ORGANIC CHEMISTRY

Ketyl radical reactivity via atom transfer catalysis

Lu Wang, Jeremy M. Lear, Sean M. Rafferty, Stacy C. Fosu, David A. Nagib*

Single-electron reduction of a carbonyl to a ketyl enables access to a polarity-reversed platform of reactivity for this cornerstone functional group. However, the synthetic utility of the ketyl radical is hindered by the strong reductants necessary for its generation, which also limit its reactivity to net reductive mechanisms. We report a strategy for net redox-neutral generation and reaction of ketyl radicals. The in situ conversion of aldehydes to α-acetoxy iodides lowers their reduction potential by more than 1 volt, allowing for milder access to the corresponding ketyl radicals and an oxidative termination event. Upon subjecting these iodides to a dimanganese decacarbonyl precatalyst and visible light irradiation, an atom transfer radical addition (ATRA) mechanism affords a broad scope of vinyl iodide products with high *Z*-selectivity.

The ketyl coupling of carbonyls offers a mechanistically inverted approach to constructing C-C bonds versus classic, polar mechanisms (*1*). However, a major limitation of this valuable method is its reliance on strong, stoichiometric reductants (e.g., Na, K, Ti) (*2–4*) to overcome the large reduction potential of carbonyls (peak cathodic potential $E_{p,c} > -2$ V versus SCE) (*5*, *6*). As shown in Fig. 1A, a powerful tool used to overcome the thermodynamic barrier for ketyl generation is Kagan's reagent (SmI_2) (*7*, *8*). This single-electron reductant can even be used catalytically when coupled with strong, stoichiometric reductants (e.g., Zn/Hg) (*9*). Recently, photochemical approaches have been applied to address this fundamental thermodynamic challenge in a complementary manner. For example, Knowles and co-workers developed a proton-coupled electron transfer strategy to reduce ketones to ketyl radicals using Ir or Ru photocatalysts (< −1.5 V), Brønsted acids, and a milder stoichiometric reductant (e.g., Hantzsch ester) (*10*, *11*). The groups of Yoon, Ngai, and Huang (*12–15*) have also shown that concerted use of Lewis acids enables photocatalytic reduction of carbonyls to access ketyl radicals and their vinylogous analogs. Additional metal-catalyzed strategies for carbonyl-alkyne coupling promote complementary reactivity (by Ni, Ru, or Ir) with alternate reductants (e.g., Et_3B, Mg, H_2) (*16–18*). However, in each of the ketyl-based strategies, a redox-neutral approach remains mechanistically unfeasible because catalysts capable of overcoming the high reduction potential of a carbonyl are necessarily also prone to reducing the resulting ketyl-coupling adduct.

Our complementary strategy, outlined in Fig. 1, addresses this challenge by replacing the carbonyl reduction step with a halogen abstraction event via an atom transfer radical addition (ATRA) mechanism. In this case, a Mn catalyst promotes mild ketyl radical formation from an in situ–generated intermediate containing a weak C-I bond. The resulting radical is capable of coupling with a range of alkynes. Catalyst turnover occurs (via formal oxidation of the ensuing vinyl radical intermediate) by atom transfer (*19*, *20*) with Mn-I, in a net redox-neutral mechanism that enables access to synthetically versatile (*21*) *Z*-vinyl halides.

In our synthetic design, we focused on addressing the challenge of ketyl radical generation from aliphatic aldehydes. We envisioned that their conversion to α-oxy iodides would benefit from hyperconjugative donation of the nonbonding oxygen electrons into the C-I antibonding orbital ($n \rightarrow \sigma^*$) to further weaken this bond. Among several α-iodo radical precursors we investigated, the α-acetoxy derivative proved simplest to generate under mild conditions. This in situ activation is performed by combining AcI (AcCl, NaI) with carbonyls [5% $Zn(OTf)_2$, 0°C, 15 min] in a modified version of Adams' nearly century-old procedure (*22*). The resulting aldehyde derivatives are conveniently handled in an aerobic atmosphere at room temperature and are stable to basic, aqueous washes without elimination. This practical synthetic accessibility allowed us to electrochemically validate our hypothesis that α-acetoxy iodides ($E_{p,c}$ = −1.1 V; fig. S2) are more easily reduced than their aldehyde precursors (> −2.2 V) (*5*) as well as other alkyl iodides (*23–26*). Next, we explored the generation of ketyl radicals—and their redox-neutral coupling with alkynes—by using a variety of atom transfer catalysts.

