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The Allyl Intermediate in Regioselective and Enantioselective Iridium-Catalyzed Asymmetric Allylic Substitution Reactions

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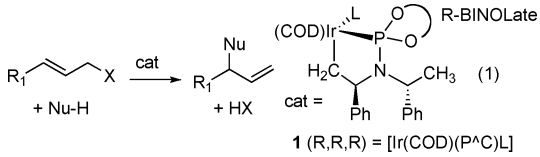
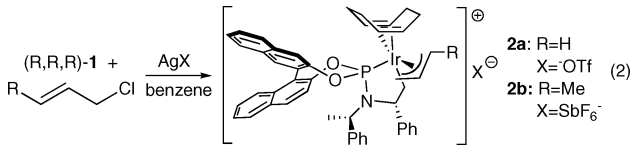
Iridium-catalyzed allylic substitution has become a powerful enantioselective method to form both carbon−heteroatom[1−5] and carbon−carbon[6−10] bonds (eq 1). When conducted with the proper combination of iridium precursor and phosphoramidite ligands, these reactions form branched substitution products with high regioselectivity and enantioselectivity.



These reactions likely occur through an allyliridium intermediate, but the composition and structure of this intermediate has been elusive. Studies from the authors' laboratory led to the isolation of a trapped form of the active catalyst, which possesses a cyclometalated phosphoramidite ligand.[11] However, kinetic studies have implied that an allyliridium complex derived from this metallacycle would be a fleeting intermediate in the catalytic system.[12] Here, we describe the independent synthesis, characterization, and reactivity of allyliridium complexes that are kinetically and chemically competent to be the elusive allyliridium intermediate. Structural data help reveal the origins of regioselectivity and explain how enantioselectivity is controlled by a stereocenter in the catalyst that is distant from that in the emerging product.

An obvious route to the potential allyliridium intermediates is the reaction of an allylic ester with [Ir(COD)(P^C)L], a stable adduct of the catalytically active metallacycle. However, treatment of [Ir(COD)-(P^C)L] (**1** in eq 1) in which L is a phosphoramidite, PPh_3 or ethylene, with allyl methyl carbonate led to no apparent reaction. This observation is consistent with a previous conclusion that the oxidative addition of an allylic carbonate is thermodynamically unfavorable.[12]

Thus, we tested the reactions of the iridium(I) complex **1** in eq 1 in which L = ethylene with more reactive allylic halides (eq 2). Treatment of this complex **1** with allyl chloride in benzene at room temperature led to the rapid formation of a new product corresponding to a singlet resonance at 125 ppm in the ^{31}P NMR spectrum of the crude mixture. Addition of AgOTf in THF to this complex generated *in situ* formed the stable allyliridium complex **2a**. After filtration of the AgCl, this complex deposited as single crystals from the reaction mixture in 55% yield upon standing at room temperature under inert atmosphere for 2 days.

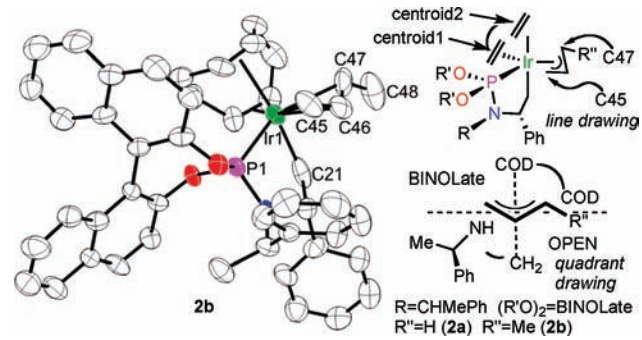


An analogous crotyl complex **2b** was prepared by similar methods. The reaction of ethylene complex **1** with *trans*-crotyl chloride in benzene, followed by abstraction of the chloride with $AgSbF_6$, generated samples of crotyl complex **2b**. Crystals suitable for X-ray diffraction formed in 30% yield upon standing at room temperature for 2 days.

