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COMMUNICATION

Catalytic enantioselective Grignard Nozaki–Hiyama methallylation from the alcohol oxidation level: chloride compensates for π-complex instability†‡

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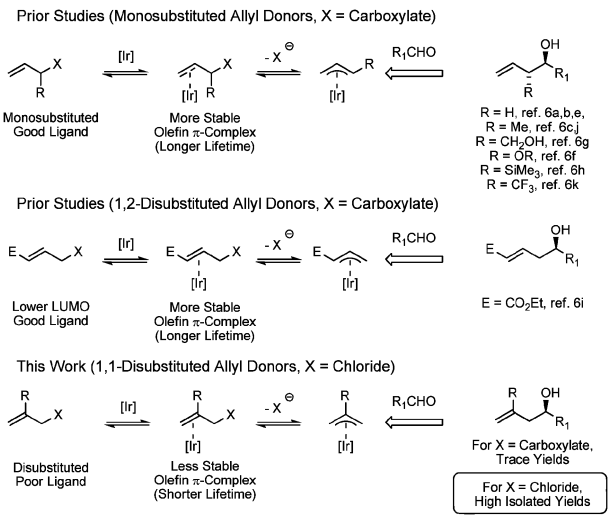
Methallyl chloride serves as an efficient allyl donor in highly enantioselective Grignard Nozaki–Hiyama methallylations from the alcohol or aldehyde oxidation level *via* iridium catalyzed transfer hydrogenation. Under identical conditions, methallyl acetate does not react efficiently. Double methallylation of 1,3-propanediol provides the C_2-symmetric adduct as a single enantiomer, as determined by HPLC analysis.

The reductive coupling of allylic chlorides to carbonyl compounds is typically conducted under Grignard conditions employing elemental magnesium as a terminal reductant.[1] To achieve enantioselective reductive coupling of allylic chlorides to carbonyl compounds, asymmetric variants of Fürstner's modification[2] of the Nozaki–Hiyama reaction may be used.[3,4] In more recent studies, hydrogen exchange between alcohols and π-unsaturated reactants was found to trigger generation of electrophile–nucleophile pairs, enabling a variety of enantioselective carbonyl allylation processes.[5,6] A remarkable feature of these transformations resides in the ability to perform carbonyl addition directly from the alcohol oxidation level in the absence of stoichiometric allylmetal reagents or (organo)metallic reductants.

One restriction associated with such iridium catalyzed carbonyl allylations relates to the requirement of allyl donors that incorporate monosubstituted olefins: higher degrees of olefin substitution are not tolerated. It has been established that the stability of late transition metal–olefin π-complex decreases with increasing olefin substitution.[7] As olefin coordination is a prerequisite to ionization, the requirement of allyl donors that incorporate monosubstituted olefins likely stems from the shorter lifetime of more highly substituted iridium–olefin π-complexes. However, in prior studies on vinylogous aldol addition,[6i] LUMO-lowering substituents were found to increase the degree of π-backbonding[8,9] thus compensating for steric destabilization of the transient π-complex arising from higher degrees of olefin substitution (Scheme 1).



Scheme 1 Better leaving groups compensate for decreased π-complex stability, facilitating π-allyl formation.

To enable efficient reactions of more highly substituted allyl donors in the absence of electronic effects, one may compensate for the shorter lifetime of the iridium–olefin π-complexes by employing a more reactive leaving group. For example, whereas methallyl acetate does not participate in efficient enantioselective iridium catalyzed carbonyl addition, methallyl chloride might serve as a feasible allyl donor.[10–12] Given the paucity of studies devoted exclusively to enantioselective carbonyl methallylation,[10h,11g,12a] this class of carbonyl additions was selected for investigation. In this account, we report that methallyl chloride does indeed participate in efficient enantioselective carbonyl methallylation from the alcohol or aldehyde oxidation level, whereas methallyl acetate does not. More significantly, this work reveals key structural–interactional features of the catalytic system that should accelerate development of hitherto inaccessible C–C bond forming transfer hydrogenations.

Our studies began with an assay of various methallyl carboxylates, sulfonates and halides employing as a catalyst the chromatographically isolated cyclometallated iridium π-allyl complex "(*R*)-**I**", which is prepared from $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPHEP, allyl acetate and 4-cyano-3-nitrobenzoic acid (Scheme 2).

