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Iridium-Catalyzed Regioselective and Enantioselective Allylation of Trimethylsiloxyfuran

Wenyong Chen and John F. Hartwig*

Department of Chemistry, University of California, Berkeley, California, 94720, United States

Abstract

We report the regioselective and enantioselective allylation of an ester enolate, trimethylsiloxyfuran. This enolate reacts in the 3-position with linear aromatic allylic carbonates or aliphatic allylic benzoates to form the branched substitution products in the presence of a metallacyclic iridium catalyst. This process provides access to synthetically important 3-substituted butenolides in enantioenriched form. Stoichiometric reactions of the allyliridium intermediate imply that the trimethylsiloxyfuran is activated by the carboxylate leaving group.

Asymmetric allylic substitution catalyzed by metallacyclic iridium phosphoramidite complexes **1** and **2**¹ forms enantioenriched materials from readily available allylic esters and a variety of heteroatom² and carbon³ nucleophiles. However, the carbon nucleophiles that undergo this process are mainly stabilized enolates.^{3a-h} Reactions of unstabilized enolates^{3i-k} have been limited to those derived from methyl ketones. Enolates of esters that undergo iridium catalyzed allylic substitutions possess a second electron-withdrawing group (EWG) to stabilize the enolate.

Trimethylsiloxyfuran **3a** is an important ester enolate because it can be used to construct butenolides, a motif found in over 13,000 natural products.⁴ High diastereo- and enantioselectivity has been achieved from the addition of **3a** to carbonyl acceptors with Lewis-acid or organic catalysts.^{4a, 5} These reactions occurred at C-5 of **3a**. Regioselective reactions at C-3 of **3a** to form enantioenriched, 3-substituted butenolides are rare.⁶

One set of palladium-catalyzed kinetic resolutions of methyl substituted allylic acetate with trimethylsiloxyfuran does occur at C-3 of the nucleophile **3a** (a of Scheme 1).⁷ In this case, the regioselectivity at the electrophile was controlled by the properties of the substrate. The attack at the less hindered end of the allyl unit led to the conjugated product.^{8, 9} This origin of regioselectivity restricts the scope of electrophiles that give one major product. Moreover, the reactions occurred with only unsubstituted trimethylsiloxyfuran. Asymmetric reactions with catalysts based on other metals could provide complementary selectivities to these palladium-catalyzed reactions. However, asymmetric allylic substitutions catalyzed by complexes of other metals with ester enolates lacking a second EWG have not been reported.

We report an iridium catalyzed allylic substitution between trimethylsiloxyfuran and prochiral electrophiles to form enantioenriched 3-substituted butenolides with high regioselectivity for the more hindered product (b of Scheme 1), including formation of the

*Corresponding Author jhartwig@berkeley.edu.

ASSOCIATED CONTENT Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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deconjugated product from reactions of cinnamyl carbonates. The process furnishes 3-substituted butenolides containing an easily functionalized terminal double bond and various aryl and alkyl groups at the stereogenic center. In addition to providing useful butenolides, this process begins to address the challenge of conducting allylic substitution with ester enolates.

Our initial studies focused on the reaction of trimethylsilyloxyfuran **3a** with cinnamyl carbonate **4a**. Table 1 summarizes the effect of several parameters on this reaction. Reactions catalyzed by complexes **1** and **2** with CsF to activate the silyl enolate formed the 3-allylated product **5a** regioselectively.^{10, 11} The reaction with catalyst **2** occurred in higher yield than the reaction with catalyst **1** (entries 1 and 2). Further assessment of fluoride activators showed that reactions conducted with ZnF₂ gave the desired product **5a** in a high 85% isolated yield with 99% ee (entry 3). The reaction with soluble fluoride salts, such as TBAF and TBAT, gave only trace amounts of the desired product (entries 4 and 5). To our surprise, this reaction also proceeded to completion without any additives, although higher catalyst loadings were needed in this case (entries 6 and 7). This final observation is consistent with studies on stoichiometric reactions of catalytic intermediates in the absence of additives described later in this paper.

