Photoredox-Catalyzed Ketyl–Olefin Coupling for the Synthesis of Substituted Chromanols

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ABSTRACT: A visible light photoredox-catalyzed aldehyde olefin cyclization is reported. The method represents a formal hydroacylation of alkenes and alkynes and provides chromanol derivatives in good yields. The protocol takes advantage of the double role played by trialkylamines (NR₃) which act as (i) electron donors for reducing the catalyst and (ii) proton donors to activate the substrate via a proton-coupled electron transfer.

Carbon–carbon and carbon–heteroatom bond-forming reactions represent powerful transformations useful for the assembly of simple as well as sophisticated molecular architectures. Among the variety of established methods reported so far, the generation of ketyl radical species by the reductive umpolung reaction of carbonyl derivatives and their application in carbon–carbon bond-forming reactions represents an appealing route for the preparation of complex molecules. The ketyl–olefin coupling, as first described by Molander and Kenny,† was promoted by samarium diiodide as a stoichiometric single-electron reducing agent and enhanced by its large reduction potential (up to −2.05 V in the presence of HMPA).‡ Alternatively, organotin compounds as reducing agents have been used in either stoichiometric§,¶ or catalytic amounts,¶ in this case requiring an additional metal hydride. Other relevant procedures involve the use of zinc/trimethylamines (NR₃) which act as (i) electron donors for reducing the catalyst and (ii) proton donors to activate the substrate via a proton-coupled electron transfer.¹⁵

Knowles and co-workers reported a catalytic protocol in which ketones are successfully reduced to ketyl radicals by the concerted transfer of both a proton and an electron.¹⁶ This phenomenon is named proton-coupled electron transfer (PCET).¹⁵

In an attempt to demonstrate the active role of proton donors in the reduction step, Knowles and co-workers also reported an asymmetricaza-pinacol cyclization of ketones and hydrazones where the binding effect of the chiral phosphoric acids led to the formation of enantiomerically enriched vicinal amino alcohols.¹¹e

Recently, our group described the photoredox-catalyzed pinacol coupling of aldehydes, ketones, and aldimines through hydrogen-bonding activation.¹²a With this work, we disclose the possibility of generating a long-lived ketyl radical using tertiary amines as the electron and proton source, replacing the combination of Hantzsch ester and diphenyl phosphate (DPP).

Based on our previous work,¹²a we envisioned the possibility of performing the ketyl radical addition on unsaturated bonds triggered by visible light, which would initiate the single-electron reduction from a photoexcited polypyridyl iridium complex to a carbonyl group (aldehyde or ketone). We postulated that the so-generated radical intermediate would be able to undergo subsequent intramolecular addition to a pendant alkene or alkyn moiety (Scheme 1).

Herein, we report the realization of this activation mode in the context of a catalytic intramolecular reductive coupling of aldehydes with alkenes and alkynes. This transformation allows the synthesis of substituted 3-benzylchroman-4-ols (5), containing a chroman unit, that exhibit anti picornavirus...
activity, commonly responsible for the upper respiratory tract infections in humans.\(^\text{16}\)

Remarkably, we observed that tertiary amines not only provided the desired products in higher yields but also proved to be crucial for the reaction to proceed.

We began our studies by evaluating conditions for the cyclization of 2-(cinnamyloxy)benzaldehyde (1a) to chromanol 2a in the presence of Ir(ppy)_2(dtbbpy)PF_6 (PC_3, 1 mol %), trialkylamines 4a−c as reductive quencher (RQ), and irradiation with a blue LED light source (11W, \(\lambda_{\text{max}} = 450\) nm). As shown in Table S1 (Supporting Information), the reaction proceeded with good yield in the presence of 2.5 equiv of tributylamine (4b, entry 5). Solvent evaluation confirmed acetonitrile to be the best solvent, whereas aprotic (entries 1 and 2) and protic (entry 3) polar solvents were shown to be unsuccessful as reaction media. Further screening of electron donors in acetonitrile confirmed Hünig base (4c) to be the best among the trialkylamines tested, providing the desired product in 80% yield (entry 6). As previously mentioned, the use of Hantzsch esters 5a and 5b alone or in combination with 10 mol% of DPP did not lead to the expected product (entries 7−10).

