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Iridium-Catalyzed Enantioselective Allylic Substitution of Unstabilized Enolates Derived from α,β-Unsaturated Ketones

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Abstract

We report Ir-catalyzed, enantioselective allylic substitution reactions of unstabilized silyl enolates derived from α,β-unsaturated ketones. Asymmetric allylic substitution of a variety of allylic carbonates with silyl enolates gave allylated products in 62–94% yield with 90–98% ee and >20:1 branched to linear selectivity. The synthetic utility of this method was illustrated by the short synthesis of an *anti*-cancer agent TEI-9826.

Keywords

asymmetric allylic substitution; unstabilized enolates; α, β-unsaturated ketones

The asymmetric alkylation of unstabilized ketone enolates is a long-standing synthetic challenge in organic chemistry.[1] One classic approach involves the SAMP and RAMP[2] chiral auxiliaries; a second, catalytic approach involves Pd-catalyzed decarboxylative allylation.[3] Both of these approaches create products containing a stereocenter α to the carbonyl group. Methods for alkylation of enolates that form products containing a stereogenic center at the β position are challenging, in part, because of the difficulty in conducting nucleophilic substitution at a secondary position. One approach to address this synthetic problem involves Ir-catalyzed asymmetric allylic substitution.[4] In contrast to the regioselectivity of Pd-catalyzed reactions,[5] the Ir-catalyzed allylic substitution occurs at the more substituted position of an allyl electrophile and, therefore, creates a stereocenter at the position β to the carbonyl group in the product.[6, 7]

However, the scope of Ir-catalyzed allylic substitution reactions with unactivated, monocarbonyl enolates is limited. Most of the allylic substitution reactions with carbon nucleophiles have been conducted with stabilized enolates.[8] The majority of reactions with unstabilized ketone enolates have been conducted with derivatives of acetophenone.[9]

α,β-Unsaturated ketones are valuable building blocks in organic synthesis because they contain two functional groups.[1] Most transformations of this class of molecule exploit its electrophilicity. Reactions in which α,β-unsaturated ketones would act as the nucleophile are less common because the enolate can undergo aldol condensation or Michael additions with another α,β-unsaturated ketone. Consistent with this assertion, Ir-catalyzed asymmetric allylic substition has not been reported with enolates derived from α,β-unsaturated ketones. Nevertheless, such a transformation would be valuable because products generated from the allylic substitution of such a reagent contain three functional groups: an electron-deficient alkene, an electron-rich alkene and a carbonyl group. A set of orthogonal reactivities of these functional groups should allow the ketone products to undergo a variety of transformations to generate valuable intermediates.

We describe Ir-catalyzed enantioselective allylic substitution reactions with unstabilized silicon enolates derived from α,βunsaturated ketones that occur in good yields and high enantioselectivities with excellent branched to linear selectivities (Figure 1). The use of KF and 18-crown-6 as the additives is the key to the development of this reaction. Under these conditions, products from competing pathways derived from the electrophilicity of the starting or product ketone were not observed. The utility of this process was illustrated by the syntheses of *syn*- and *anti*-4-methyl-pentan-2-ols and the total synthesis of TEI-9826.

We initiated our studies to identify an appropriate activator for the reactions of methyl cinnamyl carbonate **1a** with silyl enolate **2a** in the presence of [Ir(COD)Cl]$_2$ and the phosphoramidite ligand. Fluoride additives, such as KF, ZnF$_2$ or CsF and ZnF$_2$ have been shown to promote the α-arylation reactions of silyl ketene acetals and α-silyl nitriles, as well as the allylation of acetophenones.[10] Therefore, we evaluated several fluoride salts as the additive for the allylic substitution reactions of **1a** with **2a**. Treatment of carbonate **1a** (1 equiv) and silyl enolate **2a** (2 equiv) with 2 mol % [Ir(COD)Cl]$_2$ and 4 mol % (R_a,R_c,R_c)-**L** in the presence of KF (1 equiv) at 50 °C for 12 h, did not provide any of product **3a** (entry 1, Table 1), and the reaction with ZnF$_2$ as the additive also gave none of product **3a** (entry 2, Table 1). The reaction with CsF (1 equiv) gave the allylated product **3a** in only 16% yield (entry 3, Table 1). Even the reaction with CsF (0.4 equiv) and ZnF$_2$ (1.5 equiv) together provided **3a** in only 25% yield (entry 4, Table 1). We initially suspected that the low solubility of these metal fluoride salts in THF might be responsible for the low reactivity of silyl enolate **2a**.[11] However, the reactions with soluble fluoride salts, such as TASF or TBAT, led to the decomposition of the starting materials (entries 5–6, Table 1).

