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RESEARCH ARTICLE

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Radical Carbonyl Propargylation by Dual Catalysis

Huan-Ming Huang,[a] Peter Bellotti,[a] Constantin Daniliuc[a] and Frank Glorius[a]*

Dedicated to Professor Carsten Bolm on the occasion of his 60th birthday

[a] Dr. H.-M. Huang, Mr. P. Bellotti, Dr. C. Daniliuc and Prof. Dr. F. Glorius
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany
E-mail: glorius@uni-muenster.de

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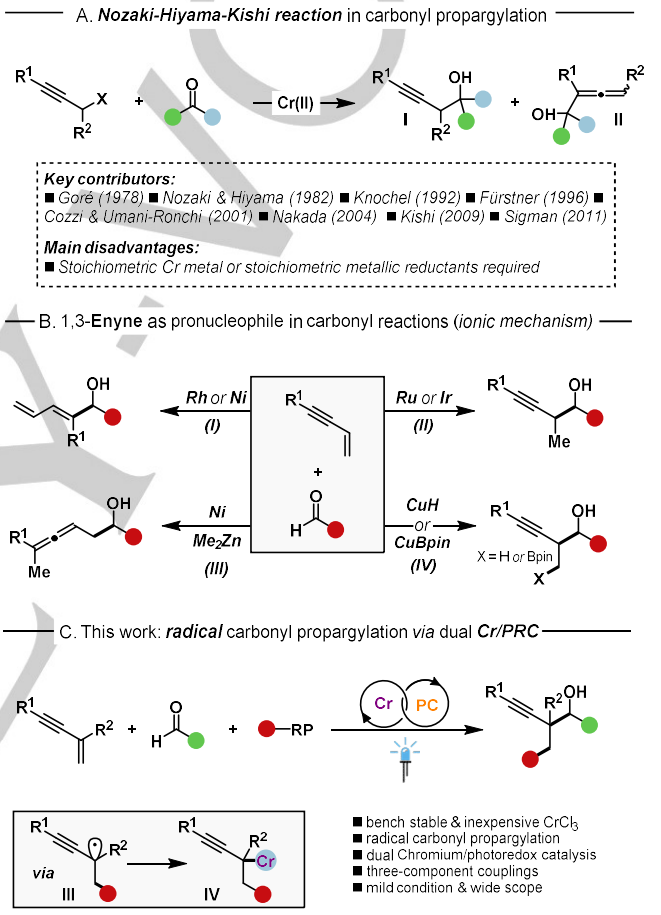
Abstract: Carbonyl propargylation has been established as a valuable tool in the realm of carbon-carbon bond forming reactions. The 1,3-enyne moiety has been recognized as an alternative pronucleophile in the above transformation through an ionic mechanism. Herein, we report for the first time the radical carbonyl propargylation *via* dual chromium/photoredox catalysis. A library of valuable homopropargylic alcohols bearing all-carbon quaternary centers could be obtained through a catalytic radical three-component coupling of 1,3-enynes, aldehydes and suitable radical precursors (*41 examples*). This redox-neutral multi-component reaction occurs under very mild conditions and shows high functional group tolerance. Remarkably, bench-stable, non-toxic and inexpensive $CrCl_3$ could be employed as a chromium source. Preliminary mechanistic investigations suggest a radical-polar crossover mechanism, which offers a complementary and novel approach towards the preparation of valuable synthetic architectures from simple chemicals.

Introduction

Addition reactions of organometallic reagents to carbonyls stand among the most fundamental chemical transformations and represent a pivotal synthetic strategy in organic chemistry since their discovery by Victor Grignard, who received the Nobel prize in 1912.[1] In this realm, carbonyl propargylation has been established as the most straightforward strategy to construct versatile homopropargylic alcohols.[2] Typically, organometallic reagents such as propargyl or allenyl metal species have to be used, thus hampering broad functional group compatibility and often requiring relatively harsh conditions.[2] Alternatively, low-valent metal-catalyzed (mediated) reductive carbonyl propargylation has become a popular class of methods.[2a] This reactive pattern is epitomized by the Nozaki-Hiyama-Kishi (NHK) reaction,[3] which has been widely explored since its discovery in 1977.[4] Thanks to the mild conditions and excellent functional group compatibility, Cr(II) mediated carbonyl propargylation has been widely investigated by Goré,[5] Nozaki & Hiyama,[6] Knochel[7] and others.[3] Fostered by the remarkable contribution in the development of catalytic NHK reactions by Fürstner and co-workers,[4d-e] Cozzi & Umani-Ronchi developed the first enantioselective chromium catalyzed carbonyl propargylation in 2000.[8] Later on, Nakada,[9] Kishi[10] and Sigman[11] further explored in this area in regard to ligand design[9,11] and total synthesis applications.[10] However, stoichiometric metallic reductants and additives could not be avoided in chromium catalyzed NHK reactions (Scheme 1A).[12]



Scheme 1. (A) Nozaki-Hiyama-Kishi reaction in carbonyl propargylation; (B) 1,3-Enyne as a pronucleophile in carbonyl reactions (ionic mechanism); (C) This work: radical carbonyl propargylation *via* dual Cr/photoredox catalysis.

