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Enantioselective Reductive Homocoupling of Allylic Acetates Enabled by Dual Photoredox/Palladium Catalysis: Access to C_2-Symmetrical 1,5-Dienes

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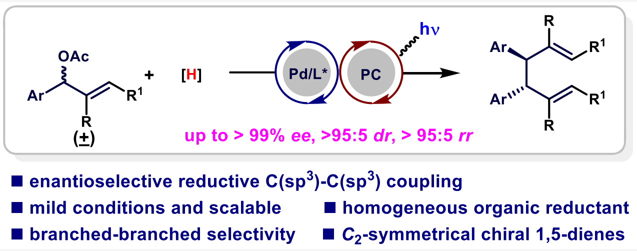
ABSTRACT: Transition-metal-catalyzed reductive coupling reactions have emerged as powerful protocols to construct C−C bonds. However, the development of enantioselective C(sp^3)−C(sp^3) reductive coupling remains challenging. Herein, we report a highly regio-, diastereo-, and enantioselective reductive homocoupling of allylic acetates through cooperative palladium and photoredox catalysis using diisopropylethylamine or Hantzsch ester as a homogeneous organic reductant. This straightforward protocol enables the stereoselective construction of C(sp^3)−C(sp^3) bonds under mild reaction conditions. A series of C_2-symmetrical chiral 1,5-dienes were easily prepared with excellent enantioselectivities (up to >99% ee), diastereoselectivities (up to >95:5 dr), and regioselectivities (up to >95:5 rr). The resultant chiral 1,5-dienes can be directly used as chiral ligands in asymmetric synthesis, and they can be also transformed into other valuable chiral ligands.



INTRODUCTION

The selective formation of C−C bonds remains one of the foremost challenges in organic synthesis. This is particularly true for the construction of C(sp^3)−C(sp^3) bonds.[1] Transition-metal-catalyzed coupling reactions between alkyl electrophiles and alkyl nucleophiles have been recognized as some of the most powerful and straightforward protocols to construct C(sp^3)−C(sp^3) bonds efficiently and stereoselectively (Figure 1a, left).[2] These traditional coupling reactions generally require preformed alkyl metals or metalloids acting as nucleophiles.[3] The reductive coupling of two alkyl electrophiles in the presence of a terminal reductant can provide a potential strategy to overcome these synthetic disadvantages (Figure 1a, right).[4] Historically, Wurtz coupling has been an important method for the homocoupling of two sp^3 carbons. However, the use of highly reactive alkali metals somewhat limited its synthetic applications.[5] In the past few decades, significant progress has been achieved in the transition-metal-catalyzed cross- or homocoupling of two electrophiles.[4] For example, Weix,[6] Gong,[7] Reisman,[8] and others[9] have established a variety of nickel-catalyzed reductive couplings of alkyl electrophiles. Despite advances, most transition-metal-catalyzed reductive couplings extensively require stoichiometric metal reductants, such as Mn(0) or Zn(0), to turn over the catalysts.[4] The development of new reduction systems would be highly desirable, and great challenges still remain. Another unsolved challenge in this field is the control of stereoselectivity.[10] Highly enantioselective reductive C(sp^3)−C(sp^3) coupling has not yet been reported.

1,5-Dienes are valuable building blocks in organic synthesis[11] and are also frequently found in numerous bioactive substances and natural products.[12] Transition-metal-catalyzed allyl−allyl coupling reactions have been proved to be powerful protocols for the synthesis of chiral 1,5-dienes.[13,14] In this field, significant advances have been made by the Morken group through Pd-catalyzed cross-coupling of allylic electrophiles and allyl boronates.[14a−d] Recently, we have been interested in the synthesis of C_2-symmetrical chiral 1,5-dienes, which are widely used as ligands in transition-metal-catalyzed asymmetric transformations (Figure 1c).[15] One of the most straightforward methods accessing 1,5-dienes is reductive homocoupling of two allylic electrophiles.[16] The most formidable challenge is the selectivity issue (Figure 1b). In the case of homocoupling of two allylic electrophiles, there are up to five kinds of selectivity issues (chemoselectivity, regioselectivity, *Z*/*E* selectivity, diastereoselectivity, and enantioselectivity). The construction of a C_2-symmetrical chiral 1,5-diene out of up to 10 isomers regio-, diastereo-, and enantioselectively is an unsolved synthetic problem to date.

Visible-light photoredox catalysis has emerged as a powerful tool to construct C−C bonds under mild and environmentally