It is known that crown ethers have high binding affinities for alkali metal ions. We anticipated that the addition of crown ethers and fluoride salts as the additives might be beneficial to the reaction. Although the reaction with CsF (1 equiv) and 18-crown-6 (1 equiv) only led to the decomposition of the starting materials (entry 7, Table 1), the reaction with added KF (1 equiv) and 18-crown-6 (1 equiv) formed the desired product **3a** in 90% yield with 96% ee and >20:1 branched to linear selectivity (entry 8, Table 1).

Table 2 shows the scope of allylic carbonate that undergoes the asymmetric allylation of carbonates **1** with silyl enolate **2a** under the developed conditions (Table 2). In general, allylic substitution of a variety of substituted cinnamyl carbonates with **2a** gave the

allylation products **3a–h** in high yield. Alkenyl- and alkyl-substituted allylic carbonates also reacted to provide the allylated products **3i–j** in good yield. Although heteroaryl-substituted allylic carbonates could potentially bind and thereby deactivate the catalyst, we found that allylic substitution of carbonates containing heteroaryl groups, such as the pyridyl or the furyl group, provided products **3k–l** in 76–83% yield. In all cases, the allylation products were obtained with >90% ee and >20:1 branched to linear selectivities. Detectable amounts of products from diallylation were not formed from these reactions.

Table 3 summarizes the scope of the silyl enolate that undergoes this substitution process. A range of silyl enolate nucleophiles with different substitution patterns at the olefin unit participated in the allylic substitution. These reactions proceeded with 91–97% ee and >20:1 branched to linear selectivities. For example, reactions of allylic carbonates with 4-methoxyphenyl or 2-thienyl-substituted enolates gave the allylation products **4a–f** in 87–94% yield and 94–97% ee. Silyl enolates containing substituents at the α or β position or both also reacted to provide the allylation products **4g–k** in 62–89% yield and 91–96% ee. The silyl enolate derived from β-Ionone also reacted to give product **4l** in 93% yield and 96% ee.

Diastereoselective allylation with chiral, nonracemic nucleophiles in the presence of enantiomerically pure catalysts is a useful approach to prepare products containing multiple stereocenters selectively. However, the inherent bias of substrates may affect the stereochemical outcome of these reactions. To investigate the diastereoselective allylation with enantioenriched nucleophiles, allylic substitution reactions of silyl enol ether **5** were conducted (Scheme 1). Allylation of methyl cinnamyl carbonate **1a** with enolate **5** gave product **7** in 61% yield, although a significant amount of branched methoxy-ether byproduct was obtained (data not shown). However, when *tert*-butyl cinnamyl carbonate **6** was used instead of **1a**, the ether byproduct was not observed. In the presence of [Ir(COD)Cl]$_2$ and (*R*)-L, the reaction of carbonate **6** with enolate **5** gave allylation product **7** in 85% yield, >50:1 diastereoselectivity and >20:1 branched to linear selectivity. When [Ir(COD)Cl]$_2$/(*S*)-L was used, product **8** was obtained in 83% yield with >50:1 diastereoselectivity and >20:1 branched to linear selectivity. The structures of **7** and **8** were confirmed by single crystal X-ray diffraction. These data demonstrated that double stereo-differentiating reactions of enantioenriched nucleophile **5** proceeded with complete catalyst control to give allylation products **7** and **8** with excellent diastereoselectivity.

syn- and *anti*-4-Methyl-pentan-2-ols are common structural motifs in many biologically active natural products.[12] Asymmetric synthesis of these structural subunits, however, has been challenging.[13] These motifs are typically prepared by a multi-step sequence starting with a component of the chiral pool (e.g. Roche ester).[14] We envisioned that diastereoselective reduction of the ketone of the allylation product, such as **3j**, could provide a simple means to synthesize either the *syn*- or *anti*- diastereomer.

