Proton-Coupled Electron Transfer in Organic Synthesis: Novel Homolytic Bond Activations and Catalytic Asymmetric Reactions with Free Radicals

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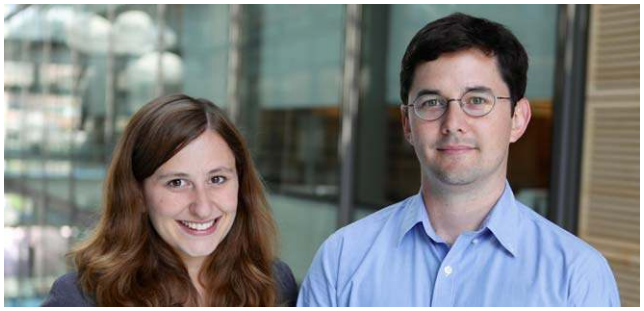
Abstract: Proton-coupled electron transfers (PCET) are unconventional redox processes in which an electron and proton are exchanged together in a concerted elementary step. While these mechanisms are recognized to play a central role in biological redox catalysis, their applications in synthetic organic chemistry have yet to be widely established. In this Account, we highlight two recent examples from our group outlining the use of concerted PCET as a platform for the development of catalytic and enantioselective reactions of neutral ketyl radicals. Central to this work was the recognition that PCET provides a mechanism for independent proton and electron donors to function jointly as a formal hydrogen atom donor competent to activate organic π systems that are energetically inaccessible using conventional H-atom transfer technologies. In addition, we found that neutral ketyls formed in the PCET event are remarkably strong hydrogen-bond donors and remain strongly associated to the conjugate base of the proton donor following the PCET event. When chiral proton donors are used, these successor H-bond complexes provide a basis for asymmetric induction in subsequent reactions of the ketyl radical.

Key words: asymmetric catalysis, radical reaction, electron transfer, free radicals, photochemistry



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Robert Knowles was born and raised in the Shenandoah Valley of Virginia and obtained his BA in chemistry from the College of William and Mary in 2003. He received his PhD in 2008 from Caltech, working in the labs of David MacMillan. After completing his doctoral studies, he was a NIH postdoctoral fellow in the labs of Eric Jacobsen at Harvard University. Since the Fall of 2011, he has been an assistant professor in the chemistry department at Princeton University.

1 Introduction

Reactions involving the concerted transfer of electrons and protons are now recognized to be key elementary steps in biological redox processes ranging from photosynthetic water oxidation and ribonucleotide reduction to C–H bond oxidation and natural product biosynthesis.[1] Consequently, over the past two decades such proton-coupled electron transfer (PCET) reactions have become a major focus of research across numerous chemical disciplines.[2] Yet to date, the potential benefits and applications of concerted PCET in synthetic organic chemistry remain largely unrecognized.[3] Our group has become interested in the potential of these mechanisms to address several long-standing challenges in the catalytic applications of free-radical intermediates in organic synthesis and asymmetric catalysis. In particular, we anticipate that the unique energetic features of concerted PCET have the potential to both enable direct radical generation from a broad number of common organic functional groups under unusually mild catalytic conditions and provide a means to associate a chiral catalyst with the resulting neutral free-radical intermediates during subsequent bond-forming events. Herein, we present a brief overview of PCET reactivity and highlight our initial results in the design and development of catalytic and enantioselective reactions of neutral ketyl radicals formed through a concerted PCET process.

2 Concerted PCET and Effective Bond Strengths

Our work in PCET was prompted by a more general interest in developing catalyst systems for reductive homolytic bond activations that are energetically inaccessible using conventional H-atom-transfer (HAT) agents. The synthetic feasibility of a given HAT process is in large part a function of the bond-strength differential between the two bonds undergoing exchange.[4] However, in the reductive

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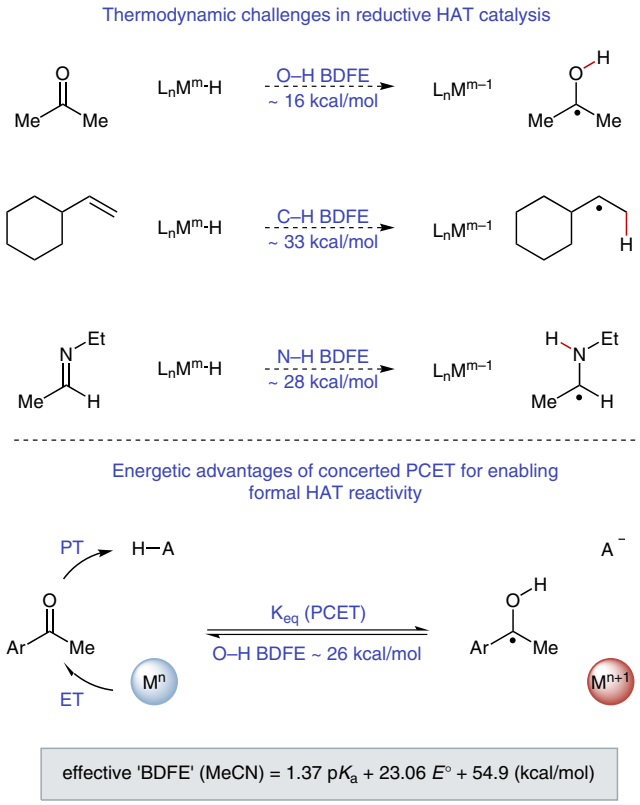
addition of H• to common organic π systems, the nascent bond to hydrogen is often extraordinarily weak as a result of destabilization by the vicinal unpaired electron (Scheme 1, b).[5] For example, the O–H bond in the ketyl of acetone exhibits a calculated bond-dissociation free energy (BDFE) of only ca. 16 kcal/mol[6] relative to ca. 105 kcal/mol[7] for the O–H bond in isopropanol, a remarkable weakening effect of more than 90 kcal/mol. Efficient HAT to these systems thus requires H• transfer from a comparably weak bond in the H-atom donor. As the weakest H-atom donors characterized to date exhibit BDFE ≥50 kcal/mol,[8] general catalytic systems that are energetically competent to activate ketones, imines, α-olefins, and many other common organic π systems are largely undeveloped[9,8a,b] (Scheme 1).



