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Communication

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Iridium-Catalyzed Enantioselective Allylic Substitution with Aqueous Solutions of Nucleophiles

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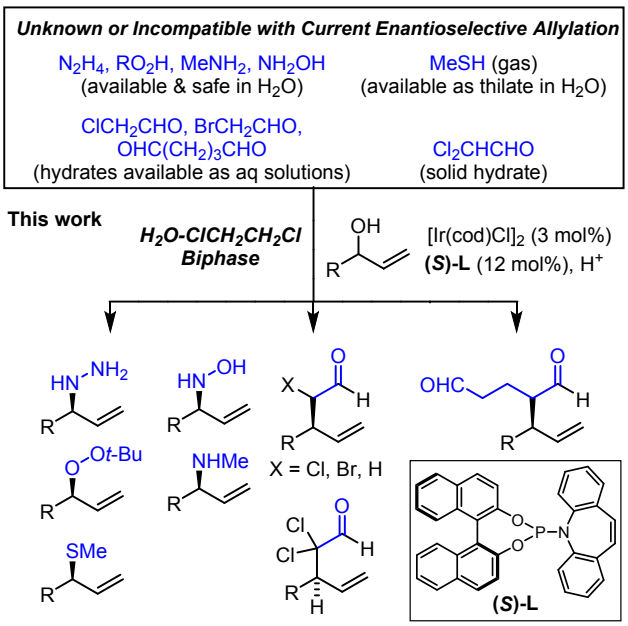
Supporting Information Placeholder

ABSTRACT: The iridium-catalyzed asymmetric allylic substitution under biphasic conditions is reported. This approach allows the use of various unstable and/or volatile nucleophiles including hydrazines, methylamine, *t*-butyl hydroperoxide, *N*-hydroxylamine, α -chloroacetaldehyde and glutaraldehyde. This transformation provides rapid access to a broad range of products from simple starting materials in good yields and up to >99% ee and 20:1 d.r. Additionally, these products can be elaborated efficiently into a diverse set of cyclic and acyclic compounds, bearing up to four stereocenters.

Enantioselective, transition metal-catalyzed allylic substitution has emerged as a powerful tool for the synthesis of chiral building blocks from simple starting materials and a wide range of nucleophiles.[1] The electrophilic nature of the η^3-organometal intermediate typically restricts the conditions to non-nucleophilic organic solvents and with few exceptions prescribes rigorous exclusion of water.[2] Yet, there are a number of highly reactive and/or unstable small molecules such as chloroacetaldehyde, hydrazines or *N*-hydroxylamine that due to their reactivity or limited stability in pure form are stored, sold, and most safely handled as aqueous solutions. To date, only protected versions of these reagents including hydroxamic acids and hydrazones have been employed in transition metal-catalyzed allylic substitution.[2d,3] Developing methods which employ the commercially available aqueous solutions of these unstable molecules, however, would significantly expand the synthetic utility of enantioselective catalysis.

In general, organocatalytic methods based on enamine catalysis or hydrogen bonding catalysts have been shown to be compatible with aqueous media.[4] For instance, aqueous chloroacetaldehyde has been employed as an electrophile in enzymatic or organocatalytic aldol reactions but its use as an nucleophile remains elusive.[5] In the field of asymmetric transition-metal catalysis, biphasic systems for enantioselective oxidations[6] and hydrogenations[7] have garnered significant attention, but transformations generating carbon-carbon bonds under aqueous conditions remain scarce.[8] Herein we report the asymmetric substitution reaction of racemic allylic alcohols with aqueous nucleophiles such as hydrazines, *N*-hydroxylamines, and α-halo-acetaldehydes catalyzed by a chiral Ir(P,olefin) complex under aqueous biphasic conditions (Scheme 1). The transformations employ aqueous solutions that the reagents are supplied in, and thus avoid laborious extraction and dehydration techniques.[9] Our approach delivers products in good yields and high regio- and enantioselectivities for nucleophiles that have been rarely employed to date.

Scheme 1. Iridium-Catalyzed Allylic Substitution Using Nucleophiles or their Hydrates in Aqueous Solutions.