As illustrated in Scheme 2, allylic substitution of methyl crotylcarbonate with enolate **10** provided ketone **11** in 81% yield, 95% ee and >20:1 branched selectivity. Reduction of ketone **11** with NaBH$_4$/CeCl$_3$[15] gave a 1:1 mixture of diastereomers **12** and **13**, reflecting a lack of inherent stereochemical bias in the reduction reaction. When reduction of ketone **11**

was conducted with the (*R*)-CBS catalyst,[16] alcohol **12** was obtained in 73% yield and with 11:1 diastereoselectivity; when the reaction was conducted in the presence of the (*S*)-CBS catalyst, diastereomer **13** formed with similar yield and diastereoselectivity (69% yield, 10:1 d.r.). Compound **12** represents the C_2–C_{10} fragment of spongidepsin.

Prostaglandins are important natural products, which have *anti*-inflammatory, antiviral and antitumor activities.[17] Because of their structural features and diverse biological activities, prostaglandins have been the subject of many synthetic studies.[18] As depicted in Scheme 3, a common structural motif in many members in the prostaglandin family is an enantioenriched cyclopentenone unit; therefore, such cyclopentenones are valuable intermediates for the synthesis of prostaglandin natural products.[19, 20] We envisioned that ring-closing metathesis[21] of the products generated from the asymmetric allylic substitution (e.g. **3**) would provide enantioenriched cyclopentenones (e.g. **14**) that could provide the basis for modular syntheses of these prostaglandin natural products.

One member of the prostaglandin family is TEI-9826.[20] Recent studies have shown that, in addition to its neuroprotective activity, TEI-9826 has significant activity against a number of cancer lines, including in vivo activity against *cis*-platin-resistant tumors when it is integrated with a lipid microsphere.[22]

An enantioselective synthesis of TEI-9826 based on asymmetric allylic substitution is summarized in Scheme 3. Starting from silyl enol ether **15** (obtained in one step from commercially available 3-penten-2-one), asymmetric allylic substitution of carbonate **16** with **15** under the standard conditions gave product **17** in 85% yield, 95% ee and 11:1 branched to linear selectivity. Ring-closing metathesis of **17** with 3 mol % of Grubbs' II catalyst **18** provided cyclopentenone **14** in 86% yield.[21] Compound **14** was then converted into TEI-9826 in 73% yield using a three-step sequence: aldol condensation with aldehyde **19**, mesylation of the resulting alcohol, and elimination of the mesylate with neutral Al_2O_3.[23] By this strategy, TEI-9826 was prepared in six steps from commercially available starting materials. This synthesis of TEI-9826 is the shortest one reported to date.

