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Very Efficient Phosphoramidite Ligand for Asymmetric Iridium-Catalyzed Allylic Alkylation

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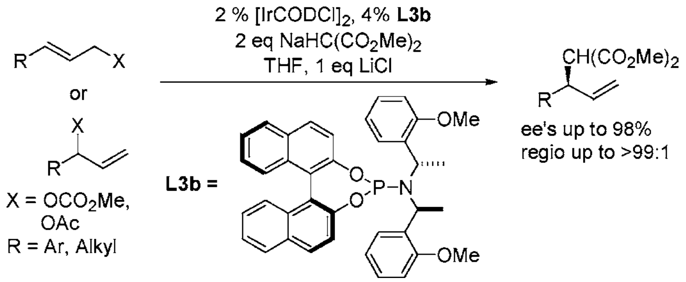
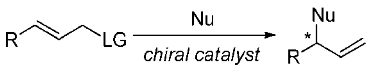
ABSTRACT



Linear or branched allylic carbonates or acetates undergo enantioselective iridium-catalyzed allylic substitution with sodium malonate. The reaction is wide in scope and affords the branched product in high yield and with high regio- (up to >99:1) and enantioselectivity (up to 98%). Ten aromatic or aliphatic substrates were successfully tested.

The asymmetric allylic substitution (eq 1) on an achiral substrate is a potentially powerful method to create new chiral centers from easily available starting material. Of particular interest are the unsymmetrically substituted allyl derivatives. They are particularly challenging substrates, because, in addition to the requirement of enantiocontrol, the problem of regioselectivity has to be solved.



(1)

Among the metals that are used for this reaction, palladium is the most widely studied.[1] However, despite the high enantioselectivities obtained with many other substrates, this metal gives preference to the linear instead of the branched product (eq 1).[2] The situation is different for complexes of Ir[3,4] Mo,[5] Ru,[6] and W,[7] which give regioselectivities in favor of branched products. Nevertheless, there is still a need for a general system that would allow the use of various types

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[1] (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 593. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, Berlin, 1999; p 833. (c) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

[2] For exceptions, see: (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471 and refs cited herein.

[3] For a review on Ir, see: Takeuchi, R. *Synlett* **2002**, 1954.

[4] (a) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263. (b) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647. (c) Takeuchi, R.; Tanabe, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1975. (d) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025. (e) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (f) Bartels, B.; Garcia-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569. (g) Bartels, B.; Helmchen, G.; Garcia-Yebra, C. *Eur. J. Org. Chem.* **2003**, 1097. (h) Fuji, K.; Kinoshita, N.; Kawabata, T.; Tanaka, K. *Chem. Commun.* **1999**, 2289. (i) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197. (j) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (k) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197. (l) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054.

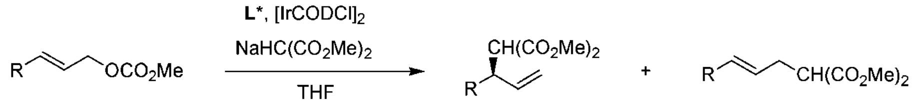
[5] (a) For a review on Mo, see: Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159 and refs cited therein. (b) See also: Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.

[6] Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059.

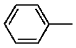
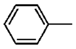
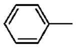
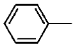
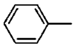
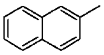
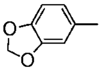
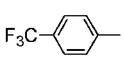
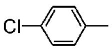
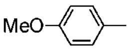
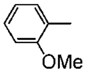
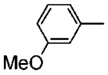
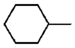
[7] Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462.

10.1021/ol048607y CCC: $27.50

Table 1. Enantioselective Ir-Catalyzed Allylic Alkylation of Carbonates[a]



1 **2** **3**

entry	substrate	**R**	ligand	additive (1eq)	*T* °C	time h	yield %[b]	**2/3**[c]	*ee* %[d]
1	**1a**		**L3b**	none	65	21.5	31	65:35	44, *R*[e]
2[f]	**1a**		**L3b**	LiCl	25	2	82	99:1	98, *R*[e]
3	**1a**		**L2b**	LiCl	25	14	28	97:3	89, *S*[e]
4	**1a**		**L1b**	LiCl	25	14	81	99:1	93, *R*[e]
5[g]	**1a**		**L3b**	LiCl	25	2	87	99:1	98, *R*[e]
6	**1b**		**L3b**	LiCl	25	20	73	99:1	96, *R*
7	**1c**		**L3b**	LiCl	30	44	70	99:1	97, *R*
8	**1d**		**L3b**	LiCl	30	65	40	92:6	94, *R*
9	**1e**		**L3b**	LiCl	35	24	90	>99:1	97, *R*[e]
10	**1f**		**L3b**	LiCl	35	24	99	>99:1	97, *R*
11	**1g**		**L3b**	LiCl	30	6	98	>99:1	79, *R*
12	**1h**		**L3b**	LiCl	30	6	58	99:1	96, *R*
13	**1i**		**L3b**	LiCl	30	65	65	93:7	98, *R*
14	**1j**	*n*-Pr—	**L3b**	LiCl	30	30	82	80:20	96, *R*

