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Journal
Journal of the American Chemical Society, 140(26)

ISSN
0002-7863

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Publication Date
2018-07-05

DOI
10.1021/jacs.8b05962

Peer reviewed

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
Cite This: J. Am. Chem. Soc. 2018, 140, 8350−8356
pubs.acs.org/JACS

Chiral Diaryliodonium Phosphate Enables Light Driven Diastereoselective α-C(sp^3)−H Acetalization

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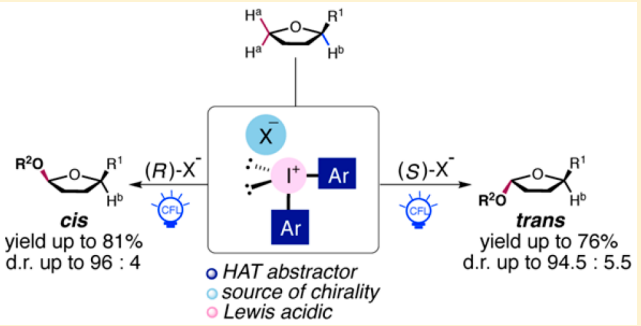
Supporting Information

ABSTRACT: C(sp^3)−H bond functionalization has emerged as a robust tool enabling rapid construction of molecular complexity from simple building blocks, and the development of asymmetric versions of this reaction creates a powerful methodology to access enantiopure sp^3-rich materials. Herein, we report the stereoselective functionalization of C(sp^3)−H bonds of cyclic ethers employing a photochemically active diaryliodonium salt in combination with an anionic phase-transfer catalyst. The synthetic strategy outlined herein allows for regio- and stereochemical control in the α-C−H acetalization of furans and pyrans using alcohol nucleophiles, thus providing the ability to control the configuration at the stereogenic exocyclic acetal carbon.



INTRODUCTION

The stereoselective functionalization of C(sp^3)−H bonds has the potential to become a powerful synthetic tool to access biologically important, stereochemically complex heterocycles.[1−3] This promise has resulted in the development of a number of transition-metal catalyzed reactions that employ directing groups to guide the metal center into close proximity with a targeted C(sp^3)−H bond.[4] Importantly, the availability of a diverse array of ligands for the modulation of reactivity, as well as the control of stereochemistry, has rendered this approach an attractive one.[5] However, in cases where either the directing group installation or access to the metal-promoted C−H activation are not feasible, the alternative radical-mediated undirected C(sp^3)−H bond functionalization strategy has been developed through the merging of hydrogen atom transfer technology (HAT) with conventional transition-metal catalysis.[6] In the latter scenario, an appropriate radical abstractor matching the polarity of the targeted C−H bond is required.[7] Since the development of related asymmetric transformations implies a considerable challenge, very few enantioselective methods that employ this technology have been reported so far.[8]