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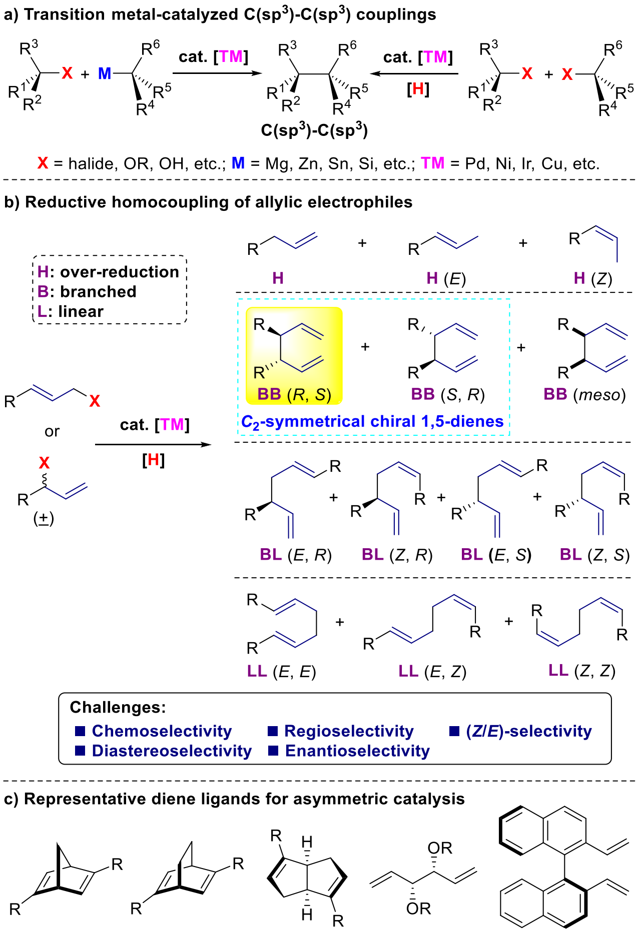


Figure 1. Transition-metal-catalyzed C(sp^3)−C(sp^3) couplings.

benign conditions.[17] The photoredox cycle could serve as a milder alternative for oxidation or reduction through single-electron-transfer (SET) processes. Dual photoredox and transition-metal catalysis has been applied to the area of reductive reactions, enabling the coupling of organohalides with the use of a homogeneous organic reducing agent.[18,19] Despite this progress, enantioselective versions are still limited.[19l,o,20] Herein, we describe a dual photoredox/Pd catalytic protocol for regio-, diastereo-, and enantioselective reductive homocoupling of allylic electrophiles (Figure 2). This cooperative catalysis strategy precludes preformed organometallic reagents and stoichiometric metal-based reductants used in the traditional C(sp^3)−C(sp^3) coupling and reductive coupling reactions. This approach allows the direct and efficient synthesis of C_2-symmetrical chiral 1,5-dienes.

We have recently achieved enantioselective photoredox/Pd-cocatalyzed allylic alkylation of the racemic allylic acetates with 4-alkyl-1,4-dihydropyridines.[21,22] During this investigation, we could observe a mixture of the reductive homocoupling of allylic acetates as the side products. 4-Alkyl-1,4-dihydropyridines serve as both the alkylation reagents for the allylic alkylation and the reductants for the reductive homocoupling. On the basis of these observations, it is believed that enantioselective homocoupling of allylic acetates can be achieved by careful selection of a reductant and catalytic system. Mechanistically, an allylic radical **A** can be generated from the corresponding allylic electrophile under photoredox conditions with the help of a reductant. Meanwhile, oxidative addition of the allylic electrophile to a Pd(0) complex delivers the Pd(II)-π-allyl species **B**. The allylic radical **A** is then trapped by the π-allyl palladium complex **B** to provide the Pd(III) complex **C**. Reductive elimination of the Pd(III) complex **C** gives a C_2-symmetrical chiral 1,5-diene as a homocoupling product (Figure 2).

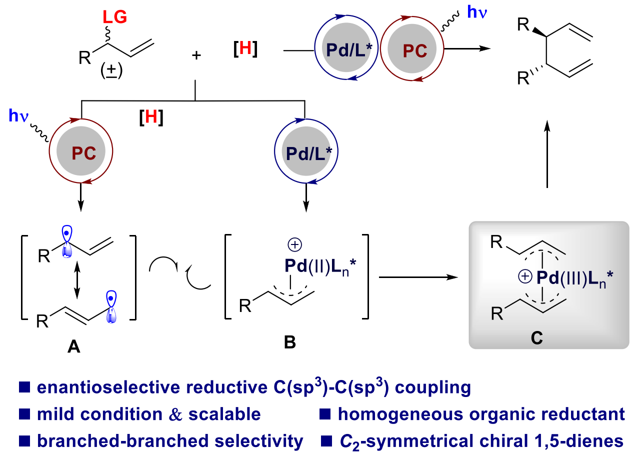
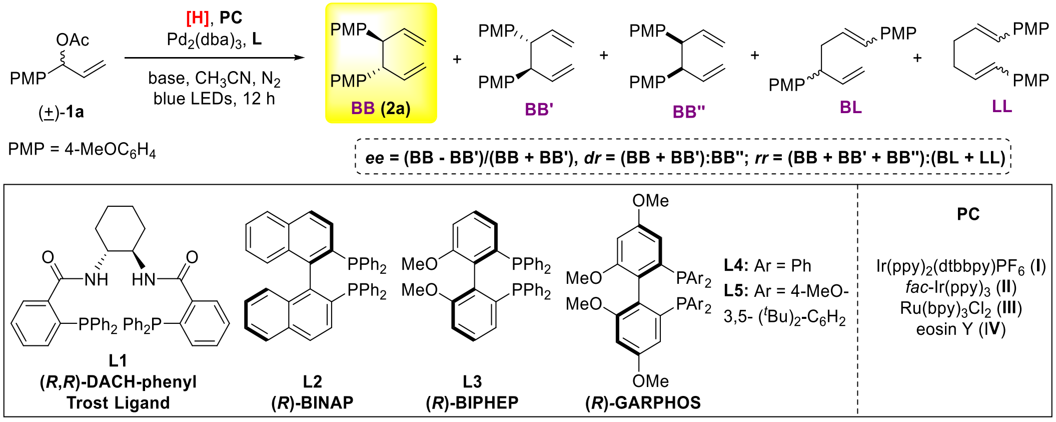


Figure 2. Rationale for photoredox/Pd-cocatalyzed reductive homocoupling of allylic electrophiles (LG = leaving group, PC = photocatalyst).

