ORGANIC LETTERS

2004
Vol. 6, No. 18
3195−3198

Rhodium-Catalyzed Enantioselective Conjugate Addition of Organoboronic Acids to α,β-Unsaturated Sulfones

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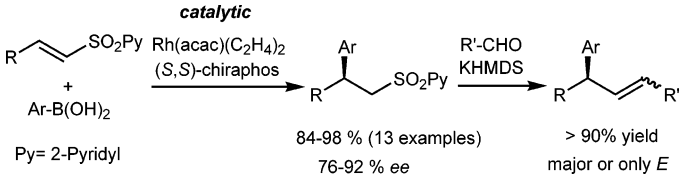
Received July 8, 2004

ABSTRACT



A general method for the enantioselective catalytic conjugate addition to acyclic α,β-unsaturated sulfones is described. Using metal-chelating α,β-unsaturated pyridyl sulfones as substrates, the rhodium-catalyzed chiraphos-mediated addition of organoboric acids takes place in excellent yield and high enantioselectivity. The subsequent elimination of the pyridylsulfonyl group by Julia–Kocienský olefination provides a novel approach to the enantioselective synthesis of allylic substituted alkenes.

Conjugate addition is undoubtedly among the most general and versatile tools in organic synthesis. Thus, it is not surprising that the development of enantioselective catalytic procedures for this cornerstone reaction has attracted much attention in recent years.[1] In this field the rhodium-catalyzed asymmetric 1,4-addition of aryl and alkenylboronic acids to enones, developed by Miyaura and Hayashi,[2] is one of the most practical methods due to the stability and availability of the boronic acid used as a nucleophile and the high enantioselectivity typically associated with this process, especially when binap is used as a chiral ligand.[3] Since the first paper published in 1997,[2a] this strategy has successfully been extended to other types of electron-deficient olefins such as α,β-unsaturated esters,[4] amides,[5] phosphonates,[6] and nitro compounds.[7]

However, despite the great versatility of sulfones in organic synthesis,[8] the development of enantioselective catalytic conjugate addition reactions to α,β-unsaturated sulfones remains an exciting challenge in asymmetric catalysis. As the closest precedent, Hayashi et al. have recently reported that α,β-unsaturated phenyl sulfones do not react with organoboron reagents under the usual rhodium-catalyzed conditions, whereas, interestingly, the reaction with the more nucleophilic aryltitanium reagents occurs with concomitant

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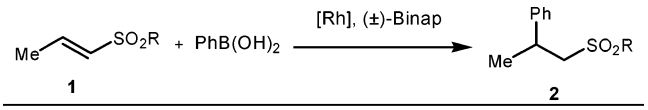
10.1021/ol048690p CCC: $27.50
Published on Web 07/31/2004

elimination of the sulfonyl group after the conjugate addition step, leading to desulfonylated alkenes as final products.[9] By using an appropriately rhodium-coordinating heteroaromatic sulfone as the key controlling moiety and chiraphos as the optimal chiral ligand, we report herein that α,β-unsaturated sulfones are excellent substrates for the rhodium-catalyzed enantioselective conjugate addition of arylboronic acids, providing β-substituted sulfones in very high yields and enantioselectivities ranging 76−92% ee.[10]

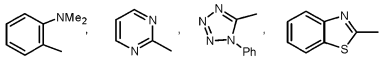
We have recently reported that the palladium-coordinating *ortho*-(dimethylamino)phenyl sulfonyl group is essential to perform intermolecular Heck reactions on α,β-unsaturated sulfones.[11] With this precedent in mind, we envisaged that this type of metal-chelating effect could be used to enhance the reactivity of α,β-unsaturated sulfones in the rhodium-catalyzed addition of organoboron reagents, as well as to suppress any possible desulfonylation process.

As a model reaction we studied the behavior of a variety of propenyl sulfones **1**, having different aromatic substitution at sulfur, under the usual experimental conditions described for the rhodium-catalyzed conjugate addition of organoboronic acids to enones:[3] $Rh(acac)(C_2H_4)_2$ (3 mol %), (±)-binap (3 mol %), $PhB(OH)_2$ (excess), dioxane/H_2O (10:1), 100 °C (Table 1).

Table 1. Rhodium-Catalyzed Reaction of Differently Substituted Propenyl Sulfones with Phenyl Boronic Acid[a]



1 2

1	R	conv. [%][a]
1a-e	Ph, 	<2
1f		>98 (74%)
1g		>98 (98%)
1h		<2

[a] Reaction conditions: $PhB(OH)_2$ (5 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol %), (±)-binap (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [a] In isolated product.

