

# Iridium-Catalyzed Enantioselective Allyl–Alkene Coupling

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**S** Supporting Information

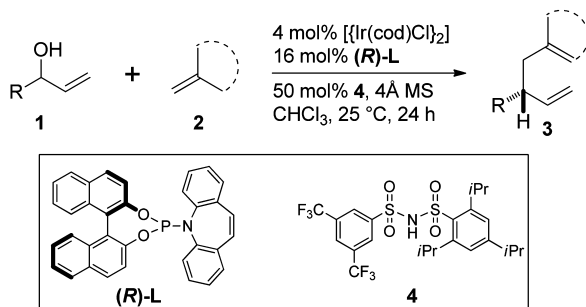
**ABSTRACT:** The direct Ir-catalyzed cross-coupling between branched, racemic allylic alcohols and simple olefins is described. This transformation is catalyzed by an Ir–(P,olefin) complex and proceeds with high site selectivity and excellent enantioselectivity. The method allows rapid access to various 1,5-dienes or trienes and was used in the catalytic asymmetric synthesis of the  $\gamma$ -secretase modulator JNJ-40418677.

Transition-metal-catalyzed allylic substitution reactions constitute one of the most versatile and efficient carbon–carbon bond formation methods in organic synthesis.<sup>1</sup> Of particular importance is the allyl–allyl cross-coupling between allyl-metal nucleophiles and allylic electrophiles, delivering synthetically valuable 1,5-dienes.<sup>2</sup> A variety of transition-metal complexes based on Pd, Cu, and Au have been used for this transformation<sup>3</sup> with only a limited number of catalytic enantioselective methods that deliver branched products. Additionally, the methods require the use of allyl metals (or metalloids), such as organo-tin<sup>3a,c</sup> and -boron<sup>4</sup> as well as Grignard<sup>5</sup> reagents. Herein, we document coupling reactions involving allyl alcohols and alkenes catalyzed by an Ir–(P,olefin) complex. The enantioselective allylic substitution approach delivers 1,5-dienes directly from branched racemic allylic alcohols with the alkene directly employed as a nucleophile (Scheme 1). The utility of this transformation is demonstrated through a facile synthesis of a  $\gamma$ -secretase modulator JNJ-40418677, a promising drug candidate for the treatment of Alzheimer's disease.

The recent pioneering work from Morken's group showcases the Pd-catalyzed regio- and enantioselective cross-coupling of allylboronic acid esters and allylic carbonates (Scheme 2).<sup>4</sup>

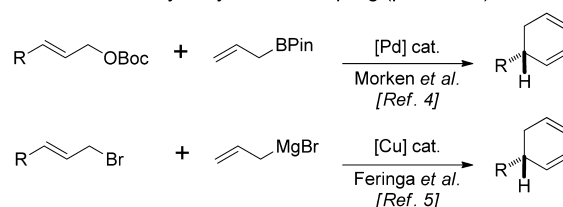
## Scheme 1. Catalytic Enantioselective Preparation of 1,5-Dienes

Enantioselective Allyl–Alkene Coupling (this work)



## Scheme 2. Metal Catalyzed Enantioselective Coupling of Allyl Partners

Enantioselective Allyl–Allyl Cross-Coupling (prior work)

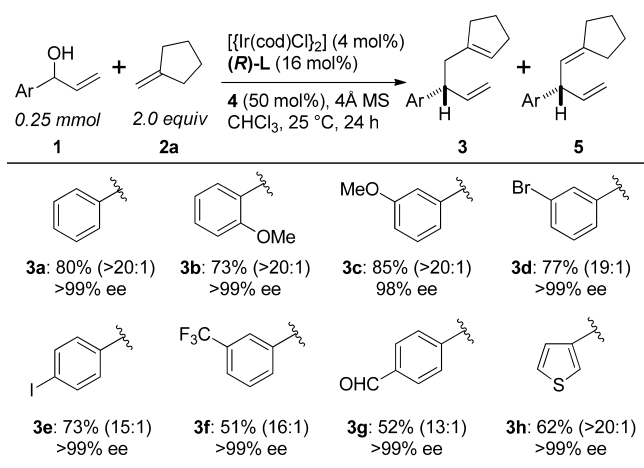


Additionally, Feringa and co-workers recently described a Cu-catalyzed asymmetric allylation of allyl bromides using allyl Grignard reagents.<sup>5</sup> Following the seminal achievements of Takeuchi, Helmchen, and Hartwig,<sup>6</sup> iridium complexes are now widely employed as catalysts in the allylic substitution reaction.<sup>7</sup> Along these lines, we have reported<sup>8</sup> a number of transformations that are characterized by high step, redox, and atom economy since they proceed by direct displacement of unactivated, branched racemic allylic alcohols.<sup>9</sup> In subsequent studies, we have sought to examine whether the putative allyl–Ir intermediate would be sufficiently electrophilic to directly engage olefins in a substitution process.<sup>10</sup> This would result in allyl–alkene coupling, a highly convenient and enantioselective C–C bond-forming transformation that would deliver 1,5-dienes without the use of any allyl-metal species in stoichiometric amounts.

