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Highly Regio- and Enantioselective Copper-Catalyzed Reductive Hydroxymethylation of Styrenes and 1,3-Dienes with CO_2

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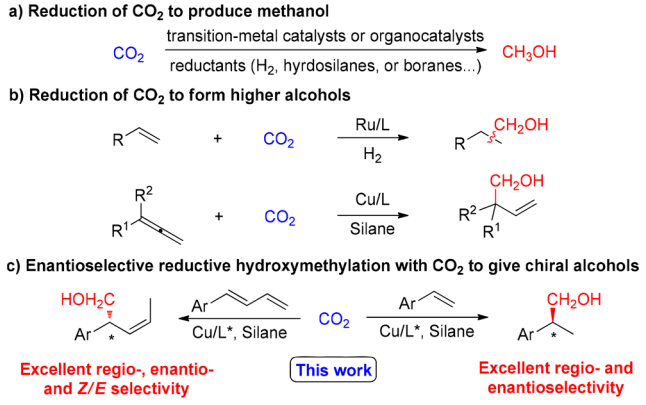
Supporting Information

ABSTRACT: Herein, we report a highly regio- and enantioselective copper-catalyzed reductive hydroxymethylation of styrenes and 1,3-dienes with 1 atm of CO_2. Diverse important chiral homobenzylic alcohols were readily prepared from styrenes. Moreover, a variety of 1,3-dienes also were converted to chiral homoallylic alcohols with high yields and excellent regio-, enantio-, and *Z*/*E*-selectivities. The utility of this transformation was demonstrated by a broad range of styrenes and 1,3-dienes, facile product modification, and synthesis of bioactive compounds (*R*)-(−)-curcumene and (*S*)-(+)-ibuprofen. Mechanistic studies demonstrated the carboxylation of phenylethylcopper complexes with CO_2 as one key step.

Carbon dioxide (CO_2) is an important and appealing C1 building block in chemical synthesis because of its nontoxicity, abundance, availability, and sustainability.[1] Over the past several decades, extensive efforts have been devoted to the transformation of CO_2 into fuels and high value-added organic chemicals.[2] Among these efforts, the catalytic reduction of CO_2 to produce methanol has received considerable attention because methanol is both a liquid fuel and a bulk chemical (Scheme 1a).[3] Furthermore, the reduction of CO_2 to form higher alcohols through C−C bond formation is highly appealing (Scheme 1b) since these products are versatile intermediates in chemical synthesis. Starting with alkenes, several groups realized the efficient Ru-catalyzed hydroformylation/reduction with CO_2 and H_2.[4] In 2015, Fujihara and Tsuji reported an elegant Cu-catalyzed reductive hydroxymethylation of allenes with CO_2 to give homoallylic alcohols.[5] The asymmetric catalytic synthesis of chiral higher alcohols with CO_2, however, remains unresolved.

Scheme 1. Reduction of CO_2 To Produce Alcohols



The catalytic asymmetric transformation of CO_2 is a well-known challenge, especially for processes involving C−C bond formation.[6] One reason is that CO_2 is difficult to activate and utilize under mild conditions due to its thermodynamic stability and kinetic inertness. Most reported examples involve CO_2 insertion into epoxides or alcohols to form chiral carbonates via enantioselective C−O bond formation.[7] The only successful examples of enantioselective C−C bond formation with CO_2 were reported by Mori and Marek.[8] Taking into consideration our continuous interest in CO_2 transformations[9] and enlightenment by the impressive achievements in CuH chemistry,[10,11] we have now realized the first enantioselective Cu-catalyzed reductive hydroxymethylation of alkenes with CO_2 (Scheme 1c) to form a series of chiral homobenzylic/allylic higher alcohols, many of which can act as key intermediates in chemical synthesis and as important precursors for medicines or other bioactive compounds.[12] Notably, high yields and excellent regio-, enantio-, and *Z*/*E*-selectivities were observed in these reactions.

To begin our investigation, we employed 4-phenylstyrene **1a** as the model substrate and $Cu(OAc)_2$ as the catalyst under 1 atm of CO_2 (Table 1). The reaction was first tested with different chiral bisphosphine ligands in cyclohexane (see Supporting Information (SI) for more information). Among them, (*R*)-DTBM-SEGPHOS was found to be the best choice in terms of enantioselective control, affording **2a** with 98:2 er (entry 1). The yield was increased drastically to 75% when the reaction temperature was elevated to 60 °C (entry 2). Although subsequent solvent screening did not improve the results (entries 3−5), further optimization showed that adding one equiv of CsOAc and lowering the concentration could further enhance the yield to 78% without diminishing the enantioselectivity (entry 6). To our delight, evaluation of silanes demonstrated that $(EtO)_3SiH$ showed excellent behavior for this transformation to produce **2a** in 94% yield and 98:2 er (entries 7−9).[13] The absolute configuration of **2a** was determined as (*S*) by X-ray crystallography of its *p*-nitro-

