CuH-Catalyzed Regio- and Enantioselective Formal Hydroformylation of Vinyl Arenes

Subhash Garhwal, Yuyang Dong, Binh Khanh Mai, Peng Liu,* and Stephen L. Buchwald*

ABSTRACT: A highly enantioselective formal hydroformylation of vinyl arenes enabled by copper hydride (CuH) catalysis is reported. Key to the success of the method was the use of the mild Lewis acid zinc triflate to promote the formation of oxocarbenium electrophiles through the activation of diethoxymethyl acetate. Using the newly developed protocol, a broad range of vinyl arene substrates underwent efficient hydroacetalization reactions to provide access to highly enantioenriched oxocarbenium electrophiles through the activation of diethoxymethyl acetate. Using the newly developed protocol, a broad range of aldehydes, alcohols, and amines with full preservation of the enantiomeric purity. Density functional theory studies support that the key C–C bond-forming event between the alkyl copper intermediate and the oxocarbenium electrophile takes place with inversion of configuration of the Cu=C bond in a backside S$_2$2-type mechanism.

Enantioselectively enriched aldehydes hold value as versatile synthetic intermediates, and as such, methods for their efficient construction are of great interest.$^{1,2}$ Among numerous synthetic approaches for their synthesis, hydroformylation of olefins represents an atom economical and cost-effective strategy.$^3$ Since the seminal discovery of “the oxo process” by Roelen in the 1930s, alkene hydroformylation has become one of the most widely employed homogeneous industrial catalytic processes, producing millions of tons of aldehyde or alcohol products from available feedstock olefins.$^{4,5}$

The adoption of hydroformylation on industrial scales can be in part attributed to the large amount of work invested in the development of efficient transition metal catalysts. However, the intrinsic challenge of enantioselective hydroformylation involves—in addition to the formation of a new stereogenic center—addressing the issues of chemoselectivity (hydroformylation versus alkene hydrogenation or overreduction to form primary alcohols) and regioselectivity (branched versus linear aldehyde products).$^6$ Accordingly, considerable effort has been exerted to develop chiral ligand-supported metal catalysts for enantioselective alkene hydroformylation. Since the first highly enantioselective vinyl arene hydroformylation reported by Stille,$^7$ various successful methods using Pt- and Rh-based catalysts have emerged for many classes of alkenes.$^8$ More recently, pioneering work from Nozaki,$^9$ Zhang,$^{10}$ Landis,$^{11}$ Clarke,$^{12}$ and others has led to the emergence of new chiral phosphine ligands, including Binaphos,$^9$ Ph-BPE,$^{10}$ Yanphos,$^{11}$ bis(diazaphospholane) (BDP),$^{12}$ Bobphos,$^{13}$ and more,$^{14}$ has enabled the development of efficient rhodium-catalyzed asymmetric hydroformylation reactions. In addition, a great deal of work has gone into inventing alternative hydroformylation methods that avoid the use of carbon monoxide gas.$^{15−17}$

Catalytic methods other than hydroformylation for the synthesis of pharmaceutically relevant chiral $\alpha$-aryl aldehydes have also been developed based on the enantioselective $\alpha$-arylation of aldehydes,$^{18}$ and photochemical deracemization.$^{19}$

While significant progress has been made in precious metal-catalyzed enantioselective olefin hydroformylation, a protocol that employs an abundant and environmentally benign base metal catalyst along with a nontoxic carbonyl source in enantioselective hydroformylation, to the best of our knowledge, has yet to be reported.$^{20}$ Nonetheless, in recent years base metal hydrides has been proven successful in various asymmetric olefin functionalizations.$^{21}$ Herein, we describe the development of a highly enantioselective formal hydro-
formylation of vinylarene copper hydride-catalyzed process that operates efficiently using a simple, commercially available ortho ester as the precursor to the active electrophile (Figure 1).

We hypothesized that a chiral alkylcopper species, generated from the highly enantioselective hydrocupration of vinyl arenes, could react with an oxocarbenium ion to afford an enantioenriched aldehyde synthon. However, given the high electrophilicity of oxocarbenium ions, we anticipated that the strongly reducing conditions required for copper hydride catalysis might be problematic. Based on our prior work on hydroalkylation, we considered the use of a protocol in which the slow in situ generation of an active electrophile might mitigate unproductive side reactions between the oxocarbenium and a silane. We envisioned that this could be accomplished through exposure of the commercially available ortho ester, diethoxy methyl acetate, to a suitable Lewis acid catalyst. The resultant oxocarbenium ion would be expected to rapidly react with alkyl copper intermediates to form hydrofunctionalized products. As these products are alkyl acetals, undesired carbonyl reduction or racemization, which plague conventional hydroformylation methods, would be precluded. The acetals thus formed could then be readily hydrolyzed to provide the corresponding aldehydes.

