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Highly Regio- and Enantioselective Reductive Coupling of Alkynes and Aldehydes via Photoredox Cobalt Dual Catalysis

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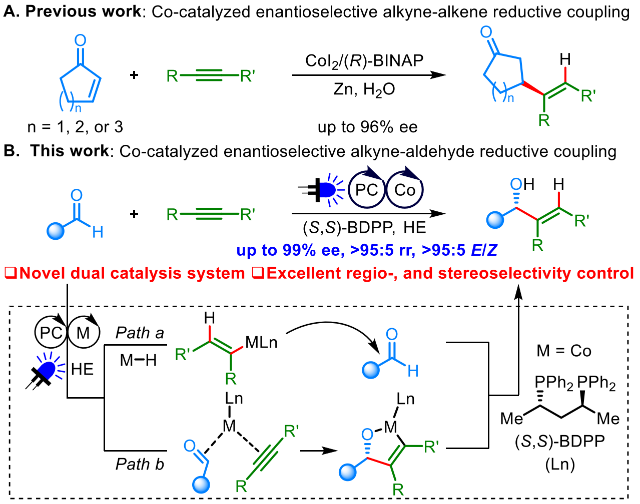
ABSTRACT: A Co-catalyzed highly regio- and enantioselective reductive coupling of alkynes and aldehydes has been developed under visible light photoredox dual catalysis. A variety of enantioenriched allylic alcohols have been obtained by using unsymmetrical internal alkynes and commercially available catalyst, chiral ligand, and reagents. It is noteworthy that this approach has considerable advantages, such as excellent regio- (>95:5 for >40 examples), stereo- (up to >95:5 *E*/*Z*), and enantioselectivity (92−99% ee, >35 examples) control, mild reaction conditions, broad substrate scope, and good functional group compatibility, making it a great improvement to enantioselective alkyne−aldehyde reductive coupling reactions.

Transition-metal-catalyzed reductive coupling reactions provide a straightforward and modular approach for the construction of complex targets from two pieces of electrophiles in the presence of reductants.[1] As asymmetric catalysis constitutes a powerful tool toward optically pure compounds, enantioselective catalytic reductive couplings have tremendous potential in the preparation of enantioenriched molecules.[2,3] The enantioselective reductive coupling of two π-components has received substantial advances in recent decades.[4] Readily available alkynes have been applied to this strategy to couple with another π-component to build a variety of substituted chiral alkenes.[5] Avoiding using vinyl halides or preformed vinyl organometallic reagents,[6] enantioselective alkyne−aldehyde reductive coupling is a promising route toward chiral allylic alcohols, which are one of the most versatile synthons in organic synthesis and key chiral skeletons in numerous pharmaceuticals and natural products. Significant advances on these reactions have been achieved with 1,3-diynes, 1,3-enynes, or alkynes as substrates by using Rh or Ni as a catalyst and H_2,[7] Et_3B,[8] silane,[9] or alcohol[10] as a reductant.[11] However, obtaining highly regio- and enantioselectivity control with simple unsymmetrical internal alkynes is still a big challenge.[12] Therefore, the development of a new efficient catalytic system for regio- and enantioselective alkyne−aldehyde reductive coupling remains highly rewarding.

Scheme 1. Enantioselective Reductive Couplings via Cobalt Catalysis



Cobalt, a low toxic, cost-effective, and earth-abundant first row metal, has been established as an excellent option in numerous transition-metal-catalyzed reactions,[13] particularly asymmetric catalysis.[14,15] In comparison, Co-catalyzed reductive couplings have not been widely developed. In this respect, couplings between two halides,[16] two alkenes,[17] alkynes and alkenes,[18] nitriles and alkenes,[19] and related reactions[20] have been developed, but no alkyne−aldehyde reductive coupling has been reported. These reactions require a stoichiometric amount of metal (Zn or Mn powder) as the reductant, and the asymmetric version is rare. One representative example is enantioselective reductive coupling of alkynes and cyclic enones to β-alkenyl ketones (Scheme 1A).[21] Since 2014, photoredox metal dual catalysis has emerged as a powerful tool to forge chemical bonds under mild conditions.[22] This synergistic catalytic strategy can circumvent the use of stoichiometric metal reductant.[23] Dual photoredox cobalt catalysis has also been applied in several types of reactions, including dehydrogenative transformations,[24] hydrofunctionalization of alkenes,[25] cycloaddition of alkynes,[26] allylation,[27] etc.[28] However, reports on the enantioselective transforma-

