

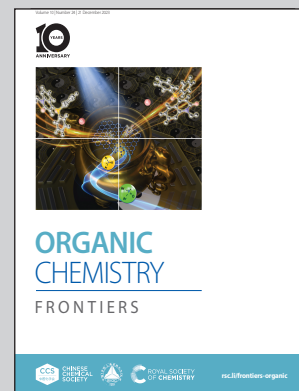
Showcasing research from Professor Ji-Bao Xia's laboratory, State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, China.

Regio- and stereoselective divergent cross-coupling of alkynes and disubstituted alkenes *via* photoredox cobalt dual catalysis

Ligand-controlled ene-type or reductive coupling of alkynes and *gem*-disubstituted alkenes has been developed by photoredox cobalt dual catalysis. Stereodefined 1,4-dienes or trisubstituted alkenes are obtained by choosing different ligands from the same intermediate.

Image credit: Zihan Xia & Lingchang Kong

As featured in:



See Hu He, Ji-Bao Xia *et al.*,
Org. Chem. Front., 2023, **10**, 6070.

Registered charity number: 207890

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2023, **10**, 6070

Regio- and stereoselective divergent cross-coupling of alkynes and disubstituted alkenes *via* photoredox cobalt dual catalysis†

 Shi-Qi Zhang,^{a,e} Yan-Lin Li,^a Kun Cui,^a Chen Chen,^{a,e} Zheng-Yang Gu,^{id} ^c Hu He^{*d} and Ji-Bao Xia^{id} ^{*a,b}

Achieving divergent synthesis from the same substrates quickly to generate different products remains an attractive objective in synthetic chemistry and the medicinal industry. Here, we report a discovery of highly selective divergent cross-coupling of alkynes and disubstituted alkenes by merging visible light photoredox and cobalt catalysis. Under otherwise identical conditions, the use of either a hemilabile P,N-ligand or a strong bidentate diphosphine ligand leads to ene-type coupling or reductive coupling of alkynes and Tulipalin A, producing stereodefined 1,4-diene or trisubstituted alkene products, respectively. The approaches feature considerable advantages for the straightforward synthesis of stereodefined multiple substituted alkenes, such as easily available substrates, low catalyst loading of an organophotocatalyst, excellent regio- and stereoselectivity, good functional group tolerance, and mild reaction conditions. Reasonable catalytic reaction pathways from the same cobaltacyclopentene intermediate have been proposed.

Received 10th August 2023,
Accepted 26th October 2023

DOI: 10.1039/d3qo01281f

rsc.li/frontiers-organic

Introduction

As essential constituents, 2-furanones (butyrolactones) have been found in over 5800 natural compounds and drug molecules and possess diverse biological activities such as anthelmintic, antiviral, antifungal, and anticancer activities (Scheme 1A).¹ Many methods have been developed to access butyrolactones, including the widely used intramolecular esterification or selective oxidation of furan derivatives.² Tulipalin A, α -methylene- γ -butyrolactone (MBL), is a structurally simple and commercially available sesquiterpene lactone present in bulb scales of tulips with antibacterial and antitumor properties.³ Bearing an exo-methylene group at the α -position of

lactone, Tulipalin A is considered as a cyclic analog of methyl methacrylate (MMA). Thus, it has been broadly used as a naturally originating vinyl monomer for the synthesis of biocompatible and biodegradable polymers.⁴ In addition, Tulipalin A has been used as a reactant in organic synthesis, such as a Michael acceptor or an electron-deficient olefin.⁵ However, it is rarely used as an efficient coupling partner in transition-metal-catalyzed cross-coupling reactions. It is suspected that the use of Tulipalin A as a simple synthon to couple with other easily accessed materials would be a straightforward and modular approach to access complex targets containing 2-furanone frameworks.

Transition-metal-catalyzed intermolecular cross-coupling of alkynes and alkenes provides a highly atom- and step-economical route to form C–C bonds with easily accessed materials in organic synthesis.⁶ The main challenge of this reaction is the control of its chemo-, regio- and stereoselectivities because diverse products can be obtained *via* a common intermediate **A** of metallacyclopentene generated from oxidative cyclometallation of alkynes and alkenes (Scheme 1B). To minimize the steric strain and reduce the regioisomeric products, less hindered monosubstituted alkenes (α -alkenes) have been mainly used as the substrates. For instance, Ru⁷- or Co-catalyzed⁸ ene-type coupling of alkynes and monosubstituted alkyl alkenes produced 1,4-dienes as the favored products *via* exocyclic β -hydride elimination followed by reductive elimination (path a). Through endocyclic β -hydride elimination followed

^aState Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, China

^bCollege of Material Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Hangzhou Normal University, Hangzhou 311121, Zhejiang, China

^cCollege of Textiles and Clothing, Key Laboratory for Advanced Technology in Environmental Protection of Jiangsu Province, Yancheng Institute of Technology, Jiangsu, China

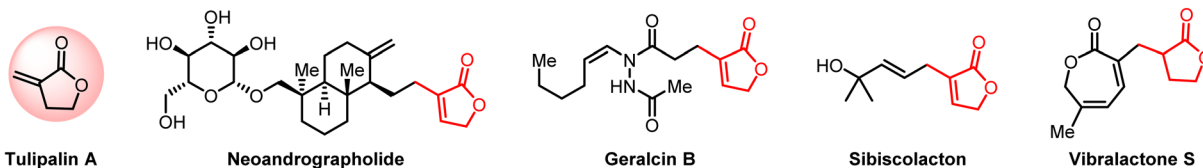
^dHangzhou SynRx Therapeutics Biomedical Technology Co., Hangzhou, 311121, China. E-mail: hehu@synrx.cn

^eUniversity of Chinese Academy of Sciences, Beijing, 100049, China

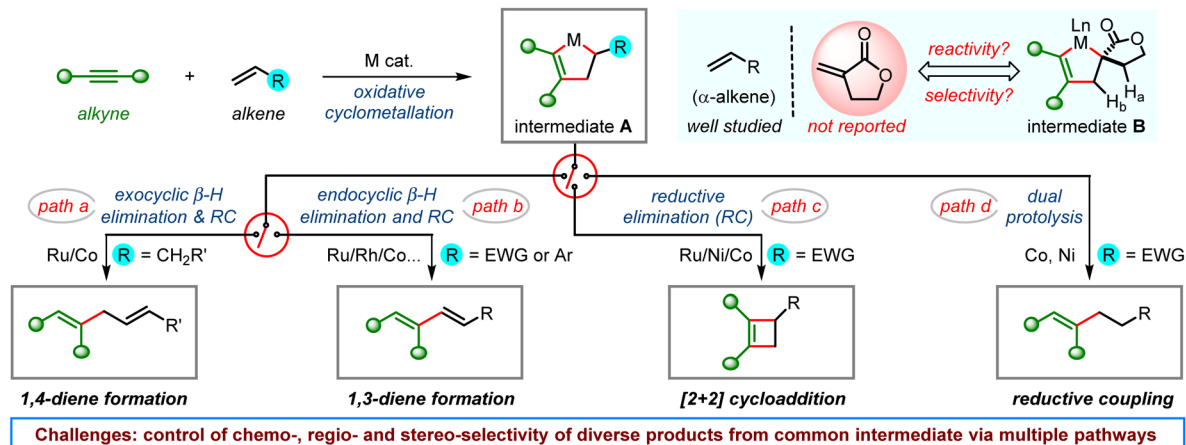
† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3qo01281f>



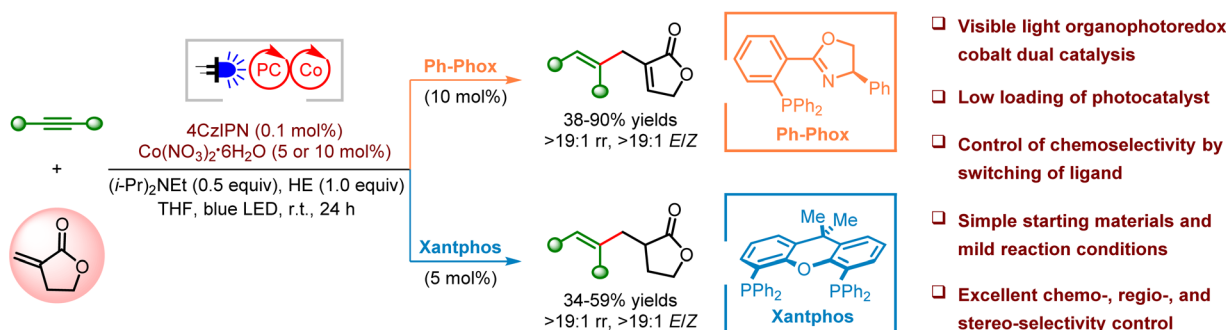
A. Selected bioactive natural products containing the dihydrofuranone or furanone motif