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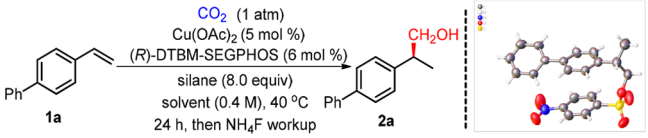
Table 1. Reaction Optimization[a]



entry	silane	solvent	yield[b]	er[c]
1	$Me(MeO)_2SiH$	CyH	20%	98:2
2[d]	$Me(MeO)_2SiH$	CyH	75%	99:1
3[d]	$Me(MeO)_2SiH$	DMF	37%	80:20
4[d]	$Me(MeO)_2SiH$	CPME	65%	98:2
5[d]	$Me(MeO)_2SiH$	EA	72%	95:5
6[d,e]	$Me(MeO)_2SiH$	CyH	78%	99:1
7[d,e]	$MePh_2SiH$	CyH	*f*	
8[d,e]	PMHS	CyH	64%	91:9
9[d,e]	$(EtO)_3SiH$	CyH	94%	98:2
10[d,e,g]	$(EtO)_3SiH$	CyH	*f*	

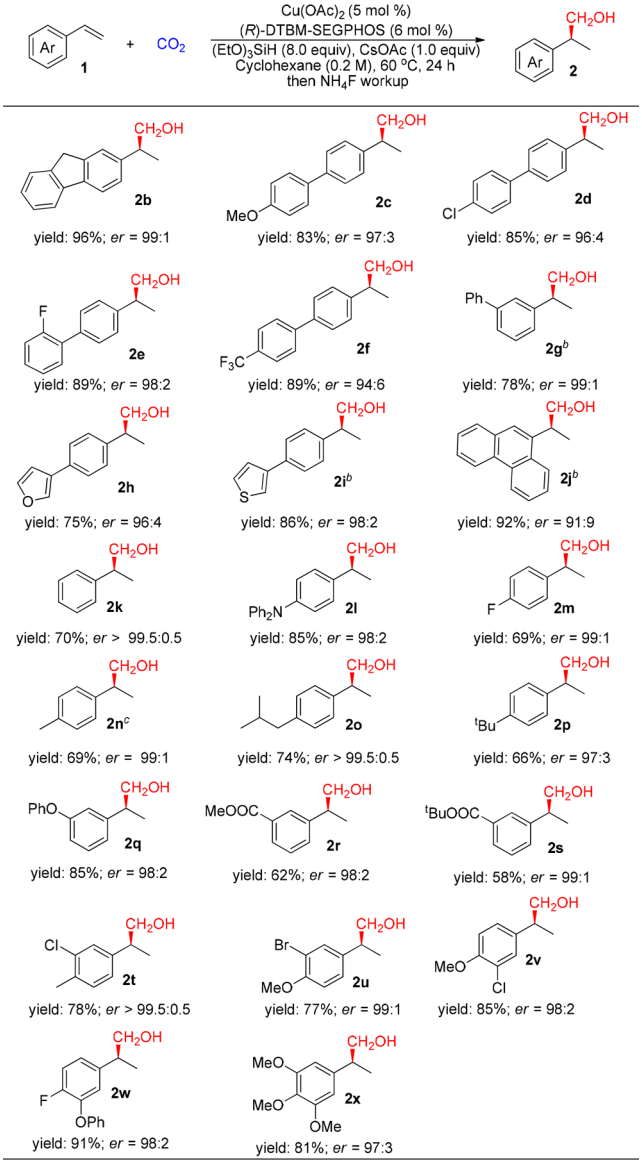
[a]0.4 mmol scale. [b]Isolated yield. [c]Enantiomeric ratio (er) determined by chiral HPLC. [d]60 °C. [e]CyH (0.2 M) with 1.0 equiv of CsOAc. [f]Not detected. [g]N_2 atmosphere (no CO_2). CyH = cyclohexane. DMF = *N*,*N*-dimethylformamide. CPME = cyclopentyl methyl ether. EA = ethyl acetate. PMHS = polymethylhydrosiloxane.

benzene-sulfonate derivative; an ORTEP diagram of this derivative is provided in Table 1.[14]

