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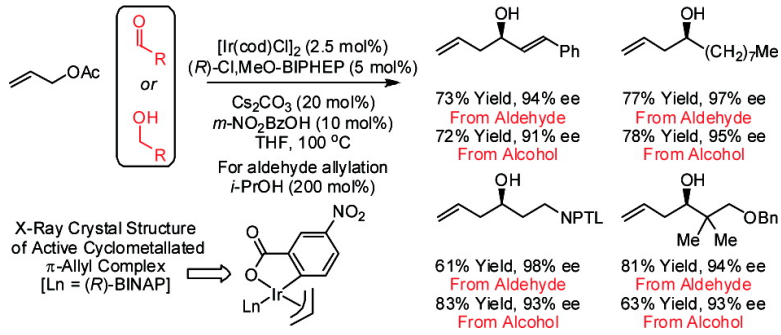

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Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition

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Abstract: Under the conditions of transfer hydrogenation employing an iridium catalyst generated in situ from $[Ir(cod)Cl]_2$, chiral phosphine ligand (*R*)-BINAP or (*R*)-Cl,MeO-BIPHEP, and *m*-nitrobenzoic acid, allyl acetate couples to allylic alcohols **1a**−**c**, aliphatic alcohols **1d**−**l**, and benzylic alcohols **1m**−**u** to furnish products of carbonyl allylation **3a**−**u** with exceptional levels of asymmetric induction. The very same set of optically enriched carbonyl allylation products **3a**−**u** are accessible from enals **2a**−**c**, aliphatic aldehydes **2d**−**l**, and aryl aldehydes **2m**−**u**, using iridium catalysts ligated by (−)-TMBTP or (*R*)-Cl,MeO-BIPHEP under identical conditions, but employing isopropanol as a hydrogen donor. A catalytically active cyclometallated complex **V**, which arises upon *ortho*-C−H insertion of iridium onto *m*-nitrobenzoic acid, was characterized by single-crystal X-ray diffraction. The results of isotopic labeling are consistent with intervention of symmetric iridium π-allyl intermediates or rapid interconversion of σ-allyl haptomers through the agency of a symmetric π-allyl. Competition experiments demonstrate rapid and reversible hydrogenation−dehydrogenation of the carbonyl partner in advance of C−C coupling. However, the coupling products, which are homoallylic alcohols, experience very little erosion of optical purity by way of redox equilibration under the coupling conditions, although isopropanol, a secondary alcohol, may serve as terminal reductant. A plausible catalytic mechanism accounting for these observations is proposed, along with a stereochemical model that accounts for the observed sense of absolute stereoinduction. This protocol for asymmetric carbonyl allylation transcends the barriers imposed by oxidation level and the use of preformed allyl metal reagents.

Introduction

Enantioselective carbonyl allylation ranks among the foremost methods used for the stereocontrolled synthesis of polyketide natural products.[1] Prevailing protocols typically rely on the use of preformed allyl metal reagents. The first carbonyl allylations employing isolable allyl boron reagents and isolable allyl silanes were described by Mikhailov and Bubnov (1964) and Hosomi and Sakurai (1976), respectively.[2] The first chirally modified allyl metal reagent, an allylborane derived from camphor, was reported by Hoffmann (1978).[3a,b] In the three decades that followed, increasingly effective protocols for asymmetric carbonyl allylation based on chirally modified allyl metal reagents emerged, including those developed by Kumada (1982),[3c] Brown (1983),[3d] Roush (1985),[3e] Reetz (1988),[3f] Masamune (1989),[3g] Corey (1989),[3h] Seebach (1987),[3i] Duthaler (1989),[3j] Panek (1991),[3k] Leighton (2002),[3l,m] and Soderquist (2005).[3n] Owing to these outstanding advances, highly enantioselective allylation is now possible for a diverse assortment of carbonyl compounds (Figure 1). However, as frequently documented,[4] the generation of stoichiometric byproducts detracts from the utility of most chirally modified allyl metal reagents. Further, the multistep syntheses required to prepare such reagents, combined with the added effort or inability to recover the chiral modifier, can pose additional barriers to their use.[5]

These issues are, in part, addressed by catalytic enantioselective protocols for carbonyl allylation, which circumvent the stoichiometric use of chiral modifiers. Following groundbreaking

(1) For reviews on enantioselective carbonyl allylation, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (c) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Hall, D. G. *Synlett* **2007**, 1644.

(2) (a) Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1874. (b) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295. (c) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1.

(3) Selected examples of chirally modified allyl metal reagents: (a) Herold, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 768. (b) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375. (c) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963. (d) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (e) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (f) Reetz, M. *Pure Appl. Chem.* **1988**, *60*, 1607. (g) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (h) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (i) Seebach, D.; Beck, A. K.; Imwinkelzied, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (j) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494. (k) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594. (l) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (m) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375. (n) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.

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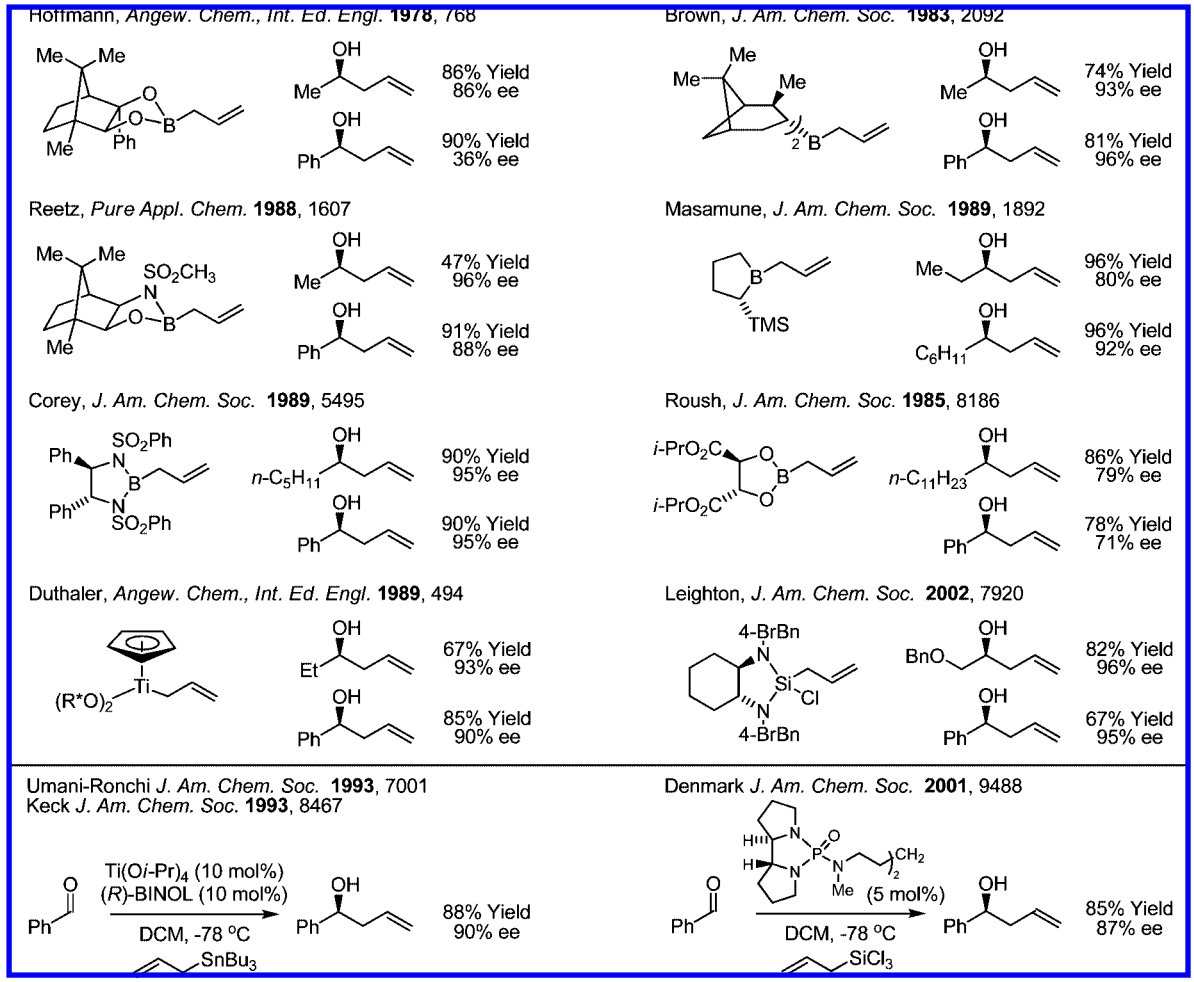