B. General overview of transition-metal-catalyzed cross-coupling of alkynes and alkenes



C. Ligand-controlled divergent photoredox Co-catalyzed cross-coupling of alkynes and Tulipalin A (This Work)



Scheme 1 Transition-metal-catalyzed selective cross-coupling of alkynes and alkenes.

by reductive elimination, 1,3-dienes were obtained using styrenes⁹ (Co catalysis) or electron-deficient alkenes (Ni,¹⁰ Rh,¹¹ Ru¹² or Pd¹³ catalysis) as the coupling partners since exocyclic β -hydride does not exist in intermediate **A** (path b). Interestingly, cyclobutenes were favored by coupling monosubstituted electron-deficient alkenes under cobalt catalysis *via* [2 + 2]-cyclization through direct C–C bond reductive elimination of **A** (path c).¹⁴ In addition, Co- or Ni-catalyzed cross-coupling of alkynes and electron-deficient alkenes easily produces multi-substituted alkenes as the reductive coupling products under reducing conditions (path d).¹⁵ Recently, a few elegant examples have been reported other than monosubstituted alkenes. Well-designed multi-substituted alkenes containing a directing group were found to be efficient coupling partners in Ru-catalyzed ene-type coupling with silyl alkynes, or propargyl or homopropargyl alcohols.¹⁶ Symmetrical cyclic alkenes have also been used in Rh- or Co-catalyzed ene-type alkyne/alkene couplings.¹⁷ On the other hand, few examples of Co-catalyzed reductive coupling of alkynes and simple electron-deficient

internal alkenes have been reported.¹⁸ We questioned whether simple Tulipalin A could be used as a versatile *gem*-disubstituted alkene to couple with alkynes, providing a direct and concise route to 2-furanone-containing stereodefined alkene targets. Two challenges have been considered in this reaction. First, a crowded spirocyclic metallacyclopentene **B** should be generated, which may cause a strong steric effect. Second, selective control of the coupling product will be attractive but difficult because intermediate **B** could possibly undergo either of the following reaction pathways, exocyclic β -H_a or endocyclic β -H_b elimination, direct reductive elimination, or reductive coupling. Photocatalysis has captured the imagination of both synthetic and medicinal chemists and has become an attractive tool in green synthesis.¹⁹ In particular, photoredox metal dual catalysis has been proved to be a powerful strategy in the synthesis of complex targets under mild reaction conditions.^{20,21} Herein, we reported for the first time a photoredox Co-catalyzed regio- and stereoselective ene-type coupling of alkynes and Tulipalin A, a *gem*-disubstituted



alkene, producing 2-furanone-containing 1,4-dienes with excellent control of geometry (Scheme 1C). Moreover, the reductive coupling of alkynes and *gem*-disubstituted alkenes has also been achieved, affording stereodefined trisubstituted alkenes using a different ligand under otherwise identical conditions.

Results and discussion

We started our research by investigating the cross-coupling of unsymmetrical 1-phenyl-1-propyne (**1**) and Tulipalin A (**2**) *via* visible light photoredox cobalt dual catalysis (Table 1). Initially, using the commercially available CoCl₂ as the catalyst, Xantphos as the ligand, and 2,4,5,6-tetrakis(carbazol-9-yl)-1,3-dicyanobenzene (4CzIPN) as the organic photocatalyst,²² the anticipated reductive coupling reaction occurred smoothly, affording the trisubstituted alkene product **3** in 65% yield with >19:1 regioselectivity (rr) and >19:1 *E/Z* stereoselectivity using Hantzsch ester (HE) as an organic reducing reagent in tetrahydrofuran (THF) under 5 W blue LED irradiation (Table 1, entry 1). After extensive screening of a variety of cobalt catalysts, an improved yield was obtained with Co(NO₃)₂·6H₂O as the metal catalyst (Table 1, entry 2, also see Table S1 in the ESI†). To our surprise, the ene-type coupling

product 1,4-diene **4** was also obtained in 5% yield under these typical reductive coupling conditions. Interestingly, the cross-coupling reaction afforded skipped diene **4** as the major product when *N,N*-dimethylformamide (DMF) was used as the solvent, indicating that the reductive coupling or ene-type coupling reaction might be possibly controlled by changing the reaction conditions (Table 1, entry 3). Since one chiral center exist in product **3**, various chiral ligands were then tested to achieve an enantioselective reductive coupling reaction. Unfortunately, low enantioselectivity control was observed with a wide range of chiral phosphine or nitrogen ligands (Table 1, entries 4 and 5; for details see Table S2 in the ESI†). To our delight, the 1,4-diene product **4** was obtained as the major product in 66% yield with >19:1 regioselectivity and >19:1 *E/Z* stereoselectivity when Ph-Phox was used as the ligand under otherwise identical conditions (Table 1, entry 6). The ligand plays an important role in the reaction. No reaction occurred with the structurally similar ^tBu-Phox as the ligand, but dppp gave a similar yield of **4** (Table 1, entries 7 and 8). The yield of product **4** was further increased to 86% after detailed optimizations of the ratio of substrates, the catalyst loadings of the cobalt catalyst and photocatalyst and the amount of HE (Table 1, entries 9–12). Notably, an excellent yield was still maintained when the

Table 1 Summary of the effects of reaction parameters on the reaction efficiency^a

Reaction scheme showing the reductive coupling of 1-phenyl-1-propyne (**1**) and Tulipalin A (**2**) to form products **3** and **4**. Conditions: 4CzIPN (2 mol%), Co catalyst (5 mol%), ligand (5 mol%), (*i*-Pr)₂NEt (0.5 eq.), HE (1.0 eq.), solvent, blue LED, r.t., 24 h. Product **3** is a trisubstituted alkene with >19:1 rr, >19:1 *E/Z*. Product **4** is a 1,4-diene with >19:1 rr, >19:1 *E/Z*. A skipped diene is also shown as 'not detected'.

Chemical structures of ligands and photocatalysts are shown below the reaction scheme:

- 4CzIPN: 2,4,5,6-tetrakis(carbazol-9-yl)-1,3-dicyanobenzene
- Hantzsch ester (HE): 1,4-dihydro-2,6-dimethyl-3,5-diepoxy-1,4-dihydropyridine
- Xantphos: 1,3-bis(diphenylphosphino)benzene
- (*R,R*)-Ph-BPE: 1,1'-bis(diphenylphosphino)ethane
- (*S*)-6-Ph-Bn-Pyox: 6-phenyl-1,2,3,4-tetrahydropyridoxin
- Ph-Phox: 1,2,3,4-tetrahydropyridoxin
- ^tBu-Phox: 1,2,3,4-tetrahydropyridoxin with a ^tBu group at the 6-position

Entry	Co catalyst	Ligand	Solvent	Yield of 3 ^b (%)	ee of 3 ^c (%)	Yield of 4 ^b (%)
1	CoCl ₂	Xantphos	THF	65	—	Trace
2	Co(NO ₃) ₂ ·6H ₂ O	Xantphos	THF	68 (59)	—	5
3	Co(NO ₃) ₂ ·6H ₂ O	Xantphos	DMF	29	—	46
4	Co(NO ₃) ₂ ·6H ₂ O	(<i>R,R</i>)-Ph-BPE	THF	17	5	<5
5	Co(NO ₃) ₂ ·6H ₂ O	(<i>S</i>)-6-Ph-Bn-Pyox	THF	11	12	Trace
6	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	5	—	66
7	Co(NO ₃) ₂ ·6H ₂ O	^t Bu-Phox	THF	0	—	0
8	Co(NO ₃) ₂ ·6H ₂ O	dppp	THF	Trace	—	62
9 ^d	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	5	—	82
10 ^{d,e}	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	<5	—	79
11 ^{d,e,f}	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	<5	—	86 (81)
12 ^{d,e,f,g}	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	<5	—	38
13 ^{d,e}	No Co catalyst	No ligand	THF	0	—	0
14 ^{d,e,f,h}	Co(NO ₃) ₂ ·6H ₂ O	Ph-Phox	THF	0	—	0

^a Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv.), Co catalyst (5 mol%), ligand (5 mol%), 4CzIPN (2 mol%), (*i*-Pr)₂NEt (0.5 equiv.), HE (1.0 equiv.), solvent (3.0 mL), 5 W blue LED, r.t., 24 h, unless otherwise noted. ^b Determined by GC with dodecane as an internal standard, and isolated yield is shown in parentheses. ^c Determined by chiral HPLC analysis. ^d With **2** (3.0 equiv.). ^e With 4CzIPN (0.1 mol%). ^f With Co(NO₃)₂·6H₂O (10 mol%) and Ph-Phox (10 mol%). ^g With HE (0.5 equiv.). ^h Without light.