The scope of the Ir-catalyzed asymmetric allylation of trimethylsilyloxyfuran in the presence of ZnF₂ is summarized in Table 2. The reaction of the electron-rich, 4-methoxy cinnamyl carbonate **4b** afforded the desired substitution product in good yield with exceptional enantioselectivity and high regioselectivity. The reactions of electron-poor substrates **4c-e** furnished the corresponding products in high yield with excellent regio- and enantioselectivities, although 3-substituted cinnamyl carbonate **4e** required 2 mol % catalyst loading for full conversion.

Reactions of aliphatic allylic electrophiles occurred with some changes to the reaction conditions. Propyl-substituted allylic carbonate **4f** gave only 18% yield of branched product **5f** with a 10:1 ratio of **5f** to linear product **6f** (entry 5). However, the reaction of the corresponding aliphatic allylic benzoate **4g** gave the branched allylation product **5f** in good yield and regioselectivity (10:1) with high enantioselectivity (entry 6) in the presence of 3 mol % catalyst **2** at 50 °C.

These conditions were suitable for a range of aliphatic benzoates. For example, crotyl substrate **4h** reacted to give the substitution product in 71% yield with excellent enantioselectivity (entry 7). Furthermore, the branched product formed selectively, even when the aliphatic substituent was branched at the carbon adjacent to the allyl unit (entry 8). The allylic substitution of dienyl benzoate **4j** with catalyst **2** yielded the product as a 1:1 mixture of constitutional isomers (entry 9), but occurred with moderate regioselectivity and high enantioselectivity when dibenzo[*a,e*]cyclooctatetraene (DBCOT) was used as a supporting ligand instead of cyclooctadiene (COD).²

The reactions of 3, 4, and 5-methyl trimethylsilyloxyfurans (**3b-d**) revealed the effect of furanyl substituents on the catalytic process. The reaction of 3-methyl trimethylsilyloxyfuran **3b** gave two products (Scheme 2). The 5-substituted linear product **6j** was isolated in 28% yield and 94% ee. The 3-substituted product was obtained as inseparable diastereomers **5j** and **5j'**. Heating the mixture of diastereomers in dichloromethane at 40 °C for 1 h led to a single diastereomer **5j** containing adjacent quaternary and tertiary stereogenic centers and linear product **6j**. Product **6j** formed by a Cope rearrangement of one of the diastereomers.¹² Thus, the 3-substituted product **5j** was ultimately isolated as a single diastereomer in 97% ee by a one-pot process involving asymmetric allylation and Cope rearrangement (Scheme 2, bottom).¹³

The reaction of 4-methyl trimethylsiloxyfuran **3c** with cinnamyl carbonate **4a** in the presence of the catalyst (*S, S, S*)-**2** also gave products from allylic substitution (Scheme 3). The reaction of **3c** produced the 3-substituted product in 47% yield, which consisted of double bond isomers **5k** and **5k'**, and the undesired 5-substituted product in 38% yield. We were able to convert isomer **5k'** to isomer **5k** with a catalytic amount of O-desmethyl quinine under mild conditions.¹⁴ Thus, the overall process furnished the 3-substituted product **5k** in 45% yield with 93% ee. Likewise, the reaction of 5-methyl trimethylsiloxyfuran **3d** gave disubstituted butenolides **5l** in an overall 88% yield with 6:1 diastereoselectivity in 99% ee after isomerization of the diastereomeric mixture of **5l'** to isomer **5l** in the presence of O-desmethyl quinine.¹⁴

The products of these substitutions contained two double bonds that underwent further functionalizations (Scheme 4). For example, the terminal double bond of **5a** underwent cross metathesis with vinyl boronate¹⁵ in the presence of the Grubbs-Hoveyda 2nd generation catalyst.¹⁶ The resulting vinyl boronate **7a** underwent Suzuki-Miyaura coupling with bromobenzene or 5-bromo-2-methylpyridine to yield **7b** or **7c** in the presence of Pd(Qphos) (crotyl)Cl. Compound **5g** was converted to **7d** by a cross metathesis with styrene catalyzed by Schrock's catalyst.¹⁷ In addition, the electron deficient double bond in **5l** served as a site for conjugate additions.¹⁸ Me₂CuLi reacted with **5l** to furnish product **7e** containing four contiguous stereogenic centers.