RESULTS AND DISCUSSION

To test our aforementioned hypothesis, we initiated our studies with racemic allylic acetate (**1a**) as an allylic electrophile. With a combination of Pd$_2$(dba)$_3$ (1.25 mol %)/(*R*,*R*)-DACH-phenyl Trost ligand (**L1**, 3 mol %) and Ir(ppy)$_2$(dtbbpy)PF$_6$ (**I**, 1 mol %) as an initial dual catalytic system, Hantzsch ester (HE) as a reductant, and K$_2$CO$_3$ as a base, the reaction proceeded smoothly under the irradiation of 45 W blue LEDs, affording the desired reductive homocoupling product (**2a**) in a good yield (86% yield determined by GC analysis; Table 1, entry 1). However, poor regio-, diastereo-, and enantioselectivities were observed (33% ee, 49:51 dr, 29:71 rr). In addition, the over-reduction product 1-allyl-4-methoxybenzene could also be detected by GC-MS, which indicated that the chemoselectivity issue of this reaction was also a great challenge. After an evaluation of chiral ligands, it was found that axially C_2 symmetrical chiral diphosphine ligands with different scaffolds, such as BINAP (**L2**), MeO-BIPHEP (**L3**), and GARPHOS (**L4**), improved the regio- and stereoselectivities remarkably (entries 2−4). When the sterically more demanding GARPHOS **L5** was employed (entry 5), excellent diastereo- and enantioselectivities (>95:5 dr, >99% ee) were achieved, although the regioselectivity (84:16 rr) needed to be improved further. We then turned our attention to the reductants and found that diisopropylethylamine (DIPEA) as the reductant had positive effects on the regio- and diastereoselectivities of this reaction (entries 6 and 7). Other photocatalysts, such as Ir(ppy)$_3$ (**II**), Ru(bpy)$_3$Cl$_2$ (**III**), and eosin Y (**IV**), were evaluated, but lower yields and regioselectivity were obtained in all cases (entries 8−10). To our delight, the replacement of K$_2$CO$_3$ with Cs$_2$CO$_3$ gave improved yields and regioselectivity (90% GC yield, 94:6 rr, entry 12). Finally, an increase in concentration of this reaction resulted in a further improved yield (96% GC yield and 92%

Table 1. Optimization of Reaction Conditions[a]



entry	PC	ligand	[H]	base	yield (%)[b]	ee (%)[c]	dr[b]	rr[b]
1	**I**	**L1**	HE	K_2CO_3	86	33	49:51	29:71
2	**I**	**L2**	HE	K_2CO_3	80	74	89:11	64:36
3	**I**	**L3**	HE	K_2CO_3	83	80	90:10	70:30
4	**I**	**L4**	HE	K_2CO_3	82	88	90:10	75:25
5	**I**	**L5**	HE	K_2CO_3	88	>99	>95:5	84:16
6	**I**	**L5**	DIPEA	K_2CO_3	74	>99	>95:5	90:10
7	**I**	**L5**	TEA	K_2CO_3	76	>99	>95:5	83:17
8	**II**	**L5**	DIPEA	K_2CO_3	63	>99	88:12	41:59
9	**III**	**L5**	DIPEA	K_2CO_3	49	>99	>95:5	48:52
10	**IV**	**L5**	DIPEA	K_2CO_3	50	>99	94:6	34:66
11	**I**	**L5**	DIPEA	K_3PO_4	85	>99	>95:5	94:6
12	**I**	**L5**	DIPEA	Cs_2CO_3	90	>99	>95:5	94:6
13[d]	***I***	***L5***	*DIPEA*	Cs_2CO_3	*96 (92)*[e]	>99	>95:5	*>95:5*

[a] Reaction conditions unless specified otherwise: a solution of **1a** (0.2 mmol), reductant (0.3 mmol), base (0.3 mmol), $Pd_2(dba)_3$ (1.25 mol %), ligand (3 mol %), and photocatalyst (1 mol %) in CH_3CN (4.0 mL) was irradiated by 45 W blue LEDs for 12 h. [b] Yields, diastereomeric ratios (dr), and regiomeric ratios (rr) were determined by GC analysis. [c] Enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase. [d] The reaction was run in 2.0 mL of CH_3CN. [e] Isolated yield.

isolated yield) and stereoselectivity (>99% ee, >95:5 dr, and >95:5 rr, entry 13).