The products of these reactions were identified as allyliridium complexes containing an intact metallacycle and a cyclooctadiene ligand by one-dimensional and two-dimensional ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, as well as X-ray diffraction. A set of ^{1}H NMR signals for the allyl ligand in **2a** were observed at 4.63, 4.22, 3.85, 3.14, and 2.71 ppm. ^{1}H resonances for the coordinated olefinic portion of the COD ligand and for the methylene protons of the metallacycle were clearly identified. Similar ^{1}H NMR resonances for **2b** were observed, save for a downfield shift of the allylic proton of the substituted terminus at 4.73 ppm. The ^{31}P NMR spectra for **2a** and **2b** consisted of a singlet near 125 ppm.

Table 1 contains an ORTEP diagram, line drawing, and quadrant diagram of the crotyl complex **2b**and metric parameters for the core

Table 1. ORTEP Diagram of **2b** and Bond Distances and Angles around Iridium for Complexes **2a** and **2b**



	distances (Å)			angles (deg)	
	2a	**2b**		**2a**	**2b**
Ir−P	2.2685(6)	2.280(3)	P−Ir−C45	86.96(8)	85.9(3)
Ir−C45	2.204(3)	2.240(10)	P−Ir−cent1	106.6	107.6
Ir−C47	2.274(3)	2.377(11)	cent1−Ir−C47	102.2	103
Ir−C21	2.125(3)	2.114(15)	C47−Ir−C45	66.4(1)	66.0(5)
Ir−cent1	2.099	2.097	cent2−Ir−P	103.8	104.6
Ir−cent2	2.244	2.215	cent2−Ir−C45	90.0	90.9
			cent2−Ir−cent1	82.3	81.4
			cent2−Ir−C47	95.8	97.3
			C21−Ir−P	75.73(8)	75.0(4)
			C21−Ir−C45	102.9(1)	102.5(5)
			C21−Ir−C47	90.9(1)	89.9(5)
			C21−Ir−cent1	85.6	86.4

of both **2a** and **2b**. An ORTEP diagram for the nearly identical structure of allyl complex **2a** is included in Supporting Information. These complexes can be considered to be severely distorted octahedra with the allyl ligand, an olefinic portion of the COD ligand, and the phosphorus of the metallacycle occupying one plane, and the other olefinic unit of the COD and a methylene of the metallacycle lying apical to this plane. The four angles involving the olefin centroid, two

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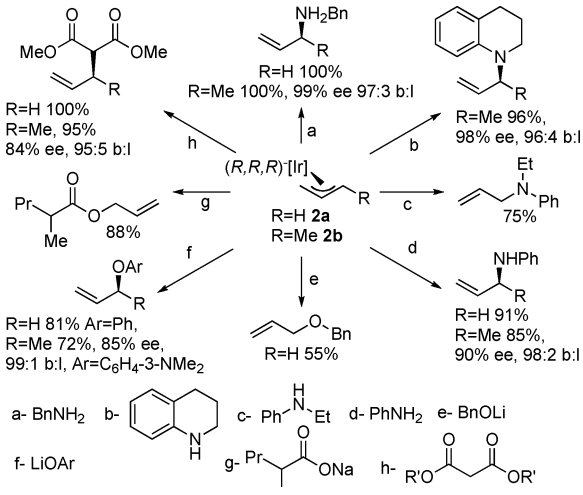
allyl termini and phosphorus atom of parent complex **2a** total 361.9°, indicating the relative planarity of these groups with the metal. The angles between the termini of the allyl group and the metallacycle methylene carbon are 90.9° (C21−Ir−C47) and 102.9° (C21−Ir−C45), indicating the apical positioning of this methylene group, and the angles between one of the olefin centroids and the terminal carbons of the allyl unit are 90.0° (cent2−Ir−C45) and 95.7° (cent2−Ir−C47), indicating the apical positioning of this olefin unit in the opposite direction. The metal−carbon distances to the two allyl termini are 2.204(3) Å and 2.274(3) Å. This 0.07 Å difference in distance reflects the trans influence of the phosphoramidite and olefin ligands on the metal−carbon bond lengths. The effect of a trans ligand on bond distances was stated to be small in the classic review on trans influence,[13] and our data are consistent with this assertion.