We found not only that the phenyl sulfone **1a** was inert under the reaction conditions but also that the same lack of reactivity was observed from the nitrogen-tethered sulfones bearing 2-(dimethylamino)phenyl (**1b**), 1,3-pyrimidinyl (**1c**), tetrazoyl (**1d**), and benzimidazoyl (**1e**) moieties. On the contrary, to our delight, the imidazoyl sulfone **1f** and the 2-pyridyl sulfone **1g** smoothly evolved under the reaction conditions to give the expected β-phenyl-substituted sulfone **2** as the only detected product. The pyridyl derivative **1g** showed the highest reactivity and provided nearly quantitative yield in pure isolated addition product (98%). Convinced that the high reactivity of this substrate was due to the coordination of the rhodium catalyst with the appropriately placed nitrogen atom[12] and not merely to electronic effects, we studied the behavior of the isomer 4-pyridyl sulfone **1h**. In accordance with the impossibility of an intramolecular rhodium-chelating effect, we found that this substrate was completely unreactive.

Having established the best substitution at sulfur in sulfones **1**, we next studied the enantioselectivity of the rhodium-catalyzed addition of phenylboronic acid to the sulfone **1g** in the presence of 3 mol % of a number of structurally varied chiral ligands (Table 2). To establish appropriate reactivity comparisons, all the reactions were stopped after 12 h under identical reaction conditions.

Interestingly, complete conversions were only obtained in the case of the P,P-bidentate ligands binap, tol-binap, and chiraphos (entries 1−3, respectively). The rest of the ligands with either P,P- (entries 4−7), P,N- (entries 8 and 9), or P,S-bidentate coordination (entries 10 and 11) proved to be much less efficient, especially the nitrogen-based ligands. An unsatisfactory reactivity was also observed in the case of using the monodentate Feringa's phosphoramidite ligand[13] (entry 12).

Concerning the enantioselectivity of the process, unlike the reported results on the rhodium-catalyzed enantioselective conjugate addition to other types of electron deficient alkenes,[2−7] in which binap proved to be the ligand of choice, in our case the highest enantioselectivity was reached using chiraphos[14] (81% ee, entry 3). It is worthy of note that the planar chiral Fesulphos P,S-ligands, recently developed by us,[15] also provided enantioselectivity similar to that obtained from chiraphos (76−81% ee), albeit the reactivity was much lower.

Having found that (*S*,*S*)-chiraphos displayed the optimal reactivity/enantioselectivity profile on the model reaction, the structural scope of this enantioselective reaction was studied (Table 3). We considered both the substitution at

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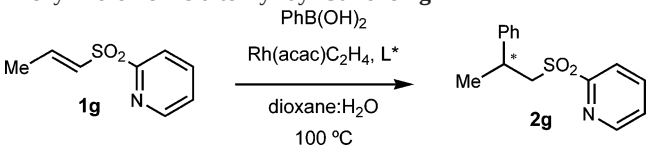
(12) For the use of the pyridyl group as a controlling chelating group in metal-mediated reactions of α,β-unsaturated pyridyl silanes, see: Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J. *J. Organomet. Chem.* **2002**, *653*, 105−113 and references therein.

(13) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481−9484.

(14) Superiority of chiraphos over binap as a chiral ligand was confirmed with other pairs of pyridyl sulfones and arylboronic acids, showing the generality of this ligand effect. For instance, the binap-mediated reaction of sulfone **1g** with *p*-fluorophenylboronic acid gave product **3** in 76% ee (84% ee using chiraphos) and the addition of phenylboronic acid to sulfone **1k** afforded **4** in 76% ee (87% ee using chiraphos).

