Remote Nickel Catalyzed Cross Coupling Arylation via PCET enabled C-C Bond Cleavage

Long Huang,[1,*] Tengfei Ji[1] and Magnus Rueping[1,2,*]

‡King Abdullah University of Science and Technology (KAUST), KAUST Catalysis Center (KCC), Thuwal 23955-6900, Saudi Arabia

†Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

KEYWORDS. Nickel catalysis, C-C bond cleavage

ABSTRACT: Cross coupling reactions for carbon-carbon and carbon-heteroatom bond formation are of great importance in modern chemical synthesis. In addition to classical cross couplings involving preformed or preactivated coupling partners, more recently breakthroughs have been made in the selective, direct coupling of abundant aliphatic carbon-hydrogen bonds using hydrogen atom transfer reactions in which the bond dissociation energy is the thermodynamic driving force. The more challenging carbon-carbon bond activation is still rather underdeveloped due to the bond inertness. Herein, we report a mild and general strategy for the activation of a diverse set of readily available cyclic alcohols for the remote and site-specific arylation of ketones via the combination of photoredox-mediated multi-site concerted proton-electron transfer (MS-PCET) and nickel catalysis. The current cross coupling proceeds with the generation of an alkoxy radical utilizing bond dissociation free energy (BDFE) as the thermodynamic driving force. Subsequently, the resulting remote carbon-centered radicals formed by C-C cleavage merge with the nickel catalytic cycle to create the challenging $C(sp^3)$-$C(sp^2)$ bonds.

■ INTRODUCTION

The cleavage of C-C bonds and subsequent functionalization by heterogeneous transition metal catalysis are particularly important for the large scale production of organic molecules and materials that are derived from non-renewable raw materials such as petroleum and natural gas.[1,2] In homogeneous catalysis, the immense scientific and commercial value of catalytic C-C bond activation is reflected in simplifying the synthetic routes for assembling complex molecules.[3-7] However, due to the challenges in activating kinetically inert and thermodynamically stable C-C single bonds, the activation of C-C bonds remains largely underexplored. One of the most common strategies to facilitate C-C bond activation is the utilization of strained molecules with ring-strain as the thermodynamic driving force (Fig. 1A).[8] Although powerful and broadly employed, its generality is limited to 3- and 4-membered ring compounds. In contrast, a mild and widely applicable solution to the long-standing challenge of C-C bond cleavage of unstrained molecules remains elusive.

Ketones are common structural features in many natural products, pharmaceuticals, organic materials, agrochemicals and small molecules of medicinal interest.[9-11] As such, a central goal in organic synthesis is the development of novel methodologies for their elaboration. In this context, substantial efforts have been devoted to the functionalization of the electrophilic *ipso* position as well as the acidic α-position of ketones. In stark contrast, efforts to develop ketone remote site functionalization have been met with only limited success.[12,13] Moreover, among the approaches developed, the location of new bond formation relative to the carbonyl group is strictly defined. Recently, the ring opening of less or none strained cycloalkanols has emerged as an alternative powerful strategy for the ketone remote sites halogenation and amination.[14-16] Despite these advances, a general solution to the remote sites arylation[17] of ketone, possessing high functional group tolerance, from readily accessible starting materials would be useful but remains to be developed.

Proton-coupled electron transfer (PCET) reactions have been shown to play a central role in the development of a wide range of chemical transformation and biological metabolism.[18,19] Recently, increased attention has been paid to their applications in organic synthesis.[20-24]

Fig. 1. Reaction development. (A) 1. Strain-releasing C-C bond cleavage of small rings (3- or 4-membered) is well precedented, however, the ring opening of unstrained molecules is elusive due to the lack of driving force; 2. Current protocol with the use of BDFE as driving force for ring-opening of various sizes (B) Mechanistic proposal for the MS-PCET enabled C-C cleavage / cross coupling *via* dual photoredox nickel catalysis.

