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O–H Hydrogen bonding promotes H-atom transfer from α C–H bonds for C-alkylation of alcohols

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The efficiency and selectivity of hydrogen atom transfer from organic molecules is often difficult to control in the presence of multiple potential hydrogen atom donors and acceptors. Herein, we describe the mechanistic evaluation of a mode of catalytic activation that accomplishes the highly selective photoredox α-alkylation/lactonization of alcohols with methyl acrylate via a hydrogen atom transfer mechanism. Our studies indicate a unique role of tetra-*n*-butylammonium phosphate in enhancing the selectivity for α C–H bonds in alcohols in the presence of allylic, benzylic, α-C=O, and α-ether C–H bonds.

Complex molecules, such as medicinal agents and natural products, often possess multiple types of C–H bonds, each with a different inherent reactivity. This intrinsic reactivity depends on a multi-faceted interplay of steric effects, inductive and conjugative influences, as well as innate strain (*1*, *2*). The intermolecular catalytic functionalization of C(sp^3)–H bonds in a selective manner represents a longstanding challenge that has inspired decades of effort within the synthetic community. Notable early studies by Bergman (*3*), as well as recent advances in selective intermolecular transition metal catalyzed C(sp^3)–H activation—including, among others, Hartwig's rhodium-catalyzed borylation of terminal methyl groups (*4*), and White's iron-catalyzed oxidation of both secondary (2°) and tertiary (3°) aliphatic C–H bonds (*5*)—highlight the importance of catalyst structure on site selectivity.

Catalyst structure has also proven critical to the selectivity of C(sp^3)–H functionalization via hydrogen atom transfer (HAT) catalysis. HAT—the effective movement of a hydrogen atom between two molecular sites—represents a ubiquitous elementary reaction step in organic chemistry (*6*–*8*). The rate of hydrogen abstraction from a C–H bond depends not only on the C–H bond dissociation enthalpy (BDE), but also on polar effects in the transition state. In 1987, Roberts noted that certain electrophilic radicals (e.g., *t*-butoxyl) preferentially abstract hydrogen from electron-rich C–H bonds, while nucleophilic radicals (e.g., amine-boryl) selectively cleave electron-deficient C–H bonds (*9*). The generality of this concept was subsequently delineated through the broad application of polarity reversal catalysis (PRC), which takes advantage of favorable polar effects to control the regioselectivity of HAT from multiple C–H groups of similar strength (*10*).

We questioned whether the basic principles of PRC could be integrated into a catalytic system for the selective activation of alcohol α-C–H bonds in the presence of a wide range of other C–H bonds (e.g., α-C=O, α-ether, allylic or benzylic C–H) (*11*, *12*). Specifically, we postulated that the selective C-alkylation of alcohols could be achieved via a photoredox-catalyzed, H-bond-assisted bond activation strategy (Fig. 1) (*13*–*15*), wherein the hydroxyalkyl C–H bond is selectively polarized and weakened via O–H hydrogen bonding.

It is well known that the strength of α C–H bonds of alcohols decreases upon deprotonation of the alcohol O–H group. This so-called "oxy anionic substituent effect" (*16*, *17*) leads to the acceleration of a wide range of organic reactions (e.g., oxyanionic [1,3] and [3,3] sigmatropic rearrangements and HAT from alkoxides (*18*)). More recently, it has been shown that intermolecular hydrogen bonding between alcohols and various acceptor molecules gives rise to a similar polarization and weakening of the adjacent C–H bond (*19*), the strength of which is reflected in the ^{13}C NMR chemical shift and the one-bond ^{13}C–^{1}H coupling constant ($^{1}J_{CH}$) (*20*, *21*). In particular, it was found that a 1 kJ/mol increase in the enthalpy of the H-bond resulted in a 0.2 Hz decrease in $^{1}J_{CH}$ for hexafluoroisopropanol complexed to various amines (*20*). On the basis of these studies, we reasoned that the efficiency and selectivity of alcohol C–H activation could be enhanced by catalytic complexation with a suitable hydrogen-bond acceptor. In particular, interaction of the hydroxyl group of an alcohol with a hydrogen-bond acceptor catalyst should increase n–σ* delocalization of the oxygen lone pair, thereby rendering the α C–H bond more hydridic (i.e., more polarized) and more susceptible to HAT by an elecrophilic radical species.