1,3-Enynes have been widely employed as alternative pronucleophiles in the carbonyl addition chemistry (Scheme 1B).[13] Carbonyl dienylation could be successfully achieved when rhodium[14] or nickel[15] are employed as catalysts (Scheme 1B - route I). In 2008, Krische and co-workers reported the first example of reductive carbonyl propargylation using a ruthenium catalyst.[16a] Moreover, elegant examples of enantioselective enyne-mediated propargylation have also been successfully achieved (Scheme 1B - route II).[16b-c] In 2013, a Ni-catalyzed three-component coupling reaction of 1,3-enynes, carbonyls, and dimethylzinc to construct allenyl alcohols was reported by Kimura (Scheme 1B - route III).[17] Later on, the elegant cross coupling reactions between 1,3-enynes and carbonyls using a

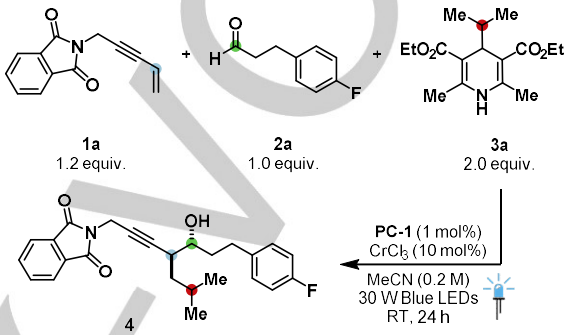
copper catalyst have been reported by Hoveyda[18a], Buchwald[18b] and others (Scheme 1B - route IV).[18c-g] 1,3-Enynes could also be used as radical acceptors to form substituted allene (1,4-adducts) or alkyne (1,2-adducts) derivatives.[19] However, catalytic radical carbonyl propargylation between 1,3-enyne and aldehyde remains an unmet challenge.[18g]

In recent years, dual catalytic manifolds have emerged as attractive tools to promote energetically unfavorable reaction steps and achieve synthetically valuable transformations under increasingly mild conditions.[20] Since 2018, our group,[21a-b] Kanai, Mitsunuma and co-workers[21c-d] have independently achieved allylation of aldehydes using dual photoredox and chromium catalysis.[21e] Compared to dual nickel/photoredox[20e-j] or copper/photoredox[20k-n] catalysis, dual chromium/photoredox catalytic mode is much less explored in synthetic chemistry, but provides a range of opportunities to achieve challenging radical-to-polar crossover-based transformations. While alkyl chromium species could also be generated,[22] propargyl chromium species have remained out of reach by means of this emerging dual catalytic system. Considering the paramount importance of NHK reactions in synthetic chemistry,[3] especially in the realm of total synthesis of natural products,[3c] we report an alternative way of generating propargylic radicals[23] using a chromium/photoredox dual catalytic manifold, achieving the catalytic radical carbonyl propargylation of aldehydes. The key step towards a successful process proved to be the selective generation of propargylic radical **III** by radical addition to 1,3-enynes, which was trapped by chromium to form intermediate **IV** (Scheme 1C). In fact, such three-component approach would enable rapid increase of complexity (two bonds formation) compared to the state of the art (Scheme 1B). Additionally, our strategy features easily accessible starting materials, tolerant reaction conditions and thus broad substrate scope.

Results and Discussion

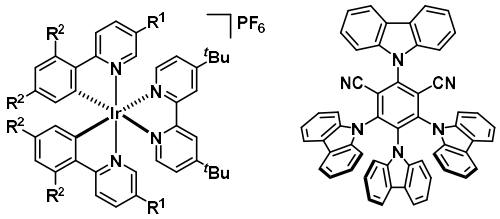
Reaction development. In analogy with previous reports from our group,[21b] we investigated the reaction of 1,3-enyne (**1a**), 3-(4-fluorophenyl)propanal (**2a**) and Hantzsch ester (**3a**, $E_{1/2}$ = 1.10 V *vs* SCE in MeCN)[24] (Table 1). After exploring different reaction conditions, the best results were accomplished with $CrCl_3$ (10 mol%), **PC-1** (1 mol%, $E_{1/2}(*Ir^{III}/Ir^{II})$ = 1.21 V *vs* SCE in MeCN) under irradiation with 450 nm light-emitting diodes (30 W blue LEDs), affording three-component coupling product **4** in 86% isolated yield with 74:26 dr (entry 1). Interestingly, when organic photoredox catalyst **4-CzIPN** ($E_{1/2}(*PC/PC^{\cdot-})$ = 1.35 V *vs* SCE in MeCN) was employed instead of **PC-1**, a comparable yield of **4** was obtained (entry 2). The use of an alternative Iridium-based photocatalyst **PC-2** ($E_{1/2}(*Ir^{III}/Ir^{II})$ = 0.66 V *vs* SCE in MeCN) or $CrCl_2$ instead of bench-stable and inexpensive $CrCl_3$ provided decreased yield (entries 3 and 4). Several common organic solvents have also been screened, revealing a moderate (1,4-dioxane and THF) to severe (DMF, acetone) detrimental influence on the yield of product **4** (entries 5-8). Predictably, control experiments showed that all the reaction components were necessary to achieve this radical three-component carbonyl propargylation coupling (entries 9-11). Additionally, a condition-based sensitivity screening demonstrated that the process can tolerate wet solvents, higher reaction temperatures and even scale-up (3.0 mmol) with minimal to negligible effect on the yield. Furthermore, commercially available dry solvents could be used under inert atmosphere without the need of additional degassing, thus simplifying the operational set-up (medium O_2). On the other hand, the absence of inert atmosphere, low light intensity and reduced temperature caused a significant decrease in yield (see radar diagram in Table 1).[25]