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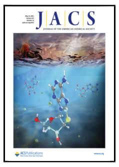

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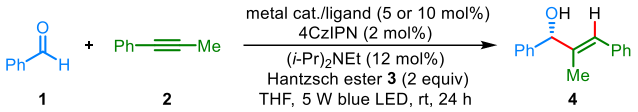
tions via synergistic photoredox cobalt catalysis have remained scarce.[29]

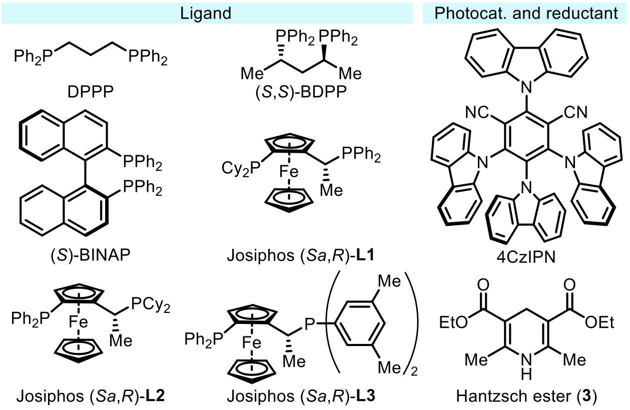
Recently, we reported a regioselective reductive coupling of 1,3-dienes and aldehydes toward homoallylic alcohols via photoredox nickel dual catalysis.[30] We suspected that application of this strategy to metal-catalyzed alkyne−aldehyde reductive coupling would deliver enantioenriched allylic alcohols in the presence of a suitable chiral ligand. Two reaction pathways are initially considered for this reaction. A metal-hydride species might be generated by oxidation of a low-valent metal catalyst with Hantzsch ester (HE) under photoredox conditions (*Path a*). Then, selective addition of aldehyde with an alkenyl metal intermediate from hydrometalation of alkyne would deliver the desired product. For an alternative pathway, metal mediated oxidative cyclometalation of alkyne and aldehyde would provide a five-membered metallacycle, which would provide the product after protolysis (*Path b*). Herein, we report a novel and practical strategy for the highly regio- and enantioselective reductive coupling of alkynes and aldehydes via visible-light photoredox cobalt dual catalysis (Scheme 1B).

We began our research by studying the reductive coupling of benzaldehyde (**1**) and 1-phenyl-1-propyne (**2**) via visible light photoredox metal dual catalysis. Initially, no desired product was observed using nickel as the catalyst with various ligands. After extensive investigations, it was gratifying that allylic alcohol **4** was obtained in 93% yield with excellent regio- and *E*/*Z* selectivity by using $CoBr_2$ as the catalyst, DPPP as the ligand, 4CzIPN as the organic photocatalyst, and Hantzsch ester (HE) **3** as the reducing agent (Table 1, entry 2). A lower yield was obtained with $CoCl_2$ as the catalyst (Table 1, entry 3). We need to mention that the ligand plays a significant role in the reaction (see Table S2 in Supporting Information). Interestingly, the reversed *E*/*Z* selectivity was observed when using an iridium photocatalyst (Table 1, entry 4). Then, various chiral biphosphine ligands were investigated to achieve the enantioselective reaction (Table 1, entries 5−9). No reaction occurred with (*S*)-BINAP as the chiral ligand (Table 1, entry 5). To our delight, excellent yield, regio- (>95:5), *E*/*Z*- (>95:5), and enantioselectivity (98% ee) were obtained by using commercially available (*S*,*S*)-BDPP as the chiral ligand (Table 1, entry 6). Several chiral Josiphos ligands (**L1−3**) were also tested affording **4** with excellent ee but lower yields (Table 1, entries 7−9). When reducing the catalyst loading from 10 mol% to 5 mol%, the catalytic efficiency can also be maintained (Table 1, entry 10, standard conditions). A similar result was also obtained with the $CoBr_2[(S,S)\text{-BDPP}]$ complex as the catalyst (Table 1, entry 11). Finally, control experiments confirmed that **4** could not be obtained without any one of the following elements: $CoBr_2$, ligand, photocatalyst, Hantzsch ester, and visible light. We want to comment that Ni-catalyzed enantioselective reductive coupling of **1** and **2** toward **4** has been studied via several systems.[8,9] Up to 86% ee has been obtained with a well-designed ferrocene-based planar chiral NHC ligand.[9c] Obviously, the best result has been achieved under our photoredox cobalt dual catalysis.