Herein, we demonstrate the selective α-activation of alcohol C–H bonds in the presence of allylic, benzylic, α-oxy and α-acyl C–H groups via a photoredox protocol, which relies on the cooperation of three distinct catalysts: an iridium-based photoredox catalyst; an HAT catalyst; and tetra-*n*-butylammonium phosphate (or TBAP), a hydrogen-bonding catalyst. On the basis of kinetic analyses, NMR structural data, and kinetic isotope effects (KIEs), we demonstrate the role of TBAP in facilitating the highly selective α hydrogen atom abstraction from alcohols.

The past several years have witnessed a dramatic increase in the application of photoredox catalysis—the use of visible light-activated organic dyes or metal complexes to facilitate single electron transfer events—to the development of organic transformations (*22*). By combining photoredox activation with organocatalysis (*23*, *24*) and nickel catalysis (*25*), we have recently highlighted the unique potential of photoredox catalysis to achieve bond constructions that are not possible with more traditional methods.

We became interested in the selectivity and efficiency of C–H bond activation in the context of our ongoing campaign to merge visible light photoredox catalysis with HAT catalysis (*26*–*29*). We have previously demonstrated the utility of thiols (S–H BDE = 87 kcal/mol) as HAT catalysts in the photoredox coupling of benzylic ethers (C–H BDE = 86 kcal/mol) with arenes (*26*) and imines (*27*). We recognized that the ability to catalytically activate stronger C–H bonds, such as those present in aliphatic alcohols and ethers (α C–H BDE > 90 kcal/mol), would hinge on the identification of a catalyst that satisfies two critical requirements: (i) homolytic cleavage of a strong substrate C–H bond must be counterbalanced by formation of a stronger H–[catalyst] bond, and (ii) selective activation of hydridic C–H bonds (i.e., bonds that are significantly polarized due to oxygen lone pair donation) must be realized. With these criteria in mind, we questioned whether it might be possible to transiently generate a hydridophilic amine radical cation from quinuclidine (**3**, Fig. 2A), which would be uniquely suited to abstraction of relatively strong, hydridic C–H bonds, while resisting α-deprotonation due to poor H–C–N orbital overlap in this rigid bicyclic structure (*30*, *31*). As outlined in Fig. 2A, we envisioned an initial excitation of the well known photocatalyst, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ [dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**1**), to $*Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ (**2**) with visible light. Reductive quenching of **2** ($E_{1/2}^{red}$ = +1.21 V vs. SCE in CH_3CN) (*32*) via oxidation of **3** ($E_{1/2}^{ox}$ = +1.1 V vs. SCE in CH_3CN) (*33*, *34*) would then afford radical cation **4** and Ir(II) (**5**). At this stage, the electrophilic quinuclidinium radical **4** should abstract a hydrogen atom from an alcohol (**6**) to afford α-hydroxy radical **7** and quinuclidinium ion **8** [H–N^+ BDE = 100 kcal/mol, (*33*)]. Nucleophilic addition of α-oxy radical **7** to an electron-deficient alkene would furnish alkyl radical **9**. Single electron reduction of this electron-deficient radical **9** by Ir(II) (**5**) ($E_{1/2}^{red}$ = –1.37 V vs. SCE in CH_3CN), would then afford the α-alkylated product **10** following protonation and lactonization, while simultaneously regenerating both the photocatalyst (**5**→**1**) and the HAT catalyst (**8**→**3**) (*35*, *36*).