In conclusion, we have developed Ir-catalyzed enantioselective allylic alkylation reactions of unstabilized silyl enolates derived from α,β-unsaturated ketones. By utilizing silyl enolate derivatives of α,β-unsaturated ketones in combination with fluoride and crown ether, we exploit their latent nucleophilicity, while avoiding side reactions that would arise from their inherent electrophilicity. These silyl enolates readily participate in asymmetric allylation to provide enantioenriched products containing a stereogenic center at the position β to the carbonyl group. The products of these reactions contain several functional groups that undergo orthogonal chemical reactions. The synthetic utility of such products was demonstrated by the synthesis of both *syn*- and *anti*-4-methyl-pentan-2-ols, as well as the synthesis of TEI-9826. Further studies of α,β–unsaturated carbonyl compounds are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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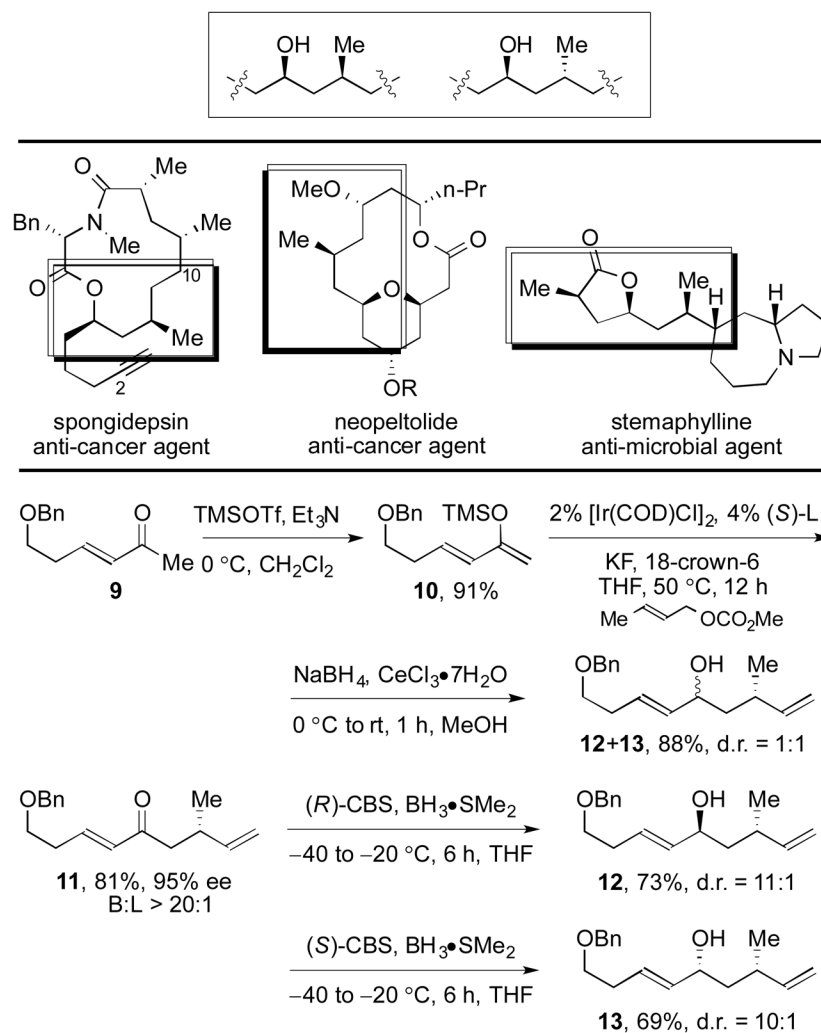23. Kobayashi Y, Murugesh MG, Nakano M, Takahisa E, Usmani SB, Ainai T. J Org Chem. 2002; 67:7110. [PubMed: 12354006]
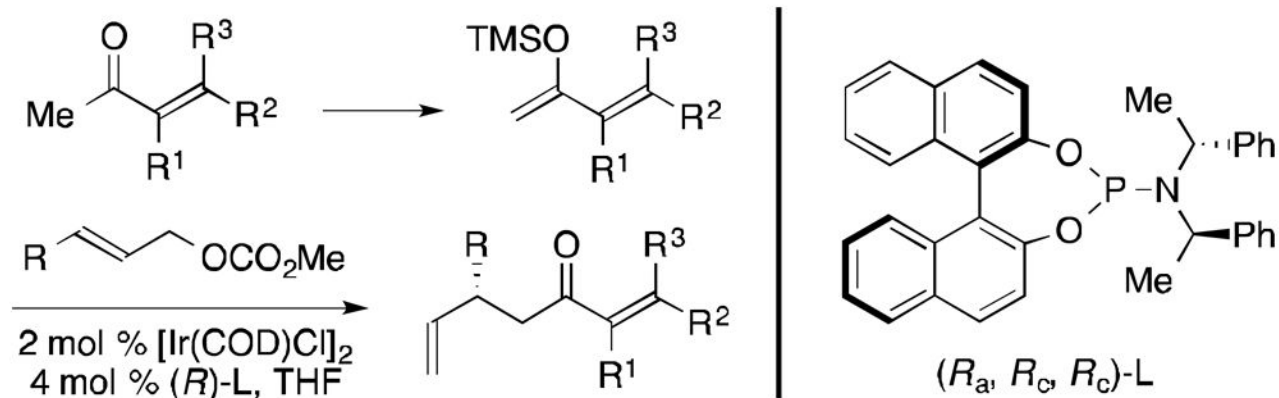
Figure 1.
Ir-Catalyzed Enantioselective Allylic Substitution of Silyl Enolates of α,β-Unsaturated Ketones
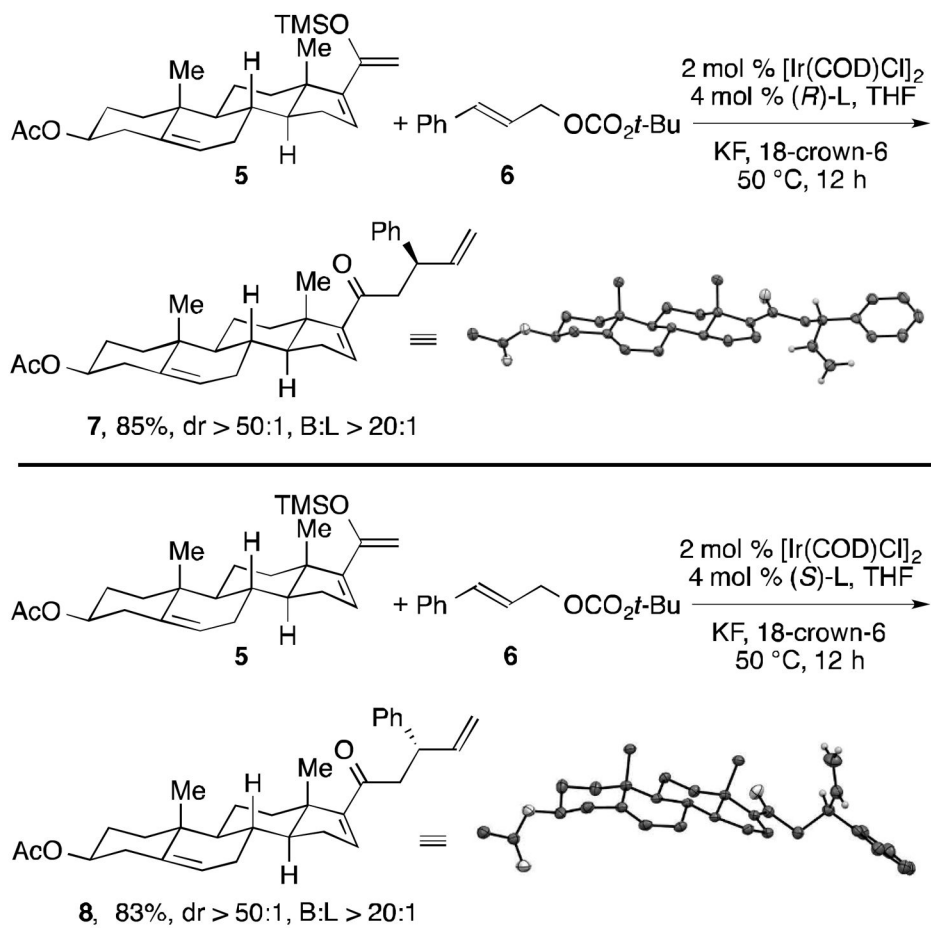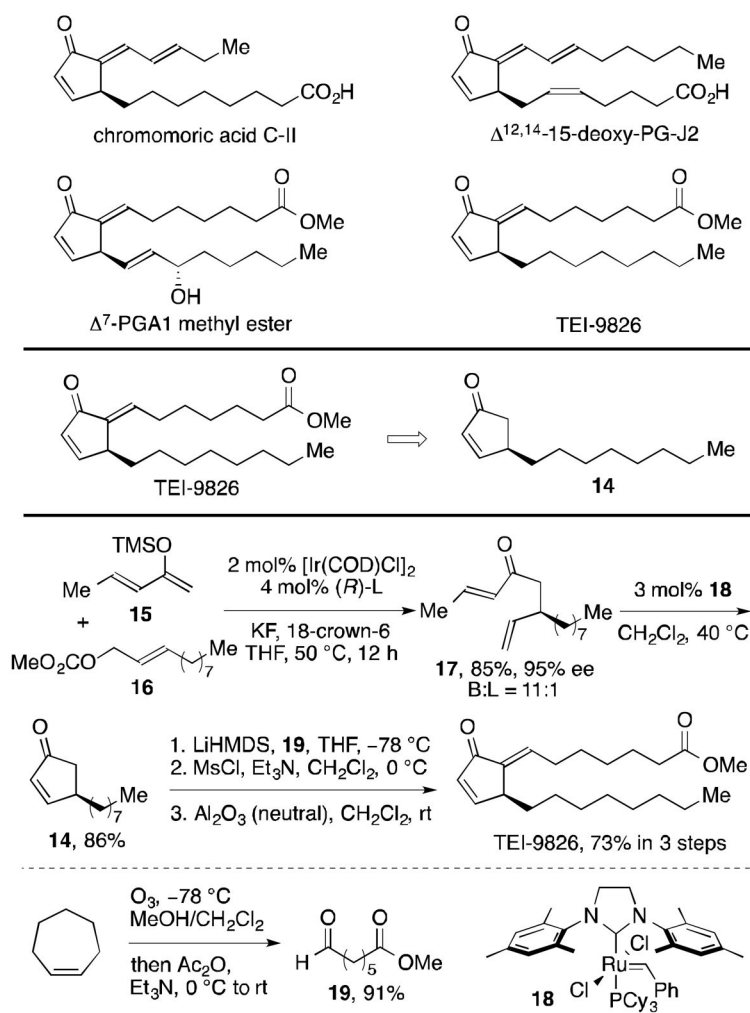
Scheme 1.
Ir-catalyzed Diastereoselective Allylic Substitution of Silyl Enolate **5**
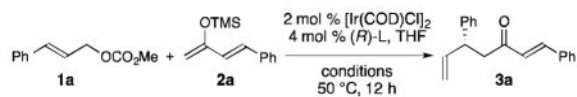
Scheme 2.
Synthesis of *syn-* and *anti*-4-Methylpentan-2-ols