Excess water can pose a challenge in transition metal-catalyzed allylic substitution not only because it can lead to decomposition of the η^3-organometal intermediate but also due to its inherent nucleophilicity.[2g,10] Thus, for a productive catalytic cycle with nucleophiles in aqueous solutions, the nucleophilic addition of water to the activated allyl-metal complex needs to be either kinetically disfavored or reversible. This makes allylic substitution reactions employing branched, unactivated allylic alcohols prime targets for the development of biphasic reactions, as nucleophilic attack by water would regenerate the starting material. With these considerations in mind, we set out to develop a general approach to biphasic allylic substitutions using the complex derived from $[Ir(cod)Cl]_2$/(*S*)-**L** and nucleophiles in aqueous solutions.[11]

Our group has previously developed an Ir(P,olefin) complex derived from phosphoramidate ligand (*S*)-**L** and iridium(I) for the displacement of allylic alcohols with various nucleophiles.[11] Key features of this catalytic system are its high robustness and its use of branched, unactivated allylic alcohols as substrates, activated by Brønsted acids.[11b] Therefore, we envisioned that this system would be well suited to explore allylic substitutions under biphasic conditions with nucleophiles that are stabilized in water and thus readily available as aqueous solutions. To demonstrate the feasibility of this approach, we initially focused on aqueous hydrazine. Chiral hydrazine derivatives are used in stereoselective

[3+2]-cycloadditions,[12] as organocatalysts,[13] and as commercialized drugs for the treatment of Parkinson's disease.[14] Hydrazine is a colorless liquid that decomposes explosively and is commonly used as a rocket fuel.[15] Thus, aqueous solutions of hydrazine find widespread applications in organic synthesis. When a 51% aqueous solution of hydrazine was used in combination with the Ir(P,olefin) complex, allylic alcohol **1a** (R = 2-Np) and 3,5-dichlorobenzoic acid as a Brønsted acid promoter adduct **2a** was obtained in 61 % yield and 94% ee (Table 1).[16] This result encouraged us to investigate aqueous solutions of various substituted hydrazine derivatives (Table 1, **2b**-**2e**). Of particular interest are substrates **2d** and **2e**. Such 1-amino piperazine and 4-amino-1,2,3-triazole derivatives have garnered significant attention from medicinal chemists and can be found in commercial drugs.[17] Due to their limited solubility in aprotic, non-nucleophilic organic solvents and the fact that they are freely soluble in water, these substrates demonstrate the synthetic power of a biphasic approach

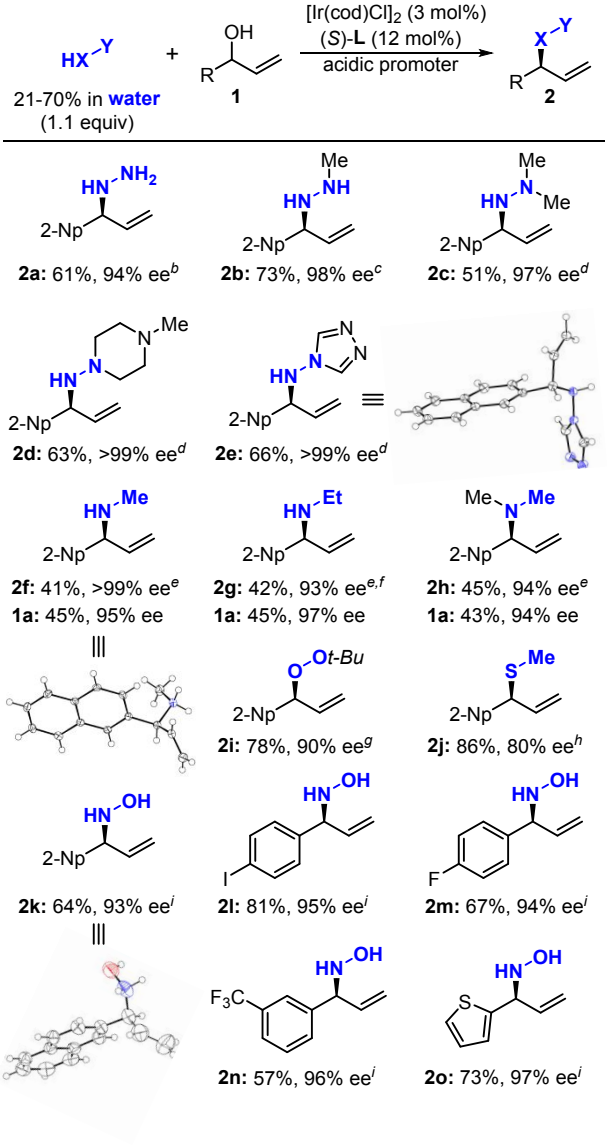
Subsequently, we examined methyl, ethyl and dimethyl amine, which are gases at room temperature but are readily available as aqueous solutions. Interestingly, for these more basic and less nucleophilic reagents, kinetic resolution of allylic alcohol **1a** was observed, and the enantioselectivity and conversion was found to strongly depend on the acidic promoter used (see supplementary information). With 3,5-dichlorobenzoic acid the corresponding secondary and tertiary amines were obtained in good yields along with the enantioenriched starting material. We then aimed to expand the scope of aqueous nucleophiles to other heteroatoms. Interestingly, *tert*-butyl hydroperoxide and sodium thiomethoxide, sold as 70% and 21% aqueous solutions respectively, afforded the corresponding adducts (**2p** and **2q**) in good yield and stereoselectivity. It is noteworthy, that the catalytic system described herein is compatible with both reductants (hydrazines)[18] and oxidants (*t*-butyl hydroperoxide).

