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Communication

Cross-Selective Aza-Pinacol Coupling via Atom Transfer Catalysis

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ABSTRACT: A cross-selective aza-pinacol coupling of aldehydes and imines has been developed to afford valuable β-amino alcohols. This strategy enables chemoselective conversion of aliphatic aldehydes to ketyl radicals, in the presence of more easily reduced imines and other functional groups. Upon carbonyl-specific activation by AcI, a photoinitiated Mn catalyst selectively reduces the resulting α-oxy iodide by an atom transfer mechanism. The ensuing ketyl radical selectively couples to imines, precluding homodimerization by a classical reductive approach. In this first example of reductive, ketyl coupling by atom transfer catalysis, Zn serves as a terminal reductant to facilitate Mn catalyst turnover. This new strategy also enables ketyl radical couplings to alkenes, alkynes, aldehydes, propellanes, and chiral imines.

Ketyl radicals provide versatility to the synthetically valuable carbonyl group by reversing its reactivity from a 2e⁻ electrophile to 1e⁻ nucleophile.[1] This polarity reversal strategy enables streamlined access to useful motifs such as 1,2-diols via pinacol coupling of carbonyls.[2−4] Similarly, β-amino alcohols—a privileged structure found in nature, catalysis, and medicine[5,6]—can be accessed by aza-pinacol coupling of an aldehyde and imine.[7] This convergent C−C coupling provides synthetic modularity and avoids regioselectivity issues associated with typical routes to β-amino alcohols via alkenes or epoxides.[5,6] Nonetheless, underlying thermodynamic and chemoselectivity challenges remain for direct aza-pinacol coupling (Figure 1). Notably, the generation of ketyl radical anions requires strong reductants (e.g., Na, Mg, Ti, Sm) with highly negative redox potentials necessary to reduce carbonyls (E_{red} > −1.9 V vs SCE),[8−12] especially aliphatic aldehydes (−2.9 V).[8] Moreover, since imines are more easily reduced (Ph: −1.9 V; Ms: −1.5 V),[9−11] it is difficult to chemoselectively generate ketyl radicals in their presence. Instead, single-electron transfer (SET) reduction of an imine—and subsequent homodimerization of the resulting α-amino radical—is typically observed (Figure 1a).[1,13]

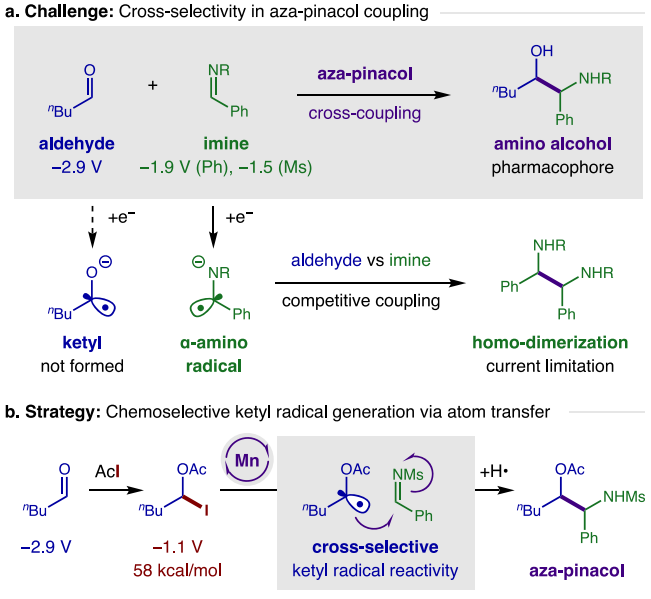

Figure 1. Design of cross-selective strategy for aza-pinacol coupling.