Table 1. Optimization of the Enantioselective Hydroacetalization(formylation) of 4-Phenyl Styrene (1a) Employing Diethoxy Methyl Acetate as the Formyl Precursor

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from above conditions</th>
<th>yield (2a) (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no Zn(OTf)$_2$</td>
<td>nr</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
<td>97</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>P1 (6 mol%)</td>
<td>98</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>no CuOAc</td>
<td>nr</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>other Lewis acids: (ZnCl$_2$, Mg(OTf)$_2$, Sc(OTf)$_3$, Ln(OTf)$_3$) (6 mol%)</td>
<td>&lt;1%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>$^t$Bu$_4$NCl or ZnCl$_2$ (6 mol%) with Zn(OTf)$_2$ (6 mol%)</td>
<td>&lt;1%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>L2 (7 mol%)</td>
<td>87</td>
<td>35:65</td>
</tr>
<tr>
<td>8</td>
<td>L3 (7 mol%)</td>
<td>80</td>
<td>25:75</td>
</tr>
<tr>
<td>9</td>
<td>L4 (7 mol%)</td>
<td>nr</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>L5 (7 mol%)</td>
<td>nr</td>
<td>-</td>
</tr>
</tbody>
</table>

"Reaction conditions: 4-Phenyl styrene (1a, 0.20 mmol, 1.0 equiv), diethoxy methyl acetate (0.30 mmol, 1.5 equiv), (MeO)$_2$MeSiH (DMMS) (0.80 mmol, 4.0 equiv), copper(1) acetate (6 mol %) and specified ligand (7 mol %), and THF (0.4 M), rt; reaction yields were estimated by $^1$H NMR analysis of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as an internal standard (see SI for details). Enantiomeric ratio (e.r.) of 2a was determined by chiral supercritical fluid chromatography (SFC). nr = no reaction."
We began by examining the reaction of 4-phenyl styrene (1a), employing diethoxy methyl acetate as the precursor to the active electrophile and a catalyst derived from (S)-DTBM-SEGPHOS, CuOAc, and dimethoxy(methyl)silane. No formation of desired product 2a was observed unless zinc triflate was added as a Lewis acid cocatalyst. Using 6 mol % of Zn(OTf)$_2$, 2a was formed in nearly quantitative yield (97% NMR yield) with a 98:2 er (Table 1, entry 2). Notably, the reaction mixture was found to exhibit complete selectivity for the formation of the branched product. Evaluating the performance of various Lewis acids revealed that Zn(OTf)$_2$ was uniquely effective, among those we tested, in promoting the formation of 2a, with other common Lewis acids failing to provide any observable product (Table 1, entry 5). The ineffectiveness of ZnCl$_2$ is particularly noteworthy and may be due to formation of ligated CuCl which cannot be converted to the copper hydride under the reaction conditions. Consistent with this hypothesis, no formation of product was observed...

**Table 2. Substrate Scope of the Enantioselective Hydroacetalization Reaction**

<table>
<thead>
<tr>
<th>R$_1$</th>
<th>R$_2$</th>
<th>CH(OEi)$_2$</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>CH(OEi)$_2$</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>CH(OEi)$_2$</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>CH(OEi)$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>2b</td>
<td>Ph</td>
<td>2c</td>
<td>2d</td>
<td>Me</td>
<td>2e</td>
<td>2f</td>
<td>Ph</td>
<td>2g</td>
</tr>
<tr>
<td>80% yield</td>
<td>98:2 e.r.</td>
<td>86% yield</td>
<td>98:2 e.r.</td>
<td>88% yield</td>
<td>99:1 e.r.</td>
<td>85% yield</td>
<td>98:2 e.r.</td>
<td>82% yield</td>
<td>99:1 e.r.</td>
<td>81% yield</td>
<td>98:2 e.r.</td>
</tr>
<tr>
<td>84% yield</td>
<td>98:2 e.r.</td>
<td>80% yield</td>
<td>96:4 e.r.</td>
<td>75% yield</td>
<td>99:1 e.r.</td>
<td>73% yield</td>
<td>96:4 e.r.</td>
<td>77% yield</td>
<td>96:4 e.r.</td>
<td>75% yield</td>
<td>97:3 e.r.</td>
</tr>
<tr>
<td>90% yield</td>
<td>98:2 e.r.</td>
<td>95% yield</td>
<td>98:1 e.r.</td>
<td>95% yield</td>
<td>98:1 e.r.</td>
<td>95% yield</td>
<td>98:1 e.r.</td>
<td>70% yield</td>
<td>98:2 e.r.</td>
<td>75% yield</td>
<td>97:3 e.r.</td>
</tr>
<tr>
<td>70% yield</td>
<td>98:2 e.r.</td>
<td>65% yield</td>
<td>96:4 e.r.</td>
<td>70% yield</td>
<td>98:2 e.r.</td>
<td>68% yield</td>
<td>94:8 e.r.</td>
<td>68% yield</td>
<td>99:3 e.r.</td>
<td>70% yield</td>
<td>99:3 e.r.</td>
</tr>
</tbody>
</table>