Encouraged by these results, *N*-hydroxylamine was also investigated as nucleophile for iridium-catalyzed allylic substitution. *N*-alkylated hydroxylamines are useful precursors for chiral nitrones and find application in the synthesis of complex molecules.[19] Similarly to hydrazine, hydroxylamine is preferably used as an aqueous solution or its hydrochloride salt since the pure compound is unstable.[20] Recently Zhao reported the enantioselective allylation of $H_2NOH{\cdot}HCl$ requiring DMSO as solvent and triethyl amine to liberate hydroxyl amine.[21] Hence, we believe the biphasic system utilizing aqueous *N*-hydroxylamine complements this approach. When a 50% aqueous solution of *N*-hydroxylamine was used in combination with the Ir(P,olefin) complex, allylic alcohol **1a** (R = 2-Np) and dibenzenesulfonamide as a Brønsted acid promoter a adduct **2k** was obtained in 64% yield and 93% ee. This transformation was found to be compatible with a series of allylic alcohols with excellent selectivity for *N*-alkylation (Table 1, and supporting information).

We next focused on the construction of carbon-carbon bonds under biphasic conditions. Since the synthesis of halogenated, biologically active molecules has been an ongoing field of research in our group,[22] we first investigated chloracetaldehyde (**3**) as nucleophile. Due to its high reactivity chloroacetaldehyde is only commercially available as a 50% aqueous solution.[23-25] Notably, the asymmetric α-functionalization of chloracetaldehyde is not known. thus, our approach provides a complementary approach to optically active chlorides which are traditionally obtained by organocatalytic α-halogenation.[26]

We found that using **1b** (R = Ph) and aqueous chloroacetaldehyde in combination with proline derived amine **A1**,[26b] ligand (*R*)-**L**, and dimethylphosphate afforded aldehyde **4b** in 82% yield, 10:1 d.r. and >99% ee. Optimization studies revealed that using solvents that give a homogenous reaction mixture such as 1,4-dioxane or acetone did not lead to any product formation, indicating that biphasic conditions were essential for this transformation. Furthermore, we found that inorganic salt additives (NaCl, Na_2SO_4, $MgSO_4$) increased the overall conversion of the reaction. Presumably, an increase of ionic strength facilitates transfer of the water-soluble aldehyde to the organic phase.[27]

Table 1. Scope of the Biphasic Iridium-Catalyzed Allylation of *N*-, *O*- and *S*-Nucleophiles.[a]



