Title

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Journal

Journal of the American Chemical Society, 137(43)

ISSN

0002-7863

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Publication Date

2015-11-04

DOI

10.1021/jacs.5b09980

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2017 March 08.

Published in final edited form as:

J Am Chem Soc. 2015 November 04; 137(43): 13972–13979. doi:10.1021/jacs.5b09980.

Iridium-Catalyzed Enantioselective Allylic Substitution of Enol Silanes from Vinylogous Esters and Amides

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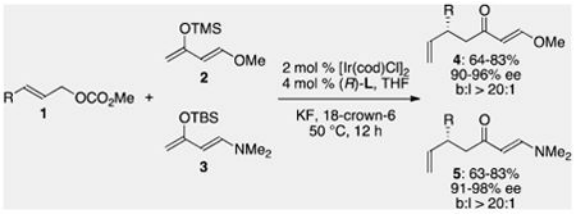
Abstract

The enol silanes of vinylogous esters and amides are classic dienes for Diels–Alder reactions. Here, we report their reactivity as nucleophiles in Ir-catalyzed, enantioselective allylic substitution reactions. A variety of allylic carbonates react with these nucleophiles to give allylated products in good yields with high enantioselectivities and excellent branched-to-linear ratios. These reactions occur with KF or alkoxide as the additive, but mechanistic studies suggest that these additives do not activate the enol silanes. Instead, they serve as bases to promote the cyclometalation to generate the active Ir catalyst. The carbonate anion, which was generated from the oxidative addition of the allylic carbonate, likely activates the enol silanes to trigger their activity as nucleophiles for reactions with the allyliridium electrophile. The synthetic utility of this method was illustrated by the synthesis of the *anti*-muscarinic drug, fesoterodine.

Graphical abstract



Introduction

Danishefsky's diene[1] and Rawal's diene[2] are widely used reagents for Diels–Alder and hetero-Diels–Alder reactions to synthesize carbocycles as well as oxygen- and nitrogen-containing heterocycles.[3] Although both dienes contain an enol silane unit that could undergo nucleophilic substitution reactions, they have rarely been used as nucleophiles for reactions besides [4 + 2] cycloadditions[4] and have not been used as nucleophiles for asymmetric allylic substitutions. Ir-catalyzed asymmetric allylations of these nucleophiles (Figure 1) would be valuable because the reaction creates a stereocenter β to the carbonyl

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Supporting Information: The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09980.

Notes: The authors declare no competing financial interest.

group, and the vinylogous ester or amide moiety in the resulting products can undergo a variety of subsequent transformations.[5,6]

Iridium-catalyzed allylic substitution[7–10] of such enol silanes would be unusual because the vast majority of prior iridium-catalyzed allylations of enolates have been conducted with stabilized enolates containing two electron-withdrawing groups on the nucleophilic carbon.[11,12] The reactions of unstabilized enolates are much less developed and have been limited in the scope of electrophile.[13] In particular, reactions of aliphatic, unstabilized enolates with aliphatic allylic esters occurred in modest yield and enantioselectivity.[13b] Moreover, the enolates of esters and amides have not undergone iridium-catalyzed allylic substitution; therefore, it was unclear if reactions of the enol silanes of vinylogous esters and amides would react like the enol silanes of α,β-unsaturated ketones that undergo iridium-catalyzed allylation or like the enol silanes of esters and amides that have, so far, given low yields of substitution products. In addition, such transformations with these nucleophiles are challenging because the product generated from the allylic substitution with these dienes contains a vinylogous ester or amide unit that could further react with the enol silanes via an addition–elimination reaction sequence to give oligomeric or polymeric products.

We report conditions by which Ir-catalyzed enantioselective allylic substitution reactions occur with unstabilized enolates derived from vinylogous esters and amides (Danishefsky's diene and Rawal's diene, Figure 1). In the presence of $[Ir(cod)Cl]_2$, the phosphoramidite (R_a,R_C,R_C)-**L** in Figure 1, KF, and 18-crown-6, these reactions proceeded smoothly to give allylated products in good yields with high enantioselectivities and excellent branched-to-linear selectivities. Mechanistic studies revealed that KF does not activate the enol silanes toward the allylic substitution. Instead, it serves as a base to promote the cyclometalation to generate the active Ir catalyst. The carbonate anion, which was generated from the oxidative addition of the allylic carbonate, appears to activate the enol silane to trigger the subsequent allylic substitution. The synthetic utility of this method was illustrated by the synthesis of the anti-muscarinic drug, fesoterodine.

Results and Discussion

Reaction Development

We began our studies by investigating suitable reaction conditions for the asymmetric allylic substitution of methyl cinnamyl carbonate (**1a**) with Danishefsky's diene (**2**). Fluoride additives can promote the α-arylation of silyl ketene acetals and α-silyl nitriles, as well as the asymmetric allylation of enol silanes derived from ketones.[13a,14] Therefore, we evaluated several fluoride salts as the additive for the reaction of **1a** with **2**. As shown in entry 1, Table 1, treatment of cinnamyl carbonate **1a** (1 equiv) and silane **2** (2 equiv) with 2 mol % $[Ir(cod)Cl]_2$ and 4 mol % of the phosphoramidite (R_a,R_C,R_C)-**L** shown in Figure 1 in the presence of CsF (1 equiv) gave product **4a** in 20% yield. The reaction did not provide any product **4a** with other fluoride salts, such as KF or ZnF_2 (entries 2–3, Table 1). When the reaction was conducted in the presence of soluble fluoride salts, such as TASF [tris(dimethylamino)sulfonium difluorotrime-thylsilicate] or TBAT (tetrabutylammonium triphenyldifluor-osilicate), only decomposition of the starting materials was observed (entries 4–5, Table 1). The reaction with the combination of CsF (1 equiv) and 18-crown-6

(1 equiv) as the additives also led to the decomposition of the starting materials (entry 6, Table 1). However, the reaction with KF (1 equiv) and 18-crown-6 (1 equiv) as additives provided product **4a** in 81% yield and 94% enantiomeric excess (ee) (entry 7, Table 1). Reactions with catalytic amounts of KF and with alternative basic additives will be discussed later in this paper.

Table 2 summarizes the scope of allylic carbonates **1** that undergo the asymmetric allylation with enol silane **2** under the developed conditions. Allylic substitution of silane **2** with a variety of substituted cinnamyl carbonates gave the allylation products **4a–i** in good yields with high enantioselectivities. Allylic carbonates containing heterocycles were tolerated under the reaction conditions. For example, reactions of the allylic carbonates substituted with a furyl, pyridyl, or indolyl group gave products **4j–l**, respectively, in 67–78% yield. Alkenyl- and alkyl-substituted allylic carbonates also reacted to provide allylated products **4m–n**, respectively, in 75–79% yield. In all cases, the allylated products were obtained with ≥90% ee and >20:1 branched-to-linear selectivity. The absolute configuration of the allylation product **4f** was determined by single-crystal X-ray diffraction.

Allylic substitutions with enol silane **3** (Rawal's diene) derived from the vinylogous amide were also explored, and the results are summarized in Table 3. In general, the reactions occurred with a wide range of allylic carbonates, including cinnamyl carbonates containing diverse electronic properties on the aryl ring, heteroaryl-substituted allylic carbonates, alkenyl-substituted allylic carbonates, and alkyl-substituted allylic carbonates. These reactions gave allylated products **5a–o** in 63–83% yield with 91–98% ee and >20:1 branched-to-linear selectivity (Table 3). Even the reaction of crotyl carbonate gave the allylation product in good yield with high branched-to-linear ratio and high enantioselectivity.

Sequential Pd-Catalyzed Isomerization and Ir-Cata-lyzed Asymmetric Allylic Substitutions

Ir-catalyzed asymmetric allylic substitutions of racemic, branched allylic esters (e.g., **6**) are valuable transformations because these branched substrates are readily accessible from commercially available materials. However, Ir-catalyzed reactions of racemic, branched allylic esters often occur with low enantioselectivities because the process occurs with retention of configuration.[11i,15] To overcome this limitation, a sequential catalytic isomerization and asymmetric allylic substitution process was previously developed to convert racemic, branched allylic carbonates to allylated products with high enantiomeric excess.[16] To evaluate whether this reaction sequence could be applicable to the asymmetric allylation with nucleophiles **2** and **3**, a series of reactions with racemic, branched carbonates **6** were performed. The results are summarized in Table 4.

The isomerization reactions of branched cinnamyl carbonates **6** were conducted in the presence of 1 mol % of $Pd(dba)_2$ and 2 mol % PPh_3. Typically, the process was complete within 1–4 h, based on ^1H NMR analysis of the crude reaction mixture. After isomerization, the reaction mixture was filtered through silica, and the resulting crude linear carbonate in THF was subjected to the Ir-catalyzed allylic substitution with silanes **2** or **3** under the standard reaction conditions. This reaction sequence provided the allylated products **4** and **5**

in 65–79% yield and 91–93% ee. Using this reaction sequence, racemic, branched cinnamyl carbonates **6** were effectively converted to enantioen-riched products **4** and **5**.

