Cobalt-Catalyzed Allylic Alkylation Enabled by Organophotoredox Catalysis

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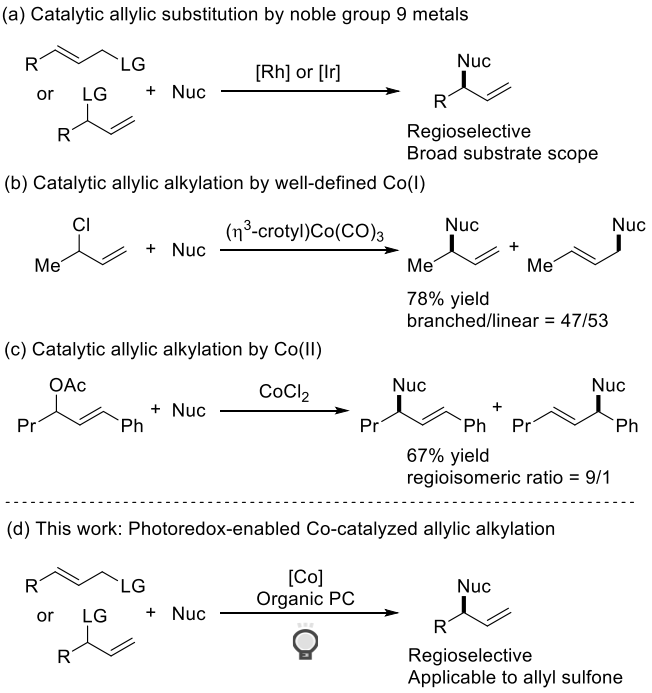
Abstract: Co-catalyzed allylic substitution reactions have long received little attention arguably because no characteristic advantage of Co catalysis over Rh or Ir catalysis was ever known. Here we describe a general and regioselective Co-catalyzed allylic alkylation using an *in situ* catalyst activation by organophotoredox catalysis. This noble-metal-free catalytic system exhibited unprecedentedly high reactivity and regioselectivity for the allylation with an allyl sulfone, for the first time representing a unique synthetic utility of a Co-catalyzed method compared to the related Rh- or Ir-catalyzed reactions.

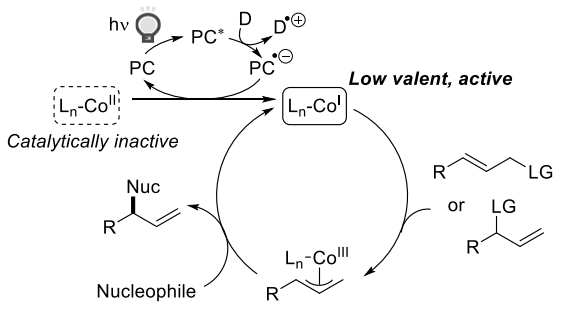
Complementary to the Pd-catalyzed Tsuji-Trost reaction,[1] catalytic allylic substitutions catalyzed by Rh or Ir complexes have been considered privileged transformations in organic synthesis due to their intrinsic tendency to afford synthetically versatile branched products.[2,3] Substantial contributions to this area, including catalysts with broader substrate scope, higher regioselectivity and enantioselectivity, have been reported by Tsuji,[4] Evans,[5] Takeuchi,[6] Helmchen,[7] Hartwig,[8] Carreira,[9] You[10] and others,[11,12] realizing transformations hitherto challenging with other metals (Scheme 1a). In addition, Breit recently disclosed photoredox/Rh dual catalysis for the allylation of amines,[13] demonstrating the prospects of group 9 metal catalysis in the context of metallaphotoredox chemistry.[14,15] On the other hand, investigations into corresponding catalysis with Co, i.e., the most abundant congener of group 9, have remained underdeveloped for decades. Contrary to the potential advantages of Co catalysis, which include lower cost and relevance to the versatile Rh and Ir catalysts, literature surveys on Co-catalyzed allylic alkylation with stabilized carbon nucleophiles revealed only few examples with inferior outcomes compared to Rh or Ir catalysis.[16] Allylic alkylations with sodium malonate catalyzed by well-defined Co(I) complexes were reported by Roustan in 1979,[16a] albeit that electrophiles were limited to allyl chlorides and that the observed regioselectivity was low (Scheme 1b). Iqbal studied $CoCl_2$-catalyzed allylic alkylations in 1993,[16b] but specific substituents on electrophiles were necessary and a mechanism mediated by an allyl cation could not be ruled out (Scheme 1c).