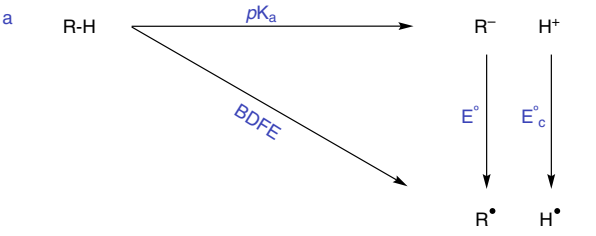
Scheme 1 Concerted PCET mechanisms and applications to thermodynamically challenging homolytic bond activations. Reported BDFE calculated at CBS-QB3 in the gas phase.[6]

Unfortunately, the rational design of more powerful HAT catalysts is complex, as illustrated by considering the energetic conventions used to define the strengths of covalent bonds. BDFE values are commonly evaluated using a thermodynamic cycle, first described by Wiberg and Breslow and later popularized by Bordwell, wherein the free energy required to heterolytically break a bond (as represented by a pK_a value) is summed together with the energies required to oxidize the resulting anion to a neutral radical and to reduce proton to H• (Scheme 2, a).[10] This formalism suggests that to further weaken the BDFE of the scissile X–H bond in a molecular H-atom donor, one must either increase its Brønsted acidity, make its conjugate base more reducing, or some combination thereof. Inconveniently, within a single molecule these two physical properties are interdependent and inversely correlated. As such, any energetic benefit derived from making a bond more acidic will be largely compensated for by a concomitant loss in the reducing ability of the resulting anion. These compensatory effects are general and typically confine specific classes of H-atom donors to a relatively narrow range of BDFE values.[2f]

However, Mayer recently pointed out that this method for conceptualizing covalent bond strengths is identical in form to the thermochemical description of multisite PCET reactions, wherein the proton and electron originate from site-separated and independent donors – a Brønsted acid and a one-electron reductant (Scheme 2, b).[2f] While no bond is physically homolyzed in such a process, Mayer noted that summing the pK_a values and redox potentials in an identical fashion provides an 'effective' bond strength, which quantitatively reflects the thermodynamic capacity of any acid–reductant combination to function jointly as a hydrogen atom donor. Significantly, in such a PCET event, the pK_a value of the proton donor and the potential of the reductant are decoupled, and can be varied independently.[11] This in turn allows the effective 'BDFE' of any given acid–reductant pair to be rationally modulated over a remarkably wide range of bond strengths (Scheme 2, c), including combinations capable of forming bonds that are >25 kcal/mol weaker than would be possible with even the weakest known molecular H-atom donors. As such, concerted PCET presents intriguing possibilities to enable formal HAT reactivity with a range of common organic functional groups that are otherwise energetically inaccessible using conventional technologies.

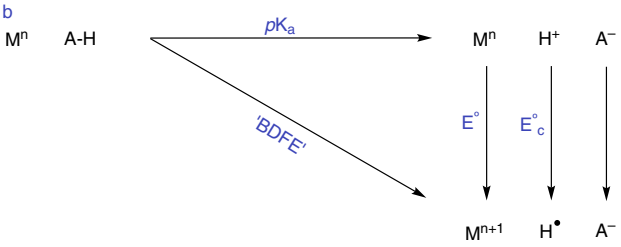
Remarkably, these enabling thermodynamic aspects of concerted PCET activation are frequently complimented by favorable kinetics.[2a,c,12] In fact, despite being intuitively unfavorable on entropic grounds, concerted PCET reactions often exhibit rates that are significantly faster than their constituent electron-transfer or proton-transfer steps in isolation (Scheme 2, d). This surprising observation follows from the fact that PCET kinetics, like those of electron transfer and HAT, are partly functions of the reaction's thermodynamic driving force.[12] The products formed directly in the concerted pathway are necessarily lower in energy than the intermediates generated in the competing stepwise pathways. The thermochemical bias to avoid higher energy intermediates along the reaction coordinate is often manifested as a diminished activation barrier for the concerted transfer. Significantly, this can enable rapid charge transfer to occur using redox catalysts whose potentials are far less energetic than the standard potentials of their substrates. This specific kinetic advantage is thought to underlie the pervasive use of PCET in biological redox catalysis,[1a,h] wherein specific hydrogen-bonding interactions and proton-transfer events modulate the rates and energetics of associated electron-transfer steps.

a



BDFE (kcal/mol) = 1.37 pK_a + 23.06 E^o + C

b



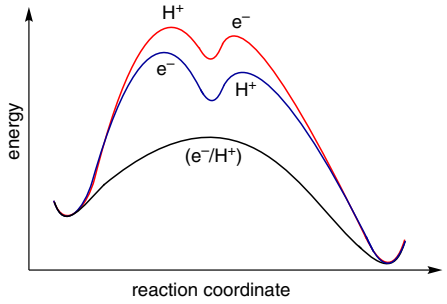
effective 'BDFE' (kcal/mol) = 1.37 pK_a + 23.06 E^o + C

c

Thermochemistry of PCET Donor Pairs

Reductant	Acid	E^o (V vs Fc)	pK_a (MeCN)	'BDFE' (kcal/mol)
$Ru^{I}(bpy)_3$	AcOH	–1.71	23.5	48
Cp^*_2Co	lutidinium	–1.47	14.1	40
Cp^*_2Co	PTSA	–1.47	8.6	33
$Ru^{I}(bpy)_3$	pyridinium	–1.71	12.5	33
$^*Ir^{III}(ppy)_3$	$(PhO)_2PO_2H$	–2.11	13	24

d



Scheme 2 (a) Thermodynamic cycle for BDFE determination in covalent bonds; (b) formalism for multisite PCET thermochemistry; (c) PCET catalyst pairs as formal H-atom donors; (d) kinetic advantages of concerted PCET.

