

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

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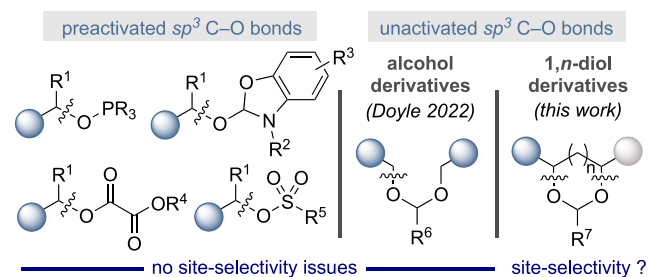


Supporting Information

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.¹ 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).^{2–6} This is

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

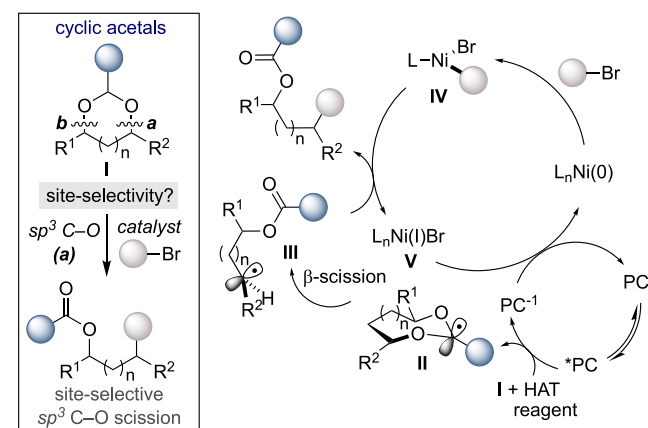


probably attributed to (a) the lower tendency of alkyl ether residues to formally act as leaving groups, (b) the remarkably high activation barrier required for effecting alkyl sp^3 C–O cleavage (~ 93 kcal·mol⁻¹),⁷ and (c) inevitable site-selectivity issues arising from the functionalization at both alkyl sp^3 C–O sites.

In recent years, metallaphotoredox scenarios have offered new conceivable pathways to challenging transformations under exceptionally mild conditions.⁸ 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,⁹ 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,*n*-diols would offer a unique opportunity for valorization of the latter ubiquitous motifs.¹⁰ 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).¹¹ 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 2. Cyclic Acetals as Manifolds for sp^3 C–O Cleavage

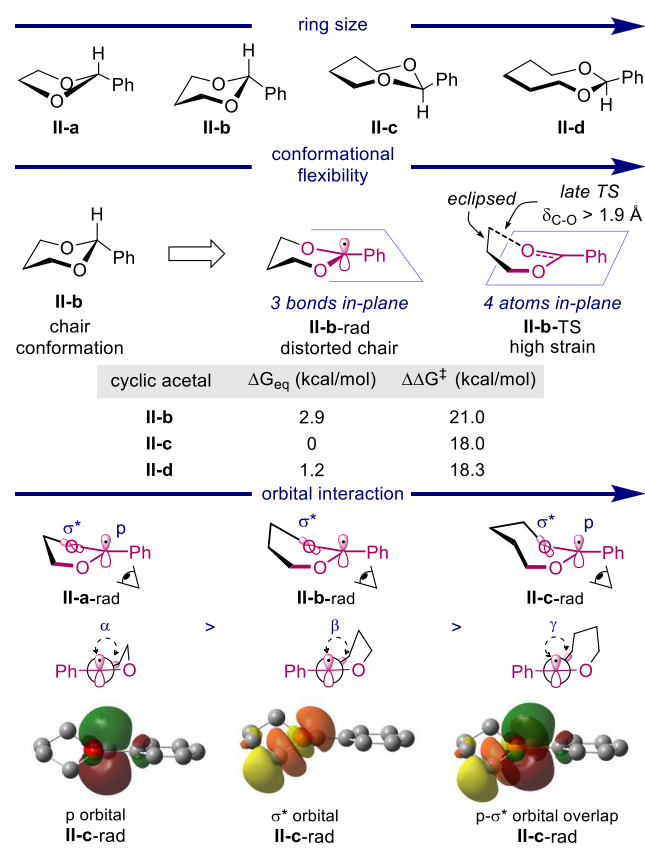


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reductive elimination. It is expected that the two catalytic cycles could be interfaced by a SET, thus recovering back the propagating catalytic species.