Table 1. Reaction Development[a]



entry	metal cat.	ligand	yield[b] (%)	rr[b]	*E*/*Z*[b]	ee[c] (%)
1	$NiCl_2$	2,2′-BPY	0	–	–	–
2	$CoBr_2$	DPPP	93	>95:5	>95:5	–
3	$CoCl_2$	DPPP	50	>95:5	>95:5	–
4[d]	$CoBr_2$	DPPP	90	>95:5	1:2	–
5	$CoBr_2$	(*S*)-BINAP	0	–	–	–
6	$CoBr_2$	(*S*,*S*)-BDPP	80	>95:5	>95:5	98
7	$CoBr_2$	Josiphos **L1**	20	>95:5	>95:5	97
8	$CoBr_2$	Josiphos **L2**	18	>95:5	>95:5	96
9	$CoBr_2$	Josiphos **L3**	31	>95:5	>95:5	97
10[e]	**$CoBr_2$**	**(*S*,*S*)-BDPP**	**80** (78)[f]	>95:5	>95:5	**98**
11[g]	$CoBr_2[(S,S)\text{-BDPP}]$		75	>95:5	>95:5	98



[a]Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), metal cat. (10 mol %), ligand (10 mol%), 4CzIPN (2 mol%), $^{i}Pr_2NEt$ (12 mol%), **3** (2 equiv), THF (3 mL), 5 W blue LEDs, rt, if otherwise noted. [b]Determined by crude ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by Chiral HPLC. [d]With $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as the photocatalyst. [e]With 5 mol% $CoBr_2$ and 5 mol% (*S*,*S*)-BDPP. [f]Isolated yield in the parentheses. [g]With 5 mol% $CoBr_2[(S,S)\text{-BDPP}]$.

With the optimal reaction conditions in hand, we then examined the generality of this enantioselective reductive coupling (Figure 1). We first investigated the scope of the alkynes. Using unsymmetrical aryl substituted internal alkynes, excellent regio- (>95:5) and enantioselectivity (98−99% ee) were obtained (**5−13**). Electronic properties have little influence on the enantioselectivity, as electron-donating (Me, OMe), electron-withdrawing (CF_3), and halide (F, Cl) substituents on the aryl ring are well tolerated. Trisubstituted aryl alkynes were also proven successful (**7**, >95:5 rr, 94:6 *E*/*Z*, 99% ee). For heteroaryl alkynes, thiophene-containing alkyne reacted smoothly affording **12** with excellent results (>95:5 rr, >95:5 *E*/*Z*, 98% ee), while pyridyl alkyne gave **13** in lower yield due to low conversion but with excellent regio- and stereoselectivity (>95:5 rr, >95:5 *E*/*Z*, 98% ee). However, relatively lower *E*/*Z* selectivities were observed when using alkynes with electron-rich aryl substituents (**6**, 82:18 *E*/*Z*, and **8**, 83:17 *E*/Z), which might be caused by corresponding *E* to *Z* isomerization by the energy transfer process (see control experiments on *E*/*Z* isomerization in the Supporting Information). This low *E*/*Z* selectivity can be dramatically improved by switching to iridium photocatalyst (**6** and **8**). With internal dialkyl alkynes as substrates, the corresponding allylic alcohol products (**14−19**) were obtained in moderate to good yields with 96−99% ee. Remarkably, excellent regioselectivity (>95:5) was obtained with these unsymmetric internal dialkyl alkynes (**15−19**). Notably, 2-butyne, the

