ChemInform Abstract: Iridium-Catalyzed anti-Diastereo- and Enantioselective Carbonyl (Trimethylsilyl)allylation from the Alcohol or Aldehyde Oxidation Level.

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Iridium Catalyzed *anti*-Diastereo- and Enantioselective Carbonyl (Trimethylsilyl)allylation from the Alcohol or Aldehyde Oxidation Level

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Abstract

Using the *ortho*-cyclometallated π-allyl iridium precatalyst (*R*)-**I** derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS and allyl acetate, enantioselective transfer hydrogenation of α-(trimethylsilyl)allyl acetate in the presence of aldehydes **2a**–**2i** mediated by isopropanol delivers products of (trimethylsilyl)allylation **4a**–**4i** in good isolated yields and with exceptional levels of *anti*-diastereoselectivity and enantioselectivity (90–99% ee). In the absence of isopropanol, but under otherwise identical reaction conditions, carbonyl (trimethylsilyl)allylation is achieved directly from alcohol oxidation level to furnish an equivalent set of adducts **4a**–**4i** with roughly equivalent isolated yields and stereoselectivities. To evaluate the synthetic utility of the reaction products **4a**–**4i**, adduct **4g** was converted to the 1,4-ene-diol **5g** via dioxirane mediated oxidative desilylation with allylic transposition, the allylic alcohol **6g** via protodesilylation with allylic transposition, and the γ-lactam **7g** via chlorosulfonyl isocyanate mediated cycloaddition.

Introduction

In connection with studies aimed at the discovery of hydrogen-mediated reductive C-C bond formations beyond hydroformylation, we recently uncovered a broad family of C-C bond forming transfer hydrogenations promoted by iridium and ruthenium catalysts.[1] A remarkable feature of these processes resides in the ability to achieve carbonyl addition from the aldehyde or alcohol oxidation level. In the former case, isopropanol or formic acid mediate reductive C-C coupling. In the latter case, dehydrogenation of the primary alcohol reactants generates aldehyde electrophiles, while simultaneously driving reductive generation of nucleophilic organometallics from unsaturated reactants. Using *ortho*-cyclometallated iridium catalysts, highly enantioselective protocols for carbonyl allylation,[2a,b,e–h,j] crotylation[2c,f,j] and *tert*-prenylation[2d,f,j] from the alcohol or aldehyde oxidation level were devised. More recently, related catalytic enantioselective methods carbonyl (hydroxy)allylation and (hydroxymethyl)allylation were developed.[3] Unlike conventional methods for carbonyl allylation,[4] these processes circumvent use of premetallated nucleophiles and metallic reductants.[1–3]

Here, using the isolated *ortho*-cyclometallated π-allyl iridium precatalyst derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS[5] and allyl acetate, we report that α-(trimethylsilyl)allyl acetate[6] **1a** couples to carbonyl compounds from the aldehyde or alcohol oxidation level, respectively, with exceptional levels of regio-, *anti*-diastereo- and

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge *via* the internet at http://pubs.acs.org.

enantioselectivity (Scheme 1). In this fashion, α-(trimethylsilyl)allyl acetate serves as a alternative to previously reported silicon-containing 1,3- or 1,1-bimetallic allyl transfer agents.[7–11] As demonstrated in the case of adduct **4g**, the products of (trimethylsilyl)allylation are readily converted to 1,4-ene-diols upon DMDO oxidation.[8h,i] Additionally, conditions for proto-desilylation with allylic transposition have been identified in the absence of a hydroxyl protecting group. Finally, upon exposure to chlorosulfonyl isocyanate, formal [3+2] cycloaddition occurs to deliver γ-lactams possessing 3 contiguous stereogenic centers as single diastereomers.

Results and Discussion

Our study began with the attempted (trimethylsilyl)allylation of benzyl alcohol **3a**. Using the *ortho*-cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS[5] and allyl acetate, neither the desired (trimethylsilyl)allylation product **4a** or resulting Peterson olefination product were detected. Using the isolated π-allyl iridium precatalyst (*R*)-**I** in the presence of cesium carbonate, the desired (trimethylsilyl)allylation product **4a** was formed along with substantial quantities Peterson olefination product. After screening various inorganic bases, it was found that Peterson olefination is suppressed using K_3PO_4 (1.0 equiv.) in the presence of water (5.0 equiv.) for reactions conducted at 70 °C. Under these conditions, α-(trimethylsilyl)allyl acetate **1a** was coupled to a structurally diverse set of aldehydes **2a**–**2i** (Table 1). In each case, good isolated yields were accompanied by exceptional levels of diastereo- and enantioselectivity. In the absence of isopropanol, but under otherwise identical conditions, (trimethylsilyl)allylation occurs directly from the alcohol oxidation level to furnish an identical set of adducts **4a–4i** (Table 2). Again, good isolated yields were accompanied by exceptional levels of diastereo- and enantioselectivity. Thus, unlike corresponding protocols involving allylmetal reagents,[7–11] carbonyl (trimethylsilyl)allylation occurs with equal facility from the alcohol or aldehyde oxidation level.