After establishing the optimal reaction conditions, we investigated the scope and limitations of this dual photoredox/Pd-catalyzed enantioselective reductive allylic homocoupling. As shown in Figure 3, this strategy was applicable to a wide range of allylic acetates bearing electronically distinct substituents at different positions of the aryl moiety, offering the corresponding C_2-symmetrical chiral 1,5-dienes **2a**−**y** in moderate to high yields (45−95%), good diastereoselectivity (85:15 to >95:5 dr), and excellent regio- and enantioselectivities (>95:5 rr and 96 to >99% ee). Specifically, allylic acetates with electron-donating groups delivered higher reactivity and diastereoselectivity in comparison to those with electron-withdrawing groups. In general, *para*- and *ortho*-substituted substrates reacted similarly, while lower yields and dr values were obtained for *meta*-substituted substrate. Furthermore, heterocycles and polycyclic aromatics, as well as heteroaromatics, which have significance in medicinal chemistry, were also applicable. The *S*,*S* configuration of **2t** was determined unambiguously by X-ray crystallography.[23]

Monosubstituted allyl substrates have been widely used in transition-metal-catalyzed enantioselective allyl−allyl coupling reactions, while unsymmetrical 1,3-disubstituted allyl substrates have been less studied.[14] In the latter case, chiral internal 1,5-dienes with *Z*/*E* selectivity would be obtained. Two major challenges may prevent the use of racemic unsymmetric 1,3-disubstituted allyl reagents in Pd-catalyzed asymmetric allylation: (a) suppression of β-H elimination side reactions[24] and (b) dynamic kinetic asymmetric transformation (DyKAT) of internal allyl electrophiles.[25] To meet these challenges and expand the scope of this reductive homocoupling further, polysubstituted allyl acetates were explored (Figure 4). We began with substrate **3a**. Under the previous optimal reaction conditions, the desired internal 1,5-diene **4a** was obtained with excellent enantio-, regio- and *E*/*Z* selectivities (>99% ee, >95:5 rr, *E*:*Z* >95:5), but the yield (36%) and diastereoselectivity (80:20 dr) were not satisfactory. Fortunately, when HE was used as a reductant instead of DIPEA, an improved yield (64%) and diastereoselectivity (89:11 dr) were observed. A series of 1-methyl-3-phenylallyl acetates with various substituents at different positions of the phenyl ring were then examined. The reaction proceeded smoothly to deliver chiral internal 1,5-dienes **4b**−**j** in moderate to high yields (63−87%) and excellent enantio-, regio-, and *E*/*Z*-selectivities (>99% ee, >95:5 rr, *E*:*Z* >95:5). The alkyl group could be ethyl (**3k**), propyl (**3l**), and pentyl (**3m**). The length of the alkyl group had little effect on the reactivity and selectivity. Cyclic allyl acetates were also suitable for the reaction and provided corresponding products **4n**−**p** in good yields (78%, 68%, and 66%, respectively) and excellent enantioselectivities (>99%, 96%, and 94% ee, respectively). Furthermore, reductive homocoupling of 1,2,3-trisubstituted allyl acetate **3q** also proceeded well to deliver the desired