Figure 1. Top: Representative examples of chirally modified allyl metal reagents for use in enantioselective carbonyl allylation. Bottom: Prototypical catalytic enantioselective carbonyl allylations.

work by Yamamoto (1991),[6] the first highly enantioselective catalytic carbonyl allylations were described by Umani-Ronchi (1993) and Keck (1993).[7a,b] Alternatively, chiral Lewis basic catalysts enable enantioselective carbonyl allylation, as demonstrated in elegant studies by Denmark (1994).[7c,d] These methods are very effective but still rely upon the use of preformed allyl metal reagents. The allyl stannanes employed in the Umani-Ronchi−Keck allylation generate stoichiometric quantities of tin byproducts, and the trichlorosilanes employed in the Denmark allylation are highly moisture sensitive and upon hydrolysis generate stoichiometric quantities of hydrochloric acid (Figure 1).

An alternate approach to catalytic carbonyl allylation involves the reduction of metallo-π-allyls derived from allylic alcohols and allylic carboxylates.[8−13] To date, palladium,[9] rhodium,[10] iridium,[11] and ruthenium[12] complexes have been reported to catalyze such carbonyl allylations. A related method for carbonyl allylation is represented by catalytic variants of the Nozaki−Hiyama−Kishi (NHK) reaction of allylic halides.[13,14] With one exception,[12] these processes require stoichiometric quantities of metallic reductants, such as SmI_2, $SnCl_2$, Et_2Zn, or Et_3B, for

(4) In Brown's allylation protocol (ref 3d), the stoichiometric generation of isopinocampheol frequently complicates isolation of the allylation product: (a) Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152. (b) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495. (c) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2004**, *69*, 6294. (d) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963. (e) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 1069. (f) Gao, D.; O'Doherty, G. A. *J. Org. Chem.* **2005**, *70*, 9932. (g) Liu, D.; Xue, J.; Xie, Z.; Wei, L.; Zhang, X.; Li, Y. *Synlett* **2008**, 1526.

(5) A notable exception involves the chirally modified allyl silanes developed by Leighton (ref 3l), for which highly efficient recovery of the chiral auxiliary is possible.

(6) To our knowledge, the first examples of enantioselective Lewis acid-catalyzed carbonyl allylation were reported by Yamamoto in 1991. While additions of substituted allylic silanes gave highly optically enriched product, only a single example of the parent allylation employing allyltrimethylsilane was given, which proceeds in 55% enantiomeric excess: Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.

(7) For catalytic asymmetric carbonyl allylation employing allyl metal reagents: (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (c) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (d) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9489.

(8) For selected reviews covering carbonyl allylation *via* umpolung of π-allyls, see: (a) Masuyama, Y. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, p 255. (b) Tamaru, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 2, p 1917. (c) Tamaru, Y. In *Perspectives in Organopalladium Chemistry for the XXI Century*; Tsuji, J., Ed.; Elsevier: Amsterdam, 1999; p 215. (d) Kondo, T.; Mitsudo, T.-a. *Curr. Org. Chem.* **2002**, *6*, 1163. (e) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, *13*, 2647. (f) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, 3599.

catalytic turnover. Carbonyl-ene processes represent another approach to carbonyl allylation and are attractive in view of their byproduct-free nature.[15] Whereas conventional Lewis acid-catalyzed variants require activated carbonyl electrophiles, recently developed nickel-catalyzed transformations exhibit complementary substrate scope.[16] Finally, metal-catalyzed allyl transfer from homoallyl alcohols represents a promising strategy for carbonyl allylation.[17]

On the basis of the concepts of hydrogenative and transfer hydrogenative C−C coupling,[18−21] we have developed a new family of catalytic carbonyl allylation methodologies wherein allenes,[22] dienes,[23] and allyl acetate[24] serve as precursors to transient allyl metal nucleophiles. These protocols enable carbonyl allylation in the absence of preformed organometallic reagents or metallic reductants. Most remarkably, transfer hydrogenative C−C coupling promotes carbonyl allylation from the aldehyde or alcohol oxidation level. In the latter case, the alcohol reactant serves as both reducing agent and aldehyde precursor. To our knowledge, these processes are among the very first examples of direct metal-catalyzed C−C couplings of alcohol and unsaturates.[25,26]

In this account, the scope of the enantioselective transfer hydrogenative carbonyl allylation employing allyl acetate is evaluated,[24] and mechanistic investigations that illuminate key features of the catalytic cycle are presented. Under the conditions of iridium-catalyzed transfer hydrogenation, allyl acetate couples to allylic alcohols **1a**−**c**, aliphatic alcohols **1d**−**l**, and benzylic alcohols **1m**−**u** to provide homoallylic alcohols **3a**−**u**, respectively, in highly optically enriched form. Under nearly identical conditions, employing isopropanol as the terminal reductant, allyl acetate couples to enals **2a**−**c**, aliphatic aldehydes **2d**−**l**, and aryl aldehydes **2m**−**u** to provide an identical set of enantiomerically enriched homoallylic alcohols **3a**−**u**, respectively. Thus, through transfer hydrogenative C−C coupling, carbonyl allylation may be achieved from the alcohol or aldehyde oxidation level. This methodology circumvents the redox manipulations often required to convert alcohols to aldehydes and bypasses the barriers imposed by the use of stoichiometrically preformed allyl metal reagents.

Results and Discussion

The initially disclosed catalytic system for transfer hydrogenative carbonyl allylation[24] employed an iridium catalyst generated in situ from $[Ir(cod)Cl]_2$ and a chelating triarylphosphine ligand. As illustrated in the coupling of allyl acetate to *p*-nitrobenzyl alcohol **1m**, it was found that optimal conversions are obtained using Cs_2CO_3 (20 mol %) and *m*-nitrobenzoic acid (10 mol %) as additives (Table 1, entry 1). Other carbonate

(9) For catalytic carbonyl allylation via reductive coupling of π-allyls based on palladium, see: (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195. (b) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577. (c) Kimura, M.; Ogawa, Y.; Shimizu, M.; Sueishi, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 6903. (d) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627. (e) Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392. (f) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 846. (g) Kimura, M.; Shimizu, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2005**, *61*, 3709. (h) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278. (i) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863.

