

# Enantioselective Formation of All-Carbon Quaternary Centers via C–H Functionalization of Methanol: Iridium-Catalyzed Diene Hydrohydroxymethylation

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**S** Supporting Information

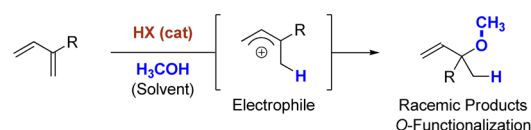
**ABSTRACT:** The first catalytic enantioselective C–C couplings of methanol (>30 × 10<sup>6</sup> tons/year) are reported. Insertion of 2-substituted dienes into the methanol C–H bond occurs in a regioselective manner to form all-carbon quaternary centers with excellent levels of enantioselectivity using an iridium–PhanePhos catalyst. Mechanistic studies corroborate a Curtin–Hammett scenario in which methanol dehydrogenation triggers rapid, reversible diene hydrometalation *en route* to regioisomeric allyliridium–formaldehyde pairs, yet single constitutional isomers are formed.

Despite impressive advances in the field of chemical synthesis, catalytic enantioselective formation of all-carbon quaternary stereocenters remains a daunting challenge.<sup>1</sup> Ideally, it would be desirable to form all-carbon quaternary stereocenters from inexpensive feedstocks in C–C bond forming processes that circumvent generation of stoichiometric byproducts. Indeed, the two largest volume applications of homogeneous catalysis, hydroformylation<sup>2</sup> and methanol carbonylation (the Monsanto/Cativa processes),<sup>3</sup> are byproduct-free C–C bond formations. In connection with our development of catalytic C–C couplings that convert lower alcohols to higher alcohols,<sup>4</sup> processes that merge the characteristics of transfer hydrogenation and carbonyl addition, we became interested in the use of methanol as a C1 feedstock in catalytic C–C coupling.<sup>4c,5</sup> Toward this end, the direct byproduct conversion of methanol to higher alcohols was achieved using allene pronucleophiles.<sup>6a</sup> Methanol-mediated couplings of more abundant  $\pi$ -unsaturated partners (dienes or  $\alpha$ -olefins) have hitherto proven elusive, and enantioselective transformations of this type appeared especially implausible.<sup>6b,7</sup>

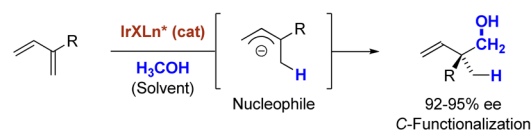
Here, we report an iridium–PhanePhos catalyst for the enantioselective C–C coupling of methanol (>30 × 10<sup>6</sup> tons/year) with 2-substituted dienes. Remarkably, mechanistic studies corroborate rapid interconversion of regio- and stereoisomeric allyliridium intermediates, yet a Curtin–Hammett selection process enables formation of single isomeric products bearing all-carbon quaternary stereocenters. Furthermore, enantiotopic  $\pi$ -facial discrimination for the reactive allyliridium isomer is efficient, resulting in high levels of enantioselectivity.<sup>8</sup> Thus, by inverting the canonical behavior of methanol in its reaction with unsaturates (etherification), enantioselective C–H functionalization of methanol is achieved for the first time (Scheme 1).

## Scheme 1. Inverting Diene Reactivity via C–C Bond Forming Transfer Hydrogenation: Enantioselective Formation of All-Carbon Quaternary Centers

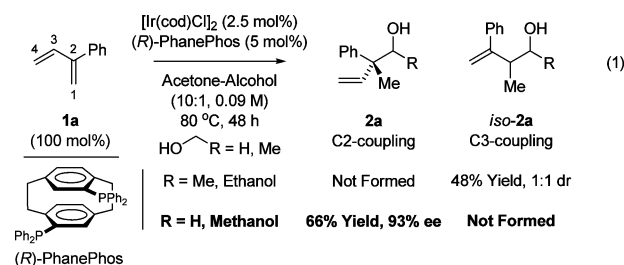
**Classical Acid-Catalyzed Etherification:** O-Functionalization of MeOH



