Diene-Ligated Iridium Complexes as Catalysts for Allylation and Methallylation Reactions of Ketones

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Abstract: An iridium-catalyzed allylation reactions of ketones using dienes as ligands has been developed. A variety of ketones underwent allylation and methallylation reactions at room temperature in good yields under these conditions. Competition experiments demonstrate that the reaction is selective for electron-deficient ketones.

Key words: iridium, allylation, diene ligands, boric acid

Dienes have been shown to be effective ligands in catalytic organometallic reactions.[1] The recent development of dienes and phosphino-olefins as ligands in transition metal catalysis has caused them to be seen as viable alternatives to phosphines.[2] In this communication we describe an iridium-catalyzed allylation and methallylation reaction of ketones with dienes as ligands. Mechanistic experiments are consistent with an open transition state for the allyl transfer event, involving participation of both a nucleophilic allyliridium complex and borate Lewis acid.

During the course of our investigation on the iridium-catalyzed allylation reaction of ketones, we screened a number of phosphines and dienes in an effort to form a nucleophilic iridium species (Table 1).[3–5] While there was no reaction with no exogenous ligand added to the $[Ir(coe)_2Cl]_2$ source (entry 1), addition of a number of bisphosphines and dienes provided the homoallylic alcohol **4a** in moderate to good yield.[6] Of the bisphosphine ligands examined, (*R*,*R*)-Me-DUPHOS gave the highest yield (entry 5). A phosphino-olefin ligand **1** (Figure 1) reported by Carreira and co-workers gave modest reactivity (entry 6).[7] Recently reported diene ligands gave a large range of reactivity. In the reactions with commercially available DOLEFIN and norbornadiene, isomerization of allylboronic ester to the 1-propenylboronic ester was the major side reaction pathway observed, resulting in low yields of homoallylic alcohol **4a** (entries 7 and 8).[8] Cyclooctadiene and diene **2** (Figure 1) provided the highest yields of the desired product (entries 9 and 10).[2b]

We sought to investigate the mechanism of the transformation and determine the key participants in the transition state for the C–C bond-forming event. We previously reported deuterium labeling studies that support the presence of a rapidly isomerizing allyliridium species and are inconsistent with direct addition of the allylic boronic ester to the ketone.[4] We therefore hypothesized that a nucleophilic allyliridium intermediate is formed in situ and subsequently reacts with the ketone.

We next sought to define a role for boric acid and the borate byproducts that are present in the reaction. In our initial studies we found that boric acid is a critical additive

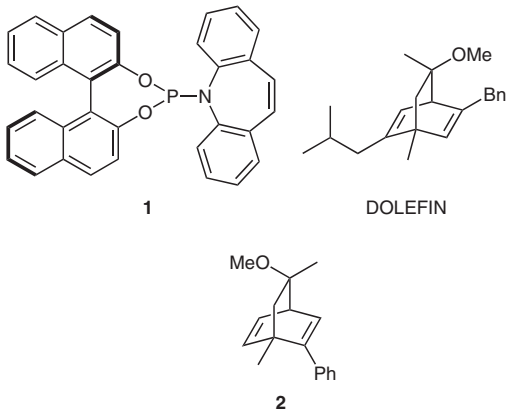
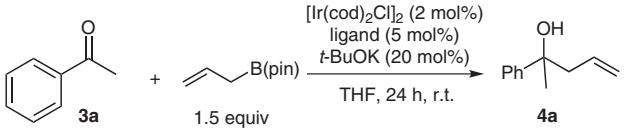


Figure 1 Diene and phosphino-olefin ligands

Table 1 Ligand Screen for Iridium Allylation of Acetophenone (**3a**)



Entry	Ligand	Yield[a] (%)
1	none	<5
2	(*R*)-BINAP	44
3	(*R*,*R*,*S*,*S*)-TANGPHOS	0
4	(*R*)-(MeO)-BIPHEP	44
5	(*R*,*R*)-Me-DUPHOS	68
6	**1**	25
7	DOLEFIN	0
8	norbornadiene	15
9	cyclooctadiene	78
10	**2**	82

[a] Isolated yield after silica gel chromatography.

