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Communication

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

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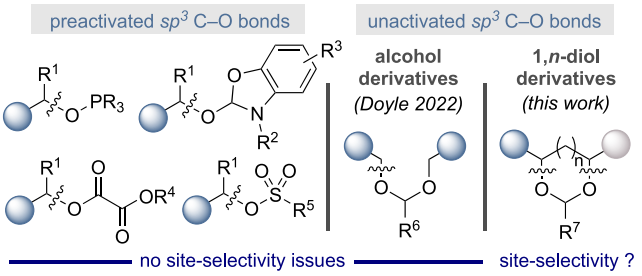
ABSTRACT: A dual catalytic manifold that enables site-selective functionalization of unactivated sp^3 C–O bonds in cyclic acetals with aryl and alkyl halides is reported. The reaction is triggered by an appropriate σ^*–p orbital overlap prior to sp^3 C–O cleavage, thus highlighting the importance of 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

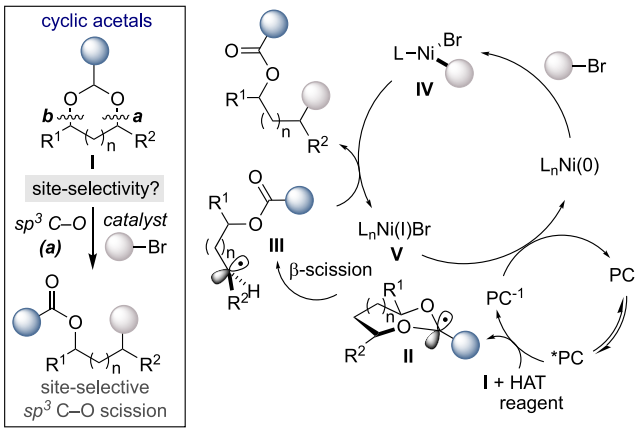
Scheme 1. sp^3 C–O Electrophiles in Cross-Coupling Events



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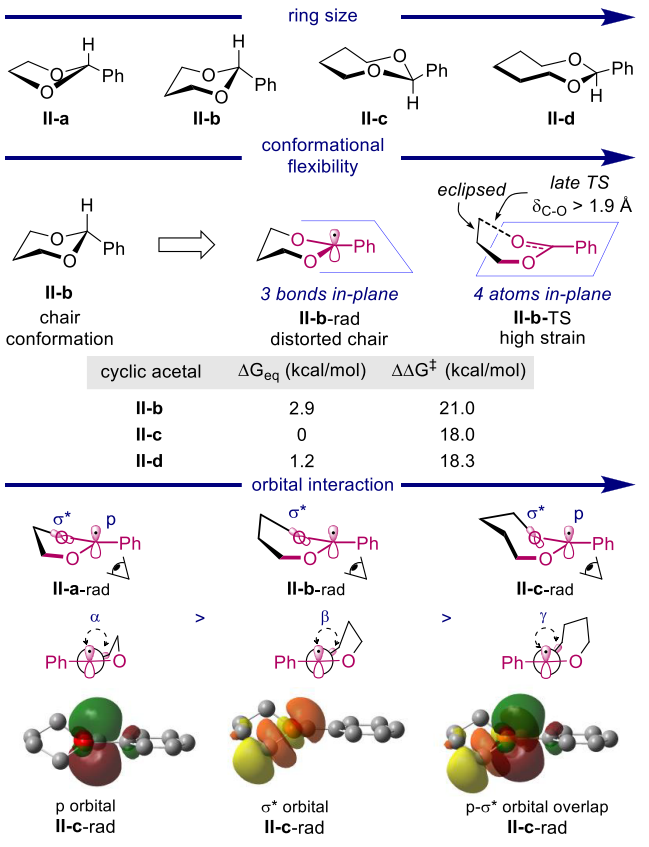
reductive elimination. It is expected that the two catalytic cycles could be interfaced by a SET, thus recovering back the propagating catalytic species.

