

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b11699 • Publication Date (Web): 21 Nov 2018

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Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes

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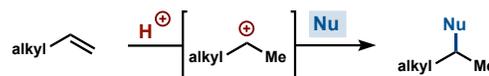
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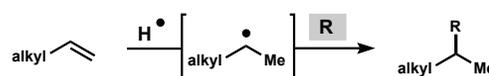
Radical hydrofunctionalization occurs with ease using metal-hydride atom transfer (MHAT) catalysis to couple alkenes and competent radicalophilic electrophiles. Traditional two-electron electrophiles have remained unreactive. Herein we report the reductive coupling of electronically-unbiased olefins with imines and aldehydes. Iron-catalysis allows addition of alkyl-substituted olefins into imines through the intermediacy of free-radicals, whereas a combination of catalytic $\text{Co}(\text{Sal}^{t\text{-Bu},t\text{-Bu}})$ and chromium salts enable a branch-selective coupling of olefins and aldehydes through the formation of a putative alkyl chromium intermediate.

Branch-selective reactions of alkyl-substituted olefins via carbocationic¹ or radical intermediates² benefits from an abundance of methods, but the analogous transformation into branched-carbanion equivalents remains underdeveloped (Figure 1). A common way to transform an olefin into a carbanion equivalent is via hydrometallation of a double bond. However, such branch-selective hydrometallation of alkenes is generally limited to styrenes, allenes, and dienes—all electronically biased systems that stabilize a developing carbon-metal bond.³ In the absence of electronic bias, steric constraints dominate: canonical metal hydrides favor linear selectivity and linear hydrometallation is predominately observed.⁴ To obtain branch-selectivity with electronically-unbiased alkenes, we have investigated M–H hydrogen atom transfer (MHAT) catalysis and subsequent capture of the nascent intermediates by a second metal complex.^{5,6,7} For example, we recently established that nickel complexes intercept $\text{Co}(\text{Sal}^{t\text{-Bu},t\text{-Bu}})$ -catalyzed MHAT cycles in a direct organocobalt to organonickel transmetalation.⁶ Similar alkyl transmetalations have been reported in non-catalytic systems between alkyl– $\text{Co}(\text{dmgBF}_2)_2\text{Py}$ and inorganic nickel,⁸ and proposed for bioorganometallic⁹ and catalytic processes.¹⁰ This alkyl transfer does not appear limited to nickel: vitamin B12-mimetics (such as $\text{Co}(\text{salen})$ derivatives) can undergo alkyl transfer to palladium,¹¹ rhodium,¹² other cobalt,¹³ platinum,¹⁴ gold,¹⁵ chromium,¹⁶ and zinc¹⁷ salts and organometallic species. Yet despite the apparent generality of this transformation, there is a paucity of preparative cross-coupling methods which leverage this reactivity.

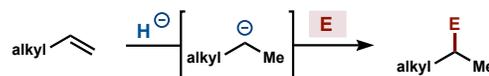
a. Olefin as carbocation surrogate - established



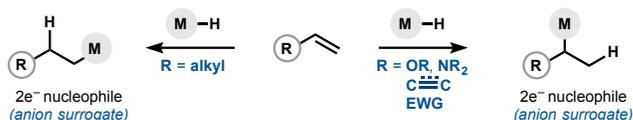
b. Olefin as radical surrogate - established



c. Olefin as anion surrogate - challenging



d. Hydrometalation leads to linear or branched 2e⁻ organometallic



e. This work

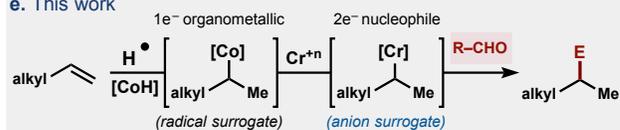


Figure 1: Transformation of olefins into carbanion equivalents by a radical/ polar crossover.