Stoichiometric reactions were conducted with the Ir-allyl complex¹⁹ to gain insight into the mode of addition and effect of additives on this addition step. The isolated Ir-allyl complex did not react with 1.5 equiv of trimethylsiloxyfuran in the presence of ZnF₂ alone (a of Scheme 5).²⁰ However, the iridium complex reacted immediately in the presence of 1.0 equiv of NBu₄OAc with or without ZnF₂ to form the product **5a** in 92% yield and 99% ee with the same absolute configuration as the product of the catalytic reaction (b of Scheme 5). This observation implies that the carbonate or benzoate generated in situ in the catalytic reaction activates the siloxyfuran. The *R* absolute configuration of the product of this stoichiometric reaction suggests that nucleophilic attack occurs at the face *anti* to the iridium fragment.

To determine if the acetate anion activated the trimethylsiloxyfuran directly or if it reacted with Ir-allyl complex to release an allylic acetate that reacted in a subsequent catalytic process, the reaction of the allyliridium complex with trimethylsiloxyfuran **3a** was conducted in the presence of 5.0 equiv of *p*-tolyl allylic acetate (c of Scheme 5). If the acetate anion led to the release of the free allylic acetate, little product from the allyl group on iridium would be observed in the presence of excess of the tolyl-substituted allylic acetate. In the event, the reaction of the Ir-allyl complex in the presence of excess of tolyl-substituted acetate formed phenyl-substituted product **5a** in 92% yield. (The *p*-tolyl product formed in only 37% yield based on *p*-tolyl allylic acetate.) This yield of phenyl-substituted product **5a** was the same as that formed in the absence of *p*-tolyl allylic acetate, and the yield of **5a** was much higher than that of *p*-tolyl-substituted product. These observations imply that the trimethylsiloxyfuran reacts directly with the Ir-allyl complex when activated by a carboxylate, not by initial release of an allylic ester.

In summary, we report an iridium-catalyzed asymmetric allylic substitution reaction with a silyl ketene acetal. The reaction between a variety of aromatic and aliphatic allylic carbonates or benzoates and trimethylsiloxyfuran proceeded smoothly to furnish 3-substituted butenolides in excellent regio- and enantioselectivity. Moreover, methyl substituted trimethylsiloxyfurans react regioselectively to form enantioenriched products. These allylation products can be converted to an array of organic building blocks by reactions at one or the other of the alkene units of the product. Stoichiometric reactions of

the allyliridium intermediate imply that the reaction proceeds by *anti* attack on the coordinated allyl ligand, as reported previously for iridium catalyzed allylic substitution with carbon and heteroatom nucleophiles,^{19a} but that the siloxyfuran is activated by coordination of the carboxylate leaving group. Further studies to expand the scope of the reaction to encompass additional silyl ketene acetals are underway in this laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