Considering these circumstances, our continuing interest in Co catalysis[17] motivated us to devise a novel Co-catalyzed allylic substitution reaction and its characteristic synthetic utility. We



Scheme 1. Allylic substitution reactions catalyzed by group 9 metals

hypothesized that low valent Co complexes generated *in situ*[18,19] should facilitate the catalytic process, and that photoredox mediated reduction[19,20] which plays a key role in photoredox/transition metal dual catalysis[14,21] might generate an active Co catalyst with intriguing reactivity (Scheme 1d). Hence, our reaction design is illustrated in Scheme 2. Under irradiation with visible light, photoredox catalyst (PC) in its excited state (PC*) oxidizes an electron donor (D). The reduced photocatalyst ($PC^{\cdot-}$) transfers one electron to Co and returns to its ground state. The low valent Co complex thus generated then engages with an allylic electrophile to form a π-allyl cobalt intermediate. A subsequent attack of the nucleophile to the π-allyl cobalt intermediate would then afford the allylated product and



Scheme 2. Mechanistic hypothesis for the allylic alkylation with cobalt and photoredox catalysis

regenerate the low valent cobalt catalyst.

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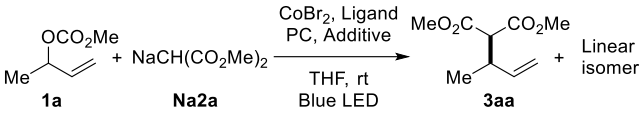
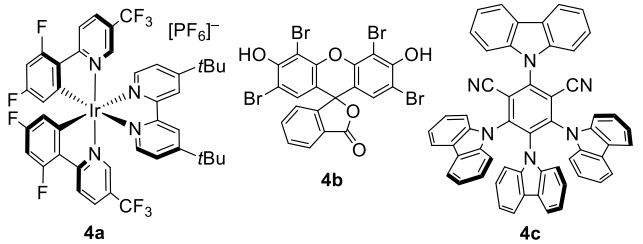
Based on this proposal, we started our investigation with the evaluation of cobalt complexes (Table 1, entries 1–3). We observed that combination of $CoBr_2$ and dppp enables the regioselective alkylation of allyl carbonate **1a** with sodium dimethyl malonate **Na2a** in the presence of $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)][PF_6]$ **4a** as a photocatalyst and Hantzsch ester (HEH) as an electron donor under blue LED irradiation (entry 2). Note that branched product **3aa** was obtained in high selectivity, suggesting similarity of this system to the Rh and Ir catalysis. Although Ir-based photosensitizers always demonstrated the best performance in previous studies,[19] the metal-free organophotocatalysts **4b** and **4c**[22] have shown even better results, comprising a noble-metal-free catalytic system (entries 4–5). An evaluation of electron donors revealed that a coordinating amine decreases the regioselectivity while $^{i}Pr_2NEt$ demonstrated superior performance to that of HEH (entries 5–7). The amount of the electron donor can be reduced to 30 mol% without loss of reactivity (entry 8) while the addition of MS4A afforded **3aa** in nearly quantitative yield under preservation of the regioselectivity (entry 9). The catalyst loading can be reduced to as low as 1.0 mol% (Co complex) and 0.10 mol% (photocatalyst) when using 1.0 equivalent of $^{i}Pr_2NEt$ (entry 10), which represents a robust protocol for large scale reactions.[23]

Table 1. Evaluation of the reaction parameters for the Co-catalyzed allylic alkylation[a]



1a Na2a 3aa

Entry	Ligand (mol%)	PC (mol%)	Additive (equiv)	Yield (%)[b]	b/l[b]
1	dppe (10)	**4a** (1.0)	HEH (0.5)	< 5	–
2	dppp (10)	**4a** (1.0)	HEH (0.5)	41	> 20/1
3	dppb (10)	**4a** (1.0)	HEH (0.5)	< 5	–
4	dppp (10)	**4b** (1.0)	HEH (0.5)	59	> 20/1
5	dppp (10)	**4c** (1.0)	HEH (0.5)	64	> 20/1
6	dppp (10)	**4c** (1.0)	DABCO (0.5)	35	2.1/1
7	dppp (10)	**4c** (1.0)	$^{i}Pr_2NEt$ (0.5)	72	> 20/1
8	dppp (10)	**4c** (1.0)	$^{i}Pr_2NEt$ (0.3)	74	> 20/1
9[c]	dppp (10)	**4c** (1.0)	$^{i}Pr_2NEt$ (0.3)	97	> 20/1
10[c,d]	dppp (1.0)	**4c** (0.10)	$^{i}Pr_2NEt$ (1.0)	91 (90)[e]	> 20/1