Scheme 3.
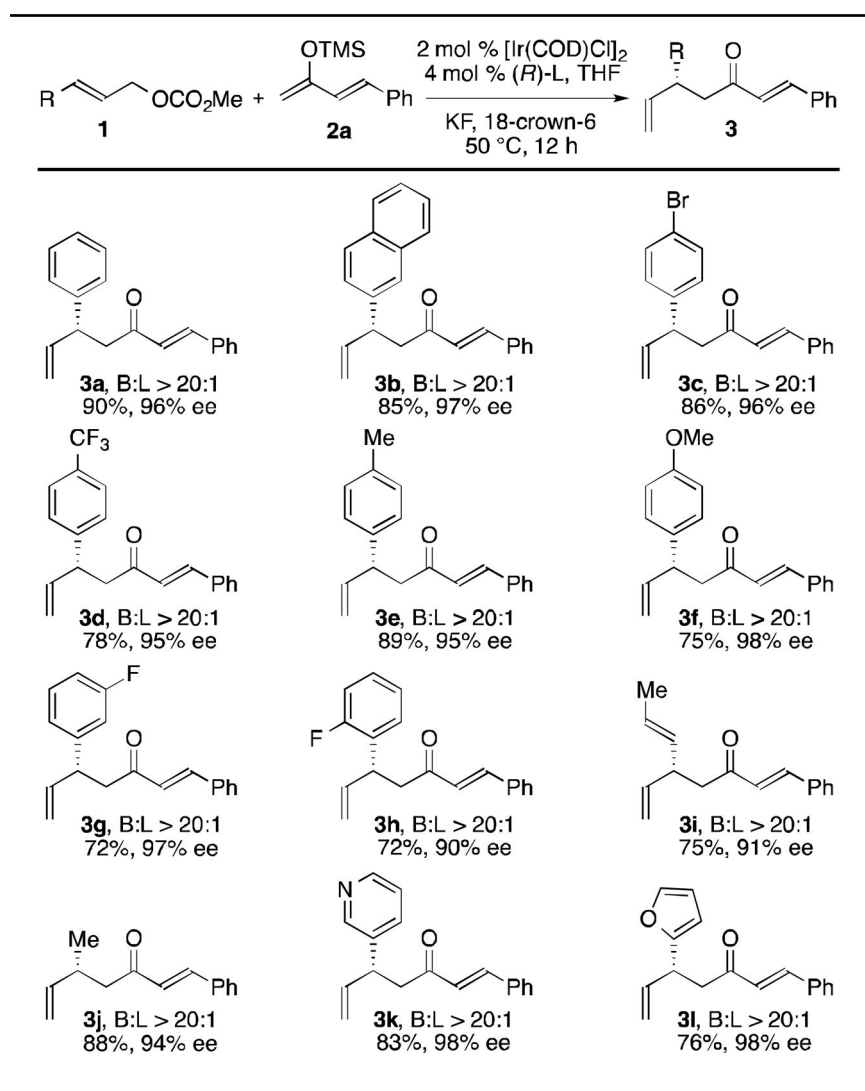Enantioselective Synthesis of TEI-9826