(10) For catalytic carbonyl allylation via reductive coupling of π-allyls based on rhodium, see: Masuyama, Y.; Kaneko, Y.; Kurusu, Y. *Tetrahedron Lett.* **2004**, *45*, 8969.

(11) For catalytic carbonyl allylation *via* reductive coupling of π-allyls based on iridium, see: (a) Masuyama, Y.; Chiyo, T.; Kurusu, Y. *Synlett* **2005**, 2251. (b) Banerjee, M.; Roy, S. *J. Mol. Catal. A* **2006**, *246*, 231. (c) Masuyama, Y.; Marukawa, M. *Tetrahedron Lett.* **2007**, *48*, 5963.

(12) For catalytic carbonyl allylation *via* reductive coupling of π-allyls based on ruthenium, see: (a) Tsuji, Y.; Mukai, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1989**, *369*, C51. (b) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.-a.; Watanabe, Y *Organometallics* **1995**, *14*, 1945.

(13) For selected examples of carbonyl allylation *via* catalytic Nozaki-Hiyama-Kishi coupling of allylic halides, see: (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Polyhedron* **2000**, *19*, 537. (c) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551. (d) Hargaden, G. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, 4235. (e) Hargaden, G. C.; O'Sullivan, T. P.; Guiry, P. J. *Org. Biomol. Chem.* **2008**, *6*, 562.

(14) For a recent review of catalytic Nozaki−Hiyama−Kishi coupling, see: Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.

(15) For reviews on carbonyl-ene reactions, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed.* **1995**, *34*, 1717. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

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(17) Sumida, Y.; Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2008**, *3*, 119, and references cited therein.

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(19) For hydrogenative C═X vinylation, see: (a) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (b) Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16040. (c) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448. (d) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873. (e) Hong, Y.-T.; Cho, C.-W.; Skucas, E.; Krische, M. J. *Org. Lett.* **2007**, *9*, 3745. (f) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280. (g) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (h) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. (i) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644.

(20) For hydrogenative aldol and Mannich addition, see: (a) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519. (b) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (c) Garner, S. A.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 5843. (d) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

(21) For hydrogenative acyl substitution via reductive hydroacylation, see: Hong, Y.-T.; Barchuk, A.; Krische, M. J. *Angew. Chem., Int. Ed.* **2006**, *128*, 6885.

(22) For hydrogenative and transfer hydrogenative carbonyl allylations employing allenes as allyl donors, see: (a) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678. (b) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (c) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705.

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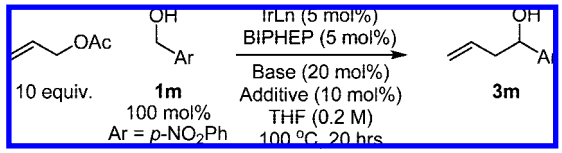
(24) For transfer hydrogenative carbonyl allylations employing allyl acetate as allyl donor, see: Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340.

(25) Formal substitution of alcohols by *C*-nucleophiles may be achieved under the conditions of hydrogen auto-transfer by way of oxidation−condensation−reduction. The alcohol−unsaturate couplings developed in our laboratory provide products of carbonyl addition, representing a formal C−H functionalization of the carbinol carbon. For recent reviews of hydrogen auto-transfer processes, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.

(26) For catalytic functionalization of carbinol C−H bonds, see: (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W. J. *J. Am. Chem. Soc.* **2005**, *127*, 10836. (b) Jiang, Y.-J.; Tu, Y.-Q.; Zhang, E.; Zhang, S.-Y.; Cao, K.; Shi, L. *Adv. Synth. Catal.* **2008**, *350*, 552.

Table 1. Selected Optimization Experiments Illustrating the Effect of Basic and Acidic Additives and Iridium Source in the Transfer Hydrogenative Allylation of *p*-Nitrobenzyl Alcohol **1m**[a]



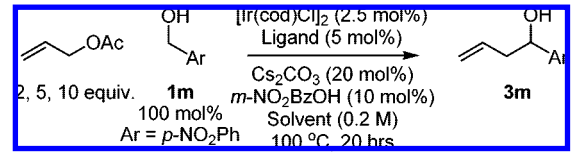
	Entry	Base	Additive	Iridium Source	Yield (%)
Additive-Base	**1**	**Cs_2CO_3**	***m*-NO_2BzOH**	**[Ir(cod)Cl]$_2$**	**80**
	2	K_2CO_3	*m*-NO_2BzOH	[Ir(cod)Cl]$_2$	21
	3	Na_2CO_3	*m*-NO_2BzOH	[Ir(cod)Cl]$_2$	15
	4	Li_2CO_3	*m*-NO_2BzOH	[Ir(cod)Cl]$_2$	12
	5	---	*m*-NO_2BzOH	[Ir(cod)Cl]$_2$	≤ 5
	6	Cs_2CO_3	---	[Ir(cod)Cl]$_2$	47
	7	---	---	[Ir(cod)Cl]$_2$	10
	8	---	*m*-NO_2BzOCs	[Ir(cod)Cl]$_2$	72
	9	Cs_2CO_3	*m*-NO_2BzOCs	[Ir(cod)Cl]$_2$	79
	10	Cs_2CO_3	*o*-NO_2BzOH	[Ir(cod)Cl]$_2$	39
	11	Cs_2CO_3	*p*-NO_2BzOH	[Ir(cod)Cl]$_2$	49
	12	Cs_2CO_3	BzOH	[Ir(cod)Cl]$_2$	39
	13	Cs_2CO_3	*p*-MeOBzOH	[Ir(cod)Cl]$_2$	42
	14	Cs_2CO_3	*m*-FBzOH	[Ir(cod)Cl]$_2$	41
	15	Cs_2CO_3	*m*-NO_2BzOMe	[Ir(cod)Cl]$_2$	47
IrLn	16	Cs_2CO_3	---	[Ir(cod)(BIPHEP)]BARF	41
	17	Cs_2CO_3	*m*-NO_2BzOH	[Ir(cod)(BIPHEP)]BARF	72

[a] All reactions were performed in 13 × 100 mm pressure tubes. The yields cited are of material isolated by silica gel chromatography. Variation in concentration or temperature resulted in diminished isolated yields of **3m**. In all cases, 0.1−5% of the corresponding *O*-allylation product is observed. See Supporting Information for further details.