Table 1. Reaction optimization for radical carbonyl propargylation[a]



Entry	*Deviation from standard conditions*	*Yield %*[b]
1	none	**95 (86)**[c]
2	**4CzIPN** instead of **PC-1**	98 (87)[c]
3	**PC-2** instead of **PC-1**	54
4	$CrCl_2$ instead of $CrCl_3$	50
5	THF as solvent	66
6	1,4-dioxane as solvent	75
7	DMF as solvent	30
8	Acetone as solvent	39
9	No **PC-1**	0
10	No $CrCl_3$	0
11	No light	0

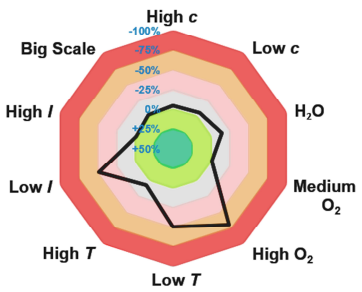
Photocatalysts



PC-1 (R^1=CF_3, R^2=F)
PC-2 (R^1=R^2=H)

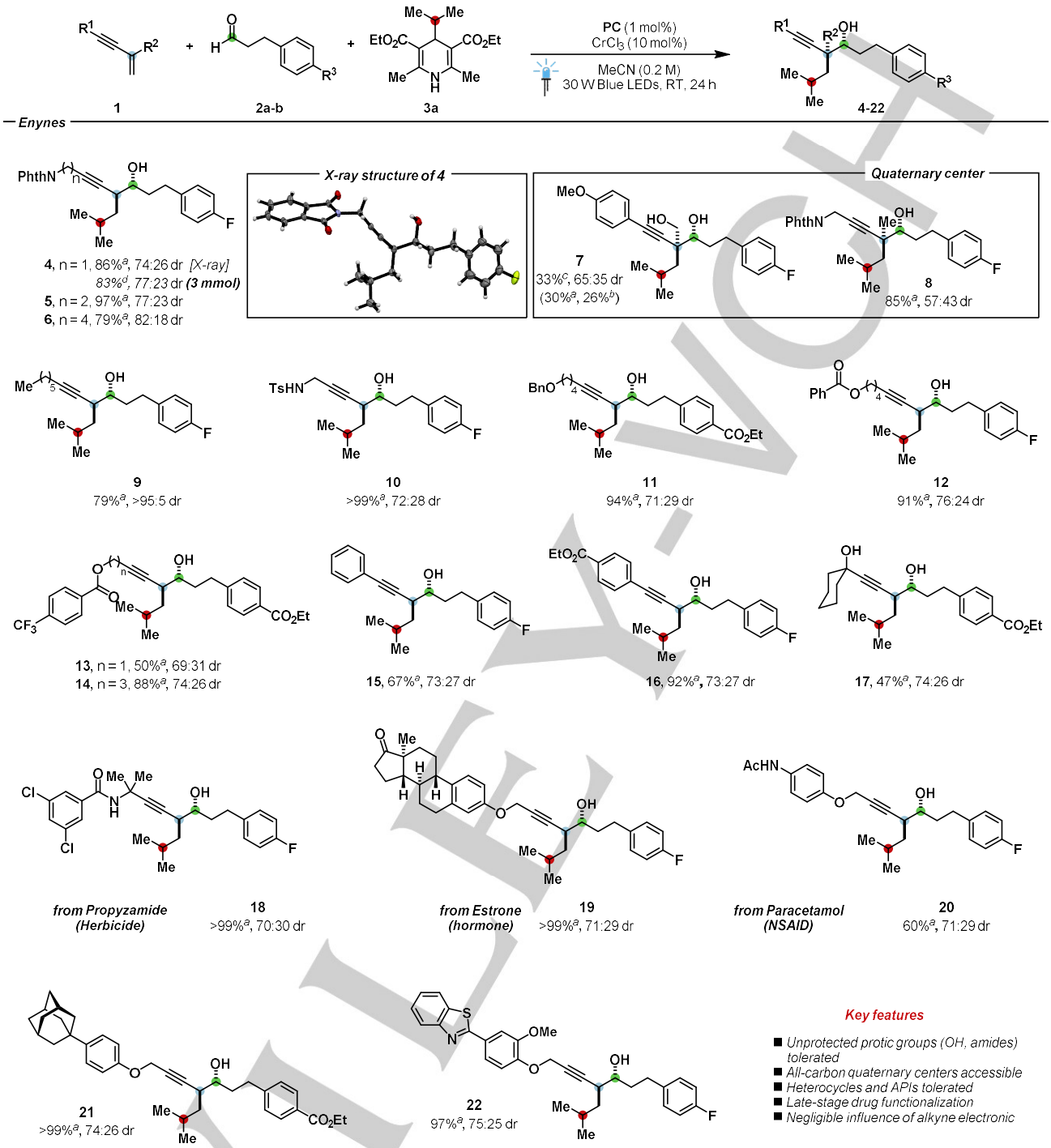
4CzIPN (PC-3)

