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Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization

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Supporting Information

ABSTRACT: The first highly enantioselective catalytic protocol for the reductive coupling of ketones and hydrazones is reported. These reactions proceed through neutral ketyl radical intermediates generated via a concerted proton-coupled electron transfer (PCET) event jointly mediated by a chiral phosphoric acid catalyst and the photoredox catalyst $Ir(ppy)_2(dtbpy)PF_6$. Remarkably, these neutral ketyl radicals appear to remain H-bonded to the chiral conjugate base of the Brønsted acid during the course of a subsequent C−C bond-forming step, furnishing *syn* 1,2-amino alcohol derivatives with excellent levels of diastereo- and enantioselectivity. This work provides the first demonstration of the feasibility and potential benefits of concerted PCET activation in asymmetric catalysis.

The rapid growth of organic photoredox catalysis has prompted a renewed interest in radical transformations initiated by outer sphere electron transfer (ET).[1] While this focus has produced many innovative and synthetically valuable reactions, few strategies for effectively controlling enantioselectivity in these processes have been reported.[2] In part, this deficit reflects the broader challenges connected with maintaining an energetically meaningful association between a radical intermediate and a chiral catalyst during the selectivity-determining steps of a catalytic cycle.

In seeking to address this limitation, we recently reported a protocol for catalytic ketyl radical generation enabled by proton-coupled electron transfer (PCET).[3,4] In these reactions, the lowest energy pathway to radical formation requires ET to a ketone acceptor from a Ru- or Ir-based redox catalyst to occur in concert with proton transfer from a phosphoric acid through the agency of a H-bond (Figure 1). In addition to enabling access to ketyls at potentials nearly 1 V less reducing than E^0 of the ketone substrates, we postulated that this key H-bonding interaction could also present new opportunities for asymmetric catalysis. Specifically, while the position of the proton within the H-bond is expected to shift from the phosphoric acid (pK_a in MeCN = 13)[5] to the ketyl (pK_a in MeCN = 20)[6] during the course of ET, we anticipated that the H-bond interface would initially remain intact (Figure 1). In analogy to the seminal work of Curran and Bach, we projected that if the successor H-bond complex between the neutral ketyl and the phosphate anion could persist on the time scale of subsequent bond-forming events, a chiral phosphate could potentially render these reactions enantioselective (Figure 1).[7,8]

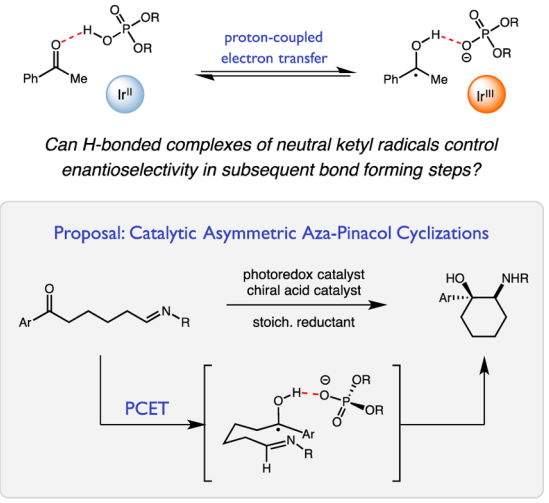

Figure 1. Precursor and successor H-bond complexes in PCET activation and application to the development of a catalytic asymmetric aza-pinacol cyclization.

Herein we report the successful realization of these ideas in the context of a catalytic and highly enantioselective intramolecular reductive coupling of ketones and hydrazones. Commonly referred to as the aza-pinacol coupling, this reaction is a particularly direct method for the synthesis of vicinal amino alcohols from simple starting materials.[9] Given the prevalence of amino alcohol derivatives in pharmaceutical agents, ligand frameworks, and natural products, many useful aza-pinacol protocols have been developed.[10,11] However, to the best of our knowledge, no catalytic asymmetric variants of this reaction have previously been reported.[12,13] The details of our synthetic studies and experimental observations consistent with the proposed mechanism are outlined below.