Our study of the Ir-catalyzed allyl–alkene coupling began by evaluating the reaction of phenyl vinyl carbinol (**1a**, Table 1) as a test substrate with several disubstituted, terminal alkenes.<sup>11</sup> Extensive investigations of reaction parameters (see Supporting Information for full details) revealed that the nature of the cocatalyst that serves to activate the alcohol was critical. In this respect, diarylsulfonimides were revealed as most suitable as Brønsted acid activators. Unsymmetrical sulfonimide **4** was identified as the ideal promoter in combination with 4 Å molecular sieves and CHCl<sub>3</sub> as solvent. It is noteworthy that trifluoromethyl groups in **4** were required for optimal acidity, while isopropyl groups on the other arene provided steric shielding needed to prevent allylic imidation by **4**. Under these conditions, linear 1,5-dienes, which are otherwise common regioisomeric byproducts in allylic substitution reactions, were not observed. The only isomeric byproducts observed are formed in 4–7% yield and correspond to 1,4-dienes **5**, which arise from competitive deprotonation modes of the putative intermediate cation.

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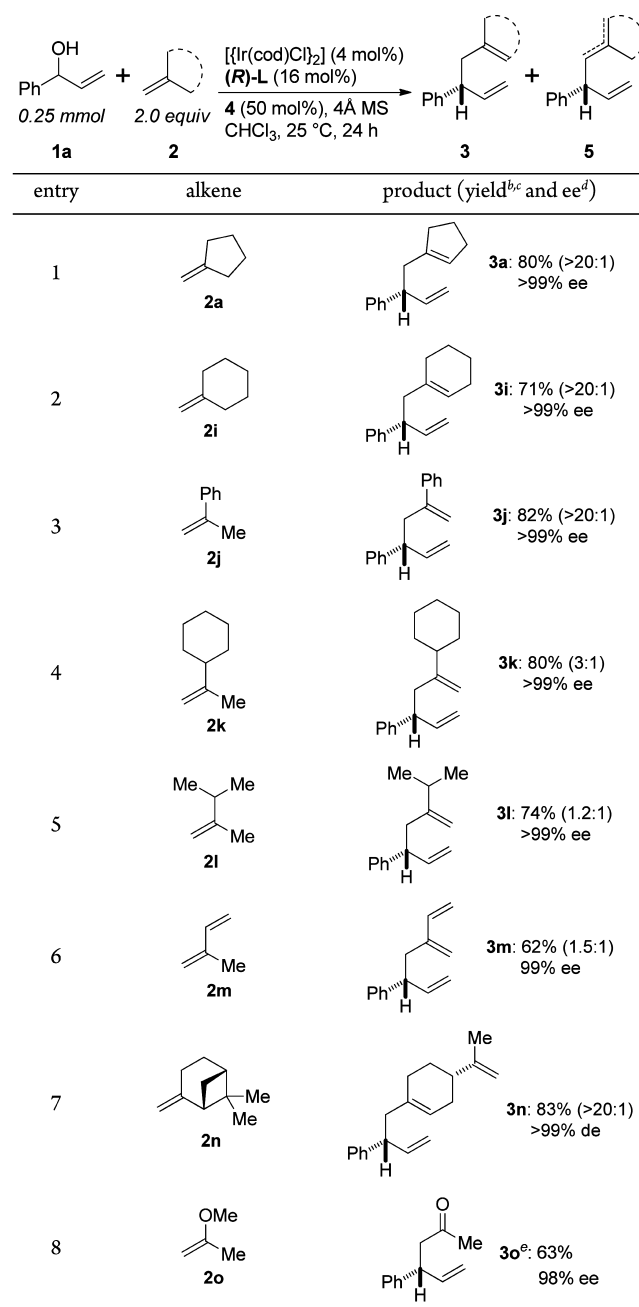
Table 1. Scope of Ir-Catalyzed Enantioselective Allyl–Alkene Coupling<sup>a,b,c,d</sup>

<sup>a</sup>Standard procedure:  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (4 mol %), (*R*)-**L** (16 mol %), substrate **1** (0.25 mmol, 1.0 equiv), alkene **2a** (0.50 mmol, 2.0 equiv), **4** (50 mol %), 4 Å MS (25 mg, 100 mg/mmol),  $\text{CHCl}_3$  (0.5 mL), 25 °C, 24 h. <sup>b</sup>Isolated yields after purification by flash chromatography. <sup>c</sup>Ratio of **3** to **5** in brackets as determined by  $^1\text{H}$  NMR integration of the crude reaction mixture. <sup>d</sup>Enantiomeric excess determined by SFC on a chiral stationary phase; absolute stereochemistry was assigned by analogy.