**This Work:** Regio- and Enantioselective C-Functionalization of MeOH



In an effort to develop enantioselective iridium-catalyzed C–C couplings of primary alcohols with dienes to form homoallylic secondary alcohols,<sup>9</sup> diverse primary alcohols were exposed to 2-phenyl-1,3-butadiene **1a** in the presence of the iridium catalyst generated *in situ* from [Ir(cod)Cl]<sub>2</sub> and various chelating chiral phosphine ligands. An astonishing observation was made: whereas the iridium–PhanePhos catalyzed reaction of ethanol with 2-phenyl-1,3-butadiene **1a** results in coupling at the diene C3-position to form *iso*-**2a** (R = Me), the corresponding reaction of methanol results in coupling at the diene C2-position to form **2a** (R = H) in 93% ee (eq 1). For both reactions, complete partitioning of C2

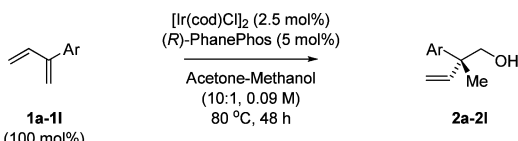
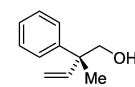
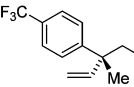
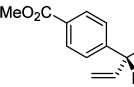
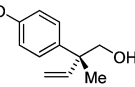
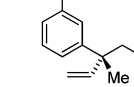
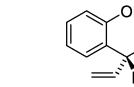
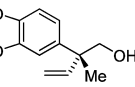
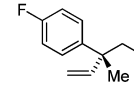
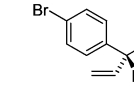
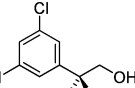
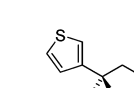
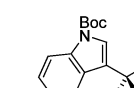


vs C3 regioselectivity is observed. Underscoring the fortuitous nature of these findings, an extensive ligand survey revealed that PhanePhos was unique in its ability to promote efficient formation of **2a** (R = H).

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**Table 1. Enantioselective Iridium-Catalyzed C–C Coupling of 2-Substituted Dienes 1a–1l with Methanol To Form Neopentyl Alcohols 2a–2l<sup>a</sup>**

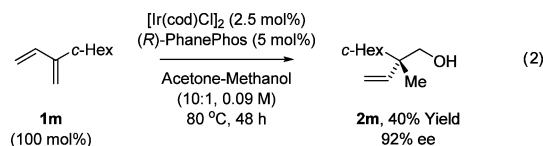
		
<b>1a</b> , R = Ph <b>1d</b> , R = 4-MeO-Ph <b>1g</b> , R = 5-benzodioxole <b>1j</b> , R = 3,5-Cl <sub>2</sub> -Ph	<b>1b</b> , R = 4-CF <sub>3</sub> -Ph <b>1e</b> , R = 3-MeO-Ph <b>1h</b> , R = 4-F-Ph <b>1k</b> , R = 3-thienyl	<b>1c</b> , R = 4-CO <sub>2</sub> Me-Ph <b>1f</b> , R = 2-MeO-Ph <b>1i</b> , R = 4-Br-Ph <b>1l</b> , R = 3-( <i>N</i> -Boc-indolyl)
 <b>2a</b> , 66% Yield 93% ee (0.15 mmol) 61% Yield, 93% ee (1 mmol) <i>X</i> -Ray (4-Br-benzoate)	 <b>2b</b> , 65% Yield 94% ee	 <b>2c</b> , 62% Yield 92% ee
 <b>2d</b> , 67% Yield <sup>b</sup> 94% ee	 <b>2e</b> , 68% Yield 94% ee	 <b>2f</b> , 60% Yield 94% ee
 <b>2g</b> , 60% Yield 94% ee	 <b>2h</b> , 67% Yield 93% ee	 <b>2i</b> , 67% Yield 94% ee (1 mmol scale)
 <b>2j</b> , 60% Yield 95% ee	 <b>2k</b> , 65% Yield 94% ee	 <b>2l</b> , 50% Yield <sup>b</sup> 95% ee

<sup>a</sup>Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See [Supporting Information](#) for further experimental details. <sup>b</sup>Acetone/methanol (1:1).