With optimized reaction conditions in hand, we first investigated the substrate scope of styrene derivatives (Table 2). For styrenes bearing a biphenyl backbone (**2b**−**2g**), a heteroarene such as furan (**2h**) or thiophene (**2i**), or a fused aromatic ring (**2j**), the desired products **2b**−**2j** could be obtained readily in both good yields (up to 96%) and excellent enantioselectivities (up to 99:1 er). Simpler styrenes, bearing either electron-donating groups (**2l, 2n-2p**) or a electron-withdrawing group (**2m, 2r, 2s**) were well tolerated, affording the homobenzylic alcohol in good yields and enantioselectivities. Polysubstituted styrene derivatives (**2t**−**2x**) were also proved to be suitable for our reaction, delivering the desired products in excellent enantioselectivities (from 97:3 er to >99.5:0.5 er) and good yields (from 77% to 91%). For some cases (**1g, 1i, 1j**), $Me(MeO)_2SiH$ showed similar behavior to $(EtO)_3SiH$. Many functional groups, including halides, amine, ether, and ester, were well tolerated, which provided huge opportunities for further transformations.

Next, we explored the substrate scope of 1,3-dienes to yield an array of chiral homoallylic alcohols. Compared to styrene derivatives, there are extra challenges for 1,3-dienes including (1) selectivity between 1,2- and 1,4-addition of the Cu−H species to the diene,[15a] (2) control of the *Z*/*E* selectivity for the remaining alkene,[15b−d] and (3) monohydroxymethylation versus over-reduction or mutlihydroxymethylation.[15e] With these challenges in mind, we further fine-tuned our reaction conditions and successfully converted a battery of (*E*)-1-phenyl-1,3-butadienes **3** to the desired 1,4-addition products **4** with high yields and excellent regio-, enantio-, and *Z*-selectivities (Table 3). Substrates with electron-rich (**3d**−**3e**) or mildly electron-withdrawing substituents (**3b**−**3c**) at the para position, as well as those with meta- (**3f**) or ortho-substituents (**3i**, **3g**, and **3h**), all provided good yields (from 63% to 91%) and good to excellent enantioselectivities (er from 90:10 to 97:3). In all these cases, >20:1 regioselectivity for 1,4-addition and >20:1 diastereoselectivity for the (*Z*)-alkene isomer were observed.

Table 2. Substrate Scope of Styrene Derivatives[a]



[a]0.4 mmol scale. Isolated yields provided. er determined by chiral HPLC. [b]$Me(MeO)_2SiH$ was used as silane reagent. [c]er of **2n** was determined from its sulfonate derivative. See SI for more details.

To shed light on the mechanism of this reaction, several experiments were carried out (Figure 1). First, silyl formate **5** could be obtained in moderate yield from $(EtO)_3SiH$ and CO_2 via copper catalysis. However, the reaction of **5** with **1o** failed to give product **2o**, demonstrating that the silyl formate may not be the active intermediate (see SI for more details). The unproductive and competitive hydrosilylation of CO_2 may also explain the requirement for a large excess of silane to obtain high conversion. Next, the stoichiometric reaction between **1m**, precatalyst mixture of $Cu(OAc)_2$ and **L3**,[13c] and $(EtO)_3SiH$ generated **L3**-ligated phenylethylcopper complex **6**[11v] in 50% yield. This organocuprate species underwent reaction with CO_2 smoothly to give the corresponding carboxylate **7** (see SI for more details). Based on these preliminary results and previous reports,[5,10,11] we propose the following possible mechanism. First, L*CuH **A** is generated in the presence of silanes. Subsequently, alkenes insert into the Cu−H bond with high regioselectivity and enantioselectivity to form species **B**, which

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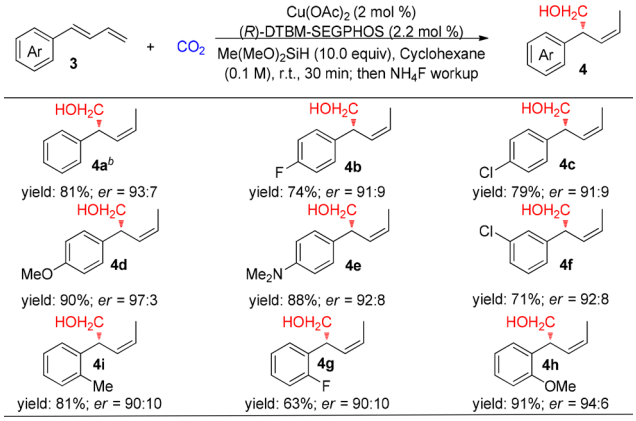
Table 3. Substrate Scope of 1,3-Dienes[a]



[a]0.5 mmol scale. Isolated yields provided. er determined by chiral HPLC. [b]Absolute configuration of **4a** was determined as (*R*,*Z*) by analogy to a compound with known absolute configuration and reported optical rotation. See SI for more details.

