Enantioselective construction of stereogenic quaternary centres *via* Rh-catalyzed asymmetric addition of alkenylboronic acids to α,β-unsaturated pyridylsulfones†

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The highly enantioselective construction of all-carbon quaternary stereogenic centres *via* Rh-catalyzed Chiraphos-mediated conjugate addition of alkenylboronic acids to β,β-disubstituted α,β-unsaturated 2-pyridylsulfones is described.

Although much progress has been achieved in recent years, the highly efficient enantioselective formation of all-carbon quaternary stereogenic centres by asymmetric catalytic methods remains a great challenge in organic synthesis.[1,2] Considering the broad scope and excellent enantioselectivities described in the last decade in the construction of tertiary stereogenic carbon centres by catalytic asymmetric conjugate addition (ACA) reactions to α,β-unsaturated carbonyls and related compounds,[3] a seemingly straightforward alternative to the enantioselective formation of quaternary stereogenic centers would be the catalytic ACA to β,β-disubstituted Michael acceptors. However, this approach must overcome a serious difficulty: the well-known reluctance of these substituted Michael substrates to undergo intermolecular conjugate addition due to steric reasons.

In fact, only very recently, in 2005, the first two catalytic enantioselective procedures based on this type of ACA process have been described, both involving Cu-mediated reactions. Thus, Hoveyda *et al.* have described the highly enantioselective addition of dialkylzinc reagents to β-aryl β-alkyl nitroalkenes,[4] while Alexakis *et al.* have reported the highly enantioselective addition of trialkylalanes to trialkyl-substituted cyclohexenones.[5] These very recent publications have prompted us to report our concomitant results in this arena. In particular, we describe herein that the Rh-catalyzed Chiraphos-mediated addition of alkenylboronic acids to β-aryl β-alkyl substituted vinyl pyridylsulfones takes place with very high enantioselectivity (88–> 99% ee). In addition, the versatile reactivity of the sulfonyl group offers wide possibilities for its further transformation into a variety of carbon functional groups having a close quaternary stereocenter.

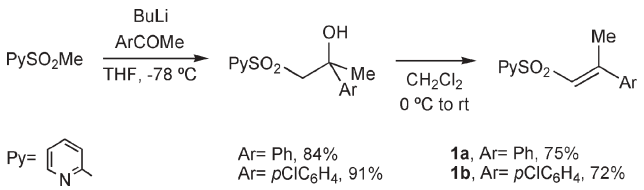
As a starting point, taking into account our previous results on the Rh-catalyzed addition of arylboronic acids to differently substituted vinyl sulfones,[6] we reasoned that using the combination of the potentially rhodium coordinating 2-pyridylsulfonyl group at the Michael acceptor (chelation-assisted effect) and a sterically low hindered nucleophile, such as alkenylboronic acids, the sluggish character of trisubstituted substrates could be overcome.

To test this hypothesis the vinyl sulfones **1a**,**b** were readily prepared in satisfactory overall yields by addition of the carbanion of pyridyl methyl sulfone to the corresponding acetophenone and further stereoselective dehydration (Scheme 1).

Unlike the behaviour of disubstituted 2-pyridylsulfones, no reaction or very low conversions (< 20%) were observed after treatment of the trisubstituted alkene **1a** with *p*-fluorophenylboronic acid in the presence of $Rh(acac)(C_2H_4)_2$ as catalyst and a variety of chiral ligands in dioxane–H_2O at 100 °C.[7] However, to our delight, a smooth and clean reaction was observed when (*E*)-styrylboronic acid was used as nucleophile and (*S*,*S*)-Chiraphos as ligand (5 mol%), reaching 65% conversion after 24 h and providing the addition product **2a** in 94% ee (HPLC, Daicel Chiralcel OD column). At that point, we confirmed that both the pyridylsulfonyl group and Chiraphos ligand were essential to the success of the conjugate addition. For instance, no reaction at all occurred either after treatment of **1a** with styrylboronic acid in the presence of Binap as ligand or after heating the phenylsulfone analogue of **1a** with styrylboronic acid under the same $Rh(acac)(C_2H_4)_2$/Chiraphos mediated reaction conditions, suggesting the participation of a key Rh-chelation effect in the case of the pyridylsulfone substrate.

We next briefly studied the scope of this enantioselective conjugate addition by using some commercially available alkenylboronic acids. The results obtained are shown in Table 1.

