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

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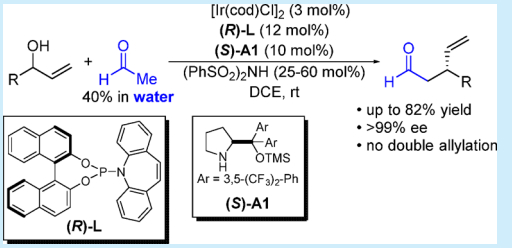
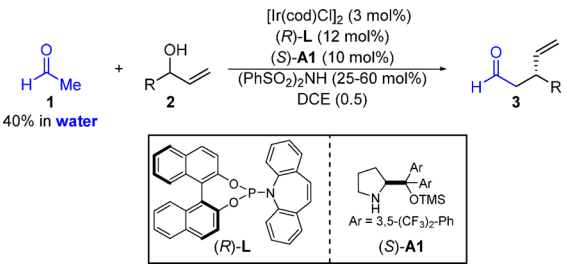
ABSTRACT: The enantioselective α-allylation of aqueous solutions of acetaldehyde using iridium- and amine-catalyzed substitution of racemic allylic alcohols is described. The method utilizes a readily available, safely handled aqueous solution of acetaldehyde and furnishes γ,δ-unsaturated aldehydes in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

The development of asymmetric transformations employing acetaldehyde as a nucleophile must overcome several factors.[5] First, 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 monofunctionalization of acetaldehyde can be challenging as the initially formed aldehyde products can often undergo downstream 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 past 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 of commercially available aqueous solutions of acetaldehyde (40 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

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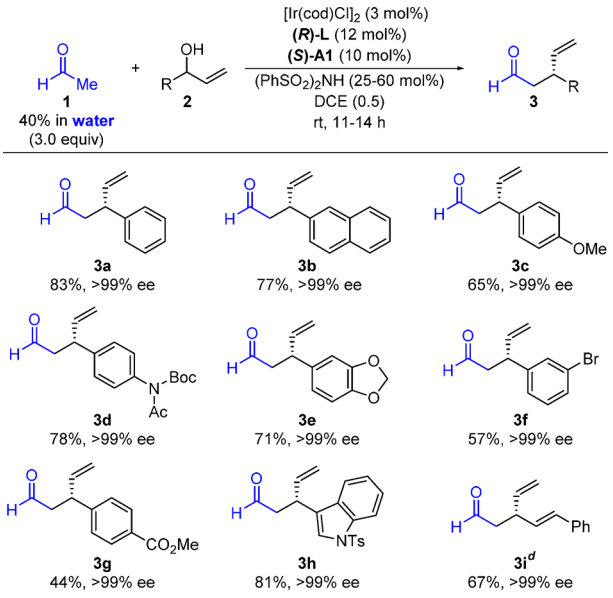
(**1**) in the presence of the catalytic complex [Ir/(*R*)-**L**], dichloroacetic acid and secondary amine (*S*)-**A1** afforded γ,δ-unsaturated aldehyde **3a** in 16% yield and excellent enantioselectivity (>99% ee). Notably, under these biphasic reaction conditions no double allylation was observed. 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 dibenzenesulfonimide in combination with [Ir/(*R*)-**L**], (*S*)-**A1** and allylic alcohol **2a** afforded product **3a** in 83% yield and >99% ee.[10]

With the 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

Table 1. Allylic Alcohol Scope of the α-Allylation of Aqueous Acetaldehyde[a−d]

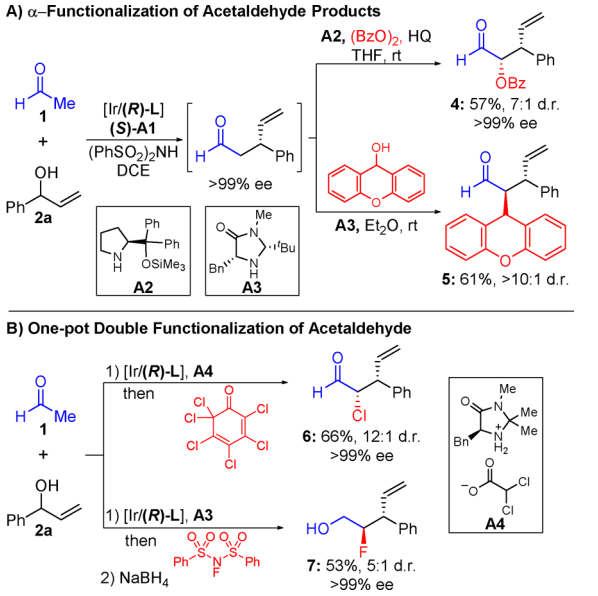


[a]Reactions run on 0.25 mmol scale under the standard conditions. [b]Yields of isolated aldehydes. [c]ee of the corresponding primary alcohol determined by SFC on a chiral stationary phase. [d]Branched/linear = 10:1.

(**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 alcohol **2h** as well as cinnamaldehyde-derived substrate **2i** were tolerated, resulting in equally high degrees of enantioinduction.

Next, we aimed to utilize this iridium-catalyzed allylation of acetaldehyde to rapidly gain access to more complex molecules (Scheme 2). 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

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



[a]For detailed experimental procedures, see the Supporting Information. [b]Diastereomeric ratios were determined by ^{1}H NMR analysis of unpurified reaction mixtures. HQ = hydroquinone.

acetaldehyde with [Ir/(*R*)-**L**] and allylic alcohol **2a** in the presence of chiral amine **A4** followed by the addition of hexachloro-2,5-cyclohexadien-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 from acetaldehyde derived allylation adducts.

To highlight the potential of the iridium-catalyzed allylation of acetaldehyde in the context of target-oriented synthesis, we undertook the formal syntheses of heliannuols C and E as well as heliespirones A and C (Scheme 3). 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. Compound **8** was treated sequentially with sodium borohydride and methoxymethyl 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 and heliespirones A and C.[19,20]

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

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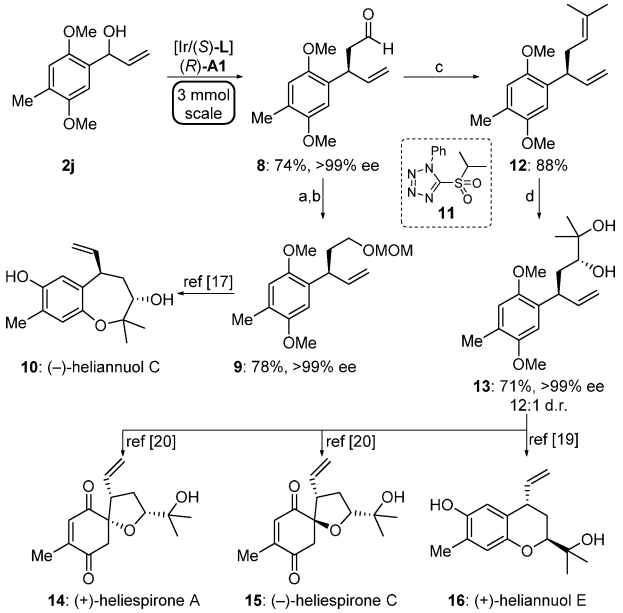
Scheme 3. Formal Syntheses of Sunflower-Derived Natural Products[a]



[a]For detailed experimental procedures, see the 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).

enantioselectivities (>99% ee). The synthetic utility of this reaction was demonstrated with the diastereoselective one-pot preparation of diverse α,β-disubstituted aldehydes and the formal syntheses of heliannuols C and E as well as heliespirones A and C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04658.

General methods, detailed experimental procedures, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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