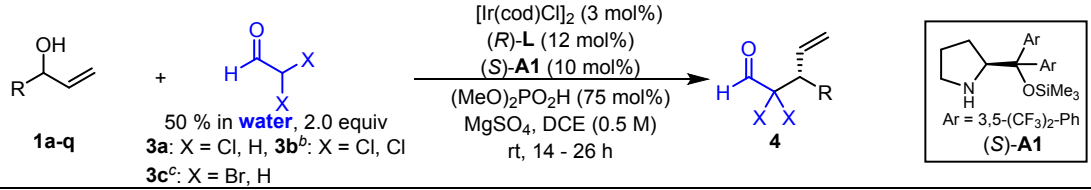
[a] 0.25 mmol scale. Isolated Yields. ee determined SFC on a chiral stationary phase. 2-Np= 2-naphthyl. [b] $(PhSO_2)_2NH$ (1.3 equiv), isolated after benzoylation. [c]DCBA (1.3 equiv), yield determined by ^1H NMR with an internal standard, isolated after acetylation. [d]DCBA (1.8 equiv). [e]2.0 equiv. of nucleophile, DCBA (2.3 equiv). [f]2.0 equiv. of nucleophile, DCBA (2.8 equiv). [g]$(PhSO_2)_2NH$ (0.5 equiv). [h]$(PhO)_2P(O)OH$ (1.8 equiv). acid. [i]$(PhSO_2)_2NH$ (1.3 equiv). DCBA = 3,5-dichlorobenzoic

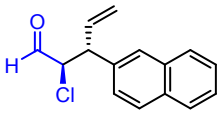
With optimized conditions in hand, the substrate scope of the reaction with regard to allylic alcohols was explored (Table 2). Electron-poor as well as electron-rich substrates were tolerated, resulting in good yields (41-81%), d.r. values between 5:1 and 20:1 and excellent enantioselectivity (>99% ee) (**4c-4j**). Additionally, hetereoaromatic allylic alcohols (**1k** and **1l**) afforded the respective products in good yields and excellent selectivities.

When dichloroacetaldehyde (**3b**), commercially available as its solid hydrate, was employed under identical reaction conditions, no

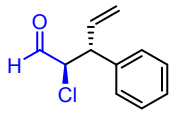
allylated product was obtained. Optimization studies revealed that for this sterically hindered aldehyde, primary amine catalysts were required. The iridium-catalyzed reaction of solid dichloroacetaldehyde hydrate, diphenylmethane amine, allylic alcohol **1a** and $Zn(OTf)_2$ as a Lewis acid promoter afforded the corresponding dichlorinated aldehyde, which was isolated as primary alcohol **4m** in 55% yield and >99% ee after reduction with $NaBH_4$. Bromoacetaldehyde could also be allylated by slight alteration of the reaction conditions and several adducts (**4n**-**4w**) could be obtained in 62–83% yield, high diastereomeric ratios (10:1–20:1 d.r.) and excellent enantioselectivity (98 - >99% ee).

Table 2. Allylic Alcohol Scope of the α-Allylation of Aqueous Chloro- and Bromoacetaldehyde.[a]