bases (K_2CO_3, Na_2CO_3, Li_2CO_3) used in combination with *m*-nitrobenzoic acid are far less effective (Table 1, entries 2−4). Use of *m*-nitrobenzoic acid in the absence of any basic additive gives only trace quantities of allylation product **3m** (Table 1, entry 5), yet use of Cs_2CO_3 in the absence of an acidic additive provides allylation product **3m** in 47% yield (Table 1, entry 6). In the absence of any additive, allylation product **3m** is generated in 10% yield (Table 1, entry 7). Logically, it was thought that Cs_2CO_3 and *m*-nitrobenzoic acid react under the coupling conditions to form cesium *m*-nitrobenzoate. Indeed, upon use of cesium *m*-nitrobenzoate as an additive, the allylation product **3m** forms in 72% yield (Table 1, entry 8). Using Cs_2CO_3 (20 mol %) and *m*-NO_2BzOCs (10 mol %), a 79% yield of allylation product **3m** is obtained (Table 1, entry 9). Thus, it indeed would appear that Cs_2CO_3 and *m*-nitrobenzoic acid serve as a source of cesium *m*-nitrobenzoate. However, just as the choice of alkali ion is critical, so is the choice of carboxylate. Among carboxylic acids, *m*-nitrobenzoic acid is unique in its ability to promote high levels of conversion (Table 1, entries 1 and 10−14). Interestingly, *m*-nitrobenzoic acid also is required for high levels of enantioselection (vide infra, Table 4). To assess whether π-complexation effects[27] account for the unique behavior of *m*-nitrobenzoic acid, methyl *m*-nitrobenzoate was used as an additive along with Cs_2CO_3 (Table 1, entry 15). The observed decrease in yield suggests such effects are not operative. Finally, cationic iridium complexes display reactivity roughly equivalent to that of the corresponding neutral complexes in both the presence and the absence of *m*-nitrobenzoic acid (Table 1, entries 1, 6, 16, and 17).

(27) For a review of the effects of olefinic additives on metal-catalyzed C−C coupling processes, see: Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

Table 2. Selected Optimization Experiments Illustrating the Effect of Allyl Acetate Loading, Solvent, and Ligand in the Transfer Hydrogenative Allylation of *p*-Nitrobenzyl Alcohol **1m**[a]



Entry	Solvent	Ligand	Allyl Acetate (mol%)	Yield (%)
1	**THF**	**BIPHEP**	**1000**	**80**
2	THF	BIPHEP	500	68
3	THF	BIPHEP	200	67
4	Dioxane	BIPHEP	200	68
5	Toluene	BIPHEP	200	13
6	DCE	BIPHEP	200	15
7	THF	PPh_3	1000	8

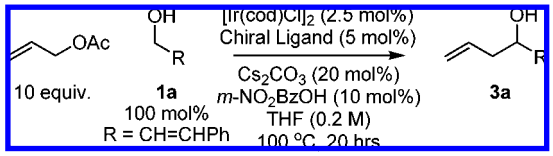
[a] All reactions were performed in 13 × 100 mm pressure tubes. The yields cited are of material isolated by silica gel chromatography. THF = tetrahydrofuran; DCE = 1,2-dichloroethane. See Supporting Information for further details.

The effects of allyl acetate loading, solvent, and ligand were evaluated under the optimum conditions cited in Table 1. Reactions conducted using 2 or 5 equiv of allyl acetate were not as efficient as those employing 10 equiv (Table 2, entries 1−3). Reactions conducted in dioxane proceed as efficiently as those conducted in THF (Table 2, entries 3 and 4). However, reactions conducted in toluene or DCE are highly inefficient (Table 2, entries 5 and 6). Finally, the bidentate phosphine ligand BIPHEP was far superior to the monodentate phosphine ligand PPh_3 under otherwise identical conditions (Table 2, entries 1 and 7).

The feasibility of highly enantioselective carbonyl allylation under transfer hydrogenation conditions was rendered uncertain due to the likelihood of product racemization by way of redox equilibration. This concern was especially germane to transfer hydrogenative carbonyl allylations from the aldehyde oxidation level, where both product and terminal reductant (isopropanol) are secondary alcohols. Gratifyingly, it was found that high levels of asymmetric induction are obtained in carbonyl allylations from the alcohol or aldehyde oxidation level. As revealed in an assay of chiral bidentate phosphine ligands in the allylation of cinnamyl alcohol **1a**, chelating triarylphosphines are required (Table 3). Among the chiral bidentate phosphine ligands screened, reactions conducted using (*R*)-Cl,MeO-BIPHEP as ligand proceed with optimal levels of conversion and asymmetric induction (Table 3, entry 1). Trace conversion to product is observed using chiral bidentate phosphine ligands possessing any degree of alkyl substitution at phosphorus. Notably, erosion of optical purity as a function of reaction time is not observed.

The highly specialized effect of *m*-nitrobenzoic acid on catalytic efficiency demanded a deeper understanding of how the structural and interactional features of this carboxylic acid are manifested. In the enantioselective coupling of allyl acetate to cinnamyl alcohol **1a** in the presence and in the absence of *m*-NO_2BzOH using (*R*)-Cl,MeO-BIPHEP as ligand, one obtains (*R*)-**3a** and (*S*)-**3a**, respectively (Table 4, entries 1 and 2). This inversion in enantioselectivity suggests that *m*-nitrobenzoic acid and the iridium center are intimately associated during the enantiodetermining carbonyl addition event. On the basis of these data, it was postulated that iridium and *m*-nitrobenzoic acid react to form an *ortho*-cyclometalated complex, which serves as the active catalyst.[28]

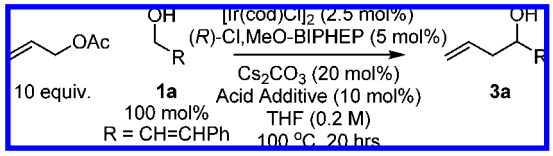
Table 3. Selected Results from an Assay of Chiral Ligand in the Transfer Hydrogenative Allylation of Cinnamyl Alcohol **1a** and Effect of Temperature on Enantiomeric Excess[a]



	Entry	T °C	Chiral Ligand	Yield (%)	ee (%)
⇨	**1**	**100**	**(*R*)-Cl,MeO-BIPHEP**	**71**	**91 (*R*)**
T °C	2	80	(*R*)-Cl,MeO-BIPHEP	61	93 (*R*)
	3	120	(*R*)-Cl,MeO-BIPHEP	59	90 (*R*)
Chiral Ligand	4	100	(*R*)-MeO-BIPHEP	69	80 (*R*)
	5	100	(*R*)-BINAP	64	90 (*R*)
	6	100	(*R*)-tol-BINAP	51	88 (*R*)
	7	100	(-)-TMBTP	59	82 (*R*)
	8	100	(*S*)-C1-TUNEPHOS	80	70 (*S*)
	9	100	(*R*)-C2-TUNEPHOS	77	77 (*R*)
	10	100	(*S*)-C3-TUNEPHOS	72	78 (*S*)
	11	100	(*S*)-C4-TUNEPHOS	57	80 (*S*)
	12	100	(*R*)-H8-BINAP	68	85 (*R*)
	13	100	(*S*)-BIPHEMP	68	80 (*R*)
	14	100	CTH-(*S*)-P-PHOS	71	86 (*S*)
	15	100	(*R*)-SOLPHOS	41	40 (*R*)
	16	100	(*S*)-SEGPHOS	69	78 (*S*)
	17	100	(*R*)-SYNPHOS	69	83 (*R*)

[a] All reactions were performed in 13 × 100 mm pressure tubes. The yields cited are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

Table 4. Selected Optimization Experiments Illustrating the Effects of Substitution of *m*-Nitrobenzoic Acid on Conversion and Enantiomeric Excess in the Transfer Hydrogenative Allylation of Cinnamyl Alcohol **1a**[a]



	Entry	Carboxylic Acid	Yield (%)	ee (%)
⇨	**1**	**$R_1 = R_2 = R_3 = H$**	**71**	**91 (*R*)**
	2	No Acid Additive	8	47 (*S*)
	3	R_1 = Me, $R_2 = R_3 = H$	18	65 (*S*)
	4	R_2 = Me, $R_1 = R_3 = H$	50	67 (*R*)
	5	R_3 = Me, $R_1 = R_2 = H$	69	91 (*R*)

[a] All reactions were performed in 13 × 100 mm pressure tubes. The yields cited are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. See Supporting Information for further details.