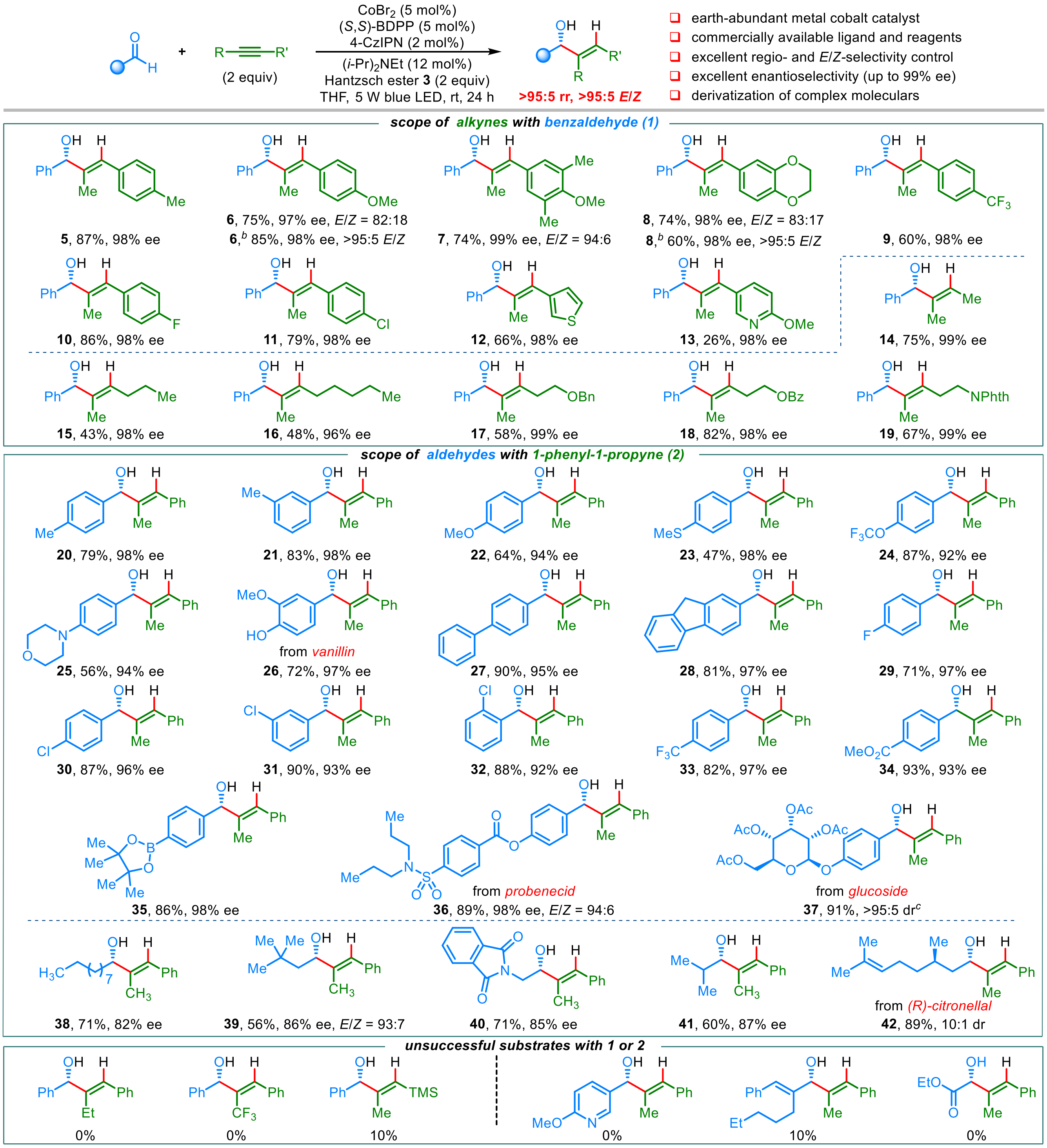


Figure 1. Reaction scope. [a]All reactions were performed with 0.2 mmol of aldehyde; isolated yield of product with >95:5 rr and >95:5 *E*/*Z* if otherwise noted; ee was determined by chiral HPLC; *E*/*Z*, rr, and dr were determined by crude ^{1}H NMR. [b]With Ir(ppy)$_2$(dtbbpy)PF$_6$ as the photocatalyst. [c]With **2** (3 equiv), **3** (3 equiv), 36 h.

smallest symmetrical internal alkyne, also reacted well affording **14** in 75% yield with 99% ee, which has a big improvement in enantioselectivity control compared to the previous Ni-catalyzed protocol (73% ee).[10]

Unfortunately, no desired product was obtained with terminal alkynes and nonmethyl substituted alkynes in this reaction (for details see Supporting Information).

Next, the scope of the aldehyde coupling partner was also explored. A variety of aromatic aldehydes were found to be efficient coupling components affording the chiral allylic alcohols with good yield and excellent regio- and enantioselectivities (**20**−**37**, >95:5 rr, 92−99% ee), exhibiting the best regio- and enantioselectivity control with the same type of substrates compared to the reported results.[8−10] Here, the mild reaction conditions are compatible with a wide range of functional groups on the aryl ring at different sites, including Me (**20** and **21**), OMe (**22**), SMe (**23**), OCF$_3$ (**24**), morpholino (**25**), phenol (**26**), electronically biased biphenyls

