A Journal of the Gesellschaft Deutscher Chemiker

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Accepted Article

Title: Trimethyl Orthoacetate and Ethylene Glycol Mono-Vinyl Ether as Enolate Surrogates in Enantioselective Iridium-Catalyzed Allylation

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201803558
Angew. Chem. 10.1002/ange.201803558

Link to VoR: http://dx.doi.org/10.1002/anie.201803558
http://dx.doi.org/10.1002/ange.201803558

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10.1002/anie.201803558

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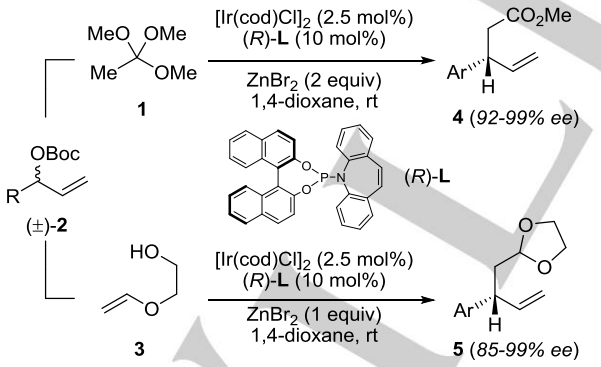
Trimethyl Orthoacetate and Ethylene Glycol Mono-Vinyl Ether as Enolate Surrogates in Enantioselective Iridium-Catalyzed Allylation

Yeshua Sempere and Erick M. Carreira*

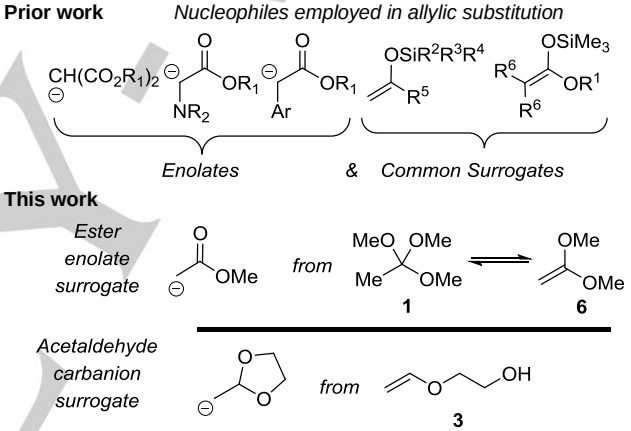
Abstract: Trimethyl orthoacetate and ethylene glycol mono-vinyl ether are employed in iridium-catalyzed, enantioselective allylation reactions. The method documented enables their convenient use as surrogates for silyl ketene acetals and silyl enol ethers to prepare γ,δ-unsaturated esters and protected aldehydes with excellent enantioselectivity. The utility of this novel method has been demonstrated by its implementation in a formal, enantioselective synthesis of the meroterpenoid (+)-conicol.

Enantioselective, iridium-catalyzed allylic substitution is a transformation that has been strategically implemented and showcased in syntheses of functionally diverse targets, including natural products and pharmaceutical agents.[1] The versatility of the reactions stems from the development of numerous robust processes, involving a wide range of heteroatom and carbon nucleophiles. Enolates and silyl ketene acetals are particularly useful nucleophiles because they provide olefin products with additional functional group handles. Herein, we disclose that trimethyl orthoacetate **1** may be used as a simple, commercially available surrogate for acetate enolates in Ir-catalyzed alkylation of racemic allylic carbonates (Scheme 1). We also disclose the use of ethylene glycol mono-vinyl ether **3** as a protected acetaldehyde enolate equivalent. The allylation reactions with each produces a diverse collection of optically active, β-substituted γ,δ-unsaturated methyl esters along with aldehydes protected as dioxolane acetals (Scheme 1)



Scheme 1. Trimethyl orthoacetate and ethylene glycol mono-vinyl ether as enolate surrogates in enantioselective iridium-catalyzed allylation reactions.