3 Concerted PCET Activation of Ketones: A Catalytic Protocol for Ketyl–Olefin Coupling and Mechanistic Investigations

Seeking to explore the ideas presented above in a useful synthetic context, we set out to develop a new PCET-based protocol for catalytic ketyl–olefin coupling.[13] Ketyls are classical radical intermediates typically derived from the one-electron reduction of carbonyl compounds that have found extensive use in synthesis.[14] However, the forcing potentials required to generate ketyls by outer-sphere electron transfer (E = –2.48 V vs. Fc in MeCN for acetophenone) has significantly limited the development of catalytic ketyl chemistry and associated asymmetric variants. We recognized that neutral ketyl generation represents a formal addition of H• to the ketone π system, resulting in the formation of an unusually weak O–H bond (O–H BDFE = 26 kcal/mol for acetophenone ketyl). While inaccessible using conventional H-atom donors, the effective bond-strength formalism suggests that such a value is readily accessible through a concerted PCET process using combinations of redox agents and proton donors whose potentials and pK_a values are energetically far removed from those of the ketone substrate. In addition to providing a new way of conceptualizing difficult homolytic bond activations, this mechanistic framework for PCET also presents novel opportunities for catalyst-controlled asymmetric induction in the reactions of the resulting radical intermediates through direct hydrogen-bonding interactions (vide infra).

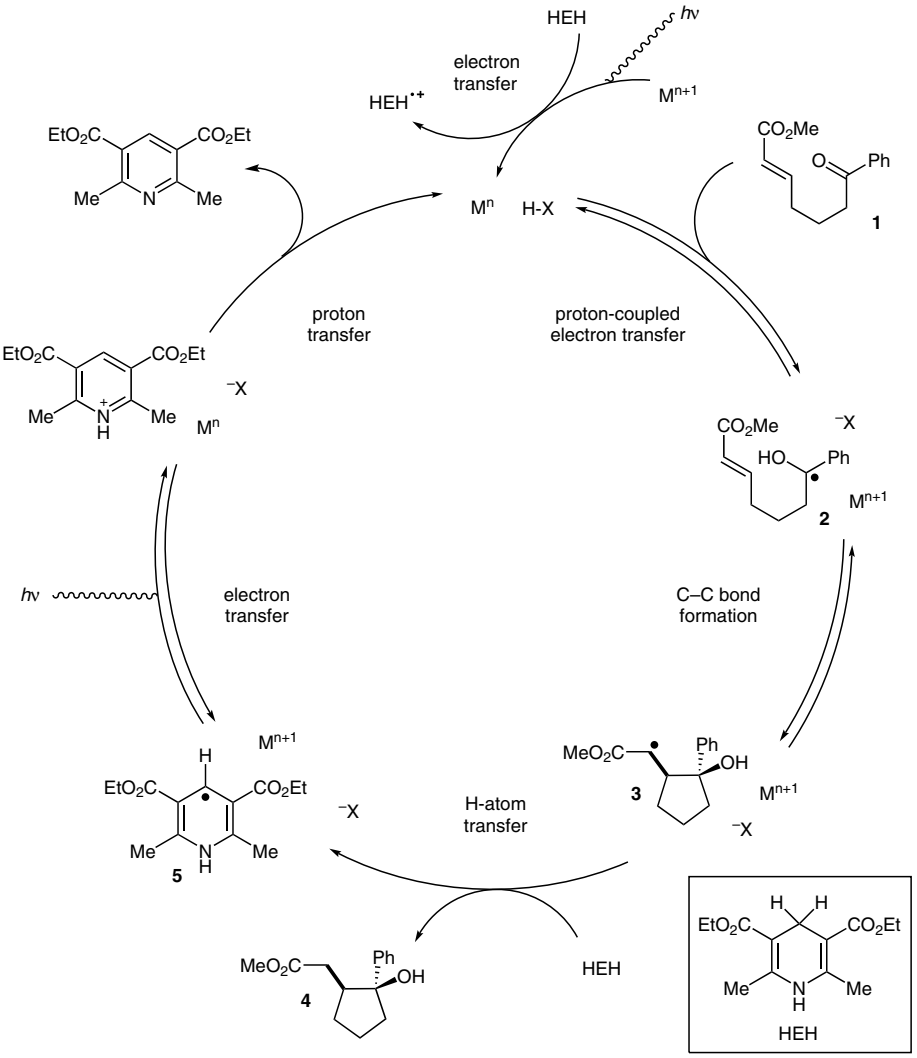
To evaluate this hypothesis, we studied the intramolecular cyclization of ketone **1** jointly catalyzed by a mild Brønsted acid and a photoredox catalyst. We envisioned a catalytic cycle (Scheme 3) initiated by visible-light excitation of the photocatalyst followed by reductive quenching of the resulting excited state by Hantzsch ester (HEH). This reduced state of the redox catalyst could then engage in PCET with a hydrogen-bonded complex of the Brønsted acid catalyst and the aryl ketone **1** substrate to generate the neutral ketyl **2**, forming a new O–H bond with a BDFE of only ca. 26 kcal/mol.[13] This radical would add conjugatively to the pendant acrylate to form a new carbocyclic ring and an α-carbonyl radical **3**. HAT from HEH to this intermediate would generate the desired closed shell product **4**. The oxidized HEH radical **5** would then regenerate the active form of the acid–reductant donor pair through electron- and proton-transfer events with the excited state of the redox catalyst and the conjugate base of the Brønsted acid.