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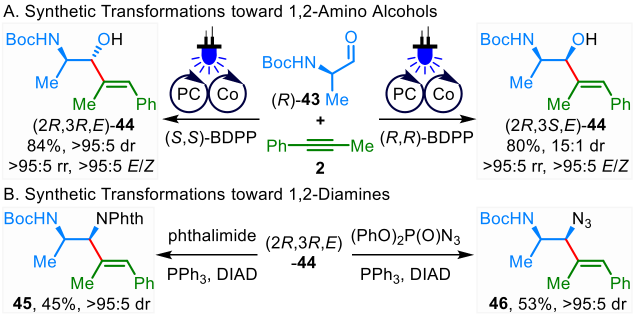
(**27** and **28**), CF$_3$ (**33**), ester (**34**), sulfanilamide (**36**), and acetal (**37**). It is noteworthy that the halogen functionalities at *ortho*-, *meta*-, and *para*-position (**29**−**32**) and boronic acid pinacol ester (**35**) remain intact after the coupling, furnishing additional reaction sites for further synthetic elaborations. Encouragingly, coupling with natural products vanillin (**26**) and aldehyde containing drug molecule derivatives (**36** and **37**) afforded the desired products in high yields with significant enantioenrichment (97−98% ee) or complete diastereocontrol (>95:5 dr), indicating the potential applicability of this reaction in late-stage functionalization or complex targets synthesis. Moreover, coupling with alkyl aldehydes, including long-chain decanal, isobutyraldehyde, and natural citronellal, also occurred smoothly leading to the products (**38**−**42**) in good yield with excellent regioselectivity (>95:5 rr), *E*/*Z* control (93:7−>95:5), and good enantio- (82−87% ee) or diastereoselectivity (10:1 dr).