Our initial investigations focused on the cyclization of ketone **1** jointly catalyzed by the photoredox catalyst $Ir(ppy)_2(dtbpy)PF_6$ and aryl phosphoric acids, employing Hantzsch dihydropyridine (HEH) as a stoichiometric reductant (Scheme 1). Drawing from our related work[3] on PCET-mediated ketyl-olefin coupling, we envisioned a plausible catalytic cycle initiated by off-cycle blue light excitation of the iridium photocatalyst. Reduction of the

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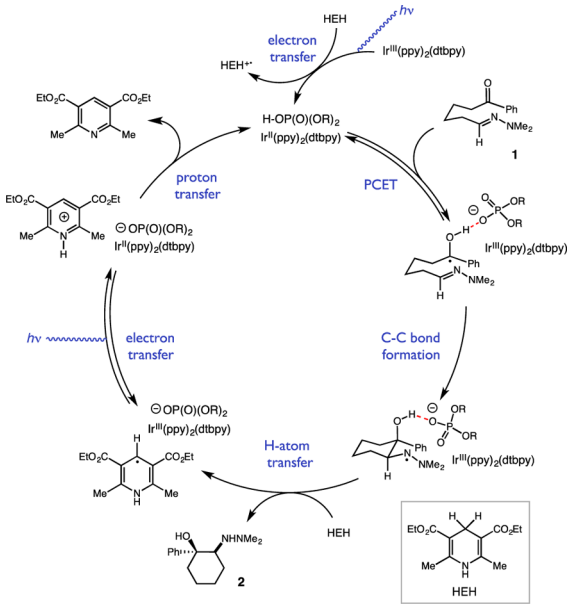
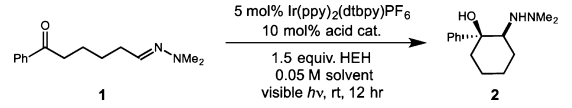
Scheme 1. Proposed Catalytic Cycle



resulting Ir^{III} excited state ($*E_{1/2}^{red}$ = 0.28 V vs Fc)[14] by a sacrificial quantity of HEH ($E_{1/2}^{ox}$ = 0.51 V vs Fc)[15] furnishes a strongly reducing Ir^{II} center ($E_{1/2}^{ox}$ = −1.89 V vs Fc)[14] which is competent to enter the catalytic cycle. Direct ET between this Ir^{II} complex and the ketone substrate ($E_{1/2}^{red}$ = −2.48 V vs Fc for acetophenone)[16] is significantly endergonic (ΔG° = +13.6 kcal/mol). However, concerted PCET to a H-bonded complex of the ketone and the phosphoric acid has a more favorable driving force[17] (ΔG° = +3.1 kcal/mol) and, based on our prior kinetic studies, is expected to present a significantly lower activation barrier.[3] During PCET, the ketyl becomes significantly more basic than the phosphoric acid, prompting a shift of the proton within the H-bond interface to furnish the neutral ketyl as a H-bonded adduct of the chiral phosphate (Figure 1). Given the characteristically rapid kinetics of radical cyclizations, we were optimistic that this noncovalent association would provide a basis for asymmetric induction in the ensuing C−C bond-forming step. Subsequent H-atom transfer (HAT) from HEH to the hydrazyl radical would then furnish the desired closed-shell product **2**. Lastly, oxidation of the resulting neutral HEH radical (calculated E^0 = −1.13 V vs Fc)[18] by the photoexcited state of the Ir^{III} catalyst would deliver an acidic pyridinium ion that can be deprotonated by the phosphate anion to close the catalytic cycle.