Beyond the initial use of malonates,[2] and derivatives of amino[3] and aryl acetic acid esters have been reported as nucleophiles in iridium-catalyzed enantioselective allylation reactions (Scheme 2).[4] However, for compounds with attenuated C-H acidity, such as esters and ketones, masked enolate equivalents are necessary. The use of silyl enol ethers and silyl ketene acetals in enantioselective iridium-catalyzed allylic substitution reactions has been reported primarily by Hartwig.[5, 6] Additionally, their use in allylic substitution has been well-documented using palladium[7] and ruthenium.[8] Interestingly, the use of the parent silyl ketene acetals derived from acetic acid esters in Ir-catalyzed allylation has not been reported.



Scheme 2. Enolates and common surrogates in enantioselective iridium-catalyzed allylation reactions.

The basis for the study we describe is the hypothesis that trimethyl orthoacetate could provide access to dimethyl ketene acetal, which might in turn participate in allylic substitution reactions with electrophilic η^3-allyl Ir(III) intermediates.[9] The classic use of orthoesters is in the Johnson-Claisen rearrangement reaction, wherein mixed ketene acetals are generated from allylic alcohols in the presence of Brønsted acids.[10] To the best of our knowledge, the use of orthoesters as nucleophiles in metal-catalyzed allylation reactions is unknown.

The iridium-P, olefin catalyst we have previously described is notable because of its robustness, and, specifically, its compatibility with a wide range of Brønsted and Lewis acids.[9b-f] Accordingly, we initially set out to identify conditions, which would lead to formation of dimethyl ketene acetal from $MeC(OMe)_3$ under conditions compatible with Ir-catalyzed allylic substitution reactions. An important consideration is that 1,1-dialkoxyalkenes can undergo polymerization when treated with electrophiles.[11] Moreover, we decided to avoid the use allylic alcohols as substrates and instead resort to allylic carbonates to avoid forming mixed ketene acetals involving **1** and the allylic alcohols.

In initial prospecting experiments, we screened a variety of conditions, including Lewis acids, such as Zn^{2+}, Fe^{3+}, In^{3+}, and

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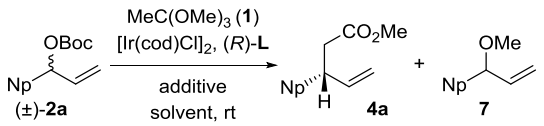
Sc^{3+}.[12] As shown in Table 1, the observations with $Zn(OTf)_2$ typify the problem faced. Thus, although **4a** was formed in high enantioselectivity, the major product of the reaction was ether **7**, formed by competitive trapping of an allyl-iridium intermediate by methanol. Interestingly, examination of other Zn(II) salts and a variety of solvents gave promising results. In particular, $ZnBr_2$ in 1,4-dioxane was found to perform well (Table 1, entries 4-6),with increasing quantities of $ZnBr_2$ having a marked positive effect on the yield of the desired product. Ultimately, the optimal conditions identified were allylic carbonate **2a** (1 equiv), $MeC(OMe)_3$ **1** (2 equiv) and $ZnBr_2$ (2 equiv) in the presence of $[Ir(cod)Cl]_2$ (2.5 mol%) and (*R*)-**L** (10 mol%) in 1,4-dioxane at room temperature for 12h. As shown in Entry 6, product **4a** was isolated in 80% yield and 97% ee.

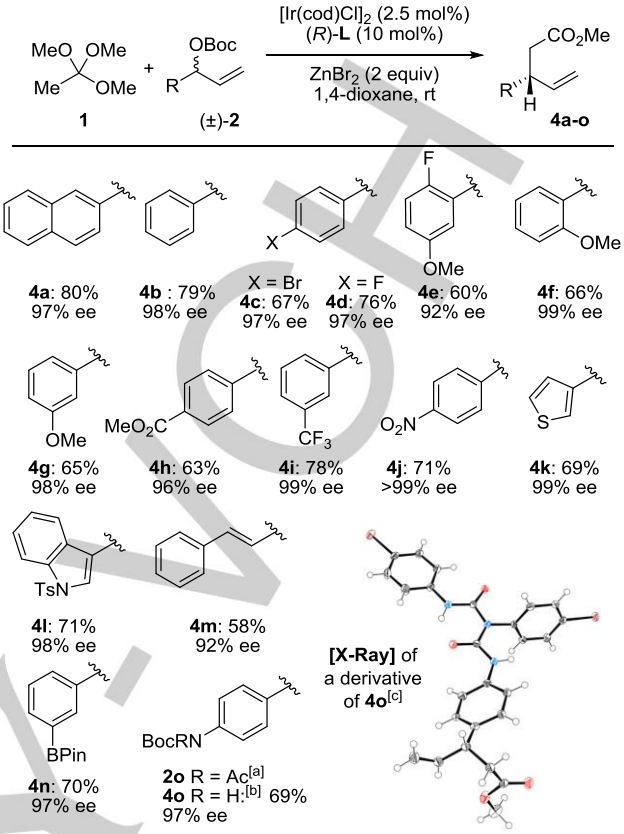
Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Additive	Equiv.	Yield **4a** [%][b]	Yield **7** [%][b]	ee [%][c]
1	$CHCl_3$	$Zn(OTf)_2$	1	18	82	86
2	$CHCl_3$	$ZnBr_2$	1	46	-	98
3	toluene	$ZnBr_2$	1	68	<5	84
4	1,4-dioxane	$ZnBr_2$	0.5	55	9	88
5	1,4-dioxane	$ZnBr_2$	1	60	7	98
6	1,4-dioxane	$ZnBr_2$	2	80	<5	97