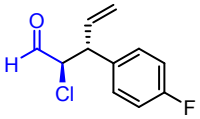




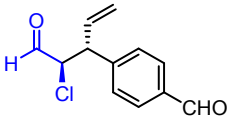
4a: 74%, 10:1 d.r.
>99% ee



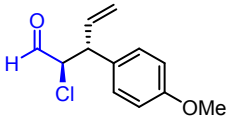
4b: 82%, 10:1 d.r.
>99% ee



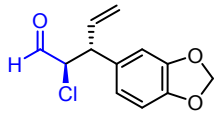
4c: 61%, 7:1 d.r.
>99% ee



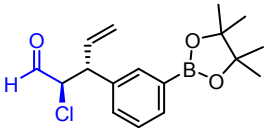
4d: 41%, 5:1 d.r.
>99% ee



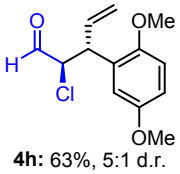
4e: 65%, 10:1 d.r.
>99% ee



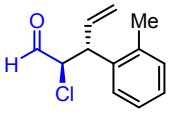
4f: 77%, 12:1 d.r.
>99% ee



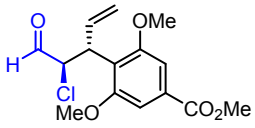
4g: 54%, 15:1 d.r.
>99% ee



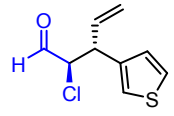
4h: 63%, 5:1 d.r.
>99% ee



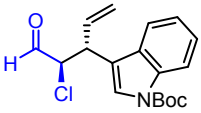
4i: 71%, 7:1 d.r.
>99% ee



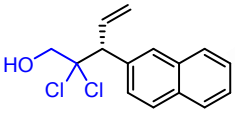
4j: 81%, 2:1 d.r.
>99% ee



4k: 73%, 10:1 d.r.
>99% ee

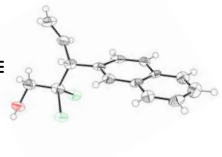


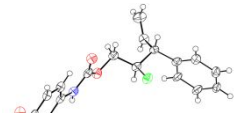
4l: 75%, 20:1 d.r.
>99% ee



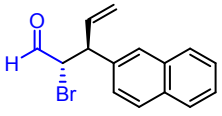
4m: 55%
>99% ee

≡

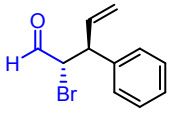




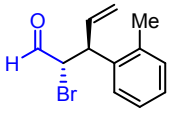
[X-Ray] of a derivative of **4b**



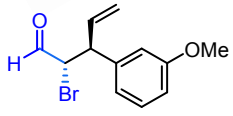
4n: 75%, 20:1 d.r.
>99% ee



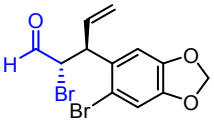
4o: 72%, 16:1 d.r.
>99% ee



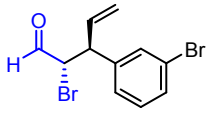
4p: 80%, 10:1 d.r.
>99% ee



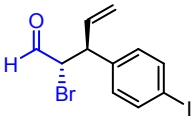
4q: 83%, 17:1 d.r.
98% ee



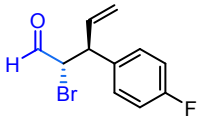
4r: 72%, 10:1 d.r.
>99% ee



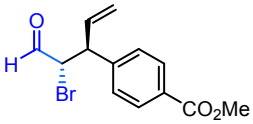
4s: 62%, 19:1 d.r.
>99% ee



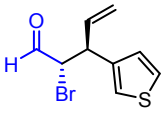
4t: 71%, 13:1 d.r.
>99% ee



4u: 75%, 14:1 d.r.
>99% ee



4v: 47%, 12:1 d.r.
>99% ee

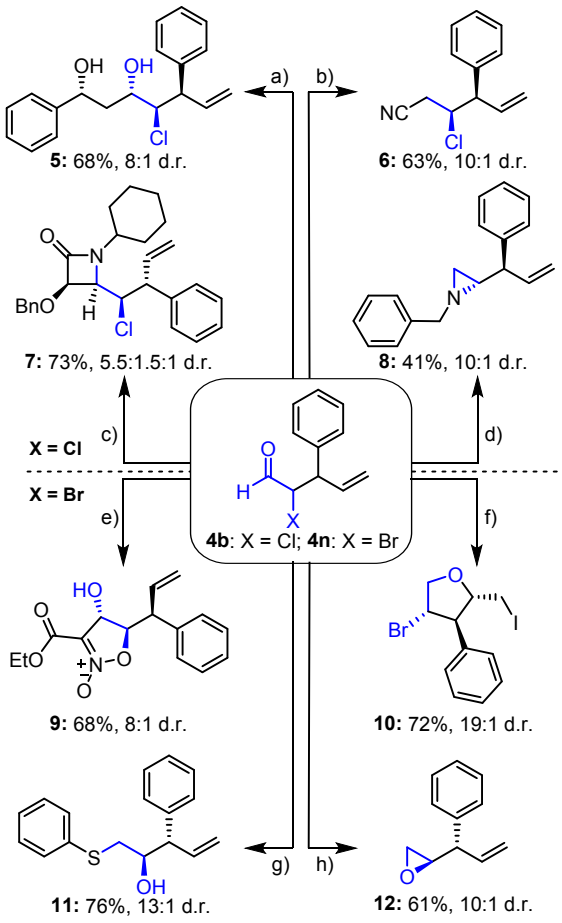


4w: 73%, 19:1 d.r.
>99% ee