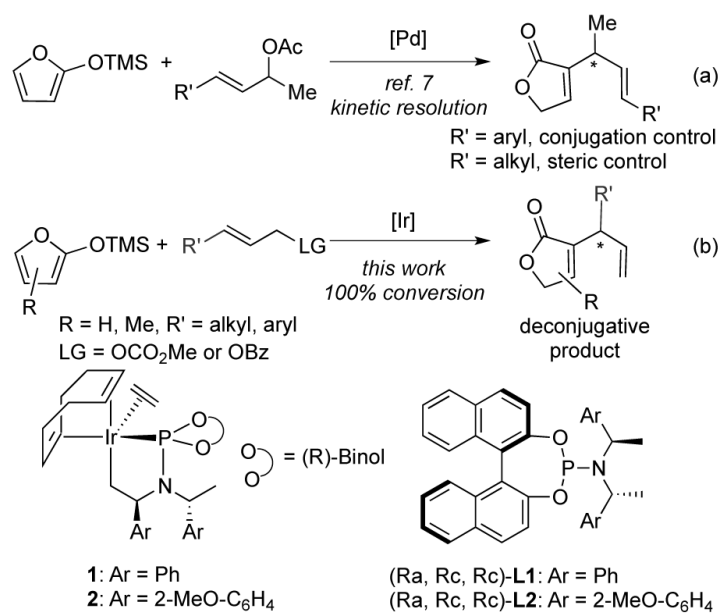
Acknowledgments

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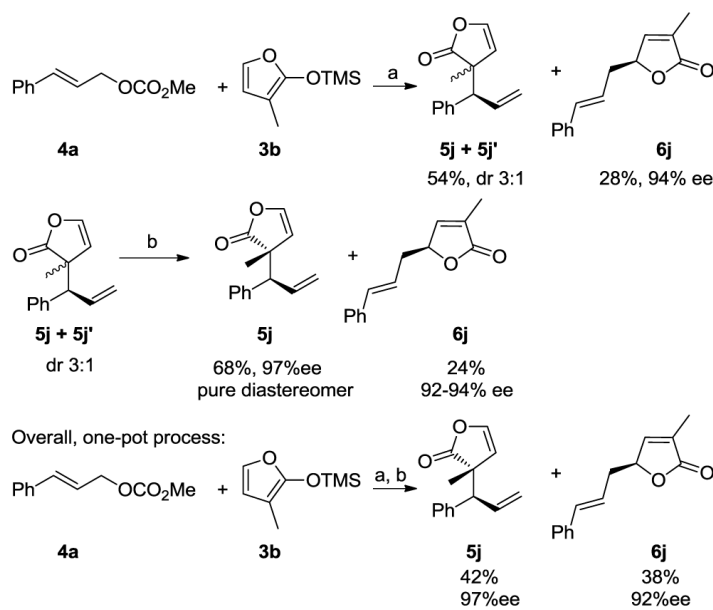
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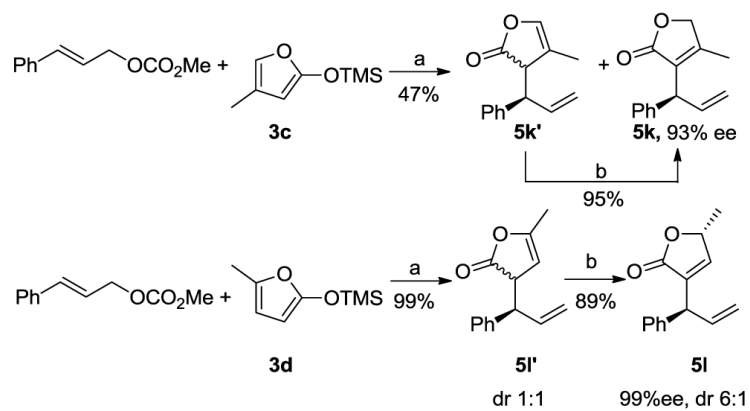
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- (9). Consistent with this origin of regioselectivity, we found that the palladium catalyzed reaction of cinnamyl acetate with **3a** failed to deliver the desired product **5a**. Instead, a mixture of 3-cinnamyl-2-furanone and **6a** formed in a combined 30% yield. See supporting information for details.
- (10). The regioselectivity for reaction at the butenolide is distinct from several processes forming products from attack at C-5. Selectivities from reactions at C-5 have been rationalized by initial [4+2] cycloadditions with an alkene or carbonyl group. In our case, the siloxyfuran activated by an anionic group is more likely reacting as an enolate, which tends to react with electrophiles at the C-3.
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- (20). To understand the effect of ZnF₂, ¹⁹F NMR experiments were conducted. The ¹⁹F NMR spectrum of the catalytic reaction (Table 1, entry 3) contained a peak at -156.9 ppm, which matches the ¹⁹F NMR resonance of TMSF. The same species was found in the mixture of ZnF₂ and TMSOAc, but not in the mixture of ZnF₂ and trimethylsiloxyfuran. These observations suggest that ZnF₂ promotes the allylic substitution reaction by reacting with the trimethylsilylcarbonate formed in the reaction to release the carbonate, which then activates the trimethylsiloxyfuran.