We initially validated our proposed alkylation protocol by subjecting 1-hexanol (**11**) and methyl acrylate to blue light in the presence of amine **3** (10 mol%) and photocatalyst **1**, which afforded after 24 hours γ-nonalactone (**12**) in 67% yield after acidic work-up (Fig. 2B). We next evaluated a range of hydrogen-bond acceptor catalysts, including the tetra-*n*-butylammonium salts of phosphate, trifluoroacetate, and diphenyl phosphate (Fig. 2B). Superior levels of product formation were achieved with catalytic TBAP (25 mol%), which provided the desired lactone in 84% yield. Initial rate kinetic analysis of the alkylation/lactonization of **11** revealed rate enhancements in the presence of each hydrogen-bonding catalyst examined, with the largest initial rate acceleration using $Bu_4NCO_2CF_3$ or $Bu_4N(PhO)_2PO_2$ (r_{rel} = 2.6 and 2.5, respectively).

We next demonstrated that a wide range of 1° and 2° alcohols undergo selective α-hydroxy alkylation with methyl acrylate in good to excellent yields using TBAP catalysis (Fig. 2C). As outlined in Fig. 3, these conditions clearly enable the selective activation of alcohol C–H bonds in the presence of various α-oxy C–H groups, including cyclic and acyclic alkyl ethers (**21**, **24** and **25**, 85%, 71% and 77% yield, respectively); silyl ethers (**23**, 73% yield); and esters (**22**, 81% yield). Moreover, excellent selectivity was achieved in the presence of both allylic and benzylic hydrogens (e.g., **26**–**29**, 70–75% yield). The selectivity of this H-bond-assisted C–H activation platform was further demonstrated via the C–H alkylation/lactonization of bifunctional steroid derivatives, which provided the corresponding lactone products in good levels of efficiency (**25** and **26**, 77% and 70%, respectively). It should be noted that electron-deficient α-benzoyloxy and α-acyl C–H bonds (**22** and **26**) are expected to be inherently deactivated toward HAT with respect to electrophilic radical HAT systems (*10*), such as quinuclidinium radical cation. In the absence of TBAP, higher levels of substrate concentration were required to achieve useful efficiencies. However, under those conditions, non-selective C–H abstraction of weaker, less hydridic C–H bonds was observed. Importantly, in all cases outlined in Fig. 3, we only observed alkylation products arising from the activation of the hydroxyalkyl C–H bonds present in the various substrates.

We next turned our attention to defining the capacity for selective α-hydroxy C–H functionalization in the presence of C–H bonds that have similar polarity and strength. Specifically we selected tetrahydrofuran (THF) as a prototypical ether substrate, which would normally undergo C–H activation via HAT with rates similar to alcohol substrates. Indeed, we found that the dual catalytic system involving quinuclidine and photoredox catalyst **1** enabled the efficient alkylation of THF with rates that were competitive with 1-hexanol in competition experiments, affording a 1.7:1 mixture of lactone and ether products (Fig. 4A) (*37*). However, the addition of 25 mol% of TBAP catalyst enabled a dramatic increase in overall reaction selectivity to afford almost exclusively the alcohol C–H alkylation product (75% lactone, 1% ether).

To further understand the role of hydrogen-bonding in this H-bond-assisted C-alkylation process, a series of computational calculations and NMR experiments were undertak-

en. These studies were to evaluate the interaction of 1-hexanol with various hydrogen-bonding catalysts (highlighted in Fig. 2B) and to determine their accompanying effect on the α-hydroxy C–H bond strength. Density functional theory (DFT) calculations, were performed using an unrestricted B3LYP functional with a 6–31G basis set. In the presence of either phosphate, diphenyl phosphate, or trifluoroacetate tetrabutylammonium salts, a BDE weakening of approximately 3 kcal/mol was calculated (see Supplementary Material). While this represents a significant change in the α-C–H BDE of 1-hexanol from 94.1 kcal/mol to 91.0 kcal/mol when bonded to the TBAP catalyst, it clearly demonstrates that BDE is not the only factor defining this HAT selectivity and bond polarization effects are likely important.