We anticipated that β -fragmentation would only be accessible if a certain degree of conformational flexibility is granted in **II** for enabling the key σ^* -p 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

Scheme 3. DFT Studies; M06-2X/6-311++G(d,p)

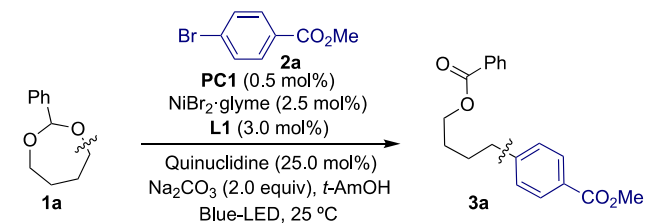


buildup of ring strain is observed as the reaction proceeds, either at the radical intermediate (**II-b-rad**) or at the highly strained transition state (**II-b-TS**). Notably, a non-negligible 2.9 kcal·mol⁻¹ stabilization was observed for **II-c-rad** when compared to **II-b-rad**, probably due to 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 CH₂-CH₂ 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 σ sp^3 linkages.

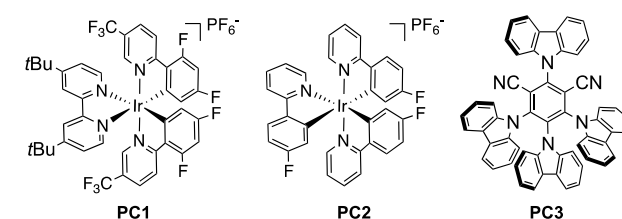
As anticipated from the DFT studies in Scheme 3, all our efforts to promote the sp^3 C-O arylation of either **II-a** or **II-b** (Scheme 3) were met with failure, corroborating the inability of five- and six-membered rings to enable the key σ^* -p orbital overlap.¹⁴ Therefore, our study continued by 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