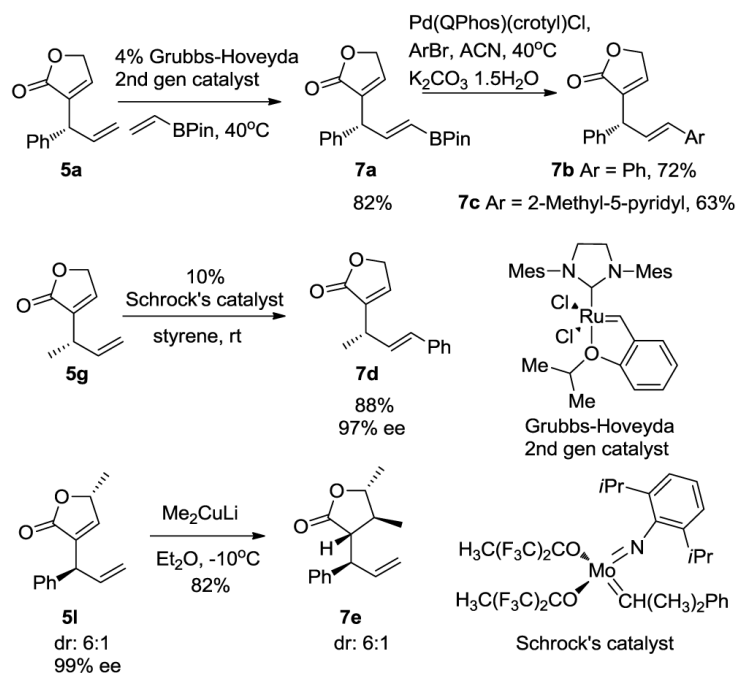
SCHEME 1.
Palladium and iridium catalyzed allylic substitution with trimethylsilyloxyfuran

**SCHEME 2.**Iridium-catalyzed allylic substitution with 3-methyl substituted trimethylsiloxyfurans^a^a (a) 2 mol % (*S, S, S*)-**2**, ZnF₂, CH₂Cl₂, 12 h; (b) 40 °C, CH₂Cl₂, 1 h

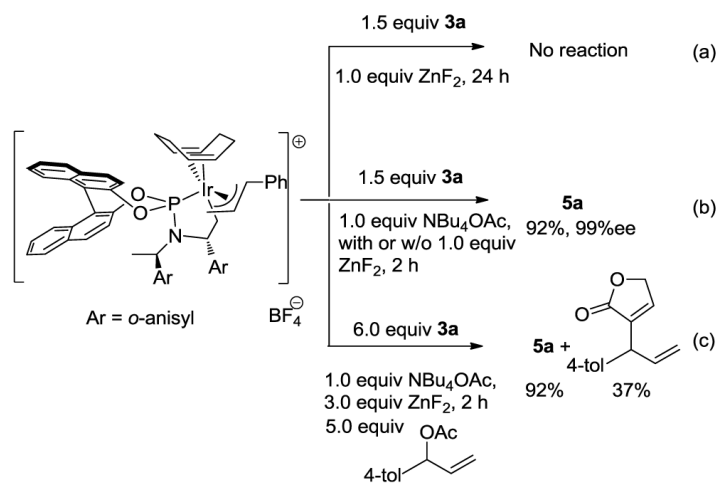
**SCHEME 3.**

Iridium-catalyzed allylic substitution with 4- and 5-methyl substituted trimethylsilyloxyfurans^a