To challenge this hypothesis, an attempt was made to isolate a catalytically relevant complex. A THF solution of $[Ir(cod)Cl]_2$ (100 mol %), (*R*)-BINAP (200 mol %), and *m*-NO_2BzOH (400 mol %) was heated to 80 °C for 3 h in the presence of Cs_2CO_3 (400 mol %). After cooling and removal of residual solid *m*-NO_2BzOCs, allyl acetate (200 mol %) was added, and the solution was heated to 80 °C for 1 h. After cooling, hexane was added to the solution, which resulted in the formation of a yellow precipitate. The precipitate was crystallized from THF−ether. Single-crystal X-ray diffraction analysis revealed the *ortho*-cyclometalated iridium(III)−π-allyl complex **V** (Figure 2). The stability of complex **V** cast doubt on its role as a catalytically relevant species. However, complex **V** serves as an active catalyst in the transfer hydrogenative carbonyl

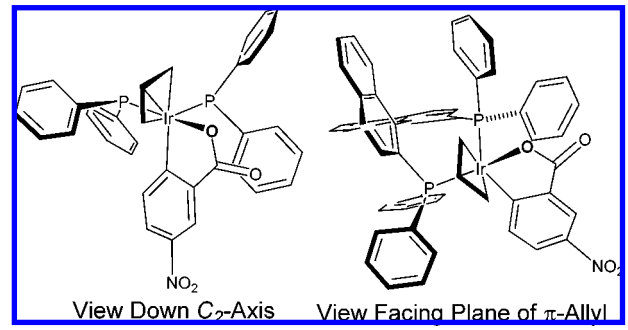
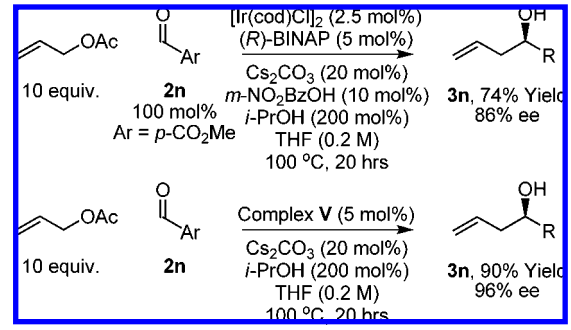


Figure 2. Structure assigned to a catalytically active *ortho*-cyclometalated iridium(III)−π-allyl complex (**V**), as determined by single-crystal X-ray diffraction analysis. The graphics are depictions of crystallographic data imported into ChemBioDraw Ultra 11.0. For clarity, the binaphthyl moiety of the structure on the left was omitted.

allylation of aldehyde **2n** under standard conditions, suggesting that complex **V** is indeed catalytically relevant. In fact, in the transfer hydrogenative carbonyl allylation of aldehyde **2n**, complex **V** provides superior conversion and optical enrichment in comparison to the analogous reaction involving generation of the catalyst in situ (Scheme 1).

Scheme 1. Experiments Corroborating Intervention of *Ortho*-Cyclometalated Iridium(III)−π-Allyl Complex **V** as a Catalytically Relevant Entity[a]



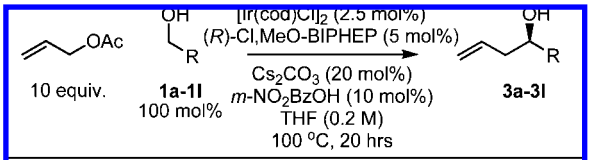
[a] All reactions were performed in 13 × 100 mm pressure tubes. The yields cited are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. See Supporting Information for further details.

Intervention of complex **V** as a catalytically relevant species also is implicated by the results of an assay of methyl-substituted *m*-nitrobenzoic acids in the enantioselective coupling of allyl acetate to cinnamyl alcohol **1a** (Table 4, entries 3−5). Whereas enantioselective coupling of allyl acetate to cinnamyl alcohol **1a** in the presence of *m*-NO_2BzOH using (*R*)-Cl,MeO-BIPHEP as ligand provides (*R*)-**3a**, the enantiomeric adduct (*S*)-**3a** is obtained in reactions conducted in the presence of 2-methyl-5-nitrobenzoic acid, where a methyl group blocks the preferred site of cyclometalation (Table 4, entries 1 and 3). Conversely, using 2-methyl-3-nitrobenzoic acid or 4-methyl-3-nitrobenzoic acid, where the preferred site of cyclometalation remains free, (*R*)-**3a** is again obtained (Table 4, entries 4 and 5).

Optimal conditions established for the enantioselective transfer hydrogenative allylation of cinnamyl alcohol **1a** were applied to allylic alcohols **1a**−**c** and aliphatic alcohols **1d**−**l** (Table 5).

(28) The *ortho*-cyclometalation of C_5Me_5−iridium complexes onto *m*-nitrobenzoate occurs at the *para*-position with respect to the nitro moiety: Kisenyi, J. M.; Sunley, G. J.; Cabeza, J. A.; Smith, A. J.; Adams, H.; Salt, N. J.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1987**, 2459.

Table 5. Ir-Catalyzed Transfer Hydrogenative Allylation of Allylic Alcohols **1a**−**c** and Aliphatic Alcohols **1d**−**l**[a]

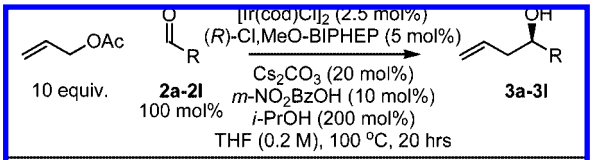


1a, cinnamyl alcohol
1b, geraniol
1c, (*E*)-non-2-en-1-ol
1d, 4-phenylbutan-1-ol
1e, nonan-1-ol
1f, isobutanol
1g, 3-(benzyloxy)-2,2-dimethylpropan-1-ol
1h, *N*-Phtl-2-aminoethan-1-ol
1i, *N*-Phtl-3-aminopropan-1-ol
1j, 2-(benzyloxy)ethan-1-ol
1k, 3-(benzyloxy)propan-1-ol
1l, 4-(benzyloxy)butan-1-ol

Entry	Alcohol	Product	Yield (%)	ee (%)
1	**1a**	**3a**	72	91
2	**1b**	**3b**	76	86
3	**1c**	**3c**	72	91
4	**1d**	**3d**	81	95
5	**1e**	**3e**	78	95
6	**1f**	**3f**	83	94[c,d]
7	**1g**	**3g**	63	93[b,c]
8	**1h**	**3h**, n = 1	51	88[c]
	1i	**3i**, n = 2	83	93[c]
9	**1j**	**3j**, n = 1	68	88[c]
	1k	**3k**, n = 2	63	94[c]
	1l	**3l**, n = 3	78	95

[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. [b] 40 h. [c] 120 °C. [d] Due to volatility, the crude product was converted to the *m*-nitrobenzoate. See Supporting Information for further details.