A distinct advantage for PCET is that unprecedented types of reactivity are often observed in comparison with conventional hydrogen atom transfer (HAT) reactions. Recent developments showed that PCET can be used to promote the C-C bond cleavage of tertiary alcohols under photoredox catalysis.[24] Thus alkyl radicals generated in this manner could in principle be merged with a nickel catalytic cycle affording a novel platform to create challenging $C(sp^3)$-$C(sp^2)$ bonds.[25]

Notably, the combination of a PCET catalytic cycle, capable of generating carbon-centered radicals *via* photo-reductive quenching, with a nickel catalytic cycle would enable the distal site-selective coupling of ketones with electrophilic coupling partners.[26-30] Such a combination proved recently successful in the amidoarylation of unactivated olefines.[31]

Owing to their highly oxidizing ability, the acridinium derived organo-photosensitizers have been successfully used to generate several classes of arene cation radicals from aromatic motifs employed commonly in the pharmaceutical development.[32-36] We therefore decided to test them as photooxidants in our desired transformation. The envisioned cross coupling with a detailed mechanism is depicted in Fig. 1B. Upon irradiation with visible light, the ground-state of **Mes-Acr-Me⁺** is promoted to its highly oxidizing singlet excited state ***Mes-Acr-Me⁺**, which undergoes a single electron transfer with the tertiary alcohol, furnishing the corresponding arene radical cation along with the reduced form of the photocatalyst **Mes-Acr-Me•**. Subsequent deprotonation (PT) and intramolecular ET reaction between the alkoxide and the radical cation would give the key alkoxyl radical species[37-43] which readily cleaves into a carbonyl moiety and a distal carbon-centered radical through scission of the neighboring C-C bond at β-position. The alkyl radical is then captured by the Ni (0) and gives an alkylnickel(I) intermediate which is expected to rapidly undergo oxidative addition with an aryl halide, generating a Ni(III) species. Reductive elimination at this stage would deliver the cross-coupled product and the Ni(I) intermediate, the latter can be reduced by the reduced form of the photocatalyst and regenerate both simultaneously, thus completing the catalytic cycle.

Photocatalyst	$E_{1/2}(\ast P/P^-)$, V vs SCE	ΔG_{ET} (kcal/mol)	Yield [%]
PC1	+ 0.77	19.1	0
PC3	+ 1.21	9.0	0
PC2	+ 1.35	5.8	0
PC4	+ 1.68	-1.8	22
PC5	+ 2.06	-10.6	86
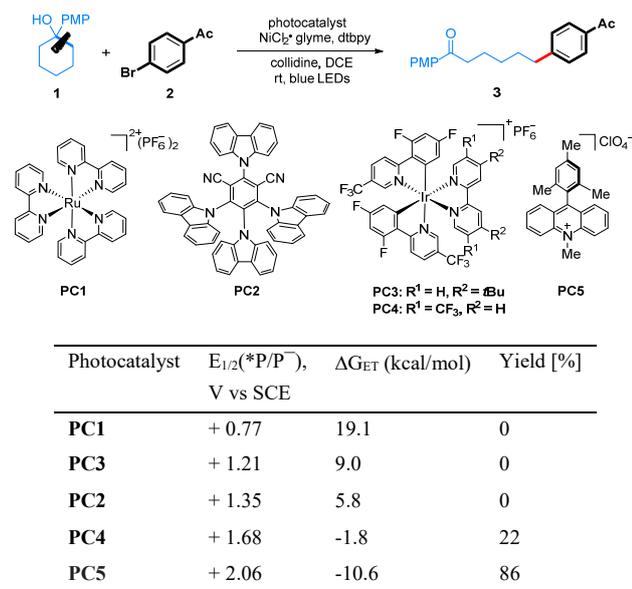
Fig. 2. Effect of photocatalyst on thermodynamics of single electron oxidation of **1** ($E_{p/2}$ = 1.57 V vs SCE).

