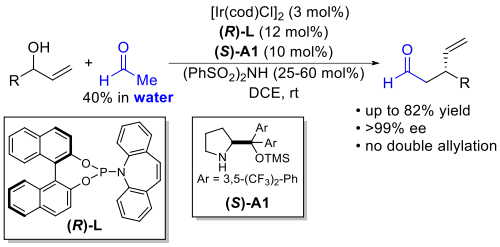
Enantioselective Iridium-Catalyzed α-Allylation with Aqueous Solutions of Acetaldehyde

Tobias Sandmeier and Erick M. Carreira*

ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland



ABSTRACT

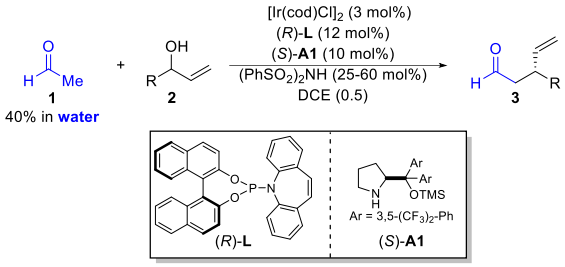
The enantioselective α-allylation of aqueous solutions of acetaldehyde using iridium- and amine-catalyzed substitution of racemic allylic alcohols is described. The method utilizes readily available, safely handled aqueous solution of acetaldehyde and furnishes γ,δ-unsaturated aldehydes in good yields and greater than 99% enantiomeric excess. The synthetic potential of the method is demonstrated with the enantioselective formal syntheses of heliannuols E and C as well as heliespirones A and C.

In recent years, enantioselective iridium-catalyzed allylic substitution reactions have found widespread attention in synthetic organic chemistry.[1] Various carbonyl-derived carbon nucleophiles have been employed to date including enolates,[2] silyl ketene acetals[3] and aldehydes.[4] However, acetaldehyde which in itself is not a carbon nucleophile but readily forms reactive enamines in the presence of amines,[5] is remarkably absent. Moreover, readily accessible masked versions of acetaldehyde such as methyl vinyl ether or vinyloxy-trimethylsilane that would provide access to unprotected, α-allylated aldehyde products have not been used in transition metal-catalyzed allylic substitution reactions. This is striking, considering that acetaldehyde is a readily available two-carbon fragment whose derived products offer numerous options for further synthetic elaborations. Recently, our group has reported ethylene glycol mono-vinyl ether as a protected acetaldehyde enolate equivalent for iridium-catalyzed allylic substitution reactions affording 1,3-dioxolane-protected aldehydes.[6] However, a transformation that provides access to the free aldehyde products would be complementary to that which we have previously reported and thus highly desirable. Herein we report the enantioselective iridium-catalyzed α-allylation of acetaldehyde (**1**) to give γ,δ-unsaturated aldehydes (Scheme 1). The products are isolated in good yields and with excellent enantioselectivities. The synthetic utility of this method is demonstrated with a series of functionalization reactions and the formal synthesis of the natural products heliannuol C and E as well as heliespirone A and C.

The development of asymmetric transformations employing acetaldehyde as a nucleophile must overcome several factors.[5] Firstly, the high reactivity of acetaldehyde, both as an electrophile and a nucleophile, can lead to low isolated yields due to self-aldolization and formation of polyacetals. Furthermore, selective mono-functionalization of acetaldehyde can be challenging as the initially formed aldehyde products can often undergo down-stream side reactions such as aldol condensation reactions. Finally, with a boiling point of 21 °C, care must be taken when handling this compound, and adding precise quantities, especially on small scale, is often challenging. Over the course of the last decade a series of organocatalytic transformations employing acetaldehyde as a nucleophile have been developed, yet its use in asymmetric transition metal catalysis remains elusive.[5,7] It has

been noted that the use commercially available aqueous solutions of acetaldehyde (40% wt/wt) could circumvent some of its inherent problems as the corresponding hydrate is less reactive and volatile.[8]