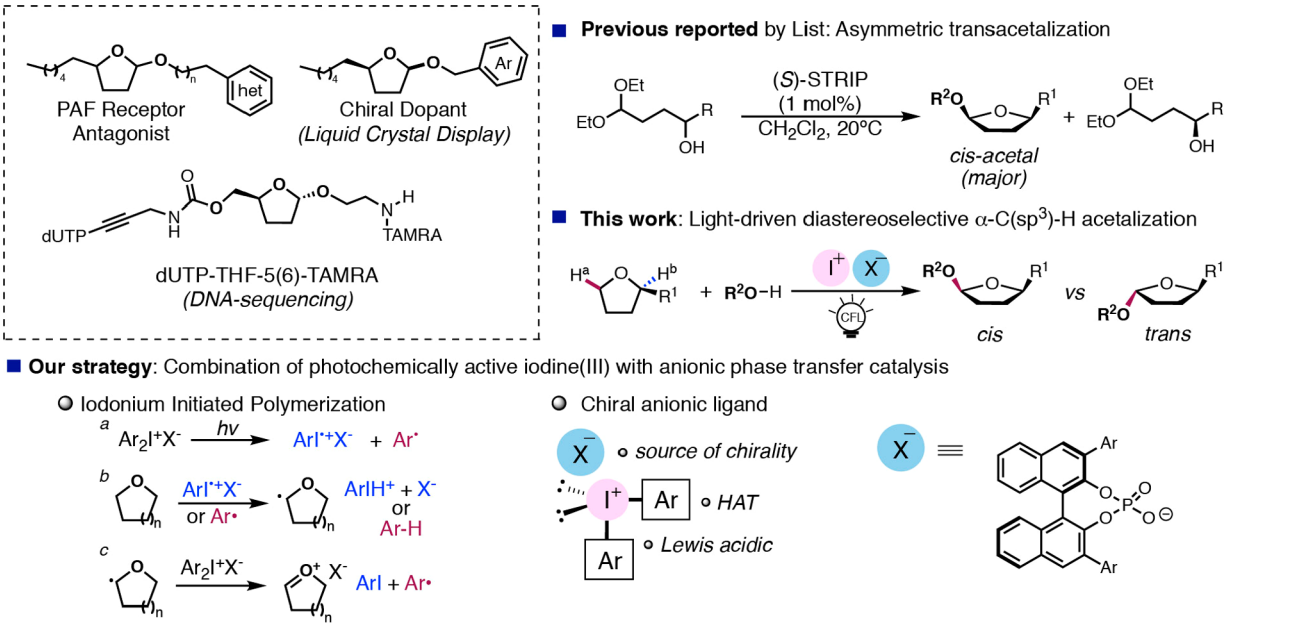
Inspired by onium salt-catalyzed polymerization reactions, we envisioned an alternative strategy for the stereoselective functionalization C(sp^3)−H bonds. In the case of diaryliodonium salts, the homolytic fragmentation into an iodonium cation radical and an aryl radical upon irradiation (254−350 nm) is proposed to initiate the polymerization (Scheme 1a).[9] These resulting radical species participate in hydrogen atom transfer (Scheme 1b) and further oxidation of the resulting ether radical to generate a cationic species (Scheme 1c) that can engage in polymerization. While trapping of the cationic species by external nucleophiles can lead to undesired termination of the polymerization, it can be employed to functionalize heterocyclic C(sp^3)−H bonds. Encouraged by diverse applications of the 2,5-disubstituted tetrahydrofuryl acetals in drug discovery,[10] liquid crystal display devices,[11] and DNA-sequencing,[12] we targeted asymmetric α-C(sp^3)−H acetalization of readily accessible chiral tetrahydrofurans through oxidative coupling with alcohols (Scheme 1). We envisioned that the outlined strategy would provide a new avenue in the stereochemical control of exocyclic acetals (*trans* versus *cis*).[13]

The successful implementation of these reagents in a stereo- and regioselective C(sp^3)−H bond functionalization requires a means to control two key steps: the HAT transfer event to mediate the regioselectivity and the nucleophilic trapping to effect the stereoselectivity. While the diaryliodonium salt might impact the regioselectivity of the HAT, its likely absence in the nucleophilic addition precludes the use of chiral iodonium reagents as stoichiometric stereocontrol element. In contrast, we hypothesized that the counterion might serve as a means to control both of the desired steps: coordination of the Lewis basic native oxygen of a cyclic ether to the iodine(III) center or the iodonium cation radical prior to C−H bond activation could enable regiocontrol through proximity of the chiral anion. Critically, we also desired that the chiral anion participate in the stereodetermining step by association with

Received: June 6, 2018
Published: June 25, 2018

DOI: 10.1021/jacs.8b05962
J. Am. Chem. Soc. 2018, 140, 8350−8356

Scheme 1. Control of Regio- and Diastereoselectivities in α-C(sp^3)−H Acetalization



a cationic electrophilic species, thereby also controlling the stereochemistry of the transformation (Scheme 1, bottom).

RESULTS AND DISCUSSION

Reaction Optimization. Key to the above strategy was previous experiments concluding that quantum yields of photoinitiated polymerization were dependent on solubility and ion pairing of the diaryliodonium salt.[14] This observation provides a basis for the hypothesis that the desired transformation might be controlled through chiral anion induced solubilization of the diaryliodonium salt. Therefore, at the outset of investigation, various reaction parameters were established using the direct coupling of **2a** with alcohol **1a** with diaryliodonium chlorides in the presence of achiral catalyst **C1** as anionic phase-transfer catalyst[15] (see Supplementary Table S1). Among these reaction parameters, irradiation was found to be essential for the α-C(sp^3)−H bond activation: a common household compact fluorescent light (CFL, 23 W) promoted the formation of **3aa** without the need for UV light. While the reaction in the absence of base gave low conversions and modest diastereoselectivity, a strong base (KOtBu) produced significant amounts of aryl ether (**B**) through the competing arylation of alcohol **1a**. On the other hand, the use of a weak base ($NaHCO_3$ or K_2CO_3) in methyl-*t*-butyl ether (MTBE) allowed for good conversions, regioselectivity, and diastereoselectivity without the competing arylation of the alcohol.

