ACS Catalysis

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Highly Enantioselective [2+2+2] Cycloaddition of Enediynes Enabled by Cobalt/Organophotoredox Cooperative Catalysis

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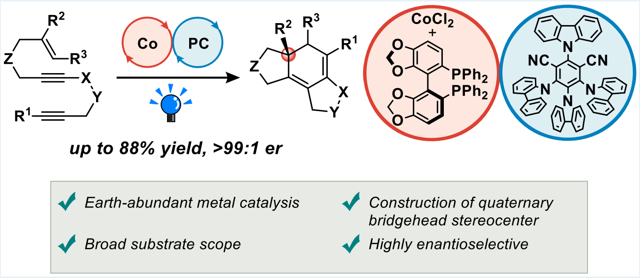
Cite This: *ACS Catal.* 2021, 11, 9479−9484

ABSTRACT: Herein, we report dual cobalt and photoredox catalysis enabled [2+2+2] cycloaddition of enediynes to produce tricyclic cyclohexadienes bearing a quaternary bridgehead carbon. A variety of enediynes were used, and the corresponding cyclohexadienes were obtained in good to high yields. The use of a chiral ligand, (*S*)-Segphos, enabled a highly enantioselective reaction allowing access to highly enantio-enriched cyclohexadienes.



KEYWORDS: *cobalt catalysis, asymmetric catalysis, metallaphotoredox, cycloaddition, enediynes*

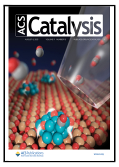
Over the past several decades, group 9 metal (Co, Rh, and Ir) catalysts have contributed to the development of [2+2+2] cycloaddition of unsaturated compounds, such as alkynes, alkenes, and nitriles, which is one of the most efficient methods for accessing polycyclic compounds in a highly atom-economical fashion.[1] In particular, the [2+2+2] cycloaddition of enediynes can provide tricyclic cyclohexadienes, which can be further transformed via functionalization of the diene moiety, allowing access to complex sp^3-rich molecules.[2] Surprisingly, although nonprecious metal catalysts have gained attention because of their economic and ecological benefits, examples of the cobalt-catalyzed [2+2+2] cycloaddition of enediynes are still very limited.[3] Cyclopentadienyl cobalt(I) complexes can facilitate the [2+2+2] cycloaddition of enediynes, although in most cases, a stoichiometric amount of cobalt is required because of the tendency of the cobalt complex to form a stable η^4-(1,3-cyclohexadiene) complex with the cyclohexadiene product.[4] Alternatively, low-valent cobalt species generated in situ from an air-stable Co^{II} salt (CoX_2) with phosphine or NHC ligands, using reductants such as Zn and Mn, can also be used for the [2+2+2] cycloaddition of enediynes, although a stoichiometric amount of cobalt salt is still required (Scheme 1A).[5] In 2013, Amatore, Aubert, Petit, and co-workers reported the [2+2+2] cycloaddition of enediynes using a catalytic amount of $CoH(PMe_3)_4$;[6] however, such Co^I complexes are difficult to handle owing to their instability.

Recently, the merger of transition-metal catalysis and photocatalysis, known as metallaphotocatalysis, has emerged as a powerful tool that enables versatile chemical transformations.[7] Rovis and co-workers, in a pioneering study, reported the [2+2+2] cyclotrimerization of alkynes catalyzed by in situ generated low-valent Co species from $CoBr_2(PCy_3)_2$ with an amine reductant in the presence of an Ir photoredox catalyst under blue LED irradiation.[8] However, the cycloaddition reaction using the Co/photoredox cooperative catalyst system is limited to the cycloaddition of 1,6-diynes and alkynes, which can also be facilitated by conventional catalyst systems such as Co^{II}/Zn, Rh^I, and Ir^I.

Our group has studied the construction of tricyclic frameworks bearing quaternary bridgehead carbons that are found in many biologically active natural products, such as 11-*O*-debenzoyltashironin, perforanoid A, and jiadifenolide.[9] Recently, we reported a Ru-catalyzed [2+2+2] cycloaddition of ene-yne-yne enediynes to provide 5−6−5 tricyclic lactones;[2b] however, the enantioselective version of this reaction has not been reported to date. Herein, we demonstrate the [2+2+2] cycloaddition of enediynes mediated by Co/photoredox cooperative catalysis, wherein a broad variety of enediynes can be used (Scheme 1B). An enantioselective reaction was also achieved using a chiral bisphosphine ligand. To the best of our knowledge, this is the first example of a highly enantioselective cycloaddition using Co/photoredox cooperative catalysis.[10]