Mechanistic Studies: Investigation of the Role of the Additives

To probe the effect of KF and 18-crown-6 on the Ir-catalyzed enantioselective allylation reaction, a series of experiments with methyl cinnamyl carbonate **1a** and enol silane **2** were conducted. As shown in Table 5, the reaction requires the presence of the catalyst and both of the additives. When the catalyst or either additive was absent, the reaction did not provide any of product **4a** (entries 1–5, Table 5). However, reactions conducted with just 0.1 equiv of KF occurred with yields and selectivities that are similar to those of reactions with 1 equiv of KF (entry 6, Table 5). The reaction with catalytic amounts of both KF (0.1 equiv) and 18-crown-6 (0.1 equiv) also afforded the allylated product **4a**, albeit in a slightly lower yield (entry 7, Table 5). Because a stoichiometric amount of KF is not required, it is unlikely that a potassium enolate (derived from KF and enol silane **2**) is the nucleophile in these reactions. This assertion is supported by NMR spectroscopy. The ^{1}H NMR signals of enol silane **2** did not change when silane **2** was treated with 1.0 equiv of KF and 1.0 equiv of 18-crown-6 in d_8-THF at 50 °C for 12 h.

We considered that KF could be facilitating the generation of the metallacyclic catalyst by serving as a base. If so, other bases should be able to replace KF, the base would not be needed in stoichiometric amounts, and a preformed metallacyclic Ir catalyst should be able to catalyze the reaction without any additive. Studies with several different bases in varying amounts are shown in Table 5. These studies showed that the allylic substitution with 0.1 equiv of KOMe and either 1.0 equiv or 0.1 equiv of 18-crown-6 provided allylated product **4a** in 43–49% yield (entries 8–9, Table 5). A significant amount of cinnamyl alcohol was also isolated from these reactions. When 4 mol % of KOMe and 0.1 equiv of 18-crown-6 were used, the amount of cinnamyl alcohol byproduct decreased to 11% (entry 10, Table 5). The formation of cinnamyl alcohol was completely suppressed by utilizing the *t*-butyl cinnamyl carbonate as the electrophile, affording product **4a** in 83% yield (entry 11, Table 5).[17]

Finally, the reaction catalyzed by the preformed metallacyclic Ir catalyst **7** was performed. The reaction of **1a** and **3** catalyzed by 4 mol % of the Ir–ethylene complex **7** in the absence of other additives formed the allylation product **5a** in 62% yield and 93% ee (Scheme 1). On the basis of these data, we conclude that KF, KOMe, and KO*t*-Bu serve as bases to promote the formation of the metallacyclic Ir catalyst, not as Lewis base to bind and activate the enol silanes.

Stoichiometric Reactions of Ir–Allyl Complexes

To gain further insight into the mechanism of the reaction, Ir–allyl complex **8** was synthesized,[8e,f] and stoichiometric reactions of complex **8** with enol silane **2** were performed (Table 6). As expected, the stoichiometric reaction did not occur in the absence of the added KF (entry 1, Table 6). However, the reaction also did not form the allylation product **4a** when the stoichiometric reaction was conducted in the presence of 1 equiv of KF and 1

equiv of 18-crown-6 for 12 h at 50 °C (entry 2, Table 6). This result is consistent with the conclusion that KF does not serve to activate enol silane **2** in the allylation reaction.

We hypothesized that the carbonate anion (generated from the oxidative addition of the allylic carbonate in the catalytic reaction) activates enol silane **2**. To probe this hypothesis, stoichiometric reactions of Ir-complex **8** and enol silane **2** in the presence of 1 equiv of Bu_4NOAc as the additive were performed.[18] This system led to complete decay of the ^1H NMR signals corresponding to allyl complex **8** after 30 min at ambient temperature and formed a 1:0.3:1 mixture of the silyl ether of allylated product **9**, allylated product **4a**, and cinnamyl acetate **10** (entry 3, Table 6). The same reaction conducted for 18 h formed a 1:0.4 mixture of **9** and **4a** (entry 4, Table 6). The reaction conducted in the presence of 1.0 equiv of KF, 18-crown-6, and Bu_4NOAc gave a 1:0.5:1 mixture of **9, 4a**, and **10** (entry 5, Table 6). After 12 h at ambient temperature, **4a** became the major component of the reaction mixture (entry 6, Table 6). Product **4a** was isolated in 78% yield, with >20:1 branched-to-linear selectivity and 92% ee. These values are similar to those of the catalytic reaction shown in Table 2, and are consistent with our hypothesis that the carbonate anion activates enol silane **2** for the subsequent addition to the allyliridium intermediate.

Resting State of the Catalyst in the Catalytic Reaction with the Catalyst Generated In Situ

To identify the resting state of the catalyst in these allylation processes, we monitored by ^{31}P NMR spectroscopy the reaction catalyzed by the system generated in situ from $[Ir(cod)Cl]_2$, (R_a,R_C,R_C)-**L**, KF, and 18-crown-6. The ^{31}P spectra were recorded after 10 min, 1 h, 2 h, and 12 h at 50 °C. The ^{31}P NMR spectra of this reaction indicated that the major iridium complex in solution is complex **A** (δ 115.6 ppm), which is catalytically inactive (Scheme 2). In the presence of a base, cyclometalated Ir-complex **B**, which is the active catalyst for the allylic substitution, is generated. However, complex **B** was not present in amounts detectable by ^{31}P spectroscopy. These data suggest that the equilibrium between the combination of acyclic complex **A** and KF and the combination of cyclometalated complex **B**, KCl, and HF lies to the side of complex **A**. Only a small amount of the active catalyst, complex **B**, is generated.

These data also suggest that the rate of the reaction with a cyclometalated Ir-complex, such as **7** in Scheme 1, should be significantly faster than the rate of the reaction with the catalyst generated in situ. Indeed, when the reaction was conducted with 4 mol % Ir–ethylene complex **7** as the catalyst, product **5a** was obtained in 75% yield with 93% ee at ambient temperature after 24 h. In contrast, the reaction with the catalyst generated in situ provided the product in <5% yield at ambient temperature after 24 h (Scheme 2).

To evaluate the generality of reactions with the cyclometalated Ir–ethylene complex **7** as the catalyst, reactions of several allylic carbonates were conducted, and the results are summarized in Table 7. Reactions with electron-rich or electron-neutral cinnamyl carbonates were complete in 24 h at ambient temperature (entries 1–3, Table 7). The rates of the reactions with less-reactive substrates, such as electron-poor or alkyl-substituted allylic carbonates, were slower at ambient temperature (entries 4–6, Table 7) but occurred to completion in 12 h at 40 °C. In general, the yield and enantioselectivity of the products

obtained from the reactions catalyzed by the cyclometalated Ir–ethylene complex **7** were comparable to those with the catalyst generated in situ. It has been shown that allylic substitution of 2-methoxy cinnamyl carbonate gave products with moderate enantioselectivity.[13b] Under the reaction conditions described in Table 3, the allylation of 2-methoxy cinnamyl carbonate with silane **3** provided product **5p** in 76% yield with 80% ee. In contrast, when the reaction was conducted at ambient temperature with the cyclometalated Ir–ethylene complex **7** as the catalyst, product **5p** was obtained in 87% yield with 87% ee. The high reactivity of complex **7** allowed the reaction to be run at 0 °C, and at this temperature, the enantiomeric excess of product **5p** improved to 89% ee (entry 7, Table 7).

Reactions with Substoichiometric Alkoxide Activator

To assess the generality of the reactions with either KOMe/18-crown-6 or Bu_4NOAc as the additive, a set of reactions of several allylic carbonates with enol silanes **2** and **3** were conducted, and the results are summarized in Tables 8 and 9. In general, allylic substitution of enol silanes **2** and **3** proceeded smoothly with either KOMe/18-crown-6 or Bu_4NOAc as the additive. The allylated products were obtained in yields, enantioselectivities, and branched-to-linear selectivities that were comparable to those obtained from the reactions conducted with KF and 18-crown-6 as the additive.