Having determined the reaction conditions for the racemic transformation, a variety of chiral phosphoric acids and diaryliodonium chlorides were evaluated in order to establish the viability of a stereoselective protocol. A screen of solvents revealed that MTBE was optimal leading to improvements in both regio- and diastereoselectivities (entry 3). The combination of achiral phosphoric acid **C1** and diaryliodonium salt **I1** resulted in unselective formation of diastereomers **3aa** and acid-labile acetal **4** without notable diastereoselectivity. In contrast, (*R*)-TRIP **C2** favored activation of the more accessible C−H_a bond giving **3aa** in higher yield with a useful diastereoisomeric ratio of 81:19 (Table 1, entries 1 vs 2). The enhanced regioselectivity in favor of abstraction of the unsubstituted C−H bond is unexpected on the basis of ionization energies (THF 9.38 eV vs 2-methylTHF 9.22 eV).[16] Nevertheless, these results clearly demonstrate that the phosphate anion has an influence in both regio- and stereoselectivity determining steps.[17]

Next, we addressed the question whether the selectivity of this process might be further altered by the nature of iodine(III) reagent and therefore examined a range of stereoelectronically different diaryliodonium chloride reagents.[18] Substitution at the *para*-position of the diaryliodonium reagent was evaluated in order to ascertain the impact of electronic changes on regio- and diastereoselectivity of the reaction. Modifications at the *para*-position of symmetric analogues had little influence on the efficiency; however, relative to the unsubstituted **I1**, a modest improvement in regioselectivity was observed with the 4-fluoro analog **I2** (Table 1, entries 3−6, and Supplementary Table S2) while maintaining good diastereoselectivity. Given the increase in regioselectivity afforded by the fluorine-substituted diaryliodonium salt, and previous reports of increased efficiency of hydrogen atom abstraction by fluorine-substituted phenyl radicals,[19] we chose to further examine fluorine substituted diaryliodonium reagents.

Previous reports using electronically unsymmetrical diaryliodonium salts in photopolymerization[20] prompted us to examine **I5** in the tetrahydrofuranyl functionalization reaction (entry 7). This fluorine containing reagent again provided an increase in regioselectivity relative to the symmetrical **I3** (entries 5 vs 7). On the basis of the hypothesis that the C−H abstraction and stereodetermining are decoupled, we sought to maintain the favorable regioselectivity afforded by *p*-fluorophenyl substitution, while modifying the *p*-methoxyphenyl moiety to gain improvements in diastereoselectivity and yield. In the event, we observed that unsymmetrical diaryliodonium reagent **I7** bearing a potential coordinating group maintained the diastereoselectivity and provided **3aa** in 82% yield with improved regioselectivity (entry 9).

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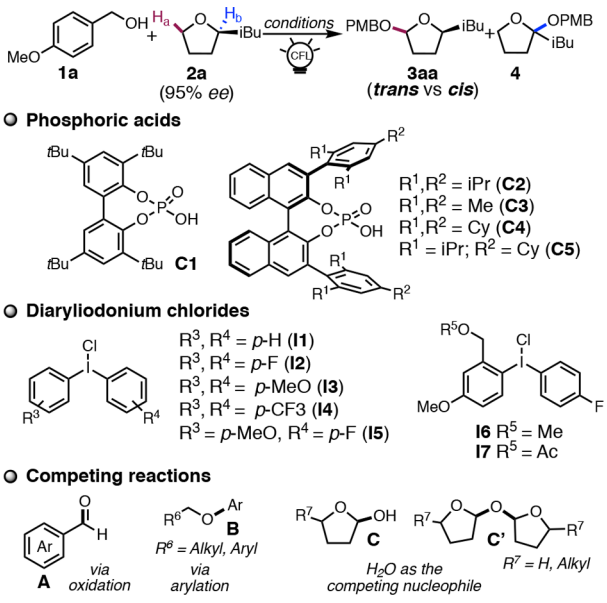
Table 1. Optimization Studies[a]



entries	CPA	[I+]	3aa/4	trans/cis	yield (3aa, %)
1[b]	**C1**	**I1**	58:42	47:53	34
2[b]	(*R*)-**C2**	**I1**	65:35	19:81	50
3	(*R*)-**C2**	**I1**	80:20	13:87	67
4	(*R*)-**C2**	**I2**	84:16	15:85	61
5	(*R*)-**C2**	**I3**	73:27	16:84	61
6	(*R*)-**C2**	**I4**	71:29	14:86	54
7	(*R*)-**C2**	**I5**	78:22	14:86	68
8	(*R*)-**C2**	**I6**	73:27	22:78	56
9	(*R*)-**C2**	**I7**	86:14	15:85	82
10	(*R*)-**C3**	**I7**	64:36	37:63	28
11	(*R*)-**C4**	**I7**	84:16	15:85	63
12	(*R*)-**C5**	**I7**	85:15	14.5:85.5[c]	81[d]
13	(*S*)-**C5**	**I7**	75:25	78.5:21.5	57
14	(*S*)-**C5**	**I1**	86:14	82.5:17.5[e]	68[d]

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (1.25 mmol), CPA (5.0 μmol), [I+] (2.50 equiv), $NaHCO_3$ (0.25 mmol), 3 Å MS, MTBE (0.20 mL, ~0.20 M), 23 W CFL, 24 h. Ratio of diastereomers (*trans*-/*cis*-**3aa**) and ratio of regioisomers (**3aa**/**4**) were determined by ^{1}H NMR. Yield of **3aa** was determined by ^{1}H NMR using internal standard 3,5-dinitrobenzene. [b]PhH instead of MTBE. [c]*cis*-**3aa**: 95% ee. [d]Isolated yield. [e]*trans*-**3aa**: 96% ee.