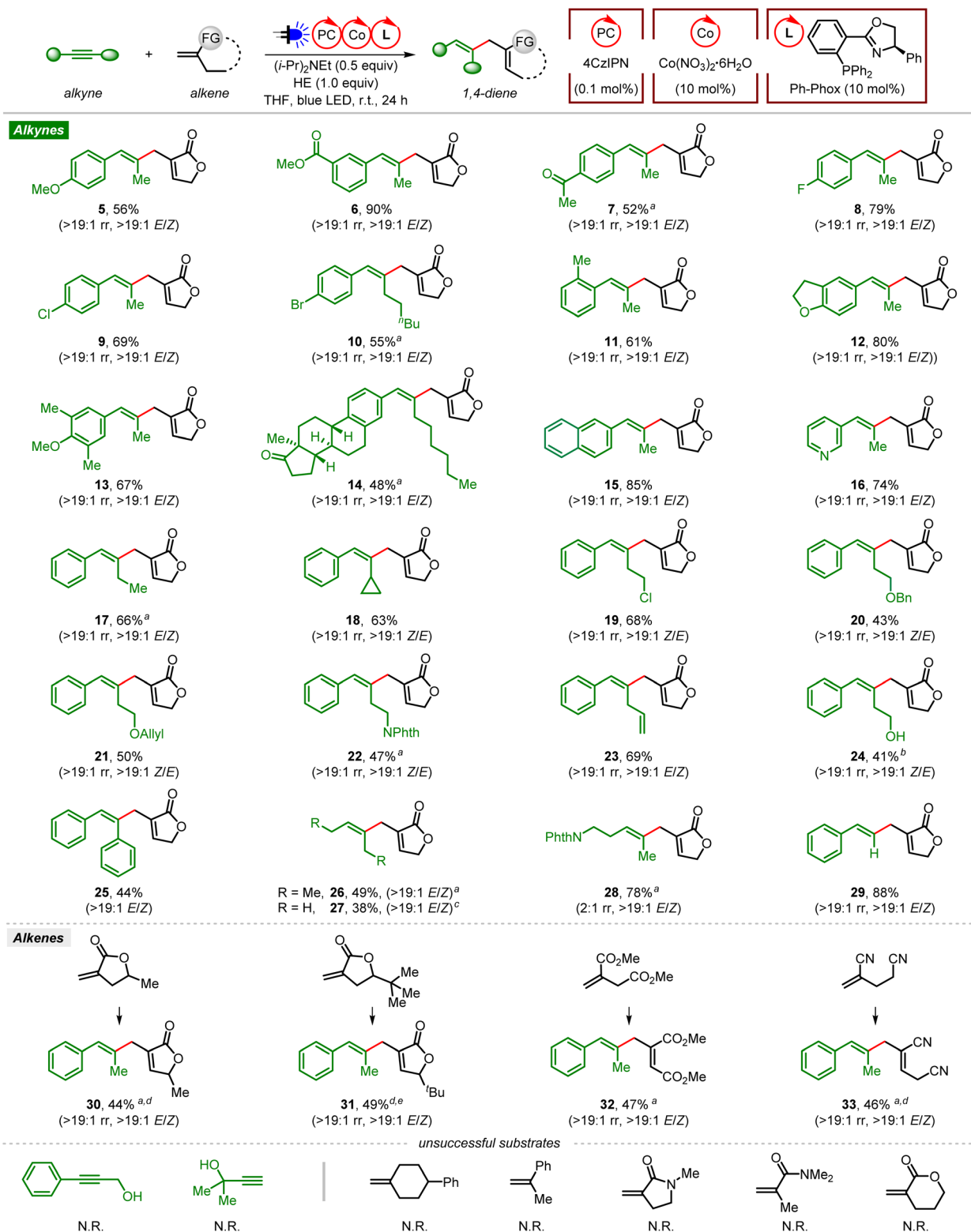


Fig. 1 Reaction scope of organophotoredox Co-catalyzed ene-type coupling of alkynes and alkenes. Reaction conditions: alkyne (0.2 mmol), alkene (3.0 equiv.), 4CzIPN (0.1 mol%), $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (10 mol%), Ph-Phox (10 mol%), $(i\text{-Pr})_2\text{NEt}$ (0.5 equiv.), HE (1.0 equiv.), THF (3.0 mL), 5 W blue LED, r.t., 24 h, isolated yield, unless otherwise noted. ^a With 4CzIPN (2 mol%). ^b With TMS-protected homopropargylic alcohol as the substrate. ^c With 2-butyne (50 equiv., 1 mL, 10 M solution in THF). ^d With DMF as the solvent. ^e With 4CzIPN-Br (2 mol%) as the photocatalyst.



catalyst loading of 4CzIPN was decreased to 0.1%. It should be noted that the 1,3-diene or cyclobutene product was not observed under the tested conditions. Finally, control experiments demonstrate that no reductive coupling or ene-type coupling product was observed in the absence of a cobalt catalyst, ligand, photocatalyst, or light, which means that they are all required for the progression of the current cross-coupling reactions (Table 1, entries 13 and 14, also see Table S8 in the ESI†).

With the optimized reaction conditions in hand, we first examined the generality of the ene-type coupling of alkynes and *gem*-disubstituted alkenes leading to 1,4-dienes *via* visible light organophotoredox cobalt dual catalysis (Fig. 1). In general, excellent regio- (>19:1 rr) and stereoselectivities (>19:1 *E/Z* or *Z/E*) were obtained. Coupling of aryl alkynes and Tulipalin A produced the desired products 5–7 in 52–90% yields, tolerating electron-donating (OMe) and electron-withdrawing (CO₂Me, Ac) groups at the *meta*- or *para*-position of the aryl ring. Halide (F, Cl, Br) groups are also tolerated to give the corresponding 1,4-dienes in good yields (8–10). Aryl methyl alkynes bearing a bulky *ortho*-methyl group on the aryl ring (11) or a multi-substituted aryl substituent reacted smoothly, indicating good steric compatibility in this transformation (12 and 13). The alkyne derived from a natural steroid was a suitable coupling partner (14), demonstrating the utility of this reaction for the late-stage functionalization of complex molecules. In addition, an internal alkyne containing a naphthalene or pyridine group was also compatible, generating the corresponding product 15 or 16 in a good yield with excellent regio- and stereoselectivity.

Besides, ene-type coupling of Tulipalin A and terminal alkyl group (ethyl or cyclopropyl) substituted phenylacetylene also occurred smoothly, giving the desired products 17 and 18. A variety of functional groups on the alkyl chain of the phenyl alkynes, such as halogen (Cl), ether (OBn, OAllyl), imide (Phth, phthalimide), and terminal alkene, were well tolerated, leading to the corresponding products in moderate to good yields (19–23). Notably, the free alcohol product 24 was obtained when trimethylsilyl (TMS)-protected homopropargylic alcohol was used as the substrate, with the removal of the TMS protecting group during isolation using flash column chromatography on silica gel.

