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Catalyst-Directed Diastereo- and Site-Selectivity in Successive Nucleophilic and Electrophilic Allylation of Chiral 1,3-Diols: Protecting Group-Free Synthesis of Substituted Pyrans**

Inji Shin, Gang Wang, and Michael J. Krische

University of Texas at Austin, Department of Chemistry, 1 University Station – A5300, Austin, TX 78712-1167 (USA)

Michael J. Krische: mkrische@mail.utexas.edu

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Introduction

The site-selective transformation of polyfunctional molecules obviates the need to install and remove protecting groups, greatly enhancing step-economy.^[1] As illustrated in the work of Kawabata,^[2] Miller,^[3] and Taylor,^[4] the site-selective modification of carbohydrates and other natural polyols provides direct access to compounds that otherwise would require numerous steps to prepare. Taking advantage of the native reducing ability of alcohols, we have developed a family of redox-triggered carbonyl additions wherein hydrogen transfer from alcohols to π -unsaturated reactants produces electrophile-nucleophile pairs *en route* to products of formal alcohol C-H functionalization *via* carbonyl addition.^[5] Among the transformations emanating from this new pattern of reactivity, the enantioselective iridium catalyzed alcohol C-allylation, which employs allyl acetate as the allyl donor, has proven particularly useful, availing exceptionally concise routes to diverse polyketide natural products.^[6,7] Remarkably, the cyclometalated π -allyliridium C,O-benzoate catalysts used in such alcohol C-allylations display a pronounced kinetic preference for primary alcohol dehydrogenation,^[8,9] enabling site-selective allylation of unprotected diols and triols with high levels of catalyst-directed diastereoselectivity.^[6h,10]

In the present study, improved methods for site-selective diol C-allylation are applied to the construction of 4-hydroxy-2,6-*cis*- or *trans*-disubstituted pyrans, which appear frequently as substructures in polyketide natural products.^[11] As documented in the review literature,^[11] the formation of complex poly-substituted pyrans is often accomplished *via* Prins cyclization, cycloetherification of olefinic alcohols triggered by electrophilic reagents (e.g.

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Correspondence to: Michael J. Krische, mkrische@mail.utexas.edu.

haloetherification), and oxa-Michael cyclization. Additionally, carbophilic metals have been shown to catalyze the cyclization of monoallylic diols to form pyrans.^[12] We envisioned a strategy for pyran formation involving iridium catalyzed diastereo- and site-selective C-allylation of chiral 1,3-diols followed by conversion of the resulting terminal olefins to the corresponding allylic acetates *via* Grubbs metathesis and, finally, metal catalyzed diastereo- and site-selective metal catalyzed O-allylation to form the pyran ring (Scheme 1). The feasibility of this approach was rendered uncertain by limitations evident in reported methods for intramolecular metal catalyzed allylic alkylation to form pyrans *via* O-allylation. Specifically, whereas formation of *cis*-2,6-disubstituted pyrans under the conditions of palladium catalyzed allylic alkylation is readily achieved, poor levels of diastereoselectivity are typically observed in attempted formations of the corresponding *trans*-isomers.^[13] Further, although intermolecular asymmetric iridium catalyzed O-allylation is known,^[14,15] only one isolated example of the cyclization of an aliphatic alcohol has been reported, which involved furan formation.^[16]

Results and Discussion

In prior work on the diastereo- and site selective C-allylation of chiral diols, a chromatographically purified cyclometalated π -allyliridium *ortho*-C,O-benzoate complex derived from [Ir(cod)Cl]₂, allyl acetate, 4-cyano-3-nitro-benzoic acid, (*R*)- or (*S*)-SEGPHOS was employed.^[6h] While use of an isolable, single component catalyst offers certain advantages, for example, allowing reactions to be conducted at lower temperatures,^[6f] generation of the catalyst *in situ* from commercial components enables rapid evaluation of structurally diverse complexes. To identify an efficient *in situ* generated catalyst for the diastereo- and site-selectivity in the C-allylation chiral 1,3-diols, the commercially available malic acid derived diol **1a** was exposed to allyl acetate in the presence of [Ir(cod)Cl]₂, various 4-substituted-3-nitro-benzoic acids, and assorted axially chiral chelating phosphine ligands. Eventually, it was found that catalyst (*S*)-Ir-**Id** derived from 4-chloro-3-nitro-benzoic acid and (*S*)-Cl,MeO-BIPHEP was optimal, providing the adduct *anti*-**2a** in 79% isolated yield as a single diastereomer, as determined by ¹H NMR analysis of the crude reaction mixture (Scheme 2).

