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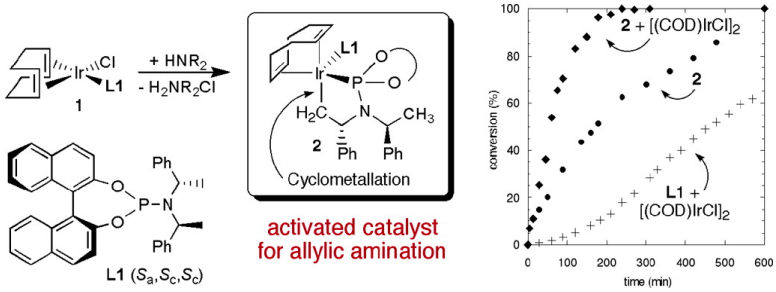

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Identification of an Activated Catalyst in the Iridium-Catalyzed Allylic Amination and Etherification. Increased Rates, Scope, and Selectivity

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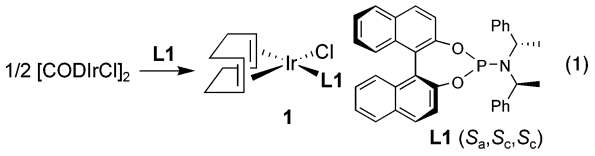
Allylic amination and etherification is an attractive convergent method to generate the α-chiral amine and ethers units that are found in a large number of single enantiomer pharmaceutical candidates and biologically active molecules. Allylic substitutions with molybdenum,[1] tungsten,[2] ruthenium,[3] rhodium,[4] and iridium catalysts[5−7] often occur to generate chiral, branched products and complement the ubiquitous palladium-catalyzed[8] reactions. We recently disclosed a highly enantioselective iridium-catalyzed reaction that forms branched allylic amines and ethers from achiral terminal allylic carbonates.[7]

Although many catalysts for allylic substitution have been developed with metals other than palladium, with few exceptions,[9] mechanistic data that reveal the identity of the active catalyst have been obtained with palladium.[10] A better mechanistic description of the allylic substitution processes with catalysts containing group 6−9 metals should allow selection of reaction conditions and ligand structures that improve rate and selectivity.

We now describe the synthesis, isolation, and characterization of an activated form of the catalyst of our allylic amination and etherification processes. An unexpected cyclometalation of a hindered phosphoramidite generates this more reactive species. This isolation of an activated catalyst has created allylic aminations and etherifications that occur faster, with higher selectivities, and with broader substrate scope. The addition of amines to terminal allylic carbonates now provides a remarkably general, efficient, and selective method to prepare α-chiral amines by C−N bond formation.

As precedented,[5c] reaction of $[Ir(COD)Cl]_2$ with **L1**[11] (eq 1), the components of the original catalyst,[7] formed the standard square-planar Ir(I) complex [CODIrCl(**L1**)] (**1**) in 90% yield. Complex **1** was fully characterized by NMR spectroscopy and X-ray diffraction.

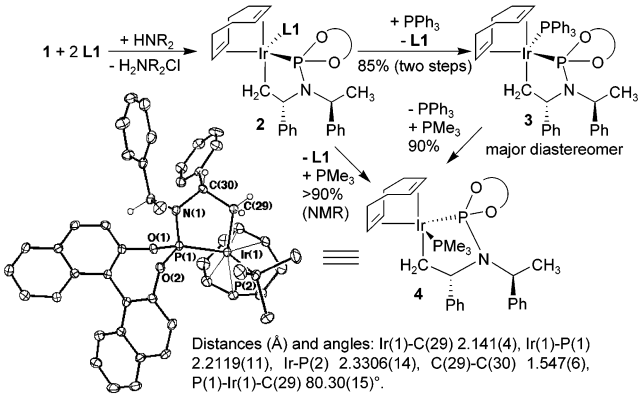


(1)

However, complex **1** did not react with an excess of methyl cinnamyl carbonate at 50 °C on the time scale of the catalytic chemistry. Thus, addition of the carbonate to square-planar **1** does not occur during the catalytic process.[12]

However, reaction of **1** at room temperature for 12 h with pyrrolidine generated a new iridium complex **2** in Scheme 1, as determined by the appearance of a single set of two doublet resonances (δ = 152.6 and 127.8 ppm, $^3J_{P,P}$ = 46.3 Hz) in the ^{31}P NMR spectrum of the reaction mixture. Reaction of complex **1** with 2 equiv of the phosphoramidite ligand (Scheme 1) and amine for 12 h generated the same compound **2** in yields greater than 90%. Our data indicate that complex **2** is formed by cyclometalation of the phosphoramidite ligand[13] at the methyl group of the amino

Scheme 1



substituent, elimination of amine hydrochloride, and coordination of a second phosphoramidite to generate a trigonal bipyramidal structure with one κ^2, P,C-bound and one typical κ^1, P-bound-phosphoramidite. ^{31}P NMR spectroscopy showed that complex **2** consisted of greater than 95% of a single diastereomer. The ^1H and ^{13}C NMR spectra of **2** were complicated by conformational changes on the NMR time scale, but the elemental composition and lack of chloride in this material were deduced by elemental analysis. The cyclometalated methylene group was identified by two ^1H signals at −0.69 and 1.75 ppm and one ^{13}C NMR signal at 15.2 ppm. The ^{13}C NMR signal was shown by DEPT ^{13}C NMR spectroscopy to result from a methylene group.