Table 6. Ir-Catalyzed Transfer Hydrogenative Allylation of Enals **2a**−**c** and Aliphatic Aldehydes **2d**−**l**[a]

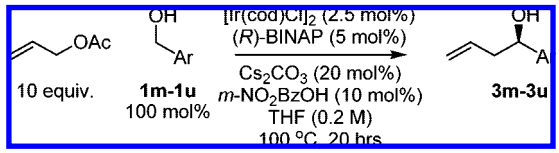


2a, cinnamaldehyde
2b, geranial
2c, (*E*)-hex-2-enal
2d, 4-phenylbutanal
2e, nonanal
2f, isobutanal
2g, 3-(benzyloxy)-2,2-dimethylpropanal
2h, *N*-Phtl-2-aminoethanal
2i, *N*-Phtl-3-aminopropanal
2j, 2-(benzyloxy)ethanal
2k, 3-(benzyloxy)propanal
2l, 4-(benzyloxy)butanal

Entry	Aldehyde	Product	Yield (%)	ee (%)
1	**2a**	**3a**	73	94
2	**2b**	**3b**	77	96
3	**2c**	**3c**	71	93
4	**2d**	**3d**	83	96
5	**2e**	**3e**	77	97
6	**2f**	**3f**	74	95[c,d]
7	**2g**	**3g**	81	94[b,c]
8	**2h**	**3h**, n = 1	51	97[c]
	2i	**3i**, n = 2	61	98[c]
9	**2j**	**3j**, n = 1	41	92[c]
	2k	**3k**, n = 2	45	96[c]
	2l	**3l**, n = 3	88	97

[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. [b] 40 h. [c] 120 °C. [d] Due to volatility, the crude product was converted to the *m*-nitrobenzoate. See Supporting Information for further details.

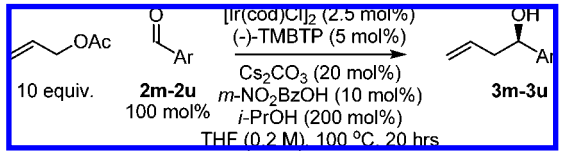
Table 7. Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohols **1m**−**u**[a]



Entry	Aryl Moiety	Alcohol	Product	Yield (%)	ee (%)
1	*p*-NO_2Ph	**1m**	**3m**	72	91
2	*p*-(CO_2Me)Ph	**1n**	**3n**	77	93
3	piperonyl	**1o**	**3o**	76	91
4	Ph	**1p**	**3p**	62	93
5	*p*-BrPh	**1q**	**3q**	74	93
6	*o*-MeOPh	**1r**	**3r**	80	92
7	*p*-MeOPh	**1s**	**3s**	73	93
8	3,5-CI_2Ph	**1t**	**3t**	61	92
9	2-(*N*-Me-indolyl)	**1u**	**3u**	55	90

[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. See Supporting Information for further details.

Table 8. Ir-Catalyzed Transfer Hydrogenative Allylation of Aryl Aldehydes **2m**−**u**[a]



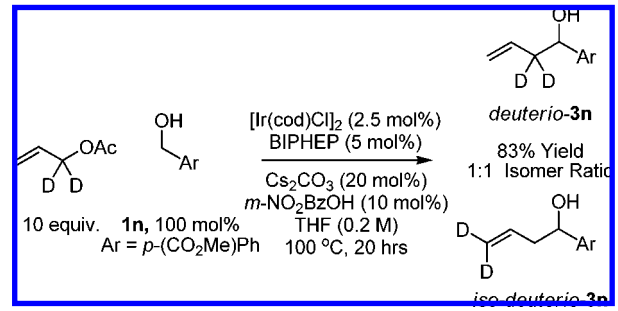
Entry	Aryl Moiety	Aldehyde	Product	Yield (%)	ee (%)
1	*p*-NO_2Ph	**2m**	**3m**	78	97
2	*p*-(CO_2Me)Ph	**2n**	**3n**	85	97
3	piperonyl	**2o**	**3o**	83	94
4	Ph	**2p**	**3p**	76	96
5	*p*-BrPh	**2q**	**3q**	77	97
6	*o*-MeOPh	**2r**	**3r**	86	95
7	*p*-MeOPh	**2s**	**3s**	75	94
8	3,5-CI_2Ph	**2t**	**3t**	76	98
9	2-(*N*-Me-indolyl)	**2u**	**3u**	82	94

[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary-phase HPLC analysis. See Supporting Information for further details.

The desired homoallylic alcohols **3a**−**l** were generated in good yield and with optical enrichments ranging from 86 to 95% enantiomeric excess. Remarkably, as demonstrated by the formation of homoallylic alcohols **3e**−**g**, aliphatic alcohols possessing secondary, tertiary and quaternary centers adjacent to the transient carbonyl moiety couple in a highly enantioselective fashion (Table 5, entries 5−7). Additionally, as demonstrated by the formation of homoallylic alcohols **3h**−**k**, aliphatic alcohols possessing both nitrogen and oxygen atoms at the carbon atoms α or β to the transient carbonyl moiety couple efficiently (Table 5, entries 8 and 9).

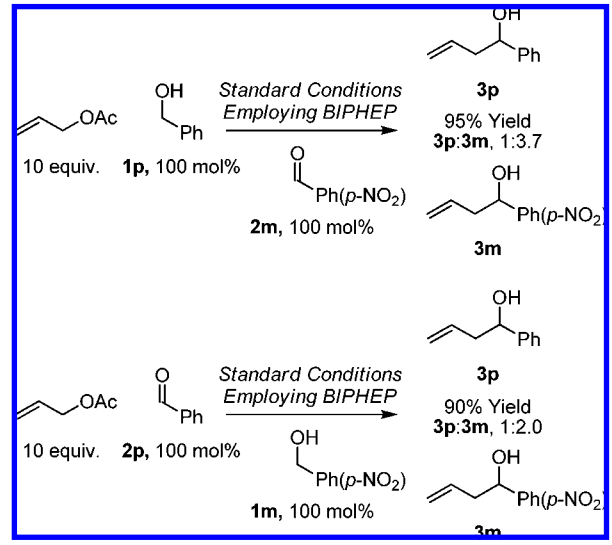
Under identical conditions, but employing isopropanol as a hydrogen donor, allyl acetate couples to enals **2a**−**c** and aliphatic aldehydes **2d**−**l** to furnish an identical set of homoallylic alcohols, **3a**−**l** (Table 6). In general, the aldehyde couplings provide slightly higher enantioselectivities. For example, formation of the homoallylic alcohol **3b** occurs in 76% isolated yield and 86% enantiomeric excess from the alcohol **1b** (Table 5, entry 2); this adduct is obtained in 77% isolated yield and 96% enantiomeric excess from the aldehyde **2b** (Table 6, entry 2). In the case of β-heteroatom-substituted aldehydes **2i** and **2k**, the homoallylic alcohols **3i** and **3k** are generated inefficiently, presumably due to elimination of the β-heteroatom group (Table 6, entries 8 and 9). Here, improved isolated yields of homoallylic alcohols **3i**,**k** are achieved by simply conducting the allylation from the alcohol oxidation level (Table 5, entries 8 and 9).