A series of control experiments demonstrated that the reaction did not take place in the absence of light, catalyst, or additive. With the optimized conditions in hand (acetonitrile, rt, 1 mol % PC_3), we began to evaluate a variety of substrates (Table 1).

As shown in Table 1, the reaction tolerates a wide variety of substituents, confirming the ability of the ketyl radical to couple to the olefin in the presence of both electron-withdrawing and -donating groups on the aromatic aldehyde moiety.

Following the development of a successful formal hydroacylation we investigated the reaction in which the olefin was replaced by an alkyne group (Table 2). Also in this case, the reaction gave the expected products (2o and 2p) in good yields.

Regarding the reaction mechanism, we propose the following: Irradiation with visible light results in the formation of the reductive species Ir^{2+}. Hünig base (i-Pr_2NEt) acts as a sacrificial electron donor; therefore, the single-electron oxidation weakens the adjacent C−H bond\(^\text{17}\) and the 1,2-H-shift becomes energetically favored. The following deprotonation through the tertiary amine provides the ammonium derivative, which is now able to engage in a proton-coupled electron transfer with the substrate, lowering its potential for Ir^{2+} reduction and generation of a neutral ketyl intermediate. Alternatively, the ammonium radical could also activate the carbonyl functionality. The ketyl radical is able to add to the unsaturated bond, forming the chroman ring and a benzyl radical which upon hydrogen atom transfer leads to the final product (Scheme 2).

| Table 1. Scope of the Reaction\(^{a−c}\) |
|------------------------------------------|

\(^{a}\) All reactions of 1 (0.12 mmol) with DIPEA (0.3 mmol) were carried out in the presence of PC 3 (1 mol %) in acetonitrile (3.0 mL) under irradiation with blue LEDs (11 W, 450 nm) for 15 h at 25 °C. \(^{b}\) Isolated yields are reported. \(^{c}\) The dr is given for anti/syn ratio. \(^{d}\) Reaction performed using 2.5 mol% of photocatalyst.

\[\text{CONCLUSIONS}\]

In conclusion, we report a ketyl−olefin coupling for the preparation of substituted 3-benzylchroman-4-ols, promoted by visible light photoredox catalysis. Importantly, we uncovered trialkylamines as a cheap and readily available alternative to the previously reported electron−proton donor system consisting of Hantzsch ester/Bronsted acid. By employing the trialkyamine/photocatalyst system, we have been able to develop an efficient intramolecular ketyl−olefin and ketyl−alkyne coupling employing readily prepared substrates. The formal hydroacylation protocol provides the chromanol derivatives in good yield under mild reaction conditions and with low catalyst...
loadings. Efforts are currently underway to expand this concept to further transformations.

## EXPERIMENTAL SECTION

**General Information.** All reactions were performed with oven-dried glassware and under an inert atmosphere (argon) unless otherwise stated. Acetonitrile was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen/argon atmosphere. Other solvents were used as purchased without further purification. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Chromatographic purification of products was carried out using silica gel (gradient pentane/EtOAc 95:5). Thin-layer chromatography was carried out in the presence of PC (1 equiv), catalyst PC (3 or 2.5 mol %), and degassed DIPEA (2.5 equiv). It was capped, evacuated, and backfilled with argon. Subsequently, degassed acetonitrile (3 mL) was added via syringe. The vial was placed in a 100 mL beaker containing a blue LED strip glued on the inner wall, and the reaction mixture was stirred for 15 h. After this time, the solvent was evaporated, and the reaction mixture was purified on silica gel (gradient pentane/EtOAc 95:5).