Sensitivity screening

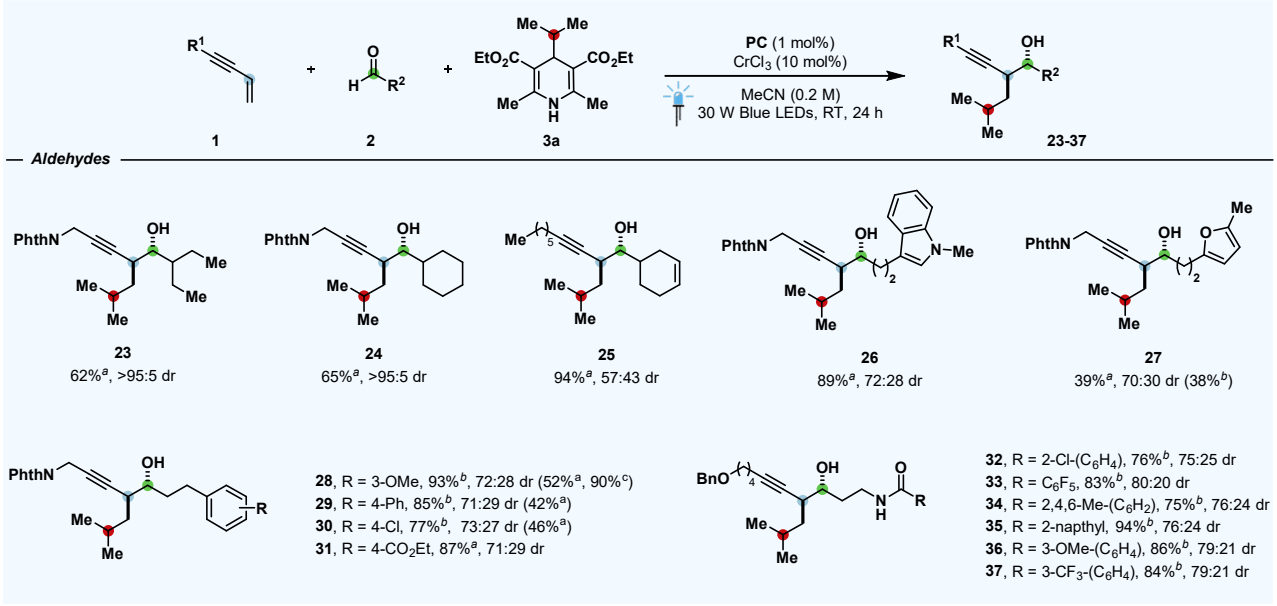


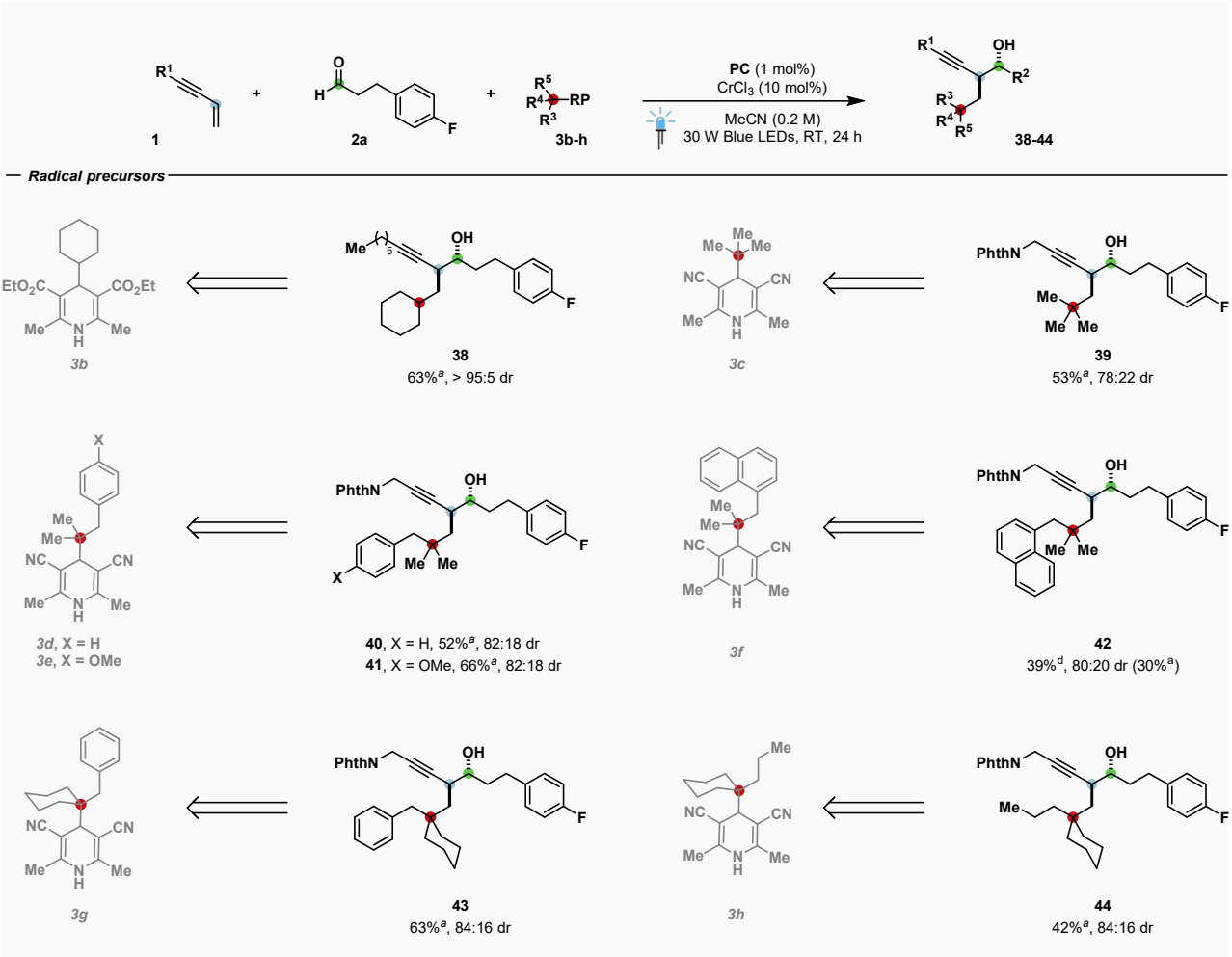
[a] Optimization of the reaction conditions: **1a** (0.24 mmol, 1.2 equiv.), **2a** (0.2 mmol, 1.0 equiv.), **3a** (0.4 mmol, 2.0 equiv.), **PC-1** (1 mol%), $CrCl_3$ (10 mol%) in MeCN (1 mL, 0.2 M) at room temperature under irradiation of 30 W blue LEDs with a cooling fan for 24 hours. [b] ^{19}F NMR yields were determined using fluorobenzene as internal standard. [c] Yields of isolated product, the diastereoisomeric ratio of product **4** is 74:26.