The mechanism for catalytic carbonyl (trimethylsilyl)allylation is analogous to that previously proposed for related crotylations.[2c] However, complete levels of *anti*-diastereoselectivity are observed in nearly all cases, suggesting carbonyl addition occurs exclusively from the (*E*)-σ-allyl through a chair-like transition structure. Notably, although the catalyst dehydrogenates primary alcohols **2a**-**2i**, the reaction products **4a–4i**, which are homo-allylic alcohols, are not oxidized under the coupling conditions and, hence, do not experience any erosion of enantiomeric purity by way of redox equilibration. This result is remarkable as 2-propanol, a secondary alcohol, is oxidized under the coupling conditions when aldehydes **3a**–**3i** are employed as reactants. As indicated in the proposed catalytic mechanism (Scheme 2), coordination of iridium to the homoallylic olefin of reaction products **4a**–**4i** provides a hexa-coordinate, 18-electron complex that cannot engage in β-hydride elimination due to the absence of an open coordination site.

To evaluate the utility of the coupling products **4a**–**4i**, adducts **4a**, **4f**, **4g** and **4i** were subjected to DMDO-mediated oxidative elimination.[8h,i] The 1,4-ene-diols **5a**, **5f**, **5g** and **5i** were produced in excellent yield with high levels of *E:Z* selectivity (Scheme 3). Proto-desilylation was attempted next. Under nearly all conditions assayed, exclusive formation of Peterson olefination products was observed. However, upon exposure of adduct **4g** to $TiCl_4$ in the presence of exogenous aldehyde, the product of proto-desilylation **6g** is generated in 73% yield with complete *E:Z* selectivity (Scheme 3). In the absence of aldehyde, Peterson olefination is again the exclusive reaction product, suggesting exogenous aldehyde protects the hydroxyl moiety of **4g** through formation of a titanium bound hemi-acetal. Notably, compound **6g** was previously prepared in 7-steps from malic acid.[12] Thus far, the protodesilylation is most efficient for the benzyl-ether containing adduct **4g** (Scheme 4).

Finally, under conditions similar to those described by Woerpel,[13] exposure of **4g**-OAc to chlorosulfonyl isocyanate delivers the product of [3+2] cycloaddition, the 4,5-*trans*-disubstituted pyrrolidinone **7g**, as a single diastereomer. Lactone formation was not observed. Formation of the **7g** suggests a mechanism involving stereoselective addition of chlorosulfonyl isocyanate to the allylsilane anti-periplanar with respect to the silyl group to generate the indicated β-silyl carbocation. Exclusive *N*-cyclization accompanied by 1,2-silyl migration delivers the 4,5-*trans*-substituted pyrrolidinone **7g**. In the absence of $NaHCO_3$, a mixture of lactone and lactam products are observed. These data suggest that partitioning of the *N*- and *O*-cyclization pathways is not dictated primarily by steric factors as proposed by Woerpel,[13b] but that the acidity of the medium plays a dominant role (Scheme 5).