The structure of crotyl complex **2b** is similar to that of **2a**. The major differences between the two structures involve the substituted terminal carbon (C47) of the allyl unit. The iridium−C47 bond length in **2b** is 0.1 Å longer than the corresponding bond in **2a**. The two angles involving the allyl termini, the iridium and the two apical ligands indicate that the allyl group in **2b** is rotated by 1.5−2°, relative to the allyl group in **2a**. These structural differences presumably result from greater steric interactions of the COD ligand with C47 in methylallyl **2b** than with C47 of allyl complex **2a**, greater electron donation by the methyl substituent, or both. Other bond lengths and angles in **2a** and **2b** agree within 0.04 Å and 1° respectively.

The competence of allyl complexes **2a** and **2b** in catalytic asymmetric allylic substitutions was assessed by studying their reactions with carbon and heteroatom nucleophiles. After reaction of **2a** and **2b** with the nucleophiles, PPh_3 was added to displace the 1-alkene product and form the known [Ir(COD)-(P^C)(PPh_3)].[11] The yields, rates, and selectivities of these stoichiometric reactions were compared to those of the reactions of methallyl methyl carbonate catalyzed by [Ir(COD)-(P^C)(C_2H_4)]. The reactions of **2a** and **2b** with eight different nucleophiles are shown in Scheme 1. The reactions occurred rapidly

Scheme 1. Reactions of Allyl Complexes **2a**,**b** with Nucleophiles[a,b]



[a] Yields and selectivities determined for reactions at room temperature for 0.5 h in THF-d_8. [b] Reactions of amines were conducted with triethylamine or $Bu_4N[OC(O)CH_3]$ as base.

at room temperature. The regioselectivities, as well as the enantioselectivities, of the stoichiometric reactions of **2b** were within 5% and 10%, respectively, of the values for the analogous catalytic reactions (see Supporting Information). Thus, **2a** and **2b** are chemically and kinetically competent to be intermediates in the catalytic processes.

The reaction of parent allyl complex **2a** with a soluble carboxylate (Scheme 1) was also studied to test the reversibility of the oxidative addition of allylic esters to **1**. Consistent with the proposed endothermicity of the oxidative addition, sodium-2-methylvalerate reacted with **2a** to form Ir(I) and the allylic ester.

The reactivity of **2a** and **2b** contrasts with that of previous allyliridium complexes. In contrast to **2a** and **2b**, previous allyliridium complexes have undergone reactions with nucleophiles at the central carbon of the allyl unit.[14,15] The structural data provide insights into the regioselectivity of attack at the two allyl termini. Consistent with data on allylpalladium complexes,[16−18] attack on allyliridium **2b** occurs at the carbon atom containing the longer M−C bond. This carbon is located trans to the ligand with the stronger trans influence.[13] However, a comparison of the structures of **2a** and **2b** imply that the effect of the trans ligand on the bond distances is smaller than the effect of the methyl substituent on this parameter.

Finally, the structure of **2b** helps explain the origin of enantioselectivity. The relationship between the stereochemistry of the allyl ligand and of the products from reaction with aniline and sodium dimethylmalonate nucleophiles is consistent with attack anti to the metal center. The enantioselectivity by iridium catalyst **1** has been shown to originate from the stereochemistry of the β-carbon in the metallacycle,[19] but this stereocenter is located far from the expected trajectory of the nucleophile. The quadrant diagram in Table 1 implies that the relay of stereochemistry from this site to the metal center to the allyl ligand occurs by orientation of the aryl group of the phenethyl substituent by the aryl group on the β-carbon. The phenethyl aryl group then blocks, in combination with the binolate group, adoption of the stereoisomer in which the methyl group of the allyl ligand would be oriented in either of the two western quadrants. The difference in steric properties of the COD and metallacycle methine hydrogen causes the allyl methyl group to occupy the southeastern quadrant that contains the less sterically demanding methine hydrogen. The allyl methyl substituent extends into solution, and this structural feature allows the reaction to occur in a similar fashion with many allylic electrophiles. Studies on the relationship between the dynamics of these allyl complexes and enantioselectivity, and the preparation of further derivatives of **2a** and **2b**, are ongoing.

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Supporting Information Available: Experimental procedures for the synthesis and reactions of **2a** and **2b** and for the catalytic reactions of *trans*-methyl crotyl carbonate. This material is available free of charge via the Internet at http://pubs.acs.org.

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