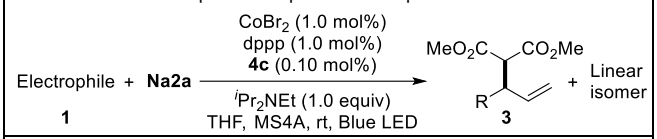


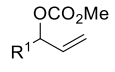
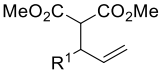
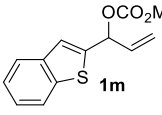
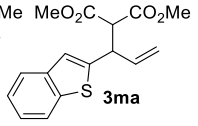
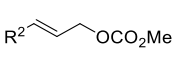
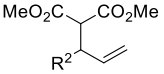
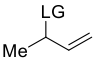
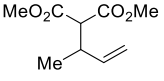
4a 4b 4c

[a] Reactions were run with **1a** (0.071 mmol), **Na2a** (2.0 equiv), $CoBr_2$ (10 mol%) in THF (0.05 M) at room temperature for 12 hours under blue LED irradiation unless otherwise noted. [b] Determined by ^1H NMR. [c] MS4A (200 g/mol) was added. [d] Reactions were run with **1a** (0.30 mmol), **2a** (2.0 equiv), $CoBr_2$ (1.0 mol%) in THF (0.2 M) for 16 hours. [e] Isolated yield. HEH: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

The substrate scope of the Co-catalyzed allylic alkylation with respect to electrophiles is summarized in Table 2. Branched allyl carbonates with alkyl substituents (**1a**–**1d**) afforded the branched products in excellent yield and regioselectivity, irrespective of the size of alkyl group (entries 1–4). Electrophiles with unsubstituted (**1e**), electron-rich (**1f**) or -deficient (**1g**–**1j**) aryl groups were also successfully employed in the desired C-C bond formation (entries 5–10). Notably, the current conditions are compatible with the C-Br bond in **1j** (entry 10). Substituents at the *ortho*- (**1k**) or *meta*-position (**1l**) did not affect the outcome of the reaction (entries 11–12). Even a heteroarene-substituted substrate (**1m**) underwent the allylic alkylation in high regioselectivity (entry 13). Linear allyl carbonates with methyl (**1n**) or phenyl (**1o**) groups exclusively afforded the branched product (entries 14, 15), suggesting negligible "memory effect"[24] in regioselectivity for this system. Allyl carbonates containing a 4-methoxyphenyl group (**1p**) or extended π system (**1q**, **1r**) produced the product in good yield while maintaining the excellent regioselectivity (entries 16–18). In terms of leaving group, allyl esters with benzoyl (**1s**) or 4-chlorophenylcarbonyl (**1t**) group afforded **3aa** in excellent yield, providing effective alternatives to methyl carbonates (entries 19–20). Substitution with an allyl sulfone (**1u**) selectively delivered the branched product (entry 21; vide infra).

Table 2. Reaction scope with respect to electrophiles[a]



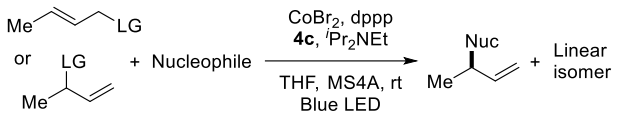
Entry	Electrophile **1**	Product **3**	Yield (%)	b/l[b]
				