Having established optimal conditions, we next investigated the substrate scope and generality of this allyl–alkene coupling protocol by using methylenecyclopentane (**2a**) as depicted in Table 1. Thus, phenyl (**3a**) as well as alkoxy-substituted (**3b** and **3c**) aromatic substrates all afforded the corresponding chiral 1,5-dienes in high yields and enantioselectivities. Incorporation of halogens (**3d** and **3e**) was also well tolerated, furnishing allyl–alkene coupling products with excellent selectivities. Although substrates possessing electron-withdrawing groups, such as trifluoromethyl (**3f**) and aldehyde (**3g**), were less reactive, reactions of these substrates still deliver products in moderate yields with excellent enantioselectivity. In addition, heteroaromatic systems, such as thiophene (**3h**), may be employed as well.<sup>12</sup>

As presented in Table 2, a wide array of alkenes readily participate as nucleophiles in this substitution reaction with allylic alcohol **1a**. Besides standard olefin substrate **2a**, methylenecyclohexane (**2i**) and  $\alpha$ -methylstyrene (**2j**) also provided the respective coupled products in good yields with superb enantio- and regioselectivities (Table 2, entries 1–3). Unsymmetrically substituted terminal alkenes (**2k** and **2l**) readily underwent the nucleophilic addition with good stereocontrol; however, as expected from the nature of this process, low regioselection was observed in these cases (Table 2, entries 4 and 5). A notable observation with respect to synthetic utility is that conjugated dienes, such as isoprene (**2m**), are also suitable for the Ir-catalyzed allyl–alkene coupling, delivering triene **3m** (Table 2, entry 6). Importantly, in each of these last three cases, the product containing a terminal olefin was preferentially formed over the more highly substituted alkene.

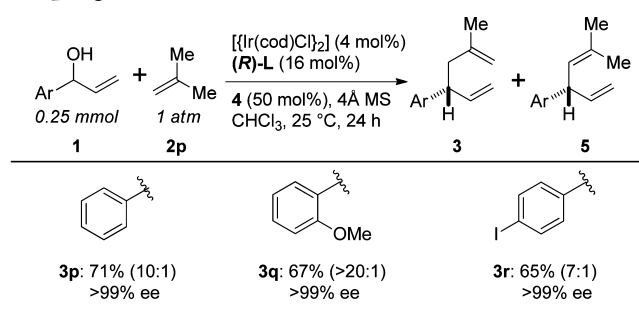
We then examined olefins which would give rise to carbocation intermediates subsequently susceptible to rearrangements. This was exemplified by the use of (–)- $\beta$ -pinene (**2n**, optical purity >99%), which gave **3n** in good yield and >99% diastereoselectivity (Table 2, entry 7). Finally, we have

Table 2. Alkene Scope of Ir-Catalyzed Enantioselective Allyl–Alkene Coupling<sup>a</sup>

<sup>a</sup>All reactions were carried out on 0.25 mmol scale under standard conditions (see Table 1 for details). <sup>b</sup>Isolated yields after purification by flash chromatography. <sup>c</sup>Ratio of **3** to **5** in brackets as determined by  $^1\text{H}$  NMR integration of the crude reaction mixture. <sup>d</sup>Enantiomeric and diastereomeric excess determined by SFC on a chiral stationary phase; absolute stereochemistry was assigned by analogy. <sup>e</sup>4.0 equiv of **2o** and  $\text{F}_3\text{CCO}_2\text{H}$  (50 mol %) instead of **4** were used without 4 Å MS.

examined the inexpensive commodity chemical 2-methoxypropene as an acetone enolate equivalent to give  $\gamma,\delta$ -unsaturated ketone (**3o**) with stereodifferentiation at the  $\beta$ -carbon (Table 2, entry 8).<sup>13</sup>

The robustness and versatility of the allyl–alkene coupling process could further be examined by the use of a gas, such as isobutene (**2p**), as a nucleophile (Table 3). When the reaction was conducted under an atmosphere of isobutene, the desired

