LETTERS 2011 Vol. 13, No. 12 3182–3185

ORGANIC

Sulfoxide—Alkene Hybrids: A New Class of Chiral Ligands for the Hayashi—Miyaura Reaction

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Received April 27, 2011



Sulfoxide—alkene hybrids are introduced as a new class of chiral heterodentate ligands for the Hayashi—Miyaura reaction. The synthesis of these ligands was achieved without the use of protecting groups. A chiral resolution was performed via simple column-chromatographic separation of the diastereomeric ligands. Both diastereomers proved to be excellent ligands in Rh-catalyzed 1,4-addition reactions, furnishing chiral products with high enantioselectivities and, remarkably, opposite stereoconfigurations.

The Rh-catalyzed 1,4-addition of boronic acids to enones, also known as the Hayashi–Miyaura reaction,¹ has been well established as an important and versatile tool for the enantioselective Michael addition.² Chiral dienes³ and most recently chiral bissulfoxides⁴ have proven very effective for achieving high levels of enantioselectivity in this type of reaction. The easy preparation⁵ and resolution of chiral diastereomeric sulfoxides, which can be performed via simple column chromatographic separation,^{4a-c,6} led us to envision novel modular hybrid ligands that combine both alkenes and sulfoxides as coordinative elements.

So far, *tert*-butylsulfinylphosphines represent the only class of chiral sulfoxide-based hybrid ligands employed in the Hayashi–Miyaura reaction,⁷ and alkene hybrid ligands are restricted to either phosphorus⁸ or nitrogen⁹ as second coordinating moiety. Herein, we report the preparation and use of the first chiral sulfoxide–alkene hybrid ligands in the Hayashi–Miyaura reaction with a direct comparative study on the relative influences of the alkenyl

and sulfoxide group on the reactivity and enantioselectivity of the Rh(I) catalyst.

Inspired by Hayashi's well-studied phosphorus-olefin hybrid ligand,^{8e,i} we designed a straightforward, protective-group free synthesis of 1 and 2 from norbornene (3) in four steps (Scheme 1). Thus, the functionalization of 3 with NBS (N-bromosuccinimide) in H₂O and subsequent Swern oxidation^{8e,i} furnished bromo ketone 4 in 55% yield. LaCl₃·2LiCl-mediated addition¹⁰ of 4-anisylmagnesium bromide to 4 followed by acidic elimination of H₂O using MsOH (methanesulfonic acid) directly gave the racemic alkene 5 with 67% overall yield without unnecessary protection-deprotection steps. Br/Li exchange on 5 using t-BuLi, subsequent transmetalation with MgCl₂, and quenching with (-)-menthyl (S)-p-toluenesulfinate (6;Andersen sulfinate)¹¹ furnished the two diastereomeric ligands 1 and 2 with 72% yield and 99% ee,¹² which could be easily separated via column chromatographic purification.¹³ No preparative HPLC separation was required.8e,i

^{$\bar{1}$}H and ¹³C NMR experiments on the Rh-complexes of **1** and **2** obtained by reacting them with $[(coe)_2 RhCl]_2^{14}$ (coe: cyclooctene; 0.5 equiv) in 1,4-dioxane- d_8 clearly proved the coordination of both the alkene and the sulfoxide moiety

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Scheme 1. Synthesis and Chiral Resolution of Ligands 1 and 2



to the Rh atom with the signals for the respective C-atoms shifted upfield and split into doublets.¹⁵

To test the efficacy and scope of 1 as a chiral ligand in the Hayashi–Miyaura reaction, we prepared the Rh complex 7 by treating 1 with $[(coe)_2RhCl]_2$ (0.5 equiv) and a

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stoichiometric amount of CsOH·H2O in 1,4-dioxane and water. The resulting in situ formed catalyst 7 (2.5 mol %) was then directly used without isolation in the 1,4-addition reactions of various aryl- and alkenylboronic acids to cyclic α,β -unsaturated carbonyl compounds (Table 1). The expected chiral addition products 8–10 were obtained with 61-99% yield and high enantioselectivities (82-97% ee) using only a slight excess of the respective boronic acid (1.2 equiv). The addition of arylboronic acids to cyclohex-2-enone typically proceeded with enantioselectivities between 90 and 93% ee. The (S)-configured products were obtained preferentially.¹⁶ Lower stereoselectivities were observed with sterically more demanding (8c; 89% ee; entry 3) or electron-rich arylboronic acids (8f; 88% ee and 8i; 82% ee; entries 6 and 9). The reactions of (E)-styryl- and (E)-4-methylstyrylboronic acid with cyclohex-2-enone gave the chiral addition products 8n-o with 61-66% yields and high enantiomeric excesses (92-95%ee; entries 14 and 15). With cyclopent-2-enone as substrate, even higher enantioselectivities were achieved (9a-i; 94-97% ee; entries 16-24). In this case, switching from aryl- to alkenylboronic acids did not result in a deterioration of the yield (9i; entry 24). The use of heterocyclic Nbenzyl maleimide as substrate led to the chiral (S)-configured addition products **10a**-c with good yields (84-88%) and high enantioselectivities (88-97% ee; entries 25-27).