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

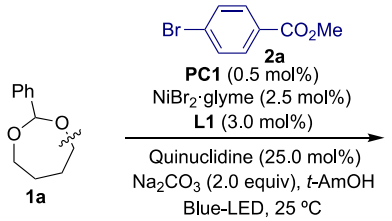
Scheme 3. DFT Studies; M06-2X/6-311++G(d,p)



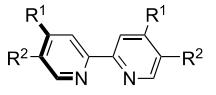
buildup of ring strain is observed as the reaction proceeds, either at the radical intermediate (**II-b-rad**) or at the highly strained transition state (**II-b-TS**). Notably, a non-negligible 2.9 kcal·mol^{-1} stabilization was observed for **II-c-rad** when compared to **II-b-rad**, probably due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

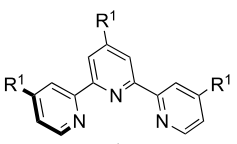
Table 1. Optimization of Reaction Conditions[a]



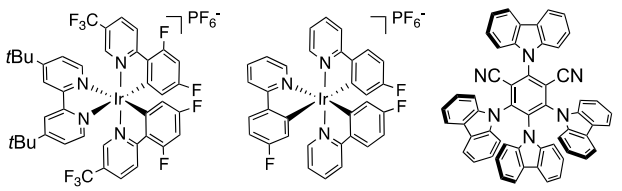
entry	deviation standard conditions	**3a** (%)[b]
1	none	85[c]
2	using **PC2**, **PC3** or $Ru(bpy)_3^{2+}$	0
3	using NiI_2	0
4	using $Ni(cod)_2$	70
5	using Cs_2CO_3	38
6	using K_3PO_4	49
7	MeCN as solvent	33
8	C_6H_6 as solvent	63
9	using **L2** as ligand	73
10	using **L3** as ligand	66
11	using **L4** 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 (R^1 = *t*Bu; R^2 = H)
L2 (R^1 = OMe; R^2 = H)
L3 (R^1 = H; R^2 = Me)



L4 (R^1 = *t*Bu)



PC1 **PC2** **PC3**

[a]Conditions: **1a** (0.40 mmol), **2a** (0.20 mmol), **PC1** (0.5 mol %), $NiBr_2$·glyme (2.5 mol %), **L1** (3.0 mol %), Quinuclidine (25.0 mol %), Na_2CO_3 (0.40 mmol), *t*-AmOH (0.20 M) under Blue-LED irradiation, 25 °C for 16 h. [b]GC yields using decane as internal standard. [c]Isolated yield.

some experimentation,[15] a protocol consisting of $NiBr_2$·glyme, **L1**, quinuclidine, and Ir[(dF,CF_3ppy)$_2$(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_2CO_3 and *t*-AmOH resulted in lower yields of **3a** (entries 5−8). Importantly, **3a** was observed in the absence of quinuclidine