During our study on the transition-metal-catalyzed cycloaddition of enediynes, we found that known catalyst systems, such as Co^{II}/Zn, Rh^I, and Ir^I, were not effective for the cycloaddition of enediyne **1a**, while the Co/photoredox

Received: May 29, 2021
Revised: July 13, 2021
Published: July 15, 2021



https://doi.org/10.1021/acscatal.1c02410
ACS Catal. 2021, 11, 9479−9484

Scheme 1. Cobalt-Mediated [2+2+2] Cycloadditions of Enediynes

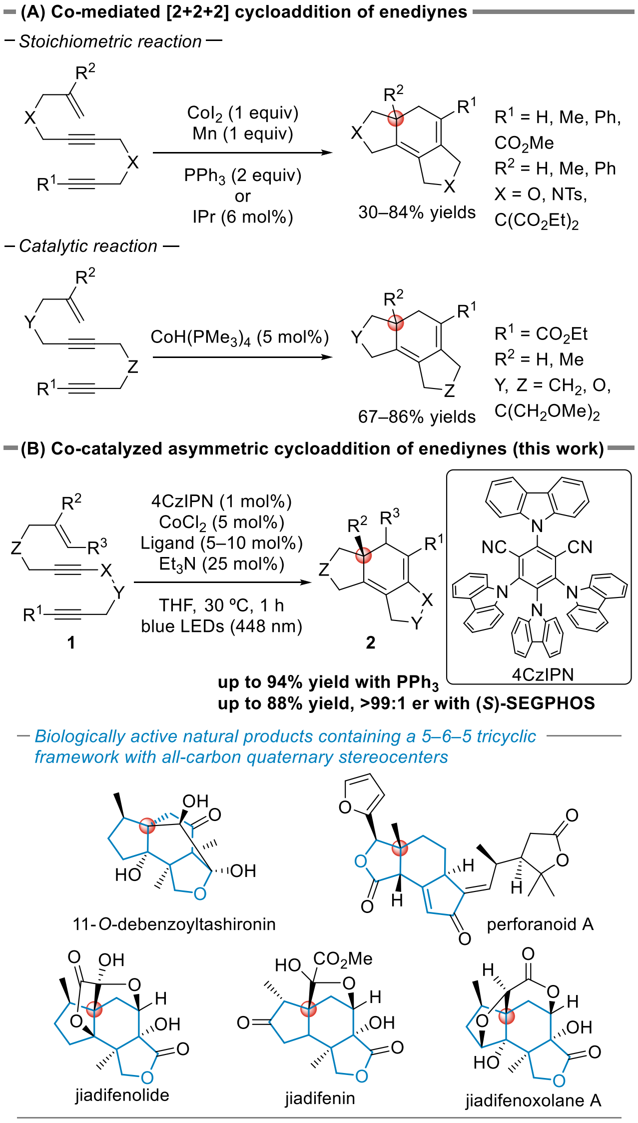
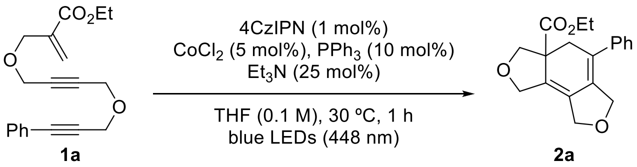


Table 1. Selected Optimization Study



entry	deviation from standard conditions	yield of **2a** [%][a]
1	none	94
2	$CoBr_2$	94
3	1 mol % $CoCl_2(PPh_3)_2$	91
4[b]	$[Ir(dF(CF_3)_2ppy)(dtbbpy)]PF_6$ instead of 4CzIPN	88
5	PCy_3 instead of PPh_3	73
6	$^{i}Pr_2NEt$ instead of Et_3N	90
7	MeCN as solvent	59
8	without $CoCl_2$, Et_3N, 4CzIPN, or light	0