Next, we examined diastereomeric **2** and its performance as a chiral ligand in the Rh-catalyzed Hayashi–-Miyaura reaction (Table 2). To our delight, we found that the corresponding Michael adducts were produced with equally high enantioselectivities and yields (79-92%; 90-99%) ee), but remarkably, the absolute configurations of the products were opposite to those obtained with **1**, clearly hinting at predominant stereocontrol through the chiral environment around the alkenyl moiety.

(12) Transmetalation with $MgCl_2$ prior to the reaction with the sulfinate was necessary to prevent epimerization at the chiral sulfur. See the Supporting Information for details.

(13) Flash column chromatography: purification/separation of the diastereomeric sulfoxide ligands from byproducts: (a) SiO₂, *n*-pentane/acetone 2:1; separation of the two diastereomeric sulfoxide ligands: (b) SiO₂, CH₂Cl₂/EtOAc 2:1.

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(16) Comparison with HPLC data from references 3d,3o, 4b, and 8i.

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Table 1.	Enantiose	lective 1	,4-Additi	on of l	Boro	nic Aci	ids to
Various	Electron-d	eficient	Alkenes	Using	1 as	Chiral	Ligand

	0	[(1)RhOH] ₂ (7 ; 2.5 mol %) R-B(OH) ₂ (1.2 equiv)	0	
		CsF (1.2 equiv)		
	ال	dioxane, rt, 1-12 h		R
			vield	
entry		product	$(\%)^a$	ee (%) ^b
1		8a: R = Ph	98	92
2		8b: $R = 2-Et-C_6H_4$	99	92
3		8c: R = 1-naphthyl	96	89 (<i>S</i>) ^c
4		8d: $R = 2$ -MeO-C ₆ H ₄	90	90
5		8e: $R = 2 - F - C_6 H_4$	88	90
6		8f: $R = 2,3-CH_2O_2-C_6H_3$	86	88
7		8g: $R = 3$ -MeO-C ₆ H ₄	93	90
8	0	8h: $R = 3-Cl-C_6H_4$	90	90
9		8i: $R = 4$ -MeO-C ₆ H ₄	85	82 $(S)^{c}$
10	∼ • _R	8j: $R = 4$ -PhO-C ₆ H ₄	90	93
11		8k: $R = 4$ -Cl-C ₆ H ₄	84	93
12		81: $R = 4 - F - C_6 H_4$	89	92
13		8m: $R = 4 - F_3 C - C_6 H_4$	80	93
14		8n: R = (<i>E</i>)-PhCH=CH	66	95
15		80: $R = (E)$ -4-MeC ₆ H ₄ -	61	92
		CH=CH		
16		9a: R = Ph	85	96 $(S)^{c}$
17		9b: R = 1-naphthyl	99	94
18		9c: $R = 2$ -MeO-C ₆ H ₄	96	96
19	0	9d: $R = 3-C1-C_6H_4$	99	96
20	\square	9e: $R = 4$ -MeO-C ₆ H ₄	88	94
21		9f: $R = 4$ -Me-C ₆ H ₄	92	96
22		9g: $R = 4$ -Cl-C ₆ H ₄	99	96
23		9h: $R = 4 - F_3 C - C_6 H_4$	93	97
24		9i: R = (<i>E</i>)-PhCH=CH	94	95
25	0	10a: R = Ph	84	$88^{d}(S)^{c}$
26	Bn∼NŬ	10b: $R = 4$ -MeO-C ₆ H ₄	88	$92^{d}(S)^{c}$
27		10c: $R = 3,5-Me_2-C_6H_3$	85	$97^{d}(S)^{c}$

^{*a*} Isolated yield of analytically pure product. ^{*b*} Determined via chiral HPLC analysis. ^{*c*} Absolute configurations determined by comparison with reported chiral HPLC data. ¹⁶ ^{*d*} Reaction time: 12 h. Compound racemizes when stored at room temperature.