[a] Molar ratio: substrate/LiCl/NaHC(CO$_2$Me)$_2$/[Ir(COD)Cl]$_2$/**L** = 1/1/2/0.02/0.04. Scale: 0.5 mmol of substrate. [b] Isolated yield. [c] Determined by 400 MHz ^{1}H NMR or GC-MS. [d] Determined by chiral GC or SFC. [e] Absolute configurations were determined by comparison with published data (ref 7); all the other configurations were attributed by analogy. [f] Performed on a 1 mmol scale. [g] Performed on a 2 mmol scale with a molar ratio: substrate/LiCl/NaHC(CO$_2$Me)$_2$/[Ir(COD)Cl]$_2$/**L** = 1/1/2/0.01/0.02.

of nucleophiles, as well as various substrates having different types of substituents (aromatic or aliphatic ones), and would be practical and cheap.

Strong π-accepting phosphoramidite monodentate ligands, such as **L1a**−**3a** (Figure 1) have recently shown their efficiency,[8] in particular in the Ir-catalyzed allylic amination reactions of allylic carbonates,[9] as well as allylic substitution of dienyl esters.[10]

In the allylic amination and etherification, using Ir and **L3a** as the chiral source, Hartwig observed an induction period; he isolated and characterized the active catalytic species.[11] Our group very recently described new phosphoramidite ligands (**L1b**−**3b**) that contain an ortho substituent on the amine part of the ligand.[12] These ligands, in particular **L3b**, gave high enantio- and regioselectivities in the Cu-

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(8) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

(9) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (b) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

(10) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116.

(11) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.

(12) Alexakis, A.; Tissot-Croset, K.; Polet, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426.

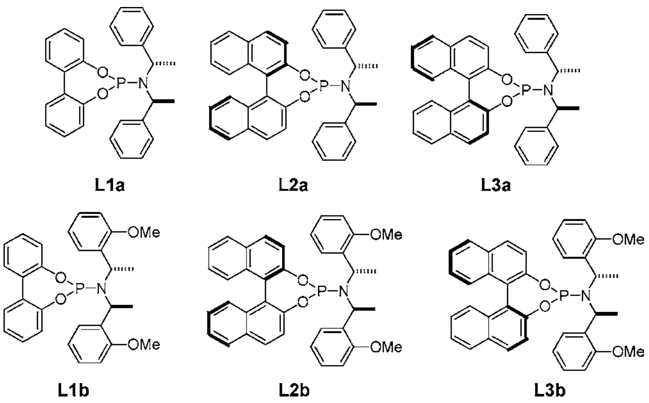


Figure 1. Chiral ligands used in this study.

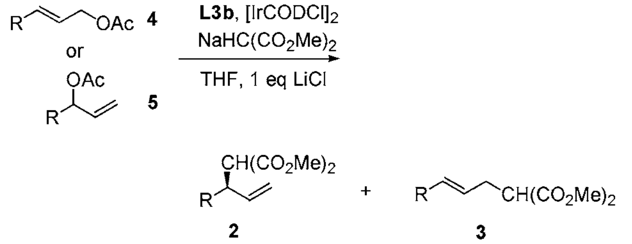
catalyzed alkylation and in the Ir-catalyzed amination of cinnamyl carbonate. No induction period was observed, which could lead to the hypothesis that **L3b** could work as a bidentate P−O hemilabile ligand. This hypothesis was supported by the fact that a *para*-methoxy group (instead of *ortho*-methoxy) does not improve the result of **L1a**−**3a**.[12]

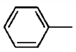
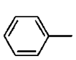
To further test the improvements brought by our new ligands and to generalize our system, we wished to try other nucleophiles, particularly malonates. It should be noticed that Helmchen had already used ligands **L1a**−**3a** in this reaction with 7−94% ee.[4e−g]