■ RESULTS AND DISCUSSION

To determine whether our designed combined catalysis is feasible, we began our investigations into the proposed PCET enabled cross coupling using cyclohexanol **1** and 4-bromoacetophenone (**2**) as model substrates. We found that the desired $C(sp^3)$-$C(sp^2)$ bond could be forged in excellent yield (86%) in the presence of Mes-Acr-Me⁺, NiCl₂•glyme (glyme = ethylene glycol dimethyl ether), 4,4'-di-tert-butyl-2,2'-bipyridine (dtbbpy), and 2,4,6-collidine in 1,2-dichloroethane (DCE) at room temperature upon irradiation with blue LEDs for 48 h (Fig. 2). Evaluation of different photocatalysts indicated that the yield of **3** strongly correlates with the endothermicity of the requisite electron transfer step (Fig. 2). Lowering the photocatalyst loading led to a decrease of the yield; this result being attributed to the degradation of the catalyst chromophore over the reaction course. It should be noted that the presence of the free hydroxyl group in the substrate is fully compatible with the current dual photoredox nickel catalysis, with no detection of aryl ether product during the overall optimization implying the dominating role of steric hindrance.[44] Furthermore, control experiments without the photocatalyst, nickel catalyst, ligand, base or visible light irradiation all gave no conversion (Table S2), emphasizing the essential role of all components in this catalytic system.

