Conformational Flexibility as a Tool for Enabling Site-Selective Functionalization of Unactivated sp^3 C–O Bonds in Cyclic Acetals

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**Cite This:** J. Am. Chem. Soc. 2022, 144, 11558−11563

**ABSTRACT:** A dual catalytic manifold that enables site-selective functionalization of unactivated sp^3 C–O bonds in cyclic acetals with aryl and alkyl halides is reported. The reaction is triggered by an appropriate σ^*−p orbital overlap prior to sp^3 C–O cleavage, thus highlighting the importance of conformational flexibility in both reactivity and site selectivity. The protocol is characterized by its excellent chemoselectivity profile, thus offering new vistas for activating strong σ sp^3 C–O linkages.

Carbon–oxygen electrophiles have recently gained momentum as alternatives to organic halides in the cross-coupling arena. Although the use of sp^2 C–O derivatives has become routine, cross-couplings of unactivated sp^3 C–O counterparts possessing β-hydrogens have received much less attention. While significant progress has been made with sp^3 C–O electrophiles bearing electron-withdrawing groups adjacent to the oxygen atom, the sp^3 C–O functionalization of unactivated alkyl ethers—arguably the simplest derivatives in the alcohol series—still remains a challenging endeavor in both two- and one-electron manifolds (Scheme 1). This is probably attributed to (a) the lower tendency of alkyl ether residues to formally act as leaving groups, (b) the remarkably high activation barrier required for effecting alkyl sp^3 C–O cleavage (~93 kcal·mol⁻¹), and (c) inevitable site-selectivity issues arising from the functionalization at both alkyl sp^3 C–O sites.

In recent years, metallaphotoredox scenarios have offered new conceivable pathways to challenging transformations under exceptionally mild conditions. Driven by this observation, we wondered whether we could harness cyclic acetals as vehicles to enable site-selective functionalization of strong σ alkyl sp^3 C–O bonds. Unlike the elegant advances realized with symmetrical acyclic acetals, the utilization of cyclic congeners not only would improve the atom economy of the overall transformation by preserving the integrity of the organic skeleton but also offer the possibility to discriminate between three similar sp^3 C–O sites, thus constituting a worthwhile endeavor for chemical invention. In addition, the ready availability of cyclic acetals from simple exposure of carbonyl compounds to 1,2-diol would offer a unique opportunity for valorization of the latter ubiquitous motifs.

We anticipated that a light-driven hydrogen atom transfer (HAT) might occur selectively at the weak acetal sp^3 C–H bond (~86.8 kcal·mol⁻¹). Subsequently, β-fragmentation would occur from II via an appropriate σ^*−p orbital overlap, enabling sp^3 C–O cleavage while delivering an open-shell species III (Scheme 2). The latter can be intercepted by Ni(II) species IV, setting the basis for C–C bond formation via

**Scheme 1.** sp^3 C–O Electrophiles in Cross-Coupling Events

**Scheme 2.** Cyclic Acetals as Manifolds for sp^3 C–O Cleavage

Received: April 28, 2022
Published: June 24, 2022
reductive elimination. It is expected that the two catalytic cycles could be interfaced by a SET, thus recovering back the propagating catalytic species.

We anticipated that $\beta$-fragmentation would only be accessible if a certain degree of conformational flexibility is granted in II for enabling the key $\sigma^*-\pi$ orbital overlap (Scheme 2). This hypothesis was assessed by DFT calculations on the phenyl-substituted 5- to 8-membered cyclic acetal series (Scheme 3, IIa–d).12 As illustrated for II-b, a significant buildup of ring strain is observed as the reaction proceeds, either at the radical intermediate (II-b-rad) or at the highly strained transition state (II-b-TS). Notably, a non-negligible 2.9 kcal mol$^{-1}$ stabilization was observed for II-c-rad when compared to II-b-rad, probably due to the distortion of the chair in the latter to accommodate the planar radical $sp^2$ carbon. A close inspection into the fragmentation transition state II-b-TS is particularly illustrative, as it confirms the difficult planarization of four atoms in a six-membered ring and a nonfavorable eclipsed conformation of the $CH_2-CH_2$ fragment. In addition, the late character of the transition state is associated with a long $sp^3$ C–O bond (ca. 2.0 Å), which introduces an extraordinary distortion in such a small ring. These observations were indirectly corroborated by a significant energy increase of 2.7–3.0 kcal mol$^{-1}$ in II-b-TS when compared to II-c-TS or II-d-TS (Scheme 3, middle). Not surprisingly, we were not able to locate II-a-TS due to the exceptional strain that might be built up in smaller ring sizes. Taken together, DFT calculations confirmed conformational flexibility as a key contributory factor for success in our targeted $sp^3$ C–O cleavage event. As part of our ongoing interest in light-induced processes and C–O bond functionalization,13 we describe the realization of this goal. Our method is characterized by its simplicity and generality across a wide number of acetals and organic halides, thus constituting an opportunity to improve our ever-growing knowledge for the activation of particularly strong $\sigma sp^3$ linkages.