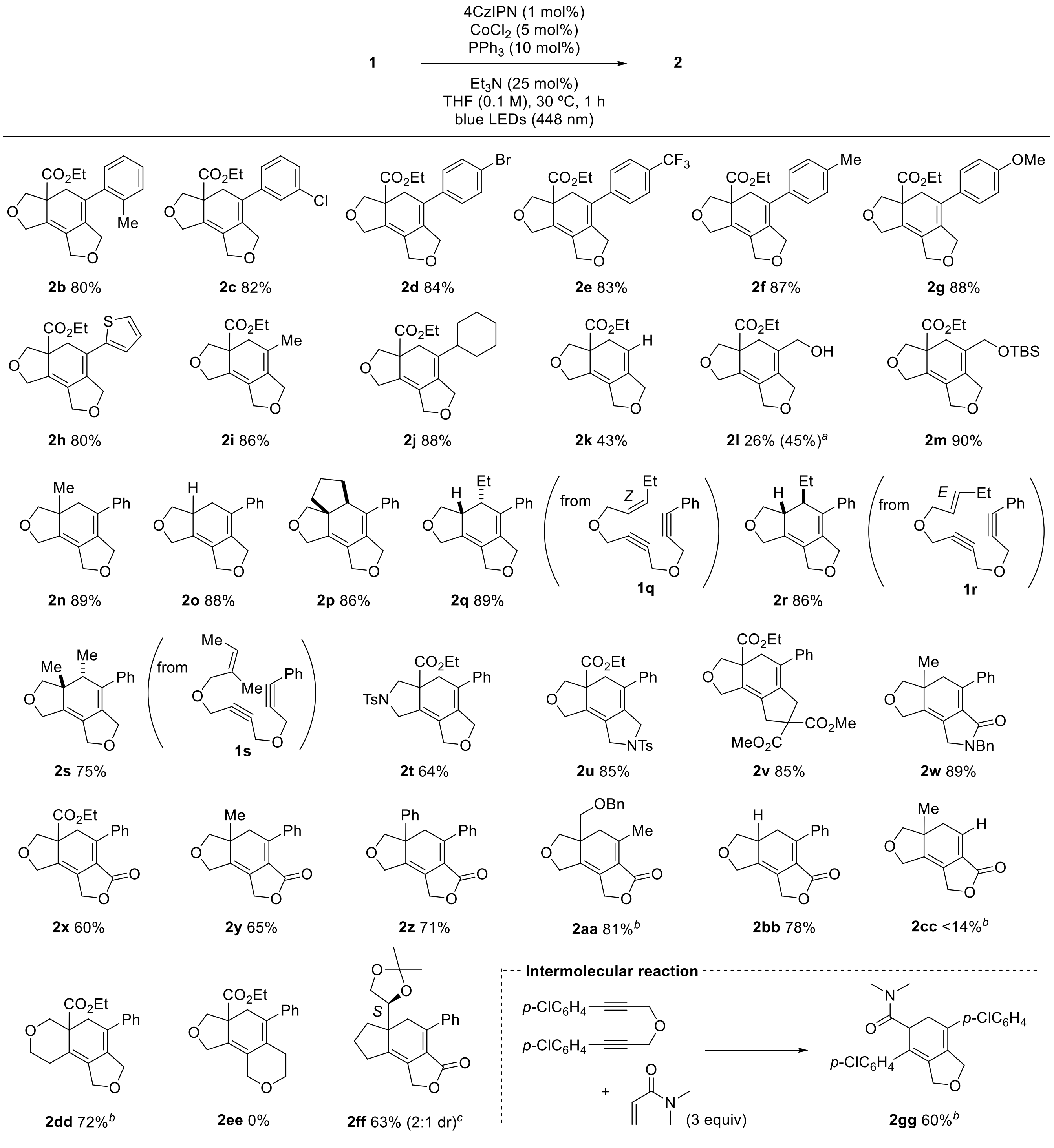
[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Using purple LEDs (385 nm) instead of blue LEDs.

cooperative catalysis gave the corresponding cyclohexadiene **2a** in good yield (Table S1). After extensively screening the reaction parameters, **2a** was obtained in 94% yield on using 1 mol % of 4CzIPN,[11] 5 mol % of $CoCl_2$, 10 mol % of PPh_3, and 25 mol % of Et_3N in THF, under blue light irradiation (448 nm) (Table 1, entry 1). The reaction using $CoBr_2$ as a precatalyst gave **2a** in 94% yield (entry 2). The amount of catalyst could be reduced to 1 mol % when $CoCl_2(PPh_3)_2$, prepared from $CoCl_2$ and PPh_3, was used, affording **2a** in 91% yield (entry 3). The reaction with $[Ir(dF(CF_3)_2ppy)(dtbbpy)]PF_6$ instead of 4CzIPN resulted in a slightly lower yield of **2a** (entry 4). Replacement of PPh_3 with several other phosphine ligands, including PCy_3, did not improve the yield of **2a** (entry 5; also see Table S4). When $^{i}Pr_2NEt$ was used as the reductant, the yield of **2a** was slightly reduced (entry 6). Switching the reaction solvent from THF to MeCN provided **2a** in a decreased yield (entry 7). The formation of **2a** was not detected in the absence of either $CoCl_2$, Et_3N, 4CzIPN, or light, demonstrating the vital role for all these components (entry 8).