Remarkably, optimization studies revealed that the effective bond-strength formalism was highly successful in predicting reaction outcomes (Table 1). Upon screening a range of acid–reductant combinations with effective 'BDFE's ranging from 45 kcal/mol to approximately 20 kcal/mol, we observed that when the effective bond strength of the acid–reductant pair was sufficiently close in energy to the strength of the ketyl O–H bond (26 kcal/mol) being formed in the PCET reaction, ketyl formation was facile irrespective of the specific acids and reductants employed (Table 1). Similarly, combinations significantly far above the 26 kcal/mol threshold failed in all cases to consume the starting materials. In accord with the prevailing theoretical models for PCET reactivity, these results strongly suggest that thermodynamic considerations are a key factor in PCET kinetics and provide strong support for the use of effective bond strengths as a

quantitative basis for rationally identifying effective PCET catalyst systems.[15]

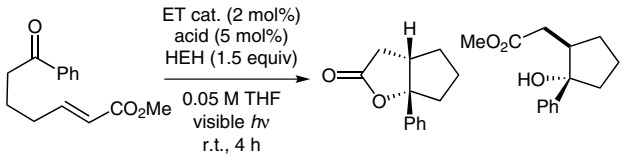
We elected to explore the substrate scope of this new process using the redox catalyst $Ru(bpy)_3(BAr^F)_2$ and diphenyl phosphoric acid as the proton donor. A range of aromatic ketone substrates could be readily activated and cyclized onto acrylate acceptors, providing *cis*-fused bicyclic butanolide products with good levels of chemical yield and diastereoselectivity (Scheme 4). Efficient ketyl addition to a styrenyl acceptor substrate was also reported. The use of 2-phenyl dihydrobenzothiazoline (BT) as a stoichiometric reductant generally resulted in higher diastereoselectivities relative to HEH, suggesting that the HAT step is partly determinant in stereoselection. Perhaps most remarkably, this PCET protocol was effective in activating electron-rich ketone substrates for which the direct electron-transfer pathway from the ruthenium(I) complex was endergonic by nearly 900 mV. This provides strong evidence for the ability of concerted PCET mechanisms to significantly expand the substrate scope of redox catalysts at a fixed potential, and bodes well for the viability of this approach in its applications to other substrate classes and transformations. However it is important to note that PCET activation of simple dialkyl ketones was not observed under any of the conditions described in Table 1, ostensibly due to the considerably weaker O–H bond in the resulting ketyls. Efforts to identify chemically compatible acid–reductant combinations with sufficiently low effective BDFE to activate these substrates are currently ongoing in our labs.

Kinetic and spectroscopic studies were consistent with a concerted PCET mechanism of ketyl formation. Luminescence-quenching studies revealed that neither acetophenone (–2.48 V vs. Fc) nor diphenyl phosphoric acid alone quenched the excited state of $Ir(ppy)_3$ (–2.11 V vs. Fc, τ = 1.9 μs, Figure 1).[16] However, solutions containing both ketone and acid resulted in efficient quenching with a first-order dependence on the concentration of each component. Furthermore, a kinetic isotope effect on the quenching rate of 1.22 ± 0.02 was observed when deuterated diphenyl phosphoric acid was employed. Together, these results discount the viability of direct electron transfer in ketyl formation, but are consistent, in principle, with



Scheme 3 Proposed catalytic cycle for ketyl–olefin coupling

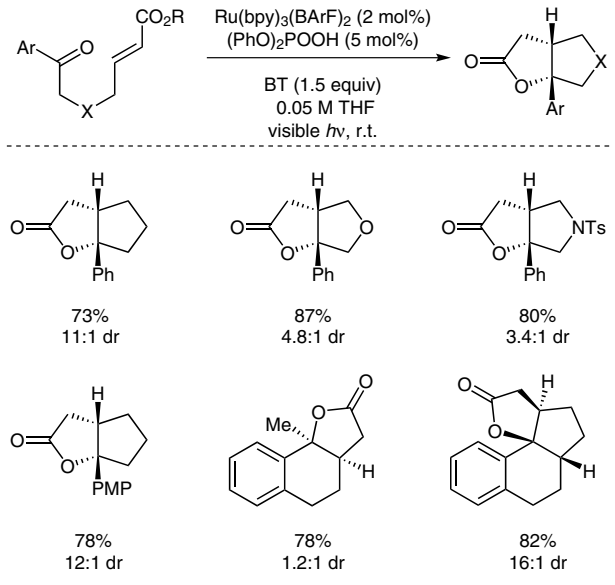
Table 1 Correlation between Effective 'BDFE' and Reaction Outcomes in Ketyl–Olefin Coupling



Acid catalyst	Electron-transfer catalyst[a]	pK_a[b]	E^{o}[c]	'BDFE'[d]	Yield (%)[e]
none	**6**	–	–	–	0
BzOH	**6**	21.5	–1.71	45	0
$Et_3N{\cdot}HBF_4$	**6**	18.8	–1.71	41	0
lutidine·HBF_4	**6**	14.8	–1.71	35	0
$(PhO)_2POOH$	**6**	13	–1.71	33	78
lutidine·HBF_4	**7**	14.8	–1.89	31	74
$(PhO)_2POOH$	**7**	13	–1.89	29	93
PTSA	**6**	8.5	–1.71	27	92
$(PhO)_2POOH$	**8**	13	–2.11	24	74

[a] Photocatalysts: **6**: $Ru^{I}(bpy)_3^{+}$, **7**: $Ir^{III}(ppy)_2(dtbbpy)$, **8**: excited state of *fac*-$Ir^{III}(ppy)_3$.
[b] In MeCN at r.t.
[c] V vs. Fc in MeCN at r.t.
[d] Effective BDFE in kcal/mol.
[e] Combined yields from GC analysis relative to a calibrated internal standard. Product ratio is ca. 5:1 in all cases, favoring the lactone.