Encouraged by these results, we evaluated a range of electrophilic coupling partners and found the scope to be broad. As summarized in Fig. 3, substrates bearing a variety of electron-deficient substituents in the *para*-position, such as ketone, ester, aldehyde, trifluoromethyl, nitrile, chlorine, bromine, sulfone and sulfonamide were well tolerated and provided the desired products in good to excellent yields (57-97%, **3-12**). Gratifyingly, less reactive electron-rich and -neutral bromoarenes are suitable substrates, delivering distally arylated ketone products in moderate to good yields (46-81%, **13-17**). Ortho and meta-monosubstituted as well as disubstituted aryl bromides were found to be competent substrates in this transformation, demonstrating the diversity of substituents that can be tolerated (81-98%, **18-20**). Notably, the efficiency of the reaction was not hampered when bicyclic aromatics such as phthalide, naphthalene and phthalimide were employed (72-86% yields, **21-23**). With respect to heteroaromatic systems, a variety of heteroaromatic substrates could be readily used, regardless of the position as well as electronic nature of the substituents. Specifically, six-membered bromopyridine and bromopyrimidine all gave good to excellent yields (63-96% yields, **24-30**). Moreover, heteroaryl bromides bearing N-Boc-indole and quinoline moieties proved to be suitable coupling partners, affording the corresponding arylated products in synthetic useful yields (38% and 67%, **31** and **32** respectively). Next, we demonstrated the synthetic potential of this method for the late-stage functionalization of structurally diverse pharmaceutical relevant substances, including celecoxib and diacetone-D-galactose derivatives which were well tolerated (71% and 84% yields, **33** and **34**). To further showcase the synthetic utility of this method, a 4 mmol scale-up reaction was performed with lower Ni and ligand loadings. The reaction proceeded smoothly to afford the desired product **8** in 77% yield. Finally, we were pleased to find that aryl iodides were effective latent electrophiles for this coupling, affording the corresponding arylated products in moderate yields (51% and 64%, **4'** and **15'** respectively).
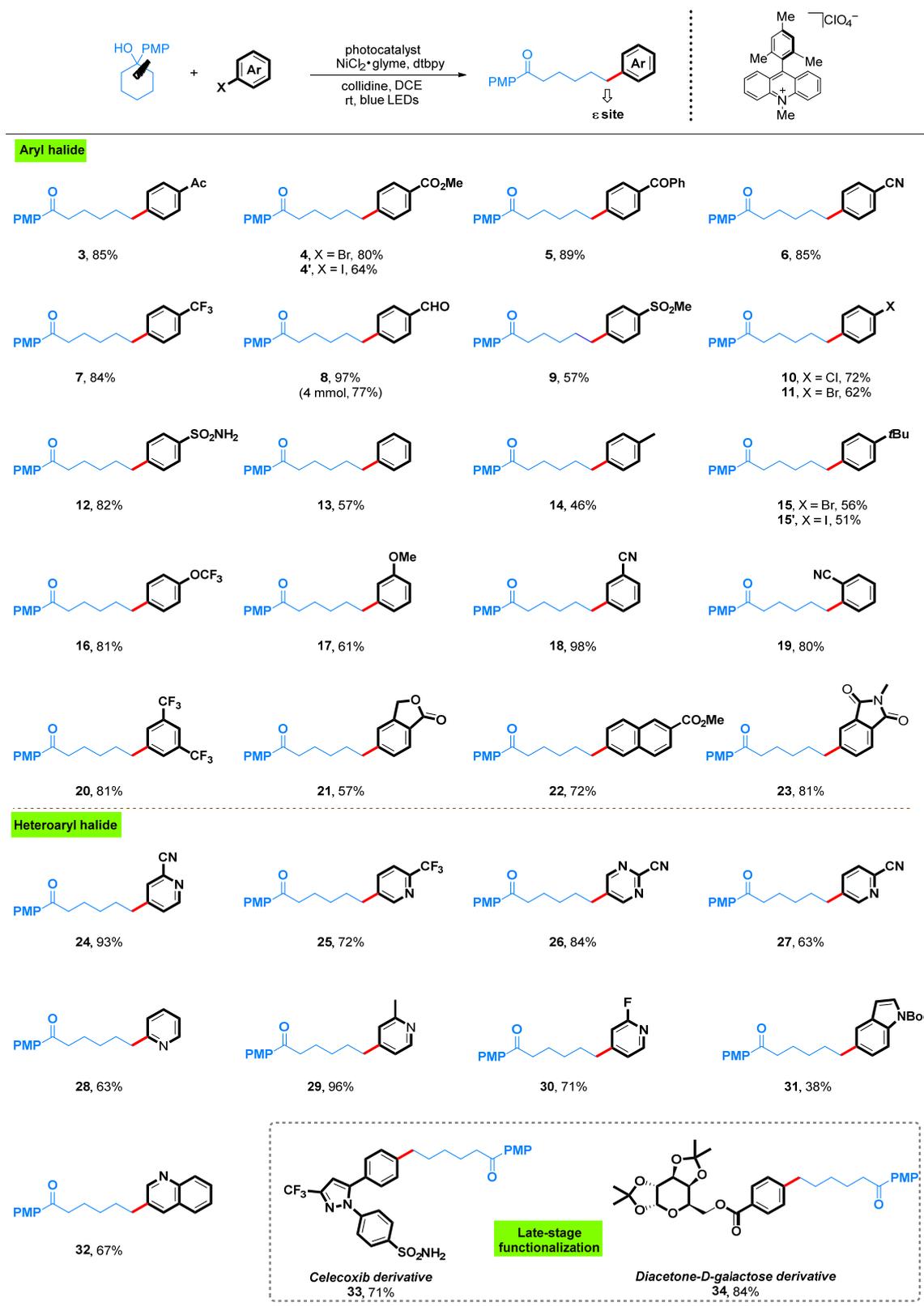
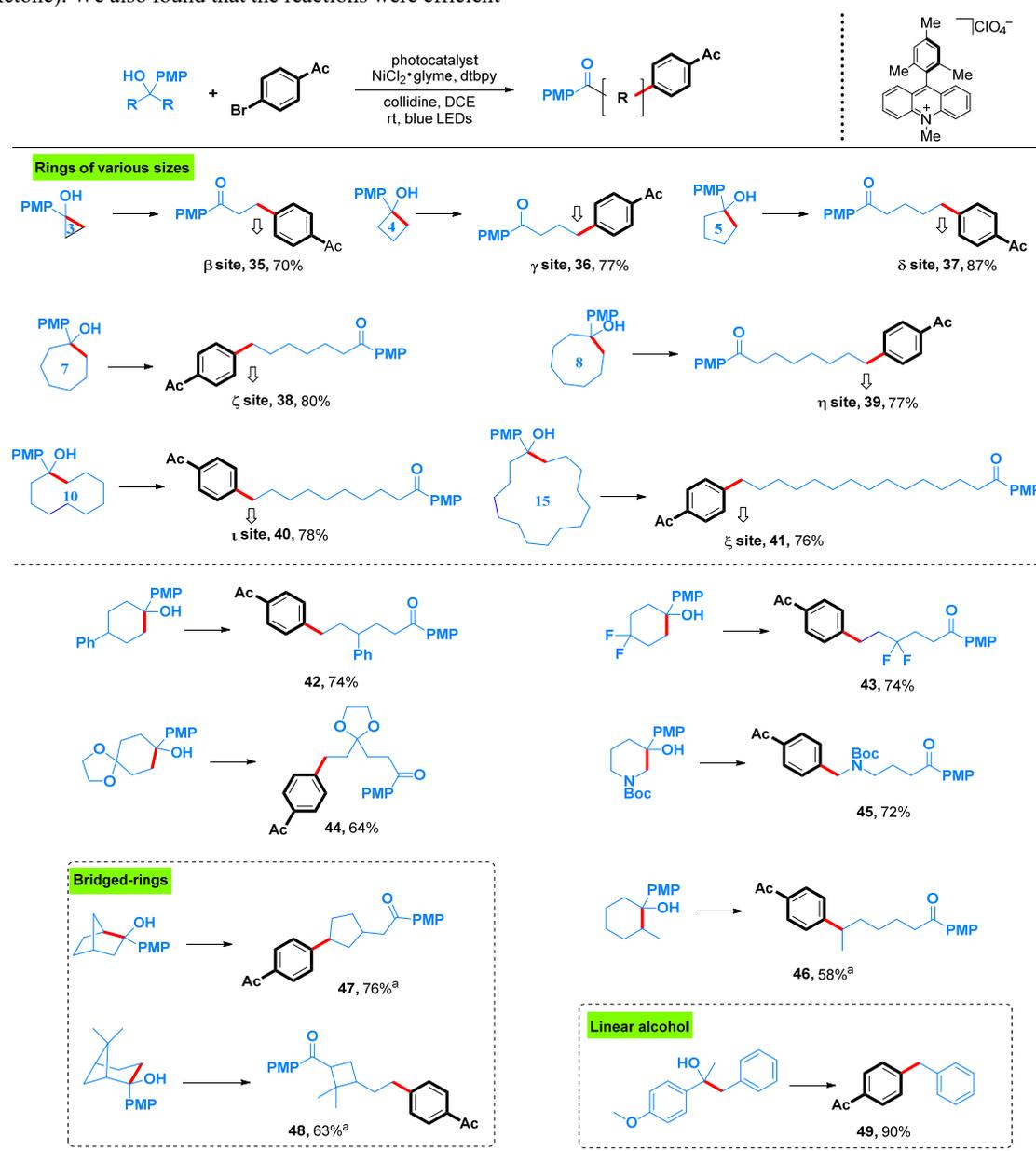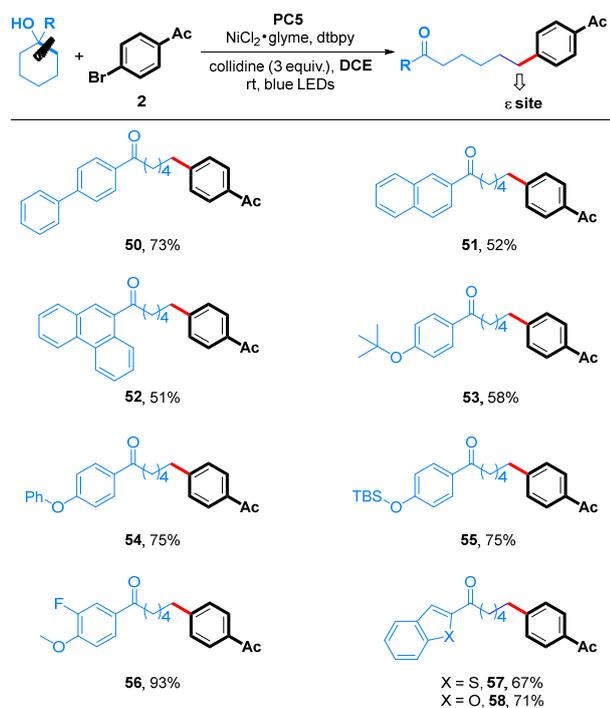**Fig. 3. Scope of aryl halides.** Unless otherwise specified, the reactions were performed on a 0.2 mmol scale under following reaction conditions: **1** (3 equiv.), **2** (1 equiv.), collidine (3 equiv.), [Acr-Mes]ClO$_4$ **PC5** (10 mol%), NiCl$_2$•glyme (20 mol%), dtbpy (25 mol%), DCE (6 ml), rt, 48-72 h, yields after purification by chromatography. PMP, *p*-methoxy phenyl group; Ac, acetyl group; Boc, *tert*-butoxycarbonyl.