NMR experiments were also performed to explore the influence of both quinuclidine and TBAP as hydrogen-bonding catalysts for 1-hexanol. In the absence of either additive, the ^{13}C NMR chemical shift of the α carbon of 1-hexanol (δC1) in $CDCl_3$ (*38*) appeared at 63.1 ppm with $^1J_{CH[hexanol]}$=141.1 Hz. Addition of an equimolar amount of quinuclidine resulted in a 0.4 ppm upfield shift ($\delta C1_{hexanol:\mathbf{3}}$=62.7 ppm) and a slight decrease in the one-bond ^{13}C–^{1}H coupling constant ($^1J_{CH[hexanol:\mathbf{3}]}$ = 140.4 Hz). For comparison, a 1:1 mixture of 1-hexanol and TBAP gave rise to a similarly upfield shift in the ^{13}C signal for C1 of 1-hexanol ($\delta C1_{hexanol:TBAP}$ = 62.6 ppm; $\Delta\delta$C1=0.5 ppm), with $^1J_{CH(hexanol:TBAP)}$ = 140.3 Hz. These data clearly indicate that both quinuclidine and TBAP can induce bond weakening of the α-C1–H of 1-hexanol via hydrogen bonding. These data are also consistent with decreased *s*-character in the hybrid carbon orbitals of the C–H bond (i.e., increased hydridicity) of hexanol upon H-bond formation (*39*).

To more thoroughly outline the factors governing both the rate and selectivity of the C-alkylation of alcohols, a suite of mechanistic experiments was undertaken. The initial rate of the reaction of 1-hexanol with methyl acrylate showed first-order dependence on $[hexanol]_{init}$ and $[acrylate]_{init}$. The observed increase in the initial rate of reaction in the presence of TBAP (Fig. 2B), coupled with first-order dependence on both reactants, implies that TBAP serves to lower the energy barrier of: (i) the C–H abstraction step (due to α-C–H bond weakening); (ii) the C–C bond forming step, i.e., addition of radical **9** to methyl acrylate (due to enhanced nucleophilicity of the H-bonded α-hydroxy radical); or (iii) a combination of both of these steps.

In order to distinguish between these three possibilities, a series of experiments was conducted to assess potential deuterium kinetic isotope effects on the C–H abstraction step of the proposed catalytic cycle. First, the rate constants for the coupling of methyl acrylate with either 3-pentanol or D-3-pentanol (**30**→**16**, Fig. 4B) were found to be identical, i.e., KIE = 1, clearly demonstrating that C–H/D abstraction from the alcohol **30** does not occur during the turnover-limiting transition state (TLTS) of our proposed catalytic cycle (Fig. 2A). However, an intramolecular competition experiment of mono-deuterated alcohol **31** afforded a mixture of deuterated and undeuterated lactones (P_D and P_H) with a 1.6:1 ratio (Fig. 4C). This result demonstrates that even though C–H/D abstraction is not rate-limiting, it represents the selectivity-determining step of the C-alkylation of hexanol **31**. The recovered starting material from this experiment did not contain any fully protonated 1-hexanol nor d_2-hexanol, confirming that C–H/D abstraction is irreversible in this process. The irreversibility of the C–H abstraction step was further confirmed by two additional experiments: first, in an intermolecular competition between 1-hexanol and di-deuterated hexanol **32** (Fig. 4D), in which no amount of mono-deuterated alcohol **31** was detected during the process; and second, in the C-alkylation of enantiopure alcohol **33** (Fig. 4E), in which no racemization of starting material was observed upon recovery of excess starting material (*40*). Taken together, these results are consistent with the mechanistic scenario (iii): a dual role of TBAP in both accelerating the C–H abstraction from alcohols and enhancing the rate of addition of the resulting radical to Michael acceptors (*41*).