With these results in hand, optimization of chiral phosphoric acid catalyst (entries 10−12, see also Supplementary Table S3) was undertaken, ultimately revealing catalyst (*R*)-**C5** and iodine(III) **I7** as the optimal combination for the formation of *cis*-acetals 3aa (entry 12). On the other hand, inversion of the absolute stereochemistry of the phosphoric acid to (*S*)-**C5** favored the generation of *trans*-**3aa** with similar diastereoselectivity, thereby demonstrating that the catalyst dominated the stereochemical outcome of the reaction (entries 13−14).

Several notable conclusions can be gleaned from observations arising from the optimization studies above. First, while it was anticipated that the iodonium reagent would impact the regioselectivity of the reaction, the observation that the chiral phosphate anion also impacts the regioselectivity implies that it is associated with the C−H abstraction event. While counteranion effects of photoinduced polymerization have been previously observed,[21] these have generally been attributed to the generation and strength of the corresponding conjugate acid. One possible explanation is that the C−H abstraction is mediated by the aryliodonium radical cation, which would be associated with the chiral counteranion, rather than the phenyl radical; although anion effects on the latter cannot be discounted.[22] Second, the observations from Table 1 clearly show the influence of the diaryliodonium species in the stereodetermining step (see also Supplementary Tables S2 and S4). The initial hypothesis that the reaction proceeds through an oxonium intermediate generated from oxidation of the tetrahydrofuranyl radical would not account for the impact of the iodonium structure on diastereoselectivity. Therefore, it seems unlikely that the transformation is proceeding via a simple chiral phosphate-paired oxocarbenium intermediate.

Substrate Scope. Having established general conditions for the desired reaction, we probed the generality of this transformation using the two variants of the optimal reaction conditions. As depicted in Scheme 2A, achiral primary and secondary alcohols **1b**−**1h** bearing a range of substituents, such as alkyl, aryl, silyl, alkynyl, boronic ester, and heterocycle, were well tolerated as the nucleophilic partner. For these reactions, control of diastereoselectivity was achieved through the chirality of **C5**. Possible double stereodifferentiation using chiral alcohols **1i** and **1j** resulted in a negligible impact upon the stereoselectivity of the reaction. Similarly, amino alcohol **1k** underwent direct acetalization forming **3ka** with excellent chemo- and diastereoselectivity. Secondary alcohols **1p** and **1s** were found to be less reactive toward C−H acetalization due to the considerable steric hindrance. The decrease in reactivity of the secondary alcohols allowed for competitive trapping by residual water and the formation of undesired acetals **C** and **C′** (see also Supplementary Table S9).

In addition to the scope of alcohols, the scope of both achiral **2b**,**2c** and optically pure cyclic ethers **2d**−**2j** was further examined (Scheme 2B). Successively increasing the steric requirements at the α-oxy position of cyclic ether ring showed a trend toward an enhanced selectivity of bond scission accompanied by an improvement in diastereoselectivity. The selective access to either *trans*- or *cis*-2,3-dideoxyfuranose derivatives **3ae**−**3ah** highlights the breadth of this reaction where a notable example is the diastereoselective and regioselective functionalization of **2h**, which possesses multiple α-oxy C−H bonds. In addition, reaction with tetrahydropyranyl substrate **2i** was also tested. In this case, we observed similar trend in regioselectivity between both α-C−H bonds but with moderate stereochemical control.