All the reactions were performed under the same conditions: $Rh(acac)(C_2H_4)_2$ (5 mol%), (*S*,*S*)-Chiraphos (5 mol%), a mixture of dioxane : H_2O (10 : 1), and 100 °C for 24 h.‡ Conversions between 45 and 77% were observed in all cases. Unfortunately, the use of a great excess of boronic acid or longer reaction times provided similar results, most likely due to the progressive decomposition of the catalyst in the harsh reaction conditions.[8] However, as the process occurs without formation of side products, both the remaining vinyl pyridylsulfone and the final conjugate addition product can be readily separated by standard



Scheme 1 Synthesis of β-aryl β-alkyl pyridylsulfones.

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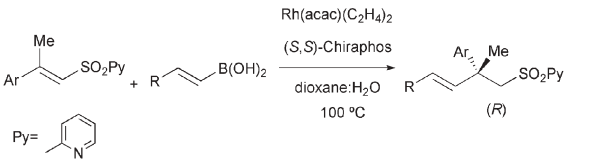
† Electronic supplementary information (ESI) available: experimental details and spectral data for new compounds, and X-ray data for compound (*R*)-**4a**. See http://dx.doi.org/10.1039/b508142d

Table 1 Rh-catalyzed asymmetric conjugate addition of alkenylboronic acids to β,β-disubstituted α,β-unsaturated pyridylsulfones



Entry[a]	Ar	R	Prod	Conv[b] (%)	Yield[c] (%), [d](%)	ee[e] (%)
1	Ph	Ph	**2a**	65	60 (88)	94
2	Ph	Me	**3a**	45	41 (85)	89
3	Ph	$PhCH_2$	**4a**	49	43 (87)	> 99
4	$pClC_6H_4$	Ph	**2b**	60	55 (91)	92
5	$pClC_6H_4$	Me	**3b**	65	59 (84)	90
6	$pClC_6H_4$	$PhCH_2$	**4b**	77	71 (89)	88

[a] Reaction conditions: alkenylboronic acid (500 mol%), (*S*,*S*)-Chiraphos (5 mol%), $Rh(acac)(C_2H_4)_2$ (5 mol%), dioxane : H_2O (10 : 1), 100 °C, 24 h. [b] Detected by ^{1}H-NMR analysis of the crude mixtures. [c] In pure isolated product. [d] In converted product. [e] Determined by HPLC (Chiralcel OD and Chiralpak AD columns).

silica gel chromatography to provide the desired conjugate addition compounds in high converted product yields (85–91%).

However, the most outstanding result was the stereochemical fidelity of the process: in all cases the enantioselectivity was very high, ranging from 88% ee (entry 6) to > 99% ee (entry 3). The (*R*) configuration of the addition product was unequivocally established by X-ray crystal diffraction analysis of compound **4a**[9] (Fig. 1).

Finally, based on the high versatility of the sulfonyl group in the formation of new C–C and C=C bonds,[10] in Scheme 2 are shown three examples illustrating the great synthetic potential of the pyridylsulfonyl addition products in the enantioselective preparation of otherwise not easily accessible functionalized compounds having quaternary allylic carbon centers. Thus, α-deprotonation of **2a** (94% ee) with KHMDS in DME at −78 °C and addition of either benzoyl chloride or ethyl chloroformate afforded in high yields the corresponding acylated product **5** or **6** as 2 : 1 mixtures of stereoisomers (Scheme 2). Further desulfonylation with activated zinc led to the ketone **7** or the ester **8** in almost quantitative yields. On the other hand, the one-step Julia–Kociensky olefination[11] reaction of the α-sulfonyl anion of **2a** with *p*-fluorobenzaldehyde afforded stereoselectively the (*E*,*E*) 1,4-diene **9** in excellent yield (89%).