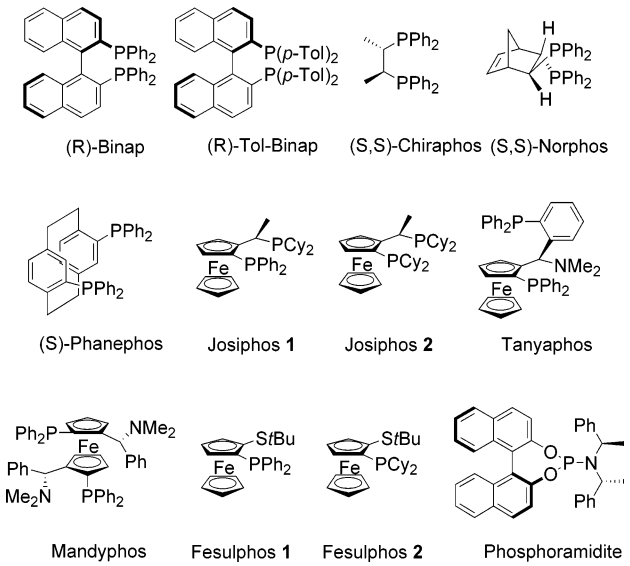
(15) (a) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679−3686. (b) García Mancheño, O.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *125*, 456−457.

Table 2. Enantioselective Rhodium-Catalyzed Addition of Phenyl Boronic Acid to Pyridyl Sulfone **1g**



entry[a]	ligand (L*)	conversion[b] (%)	yield of **2g**[c] (%)	ee (%)[d] (configuration)[e]
1	(*R*)-binap	>98	97	73 (*R*)
2	(*R*)-tol-binap	>98	92	60 (*R*)
3	(*S*,*S*)-chiraphos	>98	97	81 (*S*)
4	(*S*,*S*)-norphos	10		
5	(*S*)-phanephos	<10		
6	josiphos 1	73	68	41 (*R*)
7	josiphos 2	<10		
8	tanyaphos	<10		
9	mandyphos	<10		
10[f]	Fesulphos 1	87	78	76 (*S*)
11[f]	Fesulphos 2	70	66	81 (*S*)
12	phosphoramidite	39	31	73 (*S*)

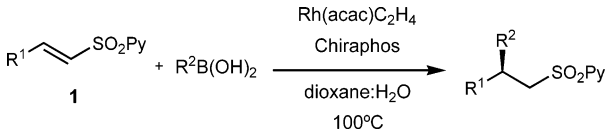
[a] Reaction conditions: $PhB(OH)_2$ (5 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol %), L* (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [b] Determined by ^1H NMR after 12 h. [c] In pure isolated product. [d] Determined by HPLC (Chiralpak AD). [e] Configuration determined by chemical correlation with the known compound (*R*)-**14**. [f] Performed with 6 mol % ligand and rhodium catalyst.



the aryl boronic acid (three electronically different reagents) and the steric bulk at the β-position on the α,β-unsaturated pyridyl sulfone (substrates **1g**, **1i**, **1j**, and **1k**).

Several conclusions are drawn from this study: (a) Complete conversions and chemical yields higher than 90% in pure isolated product were obtained in most reactions. Only the bulkier substrates **1j** and **1k** led to incomplete conversions when treated with *p*-methoxyphenyl boronic acid (>90% yield in converted product, entries 9 and 12). (b) Reasonably high and rather homogeneous asymmetric induction, ranging from 76 to 92% ee, was obtained in all reactions. (c) For each tested sulfone, the *p*-fluorophenyl boronic acid always gave the highest enantioselectivity, while

Table 3. Enantioselective Rhodium-Catalyzed Addition of Boronic Acids to α,β-Unsaturated 2-Pyridyl Sulfones



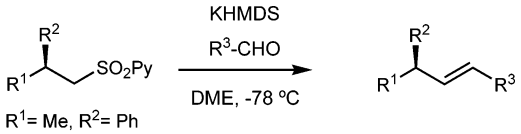
entry[a]	**1**	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	**1g**	Me	Ph	**2g**	97	81
2	**1g**	Me	pFC_6H_4	**3**	98	84
3[d]	**1g**	Me	$pMeOC_6H_4$	**4**	89	77
4[d]	**1i**	*n*Pent	Ph	**5**	98	84
5[d]	**1i**	*n*Pent	pFC_6H_4	**6**	94	87
6[d]	**1i**	*n*Pent	$pMeOC_6H_4$	**7**	92	81
7[e]	**1j**	*i*Pr	Ph	**8**	93	78
8[e]	**1j**	*i*Pr	pFC_6H_4	**9**	93	85
9[e]	**1j**	*i*Pr	$pMeOC_6H_4$	**10**	74 (94)[f]	76
10[e]	**1k**	β-Naph	Ph	**11**	96	87
11[e]	**1k**	β-Naph	pFC_6H_4	**12**	97	92
12[e]	**1k**	β-Naph	$pMeOC_6H_4$	**13**	84 (94)[f]	85

[a] Reaction conditions: $R^2B(OH)_2$ (5 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol %), chiraphos (3 mol %), dioxane/H_2O (10:1), 100 °C, 12 h. [b] In pure isolated product. [c] Determined by HPLC (Chiralpak AD or Chiralcel OD). [d] Reaction time = 24 h. [e] Performed with 5 mol % ligand and rhodium catalyst (48 h reaction time). [f] Converted product.

the *p*-methoxyphenyl boronic acid provided the lowest asymmetric induction. (d) With the exception of substrate **1j**, a slight enhancement in the enantioselectivity is observed with the increasing steric bulk of the β-substituent.

