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Dean Markovi, and John F. Hartwig

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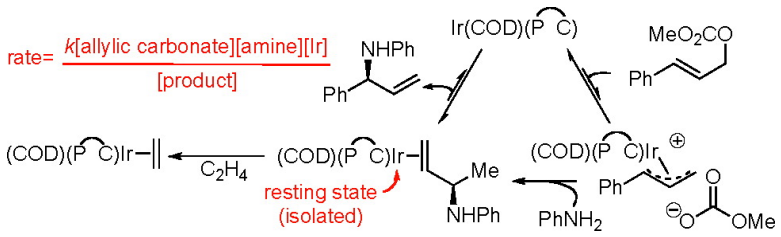

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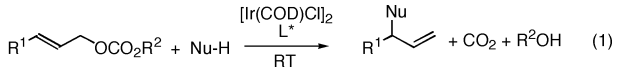
Resting State and Kinetic Studies on the Asymmetric Allylic Substitutions Catalyzed by Iridium−Phosphoramidite Complexes

Dean Marković and John F. Hartwig*

Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, and Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

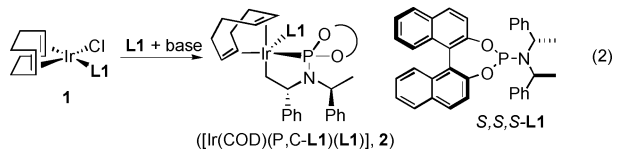
Received June 22, 2007; E-mail: jhartwig@uiuc.edu

Asymmetric iridium-catalyzed allylic substitution is emerging as a powerful method for the enantioselective construction of carbon−heteroatom[1,2] and carbon−carbon[2,3] bonds (eq 1). Despite



(1)

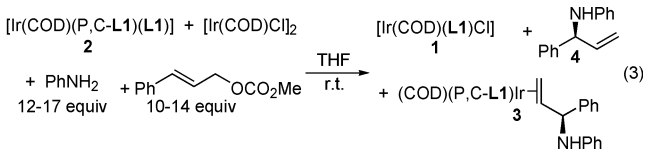
the importance of these transformations and the work of several groups in this field, mechanistic data on allylations catalyzed by iridium complexes are scarce. Our group has shown that the active catalyst contains the cyclometalated core of complex **2** in eq 2, which is generated in situ by reaction of alkylamines with [Ir(COD)Cl]$_2$ (COD = cycloocta-1,5-diene) and the phosphoramidite ligand **L1**,[4] but true intermediates in the catalytic process have not been isolated or even detected. In one of the few studies on potential iridium intermediates, Helmchen showed that an isolated, neutral allyliridium(III) complex ligated by a phosphinooxazoline ligand and two chlorides was not chemically or kinetically competent to be an intermediate in the catalytic process.[5]



(2)

Many of the assumptions about the mechanism of the iridium-catalyzed chemistry are based on the mechanism of palladium-catalyzed allylation. Palladium-catalyzed allylic substitution reactions occur by oxidative addition of an allylic ester, followed by attack of the nucleophile on the allyl intermediate.[6] The identity of each species on the palladium-catalyzed reaction pathway has been determined, and the rates of individual steps of the catalytic cycle have been measured. To connect the mechanisms of iridium- and palladium-catalyzed processes, we have sought related data on intermediates in the iridium-catalyzed processes.

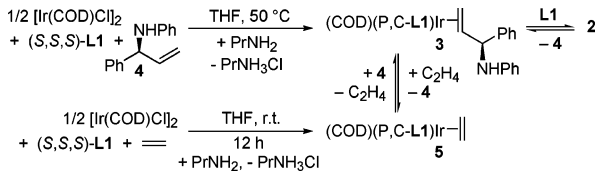
Here, we report the isolation of the resting state of the iridium catalyst and the first kinetic data on the catalytic process. In addition to implying that the resting state is a true intermediate, the kinetic data lead to the unexpected conclusion that reaction of the Ir(I) species with the allylic esters is endergonic and reversible. Moreover, the identity of the resting state has led to a convenient, single-component, activated Ir catalyst for allylic substitution.



(3)

To identify intermediates in the catalytic process, we monitored the reaction of methyl cinnamyl carbonate with aniline, benzylamine, and propylamine catalyzed by 3 mol % of the combination of [Ir(COD)Cl]$_2$ and cyclometalated **2**[4] (eq 3) by ^{31}P NMR

Scheme 1



spectroscopy and independently prepared the complex formed by aniline. The ^{31}P NMR spectrum of these reaction solutions contained two singlets of varying ratios, one at 116 ppm and one between 150 and 148 ppm. The singlet at 116 ppm corresponded to iridium complex **1**, which has been shown previously to be catalytically inactive.[4] The second singlet, whose chemical shift depended on the identity of the amine, corresponded to the resting state of the active catalyst [Ir(COD)(*P*,*C*-**L1**)(allylamine)]. The isolation and reactivity of the allylamine complex **3** formed from reaction of aniline (vide infra) imply that the iridacyclic core of the catalyst and the COD ligand remain intact during the catalytic process.