Table 1

Evaluation of Reaction Conditions for the Ir-catalyzed Asymmetric Allylic Substitution of **1a** with Silyl Enolate **2a**.

entry	conditions	yield	% ee
1	1 equiv KF	N.R.	N.D.
2	0.5 equiv ZnF_2	N.R.	N.D.
3	1 equiv CsF	16%	N.D.
4	0.4 equiv CsF, 1.5 equiv ZnF_2	25%	N.D.
5	1 equiv TASF	decomp.	N.D.
6	1 equiv TBAT	decomp.	N.D.
7	1 equiv CsF, 1 equiv 18-crown-6	decomp.	N.D.
8	1 equiv KF, 1 equiv 18-crown-6	90%	96%

Table 2

Scope of the Ir-catalyzed Asymmetric Allylation of Carbonates **1** with Silyl Enolate **2a**.

3a, B:L > 20:1
90%, 96% ee

3b, B:L > 20:1
85%, 97% ee

3c, B:L > 20:1
86%, 96% ee

3d, B:L > 20:1
78%, 95% ee

3e, B:L > 20:1
89%, 95% ee

3f, B:L > 20:1
75%, 98% ee

3g, B:L > 20:1
72%, 97% ee

3h, B:L > 20:1
72%, 90% ee

3i, B:L > 20:1
75%, 91% ee

3j, B:L > 20:1
88%, 94% ee

3k, B:L > 20:1
83%, 98% ee

3l, B:L > 20:1
76%, 98% ee

(a) Reaction conditions: carbonate **1** (0.2 mmol, 1.0 equiv), silyl enol ether **2a** (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) ee % were determined by chiral HPLC analysis.

Table 3

Scope of the Ir-catalyzed Asymmetric Allylation of Carbonates **1** with Silyl Enolates **2**.