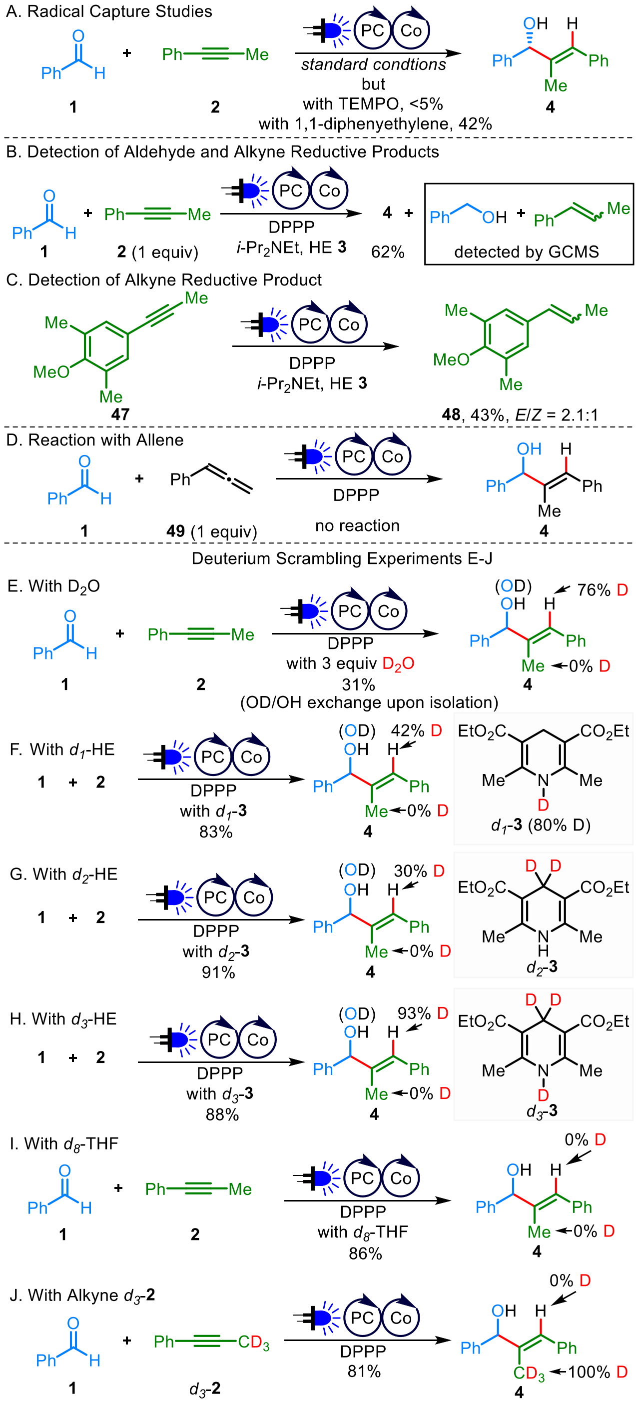
To further demonstrate the synthetic utility of the present method, diastereoselective reductive coupling of alkyne and chiral amido aldehyde (*R*)-**43** toward chiral 1,2-amino alcohol was carried out. Enantioenriched 1,2-amino alcohol (2*R*,3*R*)-**44** or (2*R*,3*S*)-**44** was easily obtained under the standard conditions with good yield and excellent regio-, *E*/*Z*-, and diastereoselectivity by using commercially available (*S*,*S*)-BDPP or (*R*,*R*)-BDPP as the chiral ligand (Scheme 2A). Next, the 1,2-amino alcohol product **44** was directly converted into 1,2-diamine **45** and 2-azide amine **46** with good stereoselectivity through Mitsunobu reaction (Scheme 2B).