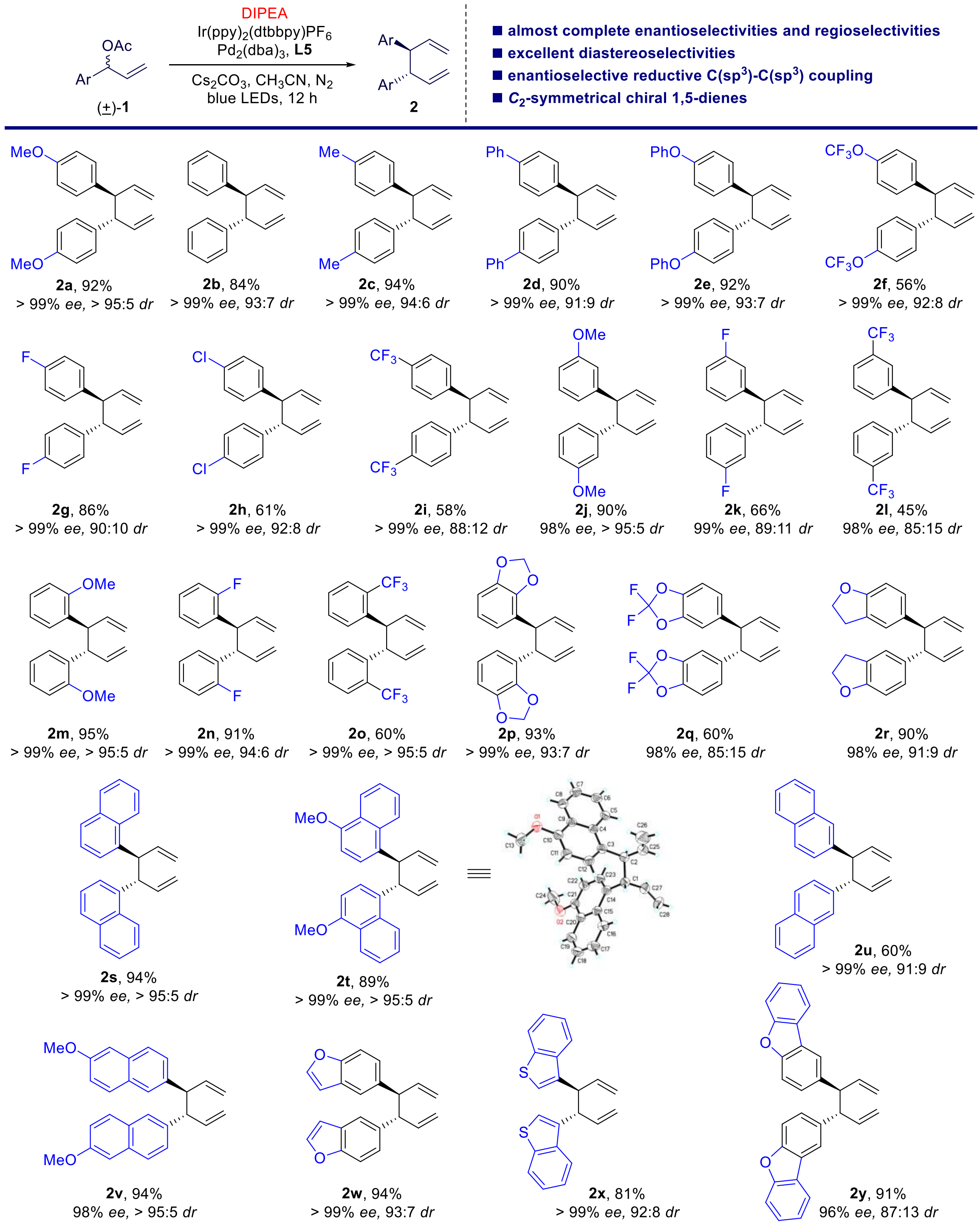


Figure 3. Scope of monosubstituted allyl acetates. Reaction conditions: a solution of **1** (0.2 mmol), DIPEA (0.3 mmol), Cs_2CO_3 (0.3 mmol), $Pd_2(dba)_3$ (1.25 mol %), ligand **L5** (3 mol %), and photocatalyst **I** (1 mol %) in CH_3CN (2.0 mL) was irradiated by 45 W blue LEDs for 12 h. Isolated yields are presented, and ee values were determined by HPLC on a chiral stationary phase. The diastereoselectivity and regioselectivity were determined by ^1H NMR. Unless otherwise noted, rr > 95:5.

product **4q** with good yield (60%) and selectivity (90% ee). Additionally, when **L2** was used as the ligand, 1,3-diphenylallyl acetate **3r** (80% yield and 92% ee) was also a valid substrate for this transformation.

To illustrate the utility of this dual catalytic enantioselective reductive homocoupling, preparative-scale reactions were performed. As shown in Figure 5a, under our established conditions, the C_2-symmetrical chiral 1,5-diene **2s** was obtained on synthetically useful scales with good yields (78% for 4 mmol scale and 66% yield for 10 mmol scale) and excellent stereoselectivities (>99% ee, >95:5 dr, and >95:5 rr). Furthermore, the resulting C_2-symmetrical chiral 1,5-dienes are synthetically valuable building blocks and could be expediently converted into a series of synthetically valuable optically active compounds. The derivatizations of **2s** were then explored. As shown in Figure 5b, hydrogenation of **2s** could be achieved