Next, we tested symmetrical internal alkynes, such as diphenylethyne, 3-hexyne and 2-butyne, in this cross-coupling reaction. They reacted smoothly with Tulipalin A, affording the corresponding products in moderate yields (25–27). When the unsymmetrical dialkyl alkyne PhthN-substituted 2-pentyne was used as the substrate, 1,4-diene 28 was obtained in 78% yield albeit with low regioselectivity (2:1 rr). Notably, the terminal alkyne phenylacetylene was also proved to be a suitable coupling partner in this reaction, producing 29 in a good yield with excellent regio- and stereoselectivity. However, no reaction occurred with internal or terminal propargylic alcohol under the standard conditions. Then the scope of *gem*-disubstituted alkenes was explored. The *O*-alpha alkyl (methyl and *tert*-butyl) substituted Tulipalin A analogs were successfully employed as the substrates, affording the desired products in moderate yields with excellent regio- and stereoselectivities (30 and 31). Linear alpha-alkyl substituted acrylate and acrylonitrile were also suitable coupling partners, leading to functionalized 1,4-

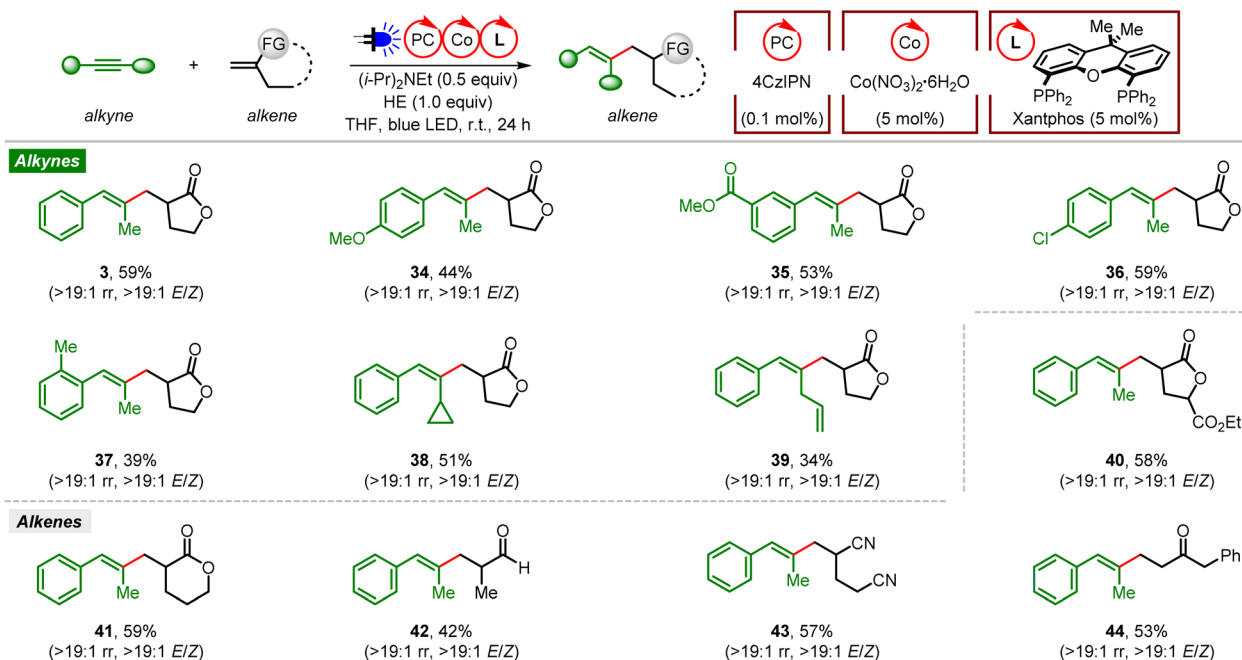


Fig. 2 Reaction scope of organophotoredox Co-catalyzed reductive coupling of alkynes and alkenes. Reaction conditions: alkyne (0.2 mmol), alkene (3.0 equiv.), 4CzIPN (0.1 mol%), Co(NO₃)₂·6H₂O (5 mol%), Ph-Phox (5 mol%), (*i*-Pr)₂NEt (0.5 equiv.), HE (1.0 equiv.), THF (3 mL), 5 W blue LED, r.t., 24 h, isolated yield.



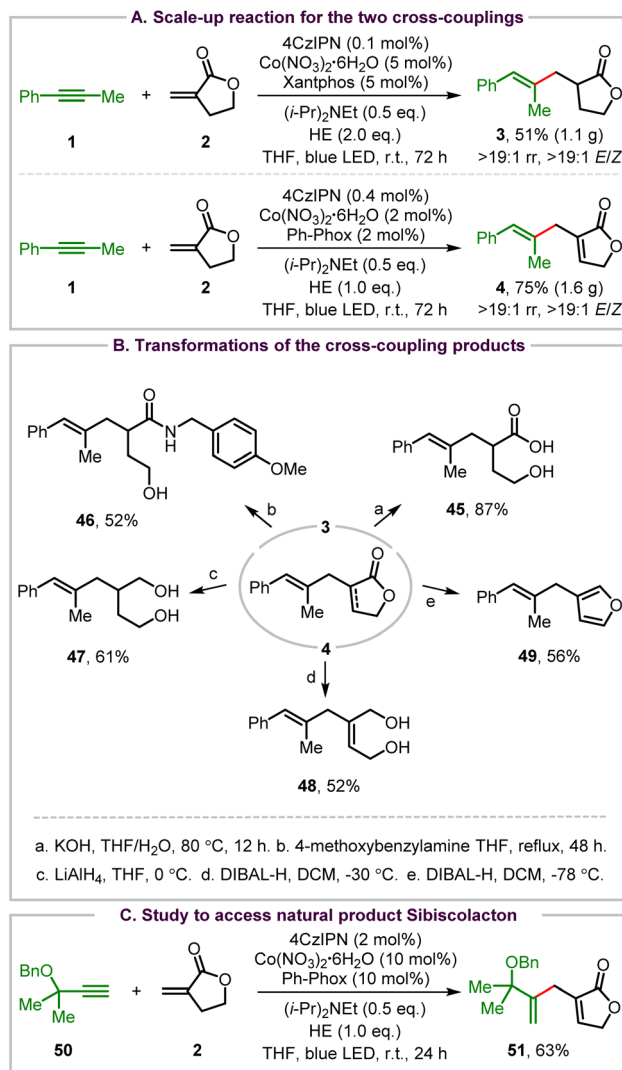
dienes with excellent regio- and stereoselectivities (**32** and **33**). A variety of other *gem*-disubstituted alkenes have also been investigated in this ene-type coupling, such as 1,1-dialkyl substituted ethene, α -methylstyrene, cyclic or linear acrylamide, and 2-methylene-5-pentanolide. Unfortunately, no desired product was observed with these substrates.

We then examined the scope of organophotoredox Co-catalyzed reductive coupling of alkynes and *gem*-disubstituted alkenes (Fig. 2). Generally, stereodefined trisubstituted alkenes were obtained with excellent regio- (>19:1 rr) and stereoselectivities (>19:1 *E/Z*). A variety of unsymmetrical aryl alkyl alkynes bearing diverse functional groups (*p*-OMe, *m*-COOMe, *p*-Cl, and *o*-Me) on different sites of the phenyl ring were found to be efficient coupling partners, affording the desired reductive coupling products in moderate yields (**34**–**37**). Similar to the ene-type coupling reaction, reductive coupling of a cyclopropane-containing alkyne and Tulipalin A produced the corresponding product **38** without ring-opening of cyclopropane. Moreover, a terminal alkene on the side alkyl chain of a phenyl alkyl alkyne was also tolerated in this reductive coupling reaction (**39**).

On the other hand, various *gem*-disubstituted alkenes were tested with 1-phenylpropyne under these conditions. Reductive coupling of alkynes with analogs of Tulipalin A or 2-methylene-5-pentanolide proved to be successful, affording the corresponding products in good yields (**40** and **41**). Methacrolein and linear α -alkyl substituted acrylonitrile were also compatible in this reaction (**42** and **43**). Furthermore, reductive coupling of 1-phenylpropyne and a simple vinyl ketone also occurred smoothly, leading to the desired product **44** in a moderate yield. Unfortunately, no reductive coupling occurred with 1,1-dialkyl substituted ethene, α -methylstyrene, or cyclic or linear acrylamide either.

A variety of synthetic transformations have been carried out to demonstrate the synthetic uses of the two organophotoredox Co-catalyzed cross-coupling reactions (Scheme 2). First, scale-up reactions of both cross-couplings were performed for the synthesis of **3** and **4** (Scheme 2A). The scale-up reductive coupling reaction produced the stereodefined trisubstituted alkene **3** in 51% yield with >19:1 regioselectivity and >19:1 *E/Z* stereoselectivity under the standard conditions. The scale-up ene-type coupling reaction also occurred smoothly, affording the desired product **4** in 75% yield without any loss of regio- and enantioselectivity control using 2 mol% Co(NO₃)₂·6H₂O/Ph-Phox as the catalyst with a slight increase of the catalyst loading of 4CzIPN (0.4 mol%).