Summary

In summary, we report a highly *anti*-diastereo- and enantioselective carbonyl (trimethylsilyl)allylation under the conditions of iridium catalyzed transfer hydrogenation employing a single-component catalyst, the *ortho*-cyclometallated complex (*R*)-**I**. Notably, identical sets of adducts **4a**–**4i** are formed with comparable levels of selectivity from the aldehyde or alcohol oxidation level in the absence of Peterson olefination. Oxidative desilylation of adducts **4a**, **4f**, **4g** and **4i** employing DMDO provides access to highly enantiomerically enriched 1,4-ene-diols **5a**, **5f**, **5g** and **5i**.[8h,i] Conditions for proto-desilylation with allylic transposition have been identified for adduct **4g** in the absence of a hydroxyl protecting group. Finally, exposure of adduct **4g** to chlorosulfonyl isocyanate delivers 4,5-*trans*-disubstituted pyrrolidinone **7g** as a single diastereomer. Future studies will focus on the development of related alcohol-unsatruate C-C couplings and related imine additions from the amine oxidation level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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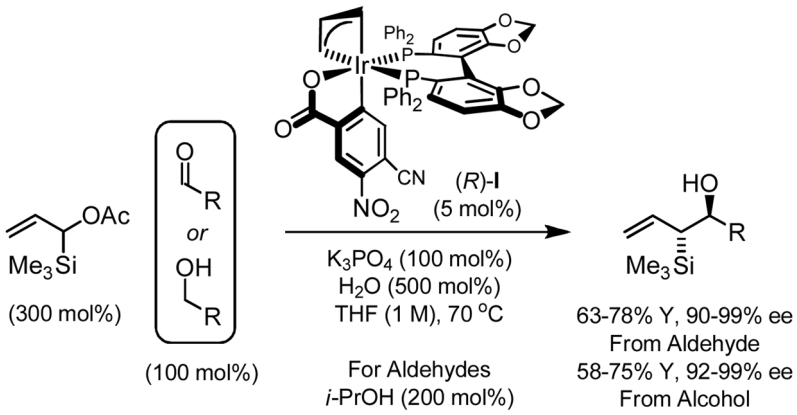
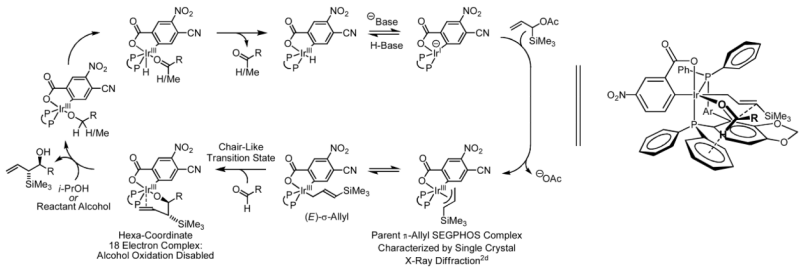


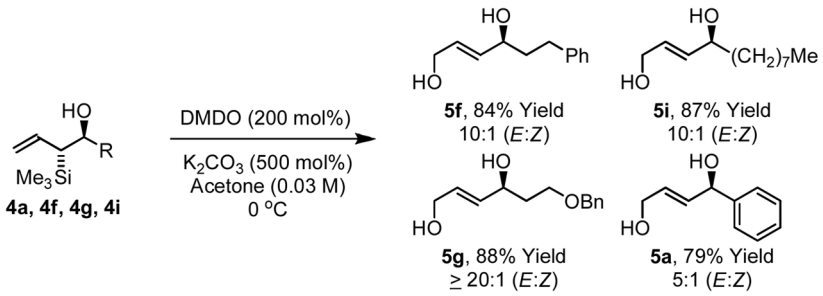
Scheme 1.

Iridium catalyzed *anti*-diastereo- and enantioselective carbonyl (trimethylsilyl)allylation from the alcohol or aldehyde oxidation Level.



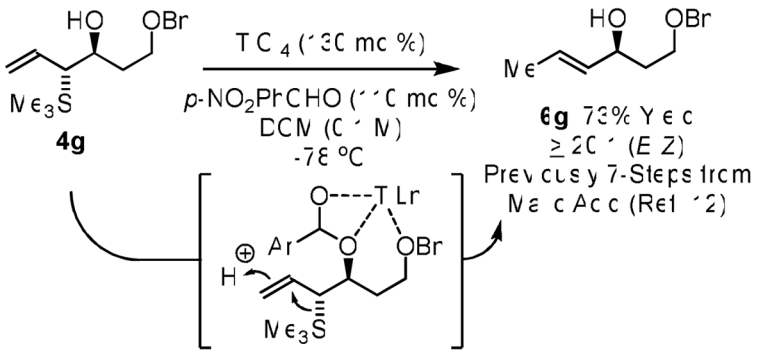
Scheme 2.

Proposed catalytic mechanism and stereochemical model for carbonyl (trimethylsilyl)allylation from the alcohol or aldehyde oxidation level.