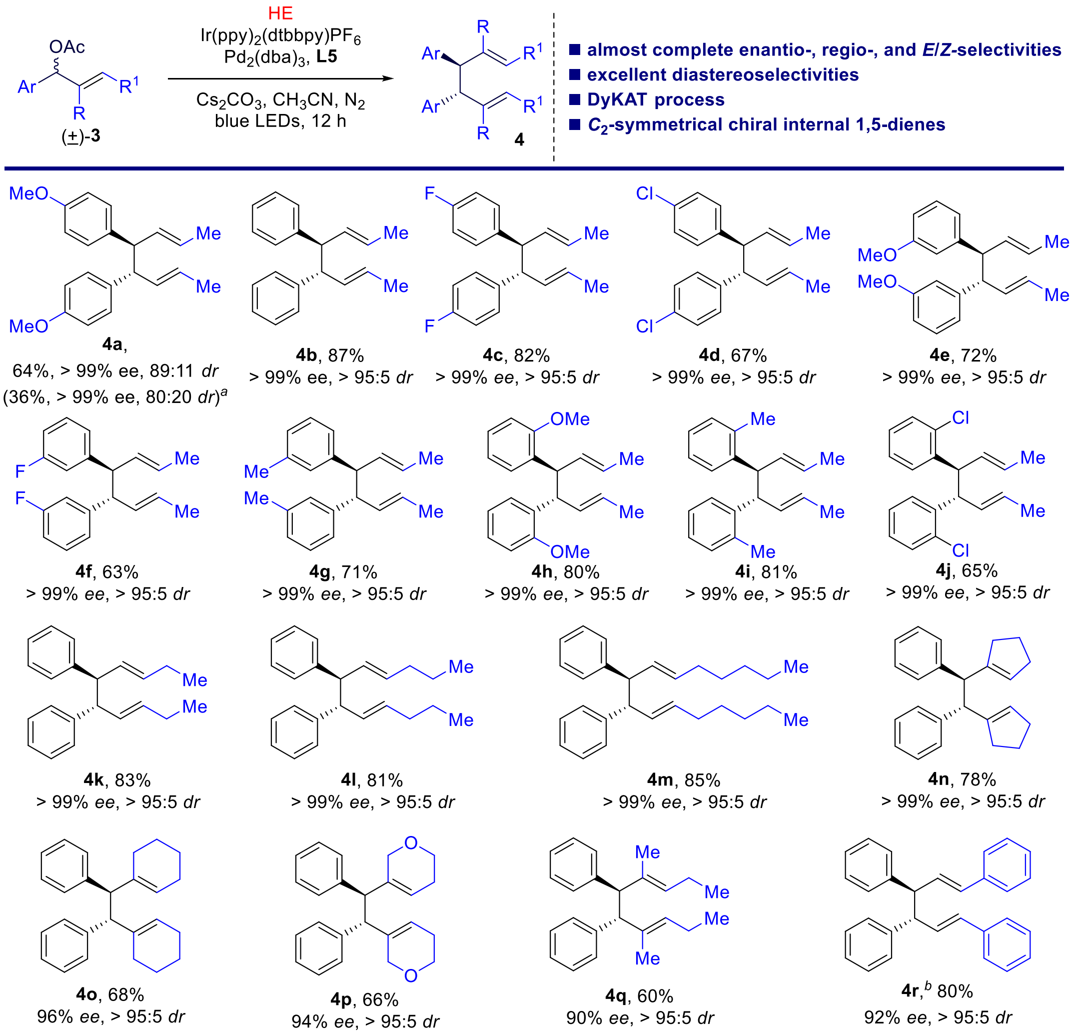


Figure 4. Scope of polysubstituted allyl acetates. Reaction conditions: a solution of **3** (0.2 mmol), HE (0.3 mmol), Cs_2CO_3 (0.3 mmol), $Pd_2(dba)_3$ (1.25 mol %), ligand **L5** (3 mol %), and photocatalyst **I** (1 mol %) in CH_3CN (2.0 mL) was irradiated by 45 W blue LEDs for 12 h. Isolated yields are presented, and ee values were determined by HPLC on a chiral stationary phase. The diastereoselectivity and regioselectivity were determined by ^1H NMR. Unless otherwise noted, rr > 95:5 and *E*/*Z* >95:5. Legend: (a) DIPEA was used; (b) **L2** was used.

efficiently using catalytic Pd/C. Hydroboration of **2s** and subsequent Suzuki cross-coupling gave **6**. The C_2-symmetrical chiral 1,6-diol **7** and 1,4-diol **9** could be synthesized from **2s** through hydroboration/oxidation or ozonolysis/reduction without affecting optical purity. In addition, **7** and **9** could be efficiently transformed into C_2-symmetrical chiral 1,6-diphenyl phosphinohexane **8** and 1,4-diphenyl phosphinobutane **10**, respectively. These results indicated the great potential of the chiral dienes in the development of valuable ligands and organocatalysts. Given that chiral dienes are highly effective ligands for transition-metal-catalyzed enantioselective reactions, the use of **2t** as a new chiral diene ligand was investagated for the Rh-catalyzed asymmetric arylation of 2-cyclohexenone **11** and *N*-tosyl imine **14** with phenylboronic acids **12** and **15** (Figure 5c). To our delight, the desired products were generated in good enantioselectivities (**13**, 90% ee; **16**, 82% ee). This result demonstrates that this class of chiral 1,5-dienes can be developed as new types of chiral diene ligands.

To gain additional insight into the reaction, we performed several control experiments (Figure 6). The photocatalyst, the palladium catalyst, and light were all essential to this reaction (Figure 6a). We investigated on−off switching of the blue LEDs of the reaction (Figure 6b). The reaction progressed smoothly upon irradiation with light, while the reaction paused during the "light-off" periods. These results reveal that this reductive homocoupling undergoes a photoredox catalysis process. Stern−Volmer quenching experiments indicate that DIPEA quenches the photoexcited catalyst **I** (Figure 6c).

The isomeric allylic acetates **1a** and **1a′** (Figure 7a, eq 1), as well as an equimolar mixture of **1a** and **1a′** (Figure 7a, eq 2), gave similar results, respectively. In addition, we synthesized π-allylpalladium complex **17**, which was subjected to this homocoupling, providing reductive homocoupling product **2b** in 53% yield (Figure 7a, eq 3). These phenomena demonstrate that a (π-allyl)palladium complex might be the key intermediate of this reaction. The intermediacy of the allylic radical was uncovered by radical trapping experiments (Figure 7b). When the radical trapping reagent 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) was added to the model reaction of **1a**, the reaction efficiency decreased dramatically, and the allyl-TEMPO adduct **18** was isolated (Figure 7b, eq 4). Meanwhile, **18** could not be detected in the absence of photocatalysis and light irradiation, which revealed

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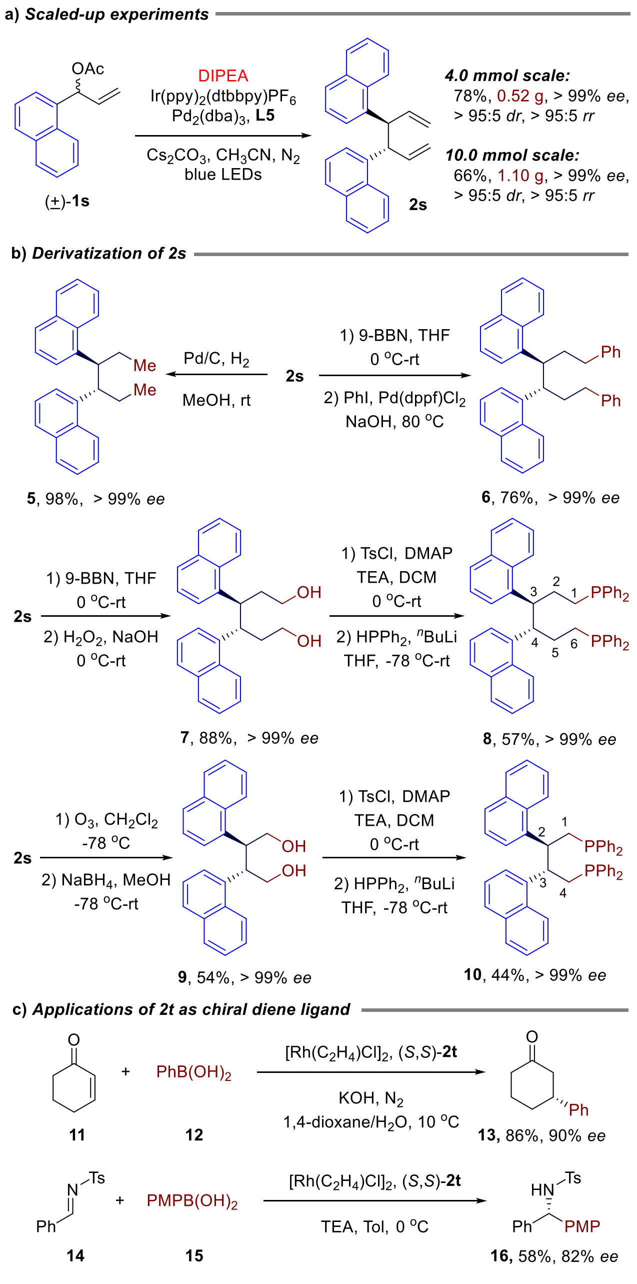