Next, the [2+2+2] cycloaddition reaction using various enediynes **1** was examined under the optimized reaction conditions (Scheme 2). Substrates bearing aryl, heteroaryl, and alkyl groups at the alkyne terminus gave the corresponding products **2b**−**2j** in high yields, while the reaction of enediyne **1k**, bearing a terminal alkyne moiety, resulted in a moderate yield of the product **2k**. Enediyne **1l** bearing a nonprotected alcohol could be transformed into **2l** in moderate yield, although the isolated yield was lesser as the column chromatography had to be repeated twice to completely remove the impurities. As an alternative method to introduce a hydroxy group, the TBS-protected substrate **1m** was successfully converted into cycloadduct **2m**. The introduction of a methyl group (**1n**) at the alkene moiety instead of the ethoxycarbonyl group did not affect the reactivity, and **2n** was still obtained in high yield. The cycloaddition of enediyne **1o** (R^2 = H) proceeded smoothly, and **2o** was obtained in high yield without the formation of any β-hydride elimination products. Enediyne **1p**, bearing a cyclopentene moiety, was successfully converted into tetracyclic cyclohexadiene **2p**. Enediynes bearing a 1,2-disubstituted or 1,1,2-trisubstituted alkene moiety were successfully transformed to the corresponding cycloadducts (**2q**−**2s**) as single diastereomers based on the stereochemistry of the double bond. With respect to the tether moieties, tosylamide, malonate, amide, and ester groups could be incorporated, affording **2t**−**2x** in good to excellent yields. Methyl, phenyl, and benzyloxymethyl groups, as well as a hydrogen atom, were successfully introduced into the alkene moiety of ester-tethered enediynes, leading to tricyclic lactones **2y**−**2bb** in good yields. The reaction of enediyne **1cc** bearing an unsubstituted propiolate terminus resulted in the formation of **2cc** in low yield, which could be ascribed to the competing intermolecular oligomerization reaction due to the relatively high reactivity of the propiolate moiety. Regarding the ring size of the cycloadducts, while 6−6−5 tricyclic cyclohexadiene (**2dd**) was successfully prepared in good yield, 5−6−6 tricyclic cyclohexadiene (**2ee**) was not obtained. The use of optically active enediyne **1ff** afforded the corresponding cyclohexadiene **2ff** in 63% yield with 2:1 dr. Notably, the intermolecular cycloaddition afforded bicyclic cyclohexadiene **2gg** in 60% yield.

There are two possible pathways for the cycloaddition of enediynes, viz., via a metallacyclopentadiene intermediate or a

Scheme 2. Scope of the [2+2+2] Cycloaddition of Enediynes 1



[a] NMR yield. [b] A substrate (enediyne or diyne) was slowly added over 1 h and the mixture was stirred for additional 10 min. [c] The reaction was performed for 2 h.

metallacyclopentene intermediate. To elucidate the reaction mechanism, the reaction of **1i**, under standard conditions, was conducted in the presence of an excess amount of methyl propargyl ether (MPE) to trap the cobaltacycle intermediate. This reaction yielded phthalan **3** in 47% yield along with **2i** in 18% yield; however, formation of cyclohexadiene **4** was not observed (Figure 1A). Moreover, intermolecular cycloaddition of enyne **5** and MPE did not proceed (Figure 1B). These results suggest that the cycloaddition of **1** is initiated by the yne-yne coupling leading to a cobaltacyclopentadiene intermediate. Next, we investigated the valence of the Co species involved in the photoinduced catalytic cycle. In the presence of a catalytic amount of $CoCl(PPh_3)_3$, the cycloaddition of **1a** proceeded smoothly without irradiation with LED light (Figure 1C). If Co^I species, such as $CoCl(PPh_3)_3$, are the active catalyst, continuous irradiation would not be required to