Reaction scope. With these results in hand, we investigated the generality of our three-component coupling with respect to different 1,3-enynes (Scheme 2). By varying the tethering length between the alkyne and phthalimido moiety, the desired products were obtained in good to excellent yields (**4-6**) and comparable levels of diastereoselectivity. Delightfully, the decrease of the radical precursor **3a** excess (see 3.0 mmol scale reaction) did not significantly impact the yield of product **4**, therefore allowing the minimization of the waste-stream. Remarkably, the reaction proved suitable for the synthesis of highly sterically congested quaternary centers (**7**, 33%) even in excellent yields (**8**, 85%). In the former case, free alcohols were tolerated, thus making the protocol suitable to generate highly decorated 1,3- (**7**) or remote diols (**17**) without the need for protective groups. In addition to long aliphatic chain derivatives (**9**), both tosylamides (**10**) and the 1,3-enyne synthesized from the herbicide propyzamide (**18**) yielded the desired products in quantitative yield. Benzyl ethers (**11**), as well as esters (**12-14**, **16**) ranging from trifluoromethyl decorated ones (**13**, **14**) to simple ethyl derivatives (**16**) smoothly afforded the desired coupling products. A variety of aryl ethers containing functional groups spanning from natural product and drugs such as estrone (**19**) and paracetamol (**20**) derivatives, adamantane (**21**) and benzothiazole (**22**) have been successfully coupled in yields ranging from 60% (**20**) to quantitative (**19, 21**), thus proving the inertness of enolizable moieties (**19, 20**) and heterocycles (**22**). Finally, these examples (**4-22**) testify that our protocol is insensitive towards the alkyne substitution, which could vary from aryl (**7**, **15**, **16**) to α-heteroatom (**4**, **8**, **10**, **13**, **17-22**) and aliphatic (**5**, **6**, **9**, **11**, **12**, **14**). The relative stereochemistry of the major diastereoisomer was confirmed by single-crystal X-ray analysis of a suitable specimen of **4**, which showed an *anti* stereochemistry between the alcohol and the appended isobutyl substituent.[26] We then evaluated the three-component manifold in the propargylation of a set of different aldehydes (**23-37**, Scheme 3, upper), which further corroborated the notion of functional group tolerance of our protocol. Both acyclic (**23**) and cyclic (**24-25**) aliphatic aldehydes afforded the desired product in moderate to excellent yields (62-94%), even in the presence of alkenes (**25**). Pleasingly, electron-rich aromatics such as indole (**26**) and furan (**27**) were tolerated, despite in the latter case the lability of the heterocyclic system deemed responsible for the reduced yield (39%). An array of 3-phenylpropanal derivatives (**28-31**) bearing both electron-donating (**28**, **29**) and -withdrawing (**30**, **31**) groups at different positions of the aromatic ring delivered the product in good to excellent yields (77-93%). Further showcasing the compatibility of the protocol with many functional groups, ranging from halides (**32**) to polyfluorinated arenes (**33**), we explored a set of aldehydes bearing variously substituted benzamides (**32-37**), which successfully yielded the corresponding propargylated products. Furthermore, these examples were performed employing **4CzIPN** instead of **PC-1** as photocatalyst, thus avoiding the use of precious iridium metal. Additionally, different radical precursors were investigated with the optimized conditions (**38-44**, Scheme 3, lower). Notably, Hantzsch nitriles (**3c-h**) could be successfully employed in our dual catalytic system and a variety of homopropargylic alcohols containing all-carbon quaternary centers (**39-44**) could be obtained in good yields. Different scaffolds such as cycloalkyl (**38**, **43**, **44**), aliphatic (**39**), phenyl (**40**, **41**, **43**), naphthyl (**42**), and methoxy (**41**) groups could all be tolerated in this three-component coupling. Unfortunately, when 4-primary alkyl-1,4-dihydropyridines – such as 4-phenethyl-1,4-dihydropyridine – were used as radical precursors, the desired product could not be obtained. According to the recent report by Molander and co-workers, the corresponding dihydropyridines (DHPs) do not undergo homolytic C−C cleavage but rather C−H homolysis, resulting in the formation of 4-alkylated pyridine byproducts.[24e] Additionally, acyl and carbomoyl radical DHPs sources have been tested according to the recent reports by Melchiorre and co-workers,[24f,g] but failed to afford any product under our standard reaction conditions.



Scheme 2. Scope with respect to 1,3-enynes. [a] **Reaction condition A**: 1,3-enyne **1** (0.24 mmol, 1.2 equiv.), aldehyde **2** (0.2 mmol, 1.0 equiv.), **3a** (0.4 mmol, 2.0 equiv.), **PC-1** (1 mol%), $CrCl_3$ (10 mol%) in MeCN (1 mL, 0.2 M) at room temperature under irradiation of 30 W blue LEDs with a cooling fan for 24 hours. [b] **Reaction condition B**: Reaction condition A was used, but **4-CzIPN** replaced **PC-1**. [c] **Reaction condition C**: aldehyde (0.4 mmol, 2.0 equiv.) and 1,3-enyne (0.2 mmol, 1.0 equiv.) were used under reaction condition A. [d] Reaction condition B was employed and **3a** was reduced (1.5 equiv. instead of 2.0 equiv.).