4a, B:L > 20:1
92%, 94% ee

4b, B:L > 20:1
93%, 96% ee

4c, B:L > 20:1
91%, 96% ee

4d, B:L > 20:1
90%, 95% ee

4e, B:L > 20:1
94%, 96% ee

4f, B:L > 20:1
87%, 97% ee

4g, B:L > 20:1
62%, 91% ee

4h, B:L > 20:1
64%, 92% ee

4i, B:L > 20:1
83%, 96% ee

4j, B:L > 20:1
89%, 96% ee

4k, B:L > 20:1
88%, 95% ee

4l, B:L > 20:1
93%, 96% ee
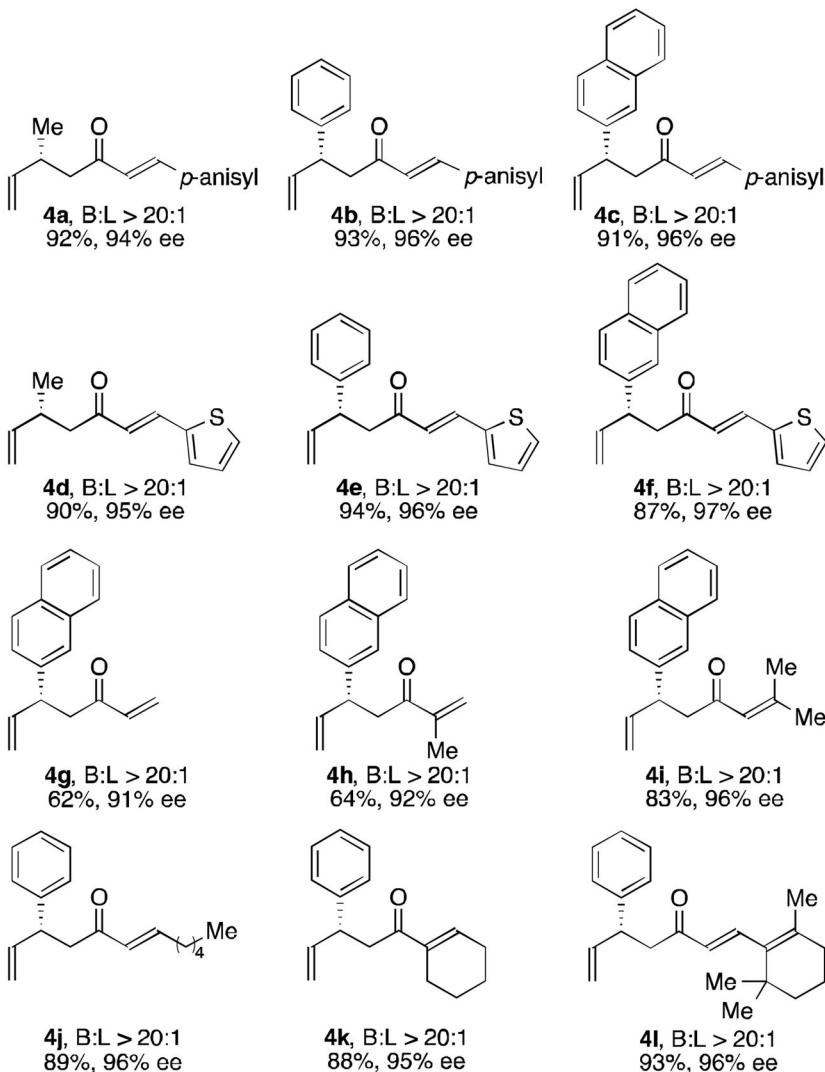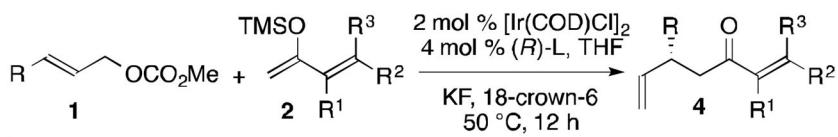
(a) Reaction conditions: carbonate **1** (0.2 mmol, 1.0 equiv), silyl enol ether **2** (0.4 mmol, 2.0 equiv), [Ir(COD)Cl]$_2$ (2 mol %), (R_a,R_C,R_C)-**L** (4 mol %), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50 °C, 8–12 h. (b) Branched to linear ratios (B:L) were determined by ^{1}H NMR analysis of the crude reaction mixtures. (c) ee % were determined by chiral HPLC analysis.