[a] Reaction conditions: (±)-**2a** (1.0 equiv), $[Ir(cod)Cl]_2$ (2.5 mol%), *(R)*-**L** (10 mol%), **1** (2.0 equiv), 0.5 M, rt. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1,4-dimethoxybenzene as internal standard. [c] Enantiomeric excess determined by supercritical fluid chromatography (SFC) with a chiral stationary phase. Np = 2-naphthyl, Boc = *tert*-butyloxycarbonyl.

We then explored the scope of the enantioselective allylation reaction with trimethyl orthoacetate (Scheme 2). Allylic carbonates bearing unsubstituted aromatic rings such as 2-naphthyl and phenyl underwent the reaction smoothly, and products were obtained in good isolated yields with excellent enantioselectivity (**4a** and **4b**). Halogenated and electron-rich substrates also performed well under the reaction conditions, leading to the corresponding ester products (**4c**-**d** and **4e**-**g**) in good yields with excellent enantioselectivity in all cases. Additionally, electron-withdrawing groups on the aromatic ring were also well tolerated (products **4h**-**j**). The use of heteroaromatic substrates was achieved, and the transformation of thienyl and indole allylic carbonates generated the corresponding γ,δ-unsaturated methyl esters enantioselectively (**4k** and **4l**). Gratifyingly, 1,4-diene (product **4m**) as well as amine- or boron- substituted aromatic substrates furnished the desired adducts with high enantioselectivity (**4n** and **4o**).



Scheme 2. Substrate scope of the enantioselective alkylation with trimethyl orthoacetate (**1**). Unless otherwise noted, all reactions were performed on a 0.20 mmol scale under the standard conditions (see Table 1, entry 6). Yields refer to isolated products after purification by chromatography on silica gel. Enantiomeric excess determined by SFC or HPLC using a chiral stationary phase. [a] Acetyl underwent cleavage under the reaction conditions. [b] Absolute configuration determined by X-ray analysis of a derivate compound.[12] [c] Derivative prepared from **4o** after Boc-group hydrolysis and reaction of the aniline produced with excess *p*-BrC_6H_4NCO. Ts = *p*-$MeC_6H_4SO_2$, Pin = pinacolate.

Encouraged by the use of $MeC(OMe)_3$ as an acetate enolate equivalent in Ir-catalyzed allylation reactions, we sought to extend the underlying concept to the use of other similar nucleophiles. Although aldehyde-derived enamines have been employed as nucleophiles in iridium-catalyzed allylation reactions,[9b-e] the use of acetaldehydes is notably absent. Generally, self-aldolization through C-C bond formation or oligomerization through C-O bond formation can occur rapidly and at the expense of product yield. However, we hypothesized that vinyl ether **3** might be capable of reacting with electrophilic η^3-allyl Ir(III) intermediates **I-1** to afford intermediate **8**, which following cyclization would yield acetal-protected aldehyde **5** (Scheme 3).

Commercially available ethylene glycol mono-vinyl ether (EGME) participated in iridium-catalyzed allylation reactions under nearly identical conditions to those already established for orthoacetates.[13] The scope of this transformation was explored as shown in Scheme 4.