Independent synthesis of the catalyst resting state **3** is summarized in Scheme 1. Reaction of allylamine **4** with the combination of **L1**, 1/2 equiv of [Ir(COD)Cl]$_2$, and propylamine to induce cyclometalation formed allylamine complex **3**. Complex **3** was challenging to isolate in pure form from this reaction but was the predominant species obtained after precipitation of side products and evaporation of solvent; complex **3** was characterized by ^{1}H, ^{31}P, ^{13}C and ^{13}C DEPT NMR spectroscopy, ^{1}H COSY, and ^{1}H−^{13}C and ^{1}H−^{31}P HMQC experiments. ^{1}H and ^{13}C NMR spectroscopy revealed the components in **3**. In particular, resonances at δ 3.59, 1.77−1.47, and 0.93 in the ^{1}H NMR spectrum and at δ 51.7 and 28.1 ppm in the ^{13}C NMR spectrum corresponding to the allylamine moiety indicated that its C=C bond is bound to iridium.

The coordinated allylamine in **3** is readily displaced by other dative ligands (Scheme 1). Addition of 1.2 equiv of **L1** to a solution of **3** generated free allylamine **4** and metallacycle **2**. Addition of ca. 40 equiv of ethylene to a J-Young NMR tube containing a THF solution of **3** generated the more stable ethylene complex **5**. Complex **5** was independently prepared in 71% isolated yield by the reaction of **L1** with 1/2 equiv of [Ir(COD)Cl]$_2$, ca. 150 equiv of ethylene, and 30 equiv of propylamine in THF (Scheme 1) in a sealed reaction vessel and was characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. This complex was stable for more than a week under nitrogen at room temperature.

The reversibility of this equilibrium and the volatility of ethylene were exploited to create a synthesis of resting state **3** in analytically pure form. Addition of *N*-phenyl allylamine **4** to ethylene complex **5** in toluene, followed by evaporation and re-addition of the solvent three times, generated pure **3** in 78% yield.

To test the competence of **3** as a true intermediate in the catalytic process, allylic aminations were conducted with 1 mol % of **3**. As summarized in eq 4, the reaction catalyzed by **3** alone led to the same product with the same branched-to-linear ratio and enantioselectivity as was formed from the combination of **2** and [Ir(COD)Cl]$_2$ or **L1** and [Ir(COD)Cl]$_2$.

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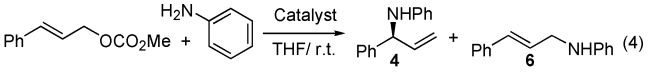
In addition, the reaction in eq 4 catalyzed by 1 mol % of the more accessible ethylene complex **5** occurred in comparable yields and ee's, and reaction with only 0.25% **5** over 8 h occurred in 83% yield. The high reactivity of **5** and high-yield, single-step synthesis from $[Ir(COD)Cl]_2$ makes this complex a convenient single-component catalyst for asymmetric allylic substitutions.



Catalyst = **3**	1%	79 %, **4/6=** 99/1, ee= 96%
5	1%	82 %, **4/6=** 99/1, ee= 96%
2/$[Ir(COD)Cl]_2$	1%/0.5%	80 %, **4/6=** 99/1, ee= 96%
$[Ir(COD)Cl]_2$/**L1**	1%/2%	77 %, **4/6=** 99/1, ee= 96%

To assess the relationship between the catalytic cycle and olefin complexes **3** and **5**, we studied their reactions with allylic esters. In contrast to Pd(0) complexes, no reaction was observed between 1.5 equiv of methyl cinnamyl carbonate and either **3** or **5**. This result indicates that the catalytic cycle does not involve complex **3**, that the amine reacts prior to the allylic carbonate, or that addition of the allylic carbonate is endothermic and reversible.