A large excess of cyclic ether was required to achieve useful yields of the desired acetals; however, a roughly equal amount of **2a** relative to the alcohol was consumed during the reaction, and the unreacted **2a** was simply recovered by distillation under vacuum. We also explored the impact of lowering the equivalents of cyclic ether on reaction outcome. With alcohols possessing reactive C−H bonds (e.g., *para*-methoxybenzyl alcohol), excess of the cyclic ether is required to overcome competing oxidation of the alcohols to the corresponding carbonyl compound **A** (see Supplementary Table S7). When alcohols less prone to C−H abstraction were employed as nucleophiles, lower equivalents of tetrahydrofuran resulted in competing arylation of the alcohol to form aryl ethers **B**, even in the absence of a strong base (see Supplementary Table S8).[23] Finally, we note that introduction of molecular sieves to the reaction medium was critical to maximizing the yield of **3aa**. In the absence of molecular sieves, residual water was identified as the competing nucleophile leading to a mixture of

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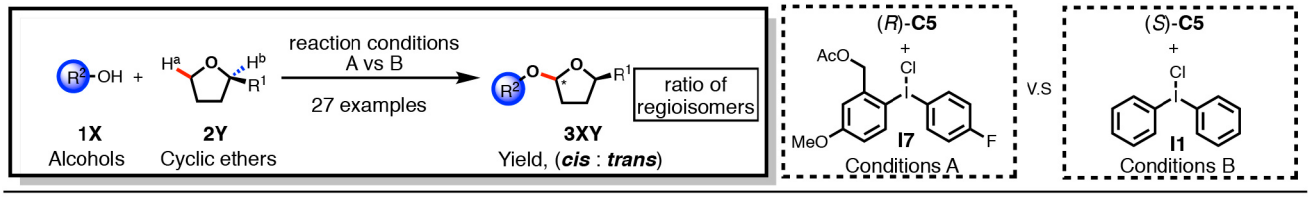
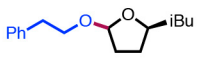
Scheme 2. Scope of Alcohols and Substituted Cyclic Ethers in Diastereoselective α-C(sp^3)−H Acetalization[a]

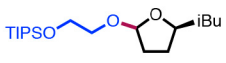


(A) Scope of alcohols

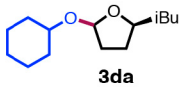
- Achiral primary & secondary alcohols



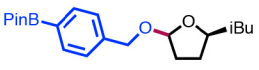
3ba
Conditions A -> 70%, (**86.5** : 13.5)
Conditions B -> 67%, (14.5 : **85.5**)



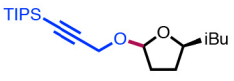
3ca
65%, (**92** : 8)
50%, (13.5 : **86.5**)



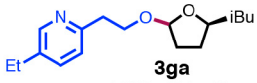
3da
42%, (**91** : 9)
47%, (10 : **90**)



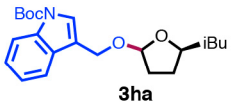
3ea
72%, (**91** : 9)
60%, (16 : **84**)



3fa
50%, (**89** : 11)
62%, (15 : **85**)

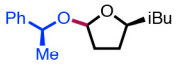


3ga
75%, (**91** : 9)
60%, (14.5 : **85.5**)

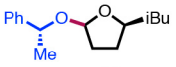


3ha
40%, (**82.5** : 17.5)
48%, (15 : **85**)

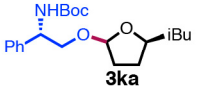
- Simple optically pure alcohols



3ia
72%, (**89** : 11)
76%, (13 : **87**)



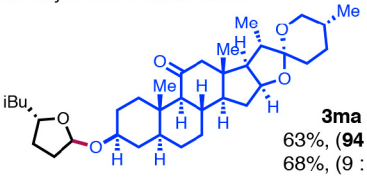
3ja
46%, (**85.5** : 14.5)
50%, (10 : **90**)



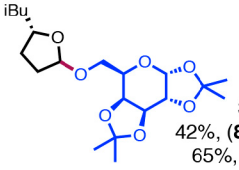
3ka
62%, (**91** : 9)
61%, (19 : **81**)

- Naturally occurred alcohols, carbohydrates & nucleosides

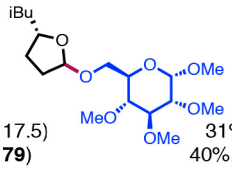
3la
57%, (**93** : 7)
53%, (9 : **91**)



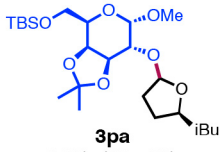
3ma
63%, (**94** : 6)
68%, (9 : **91**)



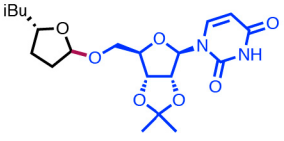
3na
42%, (**82.5** : 17.5)
65%, (21 : **79**)



3oa
31%, (**83** : 17)
40%, (11.5 : **88.5**)

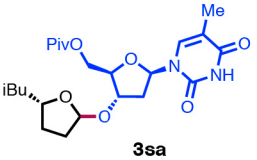


3pa
34%, (**82** : 18)
32%, (5.5 : **94.5**)



3qa
56%, (**93** : 7)
68%, (9 : **91**)