Using these conditions for *in situ* catalyst generation, the enantiomeric catalysts (*R*)- or (*S*)-Ir-**Id** were used to convert chiral 1,3-diols **1a–1c** to the diastereomeric products of C-allylation *syn*-**2a**, **2b**, **2c** and *anti*-**2a**, **2b**, **2c**, respectively (Scheme 3). In each case, good isolated yields and complete levels of catalyst-directed diastereoselectivity were observed. The site-selective dehydrogenation evident in the conversion of benzylic diol **1c** to *syn*-**2c** or *anti*-**2c** is especially noteworthy, as formation of the acetophenone should be far less endothermic than aldehyde formation, yet only trace quantities of the over-oxidized ketone product was observed. Most importantly, the diastereoselectivities observed in connection with the present protocol for *in situ* catalyst generation are uniformly better than the diastereoselectivities previously observed using related chromatographically purified catalysts.^[6h]

With the diastereomeric diols *syn*-**2a**, **2b**, **2c** and *anti*-**2a**, **2b**, **2c** in hand, conversion to the corresponding allylic acetates *syn*-**3a**, **3b**, **3c** and *anti*-**3a**, **3b**, **3c** was undertaken. Although

the unprotected 1,3-diol moieties evident in *syn*-**2a**, **2b**, **2c** and *anti*-**2a**, **2b**, **2c** posed some concerns regarding functional group compatibility, exposure of these compounds to the second generation Grubbs catalyst in the presence of *cis*-1,4-diacetoxy-2-butene delivered the desired allylic acetates *syn*-**3a**, **3b**, **3c** and *anti*-**3a**, **3b**, **3c** in excellent yields, albeit with incomplete control of alkene geometry (Scheme 4).^[17]

As the diastereomeric allylic acetates *syn*-**3a**, **3b**, **3c** and *anti*-**3a**, **3b**, **3c** each possess unprotected diol moieties, both 6-endo and 6-exo-*O*-allylation pathways are possible under the conditions of palladium catalyzed cyclization. Upon use of an achiral palladium catalyst modified by 1,1'-bis(diphenylphosphino)ferrocene, dppf, the 2,6-*cis*-pyrans were formed selectively *via* 6-exo-*O*-allylation, but with incomplete levels of diastereoselectivity and in highly variable yields. To amplify the intrinsic stereochemical bias toward the 2,6-*cis*-diastereomers, established conditions using a chiral palladium catalyst modified by (*S,S*)-1,2-diaminocyclohexane-*N,N'*-bis(2'-diphenylphosphinobenzoyl), DPPBA (Figure 1), were applied (Scheme 5).^[13b] The desired 4-hydroxy-2,6-*cis*-disubstituted pyrans 2,6-*cis*-**4a–4c** and 4-*epi*-2,6-*cis*-**4a–4c** were formed in excellent yields with complete levels of 2,6-*cis*-diastereoselectivity. These data reveal that pure olefin geometrical isomers are not required to achieve diastereoselective cyclization *via O*-allylation under the conditions of palladium catalysis, which is attributed to rapid equilibration of the π -allyl haptomers with respect to cyclization.^[18]

Given the intrinsic bias of chiral 1,3-diols *syn*-**3a–3c** and *anti*-**3a–3c** to form the 2,6-*cis*-disubstituted pyrans, preparation of the 4-hydroxy-2,6-*trans*-disubstituted pyrans 2,6-*trans*-**4a–4c** and 4-*epi*-2,6-*trans*-**4a–4c** represented a far more formidable challenge. Palladium catalysts modified by diverse chiral phosphine ligands, including (*R,R*)-DPPBA, provided highly variable diastereoselectivities in the *O*-allylation of chiral 1,3-diols *syn*-**3a–3c** and *anti*-**3a–3c**. At best, using (*R,R*)-DPPBA as ligand, a 4:1 diastereoselectivity (2,6-*trans*-**4a**:2,6-*cis*-**4a**) was observed in the *O*-allylation of the methyl-substituted diol *anti*-**3a**. Similarly, the isobutyl-substituted diol *anti*-**3b** provided a 4:1 diastereoselectivity (2,6-*trans*-**4b**:2,6-*cis*-**4b**). However, for the remaining diols, use of palladium based catalysts modified by (*R,R*)-DPPBA led to relatively poor 2,6-*trans*-diastereoselectivities.