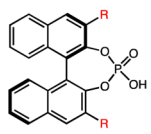
Initial experiments demonstrated that exposure of ketohydrazone **1** and 1.5 equiv of HEH to 10 mol % of diphenyl phosphoric acid and 5 mol % of $Ir(ppy)_2(dtbpy)(PF_6)$ in a THF solution irradiated by a 26-W fluorescent lamp provided hydrazinyl alcohol **2** in 91% yield as a single diastereomer after 12 h at rt (Table 1, entry 1). Encouraged by these results, we began to evaluate enantioselective cyclizations using chiral phosphoric acid derivatives. While the use of unsubstituted BINOL phosphoric acid **3** under these conditions yielded **2** in 89% yield as a racemate (Table 1, entry 2), we were excited to find that the 2-naphthyl substituted catalyst **4** delivered **2** in 30% ee (Table 1, entry 3). Further improvements were realized with 2,4,6-trisubstituted phenyl derivatives **5** and **6**, which provided **2** in 58% and 68% ee, respectively (Table 1, entries 4 and 5). TIPS-substituted acid **7** provided a more significant enhancement, furnishing **2** in 84% yield and 82% ee (Table 1, entry 6). Additional experimentation revealed triphenylsilyl-substituted

Table 1. Asymmetric Aza-Pinacol Optimization Studies[a]

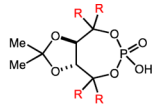


entry	acid catalyst	solvent	% yield	% ee
1	$(PhO)_2PO_2H$	THF	91	–
2	**3**	THF	89	0
3	**4**	THF	84	30
4	**5**	THF	96	58
5	**6**	THF	80	68
6	**7**	THF	84	82
7	**8**	THF	92	89
8	**9**	THF	90	0
9	**10**	THF	85	0
10	**8**	DME	90	88
11	**8**	C_6H_6	30	86
12	**8**	CH_2Cl_2	99	88
13	**8**	MeCN	77	81
14	**8**	dioxane	94	92
15[b]	**8**	dioxane	90	92

[a]Optimization reactions performed on 0.05 mmol scale. Yields and ee determinations obtained by chiral GC analysis. Visible light irradiation provided by 26-W fluorescent lamps unless otherwise noted. [b]Reaction irradiated by blue LEDs for 3 h at rt using 2 mol % of the photocatalyst.



3 R = H
4 R = 2-naphthyl
5 R = Mesityl
6 R = 2,4,6-iPr$_3$C$_6$H$_2$
7 R = iPr$_3$Si
8 R = Ph$_3$Si



9 R = Ph
10 R = 2-naphthyl

acid[19] **8** to be the most selective catalyst evaluated, increasing the enantioselectivity to 89% ee while affording the desired product in 92% yield (Table 1, entry 7). TADDOL-derived catalysts **9** and **10** were efficient, but delivered a racemic product (Table 1, entries 8 and 9). Enantioselectivity in these reactions was retained across a wide range of solvents, with CH_2Cl_2, benzene, DME, and even MeCN proving similar to THF (Table 1, entries 10−13). However, 1,4-dioxane ultimately proved optimal, yielding **2** in 94% yield and 92% ee (Table 1, entry 14). Finally, the use of blue LEDs in place of the 26-W fluorescent lamps enabled this reaction to be complete in 3 h at rt using only 2 mol % of the Ir photocatalyst, giving **2** in 90% yield and 92% ee (Table 1, entry 15). Notably, the *trans* diastereomer of **2** was not observed in any of the reactions described above. However, control experiments run under the standard screening conditions in the absence of the acid catalyst provided a 3:1 mixture of **2** and its *trans* diastereomer in 42% overall yield after 12 h, suggesting divergent mechanisms of cyclization. Reactions run in the absence of the photocatalyst under otherwise standard conditions resulted in no consumption of the starting material.