Recent strategies by Yoon, Knowles, and others to access ketyl radicals by milder reductants, such as Ru and Ir photocatalysts, entail Brønsted or Lewis acid activation of carbonyls to lower their reduction potential.[14−21] Nonetheless, such key advances remain subject to thermodynamic favorability for reducing imines versus aldehydes. To address this ongoing challenge of cross-selectivity,[1] aza-pinacol couplings typically entail either (1) intramolecularity or (2) slow addition of an α-amino radical precursor to super-stoichiometric quantities of reductant (e.g., Sm) and the less reducible, carbonyl partner.[22−26] Other recent approaches to bypass this challenge entail metal-catalyzed hydro/silyl functionalization[27−29] or reductive couplings,[30,31] alkyl-Cr addition to carbonyls,[32−34] and Sn-mediated electrochemistry.[35]

To solve the aza-pinacol coupling challenge, we proposed an alternate strategy to harness ketyl radicals by an atom transfer mechanism.[36] In this approach (Figure 1b), an aldehyde is first combined with AcI *in situ* to form an α-oxy iodide, which is nearly 2 V easier to reduce than the parent carbonyl. This improved radical precursor contains a weak C−I bond (58 kcal/mol) that may also be cleaved by iodine atom abstraction to chemoselectively form ketyl radicals of aliphatic aldehydes in the presence of more easily reduced imines. Whereas we

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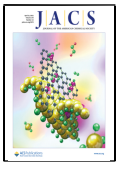

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have shown *redox-neutral* addition of ketyl radicals to alkynes afford *Z*-vinyl iodides,[36] we reasoned a suitable, terminal H-donor may now also afford *reductive* reactivity, in the form of an aza-pinacol coupling.

To test our hypothesis (Figure 2), pentanal **1** and imine **2a** were irradiated with visible light in the presence of a

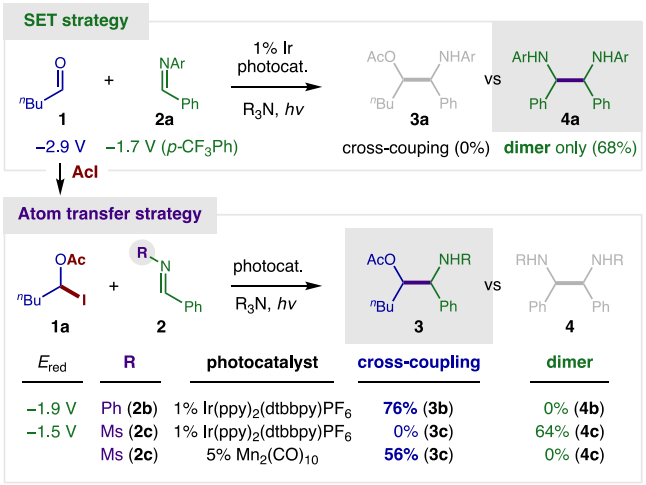
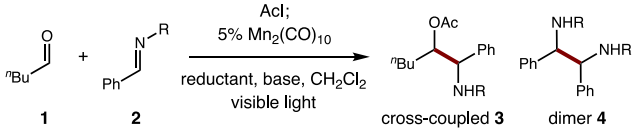


Figure 2. Development of cross-selective aza-pinacol coupling.

photocatalyst (1% $Ir(ppy)_2(dtbbpy)PF_6$) and terminal reductant (3 equiv nBu_3N). As expected from previous reports,[13] this SET strategy does not provide aza-pinacol adduct **3**, but instead affords only imine-derived homodimer **4a** (68%). Conversely, to probe our atom transfer strategy, AcI and pentanal **1** were first combined in CH_2Cl_2 at 0 °C for 15 min. The *in situ* generated *α*-oxy iodide **1a** was then subjected to imine **2b** and photocatalytic conditions. To our delight, a complete switch in reactivity is observed, wherein *cross-selective* aza-pinacol adduct **3** is now obtained exclusively (76%), without homodimer **4** (0%). Desiring an imine with a more easily removed protecting group, we replaced N-aryl imines **2a,b** with sulfonimine **2c** (R = Ms). However, this more easily reduced imine (Ms: −1.5 V vs Ph: −1.9 V)[9−11] falls within the redox window of the Ir photocatalyst (−1.5 V)[37,38] and thus yields exclusive dimerization (64% **4c**). To solve this problem, we pivoted from an SET reduction mechanism to atom transfer activation by a $Mn_2(CO)_{10}$ catalyst.[39−41] In this case, iodide **1a** and sulfonimine **2c** selectively afford cross-coupled adduct **3c** (56%) without any dimer **4** (0%).