We next turned our attention to the scope of compatible tertiary alcohols. Firstly, the deconstructive arylation method is not limited to six-membered rings, and diverse substrates containing carbocycles of various sizes were all viable in this C–C cleavage / cross coupling reaction. Accordingly, regardless of the ring strain energy, the remote arylated ketone products were obtained with carbon chains of varying lengths. For example, the highly strained 3- and 4-membered ring derivatives participated in the arylation to afford **35** and **36** in good yields (70% and 77% yield, β and γ positions of ketone). Several medium-sized rings (5-, 7- and 8-membered) formed the desired product with similar good efficiency (77-87% yield, **37-38**, δ, ζ and η positions of ketone). We also found that the reactions were efficient

for large-sized rings (10- and 15-membered), furnishing the products **40** and **41** in high yields (78% and 76% yield, ι and ξ positions of ketone). Different substituted six-membered rings were also well tolerated (**42** and **43**, both 74% yield). Furthermore, heteroatom functionality including a 1,2-ethanediol protected ketone and a Boc-protected amine could be incorporated into the carbocyclic substrates to give products **44** and **45** in good yields. Importantly, the bond scission takes place exclusively at the α-position of the *N*-Boc carbamate. In addition, excellent regioselectivity was observed for an unsymmetrical cyclic substrate, as the more stable radical intermediate is formed at the C–C bond cleavage stage (**46**).

Fig. 4. Scope of various tertiary alcohols. Unless otherwise specified, the reactions were performed on a 0.2 mmol scale under following reaction conditions: **1** (3 equiv.), **2** (1 equiv.), collidine (3 equiv.), [Acr-Mes]ClO₄ **PC5** (10 mol%), NiCl₂•glyme (20 mol%), dtbpy (25 mol%), DCE (6 ml), rt, 48-72 h, yields after purification by chromatography. ᵃIsomers were observed, and the major isomer is depicted; in all cases yields refer to the combined yield of all isomers: **46** (rr 15:1), **47** (rr 2:1), **48** (rr 2:1). PMP, *p*-methoxy phenyl group; Ac, acetyl group; Boc, *tert*-butoxycarbonyl.

This ring opening strategy can also be applied to bridged bicycles albeit with lower selectivities. For the norcamphor derived substrate, the C-C bond cleavage favors secondary over primary radical formation (**47**), however, the selectivity in the ring opening was opposite in the case of β-pinene derived substrate (**48**). We attribute the lower stability of the corresponding secondary radical to the diminished hyperconjugation effect as well as strain effect from the 4-membered ring. More pleasingly, linear alcohols can also be readily applied in this transformation (**49**).[45,46] This protocol is beneficial because the cleaved ketone can be converted into tertiary alcohols readily.