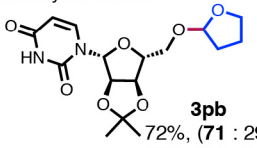
3ra
62%, (**86.5** : 13.5)
65%, (9.5 : **90.5**)



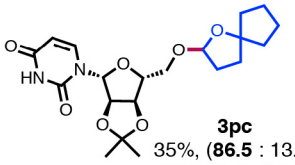
3sa
33%, (**85** : 15)
26%, (23 : **77**)

(B) Scope of cyclic ethers

- Achiral cyclic ethers

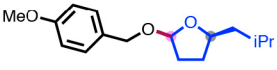


3pb
72%, (**71** : 29)
78%, (14 : **86**)



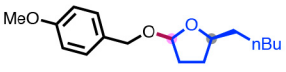
3pc
35%, (**86.5** : 13.3)
38%, (8.5 : **91.5**)

- Chiral THF & THP motifs



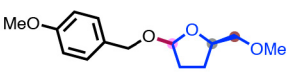
3aa
81%, (**85.5** : 14.5)
68%, (17.5 : **82.5**)

Conditions A: 85% / 15% | 86% / 14%
Conditions B



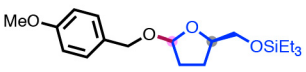
3ad
64%, (**86** : 14)
50%, (18.5 : **81.5**)

70% / 30%
75% / 25%



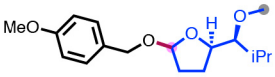
3ae
49%, (**90** : 10)
44%, (13.5 : **86.5**)

64% / 18% / 18%
62% / 19% / 19%



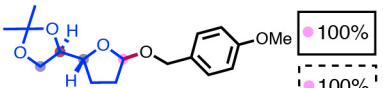
3af
35%, (**86.5** : 13.5)
40%, (13 : **87**)

87% / 13% | 85% / 15%



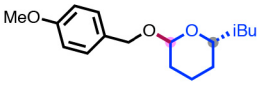
3ag
55%, (**87** : 13)
50%, (28 : **72**)

88% / 12%
88% / 12%



3ah
30%, (**96** : 4)
26%, (7: **93**)

100%
100%



3ai
24%, (16 : **84**)
20%, (**74.5** : 25.5)

84% / 16% | 81% / 19%

[a]Reaction conditions: (A) **1X** (0.10 mmol), **2Y** (2.50 mmol), (*R*)-**C5** (10.0 μmol), **I** (0.25 mmol), $NaHCO_3$ (0.50 mmol), 3 Å MS, MTBE (0.20 mL, ~0.20 M), 23 W CFL, 24 h; (B) **1X** (0.10 mmol), **2Y** (2.50 mmol), (*S*)-**C5** (10.0 μmol), **I1** (0.25 mmol), $NaHCO_3$ (0.50 mmol), 3 Å MS, MTBE (0.20 mL, ~0.20 M), 23 W CFL, 24 h. Ratio of diastereomers (*cis*-/*trans*-**3XY**) and ratio of regioisomers were determined by ^{1}H NMR. Isolated yields of **3XY** are shown.

