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Kinetic Study of Various Phosphoramidite Ligands in the Iridium-Catalyzed Allylic Substitution

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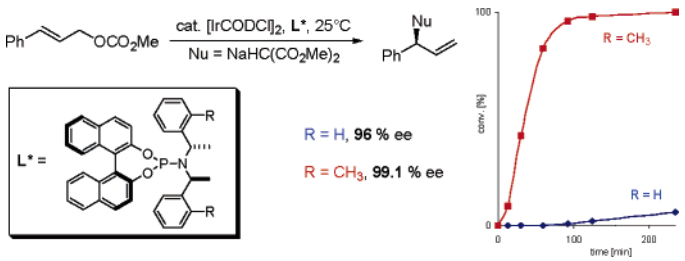
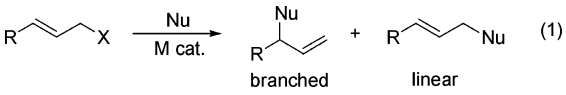
ABSTRACT



A comparative kinetic study of seven ligands is presented which clearly shows that a slight difference in the substitution pattern of the aryl group on the amine moiety of the ligand dramatically alters the activity of the resulting iridium catalyst. Ligand L6 shows the most impressive kinetics as well as the highest enantioselectivities.

Asymmetric allylic substitution (eq 1) has been shown to be a powerful method for the preparation of a wide range of chiral molecules. This reaction has generated a great deal of interest in recent years, and several methods have been developed for the control of both regio- and stereochemistry.



Among the metals that are used for this reaction, palladium has been the most widely studied.[1] The regiochemistry of this metal normally favors the linear product, although nowadays there are more and more examples of branched regioselectivity.[2] Among other metals, increasing interest is devoted to Ir[3,4] which gives regioselectivities more generally in favor of branched products.

Using $[IrCODCl]_2$ and **L1** (Figure 1) as the chiral source, Hartwig observed an induction period; he isolated and characterized the postulated catalytically active species resulting from the insertion of the iridium metal into a C−H bond of the methyl group of the amine part of **L1**.[5]

Very recently, our group described a new phosphoramidite ligand **L2** that contains two *o*-methoxy substituents on the

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(3) For a review on Ir, see: Takeuchi, R. *Synlett* **2002**, 1954−1965.

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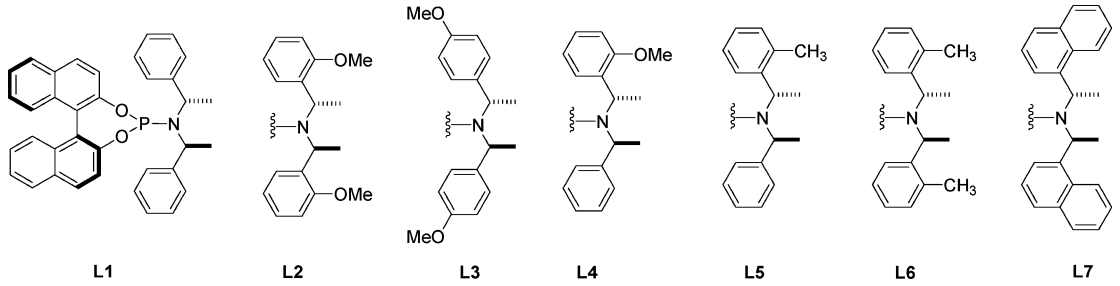
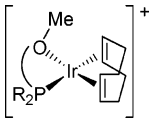


Figure 1. Chiral ligands used in this study.

amine part of the ligand. **L2** showed, both in the Ir-catalyzed allylic amination and alkylation of many allylic carbonates and acetates, a spectacular acceleration of the reaction[6] with high regio- and enantioselectivities.[7] Almost simultaneously, Helmchen tested **L2** in his conditions and also noticed acceleration as well as an improvement of the enantioselectivity compared to **L1**.[8]

At first glance, we logically assumed that the efficiency of our new ligand was due to the P−O hemilabile character (Scheme 1), although it would lead to a seven-membered metallo-ring and kick out a chloride anion.

Scheme 1. Initial Postulate Concerning the Efficiency of **L2** over **L1**

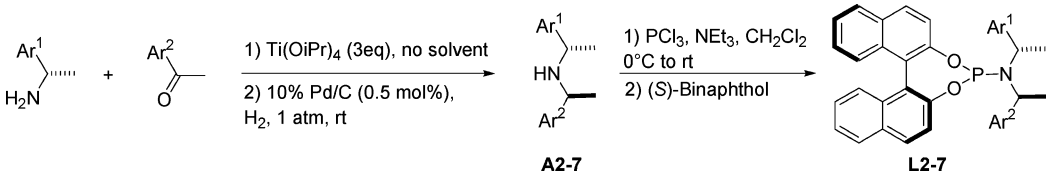


Indeed, it was legitimate to consider **L2** as a bidentate ligand, allowing a stronger positive character to enhance the oxidative addition to the substrate.[9] Preliminary calculations on the related ligand **L4**[10] could sustain such an assumption. Nevertheless, we have not been able to observe any coordination of the *o*-methoxy group by ^{1}H or ^{31}P NMR or get any crystals suitable for X-ray structure analysis.