Fig. 5. Scope of arene substituents. Unless otherwise specified, the reactions were performed on a 0.2 mmol scale under following reaction conditions: tertiary alcohol (3 equiv.), **2** (1 equiv.), collidine (3 equiv.), [Acr-Mes]ClO₄ **PC5** (10 mol%), NiCl₂•glyme (20 mol%), dtbpy (25 mol%), DCE (6 ml), rt, 48-72 h, yields of products after purification by chromatography. PMP, *p*-methoxy phenyl group; Ac, acetyl group; Boc, *tert*-butoxycarbonyl.

To further expand the scope and utility of this methodology, we next aimed to determine whether the C-C cleavage / cross coupling reaction could be extended to tertiary alcohols bearing other aromatic cores. As illustrated in Fig. 5 we found that a range of selected arene-substituted cyclohexanols, including naphthalene, phenanthrene, biphenyl, fluorinated anisole as well as *tert*-butyl, phenyl and TBS (*tert*-butyldimethylsilyl) protected phenols can serve as efficient coupling partners (**50-56**, 52-93% yield). Additionally, heteroaromatic derivatives such as benzofuran and benzothiophene derivatives also provided the desired arylated ketones under the optimized conditions (**57** and **58**, 67 and 71% respectively). To be noted, substrates with $E_{p/2}$ (Ar⁰/⁺•) below 1.38 V did not result in product formation (see SI). In view of the strong oxidizing ability of acridinium salts, it is reasonable to expect that many other aromatic systems could, at least theoretically, be suitable to undergo the C-C cleavage / cross coupling reaction. A number of

additional experiments were performed to elucidate the reaction mechanism. In order to investigate the intermediacy of the ring-opened carbon centered radical under this dual photoredox nickel catalysis, we conducted the reaction under standard conditions in the presence of TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy) as radical scavenger. As expected, the reaction was shut down completely and the formation of a distal TEMPO trapped ketone strongly supports a radical process. To get additional information, we carried out a radical clock experiment with the tertiary alcohol incorporating a cyclopropyl moiety. Upon subjection to the photocatalytic standard conditions, the radical clock ring opened product **61** was formed exclusively in moderate yield (49%, *E/Z* 2.5:1) (Fig. 6).
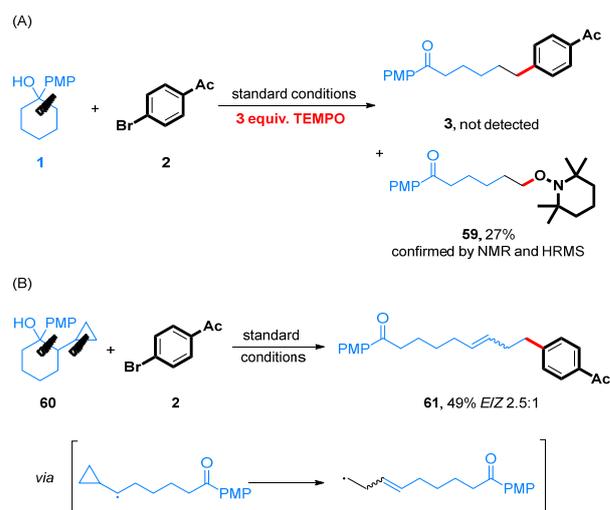

Fig. 6. Mechanistic studies. (A) Evidence for an alkyl radical mechanism, under standard conditions: 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) was used as radical trap; (B) Radical clock experiment.