Finally, compelling experimental evidence for our proposed C–H activation pathway was attained in the form of initial rate data for the conversion of cyclopropyl radical clock alcohol **35** to aldehyde **36** in the presence and absence of TBAP catalyst (Fig. 4F). Specifically, we reasoned that C–H abstraction from **35** to generate the 2-(alkoxycarbonyl)cyclopropylcarbinyl radical (rate constant for rearrangement = 5–8 × 10^{10} s^{-1} at 25°C (*42–44*)] would be rate-limiting. As such, enhancement in the rate of C–H abstraction via H-bond-assisted C–H activation should be clearly manifested in the observed rate of conversion of **35** to **36** in the presence and absence of TBAP catalyst. Indeed, under our photoredox/HAT conditions, a nine-fold rate enhancement in the rate of conversion of alcohol **35** to aldehyde **36** was observed upon addition of 25 mol% TBAP (*45*). This result clearly corroborates our mechanistic proposal, wherein TBAP facilitates C–H abstraction from alcohols via hydrogen bond activation. The activation concept presented here is likely pertinent to a wide range of C–H abstraction reactions.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
References (*46*–*83*)
Data
DFT Calculations

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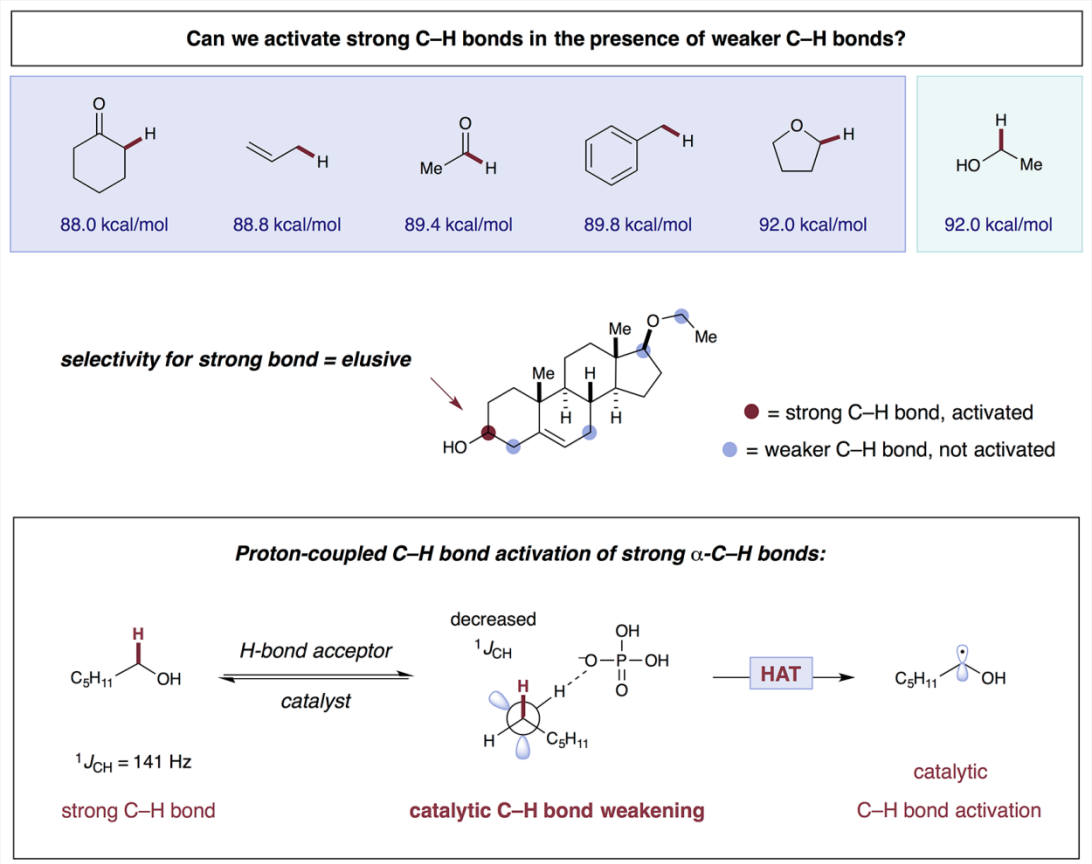

Fig. 1. Proposed hydrogen bond assisted C–H activation of alcohols. See (*13–15*) for BDE values.