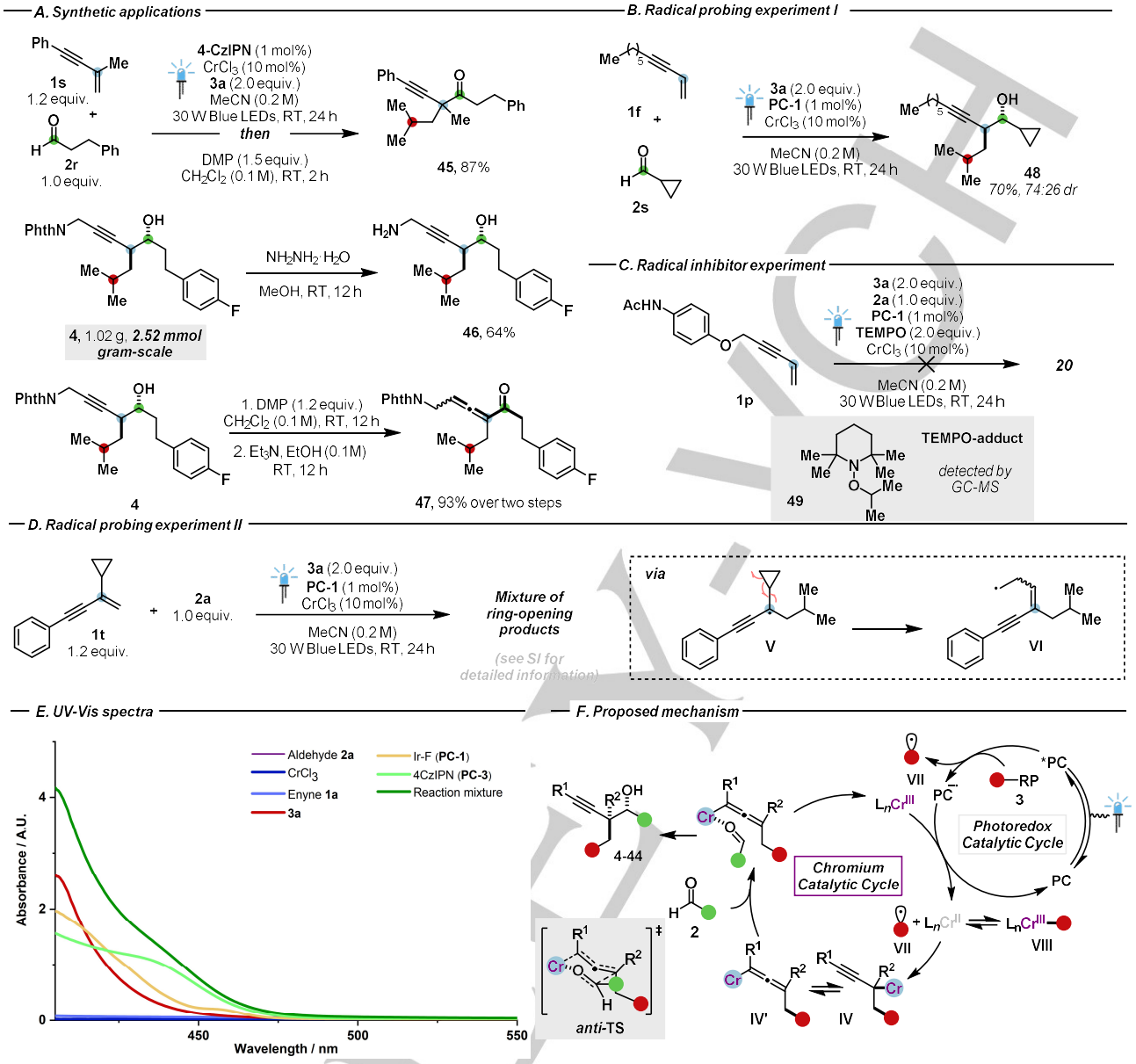




Scheme 3. Scope with respect to aldehydes and radical precursors. [a] **Reaction condition A**: 1,3-enyne **1** (0.24 mmol, 1.2 equiv.), aldehyde **2** (0.2 mmol, 1.0 equiv.), radical precursor **3** (0.4 mmol, 2.0 equiv.), **PC-1** (1 mol%), $CrCl_3$ (10 mol%) in MeCN (1 mL, 0.2 M) at room temperature under irradiation of 30 W blue LEDs with a cooling fan for 24 hours. [b] **Reaction condition B**: **4-CzIPN** was used instead of **PC-1**. [c] **Reaction condition C**: aldehyde (0.4 mmol, 2.0 equiv.) and

1,3-enyne (0.2 mmol, 1.0 equiv.) under reaction condition A. [d] **Reaction condition D**: Reaction condition A was employed and MeCN (1.0 mL, 0.2 M) was replaced with MeCN:DMF 2:1 (1.2 mL 0.17 M).