Hydrogen bonding is considered as a characteristic feature of the concerted multi-site PCET.[47] The equilibrium formation of the hydrogen-bond adduct between the cyclic alcohol and collidine base was examined by ¹H NMR spectroscopy. The ¹H NMR of 1-([1,1'-biphenyl]-4-yl)cyclohexan-1-ol **62** shows a singlet at δ_{OH} 0.96 ppm in anhydrous C₆D₆ in the absence of base. After the addition of 1 equiv. collidine, the resonance of hydroxyl proton shifts downfield to 1.15 ppm. The resonance shifts further downfield with increasing the equivalents of collidine. These results are consistent with a mechanism in which a hydrogen bonded adduct is formed between the alcohol substrate and the collidine base (Fig. 7A). Under the standard conditions, we next evaluated the C-C cleavage/cross coupling using linear alcohols with increased distance between the electron rich arene and hydroxyl group, and the corresponding products were obtained in moderate yields (**64** and **49**, 65% and 50%). Accordingly, we realized that the stabilities of the generated carbon-centered radicals *via* C-C bond cleavage (electron rich benzyl radical > neutral benzyl radical > alkyl radical) are key factors for the reaction selectivity. This result is remarkable considering that many of the linear alcohols could serve as radical precursors towards photoredox-nickel cross coupling (Fig. 7B).
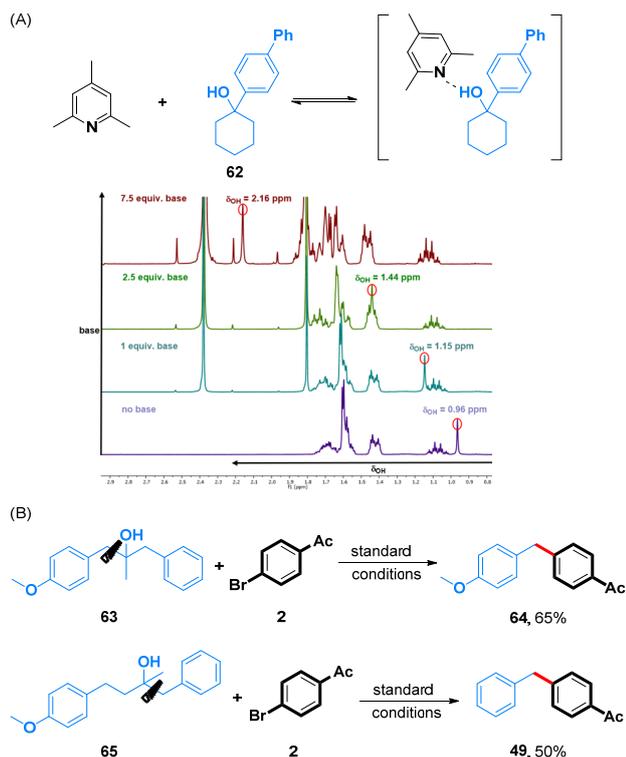
Fig. 7. (A) ^{1}H NMR spectra of substrate 1-([1,1'-biphenyl]-4-yl)cyclohexan-1-ol in C_6D_6 with various amounts of collidine. (B) Long-range MS-PCET enabled cross coupling with linear alcohols.

CONCLUSIONS

In summary, we have developed a robust method for the remote site-specific arylation of ketones from easily accessible tertiary alcohols through a photoredox-enabled MS-PCET and nickel catalysis. The use of a strongly oxidizing acridinium photocatalyst was critical in achieving high reaction efficiency. Thus, a variety of cyclic, linear as well as bridged alcohols can be effectively applied in this new C-C bond cleaving cross coupling procedure. We believe that further advances can be expected by applying this strategic design to other types of visible light mediated cross couplings *via* the C-C bond cleavage.

■ ASSOCIATED CONTENT

*Supporting Information

Experimental and computational details, full characterization of the products and spectra, Cartesian coordinates of the optimized geometries.

■ AUTHOR INFORMATION

Corresponding Author
* magnus.rueping@rwth-aachen.de
* long.huang@rwth-aachen.de
Author Contributions
Notes
The authors declare no competing financial interest.

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cycloalkanol

BDFE as driving force

Arylation