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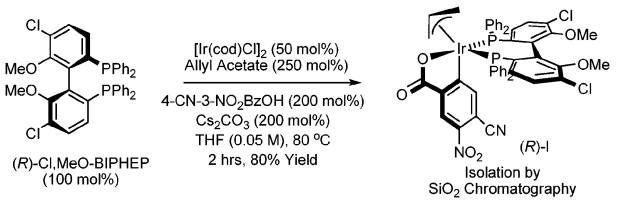
† Electronic supplementary information (ESI) available: Characterization data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS, [α]). Absolute stereochemical assignments of **3g** *via* single crystal X-ray diffraction are provided. CCDC 835997. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14392a



Scheme 2 Synthesis of iridium complex (*R*)-I.

Using benzylic alcohol **1g** as a test reactant, it was found that methallyl carboxylates delivered only trace quantities of C–C coupling product **3g**. In contrast, under identical conditions, much higher conversions were observed using methallyl chloride, an inexpensive commercial material. However, these initial experiments, which were conducted at 70 °C over 48 hours, also revealed a major side-reaction: oxidation of the initially formed methallylation product **3g** to form the conjugated dimethyl enone **4g**.[13] The formation of enone **4g** corroborates the poor coordinating ability of the methyl-substituted homoallylic olefin. Olefin dissociation at the stage of the homoallylic iridium alkoxide opens a coordination site, which induces β-hydride elimination to form a transient β,γ-enone that isomerizes to the conjugated enone **4g**.

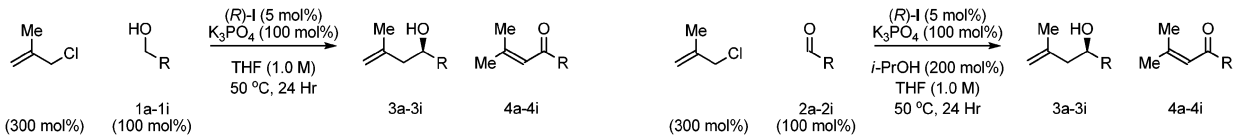
It was found that oxidation of the initially formed methallylation product **3g** to form enone **4g** is suppressed at lower temperature (50 °C) and shorter reaction times (24 hours). Under optimal conditions involving the use of catalyst (*R*)-**I** (5 mol%), methallyl chloride (300 mol%) and potassium phosphate (100 mol%) in THF (1 M) at 50 °C, benzylic alcohol **1g** is transformed to the adduct **3g** in 83% isolated yield and 96% enantiomeric excess. These conditions were applied to alcohols **1a–1i**. The products of methallylation **3a–3i** were produced in good to excellent yields and with uniformly high levels of enantioselectivity. Notably, aliphatic alcohols **1a–1d** undergo methallylation to form adducts **3a–3d** with virtually complete suppression of further oxidation to form enones **4a–4d** (Table 1).

In the presence of isopropanol (200 mol%), but under otherwise identical conditions an equivalent set of adducts **3a–3i** can be generated from aldehydes **2a–2i**. In most cases, comparable isolated yields and enantioselectivities are observed. Thus, carbonyl methallylation is achieved with equal facility from the alcohol or aldehyde oxidation level. As previously observed, competing enone formation is most evident in the case of adducts that embody allylic and benzylic secondary alcohols, which are more susceptible to β-hydride elimination (Table 1). The absolute stereochemistry of methallylation products **3a–3i** was made in analogy to that determined for bromide containing adduct **3g** by single crystal X-ray diffraction analysis using the anomalous dispersion method.