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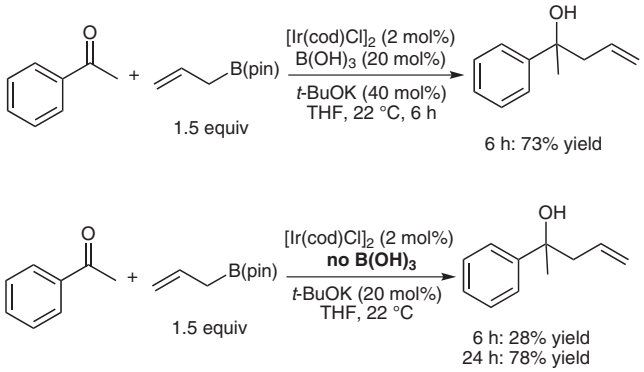
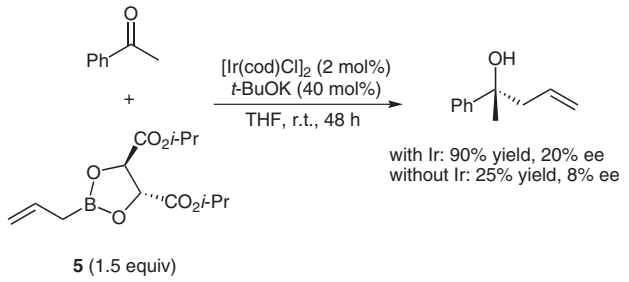
for the reaction, since in the absence of boric acid a slower reaction was observed (Scheme 1). There are several potential roles for boric acid in the reaction.[9,10] One potential role for boric acid would be to serve as a Lewis or Brønsted acid to activate the ketone.[11] In the absence of boric acid, boronate byproducts could serve as an alternative Lewis acid. Chiral boronate **5** was synthesized[12] as a mechanistic probe to determine whether or not the borate byproducts participate in the transition state for the C–C bond-forming event (Scheme 2). When boronate **5** was subjected to the reaction conditions, a modest enantiomeric excess was observed in the iridium-catalyzed reaction. Significantly, the enantiomeric excess was higher in the iridium-catalyzed reaction than the background reaction in the absence of iridium complex. These results are consistent with a transition state for the C–C bond-forming event that involves both borate ester and iridium complex. Based on all of our mechanistic data, we propose an open transition state with the boric acid or borate ester acting as a Lewis acid and an allyliridium species acting as the nucleophile. The insensitivity of this transformation to asymmetric induction from ligands on the iridium could also indirectly support an open transition state.



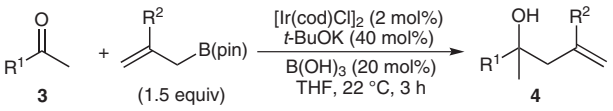
Scheme 1 Effect of boric acid on iridium allylation



Scheme 2 Reaction with chiral allylboronate

Using our optimized conditions, allylations of a variety of ketones **3** were performed, giving good yields of the homoallylic alcohol products **4** (Table 2). Electron-withdrawing (entry 2) as well as electron-donating (entry 3) substituents are tolerated with all reactions complete within three hours. Heteroaromatic ketones are also competent substrates (entries 4 and 5). Substitution on the allylic boronic ester was also tolerated. Methallylation provided