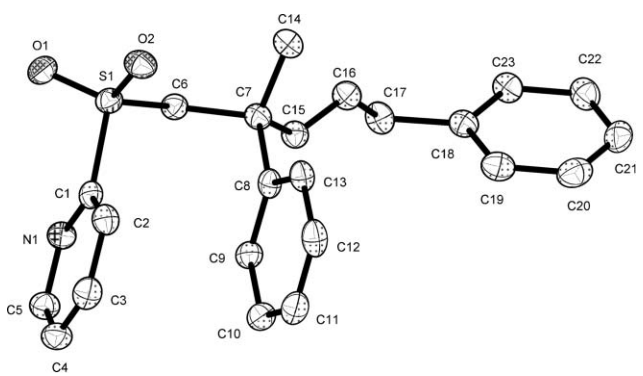
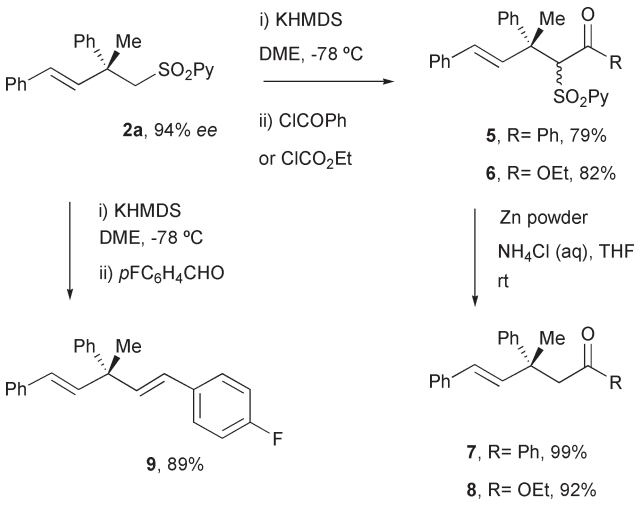


Fig. 1 ORTEP drawing of (*R*)-**4a**.



Scheme 2 Conversion of the pyridylsulfonyl group into other functional groups.

In summary, we have described the first procedure for the enantioselective construction of all-carbon quaternary stereogenic centres by a Rh-catalyzed ACA process. In particular, using $Rh(acac)(C_2H_4)_2$ as catalyst and (*S*,*S*)-Chiraphos as chiral ligand the addition of alkenylboronic acids to β-aryl β-alkyl substituted α,β-unsaturated pyridylsulfones takes place with very high enantioselectivities (88–> 99% ee). Further straightforward conversion of the pyridylsulfonyl group into typical carbon functional groups allows for the enantioselective preparation of a variety of functionalized allylic compounds having quaternary stereogenic centres. The study of other applications of the pyridylsulfonyl group as key controlling moiety in other metal-mediated processes is underway.

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Notes and references

‡ Typical experimental procedure: 5 mL of anhydrous 1,4-dioxane and 500 μL of water were sequentially added to a mixture of $[Rh(acac)(C_2H_4)_2]$ (6.5 mg, 0.025 mmol), (*S*,*S*)-Chiraphos (10.7 mg, 0.025 mmol), *trans*-styrylboronic acid (370 mg, 2.5 mmol) and the trisubstituted sulfone **1a** (129.7 mg, 0.500 mmol), previously placed under inert atmosphere (argon or nitrogen) in a Schlenk tube. The solution was stirred at 100 °C for 24 h, after which time the resulting orange mixture was cooled to rt, diluted with CH_2Cl_2 (*ca.* 3 mL) and filtered through a short pad of silica gel (eluent: CH_2Cl_2). After concentration of the filtrate, the residue was purified by flash chromatography (AcOEt : hexanes, 1 : 3) to give **2a** (109 mg, 0.3 mmol, 60% yield) and unreacted **1a** (41 mg, 32% yield).

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8 Similar or lower conversions were obtained using other rhodium catalysts, such as $Rh(cod)_2BF_4$, $Rh(cod)_2PF_6$ and $[Rh(OH)cod]_2$, or other nucleophiles, such as potassium organotrifluoroborates or trimethoxy phenyl silane.

9 Crystal data for $C_{23}H_{23}NO_2S$ (compound **4a**): M_w = 377.48, orthorhombic, crystal size 0.16 × 0.13 × 0.12 mm^3, space group $P2_12_12_1$, a = 7.9003(2), b = 14.1271(3), c = 17.2611(5) Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, V = 1926.48(8) $Å^3$, Z = 4, D_c = 1.301 g cm^{-3}, μ = 1.627 mm^{-1}, T = 100(2) K, Cu-Kα radiation (λ = 1.54178 Å), 10238 reflections measured, 3528 independent (R_{int} = 0.0291). Refinement on F^2 for 10238 reflections and 336 parameters gave GOF = 1.051, R = 0.0285, R_w = 0.0727 for $I > 2\sigma(I)$. CCDC reference number 274114. See http://dx.doi.org/10.1039/b508142d for crystallographic data in CIF or other electronic format.

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