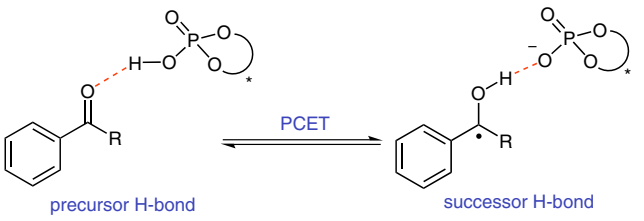
either ketyl formation through concerted PCET or a stepwise proton-transfer–electron-transfer mechanism involving rate-limiting proton transfer to the ketone to form an oxocarbenium ion followed by fast electron transfer. The latter pathway could ultimately be discounted on thermodynamic grounds, as the sizeable pK_a difference between the phosphoric acid and the ketone (13 pK_a units in MeCN)[17] would necessitate a rate constant for proton transfer that is at least $>10^6$ times too slow to be competitive with the radiative decay of the iridium(III) excited state (5.3×10^5 s^{-1}).[18] As both stepwise mechanisms could be reasonably discounted, the observed rate law and kinetic isotope effect (KIE) are most consistent with a concerted PCET mechanism for ketyl formation. In line with our original goals, this work provides proof of concept that concerted PCET reactions can serve as a viable and direct method for obtaining formal H-atom-transfer products with very weak bonds that are energetically inaccessible using more conventional approaches.



Scheme 4 Selected scope for ketyl–olefin cyclization

4 Enantioselective PCET Catalysis: Development of Catalytic Asymmetric Aza-Pinacol Cyclizations

Devising methods to associate a chiral catalyst with a neutral free radical is a long-standing challenge in asymmetric catalysis.[19] Based on the kinetic studies described above, we felt that PCET activation may provide a unique and potentially general solution to this problem. By kinetically coupling electron transfer to a specific hydrogen-bonding event, PCET ensures that radical intermediates are generated exclusively as hydrogen-bonded adducts of the conjugate base of the proton-donor catalyst (Scheme 5).[20] When chiral Brønsted acids are employed, we hypothesized that these successor H-bonding complexes might remain intact during the course of subsequent bond-forming events and thereby provide a basis for asymmetric induction.[21]



Scheme 5 Rationale for PCET-enabled enantioselective catalytic radical reactions via hydrogen bonding

The viability of this hypothesis was demonstrated in the development of an enantioselective aza-pinacol cyclization (Scheme 6).[22–25] These reductive coupling reactions between ketones and imine derivatives provide direct access to vicinal amino alcohols,[26] which are common structural motifs in pharmaceutical agents, ligand frameworks, and natural products. However, despite this synthetic potential, no catalytic or asymmetric aza-pinacol cyclizations had been previously reported in the literature.[27] Under similar conditions to our PCET-mediated ketyl–

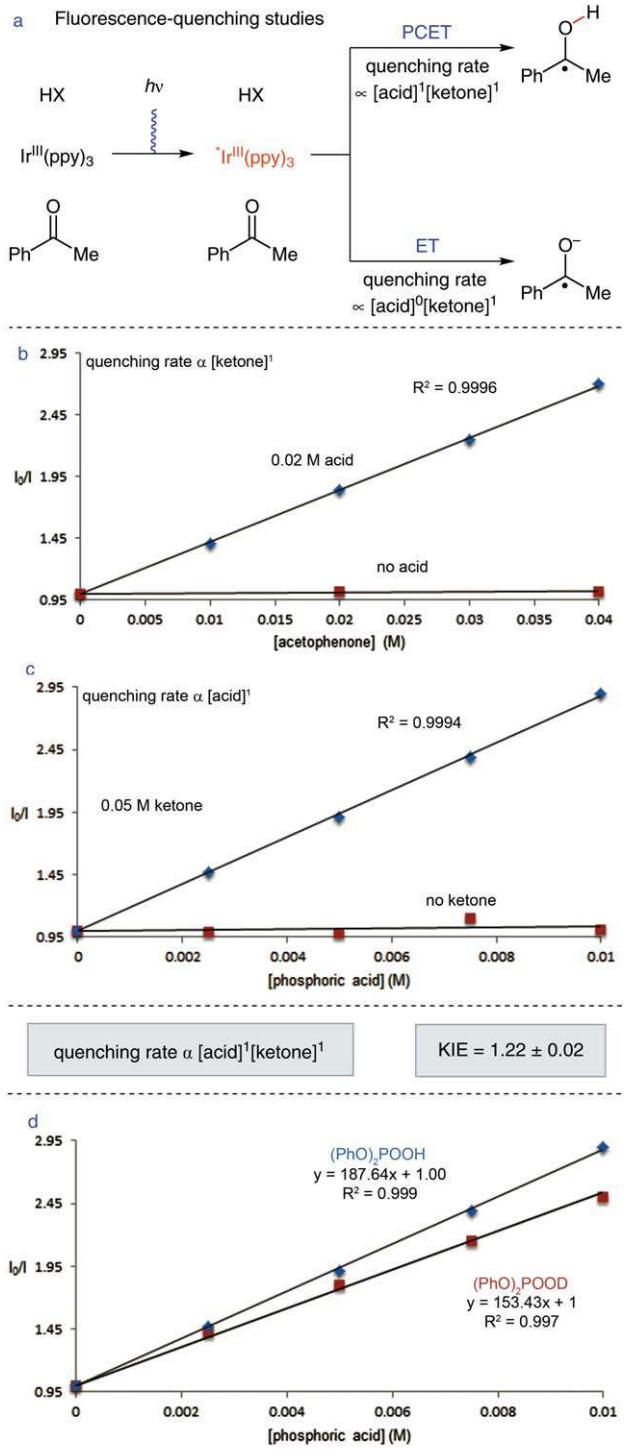
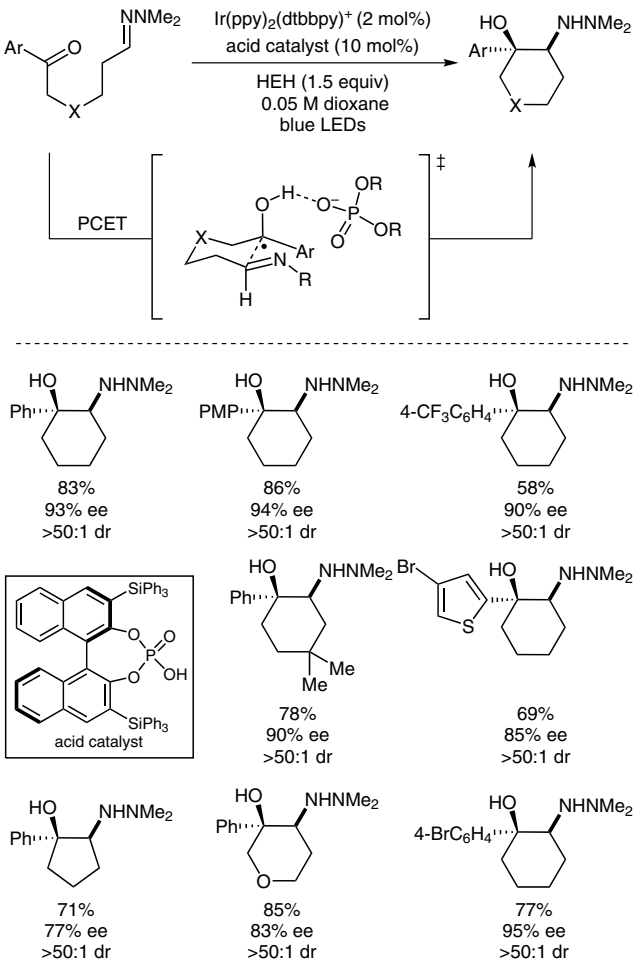