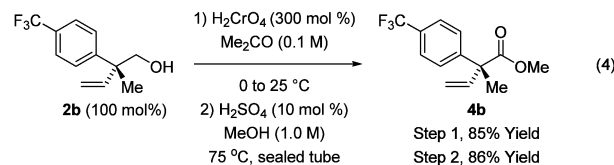
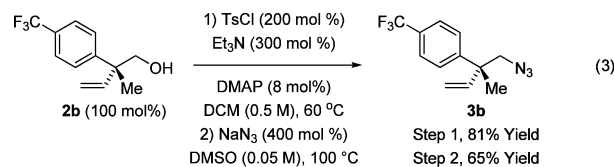
The conditions indicated for the formation of **2a** (eq 1) are the result of extensive optimization (see [Supporting Information](#)). Diene **1a** is susceptible to formation of a Diels–Alder dimerization byproduct, but this side reaction is largely suppressed at lower temperature. Because diene **1a** is far more precious than methanol, it was used as the limiting reagent even though higher yields are possible by inverting stoichiometry. Application of these conditions to 2-aryl substituted dienes **1a–1l** illustrates the scope of this process (Table 1). Dienes **1b** and **1c**, which incorporate electron-withdrawing *p*-substituted phenyl moieties, are converted to the products of hydroxymethylation **2b** and **2c**, respectively, with excellent levels of enantioselectivity. Dienes **1d–1g**, bearing phenyl groups with alkoxy substituents at the *para*-, *meta*-, and *ortho*-positions, are converted to adducts **2d–2g** with uniformly high levels of enantioselectivity. Finally, dienes incorporating halogenated phenyl moieties (**1h–1j**) and heteroaromatic rings (**1k–1l**) perform equally well. The absolute stereochemistry of the 4-bromobenzoate of adduct **2a** was determined by single crystal X-ray diffraction analysis.

The absolute stereochemistry of adducts **2b–2l** was assigned in analogy.

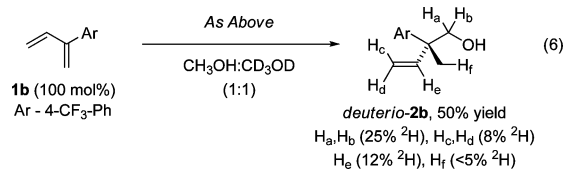
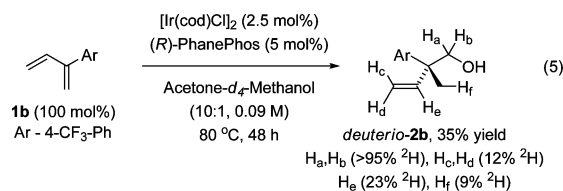
The coupling of methanol with dienes bearing alkyl substituents at the C2-position was investigated. As illustrated in the coupling of cyclohexyl-substituted diene **1m** under standard reaction conditions (eq 2), complete levels of C2-regioselectivity are accompanied by excellent levels of enantioselectivity; however, a lower isolated yield is observed. The development of improved conditions for the coupling of C2-alkyl substituted dienes is currently underway.



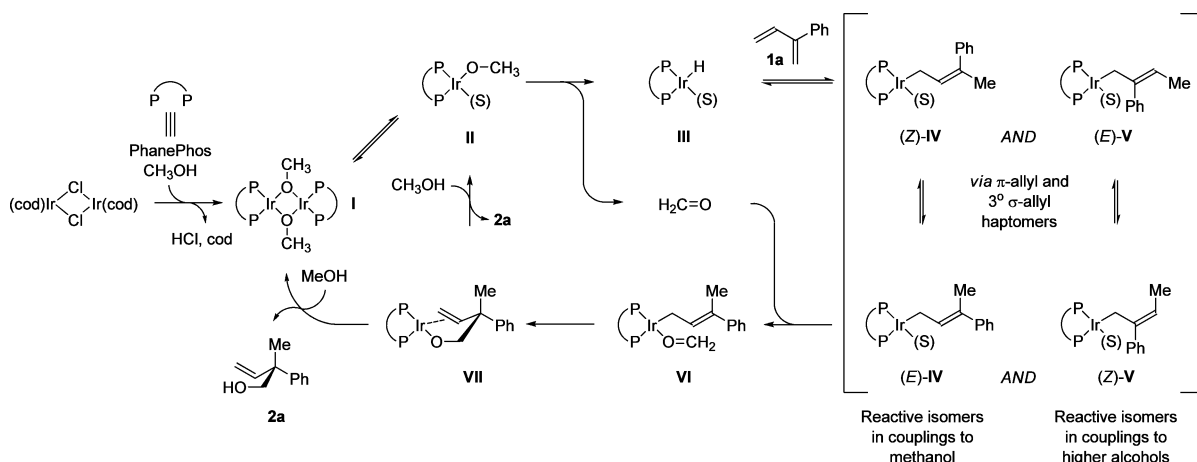
To briefly illustrate how the present coupling products may serve as building blocks in asymmetric synthesis, alcohol **2b** was converted to the corresponding *p*-toluenesulfonate and reacted with sodium azide in DMSO. Although neopentyl electrophiles are notoriously recalcitrant partners for S<sub>N</sub><sup>2</sup> reactions, azide **3b** was formed in good yield (eq 3). Additionally, Jones oxidation of neopentyl alcohol **2b** followed by Fischer esterification provides the ester **4b** (eq 4).