Further evidence for the structure of **2** was obtained by its reactions with more strongly coordinating dative ligands, such as PMe_3 or PPh_3. These reactions displaced the κ^1-phosphoramidite and generated PMe_3 and PPh_3 complexes **3** and **4** in Scheme 1 containing the κ^2-phosphoramidite of **2**. Reaction of **3** with PMe_3 also formed **4**. Complexes **3** and **4** were characterized by spectroscopic and analytic methods, and complex **4** was analyzed by X-ray diffraction. Complex **3** consisted of an 84:16 ratio of diastereomers, but complex **4** was a single diastereomer, as shown by a single set of doublets at 149.1 and −57.3 ppm ($^3J_{P,P}$ = 46.5 Hz) in the ^{31}P NMR spectrum.

Crystallographic characterization of PMe_3 adduct **4** (Scheme 1) confirmed that cyclometalation of one of the phosphoramidites had occurred at the methyl group of the amino substituent. The bite angle of this κ^2-phosphoramidite ligand is 80.30(12)°, and the Ir(1)−C(29) bond length is 2.141(4) Å.

These data imply that complex **1** does not participate directly in the catalytic cycle and that cyclometalation generates a more reactive catalyst or catalyst precursor for the allylic substitution chemistry. If the active catalyst contains a cyclometalated phosphoramidite and the cyclometalation process is slower or competitive with the catalytic cycle, then reactions catalyzed by **2** should occur faster and with equally high selectivity as reactions conducted with **1** or the combination of $[Ir(COD)Cl]_2$ and **L1**.

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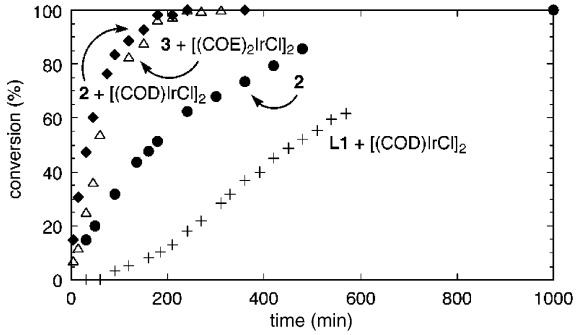
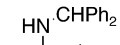


Figure 1. A comparison of the reactions of a series of iridium-phosphoramidite catalysts for the amination of cinnamyl carbonate with benzylamine in THF solvent at room temperature. Catalysts: ◆, 1 mol % **2** + 0.5 mol % $[Ir(COD)Cl]_2$; △, 1 mol % **3** + 0.5 mol % $[Ir(COE)_2Cl]_2$; ●, 1 mol % **2**; +, 2 mol % **L1** + 1 mol % $[Ir(COD)Cl]_2$. Reactions catalyzed by **2** and **3** occurred in 97% ee, and the reaction catalyzed by **L1** and $[Ir(COD)Cl]_2$ occurred in 95% ee.

Table 1. Comparison of the Original Catalyst from **L1** and $[Ir(COD)Cl]_2$ to the Activated Catalyst **2** and $[Ir(COD)Cl]_2$ for the Reaction of Methyl Cinnamyl Carbonate with Amine and Phenoxide Nucleophiles at 25 °C

Entry	Product	Catalyst	Time (h)	b / l	yield[a]	ee
1		1% **2** + $[Ir(COD)Cl]_2$	2	98/2	81%	97%
2		2% **L1** + $[Ir(COD)Cl]_2$	12	98/2	84%	95%
3		1% **2** + $[Ir(COD)Cl]_2$	10	97/3	85%	98%
4		2% **L1** + $[Ir(COD)Cl]_2$	10	–	11%[b]	–
5		0.1% **2** + $[Ir(COD)Cl]_2$	10	99/1	81%	98%
6		0.2% **L1** + $[Ir(COD)Cl]_2$	16	99/1	64%	97%
7		1% **2** + $[Ir(COD)Cl]_2$	2	99/1	81%	97%
8		2% **L1** + $[Ir(COD)Cl]_2$	24	–	<1%	–
9[c]		1% **2** + $[Ir(COD)Cl]_2$	2	95/5	75%	94%
10[c]		2% **L1** + $[Ir(COD)Cl]_2$	35	99/1	76%	94%

[a] Isolated yields. [b] Conversion. [c] Ethyl cinnamyl carbonate was used.