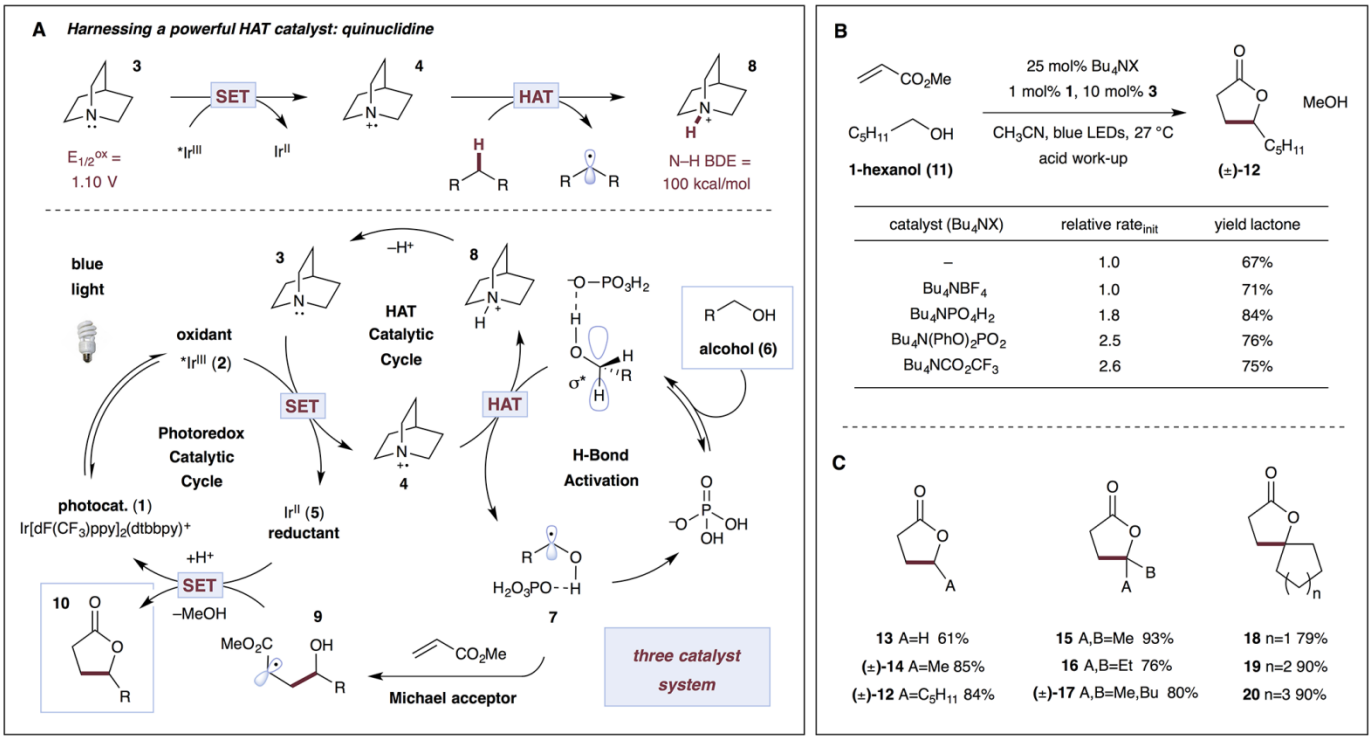

Fig. 2. Reaction development. (A) H-bond-assisted C–H activation of alcohols: proposed mechanistic pathway for the C-alkylation of alcohols with Michael acceptors. SET = single-electron transfer. HAT = hydrogen atom transfer. (B) Evaluation of hydrogen-bonding catalysts. Yield determined by ^{1}H NMR using an internal standard. (C) Selected scope of simple alcohol addition to methyl acrylate (only products are shown; experimental conditions as in B). Isolated yields are reported.