In the hope of improving catalyst-directed diastereoselectivity, the Tsuji-Trost allylation of chiral 1,3-diols *syn*-**3a–3c** and *anti*-**3a–3c** was attempted using chiral iridium catalysts.^[14,15] Here, extensive screening of reaction conditions was required to balance conversion and 2,6-*trans*-diastereoselectivity. Ultimately, it was found that the cyclometalated iridium complex modified by the indicated chiral phosphoramidite ligand (*S,S,aS*)-**L** (Figure 1) provided optimal results. In several cases, incomplete conversion was observed. It has been reported that certain additives, such as tetrahydrothiophene, and triphenylphosphine with copper(I) iodide or Pb(II) acetate, can enhance both stereoselectivity and conversion in such iridium catalyzed Tsuji-Trost allylations.^[19] However, in our hands, these additives completely suppressed the reaction.

The trends in diastereoselectivity observed in the present cyclizations can be understood on the basis of the indicated stereochemical model, as illustrated in the cyclization of *anti*-**3a** (Scheme 7). Rapid interconversion of the diastereomeric π -allyl intermediates **A/B** and **C/D**

is anticipated.^[18] For the diastereomers **A/B**, the reactive conformer **B** is *pseudo*-equatorially disposed, and cyclization occurs readily to furnish 2,6-*cis*-**4a**. For the diastereomers **C/D**, the reactive conformer **D** is *pseudo*-axially disposed and, hence, the transition state for cyclization is anticipated to be higher in energy due to developing 1,3-diaxial interactions with the relatively large metal-bound vinyl moiety. Hence, reactions that form the 2,6-*cis*-diastereomers are intrinsically more facile. Energetic partitioning of the diastereomeric reactive conformers **B** and **D** is dependent on the structural features of the chiral metal fragment. As reflected by the observed diastereoselectivities and isolated yields, one can infer that the palladium π -allyl intermediates are more reactive and, hence, less selective than the corresponding iridium π -allyl intermediates.

Conclusion

In summary, we report the protecting group-free synthesis of 4-hydroxy-2,6-*cis*- or *trans*-pyrans through successive nucleophilic and electrophilic allylations of chiral 1,3-diols **1a–1c**. Using a cyclometalated iridium catalyst generated *in situ* from commercial components, the redox-triggered C-allylation of chiral 1,3-diols **1a–1c** occurs with complete levels of catalytic directed diastereoselectivity in the absence protecting groups to deliver chiral homoallylic diols *syn*-**2a**, **2b**, **2c** and *anti*-**2a**, **2b**, **2c**, which are converted to the allylic acetates *syn*-**3a**, **3b**, **3c** and *anti*-**3a**, **3b**, **3c** using the second-generation Grubbs catalyst. Electrophilic allylation, that is, Tsuji-Trost cyclization, of the allylic acetates *syn*-**3a**, **3b**, **3c** and *anti*-**3a**, **3b**, **3c**, using a chiral palladium catalyst, delivers the 4-hydroxy-2,6-*cis*-disubstituted pyrans 2,6-*cis*-**4a–4c** and 4-*epi*-2,6-*cis*-**4a–4c** with complete levels of catalyst-directed diastereoselectivity. Formation of the corresponding 4-hydroxy-2,6-*trans*-disubstituted pyrans 2,6-*trans*-**4a–4c** and 4-*epi*-2,6-*trans*-**4a–4c** was more challenging, but serviceable diastereoselectivities could be obtained upon use of chiral palladium or chiral iridium catalysts. The pyran 2,6-*trans*-**4a** represents a synthetic intermediate in an ongoing total synthesis of the polyketide natural product swinholide, which will be reported in due course.

Experimental Section

Representative procedure for iridium catalyzed diol C-allylation

(2S,4R)-Hept-6-ene-2,4-diol (syn-2a)—To a sealed tube under an argon atmosphere charged with (*S*)-butane-1,3-diol **1a** (18 mg, 0.20 mmol, 100 mol%), [Ir(cod)Cl]₂ (3.4 mg, 0.005 mmol, 2.5 mol%), (*R*)-Cl, MeO-BIPHEP (6.5 mg, 0.01 mmol, 5 mol%), Cs₂CO₃ (13.0 mg, 0.04 mmol, 20 mol%) and 4-Cl-3-NO₂-BzOH (4.0 mg, 0.02 mmol, 10 mol%) was added freshly distilled THF (1 mL) and allyl acetate (0.22 mL, 2.0 mmol, 10 eq.). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 40 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes/EtOAc = 1:1) to furnish title compound as a light yellow oil in 70% yield (18.3 mg, 0.14 mmol, dr = >20:1).