### 3-Benzylchroman-4-ol (2a). The title compound was synthesized according to the general procedure employing 1a (0.12 mmol, 28.6 mg), 1 mol % (1.1 mg) of PC 3, and 2.5 equiv of DIPEA (38.8 mg). The product was purified by flash column chromatography: yield 80% (23 mg); δ (CDCl3) 7.36–7.19 (m, 14H), 6.94 (td, J = 7.5, 0.9 Hz, 1H), 6.90 (dd, J = 10.6, 4.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 4.51 (dd, dd, J = 9.4, 3.0 Hz, 2H), 4.23 (dd, J = 11.1, 2.6 Hz, 1H), 4.14–4.05 (m, 2H), 3.98 (dd, J = 11.1, 4.2 Hz, 1H), 2.89 (dd, J = 13.8, 8.4 Hz, 1H), 2.75–2.64 (m, 2H), 2.54 (dd, J = 13.8, 9.3 Hz, 1H), 2.40–2.29 (m, 1H), 2.28–2.17 (m, 1H), 1.92 (bs, 1H), 1.74 (bs, 1H); δ (CD3OD) 5.07 (s, 1H), 3.50 (dd, J = 6.0, 3.0 Hz, 2H), 3.01–2.86 (m, 2H), 2.40–2.26 (m, 2H), 2.27–2.17 (m, 1H), 1.92 (bs, 1H), 1.73 (bs, 1H); 13C NMR (151 MHz, CDCl3) δ 154.2, 139.1, 130.2, 129.9, 129.8, 129.1 (2C), 128.6, 128.5, 126.3 (2C), 124.1, 123.2, 120.9, 120.5, 116.9 (2C), 67.6, 64.9 (2C), 64.6, 41.5, 40.0, 34.6, 32.8; FT-IR ν max (ATR) cm$^{-1}$: 3372, 2922, 1582, 1485, 1450, 1401, 1328, 1287, 1171, 1074, 1039, 909, 748, 698; m/z (EI) 240 ([M]$^+$, 100), 91 ([PhCH$_3$]$^+$, 28); HRMS (ESI) calc’d for [C$_{16}$H$_{16}$O$_2$ + Na]$^+$ 263.10425, found 263.10419.

### 3-Benzyl-6-bromochroman-4-ol (2b). The title compound was synthesized according to the general procedure employing 1b (0.12 mmol, 38.1 mg), 2.5 mol % (2.74 mg) of PC 3, and 2.5 equiv of DIPEA (38.8 mg). The product was purified by flash column chromatography: yield 90% (28.6 mg); δ (CDCl3) 7.34–7.19 (m, 14H), 6.96 (td, J = 7.5, 0.9 Hz, 1H), 6.90 (dd, J = 10.6, 4.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 4.51 (dd, J = 9.4, 3.0 Hz, 2H), 4.23 (dd, J = 11.1, 2.6 Hz, 1H), 4.14–4.05 (m, 2H), 3.98 (dd, J = 11.1, 4.2 Hz, 1H), 2.89 (dd, J = 13.8, 8.4 Hz, 1H), 2.75–2.64 (m, 2H), 2.54 (dd, J = 13.8, 9.3 Hz, 1H), 2.40–2.29 (m, 1H), 2.28–2.17 (m, 1H), 1.92 (bs, 1H), 1.74 (bs, 1H); δ (CD3OD) 5.07 (s, 1H), 3.50 (dd, J = 6.0, 3.0 Hz, 2H), 3.01–2.86 (m, 2H), 2.40–2.26 (m, 2H), 2.27–2.17 (m, 1H), 1.92 (bs, 1H), 1.73 (bs, 1H); 13C NMR (151 MHz, CDCl3) δ 154.2, 139.1, 130.2, 129.9, 129.8, 129.1 (2C), 128.6, 128.5, 126.3 (2C), 124.1, 123.2, 120.9, 120.5, 116.9 (2C), 67.6, 64.9 (2C), 64.6, 41.5, 40.0, 34.6, 32.8; FT-IR ν max (ATR) cm$^{-1}$: 3372, 2922, 1582, 1485, 1450, 1302, 1264, 1222, 1119, 1074, 1039, 909, 748, 698; m/z (EI) 240 ([M]$^+$, 100), 91 ([PhCH$_3$]$^+$, 28); HRMS (ESI) calc’d for [C$_{15}$H$_{14}$BrO$_2$ + Na]$^+$ 271.01052, found 271.01199.