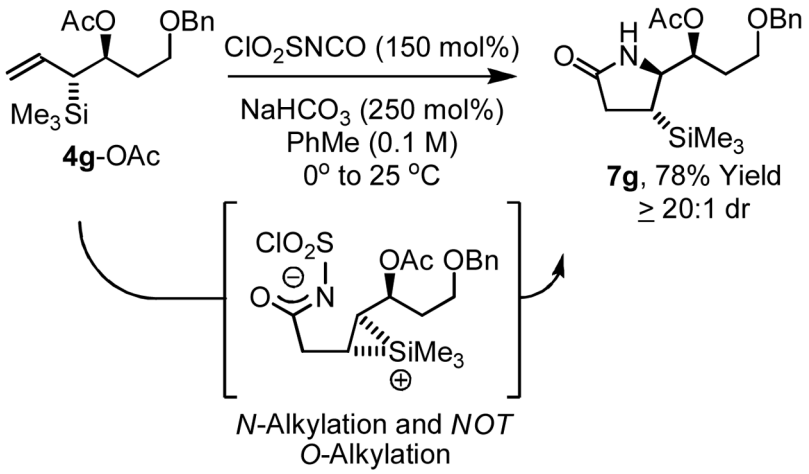
Scheme 3.

Dioxirane mediated oxidative desilylation of adducts **4a**, **4f**, **4g** and **4i** to furnish the corresponding 1,4-ene-diols **5a**, **5f**, **5g** and **5i**.



Scheme 4.

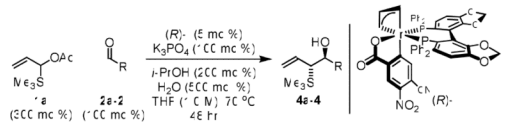
Protodesilylation of **4g** requires exogenous aldehyde to suppress Peterson olefination.

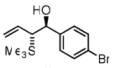
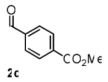
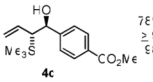
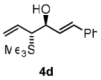
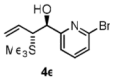
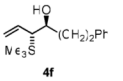
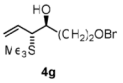
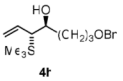
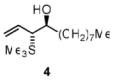


Scheme 5.
Reaction of adduct **4g** with chlorosulfonyl isocyanate to furnish the product of formal [3+2] cycloaddition **7g**.

Table 1

Enantioselective α-(trimethylsilyl)allylation from the aldehyde oxidation level.[a]

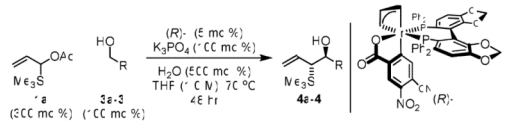


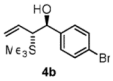
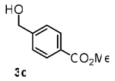
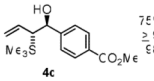
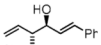
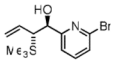
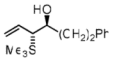
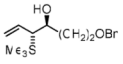
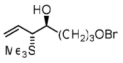
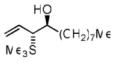
Entry	Aldehyde	Product	Yield, dr, ee%
1	 2a	 4a	71% Yield ≥ 33 : 1 dr 98% ee
2	 2b	 4b	73% Yield ≥ 33 : 1 dr 98% ee
3	 2c	 4c	78% Yield ≥ 33 : 1 dr 98% ee
4	 2d	 4d	74% Yield ≥ 33 : 1 dr 94% ee
5	 2e	 4e	66% Yield ≥ 33 : 1 dr 98% ee
6	 2f	 4f	69% Yield ≥ 33 : 1 dr 98% ee
7	 2g	 4g	63% Yield 4 : 1 dr 98% ee
8	 2h	 4h	69% Yield ≥ 33 : 1 dr 98% ee
9	 2i	 4i	72% Yield ≥ 33 : 1 dr 97% ee

[a] Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

Table 2

Enantioselective α-(trimethylsilyl)allylation from the alcohol oxidation level.[a]



Entry	Aldehyde	Product	Yield, dr, ee%
1	 3a	 4a	89% Yield ≥ 95 : 5 dr 98% ee
2	 3b	 4b	72% Yield ≥ 95 : 5 dr 98% ee
3	 3c	 4c	75% Yield ≥ 95 : 5 dr 98% ee
4	 3d	 4d	70% Yield ≥ 95 : 5 dr 92% ee[b]
5	 3e	 4e	88% Yield ≥ 95 : 5 dr 98% ee
6	 3f	 4f	85% Yield ≥ 95 : 5 dr 97% ee
7	 3g	 4g	87% Yield ≥ 95 : 5 dr 98% ee
8	 3h	 4h	89% Yield ≥ 95 : 5 dr 98% ee
9	 3i	 4i	87% Yield ≥ 95 : 5 dr 98% ee

[a] As described for Table 1.

[b] The complex modified by (*R*)-C3-TUNEPHOS was used as precatalyst.