Moreover, the addition of phenylboronic acid to heterocyclic Cbz-protected 2,3-dihydropyridin-4(1*H*)-one furnished **14** with 92% yield and 99% ee (entry 9). To rationalize the opposite stereochemical outcomes obtained with the diastereomeric ligands **1** and **2**, we propose the model outlined in Scheme 2. Since sulfinyl groups are known to be strong σ -donors to Rh,^{4b} a *trans*-configuration of the aryl group and the alkene moiety of the ligand in the complex can be assumed as it is reported for the related phosphine–olefin hybrid ligands.^{8e} The stereoselectivity is controlled by the chiral environment around the alkenyl unit, which forces the substrate via steric interactions to bind to the Rh
 Table 2. Enantioselective 1,4-Addition of Boronic Acids to

 Various Electron-Deficient Alkenes Using 2 as Chiral Ligand



^{*a*} Isolated yield of analytically pure product. ^{*b*} Determined via chiral HPLC analysis. ^{*c*} Absolute configurations determined by comparison with reported chiral HPLC data. ^{16 *d*} Reaction time: 12 h. Compound racemizes when stored at room temperature. ^{*e*} Reaction time: 12 h.

complex with its si face in the case of 1 and with its re face in the case of 2. Despite a strong coordination of the

Scheme 2. Tentative Stereochemical Model Explaining the Opposite Configurations of the Addition Products Obtained with Ligands 1 and 2



sulfinyl group to Rh the central chirality at the sulfur has only a minor influence on the observed enantioselectivities.

Finally, we examined the influence of electronic and steric modulations at the sulfoxide-olefin hybrid ligand on reactivity and enantioselectivity of the Rh complex in the Hayashi-Miyaura reaction. For this purpose, we prepared the analogues 15a-c bearing different sulfinyl moieties using subsequent addition of the corresponding Grignard reagents to (S)-TMPOO (N-tosylmethylphenyl-1.2.3-oxathiazolidine 2-oxide).¹⁷ To investigate the role of the alkenvl moiety, we prepared 16 with a more electronrich 4-dimethylaniline substituent at the C=C double bond. These ligands were then submitted to the Rhcatalyzed 1.4-addition of various arylboronic acids to cyclohexen-2-one (Table 3). Both increasing and reducing the electron-density at the sulfoxide (15a,b) led to an overall deterioration of yield and enantioselectivity (entries 1-7 of Table 3). Interestingly, the use of electron-poor arylboronic acids as nucleophiles proved advantageous to yield and enantioselectivity with both ligands (entries 4 and 7). A negative effect of electron-rich arylboronic acids on the stereoselectivity was also found with 1 as ligand (entries 6 and 9 of Table 1). With ligand 15c bearing a sterically highly congested tBu group at the sulfoxide no reaction took place at all (entry 8 of Table 3). This is probably due to a loss of coordination between the sulfinyl group and Rh. The alkenyl moiety alone is not sufficient for efficiently binding to the Rh center, thus underlining the vital role of the sulfinyl group for chelation and formation of the reactive complex. An increase of the electron-density at the C=C bond (16) led only to a deterioration of yields, without impairing the enantioselectivities (entries 9 and 10).

In summary, we have developed a concise, protectivegroup free synthesis of sulfoxide–alkene hybrid ligands. Chiral resolution is achieved via simple column chromatographic separation of the diastereomeric ligands, which can both be used in the Hayashi–Miyaura reaction, furnishing the chiral products with excellent yields, equally high enantioselectivities. and opposite stereoconfigurations. Experiments with analogues of **1** and **2** displaying different steric and electronic properties showed that coordination of the sulfinyl group represents a crucial factor for efficient chelation and formation of the reactive Rh complex. Although efficient binding of the alkenyl moiety to the Rh center is less important for the reaction to proceed, its chiral environment dictates the stereochemical outcome.

Acknowledgment. The research leading to these results has received funding from the European Research Council under the European Community's Seventh Framework





entry	ligand	product	yield $(\%)^a$	$ee (\%)^b$
1		17a: $R = 4$ -MeO-C ₆ H ₄	57	83 (<i>R</i>) ^c
2	ОМе	17b: $R = 4$ -Me-C ₆ H ₄	63	88
3	$\langle \rangle$	17c: R = Ph	69	81
4	оме 15а	17d: $R = 4-F-C_6H_4$	73	90
	Õ.			
5	S. CL	18a: $R = 4$ -MeO-C ₆ H ₄	77	84 $(R)^{c}$
6	~~~~	18b: R = Ph	84	87
7	OMe	18c: $R = 4 - F_3 C - C_6 H_4$	83	87
	150			
8	Ofference of the second	19: R = Ph	no reaction	-
9 10	Me Me Me ₂ N	20a: R = 3-MeO-C ₆ H ₄ 20b: R = 1-naphthyl	79 62	89 90 (<i>S</i>) ^c
	16			

^{*a*} Isolated yield of analytically pure product. ^{*b*} Determined via chiral HPLC analysis. See the Supporting Information for details. ^{*c*} Absolute configurations determined by comparison with reported chiral HPLC data. ¹⁶

Programme (FP7/2007-2013), ERC grant agreement no. 227763. We thank BASF AG, W. C. Heraeus GmbH, Chemetall GmbH, and Solvias AG for the generous gifts of chemicals. L.-N.G. thanks the Alexander von Humboldt Foundation for financial support.

Supporting Information Available. Experimental procedures and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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