In accordance with our design plan, we observed that several photocatalysts promote this redox-neutral alkyne coupling with ketyl radicals derived from aliphatic aldehydes (**1**), as illustrated in Fig. 1C. Expecting the nucleophilicity of α-OAc ketyl radicals to be attenuated, we explored their combination with several alkynes of varying electronic character. In particular, coupling of silyl acetylene **2** affords silyl vinyl iodide **3** (containing orthogonal handles for further synthetic manipulation) in a streamlined approach that obviates an alkynylation–Al reduction–iodination sequence. Among the atom transfer catalysts investigated, several photocatalysts afforded new, redox-neutral coupling adduct **3** preferentially over the classic, reduced coupling product **4**. These catalysts included complexes of earth-abundant, first-row metals (e.g., Mn, Fe) as well as more reducing photocatalysts (e.g., Ru, Ir; see table S1 for further details). Ultimately, a $Mn_2(CO)_{10}$ catalyst was found to provide excellent selectivity for redox-neutral coupling (**3**:**4**, >20:1) along with high *Z*:*E* diastereoselectivity (>20:1). The latter feature is notable, as there are few methods to access vinyl iodides with high *Z*-selectivity (*27*). Although Mn-mediated reactions are typically associated with oxidative mechanisms, atom transfer pathways are accessible via $Mn_2(CO)_{10}$ (*28–30*). Unlike typical photocatalysts, a photon is not necessary for turnover of the Mn catalyst. However, we observed that continual irradiation is necessary to access high efficiency and selectivity, likely due to an equilibrium between the precatalyst dimer and the active catalyst. Given the high chemo- and stereoselectivity afforded by the Mn catalyst, we decided to further explore its synthetic potential in this redox-neutral mechanism.

In our mechanistic proposal, shown in Fig. 1D, $Mn_2(CO)_{10}$ precatalyst is homolyzed to $Mn(CO)_5$ (**5**, Mn•) by irradiation with a blue LED. This 17-electron species is a competent ATRA catalyst that can abstract I• from the weak C-I bond [bond dissociation energy (BDE), 58 kcal/mol] (*31*) of in situ–generated α-acetoxy iodide **6**. Combination of the resultant ketyl radical **7** with alkyne **8** affords vinyl radical **9**. This open-shell intermediate is formally oxidized by $Mn(CO)_5I$ (**10**, [Mn]-I) via atom transfer to regenerate the Mn• catalyst (**5**), while also forming vinyl iodide **3′** in a redox-neutral mechanism (*32*). The net conversion of **6** to **3′** is exothermic because of the formation of a strong vinyl C-I bond (BDE, 61 to 68 kcal/mol). An observed post-reaction isomerization of the vinyl iodide products—from 1:1 to >20:1 *Z*:*E* selectivity—is also thermodynamically favored by up to 3 kcal/mol (*33*). This Mn-catalyzed isomerization likely occurs via an intermediate vinyl radical, which is consistent with reports of photoinduced, single-electron reduction of aryl iodides for sp^2 radical generation (*34*, *35*). This Mn-catalyzed ATRA mechanism precludes an alternate pathway, in which vinyl radical **9** is further reduced to vinyl anion **11** [$E_{p,c}$ = −0.1 V (*36*), which is at least 2 V more favorable than carbonyl to ketyl reduction] to afford allyl ester **4**. Instead, by coupling catalyst turnover with product formation, the classic reductive mechanism can be overridden by this redox-neutral pathway.

In probing the synthetic utility of this strategy, we were pleased to find that aliphatic aldehydes, which are challenging to reduce to ketyls ($E_{p,c} > -2$ V) (*5*), efficiently combine with a range of alkynes, as shown in Fig. 2. Alkynes with broad electronic character are coupled to the stabilized ketyl radicals, providing *Z*-vinyl