Scheme 2. Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohol **1n** Employing Isotopically Labeled Allyl Acetate[a]



[a] The reaction was performed in a 13 × 100 mm pressure tube. The cited yield is of material isolated by silica gel chromatography. See Supporting Information for further details.

Scheme 3. Experiments Establishing Rapid Redox Equilibration in Advance of Carbonyl Addition[a]



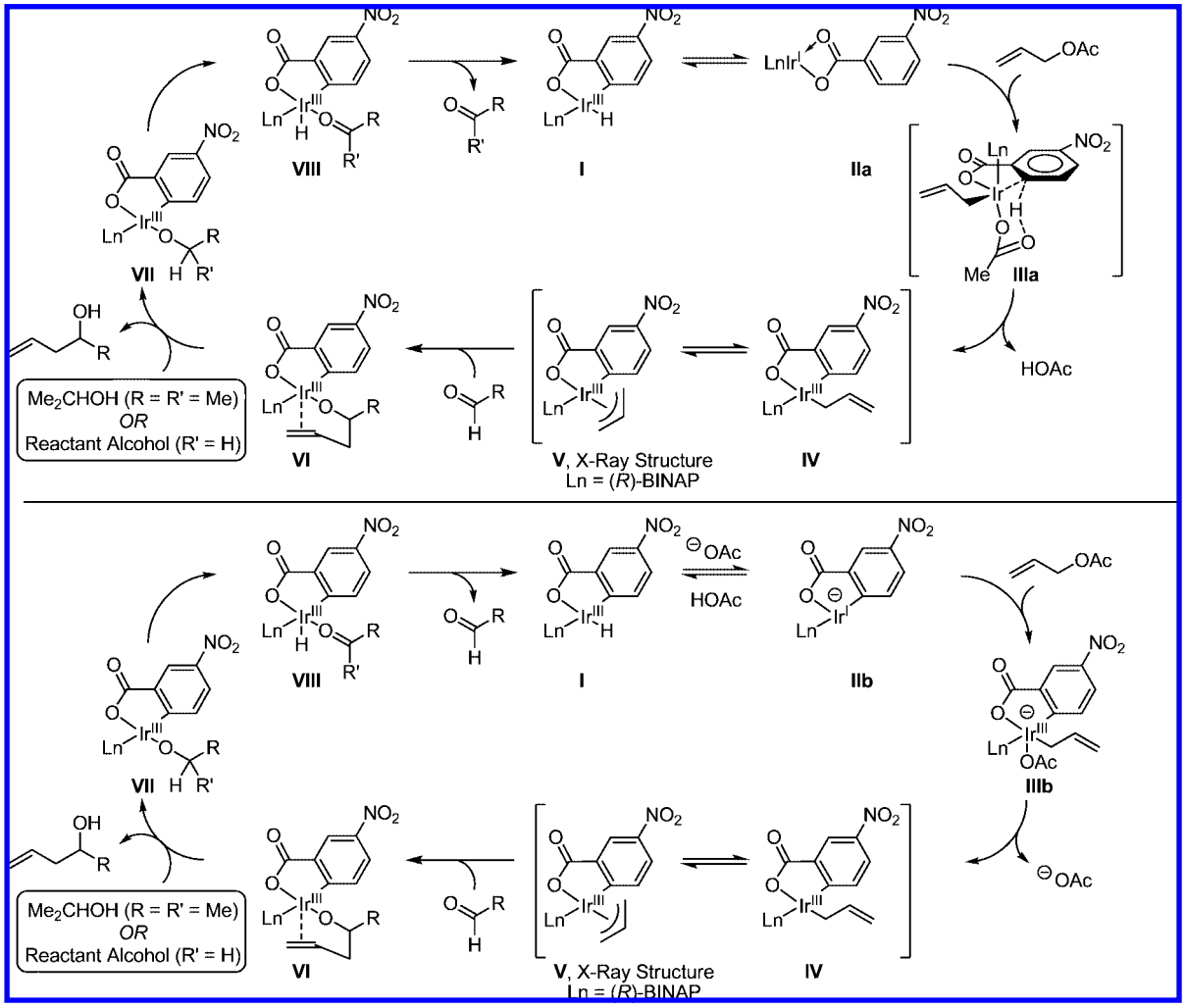
[a] All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Benzylic alcohols **1m**−**u** and aryl aldehydes **2m**−**u** also participate in transfer hydrogenative carbonyl allylation. As disclosed in our initial communication of this work,[24] benzylic alcohols **1m**−**u** are subject to allylation using an iridium catalyst generated in situ from [Ir(cod)Cl]$_2$, (*R*)-BINAP, and *m*-NO_2-BzOH in the presence of Cs_2CO_3 (Table 7). Using iridium catalysts ligated by (−)-TMBTP[29] under identical conditions, but employing isopropanol as a hydrogen donor, an identical set of homoallylic alcohols, **3m**−**u,** are prepared from the corresponding aryl aldehydes **2m**−**u** (Table 8).

Additional experiments aimed at illuminating features of the catalytic mechanism were undertaken. Transfer hydrogenative allylation of benzylic alcohol **1n** using isotopically labeled allyl

(29) (a) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

Scheme 4. Postulated Catalytic Mechanisms for the Iridium-Catalyzed Transfer Hydrogenative Coupling from the Alcohol or Aldehyde Oxidation Level (Ln = Chelating Triaryl Phosphine, e.g., (*R*)-BINAP or (*R*)-Cl,MeO-BIPHEP)



acetate[30] provides equimolar quantities of *deuterio*-**3n** and *iso-deuterio*-**3n** (Scheme 2). These results are consistent with intervention of symmetric iridium π-allyl intermediates or rapid interconversion of σ-allyl haptomers through the agency of a symmetric π-allyl. Competition experiments involving exposure of allyl acetate to equimolar quantities of **1p** and **2m** under standard conditions, employing BIPHEP as ligand, provide **3p** and **3m** in 95% yield in a 1:3.7 ratio, respectively. A very similar product distribution and yield are obtained in the analogous coupling employing equimolar amounts of **2p** and **1m**, establishing rapid redox equilibration in advance of C−C coupling (Scheme 3).

The following mechanism for iridium-catalyzed transfer hydrogenative allylation appears plausible, based upon the collective data. Association of the chelating phosphine ligand and *m*-NO_2BzOH to $[Ir(cod)Cl]_2$ delivers the iridium carboxylate **IIa**, which is in equilibrium with the *ortho*-cyclometalated complex **I**. Oxidative addition of allyl acetate to complex **IIa** should deliver an iridium carboxylate (not shown), which should be predisposed to acetate-assisted *ortho*-metalation through the six-centered transition structure **IIIa** to furnish the σ-allyl *C*,*O*-benzoate complex **IV**.[31,32] Rapid equilibration of the five-coordinate complex **IV** with the corresponding π-allyl haptomer **V** is consistent with the results of isotopic labeling (vide supra, Scheme 2). The π-allyl haptomer **V** has been characterized by single-crystal X-ray diffraction analysis (vide supra, Figure 2). Allyl transfer to the aldehyde through a closed chairlike transition structure delivers the homoallyl iridium alkoxide **VI**.[11] The configurational stability of the homoallylic alcohol is presumably due to occupation of the remaining coordination site at iridium(III) by the olefin moiety of the homoallylic

(30) Schuetz, R. D.; Millard, F. W. *J. Org. Chem.* **1959**, *24*, 297.