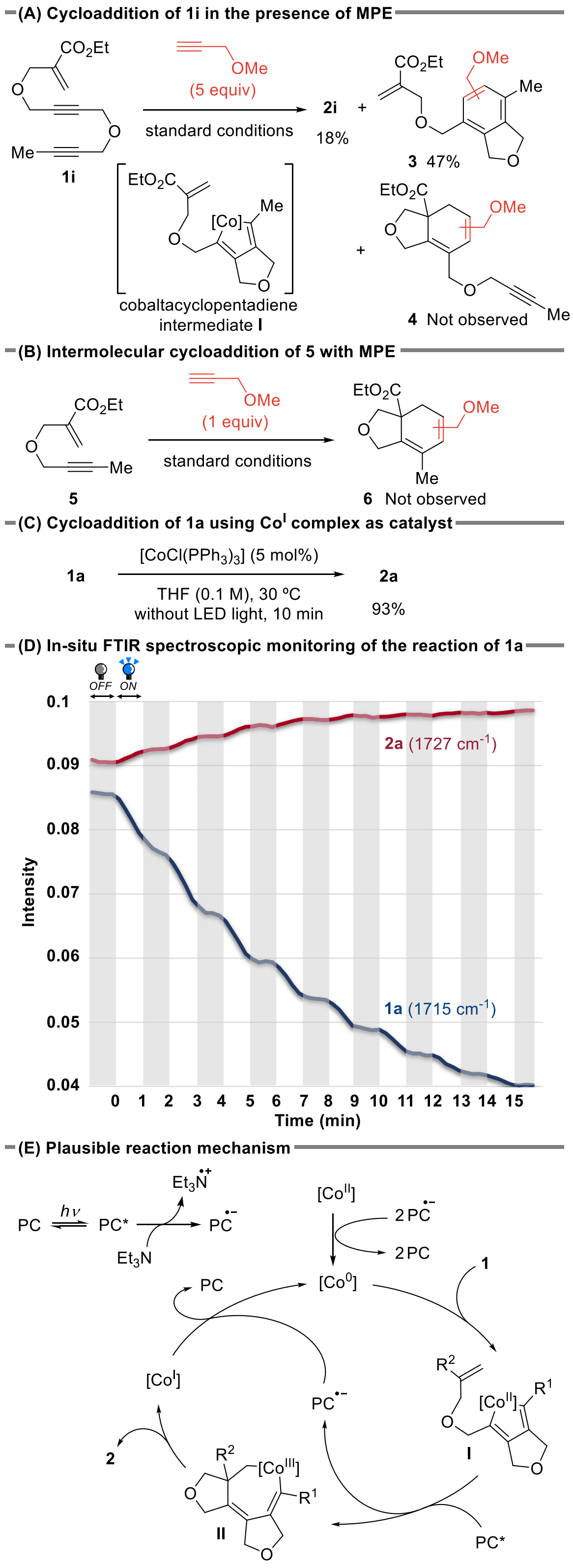
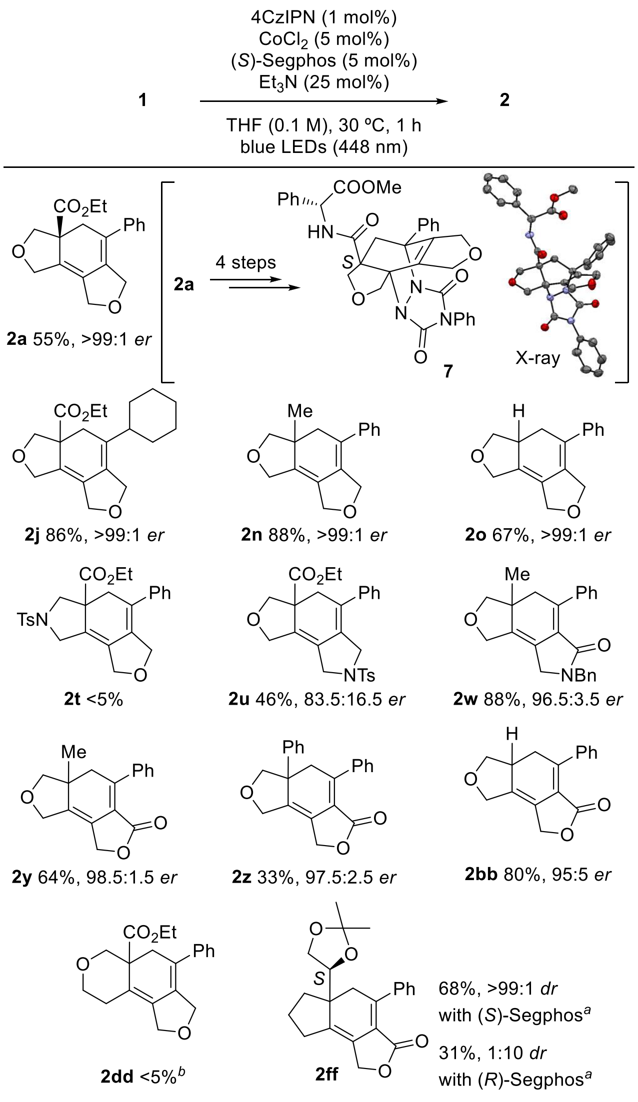