Regarding the catalytic mechanism, the regiodivergence observed in the coupling of diene **2a** with methanol vs higher alcohols suggests a Curtin–Hammett scenario wherein alcohol dehydrogenation triggers rapid, reversible diene hydrometalation to form regioisomeric allyliridium–formaldehyde pairs.<sup>10</sup> To probe the veracity of this interpretation, deuterium labeling experiments were performed. The coupling of diene **1b** with *d*<sub>4</sub>-methanol under otherwise standard conditions provides *deuterio-2b* in 35% yield (eq 5). Deuterium is retained at the carbinol position (H<sub>c</sub> = >95% <sup>2</sup>H), suggesting *deuterio-2b* is kinetically inert with respect to dehydrogenation. The

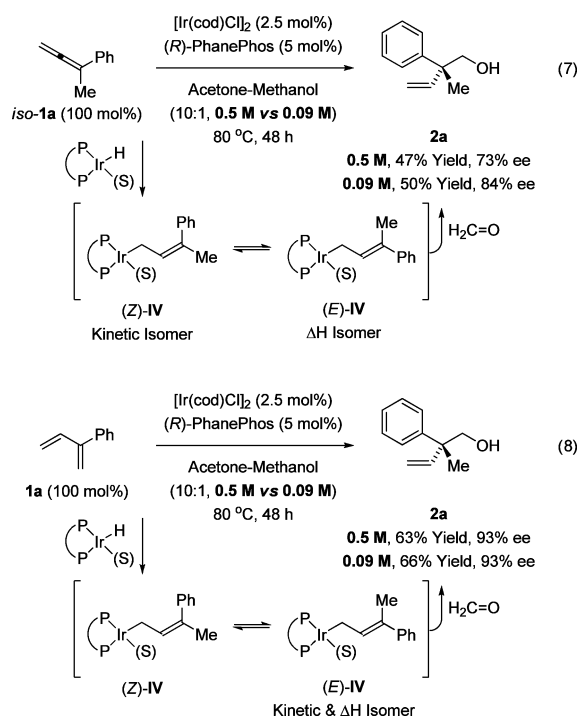


Scheme 2. General Catalytic Mechanism Accounting for Regiodivergence in the Iridium-Catalyzed Coupling of Diene 1a with Methanol vs Higher Alcohols



incorporation of deuterium at the former diene C1, C3, and C4 positions is consistent with rapid, reversible diene hydrometalation- $\beta$ -hydride elimination in advance of carbonyl addition. Incomplete transfer of deuterium is observed, which may be attributed to H–D exchange of the transient iridium hydride with adventitious water.<sup>11</sup> A competition kinetics experiment was performed in which diene **1b** was exposed to equimolar quantities of methanol and  $d_4$ -methanol (eq 6). The incorporation of deuterium at the carbinol methylene (25%  $^2\text{H}$ ) of the product *deuterio-2b* establishes a normal primary kinetic isotope effect ( $k_{\text{H}}/k_{\text{D}} = 3.0$ ). These data suggest methanol dehydrogenation is turnover-limiting. This result is not surprising given the relatively high energetic demand of methanol dehydrogenation ( $\Delta H = +84$  kJ/mol) compared to the dehydrogenation of higher alcohols, such as ethanol ( $\Delta H = +68$  kJ/mol).<sup>12</sup>