Synthetic Applications of the Allylation of Danishef-sky and Rawal Dienes

Enantioenriched 1,1-diarylalkanes are present in many biologically active natural products and pharmaceutical agents,[19] such as methoxydalbergione and mimosifoliol as well as Toviaz, Detrol LA, and Zoloft (Figure 2).[20] Because of the importance of enantioenriched 1,1-diarylalkanes in the synthesis of natural products and pharmaceutical candidates, significant effort has been devoted to the development of enantioselective methods to access these molecules.[21]

Fesoterodine and tolterodine are antimuscarinic drugs that contain an enantioenriched 1,1-diarylalkane structural motif (Figure 2). Many routes have been developed for the synthesis of tolterodine,[20] In contrast, approaches to its closely related analogue, fesoterodine, the active ingredient of Toviaz, are limited.[22,23] The enantioenriched 1,1-diarylalkane structural motif in tolterodine has been synthesized by several different asymmetric transformations, including Rh-catalyzed asymmetric addition of arylboronic acids to coumarins and Pd-catalyzed asymmetric cross coupling of aryl halides with alkyl boronates. These reactions are conducted with commercially available arylboronic acids and aryl halides.[20]

However, these methods do not translate to the synthesis of fesoterodine because the synthesis of this compound requires a polysubstituted aryl nucleophile or a polysubstituted electrophile that is not commercially available. Therefore, a multistep preparation of the requisite polysubstituted aryl halides or arylboronic acids would be required. In fact, almost all the routes to prepare enantioenriched fesoterodine rely on kinetic resolution of a racemic intermediate.[22,23]

We envisioned an alternative strategy to construct the enantioenriched 1,1-diarylalkane motif in fesoterodine that would be enabled by the iridium-catalyzed allylic substitution developed in the current study. The substituted aryl group would be formed by a [4 + 2] cycloaddition between a dienophile (e.g., ethyl propiolate) and a diene (e.g., **12**), which would be derived from compound **5**, a product of asymmetric allylic substitution with a Rawal diene as nucleophile (Scheme 3). The enantiomeric excess of compound **5** would translate to that of the 1,1-diarylalkane cycloaddition adduct.

The synthesis of fesoterodine by this strategy is shown in Scheme 3. The vinylogous amide **5a** was prepared according to the procedure described in Table 3. Compound **5a** was then converted into diene **12** with NaHMDS and TBSCl.[2] [4 + 2] Cycloaddition of diene **12** and ethyl propiolate at 50 °C in toluene provided 1,1-diarylalkane **13** in 77% yield from **5a**. DIBAL reduction of the ethyl ester of **13** gave alcohol **14**, which was then protected as the bis-TBS ether **15**. Hydro-boration and oxidation of **15**, followed by Dess–Martin oxidation[24] of the resulting primary alcohol, afforded aldehyde **16** in 77% yield over two steps. Reductive amination[25] of aldehyde **16** with diisopropyl amine and $NaBH(OAc)_3$, followed by deprotection of the two *tert*-butyldimethylsilyl (TBS) groups with tetrabutylammonium fluoride (TBAF), provided amine **17** in 76% yield. Amine **17** can be converted to fesoterodine in one step by a procedure reported by Dirat and co-workers.[22]

Conclusion

In conclusion, we have developed the Ir-catalyzed enantioselective allylic substitution of enol silanes derived from vinylogous esters and amides. Asymmetric allylation of a wide variety of allylic carbonates with silanes **2** or **3** gave vinylogous esters **4** or amides **5** in good yields with high enantioselectivities and excellent branched-to-linear selectivities. Subsequent studies revealed that the additive KF does not bind to the enol silanes and activate them for addition to the allyl intermediate. Instead, KF promotes cyclometalation to generate the active iridacyclic catalyst. The carbonate anion, which was generated from the oxidative addition of the allylic carbonate to the iridacycle, serves as the activator of the enol silanes to trigger the subsequent nucleophilic addition.[26] This conclusion allowed the development of reaction conditions for the asymmetric allylation with enol silanes **2** and **3** in the presence of acetate or alkoxide bases. The synthetic utility of this reaction was demonstrated by the enantioselective synthesis of fesoterodine through a [4 + 2] cycloaddition approach for the synthesis of the enantioenriched 1,1-diarylalkane. Further studies with these nucleophiles are currently underway in this laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support provided by the National Institutes of Health (GM-58108) is gratefully acknowledged. We thank Johnson-Matthey for gifts of $[Ir(cod)Cl]_2$. M.C. thanks Dr. Wenyong Chen for helpful discussions.

References

1. Danishefsky SJ, Kitahara T. J Am Chem Soc. 1974; 96:7807.
2. Kozmin SA, Rawal VH. J Org Chem. 1997; 62:5252.
3. (a) Kozmin SA, Green MT, Rawal VH. J Org Chem. 1999; 64:8045.(b) Huang Y, Rawal VH. J Am Chem Soc. 2002; 124:9662. [PubMed: 12175197] (c) Huang Y, Unni AK, Thadani AN, Rawal VH. Nature. 2003; 424:146. [PubMed: 12853945] (d) Unni AK, Takenaka N, Yamamoto H, Rawal VH. J Am Chem Soc. 2005; 127:1336. [PubMed: 15686341] (e) Panarese JD, Waters SP. Org Lett. 2009; 11:5086. [PubMed: 19817392] (f) Zhang Y, Danishefsky SJ. J Am Chem Soc. 2010; 132:9567. [PubMed: 20513158]
4. (a) Acocella MR, De Rosa M, Massa A, Palombi L, Villano R, Scettri A. Tetrahedron. 2005; 61:4091.(b) Attanasi OA, Favi G, Filippone P, Giorgi G, Mantellini F, Moscatelli G, Spinelli D. Org Lett. 2008; 10:1983. [PubMed: 18426219] (c) De Rosa M, Soriente A. Tetrahedron. 2011; 67:5949.
5. Liu Y, Bakshi K, Zavalij P, Doyle MP. Org Lett. 2010; 12:4304. [PubMed: 20809648] (b) Ohtani T, Tsukamoto S, Kanda H, Misawa K, Urakawa Y, Fujimaki T, Imoto M, Takahashi Y, Takahashi D, Toshima K. Org Lett. 2010; 12:5068. [PubMed: 20939604] (c) Guéret SM, Furkert DP, Brimble MA. Org Lett. 2010; 12:5226. [PubMed: 21028788] (d) Hiraoka S, Harada S, Nishida A. J Org Chem. 2010; 75:3871. [PubMed: 20459138] (e) Fujiwara K, Tanaka K, Katagiri Y, Kawai H, Suzuki T. Tetrahedron Lett. 2010; 51:4543.(f) Liu Y, Doyle MP. Org Biomol Chem. 2012; 10:6388. [PubMed: 22733346] (g) Kondratov IS, Dolovanyuk VG, Tolmachova NA, Gerus II, Bergander K, Fröhlich R, Haufe G. Org Biomol Chem. 2012; 10:8778. [PubMed: 22948733] (h) Li B, Widlicka D, Boucher S, Hayward C, Lucas J, Murray JC, O'Neil BT, Pfisterer D, Samp L, VanAlsten J, Xiang YQ, Young J. Org Process Res Dev. 2012; 16:2031.(i) Edwankar RV, Edwankar CR, Namjoshi OA, Deschamps JR, Cook JM. J Nat Prod. 2012; 75:181. [PubMed: 22257244] (j) Arnold DM, LaPorte MG, Anderson SM, Wipf P. Tetrahedron. 2013; 69:7719. [PubMed: 23976798] (k) Desrosiers JN, Kelly CB, Fandrick DR, Nummy L, Campbell SJ, Wei X, Sarvestani M, Lee H, Sienkiewicz A, Sanyal S, Zeng X, Grinberg N, Ma S, Song JJ, Senanayake CH. Org Lett. 2014; 16:1724. [PubMed: 24601851] (l) Wu B, He S, Wu Xd, Pan Yj. Planta Med. 2006; 72:1334. [PubMed: 17022005]
6. Huang P, Zhang R, Liang Y, Dong D. Org Lett. 2012; 14:5196. [PubMed: 23025242] (b) Bezenšek J, Prek B, Grošelj U, Kasunič M, Svete J, Stanovnik B. Tetrahedron. 2012; 68:4719.(c) Mizoguchi H, Oikawa H, Oguri H. Nat Chem. 2014; 6:57. [PubMed: 24345948] (d) Alper P, Azimioara M, Cow C, Mutnick D, Nikulin V, Michellys PY, Wang Z, Reding E, Paliotti M, Li J, Bao D, Zoll J, Kim Y, Zimmerman M, Groessel T, Tuntland T, Joseph SB, McNamara P, Seidel HM, Epple R. Bioorg Med Chem Lett. 2014; 24:2383. [PubMed: 24751443]
7. For recent reviews of Ir-catalyzed asymmetric allylation, see: Helmchen G, Dahnz A, Dubon P, Schelwies M, Weihofen R. Chem Commun. 2007; 675Helmchen G. Iridium Complexes in Organic Synthesis. Oro LA, Claver C. Wiley-VCHWeinheim, Germany2009:211.Hartwig JF, Stanley LM. Acc Chem Res. 2010; 43:1461. [PubMed: 20873839] Hartwig JF, Pouy MJ. Top Organomet Chem. 2011; 34:169.Liu WB, Xia JB, You SL. Top Organomet Chem. 2011; 38:155.Tosatti P, Nelson A, Marsden SP. Org Biomol Chem. 2012; 10:3147. [PubMed: 22407450] . (g) For a review of the use of phosphoramidite ligands in asymmetric catalysis, see: Teichert JF, Feringa BL. Angew Chem Int Ed. 2010; 49:2486.
8. For seminal contributions, see: Takeuchi R, Kashio M. Angew Chem Int Ed Engl. 1997; 36:263.Janssen JP, Helmchen G. Tetrahedron Lett. 1997; 38:8025.Ohmura T, Hartwig JF. J Am Chem Soc. 2002; 124:15164. [PubMed: 12487578] Kiener CA, Shu C, Incarvito C, Hartwig JF. J Am Chem Soc. 2003; 125:14272. [PubMed: 14624564] Madrahimov ST, Markovic D, Hartwig JF. J Am Chem Soc. 2009; 131:7228. [PubMed: 19432473] Madrahimov ST, Hartwig JF. J Am Chem Soc. 2012; 134:8136. [PubMed: 22486270]
9. For selected recent developments, see: Schafroth MA, Sarlah D, Krautwald S, Carreira EM. J Am Chem Soc. 2012; 134:20276. [PubMed: 23193947] Hamilton JY, Sarlah D, Carreira EM. J Am Chem Soc. 2013; 135:994. [PubMed: 23256708] Hamilton JY, Sarlah D, Carreira EM. Angew Chem Int Ed. 2013; 52:7532.Krautwald S, Sarlah D, Schafroth MA, Carreira EM. Science. 2013; 340:1065. [PubMed: 23723229] Hamilton JY, Sarlah D, Carreira EM. J Am Chem Soc. 2014; 136:3006. [PubMed: 24521052] Krautwald S, Schafroth MA, Sarlah D, Carreira EM. J Am Chem Soc. 2014; 136:3020. [PubMed: 24506196] Hamilton JY, Hauser N, Sarlah D, Carreira EM. Angew Chem Int Ed. 2014; 53:10759.Breitler S, Carreira EM. J Am Chem Soc. 2015; 137:5296. [PubMed:

25848936] . (i) For a recent application of Ir-catalyzed polyene cyclization in natural product synthesis, see: Deng J, Zhou S, Zhang W, Li J, Li R, Li A. J Am Chem Soc. 2014; 136:8185. [PubMed: 24866502]

10. (a) Chen W, Hartwig JF. J Am Chem Soc. 2012; 134:15249. [PubMed: 22954355] (b) Chen W, Hartwig JF. J Am Chem Soc. 2013; 135:2068. [PubMed: 23286279] (c) Chen W, Hartwig JF. J Am Chem Soc. 2014; 136:377. [PubMed: 24295427] (d) Chen W, Chen M, Hartwig JF. J Am Chem Soc. 2014; 136:15825. [PubMed: 25337972] (e) Chen M, Hartwig JF. Angew Chem Int Ed. 2014; 53:8691.(f) Chen M, Hartwig JF. Angew Chem Int Ed. 2014; 53:12172.
11. (a) Kanayama T, Yoshida K, Miyabe H, Takemoto Y. Angew Chem Int Ed. 2003; 42:2054.(b) Kanayama T, Yoshida K, Miyabe H, Kimachi T, Takemoto Y. J Org Chem. 2003; 68:6197. [PubMed: 12895050] (c) Bartels B, Garcia-Yebra C, Helmchen G. Eur J Org Chem. 2003; 2003:1097.(d) Schelwies M, Dübon P, Helmchen G. Angew Chem Int Ed. 2006; 45:2466.(e) Dahnz A, Helmchen G. Synlett. 2006:0697.(f) Gnamm C, Förster S, Miller N, Brödner K, Helmchen G. Synlett. 2007; 2007:0790.(g) Förster S, Tverskoy O, Helmchen G. Synlett. 2008; 2008:2803.(h) Dübon P, Schelwies M, Helmchen G. Chem - Eur J. 2008; 14:6722. [PubMed: 18576413] (i) Polet D, Alexakis A, Tissot-Croset K, Corminboeuf C, Ditrich K. Chem - Eur J. 2006; 12:3596. [PubMed: 16453353] (j) Polet D, Rathgeb X, Falciola CA, Langlois JB, ElHajjaji HS, Alexakis A. Chem - Eur J. 2009; 15:1205. [PubMed: 19072966]
12. (a) Wu QF, He H, Liu WB, You SL. J Am Chem Soc. 2010; 132:11418. [PubMed: 20677752] (b) Ye KY, He H, Liu WB, Dai LX, Helmchen G, You SL. J Am Chem Soc. 2011; 133:19006. [PubMed: 21995503] (c) Wu QF, Liu WB, Zhuo CX, Rong ZQ, Ye KY, You SL. Angew Chem Int Ed. 2011; 50:4455.(d) Liu WB, Zheng C, Zhuo CX, Dai LX, You SL. J Am Chem Soc. 2012; 134:4812. [PubMed: 22309279] (e) Wu QF, Zheng C, You SL. Angew Chem Int Ed. 2012; 51:1680.(f) Zhuo CX, Liu WB, Wu QF, You SL. Chem Sci. 2012; 3:205.(g) Zhuo CX, Wu QF, Zhao Q, Xu QL, You SL. J Am Chem Soc. 2013; 135:8169. [PubMed: 23672506] (h) Xu QL, Dai LX, You SL. Chem Sci. 2013; 4:97.(i) Zhuo CX, Wu QF, Zhao Q, Xu QL, You SL. J Am Chem Soc. 2013; 135:8169. [PubMed: 23672506] (j) Zhang X, Han L, You SL. Chem Sci. 2014; 5:1059. (k) Yang ZP, Wu QF, You SL. Angew Chem Int Ed. 2014; 53:6986.(l) Liu WB, Reeves CM, Virgil SC, Stoltz BM. J Am Chem Soc. 2013; 135:10626. [PubMed: 23829704] (m) Liu WB, Reeves CM, Stoltz BM. J Am Chem Soc. 2013; 135:17298. [PubMed: 24160327]
13. (a) Graening T, Hartwig JF. J Am Chem Soc. 2005; 127:17192. [PubMed: 16332060] (b) Weix DJ, Hartwig JF. J Am Chem Soc. 2007; 129:7720. [PubMed: 17542586] (c) He H, Zheng XJ, Li Y, Dai LX, You SL. Org Lett. 2007; 9:4339. [PubMed: 17854201]
14. (a) Hama T, Liu X, Culkin DA, Hartwig JF. J Am Chem Soc. 2003; 125:11176. [PubMed: 16220921] (b) Liu X, Hartwig JF. J Am Chem Soc. 2004; 126:5182. [PubMed: 15099101] (c) Wu L, Hartwig JF. J Am Chem Soc. 2005; 127:15824. [PubMed: 16277525]
15. Bartels B, Garcia-Yebra C, Rominger F, Helmchen G. Eur J Inorg Chem. 2002; 2002:2569.
16. Shekhar S, Trantow B, Leitner A, Hartwig JF. J Am Chem Soc. 2006; 128:11770. [PubMed: 16953612]
17. Reactions with other alkoxides such as KO*t*-Bu occurred to give product **4a** in 23% yield. Reactions with amine bases such as TBD did not provide any product **4a**.
18. It has been shown that the acetate anion of Bu_4NOAc can serve as the carbonate anion equivalent in allylic substitution reactions; see ref 10a.
19. (a) Eyton WB, Ollis WD, Sutherland IO, Jackman LM, Gottlieb OR, Magalhaes MT. Proc Chem Soc. 1962; 301(b) Eyton WB, Ollis WD, Sutherland IO, Gottlieb OR, Taveira Magalhaes M, Jackman LM. Tetrahedron. 1965; 21:2683.(c) Eyton WB, Ollis WD, Fineberg M, Gottlieb OR, Salignacde Souza Guimaraes I, Taveira Magalhaes M. Tetrahedron. 1965; 21:2697.(d) Donnelly BJ, Donnelly DMX, O'Sullivan AM, Prendergast JP. Tetrahedron. 1969; 25:4409.(e) Li F, Awale S, Tezuka Y, Esumi H, Kadota S. J Nat Prod. 2010; 73:623. [PubMed: 20307087] (f) Fu HZ, Luo YM, Li CJ, Yang JZ, Zhang DM. Org Lett. 2010; 12:656. [PubMed: 20078113] (g) Shao M, Wang Y, Liu Z, Zhang DM, Cao HH, Jiang RW, Fan CL, Zhang XQ, Chen HR, Yao XS, Ye WC. Org Lett. 2010; 12:5040. [PubMed: 20929258] (h) Takahashi M, Suzuki N, Ishikawa T. J Org Chem. 2013; 78:3250. [PubMed: 23496308]
20. For selected references: Lautens M, Rovis T. J Org Chem. 1997; 62:5246.Andersson PG, Schink HE, Österlund K. J Org Chem. 1998; 63:8067.Botteghi C, Corrias T, Marchetti M, Paganelli S,

Piccolo O. Org Process Res Dev. 2002; 6:379.Selenski C, Pettus TRR. J Org Chem. 2004; 69:9196. [PubMed: 15609955] Sörgel S, Tokunaga N, Sasaki K, Okamoto K, Hayashi T. Org Lett. 2008; 10:589. [PubMed: 18217766] Blacker AJ, Brown S, Clique B, Gourlay B, Headley CE, Ingham S, Ritson D, Screen T, Stirling MJ, Taylor D, Thompson G. Org Process Res Dev. 2009; 13:1370.Roesner S, Casatejada JM, Elford TG, Sonawane RP, Aggarwal VK. Org Lett. 2011; 13:5740. [PubMed: 21995597] Barancelli DA, Salles AG Jr, Taylor JG, Correia CRD. Org Lett. 2012; 14:6036. [PubMed: 23190249]