As anticipated from the DFT studies in Scheme 3, all our efforts to promote the $sp^3$ C–O arylation of either II-a or II-b (Scheme 3) were met with failure, corroborating the inability of five- and six-membered rings to enable the key $\sigma^*-\pi$ orbital overlap.14 Therefore, our study continued by investigating the reaction of more flexible seven-membered analogue 1a—readily accessible on a large scale by reaction of 1,4-butanediol with benzaldehyde dimethyl acetal—with 2a (Table 1). After some experimentation,15 a protocol consisting of NiBr$_2$·glyme, L$_1$, quinuclidine, and Ir[(dF,CF$_3$ppy)$_2$(dtbbpy)]PF$_6$ in t-AmOH under blue-LED irradiation afforded 3a in 85% isolated yield (entry 1). Notably, no byproducts arising from $sp^3$ C–H arylation adjacent to the oxygen atoms in 1a were detected in the crude mixtures.11 As expected, subtle changes in both photocatalyst and Ni sources had a deleterious effect (entries 2–4). Similarly, solvents and bases other than Na$_2$CO$_3$ and t-AmOH resulted in lower yields of 3a (entries 5–8). Importantly, 3a was observed in the absence of quinuclidine.
Thus suggesting the involvement of bromine radicals (BDEHBr = 86.7 kcal·mol⁻¹) as HAT reagents. While in lower yields, non-negligible reactivity was found with 2a-Cl instead. As anticipated, no product formation was observed in the absence of light, photocatalyst, or Ni catalyst (entry 14).

Next, we focused our attention to exploring the generality of our sp³ C–O functionalization of cyclic acetals (Table 2). As shown, nonsymmetrical 1,3-dioxepanes 1b and 1c posed no problems, with arylation taking place exclusively at the more substituted sp³ C–site(3b−c). Although a lower regioselectivity pattern (2:1) was observed for 5-substituted 1,3-dioxepane 1d, it is worth noting that the major isomer resulted from the activation at C4, suggesting a certain stabilization of the corresponding open-shell intermediate by hyperconjugation (3d). Equally interesting was the ability to couple disubstituted 1,3-dioxepanes or their corresponding ring-fused analogues, obtaining the targeted products 3f−k in good yields. Despite the presence of five different sp³ C–H bonds in 3l amenable for HAT, 3i was prepared in good yields. While 3j was obtained in a low 34% yield, a simple esterification of the pending hydroxyl moieties led to 3k in good yields. These results should be visualized against the challenge that is addressed due to the presence of seven nucleophilic carbinolic sp³ C–H bonds adjacent to oxygen atoms. Notably, our method could be extended to larger 8-membered dioxocanes with similar efficacy under otherwise identical reaction conditions (3l, 3m). As illustrated in Table 2 (bottom), the sp³ arylation could be applied independently on whether electron-rich or electron-poor aryl bromides were utilized as counterparts. The method showed an excellent chemoselectivity pattern, and esters (2a), nitriles (2m), ketones (2o, 2u, 2v), alkenes (2k), sulfonamides (2j), or amides (2w) could be all well-accommodated. Even heteroaryl bromides containing benzofuran, thiophen, pyridine, or quinoline cores do not interfere with productive sp³ arylation (2q and 2s−u). Interestingly, no racemization was found for compounds bearing stereocenters (2w). More interestingly, our protocol could be extended to either vinyl bromides or unactivated alkyl halides, albeit in comparable lower yields.

Encouraged by these results, we next conducted a series of control experiments to gain more insights into the intricacies of our sp³ C–O functionalization technique. Specifically, we studied the kinetic isotope effect by comparing the initial rates of 1a and 1a-d (Scheme 4, top). We observed a kH/kD = 1.0, as thus suggesting the involvement of bromine radicals (BDEHBr = 86.7 kcal-mol⁻¹) as HAT reagents. While in lower yields, non-negligible reactivity was found with 2a-Cl instead. As anticipated, no product formation was observed in the absence of light, photocatalyst, or Ni catalyst (entry 14).

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suggesting that $sp^3$ C–H bond cleavage might not be involved in the rate-determining step. In addition, 1d-$d^2$ was prepared to investigate whether an erosion in deuterium content was observed in 3d-$d^2$ due to initial HAT at the $sp^3$ C–D site followed by 1,3-HAT en route to II.18 As shown, careful spectroscopic analysis revealed 3d-$d^2$ as the only observable product, advocating the notion that HAT takes place exclusively at the acetal $sp^3$ C–H site (Scheme 4, middle).19

As displayed in Scheme 4 (bottom), we found that Ni-I—easily prepared by reacting 2a with Ni(cod)$_2$ and L1 in THF—was catalytically competent en route to 3a.

In summary, we have reported a dual catalytic strategy that harnesses the potential of cyclic ethers as manifolds for enabling an atom-economical site-selective $sp^3$alkyl C–O functionalization. Key for success is the conformational flexibility of cyclic acetics, thus leading to an appropriate $\sigma^*$$-p$ orbital overlap prior to $\beta$-fragmentation. The method is characterized by a broad scope across a wide number of cyclic acetics and aryl/alkyl halides, hence offering an opportunity to improve upon existing $sp^3$ C–O functionalization scenarios.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c04513.

Experimental procedures, $^1$H and $^{13}$C NMR spectra for all compounds, mechanistic studies, and detailed computational data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank ICIQ, FEDER/MCI-AEI/PGC2018-096839-B-100, MCIN-PID2019-110008GB-I00, European Research Council (ERC) under European Union’s Horizon 2020 research and innovation program (Grant Agreement No. 883756) for financial support. E.G.-B. thanks SGIker (UPV/EHU) for providing human and computational resources. C.R. thanks the European Union’s Horizon 2020 and innovation program under the Marie Skłodowska-Curie grant agreement (839980).

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