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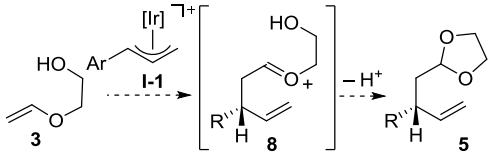
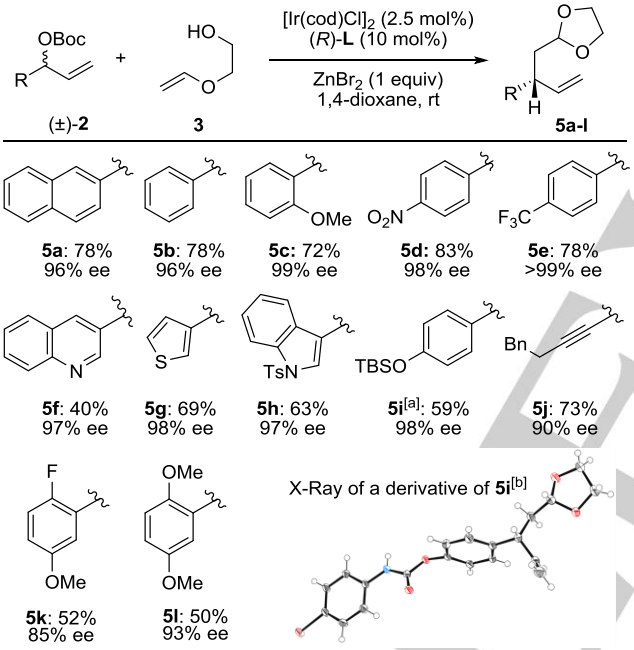


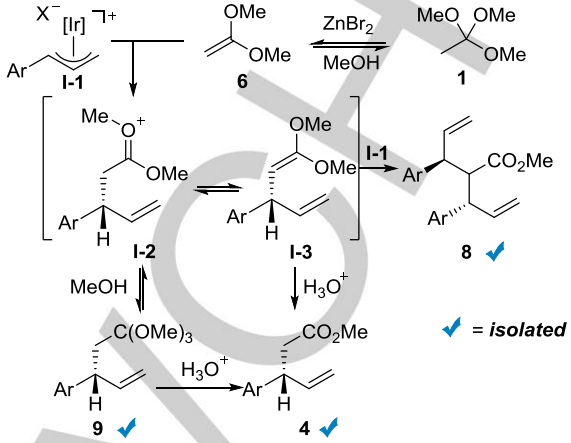
Scheme 3. Proposed mode of action of alkyl enol ether **3**.

Unsubstituted as well as alkoxy-substituted substrates provided the corresponding products (**5a-c**) in good yields and enantioselectivity. Substrates with electron-withdrawing groups proceeded with 83% and 78% yield, respectively and with greater than 98% enantioseletivity in both cases (**5d** and **5e**). Heteroaromatic substrates were also tolerated (acetals **5g** and **5h**) although the substrate possessing a quinoline ring (product **5f**) resulted in a diminished yield (40%). 1,4-Enyne substrate furnished adduct in high yield and good optical purity (**5j**). Disubstituted aromatic rings afforded the desired acetals as well, albeit only in moderate yields and with decreased enantioselectivity (**5k** and **5l**).



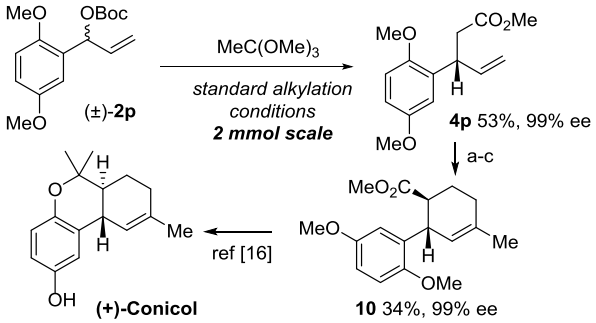
Scheme 4. Substrate scope of the enantioselective alkylation with EGME. Unless otherwise noted, all reactions were performed on a 0.25 mmol scale under the standard conditions. Yields refer to isolated products after purification by column chromatography on silica gel. Enantiomeric excess determined by SFC or HPLC using a chiral stationary phase. [a] Absolute configuration determined by X-ray analysis of a derivate compound.[12] [b] Derivative prepared from **5i** after TBS removal and reaction of the phenol produced with excess *p*-BrC_6H_4NCO.TBS = *t*-$BuMe_2Si$; Bn = Benzyl.