Table 1. Optimization of Reaction Conditions^a



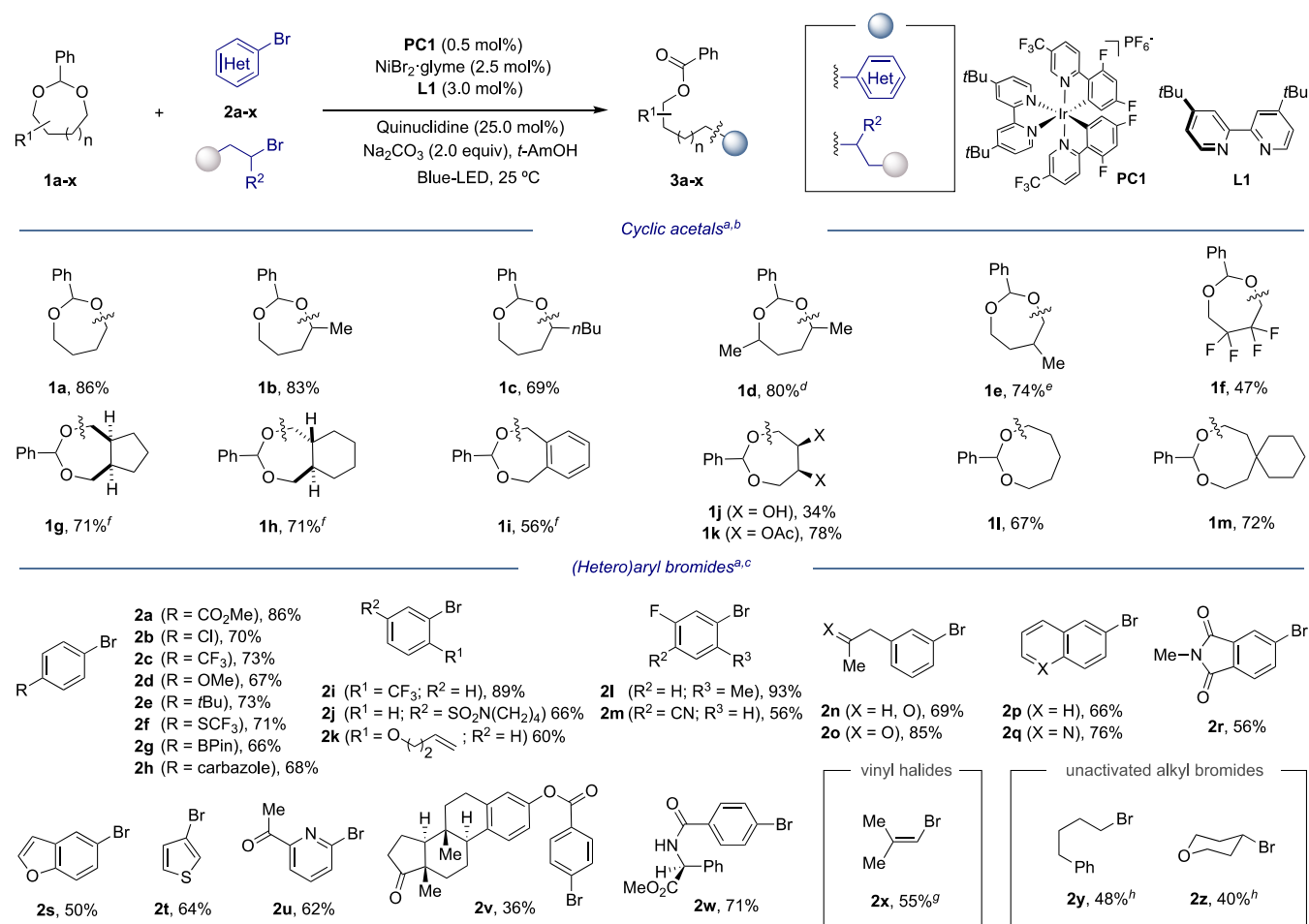
entry	deviation standard conditions	3a (%) ^b
1	none	85 ^c
2	using PC2 , PC3 or Ru(bpy) ₃ ²⁺	0
3	using NiI ₂	0
4	using Ni(cod) ₂	70
5	using Cs ₂ CO ₃	38
6	using K ₃ PO ₄	49
7	MeCN as solvent	33
8	C ₆ H ₆ as solvent	63
9	using L2 as ligand	73
10	using L3 as ligand	66
11	using L4 as ligand	11
12	using 2a-Cl as substrate	49
13	no quinuclidine	65
14	no light, no NiBr ₂ ·glyme or no PC1	0

L1 (R¹ = *t*Bu; R² = H)
L2 (R¹ = OMe; R² = H)
L3 (R¹ = H; R² = Me)
L4 (R¹ = *t*Bu)



^aConditions: **1a** (0.40 mmol), **2a** (0.20 mmol), **PC1** (0.5 mol %), NiBr₂·glyme (2.5 mol %), **L1** (3.0 mol %), Quinuclidine (25.0 mol %), Na₂CO₃ (0.40 mmol), *t*-AmOH (0.20 M) under Blue-LED irradiation, 25 °C for 16 h. ^bGC yields using decane as internal standard. ^cIsolated yield.

some experimentation,¹⁵ a protocol consisting of NiBr₂·glyme, **L1**, quinuclidine, and Ir[(dF,CF₃ppy)₂(dtbbpy)]PF₆ 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 Na₂CO₃ and *t*-AmOH resulted in lower yields of **3a** (entries 5–8). Importantly, **3a** was observed in the absence of quinuclidine

Table 2. Site-Selective sp^3 C–O Arylation and Alkylation of Cyclic Acetals

^aAs for Table 1, entry 1. ^bUsing **2a** (0.2 mmol). ^cUsing **1a** (0.4 mmol); ^d*dr* 1:1. ^e*rr* 2:1. ^f35 °C, 48 h. ^g[Ni] (5.0 mol %), dtbbpy (6.0 mol %). ^hPC1 (1 mol %), [Ni] (10 mol %), dtbbpy (12 mol %), benzene (0.2 M), 5 Å MS (30 mg), 48 h. Isolated yields, average of two different independent runs.

(entry 13), thus suggesting the involvement of bromine radicals ($BDE_{\text{HBr}} = 86.7 \text{ kcal}\cdot\text{mol}^{-1}$) as HAT reagents.^{9,16} 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).