To confirm or deny this hypothesis, we focused our attention in doing specific structural changes in the amine part of this family of ligands. Using our very efficient synthetic method leading to secondary amines,[11] we prepared several C_2- and pseudo-C_2-symmetrical amines to show the impact of *ortho* substitution of the aromatic ring in the amino part of seven different ligands (Table 1). The nonsymmetrical amines **A4** and **A5** were prepared for the sake of convenience because all of the starting materials are commercially available. The synthesis of amines **A2** and **A6** requires a chiral amine that has to be synthesized or obtained generously from BASF. The calculations on **L4** showed that a single methoxy group had the same impact as two.

With the new ligands in hand, we used them in the iridium-catalyzed allylic amination reaction using benzylamine as the nucleophile. The results of the kinetics are presented in Figure 2. Bearing a methoxy substituent in the *para* position, ligand **L3** was used to give hints concerning an eventual electronic effect. This did not seem to be the case as the

Table 1. Synthesis of C_2-Symmetrical and Pseudo-C_2-symmetrical Secondary Amines



entry	Ar^1	Ar^2	amine (dr)[a]	yield of amine[b] (%)	ligand	yield of ligand (%)
1	*o*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	**A2** (82:18)	59	**L2**	94
2	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**A3** (89:11)	47	**L3**	92
3	Ph	*o*-$MeOC_6H_4$	**A4** (82:18)	55[c]	**L4**	34[d]
4	Ph	*o*-$CH_3C_6H_4$	**A5** (92:8)	64	**L5**	82
5	*o*-$CH_3C_6H_4$	*o*-$CH_3C_6H_4$	**A6** (94:6)	64	**L6**	63
6	1-naphthyl	1-naphthyl	**A7** (94:6)	34	**L7**	74

[a] The diastereomeric ratio determined by GC−MS is shown in parentheses. [b] Isolated yield after purification by recrystallization of the corresponding hydrochloride salt. [c] Purification by chromatography. [d] Yield not optimized.

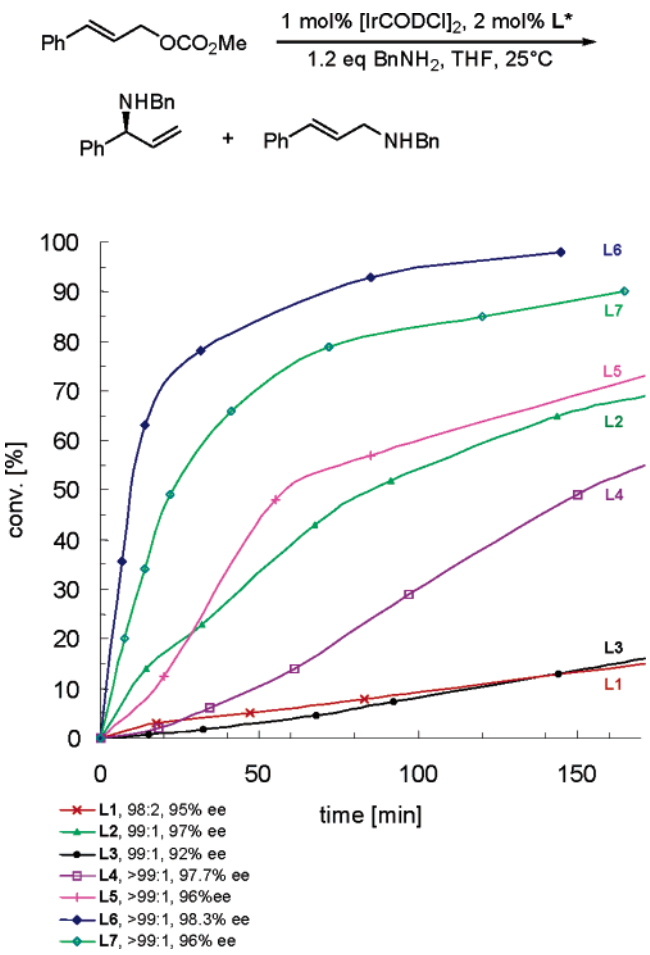


Figure 2. Comparison of the kinetics of the catalysts resulting from the corresponding ligands in the Ir-catalyzed allylic amination with benzylamine.