Representative procedure for palladium catalyzed diol O-allylation to form *cis*- or *trans*-2,6-disubstituted pyrans

(2*S*,4*R*,6*S*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*cis*-4a)—To a round bottomed flask under an argon atmosphere charged with Pd₂(dba)₃·CHCl₃ (6.2 mg, 0.06 mmol, 3 mol%) and (*S,S*)-DPPBA (12.4 mg, 0.018 mmol, 9 mol%) was added freshly distilled CH₂Cl₂ (5.2 mL). The mixture was allowed to stir at ambient temperature for 30 minutes, during which time the color of the solution changed from purple to orange. The orange solution was transferred *via* syringe to a round-bottomed flask charged with a solution of **anti-3a** (40.4 mg, 0.20 mmol, 100 mol%) and Et₃N (56 μL, 0.40 mmol, 200 mol%) in CH₂Cl₂ (15.5 mL). The reaction mixture was allowed to stir at 25 °C for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (hexanes/EtOAc = 3:2 to 2:3) to furnish the title compound as a colorless oil in 99% yield (28.2 mg, 0.198 mmol, dr = >20:1, 2,6-*cis*:2,6-*trans*).

Representative procedure for iridium catalyzed diol O-allylation to form *trans*-2,6-disubstituted pyrans

(2*S*,4*R*,6*R*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (2,6-*trans*-4a)—To a sealed tube under an argon atmosphere charged with [Ir(cod)Cl]₂ (3.1 mg, 0.003 mmol, 3 mol%) and (*S,S,aS*)-L (3.6 mg, 0.006 mmol, 6 mol%) was added TBD (7.0 mg, 0.05 mmol, 50 mol%) in THF (0.15 mL). The reaction mixture was allowed to stir at ambient temperature for 10 min, at which point a solution of **anti-3a** (20.2 mg, 0.10 mmol, 100 mol%) in THF (0.33 mL) was added *via* syringe. The reaction mixture was placed in a 90 °C oil bath and was allowed to stir for 20 h. The reaction mixture was allowed to cool to ambient temperature, and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes/EtOAc = 3:2 to 2:3) to furnish the title compound as a colorless oil in 61% yield (8.7 mg, 0.061 mmol, dr = 8:1, 2,6-*trans*:2,6-*cis*) and unreacted **anti-3a** in 21% yield (4.3 mg, 0.021 mmol), which corresponding to a 74% yield of 2,6-*trans*-4a based on recovered starting material (BRSM).

Supplementary Material

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Figure 1.
Structures of (S,S,aS) -L and (S,S) -DPPBA.

Scheme 1.

Catalyst-directed diastereo- and site-selectivity in successive nucleophilic and electrophilic allylations of chiral 1,3-diols.

Scheme 2.

Selected optimization experiments for *in situ* generation of iridium catalysts for the diastereo- and site-selective *C*-allylation of chiral 1,3-diol **1a**.

^aCited yields are of diastereomeric mixtures isolated by silica gel chromatography.

Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.

Scheme 3.

Diastereo- and site-selective C-allylation of chiral 1,3-diols **1a–1c** catalyzed by iridium.^a

^aCited yields are of diastereomeric mixtures isolated by silica gel chromatography.

Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.

Scheme 4.

Cross-metathesis of chiral diols *syn*-2a, 2b, 2c and *anti*-2a, 2b, 2c to form allylic acetates *syn*-3a, 3b, 3c and *anti*-3a, 3b, 3c.

^aCited yields are of diastereomeric mixtures isolated by silica gel chromatography. See Supporting Information for further experimental details.

Scheme 5.

Diastereo- and site-selective palladium catalyzed *O*-allylation of chiral 1,3-diols *syn*-3a–3c and *anti*-3a–3c to form 4-hydroxy-2,6-*cis*-disubstituted pyrans 2,6-*cis*-4a–4c and 4-*epi*-2,6-*cis*-4a–4c.

^aCited yields are of diastereomeric mixtures isolated by silica gel chromatography.

Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details. ^b50 °C. ^c $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ (5 mol %), (S,S)-DPPBA (15 mol%).

Scheme 6.

Diastereo- and site-selective palladium and iridium catalyzed *O*-allylation of chiral 1,3-diols *syn*-**3a–3c** and *anti*-**3a–3c** to form 4-hydroxy-2,6-*trans*-disubstituted pyrans **2,6-*trans*-4a–4c** and 4-*epi*-2,6-*trans*-**4a–4c**.

^aCited yields are of diastereomeric mixtures isolated by silica gel chromatography.

Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures.

TBD = 1,5,7,-triazabicyclo[4,4,0]dec-5-ene. See Supporting Information for further

experimental details. ^bPd₂(dba)₃-CHCl₃ (3 mol%), (*R,R*)-DPPBA (9 mol%). ^c50 °C. ^dYield based on recovered starting material.

Scheme 7.

Stereochemical features accounting for the trends in diastereoselectivity observed in the formation of 4-hydroxy-2,6-*cis*- and *trans*-pyrans 2,6-*cis*-4a and 2,6-*trans*-4a via Tsuji-Trost allylation.