Table 2 Substrate Scope of Iridium-Catalyzed Reaction

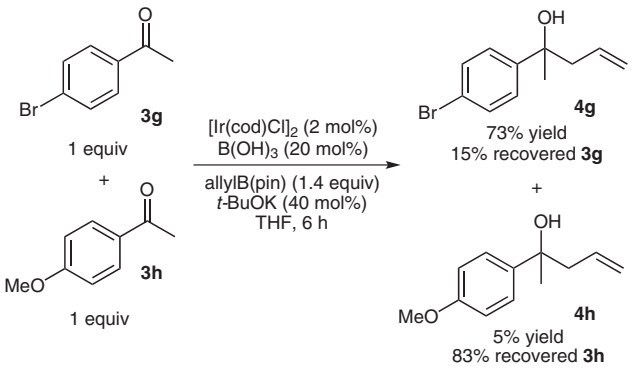


Entry	R^1	R^2	Product	Yield[a] (%)
1	Ph	H	**4a**	78
2	4-BrC_6H_4	H	**4b**	83
3	4-$MeOC_6H_4$	H	**4c**	70
4	3-pyridyl	H	**4d**	51
5	2-thienyl	H	**4e**	77
6[b]	Ph	Me	**4f**	87
7	4-BrC_6H_4	Me	**4g**	78
8[b]	4-$MeOC_6H_4$	Me	**4h**	63

[a] Isolated yield after silica gel chromatography.
[b] Reaction time was 6 h.

good yields of the substituted homoallylic alcohols (entries 6–8).

A competition experiment was performed to determine whether or not the reaction could exhibit selectivity for electronically differentiated ketones (Scheme 3).[13] Under standard reaction conditions, *p*-bromoacetophenone (**3g**) reacted preferentially over *p*-methoxyacetophenone (**3h**) giving yields of the homoallylic alcohols **4g** and **4h** of 73% and 5%, respectively. Analysis of the reaction mixture by gas chromatography also confirmed the presence of unreacted *p*-bromoacetophenone (**3g**) (15%) and *p*-methoxyacetophenone (**3h**) (83%). It can be concluded that electron-rich ketones react more slowly in this iridium-catalyzed allylation reaction.



Scheme 3 Competition experiment

In summary, we have demonstrated that a diene-ligated iridium complex allylates ketones in the presence of boric acid in good yields. Ligands have been shown to have a strong impact on the reactivity of iridium complexes. Mechanistic studies support boric acid acting as a mild Lewis acid that coordinates to the ketone, facilitating an

allyl transfer from a nucleophilic allyliridium species. Competition experiments performed showed the reaction was selective for electron-poor ketones.

All reactions were carried out in a glovebox under an atmosphere of N_2. All glassware was flame-dried prior to use. THF was degassed with argon and then passed through two 4 × 92 cm columns of anhyd neutral A-2 alumina (8 × 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 h) to remove H_2O. ^{1}H NMR spectra were recorded on CRYO-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) or DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometers. IR spectra were obtained on a Mattson Instruments Galaxy 5000 spectrophotometer. Analytical TLC was performed using silica gel 60 F254 precoated plates (0.25 mm thickness); visualization: irradiation with a UV lamp and/or staining with *p*-anisaldehyde soln. Flash chromatography was performed using silica gel 60A (170–400 mesh) from Fisher Scientific. Enantiomeric excess of the homoallylic alcohol was determined on a Berger Analytical SFC instrument using a Daicel Chiralpak AD-H column (3% MeOH, 7.6 bar, 2.5 mL/min). GC analysis was performed on a Agilent Technologies 6850 instrument using dodecane as an internal standard. Allylboronic acid pinacol ester was supplied by Frontier Scientific, Inc. and was distilled through a 15-cm Vigreux fractionating column connected to a short-path distillation head (95 °C/23 mbar) to remove $B(OH)_3$. (*R*)-BINAP, (*R*,*R*,*S*,*S*)-TANGPHOS, (*R*,*R*)-Me-DUPHOS, and $[Ir(cod)Cl]_2$ were purchased from Strem, stored in the glovebox, and used as received. Phosphino-olefin **1** and diene **2** were synthesized according to known procedures.[2b,7] DOLEFIN was purchased from Aldrich. $[Ir(coe)_2Cl]_2$ was synthesized according to a known procedure.[14] Methallylboronic acid pinacol ester was synthesized according to a known procedure.[15] *t*-BuOK was purchased from Alfa Aesar, stored in a glovebox and used as received. Chiral allylboronate **5** was synthesized according to a known procedure.[12] All ketones were purchased commercially and liquids were distilled prior to use. HRMS was performed by the University of California, Irvine Mass Spectrometry Center.