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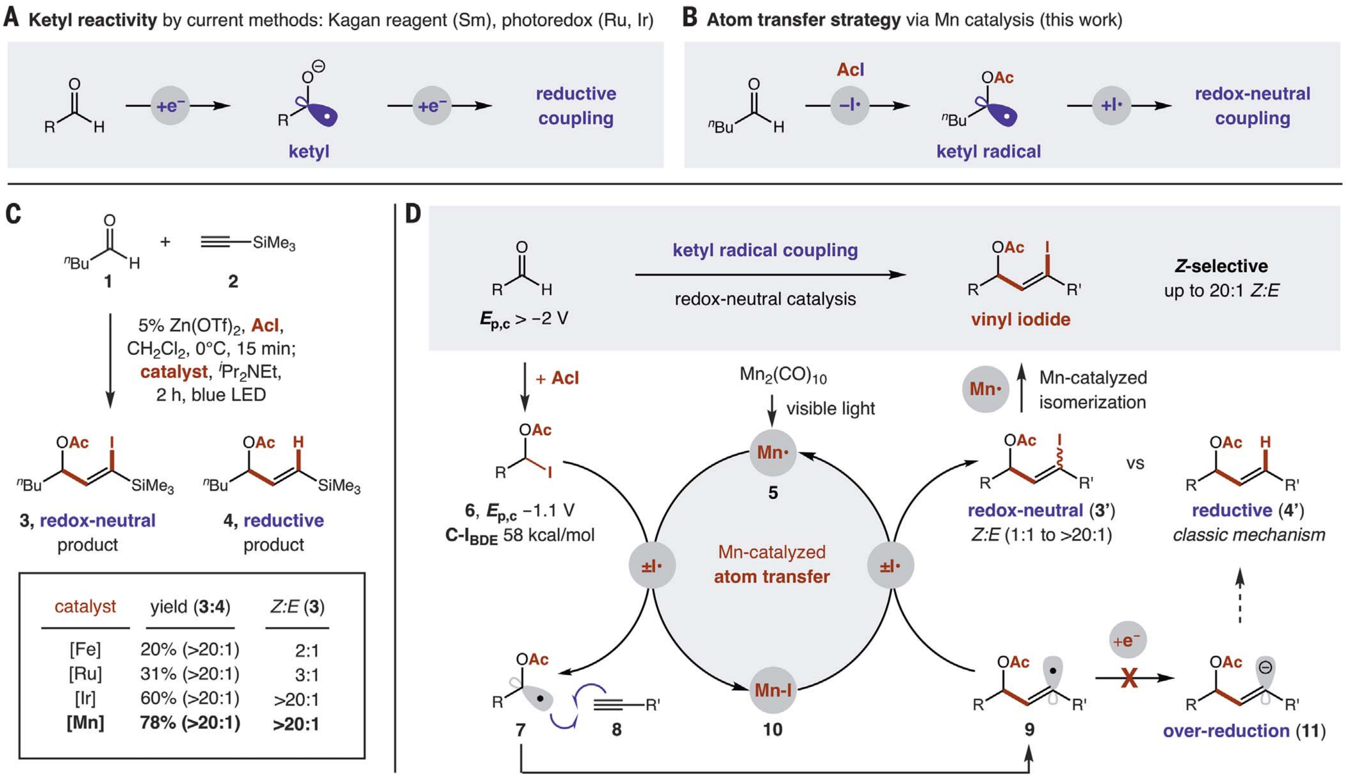

Fig. 1. Discovery of a redox-neutral ketyl radical coupling. (**A**) Current synthetic approaches to ketyl radicals rely on strong reductants that reduce both the carbonyl and subsequent radical intermediates. (**B**) An alternate strategy based on atom transfer of an α-acetoxy iodide enables milder reductive initiation, coupled with oxidative termination, to provide a redox-neutral ketyl coupling mechanism. (**C**) Several catalysts enable this atom transfer strategy, including $[CpFe(CO)_2]_2$, $Ru(bpy)_3Cl_2$, $Ir(ppy)_2(dtbbpy)PF_6$, and $Mn_2(CO)_{10}$, which provide a range of chemo- and stereoselectivities. (**D**) Proposed mechanism: Photoinitiated homolysis of $Mn_2(CO)_{10}$ occurs with visible light (blue LED). The $Mn(CO)_5$ catalyst then formally reduces the in situ formed α-acetoxy iodide via inner-sphere atom transfer. The resulting ketyl radical combines with an alkyne to form a vinyl radical, which is oxidized by the Mn catalyst to form the vinyl iodide product and regenerate $Mn(CO)_5$. This catalyst turnover step precludes an alternate reductive pathway, wherein a second reduction of the vinyl radical affords the classic, non-iodo product. ^{n}Bu, *n*-butyl; Me, methyl; ^{i}Pr, isopropyl; Et, ethyl; Ac, acetyl; $Zn(OTf)_2$, zinc trifluoromethylsulfonate; Cp, cyclopentadienyl; bpy, 2,2′-bipyridine; ppy, 2-phenylpyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridyl.