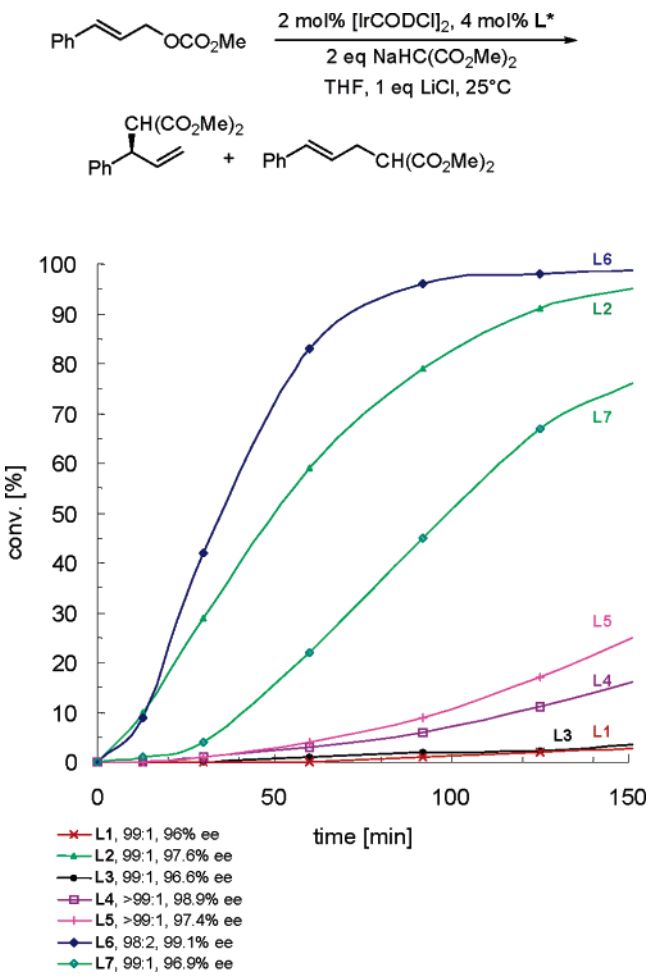


Figure 3. Comparison of the kinetics of the catalysts resulting from the corresponding ligands in the Ir-catalyzed allylic alkylation with sodium dimethylmalonate.

kinetics of **L3** is much slower than **L2**, giving a slope similar to that of **L1** (Figure 3).

We then looked to the influence of a sole *o*-methoxy substituent; the reaction showed an intermediate kinetic slope between **L2** and **L1**, which seems to be in accord to the calculations. To confirm an eventual coordination role of the substituent, we replaced the methoxy by a simple methyl group in the *ortho* position as in **L5**. This ligand gave a kinetic slope as close to the one of **L2**, suggesting that our first postulated model might be wrong. To confirm this statement, we synthesized the C_2-symmetrical ligand **L6** bearing two *o*-methyl substituents. This ligand gave a spectacular improvement of the kinetics of the reaction, allowing its completion in less than 3 h at room temperature!

For comparison, we studied the congener featuring the 1-naphthyl moiety **L7** used by Hartwig[4f,g] which gave a higher reaction rate than **L2** but less impressive than **L6**.

A similar study was conducted on the allylic alkylation. A comparable trend was detected. Ligands bearing either no substituent at all (**L1**) or a methoxy group in the *para* position (**L3**) were the slower ones. The two pseudo-C_2-symmetrical ligands, **L4** and **L5**, showed a slight improvement compared to **L1** and **L3**, although we expected **L5** to be much faster. Ligands **L2** and **L6** showed impressive results, keeping the trend we observed in the amination experiment. Once again, **L7** was less efficient in terms of kinetics.

Concerning the enantio- or regioselectivities, all the ligands gave results in the same range (92−99% ee, Figure 4), suggesting that only the kinetics of the reaction is dramatically modified by the steric bulk of the amine moiety of the ligand. Nevertheless, ligand **L6** gave the best enantioselectivities for both reactions, 98.3 and 99.1%.

This study shows that the *o*-methoxy group seems too remote to play any coordination role, but rather a steric effect, as ligand **L6** bearing no oxygen but a methyl group at the

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(9) This argument was used to justify a reaction acceleration effect in polar solvents. See ref 3 for details.
(10) Work in progress.
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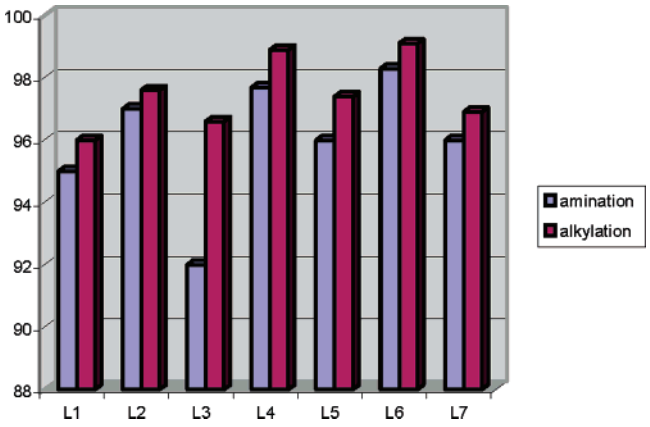

Figure 4. Recapitulative comparison of the ee's (%) resulting from the Ir-catalyzed allylic amination with benzylamine and alkylation with sodium dimethylmalonate with ligands **L1**−**L7**.

same position gave even more spectacular results. Such steric effects are well-known with phosphorus ligands where the ligand cone angle θ plays a crucial role.[12] An η^2 effect of the neighboring aryl group[13] of the amine part cannot be excluded, and further studies are currently in progress.

In conclusion, these results give interesting insights concerning slight changes in the structure of the ligands to improve not only the enantioselectivity but also the kinetics of both reactions.

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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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