Figure 1 Luminescence-quenching studies of $Ir(ppy)_3$ using acetophenone and diphenylphosphoric acid quenchers

olefin cyclizations, we found that exposure of ketohydrazones to iridium-based photocatalysts in combination with chiral phosphoric acids generated a range of cyclic *cis*-configured amino alcohol derivatives with generally excellent yields and enantioselectivities. These reactions are operationally convenient, conducted at room temperature, and often proceed to completion in under three hours upon exposure to blue LED.

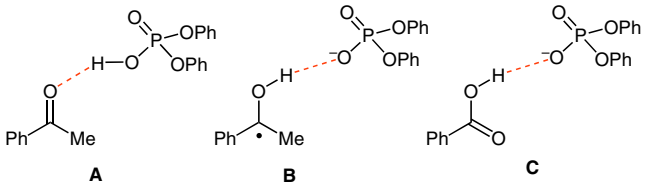


Scheme 6 Selected scope for the enantioselective aza-pinacol cyclization

Preliminary mechanistic studies are consistent with a concerted PCET mechanism of ketyl formation and a turnover-limiting and enantioselectivity-determining C–C bond-forming step. The ketyl oxygen is the most basic site in the reduced form of the substrate by ca. 7 p*K*a units in MeCN (O–H pK_a = 20.5 in MeCN),[28] and is thus the strongly preferred site of attachment for the proton originating from the phosphoric acid. Taken together with the high levels of observed enantioselectivity across a wide range of solvent dielectrics, these considerations suggested to us that the chiral phosphate anion likely remains associated with the neutral ketyl radical during C–C bond formation through the agency of a hydrogen bond.

To further evaluate the energetics of this noncovalent association, we turned to density functional theory calculations. Interestingly, we found that the proposed hydrogen-bonding interaction between the neutral ketyl radical and phosphate anion was remarkably strong [ΔE = –14.4 kcal/mol with UB3LYP/6-311+g(d,p) in dioxane solvent (CPCM)]. Not only was this adduct significantly more stable than the precursor H bond between the ketone and the phosphoric acid, but it was also more stabilized than structurally analogous complexes between the phosphate and 1-phenethyl alcohol or even benzoic acid (Scheme 7).

This surprising finding offers further support for the hypothesis that it should be possible to maintain a meaningful H-bonding interaction between the conjugate base of a chiral acid and a neutral free-radical intermediate following a PCET event, and that this association can provide an effective basis for asymmetric induction in subsequent bond-forming steps. Efforts to extend these findings to other substrate classes and asymmetric reactions are currently a focus of ongoing research in our lab.



Complex	$E_{H\text{-}bond}$ (kcal/mol)	O–H pK_a (MeCN)
A	–9.2	13
B	–14.4	20
C	–12.6	21.5

Scheme 7 Ketyl-phosphate H bond modeled with DFT calculations [UB3LYP/6-311+g(d,p) in 1,4-dioxane solvent (CPCM)]. Energies are uncorrected electronic energies.

5 Conclusions

Herein, we have outlined the design and development of novel catalytic and enantioselective reactions of neutral ketyl radicals enabled by concerted PCET activation. Our approach was founded on the hypothesis that concerted PCET can serve as an alternative mechanism for reductive H-atom transfer reactions that are difficult to realize using existing technologies. Recognizing that PCET kinetics (like those of other one-electron processes) are profoundly influenced by thermodynamic considerations, we demonstrated that Mayer's effective bond-strength formalism was a successful and enabling principle for catalyst identification. Lastly, through consideration of the unusual hydrogen-bonding properties of the neutral free radicals formed in these PCET reactions, we were able to show that these processes could be rendered enantioselective when chiral proton donors were employed. While the analysis presented here applies specifically to the activation of aryl ketone substrates, we anticipate that the elements of reaction design will also be applicable to numerous other common functional groups. We are optimistic that this line of thinking will provide new insights into the development of both homolytic bond activations that have traditionally been challenging to catalyze and asymmetric processes involving molecular recognition of neutral free-radical intermediates.