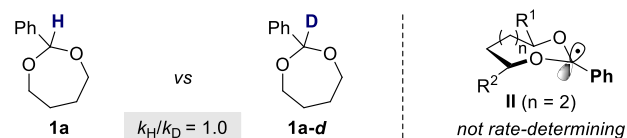
Next, we focused our attention to exploring the generality of our sp^3 C–O functionalization of cyclic acetals (Table 2). As shown, nonsymmetrical 1,3-dioxepanes **1b** and **1c** posed no problems, with arylation taking place exclusively at the more substituted sp^3 C–O site (**3b–c**). Although a lower 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**).¹⁷ 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 sp^3 C–H bonds in **1i** 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 sp^3 C–H bonds adjacent to oxygen atoms. Notably, our method could be extended to larger 8-membered dioxocanes with similar efficiency under otherwise identical reaction conditions (**3l**, **3m**). As illustrated in Table 2 (bottom), the sp^3 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 sp^3 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. The latter is particularly noteworthy given the paucity of sp^3 – sp^3 bond-forming cross-coupling reactions driven by the functionalization of unactivated alkyl sp^3 C–O bonds.³

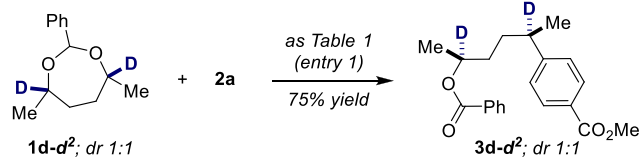
Encouraged by these results, we next conducted a series of control experiments to gain more insights into the intricacies of our sp^3 C–O functionalization technique. Specifically, we studied the kinetic isotope effect by comparing the initial rates of **1a** and **1a-d** (Scheme 4, top). We observed a $k_{\text{H}}/k_{\text{D}} = 1.0$,

Scheme 4. Preliminary Mechanistic Experiments

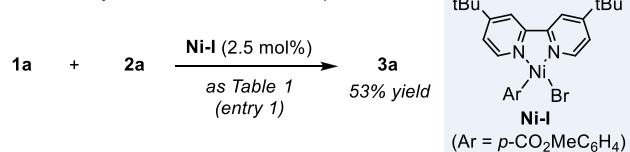
■ intermolecular kinetic isotope effect



■ arguing against competitive HAT at different sp^3 C–H sites



■ reactivity of oxidative addition complex Ni-I



suggesting that sp^3 C–H bond cleavage might not be involved in the rate-determining step. In addition, **1d-d²** was prepared to investigate whether an erosion in deuterium content was observed in **3d-d²** 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-d²** 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 acetals as manifolds for enabling an atom-economical site-selective sp^3 alkyl C–O functionalization. Key for success is the conformational flexibility of cyclic acetals, thus leading to an appropriate $\sigma^*-\text{p}$ orbital overlap prior to β -fragmentation. The method is characterized by a broad scope across a wide number of cyclic acetals 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, ¹H and ¹³C NMR spectra for all compounds, mechanistic studies, and detailed computational data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(12) All structures were optimized using Gaussian 16 at the M06-2X/6-311++G(d,p) level, introducing solvation factors with the IEF-PCM method (2-methyl-2-propanol as solvent). For more details, see [Supporting Information](#).

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(14) Despite extensive investigations by varying all experimental parameters, we were not able to detect even traces of products arising from sp³ C–O cleavage by using either six-membered 2-phenyl-1,3-dioxane or five-membered 2-phenyl-1,3-dioxolane as substrates. While this empirical observation is in full agreement with our DFT studies, thus confirming the need for conformational flexibility in the targeted sp³ C–O cleavage, it is worth noting that a single example has been described by using the latter in ref 9, albeit in low yields.

(15) See [Supporting Information](#) for details.

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(19) As expected, reaction of **1a** with **2a** in the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) resulted in ~20% of **3a-TEMPO** (as judged by GC-MS of the crude mixtures). No traces of **3a** were detected in the crude mixtures, thus indirectly confirming the radical nature of the process. Attempts at isolating **3a-TEMPO** in pure form were met with failure. See ref 15.

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