Then, selective transformations of the reductive coupling and ene-type coupling products were investigated. Hydrolysis of the reductive coupling product **3** provided γ -hydroxy carboxylic acid **45** in an excellent yield (Scheme 2Ba). And aminolysis of **3** with 4-methoxybenzylamine afforded γ -hydroxy amide **46** in a moderate yield with incomplete conversion of **3** (Scheme 2Bb). Next, reduction of the 2-furanone group of the ene-type coupling product **4** with LiAlH₄ afforded alkene-containing 1,4-diol **47** in 61% yield (Scheme 2Bc). However, reduction of 2-furanone of **4** with DIBAL-H at –30 °C generated



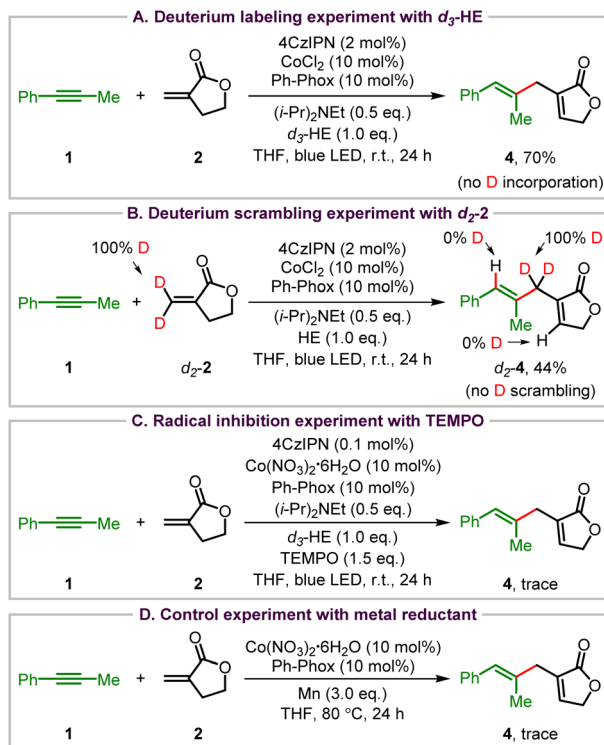
Scheme 2 Synthetic applications.

allylic diol **48** in 52% yield (Scheme 2Bd). Interestingly, a reductive isomerization of **4** took place, leading to furan-containing trisubstituted alkene **49** in 56% yield when the reaction was performed with DIBAL-H at –78 °C (Scheme 2Be).

Although 2-methyl-3-butyn-2-ol failed to produce the ene-type coupling product, its benzyl-protected derivative **50** was further tested for coupling with Tulipalin A to access the natural product sibiscolacton (Scheme 1A).²³ Interestingly but unfortunately, selective ene-type coupling at the internal sp carbon of this terminal alkyne occurred smoothly, leading to product **51** in 63% yield (Scheme 2C). This result also indicates that the regioselectivity control of an alkyne is determined by both the electronic and steric effect of the substituents.

To explore the reaction mechanism of this visible light organophotoredox Co-catalyzed cross-coupling reaction, a range of control experiments were conducted (Scheme 3). First, deuterium labeling experiments were carried out using d₃-HE with CoCl₂ as the catalyst to exclude the influence of



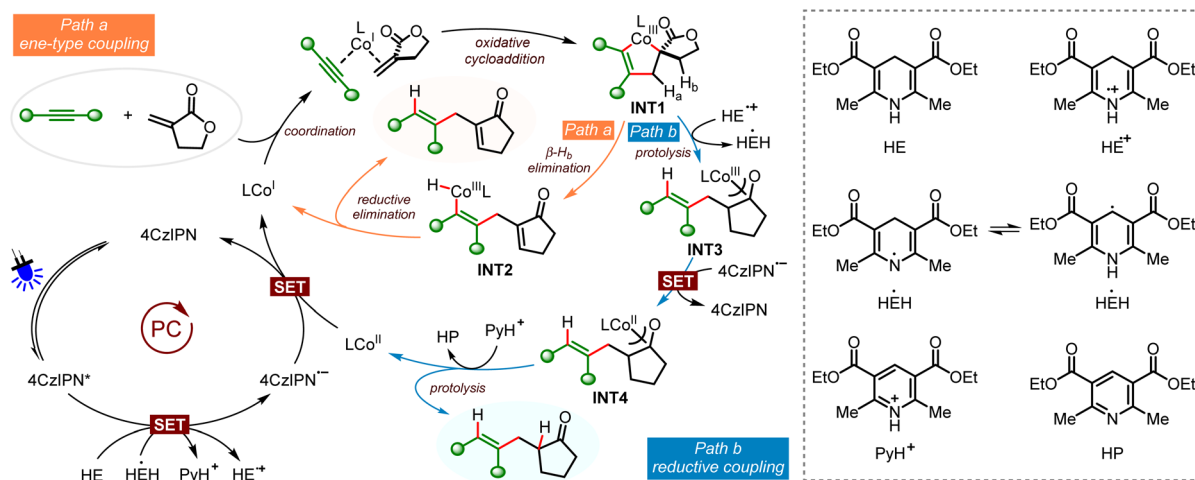


Scheme 3 Control experiments and mechanistic studies.

water in $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ under the standard conditions. The 1,4-diene **4** was obtained without any deuterium atom incorporation in the presence of d_3 -HE, indicating that HE does not provide the hydrogen atom in the ene-type coupling reaction (Scheme 3A). When d_2 -Tulipalin A (d_2 -2) was used as the coupling partner, there was no deuterium atom scrambling, with deuterium totally maintained at the methylene carbon of the Tulipalin A motif (Scheme 3B). These results demonstrate that the transfer of the allylic C–H of Tulipalin A to the alkyne triple bond might take place in this reaction. Then a radical

inhibition experiment was also carried out with 2,2,6,6-tetra-methylpiperidinyloxy (TEMPO) as the radical trapping reagent. Although the radical trapping product was not observed, the ene-type reaction was indeed suppressed, revealing that some free radical intermediates might exist in this reaction (Scheme 3C). Finally, Co-catalyzed cross-coupling of **1** and **2** was carried out using excess amounts of manganese powder as the reductant. A trace amount of **4** was observed, which indicates the high efficiency of the photoredox cobalt dual catalytic system (Scheme 3D).

Based on the control experiments and previous reports, we have proposed the possible catalytic cycles of the two coupling reactions (Scheme 4). With coupling of Tulipalin A as the example, upon irradiation with blue LED light, single electron oxidation of HE [$E_{1/2}^{\text{ox}}(\text{HE}/\text{HE}^{+\bullet}) = +0.51 \text{ V vs. Fc}^+/\text{Fc}$ in MeCN]²⁴ with photoexcited 4CzIPN^* produces $\text{HE}^{+\bullet}$ and $4\text{CzIPN}^{\bullet-}$ [$E_{1/2}^{\text{red}}(4\text{CzIPN}^*/4\text{CzIPN}^{\bullet-}) = +1.43 \text{ V vs. SCE}$ in MeCN].²² Next, reduction of the ligand coordinated $\text{Co}(\text{II})$ complex [$E_{1/2}^{\text{red}}(\text{Co}^{\text{II}}/\text{Co}^{\text{I}}) = -0.75 \text{ V vs. SCE}$ in MeCN]^{21c} with $4\text{CzIPN}^{\bullet-}$ [$E_{1/2}^{\text{red}}(4\text{CzIPN}/4\text{CzIPN}^{\bullet-}) = -1.24 \text{ V vs. SCE}$ in MeCN]²⁵ affords the low valent $\text{Co}(\text{I})$ species and regenerates 4CzIPN . Then coordination of the alkyne and Tulipalin A to the $\text{Co}(\text{I})$ species followed by oxidative cyclization gives the crowded spirocyclic cobaltacyclopentene **INT 1**, which is the common intermediate of the two cross-couplings. The selective control of the ene-type coupling or reductive coupling is achieved by using different ligands. Using hemilabile Ph-Phox as the ligand, the alkenyl $\text{Co}^{\text{III}}\text{-H}$ species **INT 2** is formed by exocyclic $\beta\text{-H}_b$ elimination (Path a). The following reductive elimination affords the 1,4-diene product and regenerates the Co^{I} catalyst. The 1,3-diene product from endocyclic β -hydride elimination is not observed, probably due to cobalt and $\beta\text{-H}_a$ is not in a *syn* coplanar arrangement. It is supposed that $\beta\text{-H}_b$ elimination is much faster than $\beta\text{-H}_a$ elimination in the spirocyclic cobaltacyclopentene **INT 1**. On the other hand, when Xantphos is used as the ligand, protolysis of **INT 1** with $\text{HE}^{+\bullet}$ takes place, generating HEH^{21c} and the α -carbonyl alkyl Co^{III}