Figure 5. Scaled-up experiments and synthetic applications.

that the radical trapping product was not formed through the directly nucleophilic addition of TEMPO to the formed (π-allyl)palladium complex (Figure 7b, eq 5). In the presence of TEMPO, the allyl radical trapping **19** was also observed in the reaction of (π-allyl)palladium complex **17** (Figure 7b, eq 6). These results suggest that an allylic radical might be generated from the (π-allyl)palladium complex with the assistance of light and the photocatalyst. In order to further confirm this conclusion, the redox potentials of allyl acetate **1b** ($E_{1/2}$ = −1.43 V vs SCE) and (π-allyl)palladium complex **17** ($E_{1/2}$ = −0.95 V vs SCE) were measured (for more details, see Figures S5 and S6). The redox potentials indicate that the allyl radical is more likely generated from (π-allyl)palladium complex **17**, which is more easily reduced than allylic acetate **1b** by the Ir(II) complex ($E_{1/2}(\mathrm{Ir^{III}/Ir^{II}})$ = −1.51 V vs SCE)[26] to give the allylic radical.

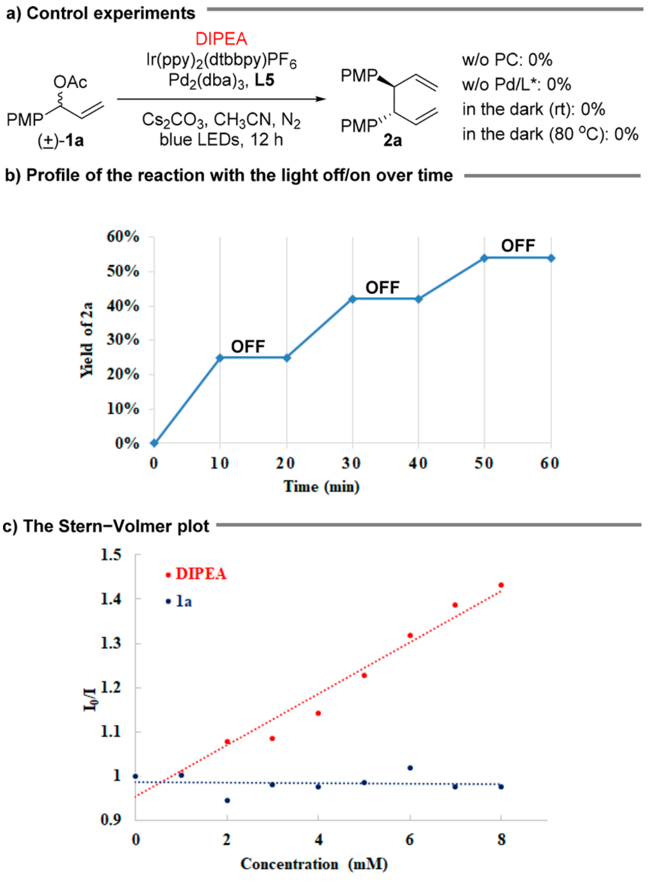

Figure 6. Control experiments and Stern−Volmer fluorescence quenching experiments.