[a] 0.25 mmol scale. Isolated yields. ee SFC on a chiral stationary phase. Diastereomeric ratios (d.r.) determined by ^1H NMR analysis of isolated products. DCE = 1,2-dichloroethane. The (*R*)-**L**, (*R*)-**A1** or (*S*)-**L**, (*S*)-**A1** ligand combination resulted in a d.r. of approximately 1:1. Reaction conditions: [b]Benzhydrylamine (0.1 equiv), $ZnBr_2$ (50 mol%), 40°C, then $NaBH_4$, MeOH. [c](*S*)-**L**, (*R*)-**A1**, $(PhSO_2)_2NH$ (50 mol%) and Na_2SO_4.

In an effort to demonstrate the synthetic versatility of the product chiral α-chloro- and α-bromoaldehydes, a variety of functionalization reactions were carried out (Scheme 2). Diverse heterocycles with various ring sizes including aziridines (**8**), tetrahydrofurans (**10**) and β-lactams (**7**) could be accessed efficiently. Addition of acetophenone to **4b** followed by *syn*-selective reduction allowed the installation of two additional stereocenters with good selectivity (product **5**). Furthermore, reduction of **4b** and **4o** to the primary alcohol with $NaBH_4$ enables the synthesis of β-chloronitrile **6** and hydroxylthio ether **11.**

Scheme 2. Functionalization of γ,δ-Unsaturaded Aldehydes[a]



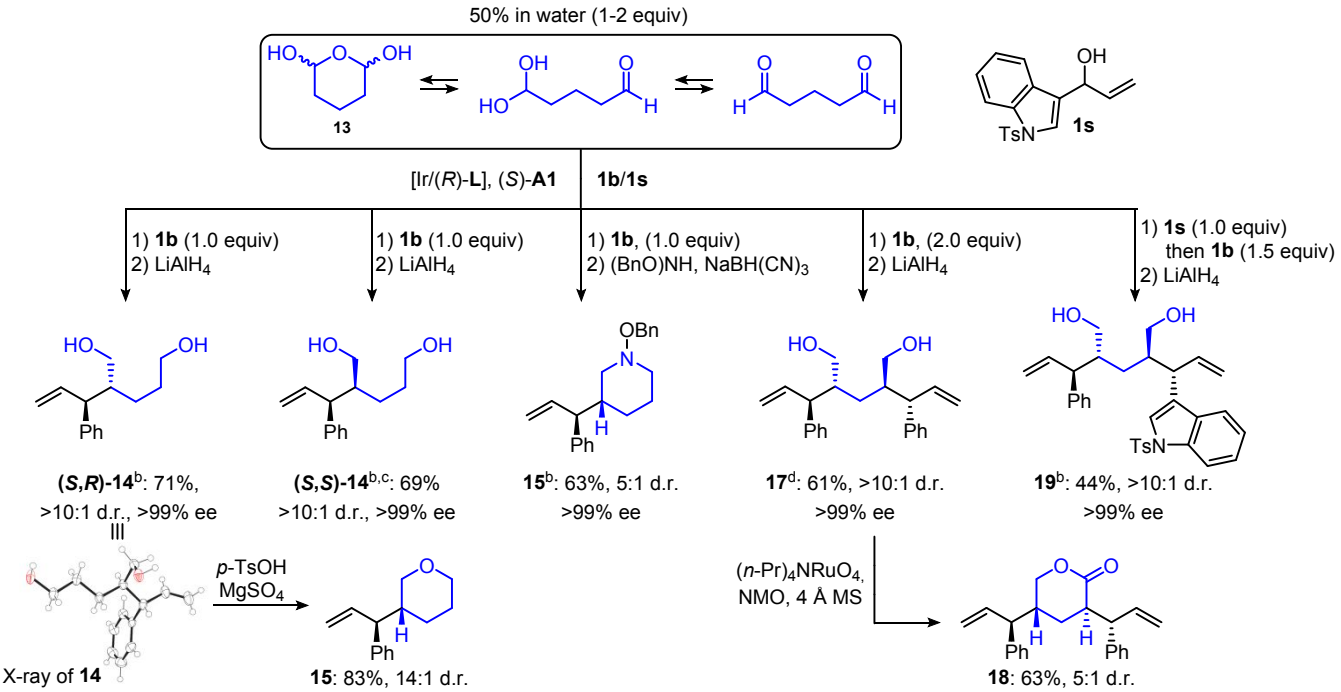
[a]Reagents and conditions: For detailed experimental procedures see supporting information. (a) 1) **4b**, acetophenone, LDA; 2) DIBAL-H. (b) 1) **4b**, $NaBH_4$; 2) Tf_2O, 2,6-lutidine, then KCN, 18-crown-6. (c) **4b**, cyclohexylamine, $MgSO_4$, then 2-(benzyloxy)acetyl chloride, NEt_3. (d) 1) **4b**, $NaBH_4$; 2) Tf_2O, 2,6-lutidine, then H_2NBn. (e) **4n**, imidazole, ethyl nitroacetate. (f) 1) **4n**, $NaBH_4$; 2) K_2CO_3, I_2. (g) 1) **4n**, $NaBH_4$; 2) PhSH, NaOH. (h) 1) **4n**, $NaBH_4$; 2) NaOH.