21. For selected references: Imao D, Glasspoole BW, Laberge VS, Crudden CM. J Am Chem Soc. 2009; 131:5024. [PubMed: 19301820] Shi BF, Zhang YH, Lam JK, Wang DH, Yu JQ. J Am Chem Soc. 2010; 132:460. [PubMed: 20017549] Pathak TP, Gligorich KM, Welm BE, Sigman MS. J Am Chem Soc. 2010; 132:7870. [PubMed: 20486685] Luan Y, Schaus SE. J Am Chem Soc. 2012; 134:19965. [PubMed: 23206197] Maity P, Shacklady-McAtee DM, Yap GPA, Sirianni ER, Watson MP. J Am Chem Soc. 2013; 135:280. [PubMed: 23268734] Cheng XF, Li Y, Su YM, Yin F, Wang JY, Sheng J, Vora HU, Wang XS, Yu JQ. J Am Chem Soc. 2013; 135:1236. [PubMed: 23305171] Harris MR, Hanna LE, Greene MA, Moore CE, Jarvo ER. J Am Chem Soc. 2013; 135:3303. [PubMed: 23414579] Zhou Q, Srinivas HD, Dasgupta S, Watson MP. J Am Chem Soc. 2013; 135:3307. [PubMed: 23425080] Do HQ, Chandrashekar ERR, Fu GC. J Am Chem Soc. 2013; 135:16288. [PubMed: 24164502] Sun C, Potter B, Morken J. J Am Chem Soc. 2014; 136:6534. [PubMed: 24564423] Takeda Y, Ikeda Y, Kuroda A, Tanaka S, Minakata S. J Am Chem Soc. 2014; 136:8544. [PubMed: 24870625]
22. Dirat O, Bibb AJ, Burns CM, Checksfield GD, Dillon BR, Field SE, Fussell SJ, Green SP, Mason C, Mathew J, Mathew S, Moses IB, Nikiforov PI, Pettman AJ, Susanne F. Org Process Res Dev. 2011; 15:1010.
23. (a) Desai SJ, Patel KM, Shah AM, Pada RS, Makwana HM. PCT Int Appl. 2011 WO 2011141932 A2. (b) Mantegazza S, Allegrini P, Attolino E. Eur Pat Appl. 2011 EP 2316817 A1. (c) Lorente Bonde-Larsen A, Gallo Nieto FJ, Ferreiro Gil JJ, Martin Pascual P. PCT Int Appl. 2013 WO 2013113946 A2. (d) Piccolo O, Giannini E, Bigini L, Gianolli E, Vigo D. PCT Int Appl. 2014 WO 2014012832 A1.
24. Dess DB, Martin JC. J Am Chem Soc. 1991; 113:7277.
25. Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. J Org Chem. 1996; 61:3849. [PubMed: 11667239]
26. We have conducted studies to investigate the role of KF with the previously reported nucleophiles in refs 10e and 10f. The results are consistent with the conclusion that it serves as a base to promote the formation of active catalyst in allylic substitution, rather than activating the nucleophile.

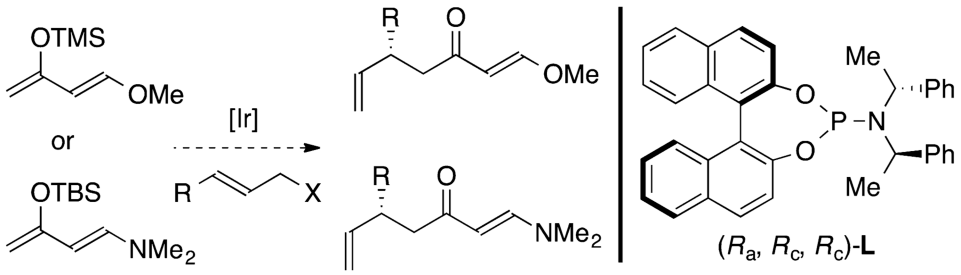


Figure 1.
Proposed Ir-catalyzed enantioselective allylic substitution with Danishefsky's diene and Rawal's diene.

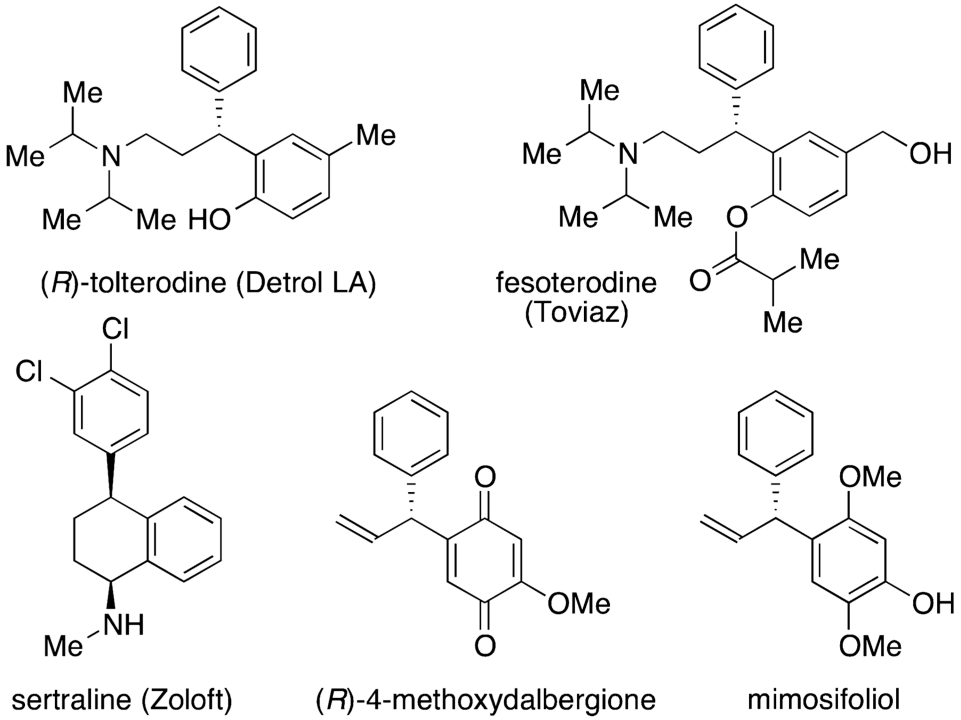
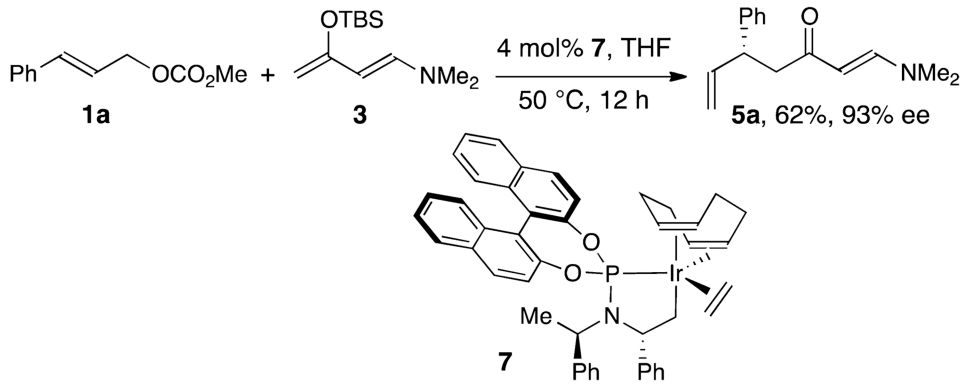
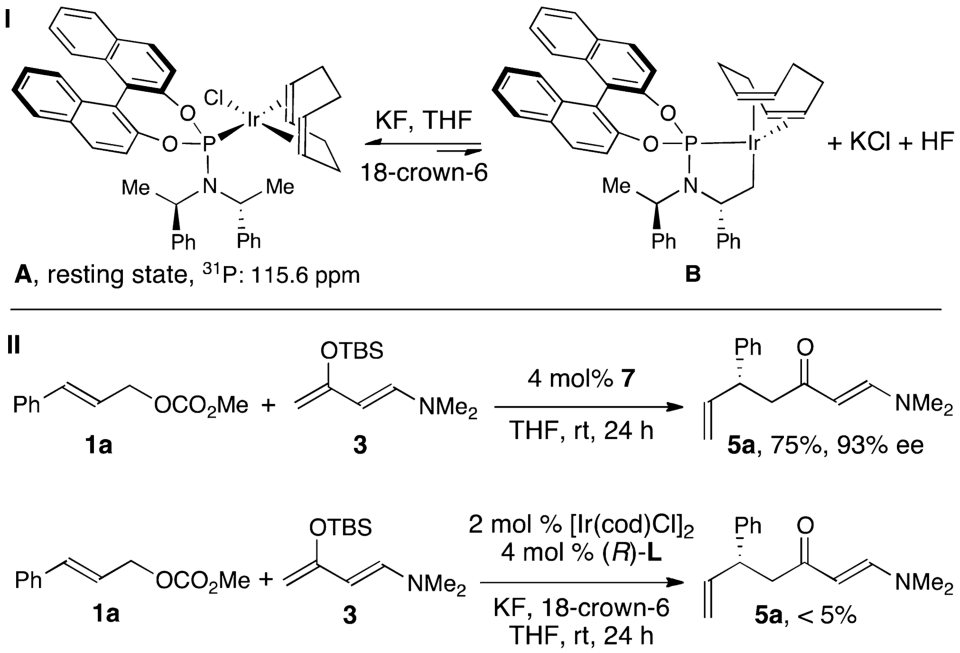


Figure 2.
Representive enantioenriched bisarylalkane containing natural products and pharmaceuticals.