On the basis of the aforementioned results and previous published work on photoredox/Pd cocatalysis,[27] a plausible mechanism is depicted in Figure 8. DIPEA ($E_{1/2}$ = +0.68 V vs SCE)[28] quenches visible-light-excited Ir(III)* ($E_{1/2}(\mathrm{Ir^{III}*/Ir^{II}})$ = +0.66 V vs SCE)[26] to generate a low-valent Ir(II) complex and the radical cation DIPEA$^{\bullet+}$.[19d,j,n,28] Meanwhile, Pd(0) oxidatively adds to the allylic acetate **1** to give a (π-allyl)Pd$^{\mathrm{II}}$ complex **A**. The single-electron reduction of **A** by an Ir(II) complex can generate the (π-allyl)Pd$^{\mathrm{I}}$ complex **B**,[27i] which can equilibrate with an allylic radical species **C** and a Pd(0) species.[27c,e] The second oxidative addition of another allylic acetate **1** to **B** would give the bis(π-allyl)Pd$^{\mathrm{III}}$ complex **D** equilibrated with bis(η^1-allyl)Pd$^{\mathrm{III}}$ complex **D′** (path a).[14a−d] Alternatively, allylic radical species **C** is trapped by (π-allyl)Pd$^{\mathrm{II}}$ complex **A** to generate **D**/**D′** (path b).[21,27a−e,g,h,j,n] Reductive elimination[14a−d] from **D**/**D′** yields the homocoupling product **2** and the Pd(I) species **E**.[21,27f,m,n,29] Finally single-electron reduction of **E** most likely by the Ir(II) complex would regenerate Pd(0).[21,27i,m,n] The Pd(III) intermediate **D**/**D′** could also be reduced to a bis(allyl)Pd$^{\mathrm{II}}$ species and then undergo a reductive elimination[14a−d] to deliver the final product **2** (for more detailed discussions, see Figures S7 and S8).[27h,k]

■ CONCLUSION

In summary, we have described a highly regio-, diastereo-, and enantioselective reductive homocoupling of allylic acetates through cooperative palladium and photoredox catalysis. DIPEA or Hantzsch ester (HE) was used as the reductant.

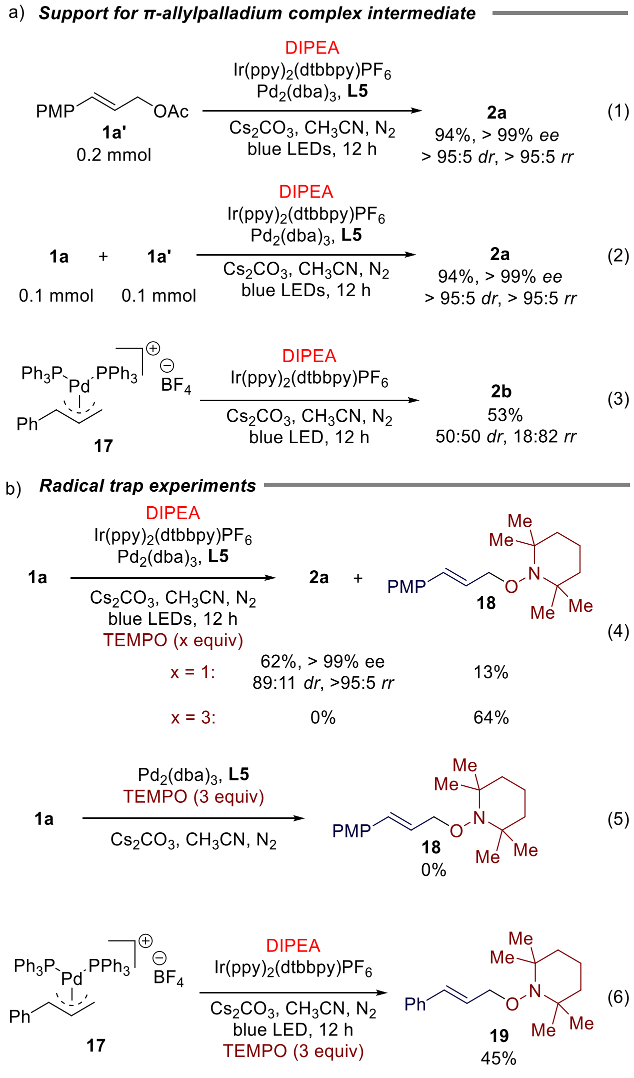

Figure 7. Mechanistic investigations.

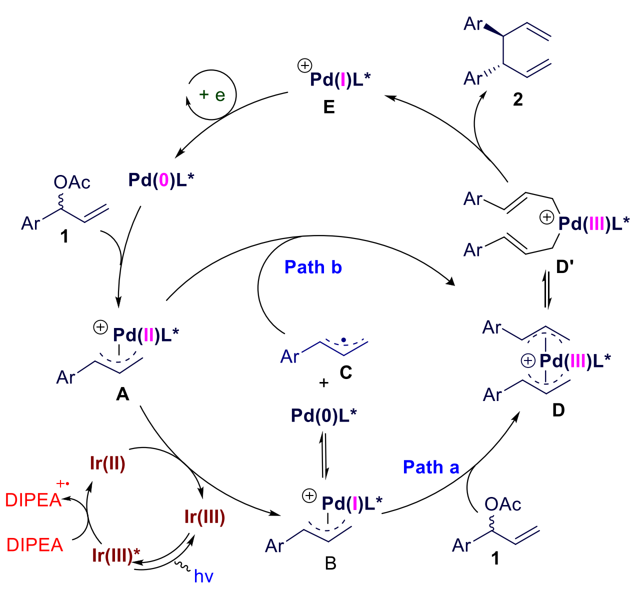

Figure 8. Proposed mechanism.

This dual catalytic protocol allows access to C_2-symmetrical chiral 1,5-dienes in optically pure form. The resultant chiral 1,5-dienes can be directly used as chiral ligands in asymmetric synthesis, and they can be also transformed into other valuable chiral ligands. Further mechanistic studies, cross-coupling variants, and synthetic applications of this photoredox/Pd-cocatalyzed enantioselective reductive coupling are underway in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06271.

> General experimental procedures and characterization data abd ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR spectral data (PDF)

Accession Codes

CCDC 2049849 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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