1	R^1 = Me (**1a**)	**3aa**	90	> 20/1
2	R^1 = ^{n}Pr (**1b**)	**3ba**	91	> 20/1
3	R^1 = ^{i}Bu (**1c**)	**3ca**	93	> 20/1
4	R^1 = CH_2CH_2Ph (**1d**)	**3da**	98	> 20/1
5	R^1 = Ph (**1e**)	**3ea**	94	> 20/1
6	R^1 = 4-Me-C_6H_4 (**1f**)	**3fa**	94	> 20/1
7	R^1 = 4-CF_3-C_6H_4 (**1g**)	**3ga**	97	> 20/1
8	R^1 = 4-CO_2Me-C_6H_4 (**1h**)	**3ha**	92	> 20/1
9	R^1 = 4-Cl-C_6H_4 (**1i**)	**3ia**	> 99	> 20/1
10	R^1 = 4-Br-C_6H_4 (**1j**)	**3ja**	85	> 20/1
11	R^1 = 2-Cl-C_6H_4 (**1k**)	**3ka**	90	> 20/1
12	R^1 = 3-Cl-C_6H_4 (**1l**)	**3la**	94	> 20/1
13			82	10/1
				
14	R^2 = Me (**1n**)	**3aa**	78	> 20/1
15	R^2 = Ph (**1o**)	**3ea**	80	> 20/1
16	R^2 = 4-OMe-C_6H_4 (**1p**)	**3pa**	75	> 20/1
17	R^2 = 4-Ph-C_6H_4 (**1q**)	**3qa**	73	> 20/1
18	R^2 = 2-naphthyl (**1r**)	**3ra**	88	> 20/1
				
19	LG = OBz (**1s**)	**3aa**	95	> 20/1
20	LG = OCO(4-Cl-C_6H_4) (**1t**)	**3aa**	96	> 20/1

21[c]	LG = SO_2Ph (**1u**)	**3aa**	91	> 20/1

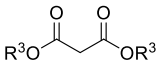
[a] Reactions were run with **1** (0.30 mmol), **2a** (2.0 equiv), $CoBr_2$ (1.0 mol%), dppp (1.0 mol%), **4c** (0.10 mol%), $^iPr_2NEt$ (1.0 equiv) and MS4A (200 g/mol) in THF (0.2 M) at room temperature for 16 hours under blue LED irradiation unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] $CoBr_2$ (2.5 mol%), dppp (2.5 mol%), **4c** (0.25 mol%) and $^iPr_2NEt$ (2.0 equiv) were used.

The substrate scope with respect to nucleophiles is summarized in Table 3. Malonate esters with larger alkyl substituents (**2b**, **2c**) underwent allylation in high yield and absolute regioselectivity (entries 1, 2). The sterically more hindered nucleophile **2d** also afforded satisfactory results in the presence of LiCl[25] (entry 3). Allylation of dibenzyl malonate derivatives (**2e**–**2g**) with **1n** efficiently proceeded in high yield and branch selectivity (entries 4–6). Malononitrile (**2h**), cyanoacetic acid derivatives (**2i**, **2j**), and phenylsulfonylacetonitrile (**2k**) were coupled with **1t** in good yield under absolute regioselectivity (entries 7–10).

Table 3. Reaction scope with respect to nucleophiles[a]



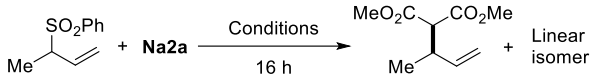
1 **Na2** **3**

Entry	Electrophile **1**	Pronucleophile **2**	Product **3**	Yield (%)	b/l[b]
					
1	**1a**	R^3 = Et (**2b**)	**3ab**	77	> 20/1
2	**1a**	R^3 = ^{i}Pr (**2c**)	**3ac**	89	> 20/1
3[c]	**1a**	R^3 = ^{t}Bu (**2d**)	**3ad**	97	16/1
4[d]	**1n**	R^3 = Bn (**2e**)	**3ne**	94	> 20/1
5[d]	**1n**	R^3 = CH_2(4-Me-C_6H_4) (**2f**)	**3nf**	92	> 20/1
6[d]	**1n**	R^3 = CH_2(4-Cl-C_6H_4) (**2g**)	**3ng**	85	> 20/1
					
7[d]	**1t**	R^4 = CN (**2h**)	**3th**	80	> 20/1
8[d]	**1t**	R^4 = CO_2Et (**2i**)	**3ti**	64[e]	> 20/1
9[d]	**1t**	R^4 = $CONMe_2$ (**2j**)	**3tj**	70[f]	> 20/1
10[d]	**1t**	R^4 = SO_2Ph (**2k**)	**3tk**	78[g]	> 20/1

[a] Reactions were run with **1** (0.30 mmol), **2** (2.0–2.2 equiv, pretreated with 2.0 equiv of NaH), $CoBr_2$ (1.0 mol%), dppp (1.0 mol%) and **4c** (0.10 mol%), $^iPr_2NEt$ (1.0 equiv) and MS4A (200 mg/mmol) in THF (0.2 M) at room temperature for 16 hours under blue LED irradiation unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] LiCl (1.0 equiv) was added. [d] $CoBr_2$ (5.0 mol%), ligand (5.0 mol%) and **4c** (0.50 mol%) were used. [e] dr = 1.0/1. [f] dr = 1.2/1. [g] dr = 1.5/1.