With optimal conditions identified, we sought to evaluate the scope of this process (Table 2). Gratifyingly, significant structural and electronic variation in the aryl ketone was tolerated. Products derived from electron-rich (**11**, **16**) and electron-poor (**12**) acetophenone derivatives were formed with similarly high levels of enantioselectivity. *Ortho*-, *meta*-, and *para*-substitution on the ring was tolerated (**13**−**15**), though the *ortho*-substituted substrate required 18 h to reach full conversion. Products derived from heterocyclic ketones such as benzofuran **17** and thiophene **18** were also successful substrates, though they

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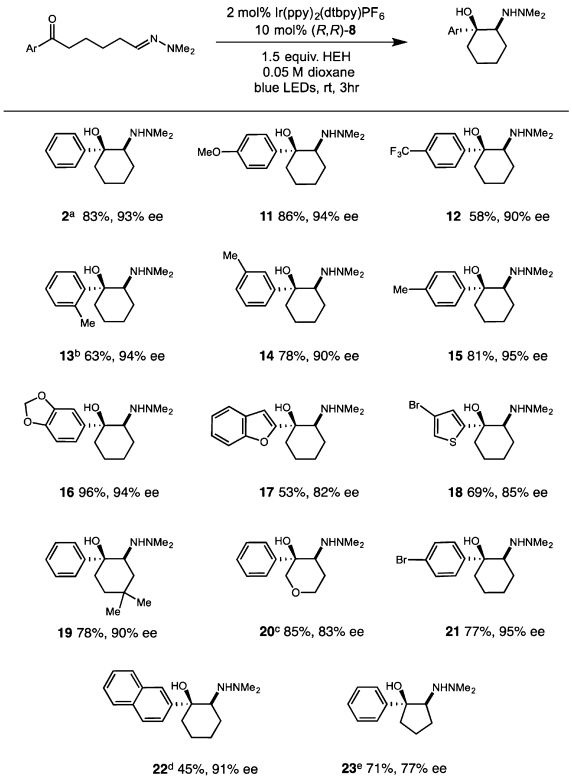
Table 2. Scope of the Asymmetric Aza-Pinacol Cyclization



Reactions run on 0.5 mmol scale unless otherwise noted. Yields are for isolated material. ee values determined by chiral GC or HPLC analysis. [a]Reaction run on 1 mmol scale. [b]Reaction run for 18 h. [c]Reaction run at −30 °C in CH_2Cl_2 for 44 h using 20 mol % **8** and 1 mol % Ir. [d]Reaction run at 0 °C in THF for 6 h. [e]Reaction run at −20 °C in THF using catalyst **6** for 48 h.

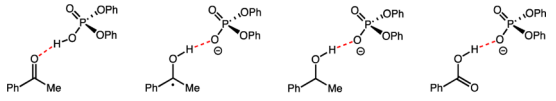
exhibited slightly diminished enantioselectivities. Substitution within the alkyl tether was possible, as demonstrated by the formation of dimethyl-substituted **19** in 78% yield and 90% ee. A substrate incorporating an ether into the ring was also viable (**20**), though 20 mol % of the Brønsted acid catalyst and lower temperatures in CH_2Cl_2 solvent (−30 °C) were required to achieve maximum selectivity (83% ee). Aryl bromide substrates could be successfully utilized, as indicated by the formation of **21** in 77% yield and 95% ee. A crystal structure of **21**•HCl was also obtained, securing the absolute configuration of the products.[20] Product **22**, which bears an extended π-system, could be cyclized in 91% ee at 0 °C in THF, but in only 45% isolated yield. Lastly, five-membered ring analog **23** cyclized in 71% yield and 77% ee at −20 °C in THF using catalyst **6** in place of **8**. Notably, the *trans* diastereomers of the indicated products were not observed. Cleavage of the N−N bond in **2** could be accomplished by hydrogenation with Raney nickel at rt in aqueous MeOH, returning the unprotected amino alcohol in 96% yield.[20]

To better understand the role of the phosphoric acid in asymmetric induction, we carried out preliminary mechanistic studies of these reactions. Reductive cyclizations of **1** using either HEH or its deuterated analog, 4,4-d_2-HEH, proceed at nearly identical rates, inconsistent with a rate-limiting HAT step.[20] As PCET activation is expected to be rapid and reversible,[3] this observation suggests that C−C bond formation is likely both the turnover-limiting and enantioselectivity-determining step in the proposed catalytic cycle. Additionally, a linear relationship between the ee of the acid catalyst **8** and the ee of the product **2** was observed,[20] suggesting the involvement of only a single molecule of the chiral phosphate in the key C−C bond-forming step.