Acknowledgment

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References and Notes

(1) (a) Meyer, T. J.; Huynh, M. H. V.; Thorp, H. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 5284. (b) Stubbe, J.; Nocera, D. G.; Yee, C.; Chang, M. *Chem. Rev.* **2003**, *103*, 2167. (c) Kaila, V. R. I.; Verkhovsky, M. I.; Wikström, M. *Chem. Rev.* **2010**, *110*, 7062. (d) Hatcher, E.; Soudachov, A.; Hammes-Schiffer, S. *J. Am. Chem. Soc.* **2004**, *126*, 5763. (e) Migliore, A.; Polizzi, N. F.; Therien, M. J.; Beratan, D. N. *Chem. Rev.* **2014**, *114*, 3381. (f) Smith, K. W.; Stroupe, M. E. *Biochemistry* **2012**, *51*, 9857. (g) Kennis, J. T. M.; Mathes, T. *Interface Focus* **2013**, *3*, 20130005. (h) Reece, S. Y.; Hodgkiss, J. M.; Stubbe, J.; Nocera, D. G. *Philos. Trans. R. Soc., B* **2006**, *361*, 1351. (i) Barry, B. A. *J. Photochem. Photobiol. B* **2011**, *104*, 60. (j) Lehnert, N.; Solomon, E. I. *J. Biol. Inorg. Chem.* **2003**, *8*, 294. (k) Neidig, M. L.; Wecksler, A. T.; Schenk, G.; Holman, T. R.; Solomon, E. I. *J. Am. Chem. Soc.* **2007**, *129*, 7531. (l) Moiseyev, N.; Rucker, J.; Glickman, M. K. *J. Am. Chem. Soc.* **1997**, *119*, 3853. (m) Derat, E.; Shaik, S. *J. Am. Chem. Soc.* **2006**, *128*, 13940. (n) Wang, Y.; Chen, H.; Makino, M.; Shiro, Y.; Nagano, S.; Asamizu, S.; Onaka, H.; Shaik, S. *J. Am. Chem. Soc.* **2009**, *131*, 6748. (o) Wang, H.; Hirao, H.; Chen, H.; Onaka, H.; Nagano, S.; Shaik, S. *J. Am. Chem. Soc.* **2008**, *130*, 7170.

(2) (a) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016. (b) Huynh, M. H. V.; Meyer, T. J. *Chem. Rev.* **2007**, *107*, 5004. (c) Costentin, C. *Chem. Rev.* **2008**, *108*, 2145. (d) Hammes-Schiffer, S.; Stuchebrukhov, A. A. *Chem. Rev.* **2010**, *110*, 6939. (e) Dempsey, J. L.; Winkler, J. R.; Gray, H. B. *Chem. Rev.* **2010**, *110*, 7024. (f) Warren, J. J.; Tronic, T. A.; Mayer, J. M. *Chem. Rev.* **2010**, *110*, 6961. (g) Hammes-Schiffer, S.; Hatcher, E.; Ishikita, H.; Skone, J. H.; Soudackov, A. V. *Coord. Chem. Rev.* **2008**, *252*, 384. (h) Costentin, C. *Chem. Rev.* **2008**, *108*, 2145. (i) Reece, S. Y.; Nocera, D. G. *Annu. Rev. Biochem.* **2009**, *78*, 673. (j) Gagliardi, C. J.; Westlake, B. C.; Kent, C. A.; Paul, J. J.; Papanikolas, J. M.; Meyer, T. J. *Coord. Chem. Rev.* **2010**, *254*, 2459. (k) Hammarstrom, L.; Styring, S. *Philos. Trans. R. Soc., B* **2008**, *363*, 1283.

(3) (a) Rosenthal, J.; Luckett, T. D.; Hodgkiss, J. M.; Nocera, D. G. *J. Am. Chem. Soc.* **2006**, *128*, 6546. (b) Yang, J. Y.; Nocera, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 8192.

(4) (a) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11. (b) Ingold, K. U. In *Free Radicals*; Vol. 1; Kochi, J. K., Ed.; Wiley: New York, **1973**, 283. (c) Russell, G. A. In *Free Radicals*; Vol. 1; Kochi, J. K., Ed.; Wiley: New York, **1973**, 69. (d) Roth, J. P.; Yoder, J. C.; Won, T.-J.; Mayer, J. M. *Science* **2001**, *294*, 2524. (e) Warren, J. J.; Mayer, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 5282.

(5) (a) Zhang, X.-M. *J. Org. Chem.* **1998**, *63*, 1872. (b) Tang, L.; Papish, E. T.; Abramo, G. P.; Norton, J. R.; Baik, M.-H.;

Friesner, R. A.; Rappe, A. *J. Am. Chem. Soc.* **2003**, *125*, 10093. (c) Brown, R. L.; Stein, S. E. *J. Am. Chem. Soc.* **1991**, *113*, 787. (d) Gou, Y.; Grabowski, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5923.

(6) BDFE from CBS-QB3 calculations. For details, see the Supporting Information.

(7) The given O–H bond strength for isopropanol is a bond-dissociation enthalpy (BDE): Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(8) (a) Choi, J. W.; Pulling, M. E.; Smith, D. M.; Norton, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 4250. (b) Estes, D. P.; Vannucci, A. K.; Hall, A. R.; Lichtenberger, D. L.; Norton, J. R. *Organometallics* **2011**, *30*, 3444. (c) Uddin, J.; Morales, C. M.; Maynard, J. H.; Landis, C. R. *Organometallics* **2006**, *25*, 5566.