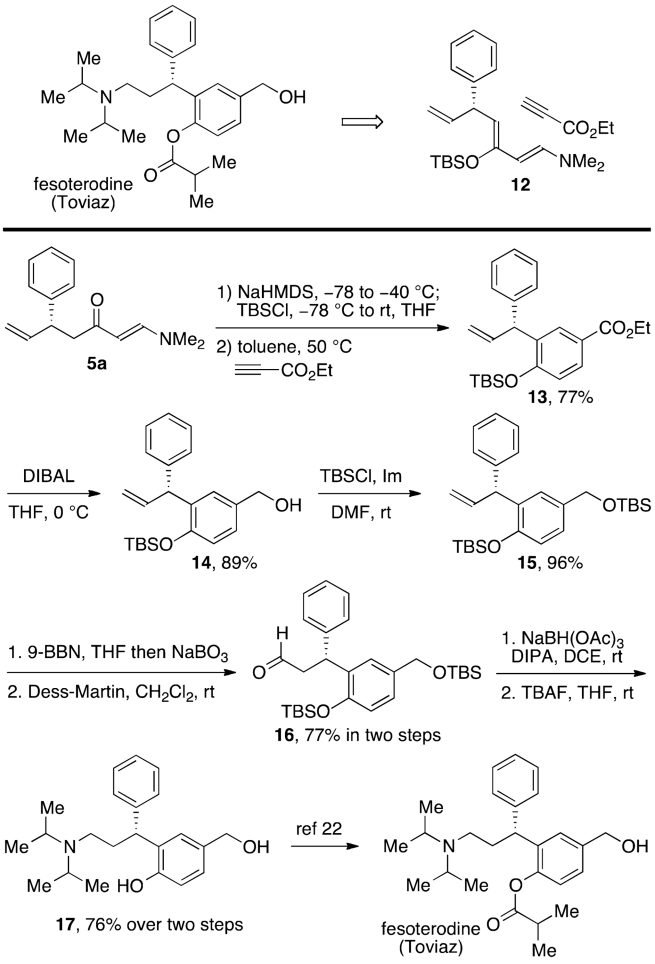
Scheme 1. Allylic Substitution of 1a with Enol Silane 3 in the Presence of the Ir–Ethylene Complex 7 as the Catalyst



Scheme 2. Analysis of the Identity and Reactivity of the Resting State of the Catalytic System[a]

[a](I) Resting state of the reaction with the catalyst generated in situ.

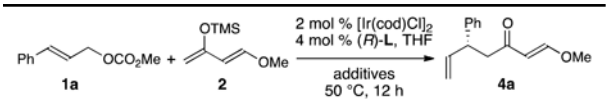
(II) Comparison of the reaction at room temperature catalyzed by the cyclometalated ethylene complex **7** and by the catalyst generated in situ.



Scheme 3. Enantioselective Synthesis of Fesoterodine

Table 1

Evaluation of the Reaction Conditions for the Ir-Catalyzed Enantioselective Allylic Substitution of Cinnamyl Carbonate 1a with Enol Silane 2[a]



entry	additives	yield[b]	% ee[c]
1	1.0 equiv CsF	20%	N.D.
2	1.0 equiv KF	N.R.	N.D.
3	0.5 equiv ZnF_2	N.R.	N.D.
4	1.0 equiv TASF	decomp.	N.D.
5	1.0 equiv TBAT	decomp.	N.D.
6	1.0 equiv CsF, 1.0 equiv 18-crown-6	decomp.	N.D.
7	1.0 equiv KF, 1.0 equiv 18-crown-6	81%	94%

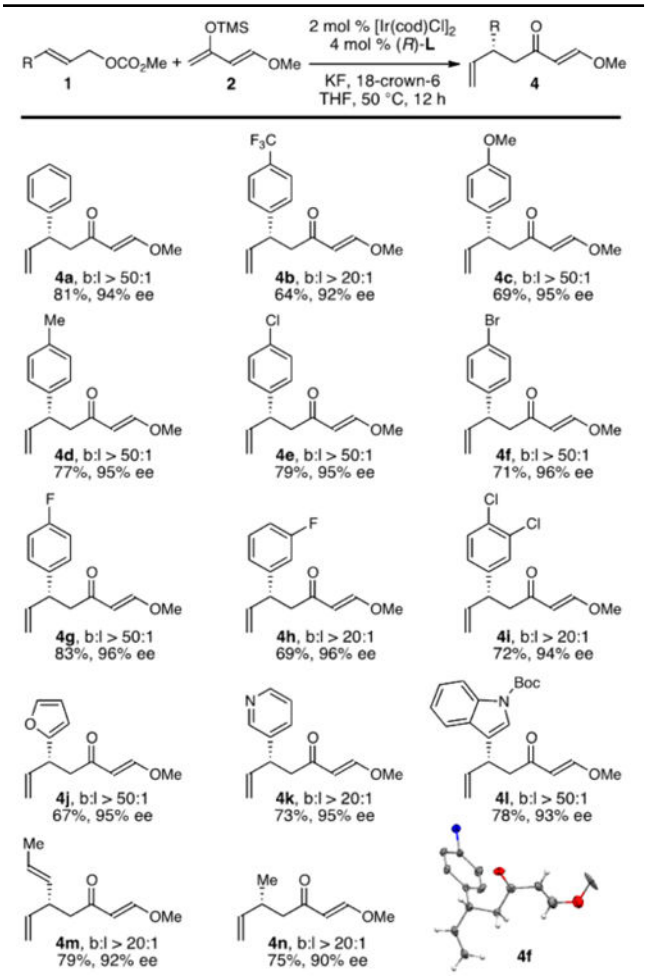
[a] Reaction conditions: cinnamyl carbonate **1a** (0.1 mmol, 1.0 equiv), enol silane **2** (0.2 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), tetrahydrofuran (THF) (0.2 mL), 50 °C, 12 h. TASF, $[(Me_2N)_3S]^+[SiMe_3F_2]^-$; TBAT, $[Bu_4N]^+[SiPh_3F_2]^-$.

[b] Isolated yields of **4a** are listed. N.R., no reaction.

[c] ee % of **4a** was determined by chiral high-performance liquid chromatography (HPLC) analysis. N.D., not determined.

Table 2

Scope of the Ir-Catalyzed Enantioselective Allylic Substitution of Allylic Carbonates 1 with Enol Silane 2[a–d]



[a]Reaction conditions: allylic carbonate **1** (0.2 mmol, 1.0 equiv), enol silane **2** (0.4 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50 °C, 12 h.

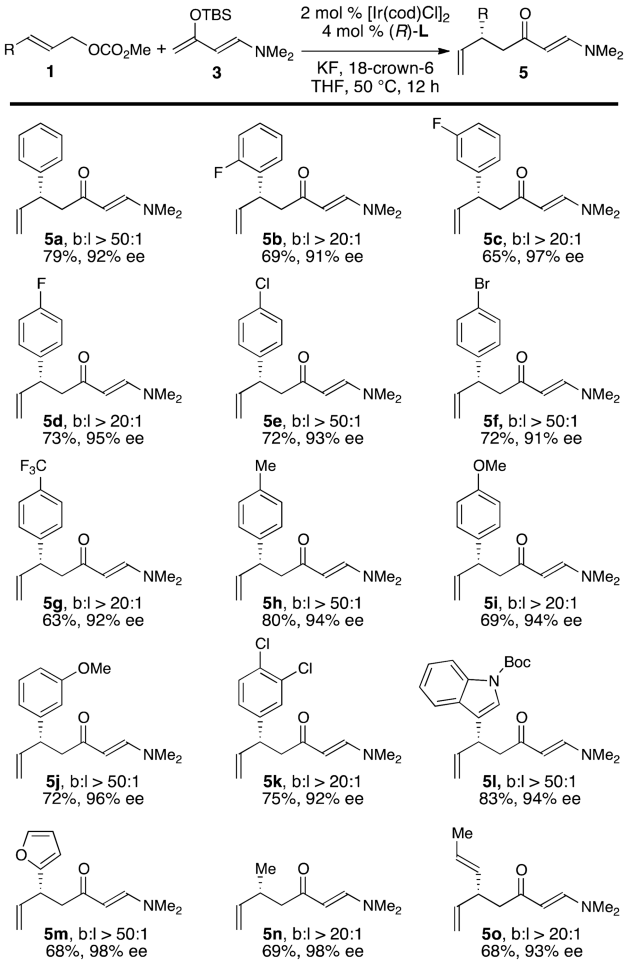
[b]Branched-to-linear ratios (b:l) were determined by ^{1}H NMR analysis of the crude reaction mixtures.