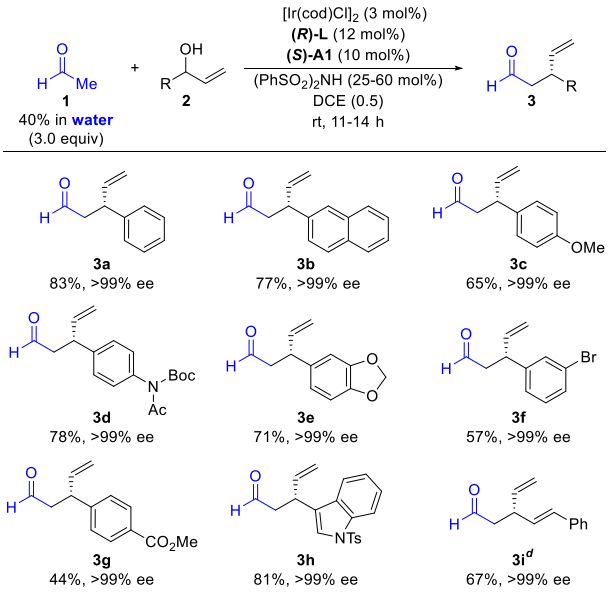
Scheme 1. Iridium-Catalyzed α-Allylation of Acetaldehyde.



Our group has recently investigated iridium-catalyzed allylic substitution reactions using aqueous solutions of nucleophiles and the iridium complex derived from $[Ir(cod)Cl]_2$ and ligand **(*R*)-L**.[9] Hence, we envisioned that our catalytic system would be uniquely suited for the enantioselective α-allylation of aqueous acetaldehyde. Initial studies revealed that the reaction of allylic alcohol **2a** with an aqueous solution of acetaldehyde (**1**) in the presence of the catalytic complex [Ir/**(*R*)-L**], dichloroacetic acid and secondary amine **(*S*)-A1** afforded γ,δ-unsaturated aldehyde **3a** in 16% yield and excellent enantioselectivity (>99% ee). Notably, under these biphasic reaction conditions no double allylation was observed. With less bulky or primary amine catalysts such as proline or benzhydrylamine, respectively, significant amounts of the bis-allylated products as well as aldol side reactions were observed. Further optimization revealed that more lipophilic Brønsted acid promoter dibenzene sulfonimide in combination with [Ir/**(*R*)-L**], **(*S*)-A1** and allylic alcohol **2a** afforded product **3a** in 83% yield and >99% ee.[10]

With optimized reaction conditions in hand, we next examined the substrate scope of this transformation with regard to allylic alcohols (Table 1). A series of electron rich (**3b**–**3e**) and electron deficient (**3f** and **3g**) allylic alcohols were found to be compatible with this transformation, affording the corresponding aldehydes in good to moderate yields and >99% enantiomeric excess. Gratifyingly, also heteroaromatic allylic alcohols **2h** and **2h** as well as cinnamaldehyde-derived substrate **2i** were tolerated, resulting in equally high degrees of enantioinduction.

Table 1. Allylic Alcohol Scope of the α-Allylation of Aqueous Acetaldehyde.[a,b,c]

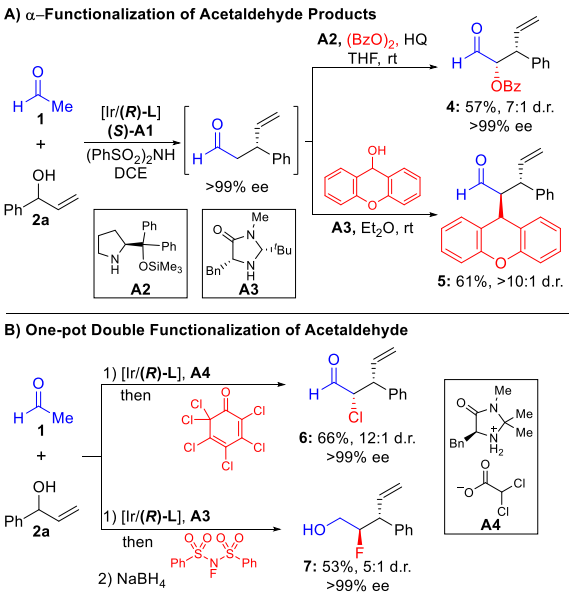


[a]Reactions run on 0.25 mmol scale under the standard conditions. [b]Yields of isolated aldehydes. [c]ee of the corresponding primary alcohol determined by SFC on a chiral stationary phase. [d]Branched/linear = 10:1.