To further extend the synthetic potential of this iridium-catalyzed α-allylation of aldehydes in biphasic media, glutaraldehyde was examined as a substrate. Like many small dialdehydes, glutaraldehyde is unstable and readily forms polymeric solids.[28] In aqueous solutions, glutaraldehyde forms cyclic hydrate **13** which can be stored for extended periods of time (Scheme 3).[29]

We found that **13** also participates in dual-catalytic α-allylation reactions with allylic alcohol **1b**. Interestingly, the reaction proceeds with high selectivity for the mono-allylated aldehyde. Since attempts to isolate the resulting dialdehyde were unsuccessful, the crude reaction mixture was reduced to the corresponding diol **14**, which could be further elaborated into tetrahydropyran **15** Alternatively, the mono-allylated aldehyde could be reductively aminated in one pot to afford piperidine **16**, demonstrating the synthetic potential of the method for the enantioselective synthesis of chiral saturated heterocycles. Additionally, we found that with an excess of allylic alcohol bis-allylated product **17** could be obtained with high enantio- and diastereoselectivity. Oxidation of diol **17** using tetrapropylammonium perruthenate afforded unsymmetrical, lactone **18**. Sequential addition of two distinct allylic alcohols, followed by reduction furnished asymmetric diol **19** in >99:1 ee and >10:1 d.r., which is remarkable considering that the reaction could in principle afford 16 different stereoisomers.

In conclusion, we have developed a biphasic aqueous system for the enantioselective iridium-catalyzed allylic substitution. This approach allows the use of readily available aqueous solutions of various nucleophiles which are otherwise highly volatile or unstable when anhydrous. These biphasic conditions rely on a robust catalyst system and allow for the synthesis of a broad range of synthetically useful chiral intermediates such as hydrazines, peroxides, *N*-hydroxylamines, α-halo-aldehydes, and diols. Their use in asymmetric transition-metal catalysis has been largely unexplored because of the requirements to use them in anhydrous forms for most other catalyst systems. We believe that the concepts disclosed in this report will serve as inspiration for other transition metal-catalyzed transformations employing these readily available, yet rarely used reagents.

Scheme 3. Iridium-Catalyzed α-Allylation of Glutaraldehyde [a]



[a]For detailed experimental procedures see supporting information. Ellipsoids shown at 50% probability. Ts = toluenesulfonyl, NMO = 4-methylmorpholine *N*-oxide. [b]2.0 equiv. of **19**. [c](*R*)-**A** was used.[d]1.0 equiv. of **19**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
General methods, detailed experimental procedures, spectral data and X-ray crystallographic data.

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Notes

The authors declare no competing financial interests.

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SYNOPSIS TOC