A collection of experimental observations enable us to propose a putative reaction mechanism for the formation of γ, δ-unsaturated esters from orthoester **1** (Scheme 5). In the first step, dimethyl ketene acetal **6** attacks the electrophilic allyl iridium species **I-1** to afford **I-2**, which may suffer either of two fates: proton loss to give **I-3** or trapping by methanol to furnish **9**. Both would lead to the isolated methyl esters following work-up procedures. The isolation and characterization of trace amounts of **8** is consistent with the presence of **I-3** participating in allylation reactions in competition with **6** (see supplementary section). The intermediacy of **I-2** is also supported by the isolation of and characterization of **9**, which was transformed into methyl ester **4** upon exposure to mild acid (aqueous NH_4Cl).



Scheme 5. Proposed mechanistic pathways. **8** and **9** were obtained using **2a** and **2e** as substrates, respectively.

In an effort to demonstrate the practicality and utility of the enantioselective method that we have described, it was applied to a formal synthesis of (+)-conicol (Scheme 6). (+)-Conicol is a naturally occurring meroterpene isolated from the ascidian *Aplidium conicum*[14] and has shown cytotoxicity against various carcinomas.[15] Starting from 2,5-dimethoxy phenyl allylic carbonate **2p**, iridium-catalyzed allylic alkylation in the presence of trimethyl orthoacetate **1** yielded ester **4p** in 53% yield with 99% ee on 2 mmol scale (Scheme 6). Alkylation of ester **4p**, followed by ring closing metathesis and subsequent epimerization of the diastereomeric mixture furnished known intermediate **10** in 34% yield over three steps. Ester **10** can be converted into (+)-conicol in a rapid manner via known procedures.[16]



Scheme 6. Enantioselective formal synthesis of (+)-Conicol. Conditions: a) 3-methylbut-3-en-1-yl trifluoromethanesulfonate (2.5 equiv.), LiHMDS (2.0 equiv.), THF, -78 ºC, 52%. b) GC-II (8 mol%), CH_2Cl_2, 68%. c) NaOMe (5 equiv.), MeOH, 65 ºC, 48 h, 95%. GC-II = Grubbs Catalyst 2nd generation.

In summary, we have disclosed an enantioselective allylic alkylation that enables the preparation of β-substituted γ, δ-unsaturated esters and protected aldehydes. The method relies on the use of trimethyl orthoacetate and ethylene glycol mono-vinyl ether as surrogates for enolates in iridium-catalyzed enantioselective allylation. This approach fills an existing gap involving the use of acetate-derived silyl ketene acetals and enol silanes from acetaldehyde. It thereby complements existing

approaches by enabling transformations with nucleophiles not requiring prior preparation. Finally, the synthetic utility of this methodology was showcased through a concise formal synthesis of meroterpenoid (+)-Conicol.

Acknowledgements

We thank the NMR and X-ray crystallography services for their assistance. We also thank the Wennemers´ group for their support with chiral chromatography. ETH Zürich and the Swiss National Science Foundation (200020_152898) are gratefully acknowledged for financial support.

Keywords: Iridium • orthoacetate • allylation • enantioselective • synthesis

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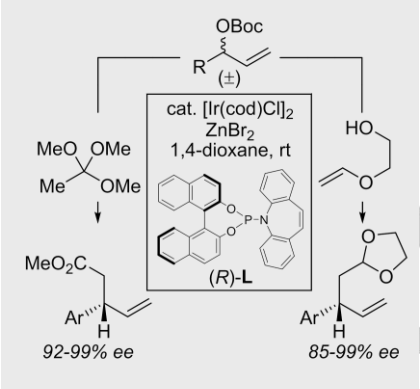
Trimethyl orthoacetate and ethylene glycol mono-vinyl ether are employed as enolate surrogates in iridium-catalyzed enantioselective allylation reactions to prepare γ,δ-unsaturated esters and protected aldehydes with excellent enantioselectivity. The utility of this novel method has been demonstrated by its implementation in a formal, enantioselective synthesis of the meroterpenoid (+)-conicol.



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