Scheme 2. Synthetic Applications


A. Synthetic Transformations toward 1,2-Amino Alcohols

B. Synthetic Transformations toward 1,2-Diamines

Scheme 3. Control Experiments


A. Radical Capture Studies

B. Detection of Aldehyde and Alkyne Reductive Products

C. Detection of Alkyne Reductive Product

D. Reaction with Allene

Deuterium Scrambling Experiments E-J

E. With D$_2$O

F. With d_1-HE

G. With d_2-HE

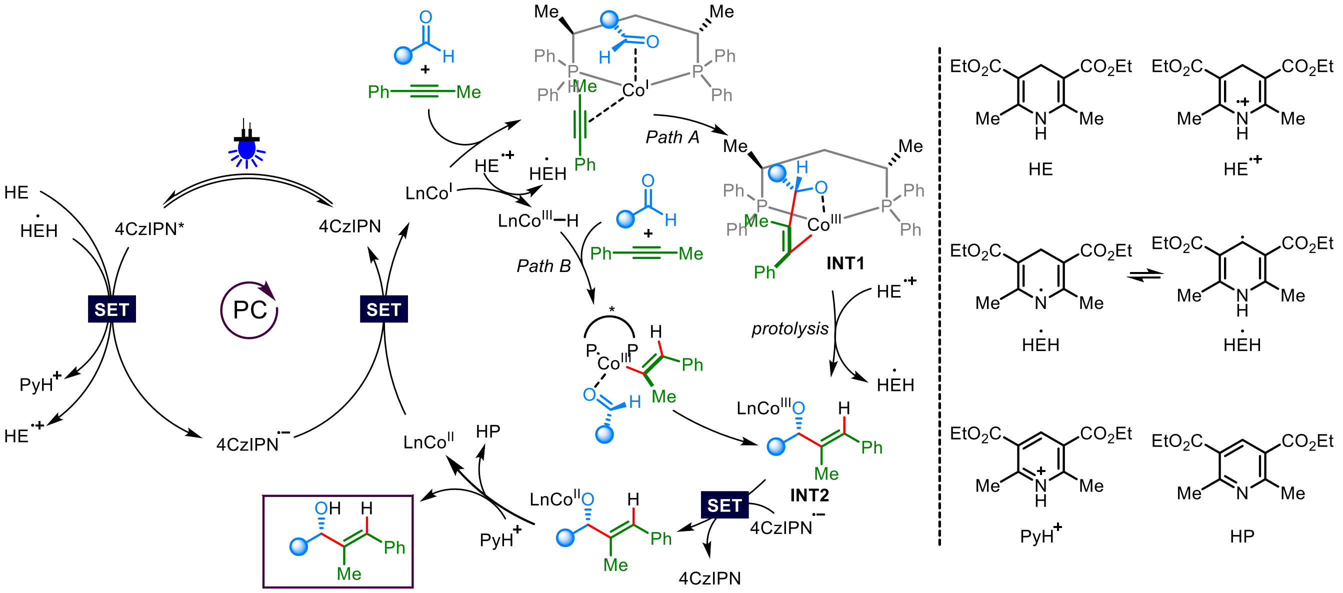
H. With d_3-HE

I. With d_8-THF

J. With Alkyne d_3-**2**

Next, control experiments were conducted to understand the mechanism of this reaction. First, radical capture studies showed that addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger inhibits the reaction while addition of ethene-1,1-diyldibenzene does not inhibit the reaction (Scheme 3A). However, we did not detect any radical capturing adduct in both cases. Considering that TEMPO may not solely act as a radical scavenger and may inhibit the reaction through another avenue, these result suggested that the reaction may not involve formation of free radical intermediate. We detected trace amounts of benzyl alcohol and alkyne semihydrogenation product during screening of the reaction conditions (Scheme 3B). Semihydrogenation of alkynes **47** was achieved in the absence of aldehyde with the same catalytic system (Scheme 3C). These results suggested that cobalt hydride species might be generated to a certain extent in the reaction. No reductive coupling product was detected with allene **49** as the coupling component, which ruled out the process in which alkyne participates in the reaction as an allene precursor (Scheme 3D).[31] In addition, a variety of deuterium scrambling experiments have been carried out with heavy water (D$_2$O), deuterated HE d_1-**3**, d_2-**3**, d_3-**3**, d_8-THF, or deuterated alkyne substrate d_3-**2** (Scheme 3E−J). The results clearly indicate the transfer of hydrogen at both the 1- and 4-postion of HE into the alkenyl hydrogen of product and suggest that an intermediate proton might exist in this reaction. Moreover, a series of Stern−Volmer fluorescence quenching experiments were performed to further understand the mechanism. We found that the emission intensity of the excited 4CzIPN* was dramatically diminished in the presence of HE **3** rather than other components, thereby indicating that

Scheme 4. Plausible Reaction Pathways



electron transfer between 4CzIPN* and HE was more favored (for details see Supporting Information).