A comparison of reactions of methyl cinnamyl carbonate with benzylamine catalyzed by complex **1**, complex **2**, and the combination of **2** or **3** with $[Ir(olefin)_2Cl]_2$ to bind the κ^1-phosphoramidite after dissociation is shown in Figure 1. Consistent with the hypothesis that the active catalyst contains a cyclometalated phosphoramidite, the reactions catalyzed by bis-phosphoramidite complex **2** occurred much faster than those catalyzed by **1** or the combination of $[Ir(COD)Cl]_2$ and **L1**. Reactions with the combination of bisphosphoramidite complex **2** or PPh_3-complex **3** and $[Ir(olefin)_2Cl]_2$ were even faster. Moreover, reactions of the cyclometalated species did not show the induction period (Figure 1) that is present during the reactions catalyzed by the combination of $[Ir(COD)Cl]_2$ and **L1**. Reactions catalyzed by **2** alone or **2** and $[Ir(COD)Cl]_2$ formed the branched amine in 97% ee.

Table 1 summarizes data that demonstrate increased rates, substrate scope, and turnover numbers with the activated catalyst. The faster rates (Figure 1 and entry 1 vs 2) allowed for increased scope with the less reactive of alkyl and benzylamines. For example, the ammonia equivalent H_2NCHPh_2 reacted slowly with methyl cinnamyl carbonate in the presence of the original catalyst, but formed the substitution product in 85% yield with 97:3 regioselectivity and 98% ee in 10 h in the presence of **2** and $[Ir(COD)Cl]_2$.

This faster rate allowed for the allylic amination to be conducted with lower catalyst loadings. Reaction of methyl cinnamyl carbonate with pyrrolidine at room temperature for 12 h in the presence of 0.1 mol % of **2** and $[Ir(COD)Cl]_2$ formed the branched allylic amine in 81% isolated yield, with 99:1 regioselectivity and 98% enantiomeric excess.

Weakly basic nitrogen nucleophiles did not react with the original system. This lack of reactivity can now be traced to an inability of these weak bases to generate the activated catalyst **2**. Thus, aniline reacted with methyl cinnamyl carbonate in the presence of **2** and $[Ir(COD)Cl]_2$ in high yield, with 99:1 selectivity for the branched isomer and in 97% ee. Likewise, sodium phenoxide reacted in the presence of isolated **2** as catalyst in less than 2 h at room temperature to form the allylic ether in 75% yield with 95:5 regioselectivity and 94% ee. This reaction required 35 h to occur in the presence of $[Ir(COD)Cl]_2$ and **L1** as catalyst.

Thus, isolation of an activated form of our original catalyst for allylic amination and etherification has led to improved activities and reaction scope for iridium-catalyzed allylic amination and etherification. An unusual mode of catalyst activation was revealed, and this finding underscores the value of delineating stoichiometric reactivity of potential catalytic intermediates.[14] Studies to identify additional reaction intermediates and to investigate further the reaction scope are in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Malkov, A. V.; Baxendale, I. R.; Dvorak, D.; Mansfield, D. J.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2737. (b) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141. (c) Glorius, F.; Neuburger, M.; Pfalz, A. *Helv. Chim. Acta* **2001**, *84*, 3178. (d) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.

(2) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.

(3) (a) Zhang, S.-W.; Mitsudo, T.-a.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, *450*, 197. (b) Cenini, S.; Ragaini, F.; Tollari, S.; Paone, D. *J. Am. Chem. Soc.* **1996**, *118*, 11964. (c) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405. (d) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059. (e) Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* **2003**, 408.

(4) (a) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012. (c) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269. (d) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882.

(5) (a) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025. (b) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (c) Bartels, B.; Garcia-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, *10*, 2569.

(6) (a) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (b) Takeuchi, R. *Synlett* **2002**, 1954.

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

(8) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(9) (a) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929. (b) Krska, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Sun, Y.; Trost, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12656.

(10) For recent studies, see: (a) Kollmar, M.; Steinhagen, H.; Janssen, J. P.; Goldfuss, B.; Malinovskaya, S. A.; Vázquez, J.; Rominger, F.; Helmchen, G. *Chem.-Eur. J.* **2002**, *8*, 3103. (b) Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Stepán Vyskocil, P. K. *Chem.-Eur. J.* **2002**, *8*, 4443.

(11) (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375.

(12) The complex formed from the dimethylamino analogue of **L1** was also unreactive toward allylic carbonates. See ref 5c.

(13) For cyclometalation of triphenyl phosphite in a related compound, see: (a) Bedford, R. B.; Castillón, S.; Chaloner, P. A.; Claver, C.; Fernández, E.; Hitchock, P. B.; Ruiz, A. *Organometallics* **1996**, *15*, 3990. (b) Reference 5c.

(14) For a previous study indicating the high activity of a 1:1 ratio of phosphite to Ir in an achiral system, see ref 6a.

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