(31) For acetate-assisted cyclometalation of iridium complexes, see: (a) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (b) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Fawcett, J.; Little, C.; Macgregor, S. A. *Organometallics* **2006**, *25*, 5976.

(32) For selected examples of carboxylate assisted cyclometalation involving other transition metal complexes, see the following. Rhodium: (a) Ito, J.-I.; Nishiyama, H. *Eur. J. Inorg. Chem.* **2007**, 1114Palladium: (b) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (c) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. Carboxylate-assisted metalation of arenes exhibits acid−base character, requiring a certain level of electron deficiency at the carbon undergoing substitution. Our data suggest that cyclometalation of *m*-nitrobenzoic acid is especially facile due to the confluence of the following effects. The nitro moiety withdraws electron density through the π-system and the σ-framework, activating the positions *ortho* and *para* to the nitro moiety. The carboxy moiety assists *ortho*-metalation by reducing the entropy of activation and through enthalpic stabilization of the product through chelation.

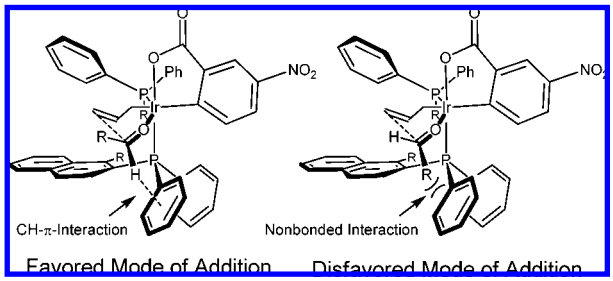


Figure 3. Proposed stereochemical model accounting for the observed sense of absolute stereoinduction, based on single-crystal X-ray diffraction data corresponding to complex **V**. The graphics are modifications based on single-crystal X-ray diffraction data corresponding to complex **V**, which were imported into ChemBioDraw Ultra 11.0. For clarity, the binaphthyl moiety has been truncated.

alcohol, which disables β-hydride elimination pathways. However, upon exchange of the homoallyl alcohol for isopropanol or a reactant alcohol, as in the conversion of **VI** to **VII**, a coordination site becomes available and β-hydride elimination ensues to deliver complex **VIII**. Dissociation of aldehyde regenerates the *ortho*-cyclometalated complex **I** (Scheme 4, top).

A related pathway that appears plausible involves proton loss from the *ortho*-cyclometalated complex **I** to deliver the anionic iridium(I) *C*,*O*-benzoate **IIb**. Such proton loss may be facilitated by stabilization of the nascent anion by the *ortho*-carboxy and the *para*-nitro moieties of the *C*,*O*-benzoate. Oxidative addition of allyl acetate provides the anionic iridium(III) σ-allyl complex **IIIb**, which upon loss of acetate delivers the neutral σ-allyl and π-allyl complexes **IV** and **V**, respectively. The remainder of the catalytic mechanism is identical to that previously described. A primary distinction between the two mechanisms resides in the fluxional versus fixed attachment of the *ortho*-*C*-benzoate linkage. In the latter mechanistic hypothesis, the *ortho*-*C*,*O*-benzoate remains intact throughout the duration of the catalytic cycle (Scheme 4, bottom).

A stereochemical model accounting for the observed sense of absolute stereoinduction is based upon the coordination mode revealed in the crystal structure of complex **V**. Complexation of aldehyde by the σ-allyl haptomer **IV** is postulated to occur at the indicated position adjacent to the *C*,*O*-benzoate. In this way, the sterically less demanding allyl moiety is placed between the naphthyl and phenyl moieties of the ligand, allowing the aldehyde to reside in a more open environment. In the favored mode of addition, the aldehyde is bound such that the aldehydic C−H bond projects into the π-face of a phenyl moiety of the ligand, giving rise to a weakly attractive aldehyde C−H π-interaction.[33] In the disfavored mode of addition, the aldehyde is bound such that the aldehydic "R group" projects into the π-face of a phenyl moiety of the ligand, giving rise to a severe nonbonded interaction (Figure 3).

Summary

A protocol for enantioselective carbonyl allylation from the alcohol or aldehyde oxidation level has been developed. An *ortho*-cyclometalated iridium complex has been established as the active catalyst. As demonstrated by the reductive coupling of allyl acetate to allylic alcohols **1a**−**c**, aliphatic alcohols **1d**−**l**, and benzylic alcohols **1m**−**u**, a broad range of alcohols are efficiently converted to highly optically enriched homoallyl alcohols **3a**−**u**. An identical set of adducts **3a**−**u** may be obtained from the aldehyde oxidation level simply by employing isopropanol as a terminal reductant. Thus, enals **2a**−**c**, aliphatic aldehydes **2d**−**l**, and aryl aldehydes **2m**−**u** are converted to adducts **3a**−**u**.

Key features of the catalytic mechanism have been elucidated. The cyclometalated complex **V**, which has been characterized by single-crystal X-ray diffraction, has been established as a catalytically relevant species. Isotopic labeling studies implicate intervention of a symmetric iridium π-allyl intermediates or rapid interconversion of σ-allyl haptomers through the agency of a symmetric π-allyl. Finally, competition experiments demonstrate rapid and reversible hydrogenation−dehydrogenation of the carbonyl partner in advance of C−C coupling. Despite facile redox equilibration of the starting alcohol and the fact that isopropanol, a secondary alcohol, may serve as terminal reductant, the resulting homoallylic alcohols **3a**−**u** experience almost no erosion of optical purity by way of redox equilibration under the coupling conditions. Plausible catalytic mechanisms that account for these observations and a stereochemical model explaining the observed sense of absolute stereoinduction are proposed.

Organic molecules, by definition, are composed of carbon and hydrogen. Hence, the ability to direct C−C coupling through the use of catalytic hydrogenation and transfer hydrogenation evokes numerous possibilities for the construction of diverse molecular architectures, circumventing use of preformed organometallic reagents. In the present case, allyl acetate serves as a surrogate to preformed allyl metal reagents in carbonyl addition. Rather than generating stoichiometric quantities of metallic byproducts—for example, molar equivalents of tin waste emanating from the use of allyl stannanes—one instead generates 1 equiv of acetic acid. Because one may conduct carbonyl addition from the alcohol oxidation level, one avoids redox manipulations often required to convert alcohols to aldehydes, thus enhancing step economy. Future studies will focus on the development of related hydrogenative and transfer hydrogenative couplings, including diastereo- and enantioselective crotylations, based on insights garnered herein.

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Supporting Information Available: Experimental details and spectroscopic data; ^{1}H NMR, ^{13}C NMR, IR, HRMS, and HPLC data for unknown compounds **3f**, **3h**, and **3i**; ^{1}H NMR, ^{13}C NMR, and HPLC data for known compounds **3a**−**e**, **3g**, and **3j**−**u**; and single-crystal X-ray diffraction data for complex **V**. This material is available free of charge via the Internet at http://pubs.acs.org.

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