Among all these reactions, the regioselective alkylation of allyl sulfone **1u** deserves special attention. Allyl sulfones are synthetically valuable electrophiles due to their ambiphilic nature.[26] However, branch-selective substitutions of allyl sulfones remain highly challenging in metal-catalyzed allylic substitution reactions.[27,28] Indeed, a comparison of the reactivity of the catalytic alkylation with **1u** revealed that only the Co-catalyzed system delivered the branched product in high yield, while Rh[5a] or Ir[6a] catalysts afforded modest conversions and/or regioselectivity under the corresponding conditions (Table 4).

Table 4. Comparison of the reactivity using allyl sulfone **1u**[a]



1u **3aa**

Entry	Conditions (mol%)	Yield (%)[b]	b/l[b]
1	$CoBr_2$ (2.5), dppp (2.5), **4c** (0.25), $^iPr_2NEt$ (200), MS4A THF, rt, Blue LED	95 (91)[c]	> 20/1
2	$Rh(PPh_3)_3Cl$ (2.5), $P(OPh)_3$ (10) THF, 30 °C	28	6.1/1
3	$[Ir(cod)Cl]_2$ (1.25), $P(OPh)_3$ (5.0) THF, 30 °C	49	> 20/1

[a] See the Supporting Information for experimental details. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield.

Regarding the mechanism, substitution of an enantiomerically enriched electrophile (*S*)-**1e** (> 99% ee) occurred by an overall retention of configuration in reduced enantiopurity (40% ee), indicating competitive η^3-η^1-η^3 interconversion of the allylcobalt before addition of nucleophiles.[29] In addition, light/dark experiments supported our mechanistic hypothesis as well as the beneficial effect of the irradiation throughout the reaction.[29]

In summary, we have developed an organophotoredox-enabled Co catalyst system for allylic alkylation. This noble-metal-free[30] system exhibits uniformly high selectivity to afford branched products for a series of C-C bond forming reactions between allylic electrophiles and soft nucleophiles. In addition, the high reactivity for the branch-selective substitution of an allyl sulfone is highly characteristic for this catalytic system, representing the first Co-catalyzed allylic substitution reaction with unique synthetic utility compared to the related Rh- or Ir-catalyzed reactions. Investigations of enantioselective reactions[31] and comprehensive study of substrate scope are currently in progress in our group.

Acknowledgements

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Keywords: allylic substitution • photoredox catalysis • cobalt • sulfone • dual catalysis

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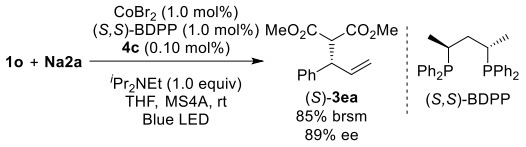

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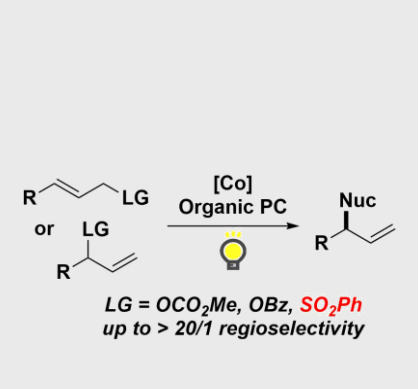
COMMUNICATION

Co-catalyzed allylic alkylation enabled by organophotoredox catalysis is described. In addition to its broad substrate scope and excellent regioselectivity, this noble-metal-free system exhibited unprecedented performance with respect to branch-selective substitution of an allyl sulfone. Thus, this study is the first representation of a unique synthetic utility of Co catalyzed allylic substitution compared to the related Rh- or Ir-catalyzed reactions.



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