To further improve this atom transfer-enabled, aza-pinacol coupling, several reaction parameters were examined (Table 1). First, including a coreductant (e.g., Hantzsch ester) affords cross-coupled adduct **3** in >20:1 chemoselectivity over dimer **4**, for three classes of imines (R = Ph, Ts, Ms, entries 1−3). Although excluding the Hantzsch reductant diminishes efficiency (10% vs 56%, entries 3−4), replacing with Zn recovers reactivity (40%, entry 5) and affords a simpler purification (separation of Zn salts versus coeluting Hantzsch pyridine). A switch from irradiation by blue LED to a broader spectrum white CFL further improves reactivity (70%, entry 6). And the hindered base, Cy_2NMe, proves superior to either iPr_2NEt or KOAc (90%, entries 6−8), suggesting its likely role as H atom donor to the transient N-radical. Finally, increased catalyst loading (15% vs 5%) affords >99% yield within 2 h (entry 9), and 1:1 stoichiometry (i.e., without excess aldehyde) also provides efficient cross-selective reactivity (entry 10).

Table 1. Reaction Optimization[a]



entry	R	light	reductant	base	yield 3	3:4
1	Ph	blue LED	Hantzsch	iPr_2NEt	28%	>20:1
2	Ts	blue LED	Hantzsch	iPr_2NEt	50%	>20:1
3	Ms	blue LED	Hantzsch	iPr_2NEt	56%	>20:1
4	Ms	blue LED	none	iPr_2NEt	10%	>20:1
5	Ms	blue LED	Zn	iPr_2NEt	40%	>20:1
6	Ms	white CFL	Zn	iPr_2NEt	70%	>20:1
7	Ms	white CFL	Zn	KOAc	29%	>20:1
8	**Ms**	**white CFL**	**Zn**	**Cy_2NMe**	**90%**	**>20:1**
9[b]	**Ms**	**white CFL**	**Zn**	**Cy_2NMe**	**99%**	**>20:1**
10[c]	Ms	white CFL	Zn	Cy_2NMe	70%	>20:1

[a]Conditions: 0.2 mmol imine, pentanal (3 equiv), AcI (2.6 equiv), 5% $Mn_2(CO)_{10}$, reductant (2 equiv), base (5 equiv), CH_2Cl_2 (1 mL), 24 h. [b]15% $Mn_2(CO)_{10}$, 2 h. [c]Aldehyde (1 equiv).

The scope and generality of this mild, cross-selective aza-pinacol coupling was then explored using a wide variety of imines and aldehydes (Table 2). For example, several *ortho-*, *meta-*, and *para*-substituted aryl aldimines were shown to be effective imine partners (**5**−**14**). Notably, an exceptionally broad range of electronically diverse substituents were tolerated, spanning Hammett constants (σ_p) of −0.3 (OMe) to +0.5 (CF_3) as well as a wide redox window,[9] including imines that may otherwise afford homodimerization via an SET manifold. Steric variation similarly does not inhibit efficiency, although *ortho* substituents strongly influence diastereoselectivity with *o*-Me groups affording *β*-amino alcohols in up to 9:1 dr (**11**, **15**). Bis-substitution is well-tolerated for both sterically (**15**) and electronically exaggerated cases, such as bis-CF_3 arene (**16**) and bis-F pyridine (**17**), again without dimerization. Lastly, a pair of mechanistic probes were investigated, containing weak, benzylic C−H bonds that may facilitate H atom transfer (HAT) to the N-radical intermediate.[42,43] However, since no remote functionalization products were observed (by either inter- or intramolecular HAT), including on the strong H atom donor, fluorene, (**18** and **19**), we conclude N-radical termination occurs more rapidly.