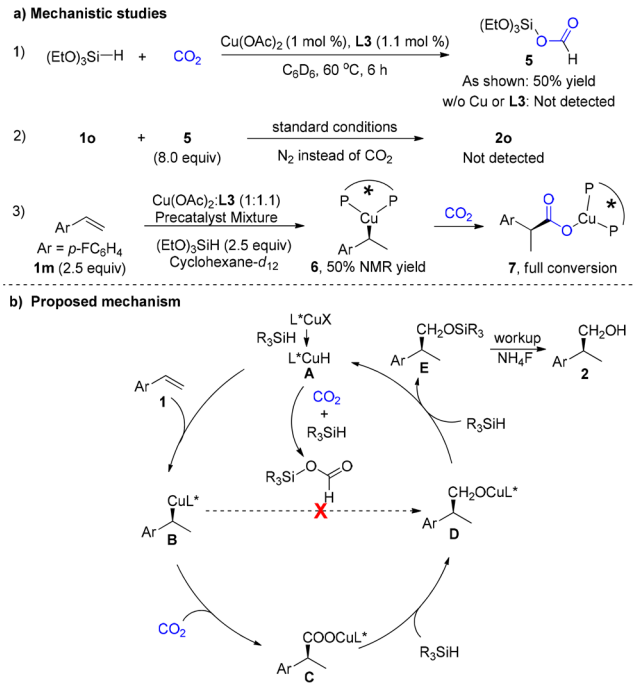
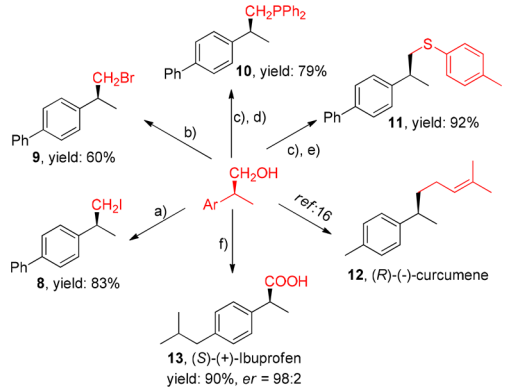


Figure 1. Mechanistic studies and proposed mechanism.

then reacts with CO_2 to give copper carboxylate **C**. Further reduction of **C** by hydrosilane produces copper alkoxide **D**.[6,15] Finally, σ-bond metathesis of **D** with hydrosilane regenerates species **A** and provides silyl ether **E**, which is converted to alcohol **2** after desilylation.

To demonstrate the utility of this transformation, several applications toward the preparation of synthetic intermediates and bioactive compounds were studied (Scheme 2). Initially, a variety of nucleophiles reacted smoothly with **2a** to generate the corresponding chiral compounds **8**−**11** in good yields. Moreover, **2n** could be easily transformed to a natural product (*R*)-(−)-curcumene **12** following reported procedures.[16] Lastly, **2o** was oxidized to the corresponding acid **13**, an important commercial drug (*S*)-(+)-ibuprofen, in excellent yield and er value. This result further demonstrates that the hydroxymethylation reaction is highly useful for synthetic and medicinal chemistry.

Scheme 2. Product Transformations and Applications[a]



[a]Reagents and conditions: (a) Ph_3P, 1*H*-imidazole, I_2, Et_2O/MeCN, 4 h; (b) Ph_3P, CBr_4, THF, r.t., 2 h; (c) TsCl, DABCO, DCM, r.t., overnight; (d) KO^{t}Bu, Ph_2PH, −78 °C−r.t., overnight; (e) *p*-MeC_6H_4SNa, EtOH; 40 °C, 16 h; (f) $NaClO_2$, TEMPO, NaClO, MeCN/phosphate buffer pH 6.7, 35 °C, 36 h. See SI for more information.

In summary, we developed the first highly regio- and enantioselective reductive hydroxymethylation of styrenes and 1,3-dienes with CO_2. Diverse chiral homobenzylic/allylic alcohols were generated from styrenes/1,3-dienes in excellent regio- and enantioselectivity. These transformations feature mild reaction conditions, broad substrate scope, and good functional group tolerance. Moreover, the desired chiral products are not only versatile building blocks in synthetic chemistry but also important intermediates for the synthesis of bioactive compounds such as (*R*)-(−)-curcumene and (*S*)-(+)-ibuprofen. More detailed mechanistic studies and the development of related enantioselective C−C bond formations with CO_2 are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b10149.

Sulfonate derivative of **2a** (CIF)

Detailed experimental procedures, spectral data, and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1569145 (a sulfonate derivative of **2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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