### General Procedure for the Synthesis of Chromanols. A Schlenk tube was charged with aldehyde 1 (1 equiv), catalyst PC 3 (1 or 2.5 mol %), and degassed DIPEA (2.5 equiv). It was capped, evacuated, and backfilled with argon. Subsequently, degassed acetonitrile (3 mL) was added via syringe. The vial was placed in a 100 mL beaker containing a blue LED strip glued on the inner wall, and the reaction mixture was stirred for 15 h. After this time, the solvent was evaporated, and the reaction mixture was purified on silica gel (gradient pentane/EtOAc 95:5).

### Table 2. Scope of the Intramolecular Ketyl–Alkyne Cyclization

| entry | prodct | yield (%) | E/Z |
|-------|--------|-----------|-----|
| 1     | Ar = m-MePh (2a) | 57 | 1:1 |
| 2     | Ar = p-OMePh (2p) | 59 | 1:1 |

"All reactions of 1 (0.12 mmol) with DIPEA (0.3 mmol) were carried out in the presence of PC 3 (2.5 mol %) in acetonitrile (3.0 mL) under irradiation with blue LEDs (11 W, 450 nm) for 18 h at 25 °C. Isolated yields are reported.

### Scheme 2. Plausible Reaction Mechanism
Brief Communication

3-Benzyl-6-fluorochroman-4-ol (2f). The title compound was synthesized according to the general procedure employing 1f (0.12 mmol, 37.7 mg), 1 mol % (1.1 mg) of PC 3, and 2.5 equiv of DPEFA (38.8 mg). The product was purified by flash column chromatography: yield 73% (25 mg); anti/ syn 1:1; 1H NMR (600 MHz, CDCl3) δ 7.36–7.14 (m, 10H), 6.95–6.77 (m, 6H), 4.48–4.47 (m, 2H), 4.29 (dd, J = 11.1, 2.7 Hz, 1H), 4.22 (ddd, J = 10.7, 3.7, 1.2 Hz, 1H), 4.15–4.04 (m, 6H), 2.88 (dd, J = 13.7, 8.4 Hz, 1H), 2.70 (dd, J = 14.0, 7.0 Hz, 1H), 2.48 (dd, J = 16.0, 9.3 Hz, 1H), 2.39 (dd, J = 16.0, 9.3 Hz, 1H).
3-Benzyl-6-methoxychroman-4-ol (2Q). The title compound was synthesized according to the general procedure employing I (0.12 mmol, 32.2 mg), 2.5 mol % (2.74 mg) of PC of 3C, and 2.5 equiv of Dipea (38.8 mg). The product was purified by flash column chromatography: yield 59% (17.7 mg); δ 1H (7.28–7.18 (m, 6H), 7.16–7.14 (m, 2H), 7.13 (s, 1H, syn); 4.14 (d, J = 11.0, 7.9 Hz, 1H, syn), 2.62–2.42 (m, 4H, 1H, syn), 2.14–2.03 (m, 1H, anti), 1.85–1.72 (m, 1H, anti), 1.48–1.39 (m, 1H, anti), 1.28–1.17 (m, 1H, anti), 1.24–1.21 (m, 1H, anti), 0.77–0.71 (m, 3H, 1H, syn); 3C NMR (100 MHz, CDCl3, δ 160.7 (2C), 155.2 (2C), 153.9, 153.1, 130.9, 128.9, 128.8, 128.0 (2C), 125.8, 125.7, 117.1, 115.6, 107.3, 106.8, 100.5 (2C), 66.3, 64.5, 64.2, 64.1, 54.3, 54.2, 42.0, 40.7, 34.2, 32.6; FT-IR νm (ATR) cm−1: 3215, 2960, 1767, 1677, 1494, 1366, 1221, 1092, 1032, 734; m/z (EI) 270 [M+], 15, 91 [PhCH2]+, 89; HRMS (EI) calcd for [C18H16O2]+ 280.1097, found 280.1096. 3-Benzyl-7-methoxychroman-4-ol (2K). The title compound was synthesized according to the general procedure employing I (0.12 mmol, 32.2 mg), 2.5 mol % (2.74 mg) of PC of 3C, and 2.5 equiv of Dipea (38.8 mg). The product was purified by flash column chromatography: yield 92% (29.8 mg); mp = 100–103 °C, C; ≈ 71; 1H NMR (400 MHz, CDCl3, δ 7.42–7.21 (m, 7H, syn), 7.20–7.12 (m, 6H, syn), 6.51 (d, J = 8.5, 2.5 Hz, 1H, anti), 5.44 (d, J = 8.5, 2.5 Hz, 1H, syn), 4.25, (d, J = 7.2, 1.7 Hz, 1H, anti), 4.15 (d, J = 11.0, 6.7 Hz, 1H, anti), 4.01–3.93 (m, 2H, syn), 3.89 (d, J = 11.0, 4.2 Hz, 1H, anti), 3.72 (s, 3H, anti), 3.69 (s, 3H, syn), 2.85 (d, J = 13.6, 7.4 Hz, 1H, syn), 2.66 (d, J = 13.7, 6.6 Hz, 1H, anti), 2.57 (d, J = 13.6, 8.0 Hz, 1H, syn), 2.46 (d, J = 13.7, 9.1 Hz, 1H, anti), 2.32–2.14 (m, 1H, syn), 2.14–2.03 (m, 1H, anti), 1.74–1.58 (m, 1H, anti); 13C NMR (100 MHz, CDCl3, δ 166.0 (2C), 152.5, 139.6, 139.5, 131.1, 130.9, 128.9, 128.8, 128.0 (2C), 125.8, 125.7, 117.1, 115.6, 107.3, 106.8, 100.5 (2C), 66.3, 64.5, 64.2, 64.1, 54.3, 54.2, 42.0, 40.7, 34.2, 32.6; FT-IR νm (ATR) cm−1: 3215, 2960, 1767, 1677, 1494, 1366, 1221, 1092, 1032, 734; m/z (EI) 270 [M+], 15, 91 [PhCH2]+, 89; HRMS (EI) calcd for [C18H16O2]+ 280.1097, found 280.1096.