^a (a) 2 mol % (*S, S, S*)-**2**, ZnF₂, CH₂Cl₂, 12 h; (b) 20 mol % O-desmethyl quinine, CH₂Cl₂, 12 h

**SCHEME 4.**Derivatization of the butenolide product^a

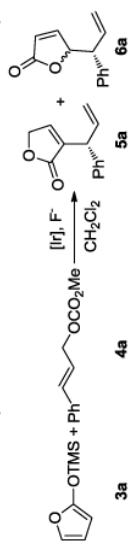
a See supporting information for experimental details. All yields reported here are isolated yields. Diastereomeric ratio was determined from ¹H NMR spectra of the crude reaction mixtures. ee was determined by chiral HPLC analysis.



SCHEME 5.
Stoichiometric reactions of the cinnamyl iridium intermediate with trimethylsiloxyfuran

TABLE 1

Effect of catalyst and fluoride source on the Ir-catalyzed allylic substitution of trimethylsilyloxyfuran^a



Entry	Cat. ^b	Fluoride	Yield(%) ^c	5a:6a ^d	ee(%) ^e
1	1	CsF	13	-	-
2	2	CsF	32	20:1	99
3	2	ZnF ₂	87(85)	20:1	99
4 ^f	2	TBAF	trace	-	-
5	2	TBAI	trace	-	-
6	2	None	40	20:1	99
7 ^g	2	None	89	20:1	99

^aSee supporting information for experimental details.

^b1 mol % Ir catalyst was used unless otherwise noted.

^cThe yield was determined by ¹H NMR analysis with mesitylene as the internal standard. The value in parentheses corresponds to the isolated yield.

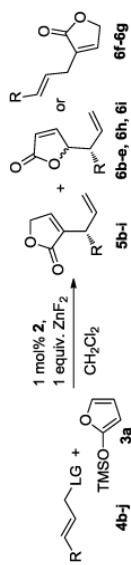
^dThe ratio was determined by ¹H NMR analysis of crude reaction mixtures.

^eThe ee was determined by chiral HPLC.

^f1-phenylallyl alcohol was formed in 69% yield.

^g2 mol % Ir catalyst was used.

TABLE 2

Iridium-catalyzed allylic substitution of trimethylsilyloxyfuran 3a^a

Entry	R (4)	LG	Yield (%) ^b	5/6 ^c	ee ^d (%)
1	4-MeO-C ₆ H ₄ (4b)	OCO ₂ Me	5b, 70	20:1	98
2	4-F-C ₆ H ₄ (4c)	OCO ₂ Me	5c, 83	20:1	95
3	4-Cl-C ₆ H ₄ (4d)	OCO ₂ Me	5d, 78	20:1	97
4 ^e	3-F-C ₆ H ₄ (4e)	OCO ₂ Me	5e, 91	20:1	97
5 ^f	n-Propyl (4f)	OCO ₂ Me	5f, 18	10:1	99
6 ^{f,g}	n-Propyl (4g)	OBz	5f, 80	10:1	96
7 ^{f,g}	Methyl (4h)	OBz	5g, 71	10:1	97
8 ^g	Cyclohexyl (4i)	OBz	5h, 60	8:1	94
9	1-propenyl (4j)	OCO ₂ Me	5i, 90	1:1	-
10 ^h	1-propenyl (4j)	OCO ₂ Me	5i, 83	3:1	99

^aSee supporting information for experimental details.^bIsolated yield^cRatio was determined by ¹H NMR analysis of the crude reaction mixtures.^dee was determined by chiral HPLC analysis.^e2 mol % Ir catalyst 2 was used.^fThe products 6 are 3-substituted linear products.^gThe reaction was conducted with 3 mol % Ir catalyst 2 at 50 °C.^h2 mol % [(dcbot)IrCl]₂ was used.