Our work began with the simple addition of sodium malonate onto carbonate **1a** under the classical experimental conditions (4% Ir catalyst and 4% ligand).[4g] The reaction was very slow, even at 60 °C, and led to low regio- and enantioselectivities (Table 1, entry 1). The observation by Helmchen[4e] and Fuji[4h] that lithium chloride gave a strong salt effect, improving both the regio- and the enantioselectivity, led us to add 1 equiv of lithium chloride early in the reaction. An impressive acceleration of the reaction, together with an improvement of the regio- (99:1) and enantioselectivity (98%), was obtained (entry 2). Even a lower catalyst loading (2% Ir catalyst) did not seem to be deleterious (entry 5). This result demonstrates again the efficiency of the new ligand **L3b**, bearing the *ortho*-methoxy group, as compared to **L3a**, which in the case of cinnamyl derivative gave 86% ee and a 91:9 ratio.[4g]

Comparison of ligands **L3b** (*S*,*SS*) and **L2b** (*R*,*SS*) clearly shows a matched/mismatched situation, with **L2b** being the mismatched one (only 89% ee). It should be noted that the inversion of the binaphthol part of the ligand translates into an inversion of stereochemistry on the resulting allylic adduct. Interestingly, the simpler ligand **L1b** affords a relatively high ee (93%). The absolute stereochemistry of the adduct corresponds to the one obtained with the matched ligand **L3b**. Thus, the biphenol part of the atropoisomerically flexible ligand **L1b** seems to adopt the same atropoisomeric configuration as the (*S*)-binaphthol of **L3b**. This behavior is similar to that observed in Cu-catalyzed reactions, where the induced atropoisomerism of the biphenol part has the same configuration as the matched binaphthol configuration of the binaphthyl-type ligand.[13]

Table 2. Ir-Catalyzed Allylic Alkylation of Acetates with Ligand **L3b**[a]

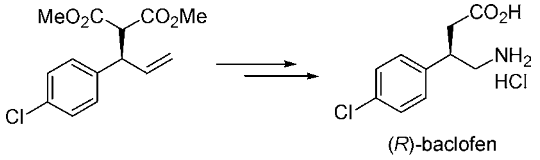


entry	substrate	R	*T* °C	time h	yield %[b]	2/3[c]	*ee* %[d]
1	**4a**		25	21.5	79	99:1	97[e]
2	**4b**	*n*-Pr—	25	60	21	91:9	94
3	**4b**	*n*-Pr—	30	66	87	87:13	97
4	**4b**	*n*-Pr—	42	15	71	86:14	97
5	**4b**	*n*-Pr—	55	18	82	82:18	97
6	**5a**		25	3	81	>99:1	10

[a] Molar ratio: substrate/LiCl/NaHC(CO_2Me)$_2$/[Ir(COD)Cl]$_2$/**L3b** = 1/1/2/0.02/0.04. Scale: 0.5 mmol of substrate. [b] Isolated yield. [c] Determined by 400 MHz ^{1}H NMR or GC-MS. [d] Determined by chiral GC or SFC. [e] Performed on a 1 mmol scale.

We then successfully tested other allylic substrates, showing that the reaction was general for every substrate, whatever the electron demand on the aromatic substituents.[5] The only exception was for the *ortho*-methoxy derivative **1h**. This suggests that the O-coordinating ability of the methoxy group on the substrate competes with the *ortho*-methoxy of the ligand (entry 11). Of particular interest is the substrate bearing a *para*-Cl substituent, **1f**, which is known to lead to the therapeutically useful GABA$_B$ receptor agonist (*R*)-baclofen hydrochloride (Scheme 1) in high yield and enantioselectivity.[14] The reaction is equally effective with substrates having a primary (entry 14) or a secondary (entry 13) alkyl substituent.

Scheme 1. Synthesis of (*R*)-Baclofen According to Ref 14b



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(13) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375.

(14) (a) Corey, E. J.; Zhang, F.-Y *Org. Lett.* **2000**, *2*, 4257. (b) Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275.

Allylic carbonates are usually the substrates of choice, whereas allylic acetates are used less often due to their lower reactivity and selectivity. In our case, the reaction on linear allylic acetates did not seem to be different, except for a slight decrease in rate (Table 2, entry 1). Thus, the substrate **4b** needs to be heated to complete the reaction. The effect of raising the temperature did not affect the enantioselectivity but affected instead the regioselectivity (entries 2−5). Finally, we also tested a branched substrate **5a**. However, the enantioselectivity dropped dramatically, showing that the isomerization of the Ir π-complex is a very slow process, a result also observed by Helmchen and Moberg.[4e,14]

In conclusion, we have found that our new phosphoramidite ligands **L1b**−**3b** are excellent for the Ir-catalyzed allylic substitution in terms of regio- and enantioselectivity and in the wide scope of applicability. Ligand **L3b** appears to be the best for this purpose. This efficiency may probably be ascribed to their bidentate P−O nature, due to the presence of the *ortho*-methoxy group.

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Supporting Information Available: Experimental details, chromatograms, and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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