Scheme 4 The proposed reaction pathway.



species **INT 3**, which can be stabilized by the isomerized cobalt enolate (Path b). Next, the strong electron donor HEH^+ ($E^{\text{ox}} = -1.13 \text{ V vs. SCE}$) can also donate a radical to 4CzIPN^* , leading to $4\text{CzIPN}^{\cdot-}$ and the pyridinium ion PyH^+ .²⁶ Furthermore, single electron reduction of Co^{III} species **INT 3** with $4\text{CzIPN}^{\cdot-}$ affords Co^{II} species **INT 4** [$E_{1/2}^{\text{red}}(\text{Co}^{\text{III}}/\text{Co}^{\text{II}}) = -0.51 \text{ V vs. Fe}^+/\text{Fe}$] and 4CzIPN .²⁷ Finally, protonation of the alkyl $\text{Co}(\text{II})$ species **INT 4** with PyH^+ produces a stereodefined alkene as the reductive coupling product and HP as the by-product. It is surprising and interesting that the β -hydride elimination occurs efficiently under this photoredox reductive conditions in the presence of a suitable ligand.

Conclusions

In summary, we reported here the first general method of ligand-controlled ene-type or reductive coupling of alkynes and *gem*-disubstituted alkenes *via* visible light organophotoredox cobalt dual catalysis. Using the natural product Tulipalin A and other *gem*-disubstituted alkenes to couple with internal or terminal alkynes, functionalized 1,4-dienes have been obtained *via* ene-type coupling in moderate to good yields with excellent chemo-, regio-, and stereoselectivities using a PHOX ligand. Similarly, stereodefined trisubstituted alkenes were synthesized *via* reductive coupling with Xantphos as the ligand under otherwise similar conditions. Notably, as low as a thousandth of a commercially available organic photocatalyst has been used to efficiently catalyze the two coupling reactions. In general, this study shows that coupling of alkynes with multi-substituted alkenes is much difficult compared to well-studied monosubstituted alkenes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (22271296 and 21772208), the Major Science and Technology Project of Gansu Province (22ZD6GA003), the Natural Science Foundation of Jiangsu Province (BK20201193), and the Major Program of the Lanzhou Institute of Chemical Physics (No. ZYFZFX-1).

References

- (a) B. H. B. Kwok, B. Koh, M. I. Ndubuisi, M. Elofsson and C. M. Crews, The Anti-Inflammatory Natural Product Parthenolide from the Medicinal Herb Feverfew Directly Binds to and Inhibits I κ b Kinase, *Chem. Biol.*, 2001, **8**, 759–766; (b) R. R. A. Kitson, A. Millemaggi and R. J. K. Taylor, The Renaissance of α -Methylene- γ -butyrolactones: New Synthetic Approaches, *Angew. Chem., Int. Ed.*, 2009, **48**, 9426–9451; (c) R. Lagoutte, C. Serba, D. Abegg, D. G. Hoch, A. Adibekian and N. Winssinger, Divergent Synthesis and Identification of the Cellular Targets of Deoxyelephantopins, *Nat. Commun.*, 2016, **7**, 12470–12480; (d) J. Hur, J. Jang and J. Sim, Review of the Pharmacological Activities and Recent Synthetic Advances of γ -Butyrolactones, *Int. J. Mol. Sci.*, 2021, **22**, 2769–2817.
- (a) A. Hashem and E. Kleinpeter, The Chemistry of 2(5H)-furanones, *Adv. Heterocycl. Chem.*, 2001, **81**, 107–165; (b) T. G. Elford and D. G. Hall, Advances in 2-(Alkoxyacetyl)allylboration of Carbonyl Compounds and Other Direct Methods for the Preparation of α -Exo-Alkylidene γ -Lactones, *Synthesis*, 2010, 893–907; (c) B. Mao, M. Fananas-Mastral and B. L. Feringa, Catalytic Asymmetric Synthesis of Butenolides and Butyrolactones, *Chem. Rev.*, 2017, **117**, 10502–10566; (d) K. J. R. Murauski, A. A. Jaworski and K. A. Scheidt, A Continuing Challenge: N-Heterocyclic Carbene-Catalyzed Syntheses of γ -Butyrolactones, *Chem. Soc. Rev.*, 2018, **47**, 1773–1782; (e) W. Liu and N. Winssinger, Synthesis of α -Exo-Methylene- γ -Butyrolactones: Recent Developments and Applications in Natural Product Synthesis, *Synthesis*, 2021, **53**, 3977–3990.
- (a) J.-P. Lepoittevin, V. Berl and E. Giménez-Arnau, α -Methylene- γ -Butyrolactones: Versatile Skin Bioactive Natural Products, *Chem. Rec.*, 2009, **9**, 258–270; (b) J. McCluskey, M. Bourgeois and R. Harbison, Tulipalin A Induced Phytotoxicity, *Int. J. Crit. Illn. Inj. Sci.*, 2014, **4**, 181–183.
- (a) S. Agarwal, Q. Jin and S. Maji, in *Biobased Monomers, Polymers, and Materials*, American Chemical Society, 2012, vol. 1105, ch. 13, pp. 197–212; (b) M. Mousa, H. Bergenudd, A. L. Kron and E. Malmström, Biobased Lactones-Exploring Their Free-Radical Polymerization and Polymer Properties, *Macromolecules*, 2021, **54**, 6127–6134; (c) K. Onita, M. Onishi, T. Omura, T. Wakiya, T. Suzuki and H. Minami, Preparation of Monodisperse Bio-Based Polymer Particles Via Dispersion Polymerization, *Langmuir*, 2022, **38**, 7341–7345.
- (a) A. Arcadi, M. Chiarini, F. Marinelli, Z. Berente and L. Kollár, Palladium-Catalyzed Arylation of α -Methylene- γ -Butyrolactones: 3-Benzylfuran-2(5H)-ones Vs (Z)-Benzylidene- γ -Butyrolactones and Their Reduction to 3-Benzyl- γ -Butyrolactones, *Org. Lett.*, 2000, **2**, 69–72; (b) K. Tsuchikama, Y. Kuwata and T. Shibata, Highly Enantioselective Construction of a Chiral Spirocyclic Structure by the [2+2+2] Cycloaddition of Dienes and Exo-Methylene Cyclic Compounds, *J. Am. Chem. Soc.*, 2006, **128**, 13686–13687; (c) R. J. Mayer, P. W. A. Allihn, N. Hampel, P. Mayer, S. A. Sieber and A. R. Ofial, Electrophilic Reactivities of Cyclic Enones and α,β -Unsaturated Lactones, *Chem. Sci.*, 2021, **12**, 4850–4865.
- (a) M. Jeganmohan and C.-H. Cheng, Cobalt- and Nickel-Catalyzed Regio- and Stereoselective Reductive Coupling of Alkynes, Allenes, and Alkenes with Alkenes, *Chem. – Eur. J.*,