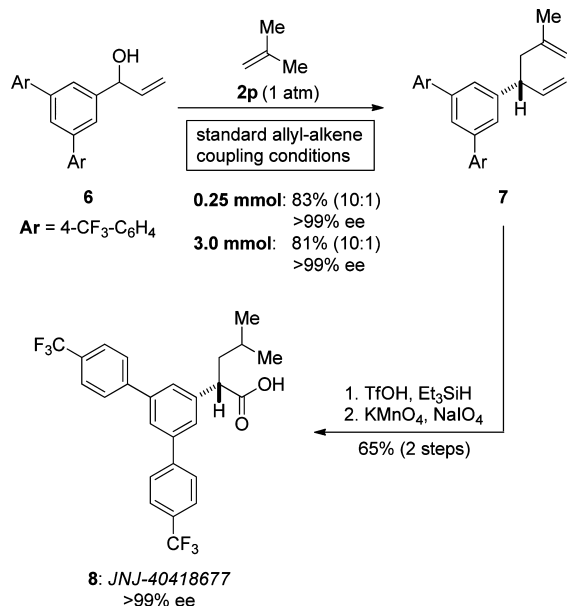
**Table 3. Ir-Catalyzed Enantioselective Allyl–Alkene Coupling with Isobutene<sup>a,b,c,d</sup>**

<sup>a</sup>All reactions were carried out on 0.25 mmol scale under standard conditions (see Table 1 for details); isobutene (1 atm, balloon).

<sup>b</sup>Isolated yields after purification by flash chromatography. <sup>c</sup>Ratio of **3** to **5** in brackets as determined by <sup>1</sup>H NMR integration of the crude reaction mixture. <sup>d</sup>Enantiomeric excess determined by SFC on a chiral stationary phase; absolute stereochemistry was assigned by comparison (**3p**) and analogy.

allyl–alkene coupling was readily achieved. In addition to the phenyl allylic alcohol (**3p**), alkoxy substituted (**3q**) as well as halogenated (**3r**) aromatic substrates all underwent the desired transformation.

To demonstrate the synthetic utility of the new method, we applied the catalytic allyl–alkene coupling to the synthesis of a potent, orally bioavailable  $\gamma$ -secretase modulator JNJ-40418677 (**8**) (Scheme 3), developed by Johnson & Johnson as a

**Scheme 3. Enantioselective Synthesis of JNJ-40418677**

promising drug candidate for the treatment of Alzheimer's disease.<sup>14</sup> Accordingly, upon exposure of allylic alcohol **6** to the standard reaction conditions under an atmosphere of isobutene (**2p**), 1,5-diene **7** was obtained in good yield and excellent enantioselectivity. Subsequent chemoselective ionic reduction of the disubstituted alkene, followed by oxidative cleavage of the remaining terminal olefin, efficiently provided **8**. The preparative utility of this method was further showcased by conducting the allyl–alkene coupling on a larger scale (1.27 g of **6**, 3.0 mmol scale), employing a reduced amount of catalyst

(3/12 mol % Ir/(**R**)-**L**) to afford the product with comparable yield and selectivity.<sup>15</sup>

In summary, we have documented a new Ir-catalyzed, enantioselective allylic substitution which employs racemic secondary alcohols and readily accessible alkenes as nucleophiles to afford chiral 1,5-diene products in good yields and excellent enantioselectivities. It is noteworthy that the allyl–alkene coupling described represents an atom economical method that, unlike common alternatives, does not require any stoichiometric allyl-metal reagents or prior activation of the allylic alcohol partner. The synthetic potential of this transformation has been demonstrated in a concise preparation of  $\gamma$ -secretase modulator JNJ-40418677. Further studies regarding the expansion of the substrate scope and development of related transformations, as well as further applications of the method, are ongoing and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data for all reactions and products, including <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(11) 2,2-Disubstituted alkenes were required; mono-, 1,2-di-, or trisubstituted alkenes were unreactive under the described reaction conditions.

(12) At the current level of development aliphatic allylic alcohols are not substrates for the substitution reaction described herein. In addition, allylic alcohol substrates bearing substituents on the vinyl group (at C2 and C3) were unreactive under these conditions.

(13) Similar products were obtained using Ir-catalyzed allylation of enamines and silyl ketone enolates; see refs 7i and 7k.

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(15) Sulfonimide promoter **4** was recovered in high yield (91%) by increasing the eluent polarity after elution of the product during flash chromatography. See Supporting Information for details.