iodides in up to 20:1 diastereomeric ratio. For example, alkynes with highly electron-releasing substituents, such as $SiEt_3$ or BPin, are competent partners (**12**, **13**), affording versatile vinyl silanes or boronates (*37*, *38*). Aryl alkynes and 1,3-enynes afford valuable styrene and diene adducts (**14**, **15**), and electron-deficient propiolates also undergo ketyl coupling to merge these electrophiles (**16**, **17**).

In addition to conjugated alkynes, we found propargyl esters to be suitable ketyl radical acceptors that afford *Z*-vinyl iodide **18**, which contains orthogonal allyl esters. An internal competition between alkynes (alkyl- versus ester-substituted) selectively converts the propiolate alkyne to vinyl iodide **19**, leaving the unsubstituted alkyne intact. The mild, radical addition conditions are also tolerant of alcohols (**20**) and ketones (**21**, **22**), illustrating the orthogonality and synthetic utility of this ATRA-based strategy.

To further demonstrate the functional group compatibility of this ketyl-alkyne coupling, we also explored a wide range of aliphatic aldehydes. Aldehyde-derived ketyl radical precursors with both small (**23**) and large (**24**) steric footprints provide *Z*-vinyl iodides in >20:1 selectivity. The tolerated functionality on the aldehyde component includes arenes of varying electronic character (**25**–**27**), ethers (**28**–**29**), and amides (**30**–**32**). Alkyl halides (e.g., Cl, **33**; I, **34**) are also tolerated in the reaction, illustrating selective reaction of the Mn catalyst with the hyperconjugatively activated α-acetoxy iodides.

Finally, although some ketone-derived ketyl radicals are too hindered for efficient cross-coupling, we found that trifluoroacetone provides efficient access to *Z*-vinyl iodide **35** bearing an adjacent tertiary ester. Electron-rich alkenes are also capable of ketyl radical coupling, including those substituted with Si (**36**) or B (**37**). An antioxidant, vitamin E, was also incorporated in the alkyne acceptor (**38**) without inhibiting this mild ketyl radical coupling.

Our mechanistic hypothesis for the redox-neutral catalytic reaction described above is supported by reaction intermediate isolation and resubjection, competition experiments, and kinetic measurements (Fig. 3). To probe the origin of the high *Z*:*E* diastereoselectivity, we monitored product formation of vinyl iodides **12** and **16** over the reaction course (Fig. 3A). In each case, we observed rapid product formation (>70% yield) within 15 min, albeit with modest *Z*:*E* selectivity (7:1, 1:1). For the first 2 hours, product yields remained within 5 to 10% of their 15-min values, but *Z*:*E* selectivity increased markedly (>20:1, 14:1), suggesting a product isomerization mechanism. Additional evidence of post-reaction epimerization was found when a 1:1 mixture of vinyl iodide **16** was resubjected to the Mn photocatalyst for 2 hours, affording the *Z*-isomer selectively: 4:1 (10% catalyst) or >20:1 (20% catalyst) (Fig. 3B).

Further insights were obtained for each elementary step of the atom transfer radical addition via the mechanistic experiments shown in Fig. 3. First, a competition experiment between an electron-poor and an electron-rich alkyne resulted in exclusive ketyl radical coupling to the electron-deficient propiolate alkyne (**16** versus **12**), indicating that the α-OAc radical has nucleophilic character (Fig. 3C). Next, we validated the viability of the key oxidation step required for catalyst turnover by stoichiometric trapping of an aryl radical with