(9) For selected examples of HAT to olefins from metal hydrides, see: (a) Halpern, J. *Pure Appl. Chem.* **1986**, *58*, 575; and references cited therein. (b) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300. (c) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884. (d) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304.

(10) (a) Wiberg, K. B.; Foster, G. *J. Am. Chem. Soc.* **1961**, *83*, 423. (b) Breslow, R.; Balasubramanian, K. *J. Am. Chem. Soc.* **1969**, *91*, 5182. (c) Breslow, R.; Chu, W. *J. Am. Chem. Soc.* **1973**, *95*, 411. (d) Jaun, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 5741. (e) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229. (f) Wayner, D. M.; Parker, V. D. *Acc. Chem. Res.* **1993**, *26*, 287. (g) Tilset, M.; Parker, V. D. *J. Am. Chem. Soc.* **1989**, *111*, 6711. (h) Tilset, M.; Parker, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 2843. (i) Parker, V. D.; Handoo, K. L.; Roness, F.; Tilset, M. *J. Am. Chem. Soc.* **1991**, *113*, 7493.

(11) Waidmann, C. R.; Miller, A. J. M.; Ng, A. C.-W.; Scheuermann, M. L.; Porter, T. R.; Tronic, T. A.; Mayer, J. M. *Energy Environ. Sci.* **2012**, *5*, 7771.

(12) (a) Mayer, J. M. *Acc. Chem. Res.* **2001**, *44*, 36. (b) Costeintin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* **2007**, *129*, 9953. (c) Sjodin, M.; Styring, S.; Wolpher, H.; Xu, Y.; Sun, L.; Hammarstrom, L. *J. Am. Chem. Soc.* **2005**, *127*, 3855. (d) Osako, T.; Ohkubo, K.; Taki, M.; Tachi, Y.; Fukuzumi, S.; Itoh, S. *J. Am. Chem. Soc.* **2003**, *125*, 11027. (e) Schrauben, J. N.; Cattaneo, M.; Day, T. C.; Tenderholt, A. L.; Mayer, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 16635.

(13) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022.

(14) For examples of ketyl reactions in synthesis, see: (a) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140.

(15) This analysis does not include the thermochemical impact of the H-bonding interactions, which can play a substantive role in the overall thermochemistry of PCET reactions in the low-driving force regime. See also ref. 22.

(16) For pioneering studies of on the activation of aryl ketones towards electron transfer using strong Brønsted acids, see: (a) Fukuzumi, S.; Chiba, M.; Tanaka, T. *Chem. Lett.* **1989**, *18*, 31. (b) Fukuzumi, S.; Ishikawa, K.; Hironaka, K.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1987**, 751.

(17) For the pK_a value of protonated acetophenone in MeCN, see: (a) Kolthoff, I. M.; Chantooni, M. K. *J. Am. Chem. Soc.* **1973**, *95*, 8539. For pK_a values of phosphoric acids in MeCN, see: (b) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

(18) Dixon, I. M.; Collin, J.; Sauvage, J.; Flamigni, L.; Encinas, S.; Barigelletti, F. *Chem. Soc. Rev.* **2000**, *29*, 385.

(19) For synthetic examples of hydrogen bonding interactions with open shell species, see: (a) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259. (b) Bach, T.; Bergmann, H.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2302. (c) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (d) Aechtner, T.; Dressel, M.; Bach, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5849. (e) Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. *Nature (London, U.K.)* **2005**, *436*, 1139. (f) Müller, C.; Bauer, A.; Bach, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 6640. (g) Müller, C.; Bauer, A.; Maturi, M. M.; Cuquerella, M. C.; Miranda, M. A.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 16689.

(20) For an alternative approach using chiral Lewis acid activation, see: Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392.

(21) For a discussion of the energetic role of precursor and successor H bonds in PCET reactions, see: Mader, E. A.; Mayer, J. M. *Inorg. Chem.* **2010**, *49*, 3685.

(22) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735.

(23) For examples of asymmetric photoredox catalysis, see: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600. (d) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (e) Pirnot, M. T.; Rankic, D. A.; Martin, D. B.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (f) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521. (g) Bergonzini, G.; Schindler, C.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. *J. Chem. Sci.* **2013**, *5*, 112.

(24) For examples of H-bond activation in asymmetric radical additions to imine derivatives, see: (a) Cho, D. H.; Jang, D. O. *Chem. Commun.* **2006**, 5045. (b) Kim, S. Y.; Kim, S. J.; Jang, D. O. *Chem. Eur. J.* **2010**, *16*, 13046.

(25) For a recent example of catalytic asymmetric ketyl reactivity, see: Streuff, J.; Feurer, M.; Bichovski, P.; Frey, G.; Gellrich, U. *Angew. Chem. Int. Ed.* **2012**, *51*, 8661.

(26) Burchak, O. N.; Py, S. *Tetrahedron* **2009**, *65*, 7333.

(27) For selected examples of aza-pinacol reactions in synthesis, see: (a) Nicolaou, K. C.; Hao, J.; Reddy, M.; Rao, P.; Rassias, G.; Snyder, S.; Huang, X.; Chen, D.; Brenzovich, W.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897. (b) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382.

(28) The pK_a values of neutral ketyl radicals in MeCN can be estimated from the BDFE of the ketyl O–H bond (26 kcal mol^{-1}) and the reduction potential of acetophenone in MeCN (–2.48 V vs. Fc). See: (a) Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223. (b) Hayon, E.; Ibata, T.; Lichtin, N. N.; Simic, M. *J. Phys. Chem.* **1972**, *76*, 2072.