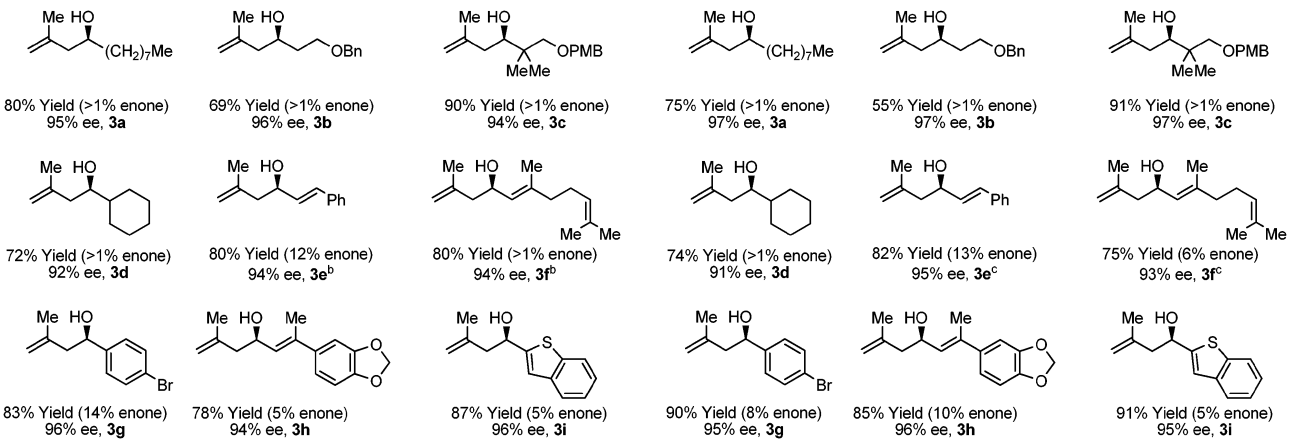
To showcase the utility of this methodology, double enantioselective methallylation of 1,3-propanediol was attempted under standard conditions.[14] The corresponding C_2-symmetric diol **6** is produced in 66% isolated yield as a single enantiomer, as the minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer of the product.[15] Diol **6** was converted to acetonide **7** and subjected to ozonolysis to provide the formal product of double acetone aldol addition **8** (Scheme 3).

The present study suggests that methallyl acetate does not serve as an efficient allyl donor due to the lower stability and, hence, shorter lifetime of the iridium–olefin π-complex that precedes formation of the requisite π-allyliridium complex.

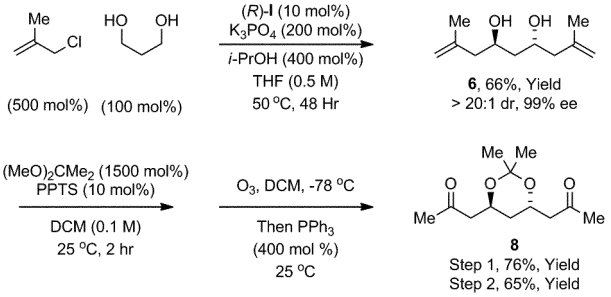
Table 1 Enantioselective carbonyl allylation from the alcohol or aldehyde oxidation level[a]



1a, R = $(CH_2)_7Me$ **1b**, R = $(CH_2)_2OBn$ **1c**, R = CMe_2CH_2OPMB **2a**, R = $(CH_2)_7Me$ **2b**, R = $(CH_2)_2OBn$ **2c**, R = CMe_2CH_2OPMB
1d, R = *c*-C_6H_{11} **1e**, R = CH=CHPh **1f**, R = geranyl **2d**, R = *c*-C_6H_{11} **2e**, R = CH=CHPh **2f**, R = geranyl
1g, R = 4-BrC_6H_4 **1h**, R = piperonyl **1i**, R = 2-benzothienyl **2g**, R = 4-BrC_6H_4 **2h**, R = piperonyl **2i**, R = 2-benzothienyl



[a] See ESI† for detailed experimental procedure. [b] 200 mol% isopropanol. [c] 400 mol% isopropanol.



Scheme 3 Double methallylation of propanediol to form the C_2-symmetric adduct **8**.

Through the use of methallyl chloride, which incorporates a more reactive leaving group, ionization to form the π-allyliridium complex becomes more rapid, compensating for the shorter lifetime of the more highly substituted olefin π-complex. Based on this insight into the requirements of the catalytic process, highly enantioselective Grignard-Nozaki–Hiyama methallylation is achieved from the alcohol or aldehyde oxidation levels in the absence of stoichiometric metallic reagents or reductants. Future studies will focus on the development of related alcohol–alkyl halide C–C couplings.

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