Figure 1. Mechanistic study.

promote the reaction because the Co^{I} species, generated from the Co^{II} species during the initial irradiation, would facilitate the reaction without any further irradiation. To test this hypothesis, we performed a real-time analysis of the reaction of **1a** using in situ FTIR spectroscopy. The reaction profiles under alternating periods of irradiation and darkness are shown in Figure 1D. The intensity of the absorptions derived from the ester carbonyl groups of **1a** and **2a** was reduced or increased during irradiation, while the transformation of **1a** into **2a** was suppressed during darkness. This result implies that the Co^{I} species is not generated in this catalytic system. On the basis of these results, we propose a plausible reaction mechanism, as shown in Figure 1E. At the initial stage of the reaction, the photoinduced reduction of a Co^{II} precatalyst occurred to produce Co^{0} species. The yne-yne coupling facilitated by the Co^{0} catalyst generates the cobaltacyclopentadiene intermediate **I**. Subsequent photoinduced oxidation and insertion of the pendant alkene into the $Co{-}Csp^{2}$ bond provides the intermediate **II**, which on reductive elimination furnishes **2** and the Co^{I} species. Finally, the Co^{0} species is restored by photocatalyst-mediated reduction of the Co^{I} species. This mechanism is consistent with the fact that the reaction can be regulated by turning ON and OFF the light, as originally suggested by Rovis et al.[8a]

Scheme 3. Enantioselective [2+2+2] Cycloaddition of Selected Substrates



[a] The reaction was performed for 2 h. [b] Enediyne was slowly added over 1 h and the mixture was stirred for additional 10 min.

Finally, we investigated the enantioselective version of this reaction using a chiral ligand. Several chiral biaryl bisphosphine ligands were examined for the cycloaddition of **1a**, leading to the identification of (*S*)-Segphos as the most appropriate ligand for enabling a highly enantioselective cycloaddition reaction (Table S4). The results of the enantioselective cycloaddition using the selected substrates are summarized in Scheme 3. A variety of enediynes were applicable and the enantio-enriched 5−6−5 tricyclic products were obtained in moderate to high yields with excellent enantioselectivities. However, several enediynes such as **1s**, **1t**, and **1dd** failed to undergo the cycloaddition. The intermolecular cycloaddition also did not proceed with (*S*)-Segphos. Considering that the reactivity seems to be affected by the structure around the alkene moiety in the intramolecular reaction, it might be assumed that the alkene insertion process is problematic due to the relatively narrow cavity of the Co-Segphos complex which enables the high enantioselectivity. The absolute configuration of (*S*)-**2a** was determined by X-ray diffraction analysis of **7**, which was prepared from **2a** (>99:1 er) in four steps (Scheme S2).[12] Moreover, the reaction of (*S*)-**1ff** using (*S*)-Segphos furnished **2ff** with excellent diastereoselectivity (>99:1 dr). In contrast, the use of (*R*)-Segphos afforded **2cc** with 1:10 dr, albeit in low yield, indicating that the stereoselectivity of the quaternary bridgehead carbon is controlled by the catalyst rather than the substrate.

In conclusion, we have developed a [2+2+2] cycloaddition of enediynes mediated by cobalt and photoredox cooperative catalysis. Several control experiments suggest that the reaction proceeds via the cobaltacyclopentadiene intermediate formed by the yne-yne coupling mediated by the Co catalyst. In addition, highly enantioselective cycloaddition was achieved using (*S*)-Segphos as a chiral ligand.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02410.

Additional tables of optimization data, experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds (PDF)

Crystallographic data for **7** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was partially supported by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) from AMED under Grant Number JP21am0101099) and JSPS KAKENHI (Grant Number JP21K05051).

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(12) X-ray crystallographic data for compound **7** have been deposited with the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under code CCDC2083437. For details, see the Supporting Information.