A mechanism involving addition of allylic carbonate triggered by coordination of amine is unlikely because binding of amine to the [Ir(COD)(*P*,*C*-**L1**)] core would generate an 18-electron complex that should be less reactive than [Ir(COD)(*P*,*C*-**L1**)] toward oxidative addition. An alternative mechanism that starts with allylamine complex **3** and occurs by formation of an allyl intermediate by endothermic and reversible addition of the allylic carbonate is shown in Scheme 2. By this mechanism, the reversible addition of the allylic carbonate is followed by irreversible formation of the allylamine complex **3**. The full rate equation corresponding to this pathway is provided in Supporting Information; a simplified equation based on the greater stability of **3** versus unsaturated **6** and the greater stability of **3** and the allylic carbonate versus the proposed allyl intermediate **7** is provided in eq 5.

$$\frac{d[\mathrm{P}]}{dt} = \frac{k_1 k_2 k_3 [\mathrm{S}][\mathrm{A}][\mathrm{Ir}]_{\mathrm{tot}}}{k_2 k_3 [\mathrm{S}][\mathrm{A}] + k_3 k_{-1} [\mathrm{A}][\mathrm{P}] + k_{-1} k_{-2} [\mathrm{P}]} \qquad (5)$$

This equation shows that a reaction via Scheme 2 with reversible dissociation of the allylamine and reversible addition of the allylic carbonate (the $k_{-1}k_{-2}$[P] term being the largest in the denominator) would be first-order in substrate [S], nucleophile [A], and Ir catalyst [Ir] and would be inverse first-order in the allylamine product [P].

Kinetic data were obtained by ^{1}H NMR spectroscopy at 50 °C with benzene-d_6 as solvent and 1 mol % of the allylamine adduct **3** as catalyst. Complex **3** was generated in situ from complex **5** and 500 equiv of allylamine **4** (vide supra) to ensure full conversion of **5** to **3** and an essentially constant concentration of **4** throughout the reaction. Plots of k_{obs} versus [aniline], k_{obs} versus [Ir complex **5**], and k_{obs} versus 1/[allylamine **4**] (or their double reciprocals) were all linear (see Supporting Information). Second-order rate constants calculated from the three sets of experiments conducted under pseudo-first-order conditions are provided in Table S1 and are indistinguishable ($0.11 \pm 0.1\ s^{-1}\ M^{-1}$). These data are consistent with the mechanism in Scheme 2 involving endothermic, reversible reaction of **3** with the allylic carbonate, followed by reaction of the resulting intermediate with the amine nucleophile.

Finally, the observation of coordinated product allows one to relate the stability of the diastereomeric allylamine complexes to the enantioselectivity of the catalytic process. Although the addition of amine to the likely allyl intermediate is exergonic, the Hammond postulate implies that the relative stabilities of the allylamine adducts should bear some relationship to the relative rates of formation of these amines. Most striking, allylamine (*R*)-**4** (Table 1), which is the minor enantiomer formed by the catalytic process, binds roughly 70 times more weakly to the iridium fragment generated from (*S*,*S*,*S*)-**L1** than does (*S*)-**4**. If these relative binding constants directly correspond to the relative rates for formation of the two enantiomers, the enantiomeric excess would be 97%. This value is within experimental error of the 96% ee (eq 4) obtained from the amination of cinnamyl carbonate with aniline catalyzed by the metallacyclic catalysts.

Scheme 2

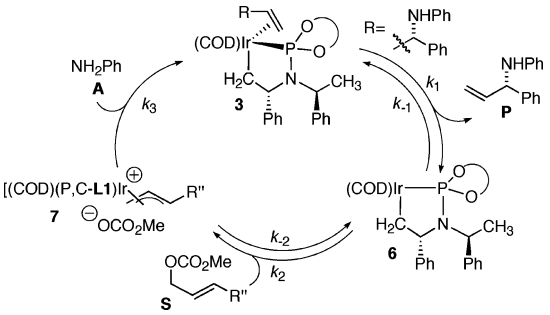
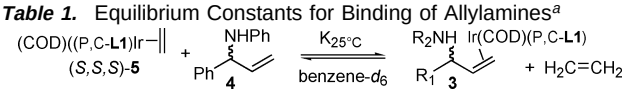


Table 1. Equilibrium Constants for Binding of Allylamines[a]



config of **4**	$K_{25\ °C} \times 10^4$	$K_{rel\ (25\ °C)}$
S	220	73
R	3	1

[a] Reactions were conducted in NMR tubes containing *tert*-butylbenzene as internal reference for ^{1}H NMR spectroscopy and $OPPh_3$ as external reference for ^{31}P NMR spectroscopy.

Thus, these studies provide a detailed insight into the mechanism of iridium-catalyzed allylation and point to further methods to improve the iridium catalyst. Studies to develop next-generation catalysts will be the subject of future studies.

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Note Added after ASAP: The version posted on Aug 29, 2007 had an error in the thirteenth paragraph, second sentence, which was corrected in the version posted Sep 7, 2007.

Supporting Information Available: Experimental procedures, spectroscopic data, full rate equations, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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