[c]Yields of isolated products are listed (the average of at least two runs).

[d]Enantiose-lectivities were determined by chiral HPLC analysis.

Table 3

Scope of the Ir-Catalyzed Enantioselective Allylic Substitution of Allylic Carbonates 1 with Enol Silane 3[a–d]



[a]Reaction conditions: allylic carbonate **1** (0.2 mmol, 1.0 equiv), enol silane **3** (0.4 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50 °C, 12 h.

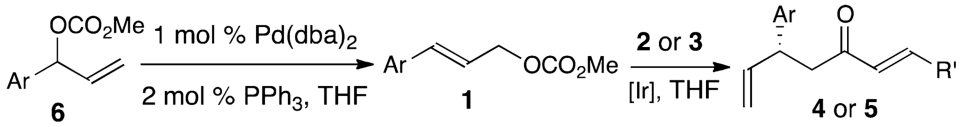
[b]Branched-to-linear product ratios (b:l) were determined by ^{1}H NMR analysis of the crude reaction mixtures.

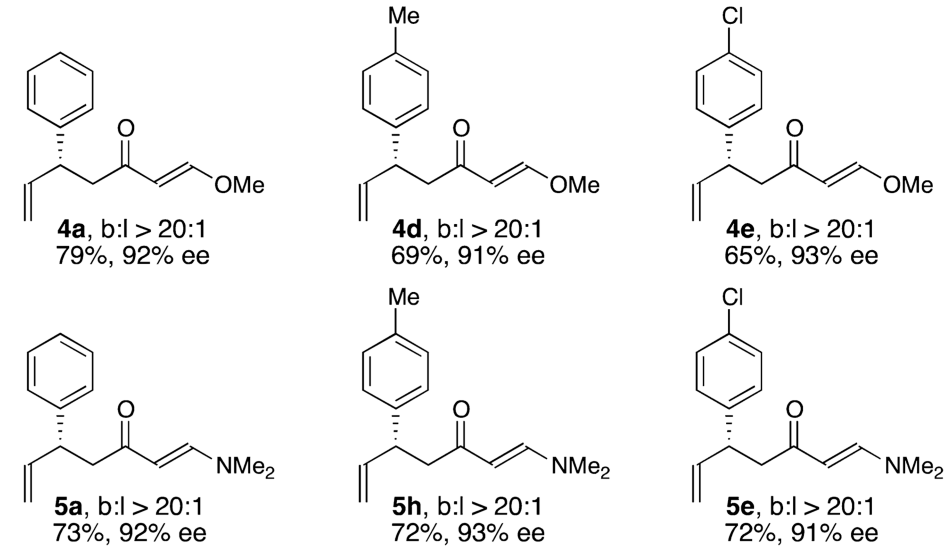
[c]Yields of isolated products are listed (the average of at least two runs).

[d]Enantiose-lectivities were determined by chiral HPLC analysis.

Table 4

Sequential Pd-Catalyzed Isomerization of Branched Allylic Carbonates 6 and Ir-Catalyzed Asymmetric Allylic Substitutions[a]

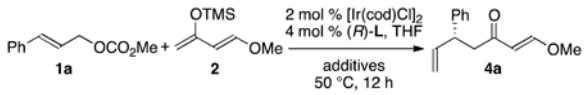




[a]Reaction conditions. Step 1: allylic carbonate **6** (0.4 mmol), $Pd(dba)_2$ (1 mol %), PPh_3 (2 mol %), THF, rt. Step 2: enol silane **2** or **3** (0.8 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), KF (1 equiv), 18-crown-6 (1 equiv), THF (0.8 mL), 50 °C, 12 h.

Table 5

Evaluation of the Effect of Additives on the Ir-Catalyzed Enantioselective Allylic Substitution of Carbonate 1a with Enol Silane 2[a,b]



entry	additives	yield
1	1.0 equiv KF, 1.0 equiv 18-crown-6	81%
2	no additives (no KF and 18-crown-6)	N.R.
3	no catalyst, 1.0 equiv KF, 1.0 equiv 18-crown-6	N.R.
4	1.0 equiv KF, no 18-crown-6	N.R.
5	no KF, 1.0 equiv 18-crown-6	N.R.
6	0.1 equiv KF, 1.0 equiv 18-crown-6	76%
7	0.1 equiv KF, 0.1 equiv 18-crown-6	69%
8	0.1 equiv KOMe, 1.0 equiv 18-crown-6	43%
9	0.1 equiv KOMe, 0.1 equiv 18-crown-6	49%
10	4 mol % KOMe, 0.1 equiv 18-crown-6	69%
11[c]	4 mol % KOMe, 0.1 equiv 18-crown-6	83%
12	0.1 equiv KOt-Bu, 0.1 equiv 18-crown-6	23%

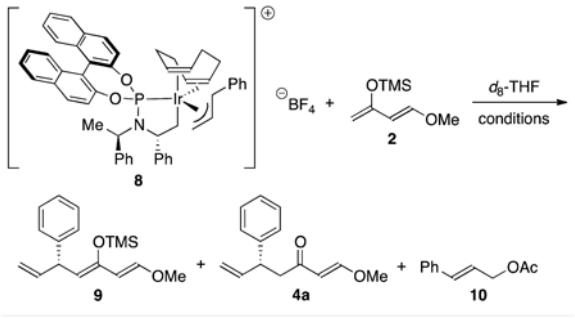
[a] Reaction conditions: cinnamyl carbonate **1a** (0.1 mmol, 1.0 equiv), enol silane **2** (0.2 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), THF (0.2 mL), 50 °C, 12 h.

[b] Isolated yields were listed.

[c] *t*-Butyl cinnamyl carbonate was utilized.

Table 6

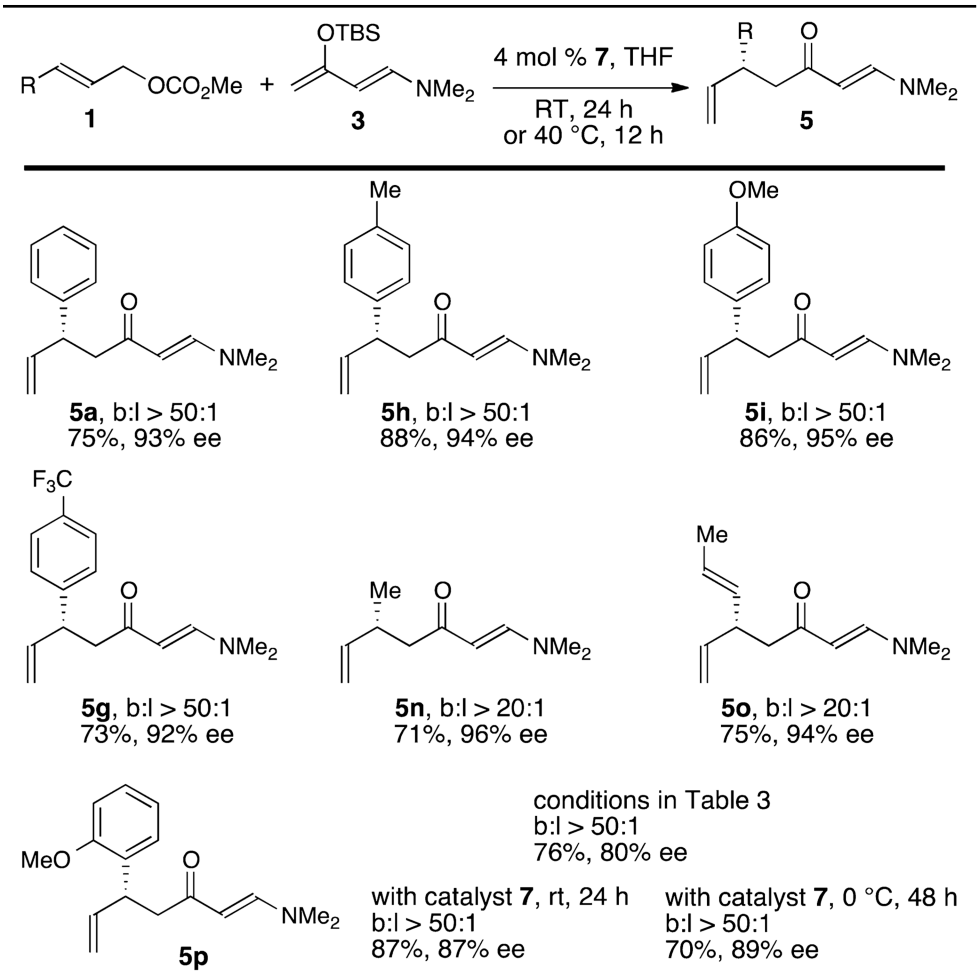
Stoichiometric Reactions of Ir–Allyl Complex 8 with Enol Silane 2



entry	conditions	ratio (9/4a/10)
1	no KF, 1.0 equiv 18-crown-6, 50 °C, 12 h	N.R.
2	1.0 equiv KF, 1.0 equiv 18-crown-6, 50 °C, 12 h	N.R.
3	no KF, no 18-crown-6, 1 equiv Bu_4NOAc, rt, 0.5 h	1:0.3:1
4	no KF, no 18-crown-6, 1 equiv Bu_4NOAc, rt, 18 h	1:0.4:0
5	1.0 eq KF, 1.0 eq 18-crown-6, 1 eq Bu_4NOAc, rt, 0.5 h	1:0.5:1
6	1.0 eq KF, 1.0 eq 18-crown-6, 1 eq Bu_4NOAc, rt, 12 h	0:10:1