To critically probe the chemoselectivity of this cross-selective coupling, we designed a series of experiments examining imines with acid-labile or easily reducible groups that would not be tolerated under typical SmI_2, photocatalytic, or other highly reducing conditions. In each of these cases, aza-pinacol coupling was the exclusive product observed. For example, benzofuran (**20**), acetal (**21**), aryl nitrile (**22**), and aryl iodides (**23**−**25**) all remain intact. Most notably, benzophenone (**26**; −1.3 V)[44] is unperturbed despite its less negative potential than the imine (−1.5 V), or the aldehyde (−2.9 V) that is chemoselectively converted to a ketyl radical.

Next, a range of aliphatic aldehydes were investigated to determine the generality of *β*-amino alcohols accessible by this ketyl coupling. Steric effects appear minimal as both smaller acetaldehyde (**27** and **28**) and larger isobutyraldehyde (**29**) provide similar efficiency, with the imine partner having a stronger stereoselectivity influence (**28**; 10:1 dr with *o*-tolyl imine). As further chemoselectivity probes, reductively prone

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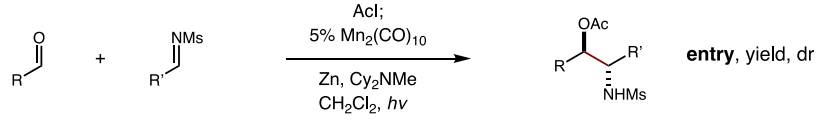
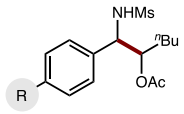
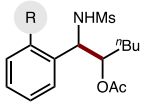
Table 2. Scope, Generality, and Chemoselectivity of Catalytic, Atom Transfer, Cross-Aza-Pinacol Coupling



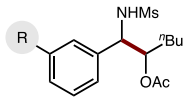
Imines



R = CF_3, **5**, 92%, 2:1
Br, **6**, 89%, 3:1
H, **3**, 90%, 3:1
Me, **7**, 75%, 3:1
OMe, **8**, 54%, 3:1

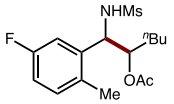


R = F, **9**, 90%, 1:1
Br, **10**, 79%, 3:1
Me, **11**, 81%, 7:1

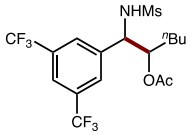


R = Br, **12**, 71%, 2:1
Me, **13**, 79%, 3:1
OBn, **14**, 79%, 3:1

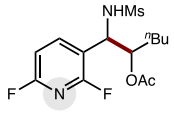
H-atom transfer (HAT) probes



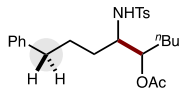
15, 70%, 9:1[b]



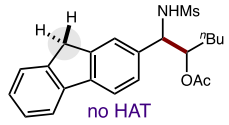
16, 71%, 1:1



17, 91%, 1:1[b]

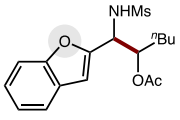


18, 50%, 1:1[c,d]

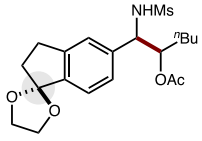


19, 55%, 3:1[b]

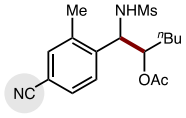
chemoselectivity probes



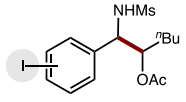
20, 52%, 2:1



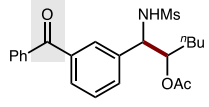
21, 66%, 3:1



22, 64%, 4:1[b]

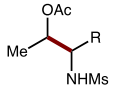


ortho-I: **23**, 56%, 2:1[b]
meta-I: **24**, 87%, 2:1[b]
para-I: **25**, 83%, 3:1[b]