$^a$Reported yields are the average of two isolated yields, using 0.50 mmol of vinyl arene substrate and 0.75 mmol of diethoxy methyl acetate.

$^b$Reaction time 24 h. Cu(OAc)$_2$ (10 mol %), (S)-DTBM-SEGPHOS (12 mol %), and reaction time 24 h. Vinyl arene substrate used as a 9:1 mixture of E/Z-isomers; enantiomeric ratio (e.r.) was determined by chiral SFC. $^c$Enantiomeric ratio determined for aldehyde, $^d$Enantiomeric ratio determined for alcohol.
electron density led to products with slightly decreased enantioselectivities. The use of vinyl arenes with increased copper is responsible for the hydroacetalization reaction and electronically varied vinyl arenes. Hydroacetalization, we next examined the scope of vinylarene.

A control experiment in the absence of (Table 1, entry 7 -Ph-BPE resulted in a lower yield and enantioselectivity of S,S selectivity as that obtained using a mixture of CuOAc and (5.0 equiv), acetonitrile, rt, 1 h. Another reaction could also be used and afforded 3d when exogenous chloride was added (8Bu4NCl or ZnCl2) along with Zn(OTf)2 (Table 1, entry 6). The previously described complex (S)-DTBM-SEGPHOS)CuOAc (P1) could also be used and afforded 2a in similar yield and selectivity as that obtained using a mixture of CuOAc and (S)-DTBM-SEGPHOS. A control experiment in the absence of CuOAc provided no product, supporting the notion that copper is responsible for the hydroacetalization reaction and ruling out a potential ligated zinc-catalyzed pathway. Finally, the use of other bidentate chiral (bis)phosphine ligands such as (S,S)-Ph-BPE resulted in a lower yield and enantioselectivity of 2a (Table 1, entry 7–8).

Having established useful conditions for enantioselective hydroacetalization, we next examined the scope of vinylarene (Table 2) that could be accommodated. A variety of electronically varied vinyl arenes—both electron-rich and -deficient—afforded the α-aryl acetalts in good yields and enantioselectivities. The use of vinyl arenes with increased electron density led to products with slightly decreased enantioselectivity (2h, 2i, and 2k). Functional groups, such as aryl halides (2d, 2e, 2j), an alcohol (2m), ethers (2g, 2i, 2r, 2p), an amine (2k), an ester (2y), and a tertiary amide (2q), were all found to be compatible with the protocol. Vinyl arenes containing a pyridine (2t), carbazole (2n), thiophene (2v), piperidine (2k), pyrrole (2x), and benzofuran (2o) unit efficiently underwent the hydroacetalization reaction to provide the corresponding α-aryl acetals in good yield and excellent enantioselectivity. The scope of the hydroacetalization reaction was found to extend to β-Substituted styrenes as well, with compounds 2w, 2x, and 2y successfully produced with high levels of enantioselectivity.

One limitation of this methodology is the competitive formation of unusual dearomatized products when ortho substituted substrates were employed (Scheme S11). Dearomatized products were also observed to form when trans/β-methylstyrene and several vinyl heteroarenes were used as substrates (Scheme S11). Due to instability of the dearomatized product, we were unable to isolate and fully characterize these dearomatized products. Nonetheless, DFT calculations support a competing pathway for dearomative electrophilic addition for ortho-substituted styrenes (Scheme S13).

We found that the α-aryl acetalts produced by the above-described protocol could be converted to the corresponding aldehydes (3a–b) by treatment with a formic acid and pentane mixture (1:1) for 1 h at room temperature (Scheme 1). Importantly, this procedure was found to preserve enantio-purity, enabling the possibility of further derivatization to a variety of enantiomerically enriched products. Hydride reduction (3c–d) or reductive amination (3e–f) of aldehyde products could be efficiently carried out to provide alcohols or amines with high levels of enantiomeric purity. In addition, it has been reported that oxidation of α-aryl aldehydes to the corresponding carboxylic acids occurs without deterioration of enantiomeric purity. These resulting compounds have applications as nonsteroidal anti-inflammatory drugs. The absolute configuration of the products was assigned by comparing the specific optical rotation values of 3a, 3b, and 3d to those in the literature.