- 2008, **14**, 10876–10886; (b) G. Hilt, Hydrovinylation Reactions–Atom-Economic Transformations with Steadily Increasing Synthetic Potential, *Eur. J. Org. Chem.*, 2012, 4441–4451; (c) P. Gandeepan and C.-H. Cheng, Cobalt Catalysis Involving π Components in Organic Synthesis, *Acc. Chem. Res.*, 2015, **48**, 1194–1206; (d) M. Hirano, Recent Advances in the Catalytic Linear Cross-Dimerizations, *ACS Catal.*, 2019, **9**, 1408–1430.
- 7 (a) B. M. Trost, On Inventing Reactions for Atom Economy, *Acc. Chem. Res.*, 2002, **35**, 695–705; (b) B. M. Trost and A. Indolese, Ruthenium-Catalyzed Addition of Alkenes to Acetylenes, *J. Am. Chem. Soc.*, 1993, **115**, 4361; (c) H. Butenschön, Construction of Carbon Frameworks with the Help of Ruthenium Complexes: 1,5-Cyclooctadiene as a Reagent in Transition Metal Catalyzed Reactions, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 636–638; (d) B. M. Trost, A. B. Pinkerton, F. D. Toste and M. Sperrle, Synthesis of 1,1-Disubstituted Alkenes Via a Ru-Catalyzed Addition, *J. Am. Chem. Soc.*, 2001, **123**, 12504–12509; (e) B. M. Trost and J.-P. Surivet, An Atom-Economic Three-Carbon Chain Extension to Give Enamides, *Angew. Chem., Int. Ed.*, 2001, **40**, 1468–1471; (f) A. C. Gutierrez and T. F. Jamison, Continuous Photochemical Generation of Catalytically Active $[\text{CpRu}]^+$ Complexes from $\text{CpRu}(\eta^6\text{-C}_6\text{H}_6)\text{PF}_6$, *Org. Lett.*, 2011, **13**, 6414–6417; (g) B. M. Trost, D. C. Koester and A. N. Herron, Stereocontrolled Synthesis of Vinyl Boronates and Vinyl Silanes Via Atom-Economical Ruthenium-Catalyzed Alkene–Alkyne Coupling, *Angew. Chem., Int. Ed.*, 2015, **54**, 15863–15866.
- 8 (a) G. Hilt and J. Treutwein, Cobalt-Catalyzed Alder–Ene Reaction, *Angew. Chem., Int. Ed.*, 2007, **46**, 8500–8502; (b) G. Hilt, F. Erver and K. Harms, Regioselective Cobalt-Catalyzed Alder-Ene Reaction toward Silicon- and Boron-Functionalized Building Blocks, *Org. Lett.*, 2011, **13**, 304–307; (c) F. Erver and G. Hilt, Cobalt- Versus Ruthenium-Catalyzed Alder–Ene Reaction for the Synthesis of Credneramide A and B, *J. Org. Chem.*, 2012, **77**, 5215–5219.
- 9 S. Mannathan and C.-H. Cheng, Cobalt-catalyzed Regio- and Stereoselective Intermolecular Enyne Coupling: An Efficient Route to 1,3-Diene Derivatives, *Chem. Commun.*, 2010, **46**, 1923–1925.
- 10 H. Horie, I. Koyama, T. Kurahashi and S. Matsubara, Nickel-Catalyzed Intermolecular Codimerization of Acrylates and Alkynes, *Chem. Commun.*, 2011, **47**, 2658–2660.
- 11 Y. Shibata, M. Hirano and K. Tanaka, Rhodium-catalyzed Regio- and Stereoselective Codimerization of Alkenes and Electron-Deficient Internal Alkynes Leading to 1,3-Dienes, *Org. Lett.*, 2008, **10**, 2829–2831.
- 12 (a) T. Nishimura, Y. Washitake and S. Uemura, Ruthenium/Halide Catalytic System for C-C Bond Forming Reaction between Alkynes and Unsaturated Carbonyl Compounds, *Adv. Synth. Catal.*, 2007, **349**, 2563–2571; (b) N. M. Neisius and B. Plietker, The Ruthenium-Catalyzed Hydrovinylation of Internal Alkynes by Acrylates: An Atom Economic Approach to Highly Substituted 1,3-Dienes, *Angew. Chem., Int. Ed.*, 2009, **48**, 5752; (c) J. Zhang, A. Ugrinov, Y. Zhang and P. Zhao, Exploring Bis(Cyclometalated) Ruthenium(II) Complexes as Active Catalyst Precursors: Room-Temperature Alkene–Alkyne Coupling for 1,3-Diene Synthesis, *Angew. Chem., Int. Ed.*, 2014, **53**, 8437–8440.
- 13 A. T. Lindhardt, M. L. H. Mantel and T. Skrydstrup, Palladium-Catalyzed Intermolecular Ene–Yne Coupling: Development of an Atom-Efficient Mizoroki–Heck-Type Reaction, *Angew. Chem., Int. Ed.*, 2008, **47**, 2668–2672.
- 14 M. M. Parsutkar, V. V. Pagar and T. V. RajanBabu, Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives, *J. Am. Chem. Soc.*, 2019, **141**, 15367–15377.
- 15 (a) A. Herath, B. B. Thompson and J. Montgomery, Catalytic Intermolecular Reductive Coupling of Enones and Alkynes, *J. Am. Chem. Soc.*, 2007, **129**, 8712–8713; (b) S. Mannathan and C.-H. Cheng, Synthesis of Trans-Disubstituted Alkenes by Cobalt-Catalyzed Reductive Coupling of Terminal Alkynes with Activated Alkenes, *Chem. – Eur. J.*, 2012, **18**, 11771–11777; (c) M. J. González and B. Breit, Visible-Light-Driven Intermolecular Reductive Ene–Yne Coupling by Iridium/Cobalt Dual Catalysis for $\text{C}(\text{Sp}^3)\text{–C}(\text{Sp}^2)$ Bond Formation, *Chem. – Eur. J.*, 2019, **25**, 15746–15750; (d) P. Rai, K. Maji and B. Maji, Photoredox/Cobalt Dual Catalysis for Visible-light-mediated Alkene–Alkyne Coupling, *Org. Lett.*, 2019, **21**, 3755–3759; (e) S. Gao, C. Liu, J. Yang and J. Zhang, Cobalt-Catalyzed Electrochemical Reductive Coupling of Alkynes and Alkenes, *Chin. J. Org. Chem.*, 2023, **43**, 1559–1565.
- 16 (a) B. M. Trost and J. J. Cregg, Ruthenium-Catalyzed Alkene–Alkyne Coupling of Disubstituted Olefins: Application to the Stereoselective Synthesis of Trisubstituted Encarbamates, *J. Am. Chem. Soc.*, 2015, **137**, 620–623; (b) S. M. Rummelt, G.-J. Cheng, P. Gupta, W. Thiel and A. Fürstner, Hydroxy-Directed Ruthenium-catalyzed Alkene/Alkyne Coupling: Increased Scope, Stereochemical Implications, and Mechanistic Rationale, *Angew. Chem., Int. Ed.*, 2017, **56**, 3599–3604; (c) S. Kiyota, S. In, N. Komine and M. Hirano, Regioselectivity Control by Added MeCN in Ru(0)-Catalyzed Cross-Dimerization of Internal Alkynes with Methyl Methacrylate, *Chem. Lett.*, 2017, **46**, 1040–1043.
- 17 (a) D. Zhang, M. Li, J. Li, A. Lin and H. Yao, Rhodium-catalyzed Intermolecular Enantioselective Alder–Ene Type Reaction of Cyclopentenes with Silylacetylenes, *Nat. Commun.*, 2021, **12**, 6627–6634; (b) G. Hilt, A. Paul and J. Treutwein, Cobalt Catalysis at the Crossroads: Cobalt-Catalyzed Alder–Ene Reaction Versus [2+2] Cycloaddition, *Org. Lett.*, 2010, **12**, 1536–1539.
- 18 (a) C.-H. Wei, S. Mannathan and C.-H. Cheng, Enantioselective Synthesis of β -Substituted Cyclic Ketones Via Cobalt-Catalyzed Asymmetric Reductive Coupling of Alkynes with Alkenes, *J. Am. Chem. Soc.*, 2011, **133**, 6942–6944; (b) K. Cui, Y.-L. Li, G. Li and J.-B. Xia, Regio- and Stereoselective Reductive Coupling of Alkynes and Crotononitrile, *J. Am. Chem. Soc.*, 2022, **144**, 23001–23009.