DOI: 10.1021/jacs.8b05962
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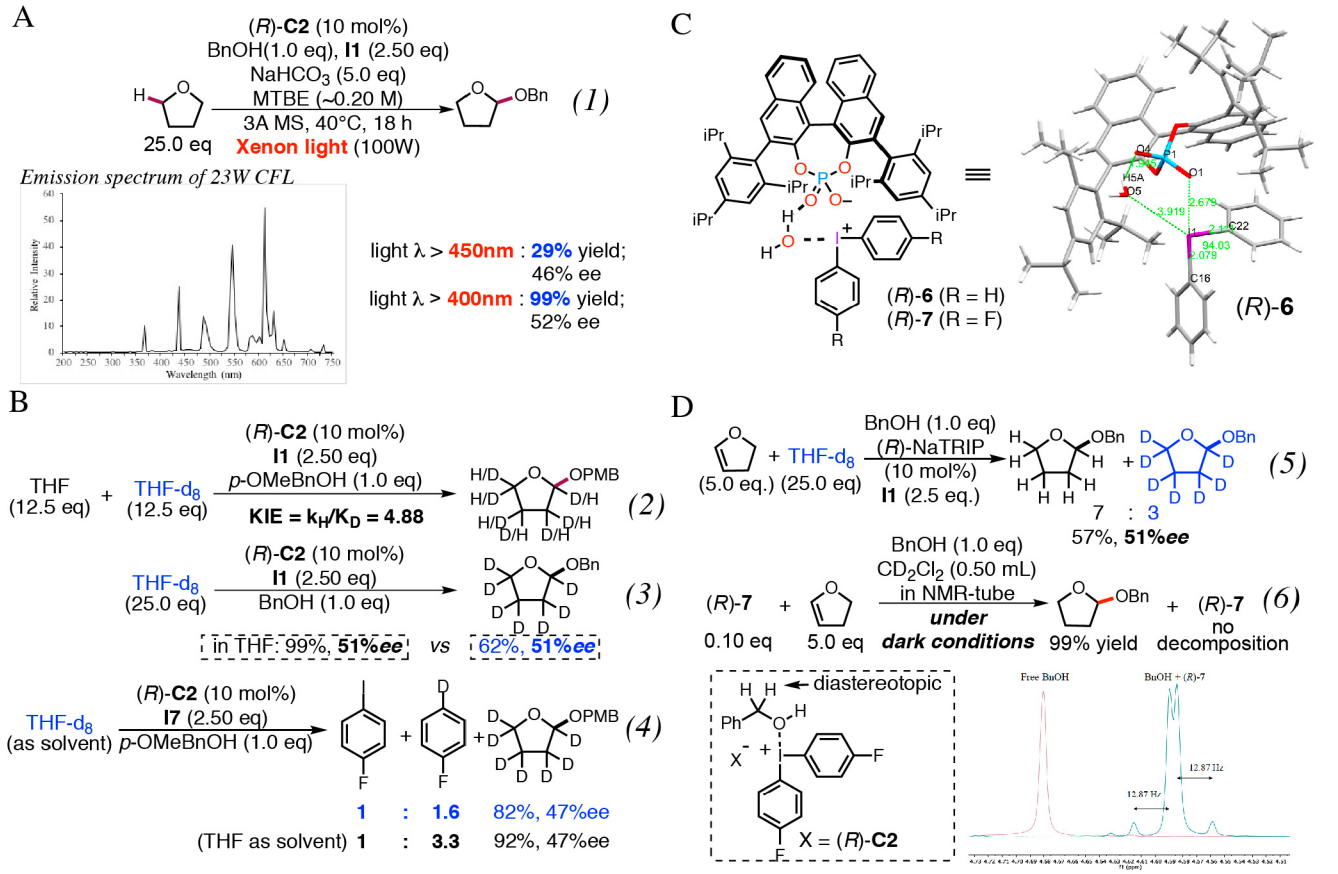
Scheme 3. Investigation of Mechanism



mono- and bis-acetals as side products **C** and **C′** (see Supplementary Table S9)

Mechanistic Studies. Functionalization reactions of THF were explored in order to gain a better understanding of the mechanistic pathway and origin of the observed selectivities (Scheme 3). Since irradiation was essential for any of the C−H bond cleavage events, we determined the UV−Vis spectra of various diaryliodonium salts. Consistent with previous reports, these salts displayed relatively weak absorptions in the near UVA region (Figure S2−S5). The employed CFL showed emission range of 360−440 nm; however, previous reports have suggested appreciable quantum yield of photolysis can occur at wavelengths >300 nm at the tail end of the absorption band of the diaryliodonium salts.[21b] Indeed, experiments conducted with filtered light from a 100 W xenon lamp showed that wavelengths in the low 400 nm range effectively promoted the transformation (Scheme 3A).

Having established a light-driven process as critical for the transformation, we next explored the C−H functionalization event. The measured competition deuterium kinetic isotope effect (KIE = 4.88, Scheme 3B, eq 2) is comparable to that previously measured for processes involving phenyl radical abstraction from THF.[24] On the other hand, use of THF-d_8 as a substrate did not influence the stereochemistry of the transformation, which indicates that the C−H abstraction is decoupled from the stereodetermining step (Scheme 3B, eq 3). Consistent with this conclusion, although both arenes of iodine(III) species can act as the HAT abstractors, the selectivity of their homolytic cleavage gave no notable influence on the stereochemical outcome of the transformation (Scheme 3B, eq 4, see also Supplementary eqs S4 and S5).

The results above are consistent with a C−H functionalization event likely occurring by a light induced H-atom abstraction that is separate from the C−O bonding forming event; therefore, we sought to gain insight into the mechanism of the stereodetermining C−O bond forming reaction. A control experiment using complex (*R*)-7 in the absence of benzyl alcohol led to the identification of 2,3-dihydrofuran as a potential intermediate in the transformation (Supplementary eq S11). Consistent with this hypothesis, under identical reaction conditions, utilizing benzyl alcohol and 2,3-dihydrofuran as the ether substrate, we observed the formation of desired acetal without decomposition of (*R*)-7 (Scheme 3D, eq 6, see also Supplementary eq S15). Moreover, almost identical stereochemical outcome was observed starting with either 2,3-dihydrofuran or THF (Scheme 3D, eq 5). Finally, the stereoselectivity outcome of these transformations was significantly different from that obtained using conventional Brønsted acid catalysis,[25] in which the product was formed in lower enantiomeric excess (Supplementary eq S17).