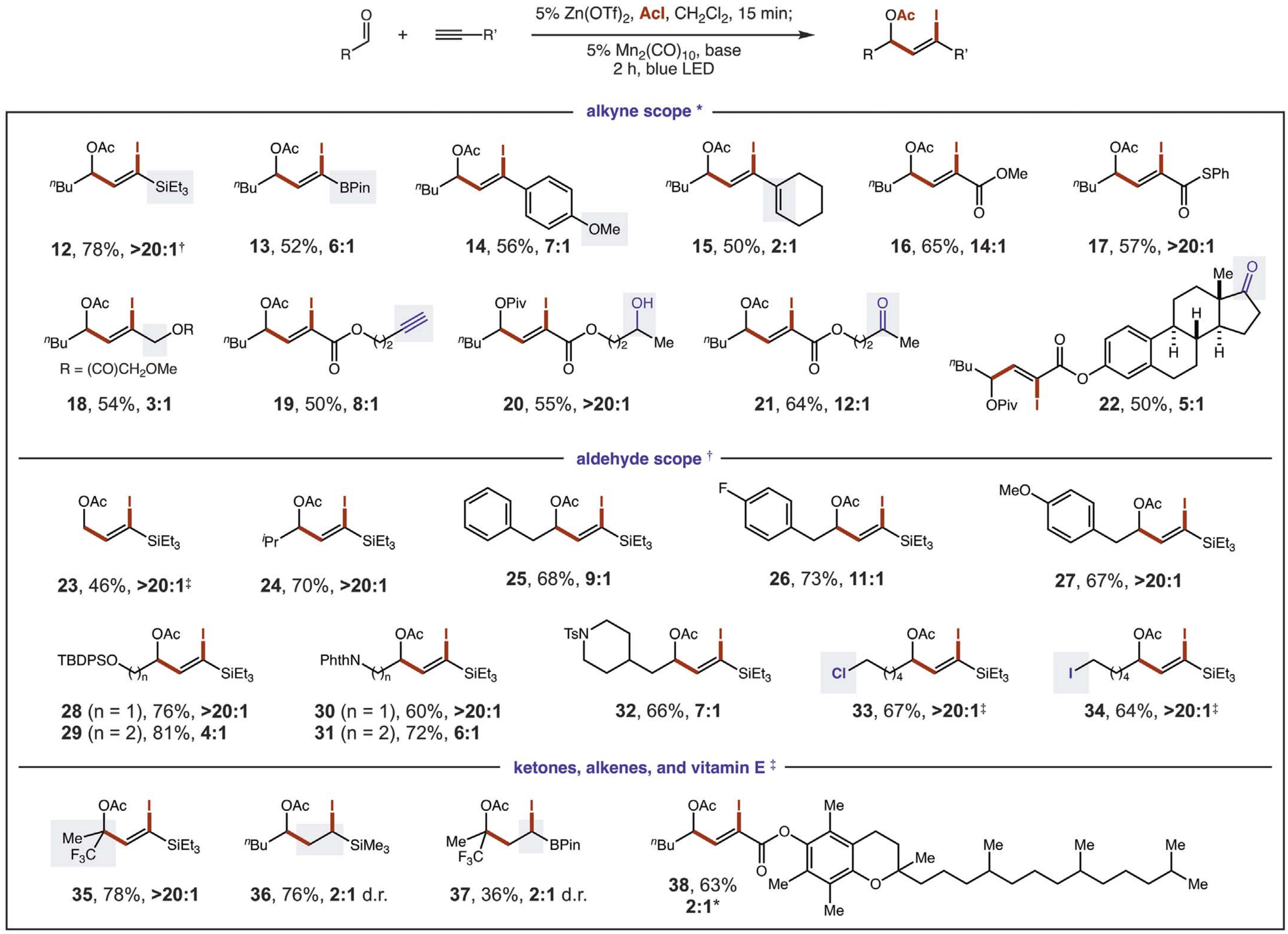

Fig. 2. Synthetic scope of redox-neutral ketyl radical coupling. See supplementary materials for experimental details. Isolated yield and *Z*:*E* ratio are indicated below each entry. *20% $Mn_2(CO)_{10}$, 1 equiv KOAc. †5% $Mn_2(CO)_{10}$, 0.5 equiv $^{i}Pr_2NEt$. ‡10% $Mn_2(CO)_{10}$. Abbreviations: Ac, acyl; Pin, pinacol; Piv, pivaloyl; TBDPS, *tert*-butyldiphenylsilyl; Phth, phthalyl; Ts, toluenesulfonyl; BPin, bis(pinacolato)diboron.