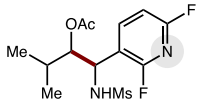


26, 68%, 2:1[b]

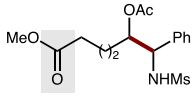
Aldehydes



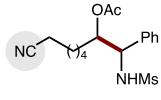
R = Ph, **27**, 63%, 3:1
o-tolyl, **28**, 60%, 10:1[b]



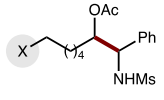
29, 73%, 1:1[b]



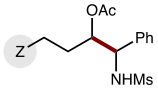
30, 70%, 3:1[b]



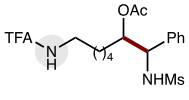
31, 70%, 3:1[b]



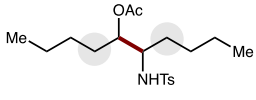
X = Cl, **32**, 74%, 3:1
I, **33**, 54%, 3:1[b,c]



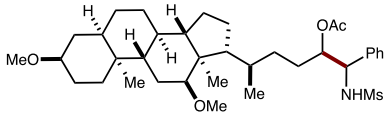
Z = ^{t}BuPh$_2$SiO, **34**, 68%, 3:1[d]
PhthN, **35**, 50%, 2:1



36, 65%, 3:1[b]



37, 54%, 1:1[c,d]

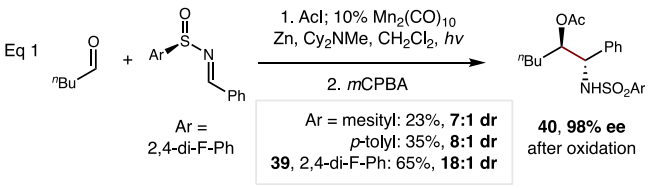


38 (from deoxycholic acid), 60%, 3:1[d]

[a]0.2 mmol imine, aldehyde (3 equiv), AcI (2.6 equiv), 5% $Mn_2(CO)_{10}$, Zn (2 equiv), Cy_2NMe (5 equiv), CH_2Cl_2, (1 mL), 2 × 23W white CFL, 24 h. [b]10% $Mn_2(CO)_{10}$. [c]iPr_2NEt instead of Cy_2NMe. [d]With Hantzsch ester (0.75 equiv). See SI for full details.

functionality was also preserved on the aldehyde component, including esters, nitriles, and alkyl halides (**30**−**33**). Synthetically useful heteroatom substitution is also tolerated, such as ethers, imides, and amides (**34**−**36**), including within a natural product derivative of deoxycholic acid (**38**). Conversely, both the aldehyde and imine partners may also be entirely aliphatic (**18**, **37**).[45]

Given the strong influence of the imine on controlling diastereoselectivity, we sought to access a single enantiomer of *β*-amino alcohols by use of a chiral auxiliary (eq 1).[46,47] To this



end, we found S-aryl sulfinimines enable more efficient radical-coupling than the S-*t*Bu analog (<10%). Moreover, 2,4-di-*F*-phenyl sulfinyl aldimine affords superior stereoselectivity (18:3:3:1 dr **39**; 18:1 dr at C−N stereocenter) vs typical variants: mesityl (7:1 dr) or tolyl (8:1 dr). Oxidation of the auxiliary by *m*CPBA then affords protected sulfonamide **40** in >98% ee.