Based on our experimental findings, we hypothesize that the reaction proceeds through the catalytic cycle shown in Figure 2A. CuH complex (A) undergoes enantioselective hydrocupration of styrene substrate 1 to generate the Cu-alkyl intermediate (B), which goes on to react stereospecifically with oxocarbenium intermediate 5. This leads to the formation of acetal product 2, as well as ligated CuOAc (D). D can then be transformed to the active CuH catalyst through the reaction with DMMS ((MeO)2MeSiH).

The proposed catalytic cycle was investigated using density functional theory (DFT), including both the Zn-promoted ionization and the Cu-catalyzed hydrocupration steps. The DFT calculations were performed at the M06/6-311+G(d,p)–SDD(Cu, Zn)/SMD(THF)//B3LYP-D3/6-31G(d)–SDD(Cu, Zn) level of theory with the (S)-DTBM-SEGPHOS (L1)-supported Cu catalyst and p-methylstyrene 1b as the model substrate (see the Supporting Information for Computational Details). Calculations revealed that when the Zn(II) tetrahydrofuran complex was used as a catalyst, the generation of oxocarbenium ion 5 is thermodynamically favorable (ΔG = −10.9 kcal/mol) with a low activation barrier (ΔG‡ = 8.9 kcal/mol) via TS-1 (Figure 2B).

Upon the generation of (R)-Cu-alkyl intermediate 9 via the highly enantioselective hydrocupration (TS-2) of substrate 1b by CuH catalyst 7, 30, 31 9 forms a weak van der Waals (vdW) complex with the oxocarbenium ion. From the vdW complex 10, our DFT calculations support that the electrophilic addition of 5 to 9 takes place through a stereoinertive S_{2}2-type mechanism, i.e., backside electrophilic substitution via TS-3 (Figure 2D). This S_{2}2 pathway is calculated to occur readily with an activation barrier of 1.8 kcal/mol relative to Cu-alkyl intermediate 9. The stereochemical outcome of this most favorable pathway (shown in black in Figure 2C) is consistent...
with the absolute configuration of the hydroacetalization products observed experimentally. We located a transition state (TS-4) leading to the formation of the enantiomer of 2b via a stereoretentive S_E_2-type process. However, the activation barrier for TS-4 is 2.9 kcal/mol higher in energy than the stereoinvertive substitution TS-3.

Beyond the aforementioned S_E_2 mechanisms, several alternative pathways were considered. The oxocarbenium addition to the Cu center (TS-5) to form Cu(III) intermediate 11 and subsequent stereospecific C−C reductive elimination (TS-6) was predicted to occur with a significantly higher barrier relative to TS-3 (ΔΔG‡ = 15.8 kcal/mol). A dearomative electrophilic addition to the ortho position of 9 (TS-7) requires a barrier that is 3.6 kcal/mol higher relative to TS-3. Formation of dearomatized intermediate 12 via 1,3-Cu migration^{25,33} is unlikely because 12 is 13.2 kcal/mol less stable than TS-3. Taken together, the DFT calculations support that the acetalysis of Cu-alkyl intermediate 9 takes place via a stereoinvertive S_E_2-type mechanism involving electrophile 5 generated from the facile Zn-catalyzed ionization of orthoester 4.

In summary, we have disclosed a CuH-catalyzed enantioselective formal hydroformylation of vinyl arenes, providing access to α-aryl acetal and aldehyde derivatives with high levels of enantioselectivity. This method was found to be tolerant of various functional groups and heterocycles. DFT computational modeling suggests a key role for the catalytic Lewis acid zinc(II) trflate in the activation of the orthoester electrophile to form a highly reactive oxocarbenium ion. Beyond this, calculations demonstrate that the enantioenriched alkyl copper intermediate generated from enantioselective alkene hydrocupration reacts with in situ formed oxocarbenium ion through a stereospecific invertive S_E_2-type mechanism to yield α-aryl acetals as product. We anticipate that the results presented in this study may have implications in the design of other base metal catalyzed hydroformylation processes.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c04287.

Experimental procedures and characterization data for all new compounds, including NMR spectra, SFC traces, computational details, and Cartesian coordinates of all computed structures (PDF)
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Notes
The authors declare no competing financial interest.

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