Interestingly, the 2-pyridylsulfonyl group not only is essential for achieving the rhodium-catalyzed conjugate addition, but its basic elimination by Julia−Kocienski olefination reaction provides a practical alternative for the introduction of a C−C double bond.[16] As shown in Table 4, the treatment of several enantioenriched β-substituted pyridyl

Table 4. Elimination of the Pyridylsulfonyl Group by Julia−Kocienski Olefination



2g, R^1= Me, R^2= Ph
3, R^1= Me, R^2= pFC_6H_4
5, R^1= *n*Pent, R^2= Ph

entry	sulfone	R^3	alkene	*E*/*Z* ratio[a]	(*E*)-isomer yield[b] (%)
1	**2g**	Ph	**14**	>99/<1	93
2	**2g**	pFC_6H_4	**15**	90/10	81
3	**2g**	PhC_2H_2	**16**	87/13	89[c]
4	**2g**	*i*Pr	**17**	65/35	48
5	**3**	Ph	**18**	>99/<1	92
6	**5**	Ph	**19**	>99/<1	91

[a] Determined by ^1H NMR from the crude mixtures. [b] In pure (*E*)-alkene after silica gel chromatography. [c] As an 87:13 mixture of *E*/*Z* isomers.

sulfones with KHMDS in DME at −78 °C, followed by addition of an aromatic (entries 1, 2, 5, and 6), aliphatic (entry 4), or α,β-unsaturated aldehyde (entry 3), afforded the corresponding alkene in excellent yield, usually with high (*E*)-stereoselectivity. The enantiopurity of alkene **14** was confirmed by HPLC (Chiralcel OD) to be identical to that of the sulfone precursor **2g** (81% ee) proving that, as expected,[16a] this olefination process occurs without racemization at the β-stereogenic carbon. On the other hand, since (*R*)-**14** is a known compound,[17] this chemical correlation allowed us to establish the (*S*)-configuration of the chiral sulfone **2g** obtained in the Rh-chiraphos-catalyzed addition step.[18]

From a synthetic point of view, this two-step enantioselective synthesis of allylic substituted alkenes constitutes an interesting alternative to the direct enantioselective metal-catalyzed allylic substitution of allylic alcohols derivatives with stabilized enolates.[19] On the other hand, unlike processes involving π-allylic species, this approach avoids any regiochemical uncertainty in the formation of the C−C double bond. For instance, this point is well illustrated in Table 4 by the unambiguous synthesis of the regioisomers **15** and **18** (entries 2 and 5).

In conclusion, we have developed, to the best of our knowledge, the first catalytic procedure of enantioselective conjugate addition of carbon nucleophiles to α,β-unsaturated sulfones. The success of this Rh-catalyzed addition of boronic acids relies heavily on the use of α,β-unsaturated 2-pyridyl sulfones as key rhodium-coordinating substrates and chiraphos as the optimal chiral ligand. This methodology has a broad scope regarding both the arylboronic acid and the sulfone substrate, affording the conjugate addition products in excellent yields (usually >90%) and high enantioselectivities (76−92% ee). The efficient elimination of the pyridylsulfonyl group by Julia−Kocienski olefination offers a new approach to the enantioselective synthesis of allylic substituted alkenes.

Acknowledgment. This work was supported by the MCyT (Projects BQU2000-0226 and BQU2003-0508). P.M. thanks the MCyT for a predoctoral fellowship. Prof. José L. García-Ruano is gratefully acknowledged for unrestricted access to the HPLC equipment of his group. We also thank Solvias for the generous gift of several chiral ligands.

Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Knochel, P.; Schwink, L. *Chem. Eur. J.* **1998**, *4*, 950−968.

(18) By chemical analogy, the rest of chiral sulfones obtained using (*S*,*S*)-chiraphos as a ligand (compounds **3**−**13**) are also supposed to have the same configuration, as shown in Table 3.

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