A catalytic mechanism consistent with the collective data has been proposed (Scheme 2). Exposure of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  to PhanePhos in the presence of methanol provides the methoxy-bridged dimer **I**,<sup>12c,d,13</sup> which exists in equilibrium with the monomeric iridium methoxide complex **II**.  $\beta$ -Hydride elimination of **II** generates the iridium hydride **III** and formaldehyde.<sup>12</sup> Reversible diene hydrometalation provides an equilibrating mixture of regioisomeric allyliridium complexes **IV** and **V**. Complexation of formaldehyde occurs exclusively by way of the 1,1-disubstituted allyliridium isomers **IV** to form the formaldehyde complex **VI**. Carbonyl addition then provides the homoallylic iridium alkoxide complex **VII**, which upon methanolysis releases the product of hydrohydroxymethylation **2a** and regenerates the iridium methoxide complex **I** or **II** to close the catalytic cycle. The regiodivergence observed in the coupling of diene **2a** with methanol vs higher alcohols may be rationalized as follows. The 1,1-disubstituted allyliridium species (*E*)-**IV** is both thermodynamically preferred and, in the case of formaldehyde addition, kinetically more reactive. Higher alcohols, and therefrom higher aldehydes, impose greater steric congestion, raising the energy of the transition state for carbonyl additions that form all-carbon quaternary centers. Consequently, in addition to higher aldehydes, the 1,2-disubstituted allyliridium isomers **V** are kinetically more reactive. Rapid, reversible diene hydrometalation, as corroborated by deuterium labeling (eq 5), replenishes whichever allyliridium isomer that is consumed.

Scheme 3. Diene Hydrometalation Delivers the Allyliridium Isomer That Is Both Kinetically and Thermodynamically Preferred<sup>a</sup>

<sup>a</sup>Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

High levels of enantioselectivity in the formation of adducts **2a–2m** require intervention of a single allyliridium geometrical isomer if carbonyl addition occurs in a stereospecific manner through a closed 6-centered transition structure. As dienes bearing sterically demanding groups at the 2-position predominantly reside in the *s-cis* conformation,<sup>14</sup> the hydrometalation of dienes **1a–1m** should display a kinetic preference for formation (*E*)-**IV**, which is presumed to be thermodynamically more stable than (*Z*)-**IV**. The coupling of allene *iso-1a* provides a unique opportunity to test this hypothesis (Scheme 3, eq 7). Hydrometalation of allene *iso-1a* should occur predominantly from the olefin  $\pi$ -face that is “*syn*” with respect

to the relatively small methyl moiety. Thus, for allene *iso*-1a, hydrometalation to form (*Z*)-IV is kinetically preferred. Enantioselectivities in the coupling of allene *iso*-1a are concentration dependent and improve with decreasing concentration. These data corroborate a scenario wherein isomerization of the kinetic allyliridium isomer (*Z*)-IV to the more stable isomer (*E*)-IV occurs at a rate that is only slightly faster than formaldehyde addition. For the corresponding diene pronucleophile 1a, enantioselectivity is insensitive to concentration, consistent with the hypothesis that (*E*)-IV is both kinetically and thermodynamically preferred (Scheme 3, eq 8).

To summarize, by unlocking the native reducing ability of methanol, one can override the canonical  $S_N1$  pathways observed in reactions with dienes, that is, *O*-alkylation, and instead activate catalytic mechanisms for C-alkylation. Furthermore, as demonstrated by the regio- and enantioselectivities evident in the present report, mediation of the catalytic process by transition metals enables unique isomer selectivities manifesting in the asymmetric formation of all-carbon quaternary centers, and the first enantioselective C–C couplings of methanol.<sup>15</sup> Future studies will focus on the development of related transfer hydrogenative C–C bond formations, including the byproduct-free coupling of alcohols with  $\alpha$ -olefins.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09333.

Experimental procedures and spectral data. HPLC traces corresponding to racemic and enantiomerically enriched samples. Single crystal X-ray diffraction data for the 4-bromobenzoate of compound 2a (PDF)

Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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