discrimination than the *p*-tolylsulfinyl group and equal to the *tert*-butyl group in the Corey–Chaykovsky reaction of chiral sulfinylimines and in the organocatalytic allylation of acyl hydrazones.[16a] A temperature effect study on the stereochemical outcome of the reaction done with ligand **4** shows that the ee drops from 84% ee at 40 °C (Table 1, entry 4) to 50% at 60 °C (Table 1, entry 6). Finally, the excellent result obtained with ligand **5**, derived from cinnamylamine, highlights the importance of the substituent at the terminal position of the olefin in this kind of ligand (Table 1, entry 7). Fixing the best temperature at 40 °C, we conducted a solvent effect study using the best ligand **5** (Table 1, entries 8 and 9). Interestingly, using 1,4-dioxane or methanol as solvents, the desired product **8** was obtained as a single enantiomer, with 93 and 95% yield respectively.

Table 2 Substrate scope of the enantioselective Rh-catalyzed 1,4-addition using sulfolefin **5**[a]

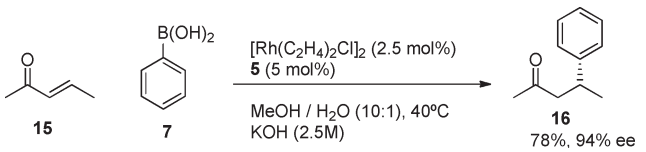


Entry	Starting enone	Product	Solvent	Yield (%)[b]	ee (%)[c]
1	 **6**	 **8**	Toluene	98	90
2			Methanol	93	99
3	 **9**	 **12**	Toluene	91	99
4			Methanol	93	99
5	 **10**	 **13**	Toluene	83	84
6			Methanol	92	96
7	 **11**	 **14**	Toluene	94	99
8			Methanol	96	99

[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 OD-H column.

Owing to the excellent results obtained with sulfolefin **5**, we decided to determine the substrate scope of the reaction using various cyclic enones in methanol and also in toluene as it is described as the best solvent for this transformation in the literature, and the results obtained are summarized in Table 2.

In the case of cyclopentenone **9**, adduct **12** was obtained as a single enantiomer both in toluene and methanol with 91 and 93% yield, respectively (Table 2, entries 3–4). On the contrary, in the case of cycloheptenone **10**, the product **13** was obtained with only 84% ee in toluene (Table 2, entry 5), while in methanol the reaction was highly selective allowing the formation of **13***R* in 96% ee and 93% yield (Table 2, entry 6). The reaction is not limited to unsaturated cyclic alkenones, as the reaction of phenyl boronic acid with the unsaturated lactone **11** leads to the



Scheme 2

γ-valerolactone derivative **14***R* as a single enantiomer, both in toluene and in methanol, with excellent yields in both solvents (Table 2, entries 7 and 8). The Rh-catalyzed 1,4-adition of aryl boronic acids to acyclic unsaturated ketones is a more challenging task, and most of the catalysts described in the literature afford the addition product with only moderate enantioselectivity. Based on the excellent catalytic behavior of ligand **5**, with cyclic substrates, we decided to prove its capacity in acyclic substrates. We were pleased to find that addition of phenyl boronic acid to 3-pentenone **15**, afforded the desired 4-phenylpentan-2-one **16** in 78% yield and an interesting 94% ee (Scheme 2), which represents one of the highest enantioselective processes described to date.

In order to gain a better insight into the mechanism of the described process, and to unravel the motives of the high enantioselectivity observed, we conducted some structural studies in solution. Together with the alkene moiety, the sulfolefin ligands possess three other heteroatoms, which can coordinate to the rhodium, namely the nitrogen, sulfur, and oxygen. Considering only the sulfinyl moiety (S–O) of the sulfinamide, and in analogy with the sulfoxide group, one can predict an S-coordination mode to the rhodium. In this regard, the α-protons to the sulfinyl group serve as excellent reporters for the determination of the coordination mode of the sulfinyl group by ^{1}HNMR spectroscopy.[3a,8] Therefore, ligand **1** with three methinic protons constitutes an ideal ligand for our purpose. Reaction of 1 equiv. of ligand **1** with 0.5 equiv of $[Rh(C_2H_4)Cl]_2$ in deuterated methylene chloride leads to the immediate formation of the rhodium complex. The most significant characteristics of the Rh-complex are the downfield chemical shift of the methylsulfinyl group from 2.5 pp to 3.7 ppm, and a 3 ppm upfield chemical shift of the olefinic protons from 6 ppm to 3 ppm (see the supporting information†). These data are pointing out that the sulfolefins act as bidentate ligands, coordinating to the rhodium atom through the olefin and sulfinyl sulfur.

In conclusion, we have developed an efficient approximation to mixed olefin/sulfinamide ligands enclosing a chiral sulfur atom as the sole chiral center. The high modularity of the reported design, allows a rapid optimization of the substituent at the sulfinyl sulfur, and permits the synthesis of an efficient catalyst for the Rh-catalyzed 1,4-addition of boronic acids to electron deficient olefins. The new catalyst displays a high substrate scope, as the addition adducts from cyclopentenone, cyclohexenone, cycloheptenone, and unsaturated lactone are usually obtained as a single enantiomer. Importantly, the new catalyst exhibits also high enantioselectivity in the addition of boronic acids to the more challenging linear unsaturated ketones. Additionally, along with tailoring of the steric and electronic character of the sulfinyl substituent, the use of the DAG-methodology allows the synthesis of both enantiomers of the "sulfolefin" ligands in an enantiodivergent manner. The application of the present approximation for the synthesis of other enantiopure sulfolefins, as well as their applications in other metal promoted enantioselective processes, are being actively investigated in our laboratories, and will be reported in due course.

Acknowledgements

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