[Mn]-I to form Ar-I (Fig. 3D). The sp^2 C• radical precursor, diazonium **39**, affords aryl iodide **40** in 70% yield when combined with $Mn(CO)_5I$ and eosin Y photocatalyst (3% without light, 68% with only thermal initiation). Next, the rate of atom transfer was compared to known radical clocks (*39*) appended to propiolate (Fig. 3E). For each of the three intramolecular traps investigated, only atom transfer (i.e., vinyl C-I termination, **41**–**43**) was observed, in lieu of radical cyclization, which occurs rapidly with these acceptors ($>1 \times 10^8$ s^{-1}). Finally, cascade reactions were facilitated by incorporation of intramolecular traps within the ketyl radical precursors (Fig. 3F). Unlike the radical clock experiments that did not manifest cyclization, these ring closures occurred selectively, albeit with divergent outcomes dependent on the hybridization of the coupled radical intermediate. For example, alkyne **44**, which forms an sp^2 C•, selectively traps iodine, affording two-component coupling product **45**, even in the presence of alkyne traps (e.g., $-CO_2Et$, $-SiEt_3$). Alternatively, an sp^3 C• formed by ketyl radical cyclization of alkene **46** selectively combines with Et_3Si-alkyne to afford three-component coupling product **47**. In this case, intramolecular sp^3 to sp^3 translocation of the carbon radicals (α-OAc to α-CO_2Et) precedes intermolecular trapping of the alkyne. The resultant sp^3 C• is long-lived enough (or exists as a living radical) (*40*) to then combine with an alkyne, forming an sp^2 C• that is rapidly trapped as the vinyl iodide.

Finally, to demonstrate the synthetic utility of these functionally rich ketyl-alkyne adducts (bearing a geminal vinyl iodide/silane), we manipulated the atom transfer product **3**, as shown in Fig. 4. First, Pd-catalyzed cross-coupling of the vinyl iodide with a range of boronic acids afforded alkylation (**48**), vinylation (**49**), and arylation (**50**–**52**) products with complete stereoretention. Next, the resulting *E*-vinyl silane **48** was converted to a *Z*-vinyl iodide with *N*-iodosuccinimide (NIS), and subsequent arylation with $PhB(OH)_2$ afforded **53** via a modular, five-component coupling. We expect that this atom transfer method for accessing ketyl radicals—and selectively combining them with an electronically diverse range of π-acceptors—through the use of earth-abundant metal catalysts will have broad utility in various synthetic arenas.