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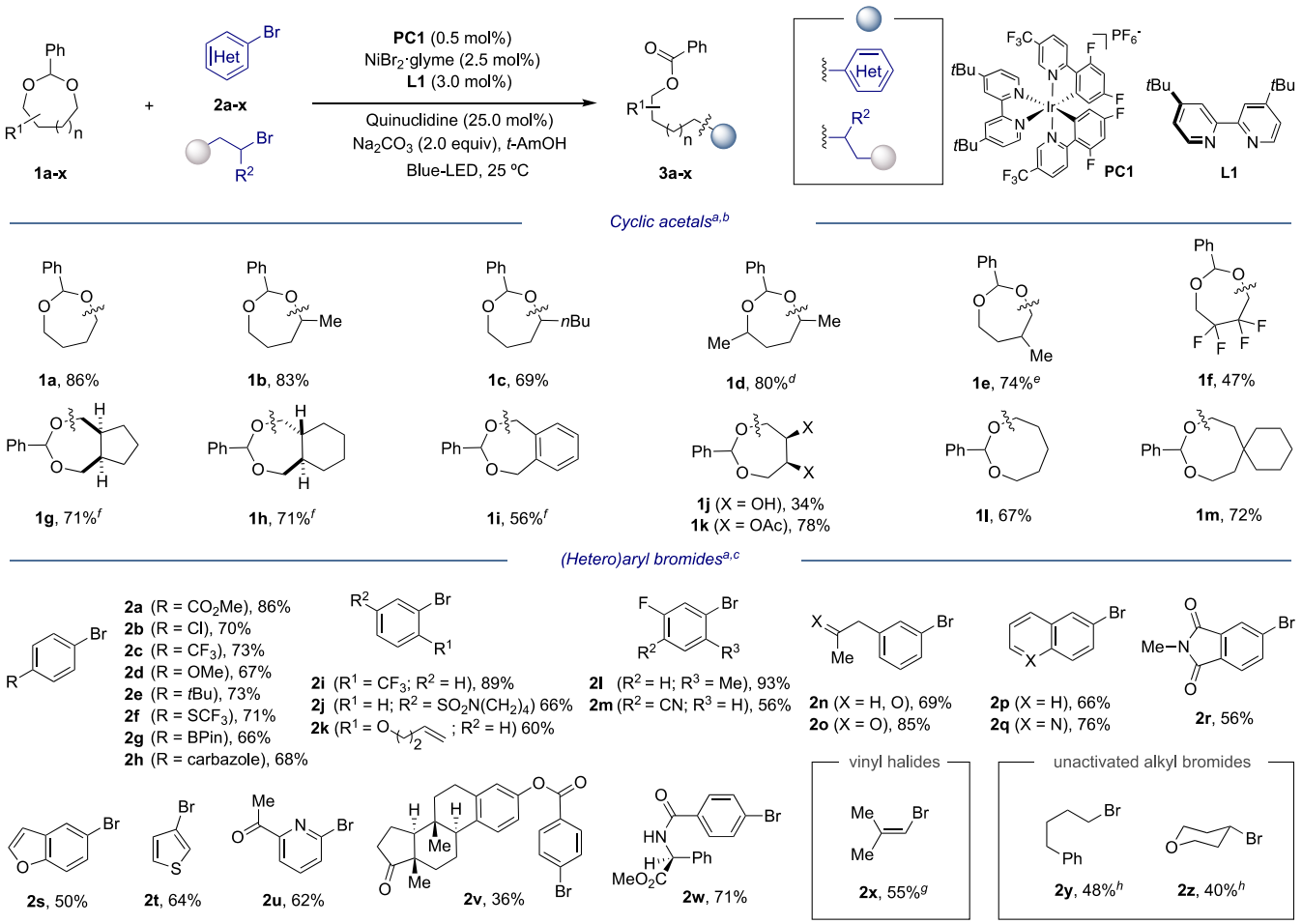
Table 2. Site-Selective sp^3 C−O Arylation and Alkylation of Cyclic Acetals



[a]As for Table 1, entry 1. [b]Using **2a** (0.2 mmol). [c]Using **1a** (0.4 mmol); [d]*dr* 1:1. [e]*rr* 2:1. [f]35 °C, 48 h. [g][Ni] (5.0 mol %), dtbbpy (6.0 mol %). [h]**PC1** (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_{HBr} = 86.7 kcal·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 efficency 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_H/k_D = 1.0,

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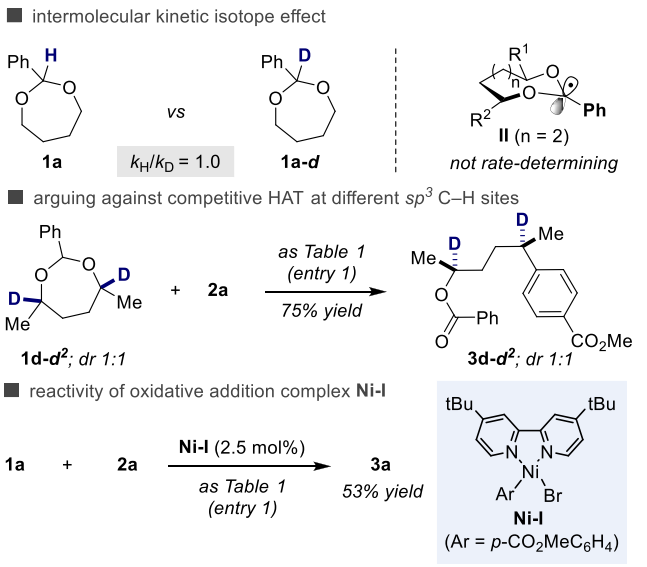
Scheme 4. Preliminary Mechanistic Experiments



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 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 σ^*−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, ^{1}H and ^{13}C NMR spectra for all compounds, mechanistic studies, and detailed computational data (PDF)

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Author Contributions

$^{\perp}$C.R. and L.T. contributed equally to this work

Notes

The authors declare no competing financial interest.

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(15) See Supporting Information for details.

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