2-Phenylpent-4-en-2-ol (4a); Typical Procedure for Allylation Reactions with $[Ir(coe)_2Cl]_2$ (Table 1)

In a flame-dried 5-mL round-bottom flask in a glovebox, $[Ir(coe)_2Cl]_2$ (9 mg, 0.010 mmol, 0.02 equiv) and cyclooctadiene (3 mg, 0.025 mmol, 0.05 equiv) were stirred in THF (1 mL) for 3 h. After 3 h, *t*-BuOK (11 mg, 0.10 mmol, 0.2 equiv), acetophenone (**3a**, 58 μL, 0.50 mmol, 1 equiv), allylboronic acid pinacol ester (140 μL, 0.75 mmol, 1.5 equiv), and 1,4-bis(trifluoromethyl)benzene (79 μL, 0.50 mmol, 1 equiv) (as an internal standard) were added. The mixture was capped with a septa and stirred in the glovebox at r.t. for 24 h. The reaction was removed from the glovebox and quenched with sat. NH_4Cl soln (1 mL) and stirred for 10 min. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography (silica gel, pentane–Et_2O, 90:10) afforded **4a** (63 mg, 78%) as a colorless oil.

2-Phenylpent-4-en-2-ol (4a); Typical Procedure for Allylation Reactions with $[Ir(cod)Cl]_2$ (Table 2)

To a flame-dried 5-mL round-bottom flask in a glovebox was added $[Ir(cod)Cl]_2$ (7 mg, 0.010 mmol, 0.02 equiv), *t*-BuOK (22 mg, 0.20 mmol, 0.4 equiv), boric acid (6.2 mg, 0.10 mmol, 0.2 equiv), THF (1 mL), acetophenone (**3a**, 58 μL, 0.50 mmol, 1 equiv), and allylboronic acid pinacol ester (140 μL, 0.75 mmol, 0.5 equiv). The mixture was capped with a septa and stirred in the glovebox at r.t. for 3 h. The reaction was removed from the glovebox and quenched with sat. NH_4Cl soln (1 mL) and stirred for 10 min. The aqueous layer was extracted Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography (silica gel, pentane–Et_2O, 90:10) afforded **4a** (63 mg, 78%) as a colorless oil. Compounds **4c**,**f**,**g** were purified using $AgNO_3$-impregnated silica gel.[16] Characterization data for compounds **4a**–**c**,[17] **4d**,**e**,[4] and **4f**[18] have been previously reported.

2-(4-Bromophenyl)-4-methylpent-4-en-2-ol (4g)

IR (thin film): 3467, 3074, 2978, 1487 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 2 H), 7.33 (s, *J* = 8.4 Hz, 2 H), 4.90 (s, 1 H), 4.74 (s, 1 H), 2.60 (d, *J* = 13.4 Hz, 1 H), 2.49 (d, *J* = 13.4 Hz, 1 H), 2.38 (s, 1 H) 1.54 (s, 3 H), 1.43 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.3, 142.4, 131.3, 127.0, 120.6, 116.3, 73.2, 52.1, 31.0, 24.5.

HRMS (TOF MS APCI+): *m*/*z* $[M + NH_4]^+$ calcd for $C_{12}H_{19}BrNO$: 272.0650; found: 272.0648.

2-(4-Methoxyphenyl)-4-methylpent-4-en-2-ol (4h)

IR (thin film): 3474, 3072, 2974, 1512, 1248 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 6.7, 2.1 Hz, 2 H), 6.87 (dd, *J* = 6.7, 2.1 Hz, 2 H), 4.90 (s, 1 H), 4.75 (s, 1 H), 3.81 (s, 3 H), 2.62 (d, *J* = 13.3 Hz, 1 H), 2.51 (d, *J* = 13.3 Hz, 1 H) 2.33 (s, 1 H), 1.56 (s, 3 H), 1.43 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 142.9, 140.4, 126.1, 115.8, 113.5, 73.2, 55.4, 52.3, 30.9, 24.5.

HRMS (TOF MS APCI+): *m*/*z* $[M + NH_4]^+$ calcd for $C_{13}H_{22}NO_2$: 224.1651; found: 224.1652.

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