Table 7

Enantioselective Allylic Substitution with Ethylene Complex 7 as the Catalyst[a–d]



[a]Reaction conditions: allylic carbonate **1** (0.2 mmol, 1.0 equiv), enol silane **3** (0.4 mmol, 2.0 equiv), **7** (4 mol %), THF (0.4 mL), rt for 24 h or 40 °C for 12 h.

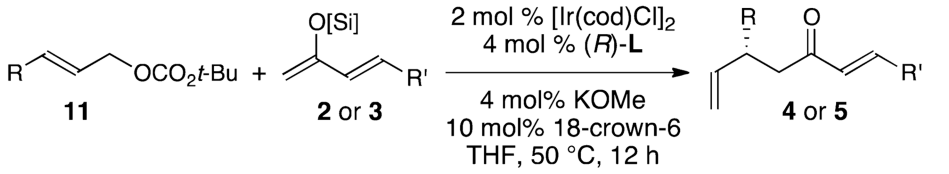
[b]Branched-to-linear product ratios (b:l) were determined by ^{1}H NMR analysis of the crude reaction mixtures.

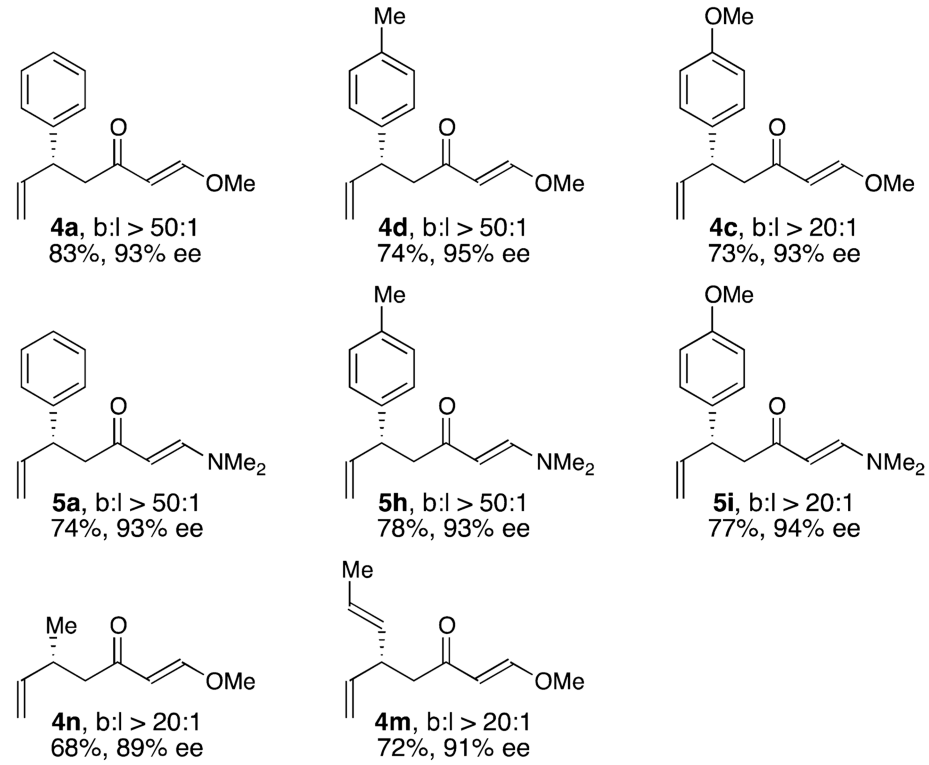
[c]Yields of isolated products are listed.

[d]Enantioselectivities were determined by chiral HPLC analysis.

Table 8

Ir-Catalyzed Enantioselective Allylic Substitution with KOMe and 18-Crown-6 as the Additives[a–e]





[a]Reaction conditions: allylic carbonate **16** (0.2 mmol, 1.0 equiv), enol silane **2** or **3** (0.4 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), KOMe (4 mol %), 18-crown-6 (10 mol %), THF (0.4 mL), 50 °C, 12 h.

[b]Branched-to-linear product ratios (b:l) were determined by ^{1}H NMR analysis of the crude reaction mixtures.

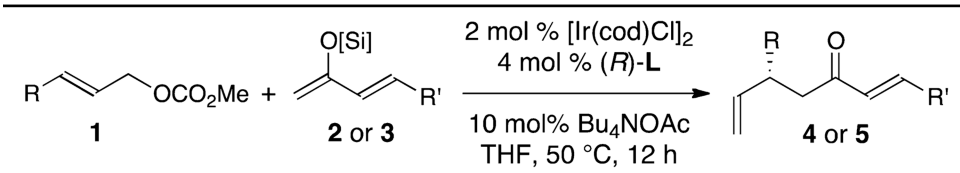
[c]Yields of isolated products are listed.

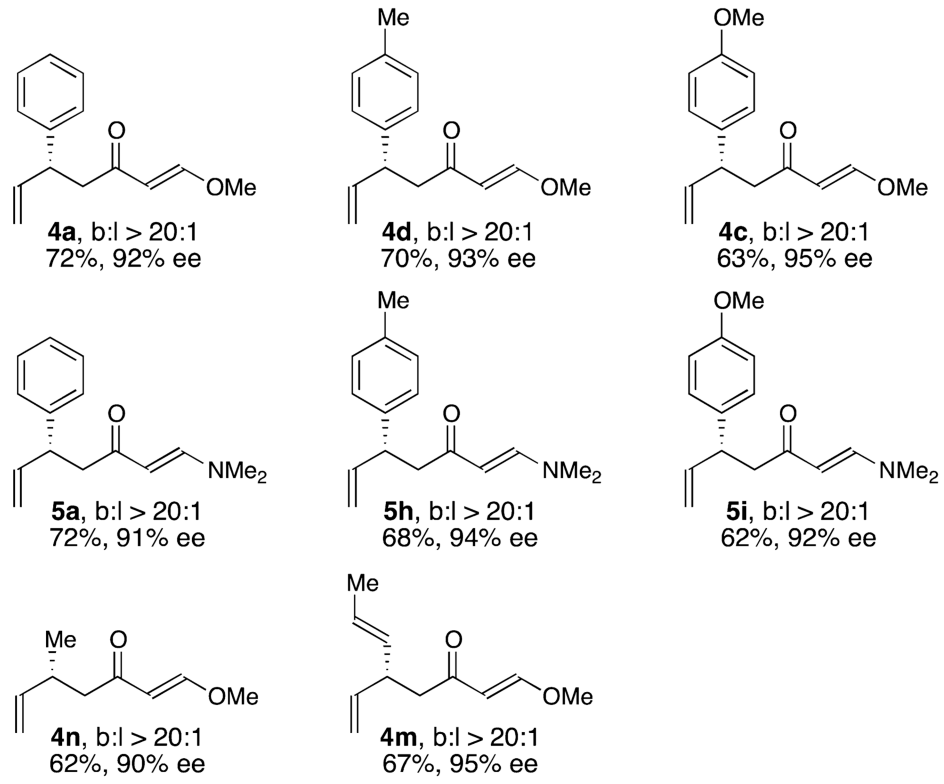
[d]Enantioselectivities were determined by chiral HPLC analysis.

[e]*t*-Butyl allyl carbonates **11** were utilized to suppress the formation of allylic alcohol side products.

Table 9

Ir-Catalyzed Enantioselective Allylic Substitution with Bu_4NOAc as the Additive[a–d]





[a]Reaction conditions: carbonate **1** (0.2 mmol, 1.0 equiv), enol silane **2** or **3** (0.4 mmol, 2.0 equiv), $[Ir(cod)Cl]_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), Bu_4NOAc (10 mol %), THF (0.4 mL), 50 °C, 12 h.

[b]Branched-to-linear product ratios (b:l) were determined by ^1H NMR analysis of the crude reaction mixtures.

[c]Yields of isolated products are listed.

[d]Enantioselectivities were determined by chiral HPLC analysis.