Next, we aimed to utilize this iridium-catalyzed allylation of acetaldehyde to rapidly gain access to more complex molecules. To this end, allylic alcohol **2a** was reacted with acetaldehyde under the previously established conditions

and the crude reaction mixture was treated with a second amine catalyst and an electrophile. This two-step procedure gave access to α-oxygenated[11] and α-alkylated[12] products **4** and **5**, respectively, in good yields and diastereomeric ratios. Encouraged by these results, we envisioned that such transformations could also be carried out in a one-pot procedure wherein one amine catalyst controls two sequential α-functionalization reactions. Gratifyingly, treatment of acetaldehyde with [Ir/(***R***)-**L**] and allylic alcohol **2a** in the presence of chiral amine **A4** followed by the addition of hexachloro-2,5-cycloheydien-1-one afforded α-chlorinated aldehyde **6** in good yield and high stereoselectivity. Similarly, fluorinated product **7** could be obtained when **A3** and *N*-fluorobenzesulfonimide were employed.[13] Hence, we have established conditions for the rapid generation of molecular complexity starting for acetaldehyde derived allylation adducts.

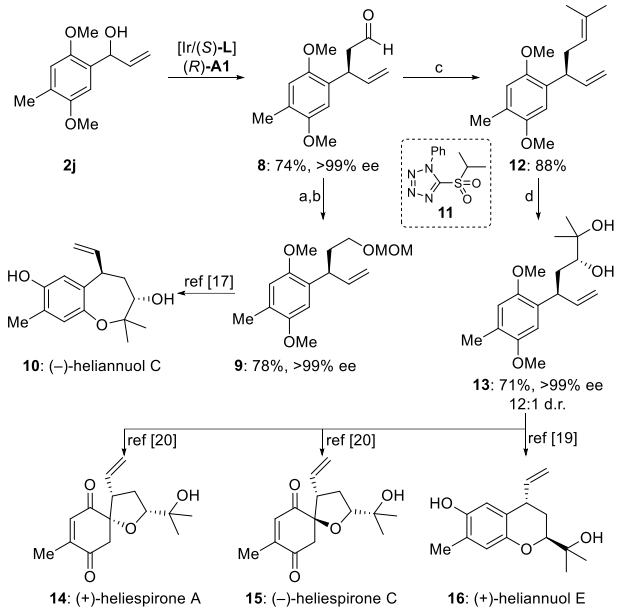
Scheme 2. Preparation of α,β-Disubstituted Aldehydes.[a]



[a]For detailed experimental procedures, see supporting information. HQ = hydroquinone.

To highlight the potential of the iridium-catalyzed allylation of acetaldehyde in the context of target-oriented synthesis, we undertook the formal syntheses of heliannuol C and E as well as heliespirone A and C. These sesquiterpenes were isolated from the cultivated sunflower *Helianthus annuus* and display herbicidal activity in bioassays rendering them potential scaffolds for the development of new and selective pesticides.[14-16] Starting from commercially available 2,5-dimethoxy-4-methylbenzaldehyde allylic alcohol **2j** was prepared in one step by addition of vinylmagnesium bromide. Subsequent iridium-catalyzed allylation under the established conditions afforded *γ*,*δ*-unsaturated aldehyde **8** in 74% yield. **8** was treated sequentially with sodium borohydride and methoxy methyl chloride (MOM-Cl) to furnish protected alcohol **9** which can be converted into (–)-heliannuol C, following a sequence reported by Shishido and co-workers.[17] Additionally, diene **12** was prepared from aldehyde **8** using a modified Julia-Kocienski olefination.[18] Subsequent Sharpless dihydroxylation afforded diol **13** in a highly diastereoselective manner. Compound **13** was used by Liu and co-workers as a key intermediate for the total synthesis of heliannuol E as well as heliespirone A and C.[19,20]

Scheme 3. Formal Syntheses of Sunflower-Derived Natural Products[a]



[a]For detailed experimental procedures, see supporting information. Reagents and conditions: (a) $NaBH_4$, CH_2Cl_2/MeOH (2:1). (b) MOM-Cl, DIPEA, CH_2Cl_2. (c) LiHMDS, **13**, THF. (d) AD-mix-β, methanesulfonamide, *t*-BuOH/H_2O (1:1).

In conclusion, we have developed conditions for the enantioselective *α*-allylation of acetaldehyde under biphasic conditions. It is noteworthy, that the transformation employs readily available, aqueous solutions of acetaldehyde, rendering it operationally simple an atom economic. A series of γ,δ-unsaturated aldehydes could be synthesized with excellent enantioselectivities (>99% ee). The synthetic utility of this reactions was demonstrated with the diastereoselective one-pot preparation of diverse α,β-disubstituted aldehydes and the formal syntheses of heliannuol C and E as well as heliespirone A and C.

AUTHOR INFORMATION

Corresponding Author

*E-mail: erickm.carreira@org.chem.ethz.ch

Notes

The authors declare no competing financial interest.

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