These observations suggest two possibly competing pathways for C−O bond formation: direct trapping of the initially formed ion-paired oxonium intermediate **4** to give the product **3** or conversion of **4** to the dihydrofuran, which undergoes acid mediated conversion to **3**. The difference in stereoselectivity observed between phosphoric acid-catalyzed reaction in the presence and absence of the diaryliodonium salt and the impact of diaryliodonium salt structure on selectivity from the tetrahydrofuranyl starting materials suggest that the diary-

DOI: 10.1021/jacs.8b05962
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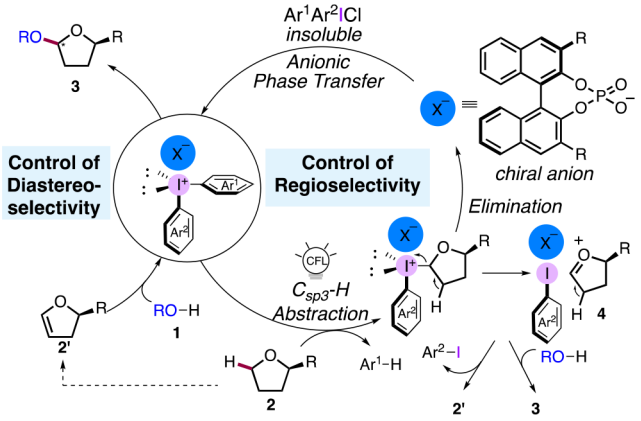
liodonium reagent is intimately involved in the C−O forming step. Notably, interaction between the alcohol and chiral phosphate-paired diaryliodonium complex (*R*)-**7** was detected by ^{1}H NMR spectroscopy (Scheme 3D). All together, these results support the putative mode of hydroalkoxylation of an enol ether catalyzed by the chiral phosphate-paired Lewis-acidic diaryliodonium species (Scheme 4). This hypothesis is

Scheme 4. Putative Mechanism



consistent with the observation that, while the stereoselectivity is not impacted by the selectivity of iodonium aryl cleavage, the identity of the intact diaryliodonium reagent influences the stereocontrol and is therefore involved in the stereodetermining step.

The structure of the iodine(III)−phosphoric acid ion pair (*R*)-**6** was unambiguously established by X-ray crystallography (Scheme 3C).[26] The water bound structure of (*R*)-**6**, featuring an ionic interaction (I(1)−O(1) = 2.679 Å),[27] demonstrates the viability of coordination of the alcohol to the Lewis acid iodine(III) center (Scheme 3D).[28] The interaction between the alcohol and the chiral phosphate might enhance the acidity of the alcohol and places the alcohol in the chiral environment created by the phosphate allowing for diastereoselective enol ether hydroalkoxylation.[25a,29]

CONCLUSION

In summary, we have elaborated an unprecedented protocol for the stereoselective α-C(sp^3)−H acetalization of cyclic ethers. A combination of the anionic phase-transfer concept together with the photochemical properties of iodonium salts was harnessed to enable site-selective C−H bond activation. Using this catalyst system, the chirality of the chiral phosphate allows for the selective formation of *trans*- and *cis*-acetals with high functional group compatibility and excellent scope. More broadly, the observation that chiral phosphate anions can be paired with diaryliodonium reagents in stereoselective processes suggests that this strategy could be leveraged to control other radical-mediated asymmetric transformations involving these reagents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b05962.

Crystallographic data for compound (*R*)-**6** (CIF)

Materials and methods, synthetic and characterization procedures, supplementary figures, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank NIGMS (R35 GM118190) for support of this work. B.Y. is grateful to the Swiss National Science Foundation (SNSF) for a postdoctoral mobility fellowship (P2ELP2_158881). We thank Jingjing Yang and Nichlolas Settineri (UC Berkeley) for X-ray crystallography assistance. We thank Dr. Vaneet Saini (Novartis) for help with the preparation of chiral cyclic ethers. We thank Dr. Ming Gong for help with Xenon light equipment and Dr. Miao Zhang for help with HRMS and IR studies. Metrical parameters for the structures of compound (*R*)-**6** are available free of charge from Cambridge Crystallographic Data Centre under reference number CCDC 1580352 with all other data available in the supplement.

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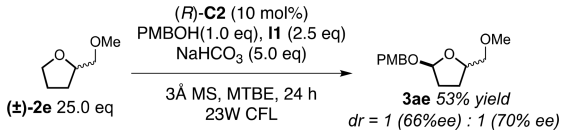

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