We next sought to examine if other classes of *reductive* ketyl radical couplings could also be enabled by these mild atom transfer conditions (Figure 3). To complement our previous, *redox-neutral* ketyl couplings with alkynes (yielding *Z*-vinyl iodides),[36] we were pleased to find inclusion of Zn as a terminal reductant instead affords *E*-allyl acetate **41**. Notably, these mild conditions do not over-reduce the acrylate product. Separately, addition to acrylates yield *γ*-acetoxy ester **42** via a ketyl coupling that was not observed under redox-neutral conditions. Lastly, pinacol cross-coupling of pentanal with more easily reduced glyoxylate (−1.4 V)[48] affords *α*-hydroxy-

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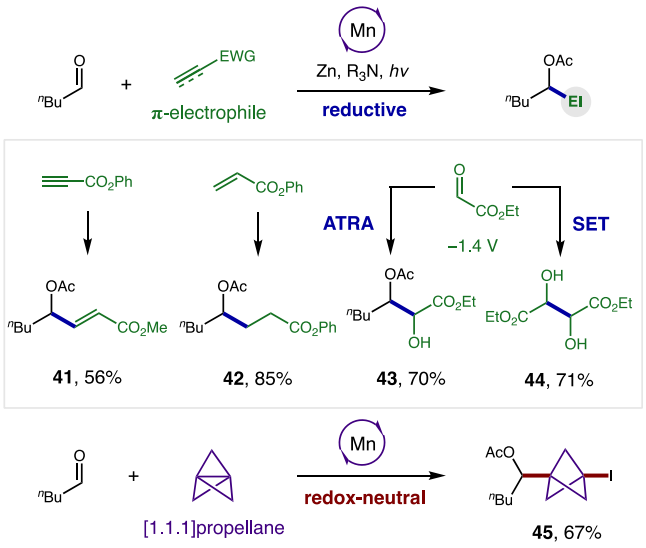

Figure 3. Additional classes of ketyl couplings enabled by atom-transfer catalysis.

β-acetoxy ester **43**. This unique *cross*-selectivity of our atom transfer strategy is highlighted by divergent reactivity compared to SET-mediated photocatalysis,[49] which exclusively yields homodimeric tartrate **44**. Finally, given significant recent interest in the medicinal utility of bicyclo(1.1.1)pentane bioisosteres,[50,51] we tested [1.1.1]propellane as a ketyl coupling partner via both reductive and Zn-free conditions. Interestingly, both pathways yield redox-neutral adduct **45** exclusively, indicating the rapid rate of iodine atom trapping by the bicyclopentyl radical and stability of the resulting alkyl iodide in this first ketyl-propellane coupling.

Mechanistic studies were conducted to elucidate the nature of the key reductive turnover step in this Mn-catalyzed transformation. Unlike our previous *redox-neutral* studies, wherein radical rebound abstracts I• from [Mn]−I,[36] catalyst turnover in this *reductive* process necessitates that a mild reductant liberates I^- to regenerate the 17-electron [Mn•] complex. Mindful of redox data indicating Zn may not be strong enough to reduce [Mn]−I, we were especially curious about this selective reduction event. To investigate the role of Zn in catalyst turnover, we first employed the proposed intermediate, $(CO)_5MnI$, as a catalyst instead of $Mn_2(CO)_{10}$ (Figure 4a). Interestingly, under photolytic conditions in the absence of Zn, we observed Cy_2NMe can activate [Mn]−I to afford a 25% yield, likely via an electron-donor−acceptor (EDA) complex. However, addition of both Zn and amine significantly improves efficiency (66% yield), suggesting a productive interplay of all three components. This hypothesis was further supported by UV−vis analysis (Figure 4b). Background absorption spectra were obtained for $Mn_2(CO)_{10}$ (λ_{max} = 343 nm, yellow line) and $(CO)_5MnI$ (λ_{max} = 300 nm, orange line). Notably, the diagnostic absorption at 343 nm was not observed for combination of $(CO)_5MnI$ and Zn alone (gray line). However, when all three components were combined ([Mn]−I, Zn, Cy_2NMe), the signal was restored (blue line). Further evidence that an EDA complex promotes this reduction is a concentration-dependent loss of the [Mn]−I signal with increasing [Cy_2NMe], along with formation of a new 250 nm peak (see SI). Together, these experiments illustrate the combined action of both Zn and amine in reducing [Mn]−I to [Mn•] and enabling catalyst turnover.