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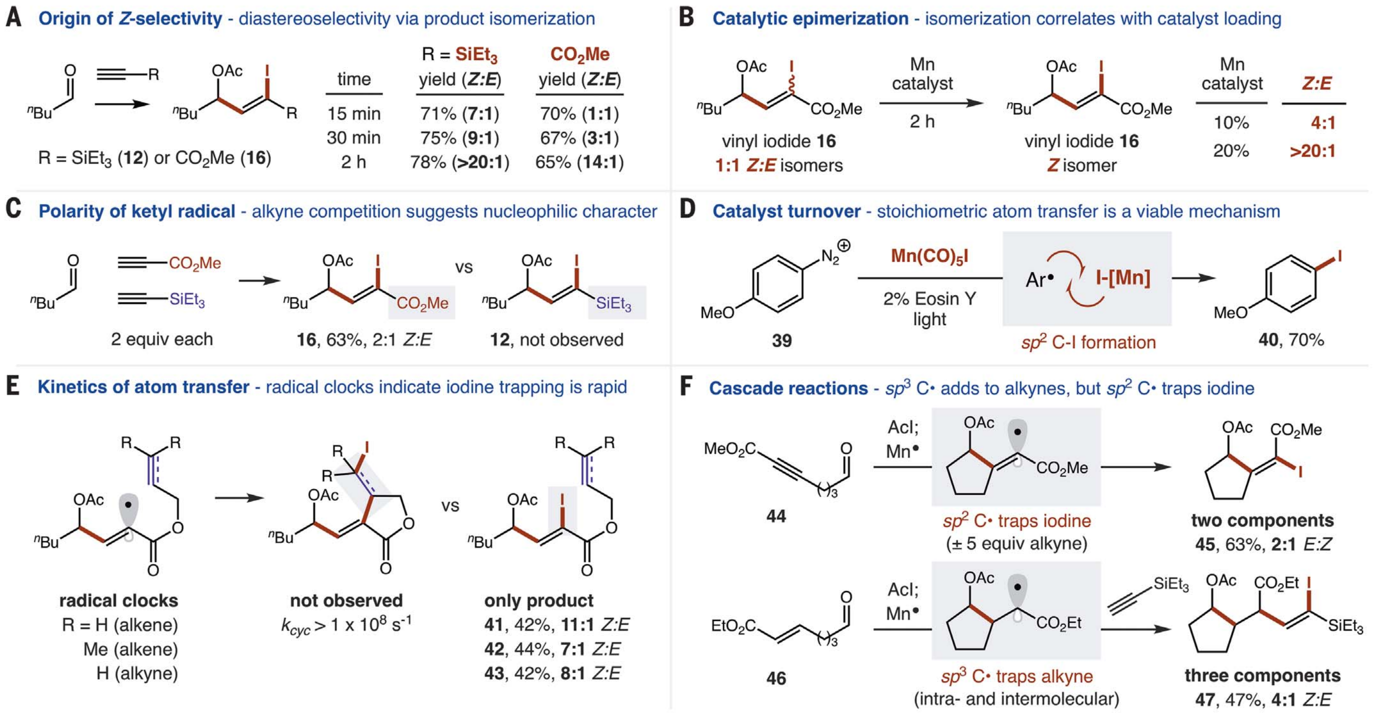
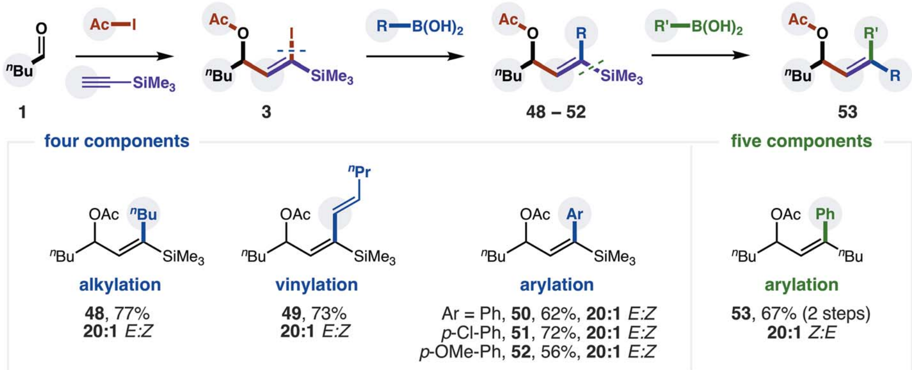


Fig. 3. Mechanistic experiments. (**A**) *Z*:*E* selectivity increases over the reaction course for both alkyne classes, suggesting a product isomerization pathway. (**B**) A 1:1 mixture of vinyl iodide isomerizes to increased ratios of the *Z*-isomer correlating with Mn catalyst loading, illustrating the catalyst's role in isomerization. (**C**) Selective combination with an electron-deficient alkyne indicates that the ketyl radical is nucleophilic. (**D**) The catalyst turnover step involving sp^2 C-I formation is recapitulated by trapping an aryl radical with [Mn]-I to form Ar-I. (**E**) Selective recombination of the vinyl radical with I• (versus intra-molecular traps) suggests that this step is rapid. (**F**) Intramolecular traps with sp^2 or sp^3 C• intermediates afford either two- or three-component cascade couplings.

Fig. 4. Synthetic utility of the atom transfer product. Silyl vinyl iodide **3** was coupled to alkyl, vinyl, and aryl boronic acids with 10% Pd(PPh$_3$)$_2$Cl$_2$ in a net four-component coupling. The resulting *E*-vinyl silane was converted to a *Z*-vinyl iodide with NIS, then also coupled with phenyl boronic acid in a net five-component coupling.



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SUPPLEMENTARY MATERIALS

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Figs. S1 to S9
Tables S1 to S4
NMR Spectra
References (*41*–*60*)

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Ketyl radical reactivity via atom transfer catalysis

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Iodine smooths the way to ketyl radicals

Chemists typically transform carbonyl compounds through polar two-electron reactions. It is also possible to pursue radical coupling strategies by adding just one electron to form a ketyl group. However, the strong reductant supplying that electron often limits the reaction's versatility. Wang *et al.* report a mild means of forming ketyls by first adding acetyl iodides across the C=O bond (see the Perspective by Blackburn and Roizen). A photoactivated manganese catalyst then temporarily pulls the iodine away, leaving a ketyl to couple with alkynes. The iodine then returns to one of the alkyne's carbons, stabilizing the product but remaining poised for further transformations.

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