Based on the control experiments, a preliminary mechanism is proposed in Scheme 4. Upon irradiation with visible light, photoexcited 4CzIPN* accepts one electron from HE [$E_{1/2}^{\mathrm{ox}}$ (HE/HE$^{\bullet+}$) = 0.51 V vs Fc$^+$/Fc in MeCN][32] to afford 4CzIPN$^{\bullet-}$ [$E_{1/2}^{\mathrm{red}}$ (4CzIPN*/4CzIPN$^{\bullet-}$) = −1.21 V vs SCE in MeCN],[33] which can reduce ligand coordinated Co(II) complex [$E_{1/2}^{\mathrm{red}}$ (Co$^{\mathrm{II}}$/Co$^{\mathrm{I}}$)= −0.75 V vs SCE in MeCN][26a] to low valent Co(I) species via single electron transfer (SET).[25b] Then, the coordination of alkyne at the equatorial position and aldehyde with its *Re* face at the axial position of the Co(I) center followed by oxidative cyclization gives oxacobaltacyclopentene intermediate **INT1** (Scheme 4, *Path A*).[34] The following protonation by HE$^{\bullet+}$ produces the allylic cobalt alkoxide **INT2** and neutral HEH radical.[26a] Subsequently, the strong electron donor HEH radical (E^{ox} = −1.13 V versus SCE) can donate one electron to photoexcited 4CzIPN* to afford pyridinium ion PyH$^+$ and 4CzIPN$^{\bullet-}$,[35] which reduce Co(III)-alkoxide to Co(II)-alkoxide to achieve the second photocatalytic cycle.[36] The final protolysis by PyH$^+$ would deliver the corresponding allylic alcohol product. The corresponding pyridine compound (HP) has been isolated as a byproduct. Alternatively, we cannot exclude another reaction pathway involving addition of aldehyde with alkenyl cobalt species from hydrometalation of alkyne with cobalt(III) hydride, which is generated from oxidation of Co(I) species via proton reduction of HE$^{\bullet+}$ under photoredox conditions (Scheme 4, *Path B*).[25b]

In summary, we have disclosed the first synergistic visible light photoredox Co-catalyzed highly regio- and enantioselective reductive coupling of alkynes and aldehydes toward chiral allylic alcohols under mild conditions. This convenient method uses commercially available catalyst, chiral ligand, and reagents, delivering enantioenriched allylic alcohols with excellent regio- (>95:5), *E*/*Z*- (up to >95:5), and enantioselectivity (up to 99% ee). Remarkably, excellent regioselectivity has been achieved with unsymmetrical internal dialkylalkynes as substrates. The broad scope and good functionality tolerance of this novel method have been applied in the diastereoselective synthesis of 1,2-amino alcohols. Further application and mechanistic clarification of this strategy are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03527.

Experimental procedures, characterizations and analytical data of new compounds; and spectra of NMR and HPLC for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(36) Alternatively, it is also possible that the HEH radical (E^{ox} = −1.13 V versus SCE.) directly donates one electron to Co(III) generating Co(II) and pyridinium ion PyH^+. For [E^{red}(Co^{III}/Co^{II}) = −0.51 V vs Fc^+/Fc], see: Elgrishi, N.; Kurtz, D. A.; Dempsey, J. L. Reaction parameters influencing cobalt hydride formation kinetics: implications for benchmarking H_2-evolution catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 239.

■ NOTE ADDED AFTER ASAP PUBLICATION

The figure of Ligand, Photocat. and reductant was added to Table 1 on May 6, 2021.