- 19 (a) J. Xuan and W.-J. Xiao, Visible-Light Photoredox Catalysis, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828–6838; (b) N. Corrigan, S. Shanmugam, J. Xu and C. Boyer, Photocatalysis in Organic and Polymer Synthesis, *Chem. Soc. Rev.*, 2016, **45**, 6165–6212; (c) M. D. Kärkäs, J. A. Porco Jr. and C. R. J. Stephenson, Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis, *Chem. Rev.*, 2016, **116**, 9683–9747; (d) B. Chen, L.-Z. Wu and C.-H. Tung, Photocatalytic Activation of Less Reactive Bonds and Their Functionalization Via Hydrogen-Evolution Cross-Couplings, *Acc. Chem. Res.*, 2018, **51**, 2512–2523; (e) L. Chang, Q. An, L. Duan, K. Feng and Z. Zuo, Alkoxy Radicals See the Light: New Paradigms of Photochemical Synthesis, *Chem. Rev.*, 2022, **122**, 2429–2486; (f) N. Holmberg-Douglas and D. A. Nicewicz, Photoredox-Catalyzed C–H Functionalization Reactions, *Chem. Rev.*, 2022, **122**, 1925–2016; (g) S. P. Pitre and L. E. Overman, Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis, *Chem. Rev.*, 2022, **122**, 1717–1751.
- 20 (a) K. L. Skubi, T. R. Blum and T. P. Yoon, Dual Catalysis Strategies in Photochemical Synthesis, *Chem. Rev.*, 2016, **116**, 10035–10074; (b) J. A. Milligan, J. P. Phelan, S. O. Badir and G. A. Molander, Alkyl Carbon–Carbon Bond Formation by Nickel/Photoredox Cross-Coupling, *Angew. Chem., Int. Ed.*, 2019, **58**, 6152–6163; (c) H.-H. Zhang, H. Chen, C. Zhu and S. Yu, A Review of Enantioselective Dual Transition Metal/Photoredox Catalysis, *Sci. China: Chem.*, 2020, **63**, 637–647; (d) F.-D. Lu, J. Chen, X. Jiang, J.-R. Chen, L.-Q. Lu and W.-J. Xiao, Recent Advances in Transition-Metal-Catalysed Asymmetric Coupling Reactions with Light Intervention, *Chem. Soc. Rev.*, 2021, **50**, 12808–12827; (e) K. Kwon, R. T. Simons, M. Nandakumar and J. L. Roizen, Strategies to Generate Nitrogen-Centered Radicals That May Rely on Photoredox Catalysis: Development in Reaction Methodology and Applications in Organic Synthesis, *Chem. Rev.*, 2022, **122**, 2353–2428.
- 21 (a) K.-H. He, F.-F. Tan, C.-Z. Zhou, G.-J. Zhou, X.-L. Yang and Y. Li, Acceptorless Dehydrogenation of N-Heterocycles by Merging Visible-Light Photoredox Catalysis and Cobalt Catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 3080–3084; (b) S. M. Thullen and T. Rovis, A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System, *J. Am. Chem. Soc.*, 2017, **139**, 15504–15508; (c) J. Hou, A. Ee, W. Feng, J.-H. Xu, Y. Zhao and J. Wu, Visible-Light-Driven Alkyne Hydro-/Carboxylation Using CO₂ Via Iridium/Cobalt Dual Catalysis for Divergent Heterocycle Synthesis, *J. Am. Chem. Soc.*, 2018, **140**, 5257–5263; (d) Q.-Y. Meng, T. E. Schirmer, K. Katou and B. König, Controllable Isomerization of Alkenes by Dual Visible-Light-Cobalt Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 5723–5728; (e) M. Kojima and S. Matsunaga, The Merger of Photoredox and Cobalt Catalysis, *Trends Chem.*, 2020, **2**, 410–426; (f) À. Cristófol, B. Limburg and A. W. Kleij, Expedient Dual Co/Organophotoredox Catalyzed Stereoselective Synthesis of All-Carbon Quaternary Centers, *Angew. Chem., Int. Ed.*, 2021, **60**, 15266–15270; (g) M.-J. Zhou, L. Zhang, G. Liu, C. Xu and Z. Huang, Site-Selective Acceptorless Dehydrogenation of Aliphatics Enabled by Organophotoredox/Cobalt Dual Catalysis, *J. Am. Chem. Soc.*, 2021, **143**, 16470–16485; (h) W.-L. Yu, Z.-G. Ren, K.-X. Ma, H.-Q. Yang, J.-J. Yang, H. Zheng, W. Wu and P.-F. Xu, Cobalt-Catalyzed Chemoselective Dehydrogenation through Radical Translocation under Visible Light, *Chem. Sci.*, 2022, **13**, 7947–7954; (i) H. Jiang, X.-K. He, X. Jiang, W. Zhao, L.-Q. Lu, Y. Cheng and W.-J. Xiao, Photoinduced Cobalt-Catalyzed Desymmetrization of Dialdehydes to Access Axial Chirality, *J. Am. Chem. Soc.*, 2023, **145**, 6944–6952; (j) A. Suzuki, Y. Kamei, M. Yamashita, Y. Seino, Y. Yamaguchi, T. Yoshino, M. Kojima and S. Matsunaga, Photocatalytic Deuterium Atom Transfer Deuteration of Electron-Deficient Alkenes with High Functional Group Tolerance, *Angew. Chem., Int. Ed.*, 2023, **62**, e202214433; (k) H. Yan, Q. Liao, Y. Chen, G. G. Gurzadyan, B. Lu, C. Wu and L. Shi, Photocatalytic Metal Hydride Hydrogen Atom Transfer Mediated Allene Functionalization by Cobalt and Titanium Dual Catalysis, *Angew. Chem., Int. Ed.*, 2023, **62**, e202302483; (l) Z. Jia and S. Luo, Visible Light Promoted Direct Deuteration of Alkenes Via Co(III)-H Mediated H/D Exchange, *CCS Chem.*, 2023, **5**, 1069–1076; (m) Y.-L. Li, S.-Q. Zhang, J. Chen and J.-B. Xia, Highly Regio- and Enantioselective Reductive Coupling of Alkynes and Aldehydes Via Photoredox Cobalt Dual Catalysis, *J. Am. Chem. Soc.*, 2021, **143**, 7306–7313.
- 22 (a) H. Uoyama, K. Goushi, K. Shizu, H. Nomura and C. Adachi, Highly Efficient Organic Light-Emitting Diodes from Delayed Fluorescence, *Nature*, 2012, **492**, 234–238; (b) J. Luo and J. Zhang, Donor–Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic C(Sp³)-C(Sp²) Cross-Coupling, *ACS Catal.*, 2016, **6**, 873–877.
- 23 (a) B. Li, J.-B. Lee, K. Hayashi, Y. Ito, W.-J. Sun, X. Wang, Y. Kano and T. Hayashi, Two New Monoterpenes from *Sibiraea angustata*, *J. Nat. Med.*, 2010, **64**, 89–92; (b) Y. Deng, J.-Q. Zhao, L.-J. Mei and Y.-D. Tao, Two New Monoterpenes from *Sibiraea laevigata*, *J. Asian Nat. Prod. Res.*, 2017, **19**, 877–883.
- 24 (a) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong and R. R. Knowles, Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization, *J. Am. Chem. Soc.*, 2013, **135**, 17735–17738; (b) R. A. Aycock, D. B. Vogt and N. T. Jui, A Practical and Scalable System for Heteroaryl Amino Acid Synthesis, *Chem. Sci.*, 2017, **8**, 7998–8003; (c) P.-Z. Wang, J.-R. Chen and W.-J. Xiao, Hantzsch Esters: An Emerging Versatile Class of Reagents in Photoredox Catalyzed Organic Synthesis, *Org. Biomol. Chem.*, 2019, **17**, 6936–6951; (d) J. A. Leitch, T. Rossolini, T. Rogova and D. J. Dixon, α -Tertiary Dialkyl Ether Synthesis Via Reductive



- Photocatalytic α -Functionalization of Alkyl Enol Ethers, *ACS Catal.*, 2020, **10**, 11430–11437.
- 25 E. Speckmeier, T. G. Fischer and K. Zeitler, A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor–Acceptor Cyanoarenes, *J. Am. Chem. Soc.*, 2018, **140**, 15353–15365.
- 26 G. Park, S. Y. Yi, J. Jung, E. J. Cho and Y. You, Mechanism and Applications of the Photoredox Catalytic Coupling of Benzyl Bromides, *Chem. – Eur. J.*, 2016, **22**, 17790–17799.
- 27 N. Elgrishi, D. A. Kurtz and J. L. Dempsey, Reaction Parameters Influencing Cobalt Hydride Formation Kinetics: Implications for Benchmarking H₂-Evolution Catalysts, *J. Am. Chem. Soc.*, 2017, **139**, 239–244.