While these observations are consistent with a mechanism in which the phosphate remains associated with the substrate radical during C−C bond formation, the exact position of the proton and its associated H-bonding network are challenging to assess experimentally. However, several factors lend support to the proposal indicated in Figure 1. Foremost, the ketyl is the most basic functionality present in the reaction mixture with a pK_a of 20 in MeCN. By way of comparison, the pK_a's of the conjugate acids of the biaryl phosphate and the dimethyl amine of the hydrazone are 13 and ∼14, respectively, in MeCN.[5,21] Based on the work of Raines and More O'Ferall, the sp^2 nitrogen of the hydrazone is anticipated to be weakly basic (pK_a <0.7 in H_2O for the hydrazonium ion).[22] As such, at equilibrium, the proton is expected to be covalently associated with the ketyl oxygen in the reduced form of the substrate. Additionally, based on these pK_a values, endergonic proton transfer from the ketyl to these functional groups would incur a kinetic penalty commensurate with or greater than the activation barriers reported for C−C bond formation in similar radical cyclizations to imine-type acceptors.[23]

Despite its relative basicity within these reactions, the ketyl intermediate is comparatively acidic in absolute terms, with a pK_a value similar to that of benzoic acid (BzOH pK_a in MeCN = 21.5).[24] This suggests that the proposed H-bond between the ketyl and the phosphate anion may be strong. To address this question directly, we evaluated the relative energetics of these noncovalent complexes using density functional theory (Table 3).[20] These calculations revealed that the acetophenone ketyl-

Table 3. DFT Evaluation of Ketyl-phosphate H-Bonding



complex	$\Delta E_{\text{H-bond}}$ [a,b]	*d* OH···O (Å)[a]	O−H pK_a(MeCN)	Mulliken charge (H)[a]
A	−9.2	1.642	13	0.39
B	−14.4	1.629	20	0.59
C	−10.4	1.737	∼38[c]	0.51
D	−12.6	1.551	21.5	0.60

[a]Calculated at UB3LYP/6-311+g(d,p) in 1,4-dioxane solvent (CPCM). See Supporting Information for computational details. [b]Energies are uncorrected electronic energies in kcal•mol^{-1}. [c]pK_a for *t*BuOH in MeCN, see reference 17a.

diphenyl phosphate H-bond (complex **B**) is significantly stronger than the precursor H-bond formed between the ketone and the phosphoric acid prior to PCET (complex **A**). More strikingly, comparisons with the H-bonded complexes of the phosphate with structural analogs 2-phenethyl alcohol (complex **C**) and benzoic acid (complex **D**) revealed that the ketyl was the strongest H-bond donor in the series. These findings support the hypothesis that the ketyl phosphate H-bond complexes are strongly stabilizing and may persist with an appreciable lifetime following radical generation.[25,26]

In conclusion, we have demonstrated the first catalytic protocol for enantioselective aza-pinacol cyclizations. By kinetically coupling ET to a H-bonding event between the substrate and a chiral acid, PCET activation enables the generation of

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radical intermediates as catalyst-bound adducts. The surprising stability of these noncovalent complexes allows them to effectively serve as a basis for asymmetric induction in a subsequent C−C bond-forming step. We anticipate that these features of PCET activation will be transferable to other substrate classes and transformations, providing new opportunities for the further development of catalytic asymmetric radical chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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