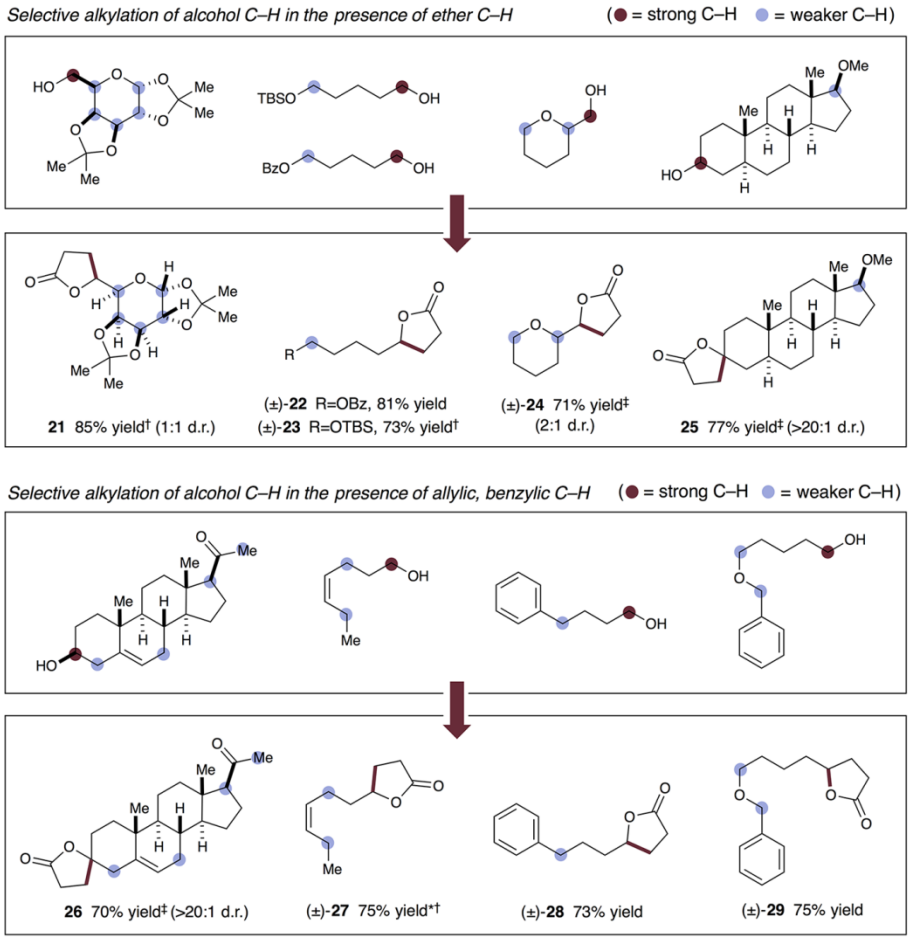

Fig. 3. Selected alcohol scope for H-bond-assisted C–H activation. Additions to methyl acrylate were carried out at 27°C for 24 hours, unless otherwise noted. Isolated yields are reported. See SM for detailed experimental procedures and full scope of alcohols/Michael acceptors. †40 hours reaction time. ‡48 hours reaction time. *1:1 mixture of *E/Z* isomers. No alkylation of positions marked with blue circles observed in any case.