Applications and Preliminary Mechanistic Investigation. Our methodology towards homopropargylic alcohols offers a straightforward platform to access motifs such as homopropargylic ketones and propargylated amines, which are key motifs in many drugs (*e.g*. Oxybutynin and oxotremorine). Delightfully, homopropargylic ketone **45** could be obtained in 87% yield through this three-component coupling reaction and sequential simple oxidation in one step. Additionally, the free propargylic amine product **46** could be obtained in 64% yield through the straightforward Ing-Manske procedure, without the need of chromatographic purification (Scheme 4A). We envisaged that homopropargylic alcohols can offer a gateway towards α-allenyl ketones and alcohols, which are highly prevalent scaffolds in carotinoids and terpenoids natural products (*e.g.* Mimulaxanthin or Icariside B_1).[27] Indeed, straightforward oxidation-isomerization sequence delivered the allene **47** in high yield, thus testifying the feasibility of our protocol towards its utilization in synthetic endeavors. To shed light on the possible reaction mechanism, cyclopropanecarboxaldehyde (**2s**) was subjected to the optimized reaction conditions, product **48** was obtained in good yield and no cyclopropane ring opening was observed, speaking against the intermediacy of ketyl radical intermediates in the coupling process, in addition to unfavorable redox potentials (Scheme 4B).[28] Additionally, the radical scavenger TEMPO (2 equivalents) was added to the standard reaction, causing the disturbance of the catalytic manifold (desired product **20** could not be detected), while *i*Pr-TEMPO adduct **49** was detected (Scheme 4C). This suggests that the reaction may proceed through a radical-based mechanism. We also synthesized 1,3-enyne **1t** containing a three membered ring, which delivered – under the optimized conditions – a mixture of ring-opening products arising from intermediate **V** collapsing toward radical intermediate **VI** (Scheme 4D), therefore unequivocally suggesting the intermediacy of propargyl radicals. Finally, UV-visible (Scheme 4E) and Stern-Volmer experiments (see supporting information for details) were performed and the results clearly show that only the photoredox catalyst (either **PC-1** or **4-CzIPN**) absorbs visible light in the reaction system and the photoluminescence can be quenched exclusively by Hantzsch ester **3a**. Based upon these preliminary mechanistic results and our previous study,[21b] we propose that alkyl radical **VII** is generated from a suitable radical precursor following reductive quenching of the photoexcited **PC-1** or **4-CzIPN** (Scheme 4F). Then the $L_nCr(III)$ species is reduced *in situ* to $L_nCr(II)$ ($E_{1/2}$ = −0.65 V *vs* SCE in H_2O, $E_{1/2}$ = −0.51 V *vs* SCE in DMF)[77] by the reduced photocatalyst $PC^{\cdot-}$ (for instance, organic dye **4CzIPN**, $E_{1/2}$ ($PC/PC^{\cdot-}$) = −1.21 V *vs* SCE in MeCN;[29] **PC-1**, $E_{1/2}(Ir^{II}/Ir^{III})$ = −1.37 V *vs* SCE in MeCN[30]). The alkyl radical **VII** could either reversibly add to a low-valent $L_nCr(II)$ species to form the resting state Cr(III)-alkyl complex **VIII** or add to 1,3-enynes to generate a propargylic radical in equilibrium with its allenyl equivalent. After radical capture by the $L_nCr(II)$ species, propargylic Cr(III) intermediate **IV** and allenic species Cr(III) **IV'** are generated. Interestingly, when attempting to obtain macrocyclic alcohols using a designed 1,3-enyne containing an aldehyde functional group in the end through cascade reaction by dual chromium/photoredox catalysis, no macrocyclization could be observed. Instead, we obtained a mixture of acyclic alkyne and allene radical addition products, which suggest the existence of intermediates **IV** and **IV'** (see supporting information for details). Finally, either **IV** or **IV'** can react with suitable aldehydes **2** to yield the final homopropargylic products (**4**-**44**) through an *anti*-transition state, which accounts for the observed diastereoselectivity. The reduced diastereoselectivity of the process upon reacting polysubstituted enynes (**8,** 57:43 dr) can be tentatively ascribed to the lowered energetic difference between the *anti*- and *syn*-transition states due to increased steric demand of the substituents (see supporting information for details).



Scheme 4. Preliminary Mechanistic Investigation. A. Synthetic application; B. Radical probing experiment I; C. Radical inhibitor experiment; D. Radical probing experiment II; E. UV-Vis spectra. Reaction mixture refers to Table 1 – entry 2; F. Proposed mechanism. DMP = Dess-Martin Periodinane; TEMPO = (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl.

Conclusion

In summary, we have demonstrated for the first time a mild and scalable radical carbonyl propargylation *via* dual chromium/photoredox catalysis with excellent functional group tolerance. This redox-neutral method provides an alternative strategy to carbonyl propargylation chemistry, enabling the generation of a library of homopropargylic alcohols bearing highly congested structures in good to excellent yields. Preliminary mechanistic studies are suggestive of a radical-polar crossover mechanism through the intermediacy of either propargyl- or allenyl-Cr(III) species. We anticipate that this strategy along with other reports will serve as an innovative multi-component reaction and will inspire chemists to revisit the synthetic potential of organochromium chemistry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: radical-polar • carbonyl • propargylation • dual catalysis • chromium

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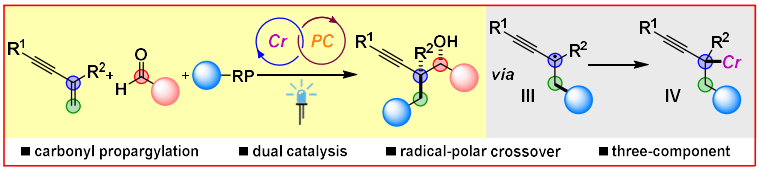

Herein, we report for the first time the radical three-component carbonyl propargylation between 1,3-enynes, aldehydes and suitable radical precursors *via* dual chromium/photoredox catalysis. This redox-neutral reaction occurs under very mild conditions, shows high functional group tolerance and represents a complementary novel approach for preparing valuable synthetic architectures from simple chemicals.

Institute and/or researcher Twitter usernames: @GloriusGroup