To further elucidate the role of amine in enabling reduction, CV analysis confirms that Zn (−1.0 V) reduction of either $(CO)_5MnI$ ($E_{p/2}$: −1.1 V) or $Mn_2(CO)_{10}$ ($E_{p/2}$: −1.2 V) is thermodynamically disfavored (Figure 4c). Conversely, a 100 mV anodic shift in reduction potential was observed upon addition of Cy_2NMe to $(CO)_5MnI$ ($E_{p/2}$: −1.0 V), indicating the [Mn]−I:NR_3 EDA complex facilitates milder reductive turnover of the Mn catalyst. Intriguingly, these results suggest photoinitiation may not be required, which we have validated by a pair of additional experiments conducted in the absence of light (Figure 4d). First, since [Mn•] generation from $Mn_2(CO)_{10}$ is dependent on visible light homolysis of the Mn−Mn bond, minimal product was observed (10%) without this initiation. However, when proposed intermediate [Mn]−I,

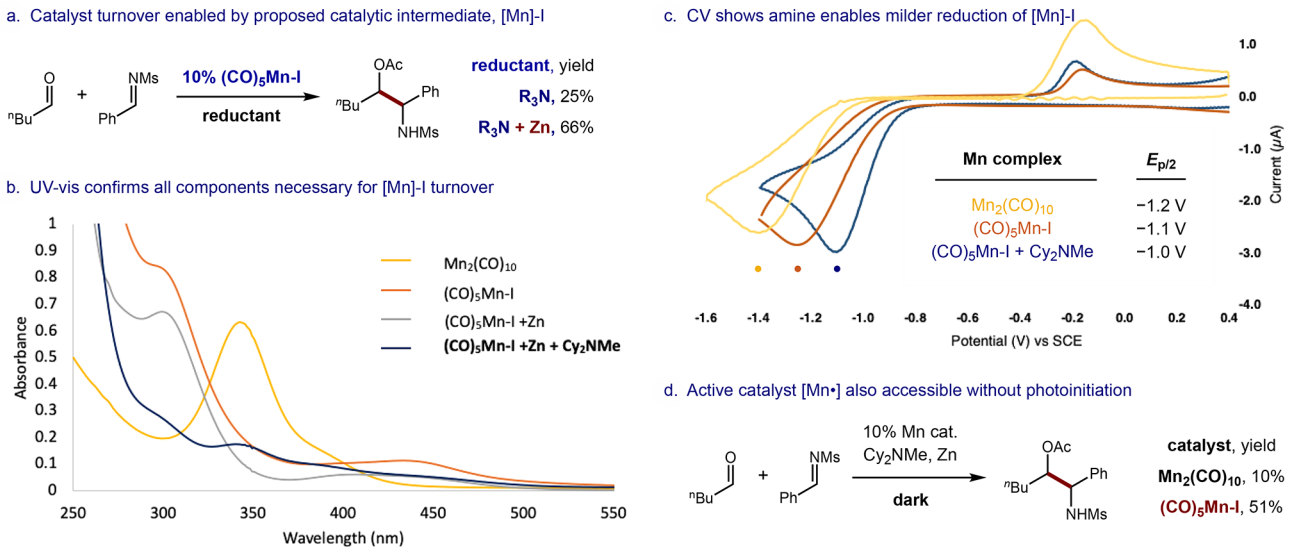

Figure 4. Mechanistic experiments probing Mn catalyst turnover.

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Zn, and amine were combined to initiate generation of the active [Mn•] species, reactivity was observed in the dark (51%). These data suggest photolysis is required only for initiation and when [Mn•] dimerization ($k = 9.5 \times 10^8$ M^{-1} s^{-1})[52] occasionally outcompetes ketyl radical generation by iodine abstraction.