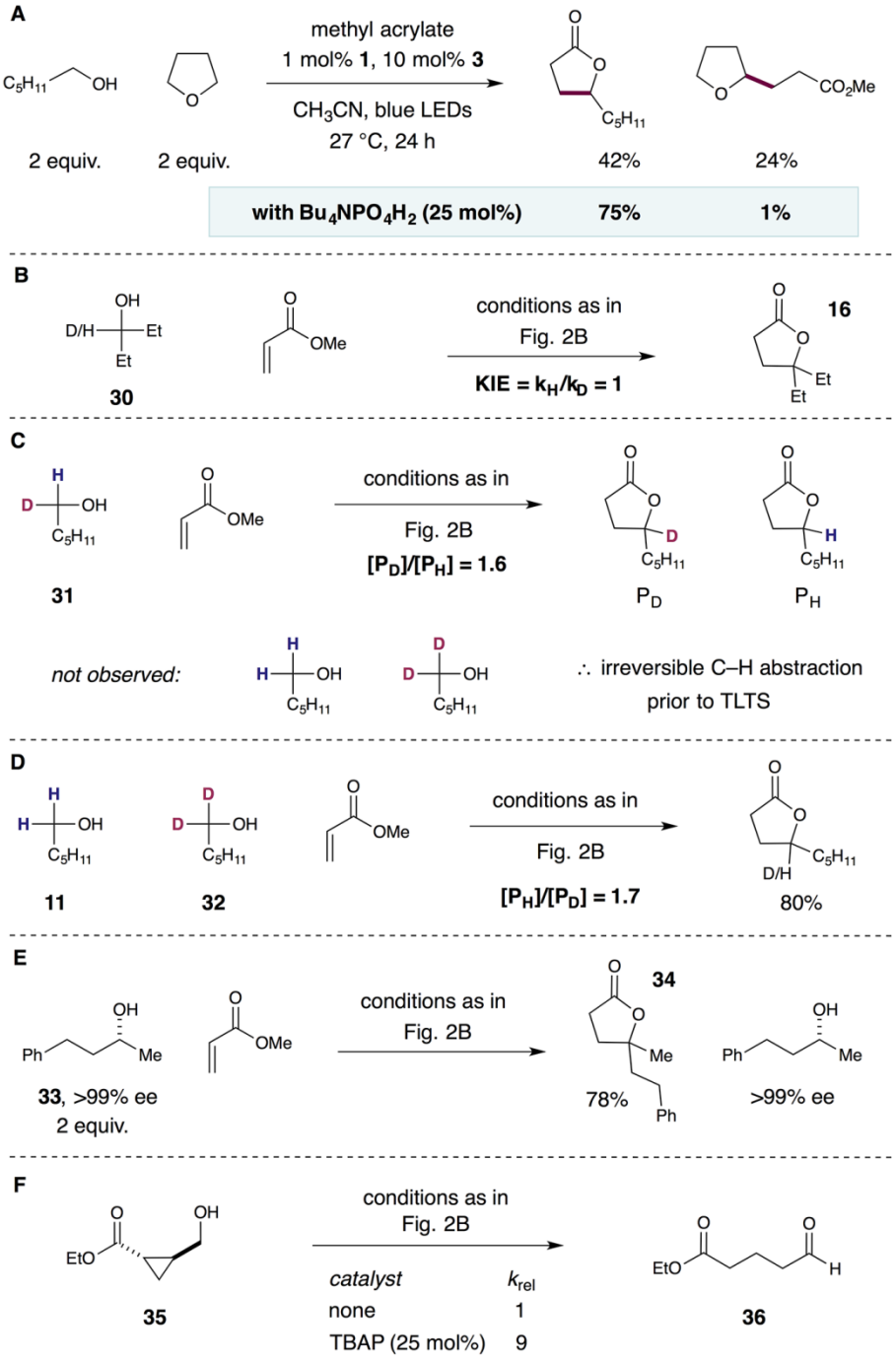

Fig. 4. Mechanistic studies. (**A**) H-bond-dependent selectivity of α-oxy C–H alkylation. (**B**) Kinetic isotope effect determined from two parallel kinetic analyses. (**C**) Kinetic isotope effect determined from intramolecular competition experiment. (**D**) Kinetic isotope effect determined from intermolecular competition experiment. (**E**) Evaluation of the enantiomeric excess of unreacted alcohol under standard C-alkylation conditions. (**F**) Effect of TBAP on the rate of C–H abstraction from **35**.