3-Benzyl-4-ol (2M). The title compound was synthesized according to the general procedure employing I (0.12 mmol, 32.2 mg), 2.5 mol % (2.74 mg) of PC of 3C, and 2.5 equiv of Dipea (38.8 mg). The product was purified by flash column chromatography: yield 86% (32.7 mg); anti/syn 1:8.1; 1H NMR (600 MHz, CDCl3, δ 7.45 (d, J = 7.2 Hz, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.35–7.18 (m, 26.7H), 7.12–7.09 (m, 3H), 6.97–6.85 (m, 5.4H, 4H, 1H, syn), 4.41 (bs, 1H, anti), 4.27 (d, J = 11.2, 2.3 Hz, 1H, anti), 4.14–4.06 (m, 2H, syn), 4.00 (d, J = 10.8, 3.5, 1.5 Hz, 1H, syn), 3.96–3.93 (m, 1H, anti), 3.70 (d, J = 12.4, 1.8 Hz, anti), 2.91 (d, J = 11.9, 7.5, 3.2 Hz, 1H, syn), 2.79 (dq, J = 12.4, 2.3 Hz, 1H, syn), 2.00 (bs, 1H, anti), 1.80 (bs, 1H, syn); 13C NMR (151 MHz, CDCl3, δ 171.4 (2C), 142.7, 142.4, 142.3 (2C), 130.9, 130.5, 130.0, 129.9, 128.9 (2C), 128.8 (2C), 128.1 (2C), 127.9, 127.8, 126.8, 126.7, 126.6, 124.0, 122.5, 121.0, 120.5, 117.1, 116.9, 65.8, 64.1, 64.0, 63.1, 49.6, 42.9, 43.0, 41.9; FT-IR νm (ATR) cm−1: 3306, 2927, 2972, 1619, 1516, 1491, 1446, 1318, 1226, 1117, 1014, 972, 755; m/z (EI) 167 ([PhCH3]+), 59, 151 ([Me–Ph]+), 28; HRMS (EI) calcd for [C18H15O]+ 236.14578, found 236.14636.
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