Merging the insights from these experiments, a proposed mechanism is illustrated in Figure 5. Upon selective *in situ*

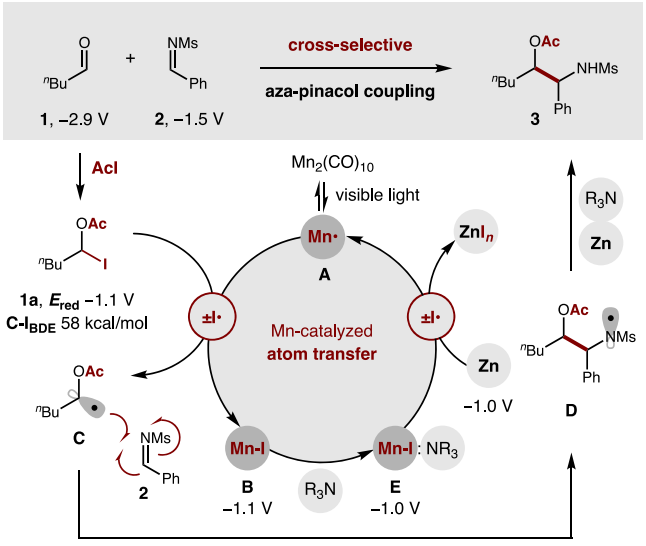

Figure 5. Proposed mechanism of Mn-catalyzed aza-pinacol coupling.

activation of aldehyde **1** by AcI, this least reducible component is transformed into the most easily reduced, α-oxy iodide **1a** (−2.9 V to −1.1 V). To initiate catalysis, visible light homolysis of the weak Mn−Mn bond of $Mn_2(CO)_{10}$ provides $(CO)_5Mn•$ (**A**). Ketyl radical generation is chemoselectively accomplished by iodine atom transfer of the weak C−I bond (58 kcal/mol)[36] by **A** to form $Mn(CO)_5I$ (**B**). The resulting α-acyloxy radical **C** selectively cross-couples to imine **2** (or other π-acceptors, such as alkynes, alkenes, aldehydes, and propellane) to form N-centered radical **D** (or corresponding C-radical). This electron-deficient amidyl radical is then terminated via either (i) SET reduction by Zn and R_3N (both are necessary) or (ii) HAT from the polarity-matched α-amino C−H of Cy_2NMe.[53,54] This final step occurs more rapidly than intramolecular HAT from even weak, benzylic C−H bonds, to afford aza-pinacol adduct **3**. Finally, catalyst turnover of $(CO)_5MnI$ (**B**) is mediated by R_3N (via EDA complex **E**), whose ground state reduction potential is lowered by 100 mV (−1.1 V to −1.0 V), allowing Zn to serve as a mild, chemoselective reductant. The regenerated catalyst **A** may propagate nonphotolytic catalytic cycles until dimerization to $Mn_2(CO)_{10}$ necessitates visible light homolysis to reinitiate the catalytic cycle.

In summary, a cross-selective aza-pinacol coupling has been developed for the synthesis of β-amino alcohols. An atom transfer catalytic approach enables chemoselective reduction of aldehydes to ketyl radicals in the presence of more easily reduced imines. This atypical selectivity facilitates cross-coupling reactivity and precludes homodimerization of the imine partner, as might otherwise be observed under typical reductive manifolds. A wide range of β-amino alcohols are accessed, including valuable chemoselectivity probes containing acid- and reductant-sensitive groups that would not otherwise be tolerated by Sm, Na, or strong photoreductants. The synthetic utility of this strategy is further illustrated by ketyl couplings of alkynes, alkenes, aldehydes, [1.1.1]-propellane, and stereoselective aza-pinacol coupling with chiral sulfinimine. This represents the first *reductive* version of our Mn-catalyzed, atom transfer strategy for accessing ketyl radical reactivity. Mechanistic studies illustrate the shared role of Zn and amine in Mn catalyst turnover and the rapid rates of termination of the radical relay. We envision this strategy will enable further discovery of nonclassical ketyl radical couplings via atom transfer mechanisms.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site at DOI: The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00886.

Experimental procedures and characterization for all new compounds; ^1H and ^{13}C NMR spectral data (PDF)

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Notes

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