The capacity to form cobalt organometallics via MHAT followed by cage-collapse^{6,18,19,20} prompted us to explore transmetalation partners that might lead to otherwise inaccessible branched products. Here we show that olefins can be added to imines and aldehydes to form $\text{sp}^3\text{-sp}^3$ bonds. The former reaction with an activated electrophile occurs under standard MHAT catalysis, whereas the latter reaction requires interception of MHAT intermediates with chromium salts (Figure 1e). This transformation expands the current scope of olefins as carbanion surrogates²¹ which has heretofore required the use of electronically-activated olefins, such as styrene, allenyl, or dienes. Alkyl-substituted olefins, in contrast, react with carbonyls at the least-substituted position through a Prins mechanism,²² or undergo iron-catalyzed hydromagnesiation reactions to form linear nucleophiles.^{23,24,25}

We initially investigated the Markovnikov addition of alkenes into carbonyl derivatives by utilizing the intermediacy of the free radicals and noticed that productive reactions

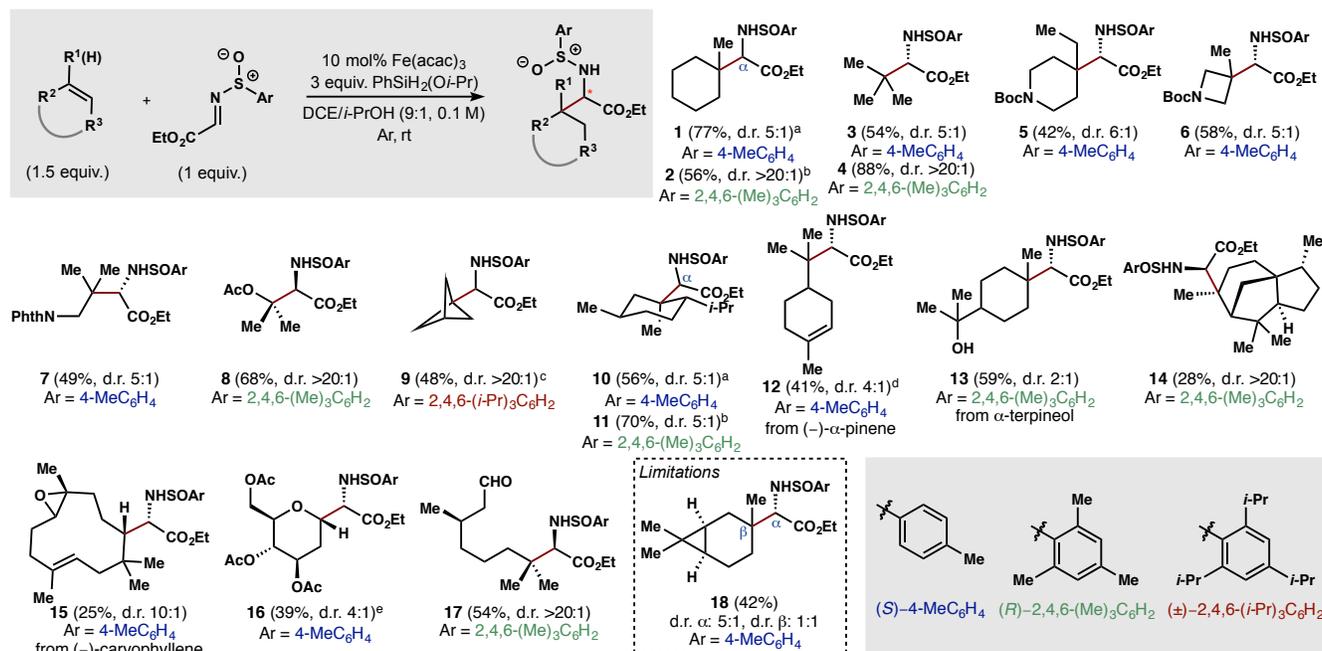


Figure 2. Alkyl radicals generated by MHAT add to chiral sulfinimines. d.r. of two major diastereomers reported. ^astereochemistry at the α -carbon is (*S*). ^bstereochemistry in the α -carbon is (*R*). ^cMn(dpm)₃ instead of Fe(acac)₃ was used. ^dcontains 15% unrearranged pinene product and its diastereomer. ^e3 equiv. of olefin used.

were only obtained with standard radicalophiles, such as radical-stabilizing imines. Glyoxylimines are preceded as radical acceptors,^{26,27} and chiral sulfinyl auxiliaries can be used to impart stereocontrol. Although the competitive reduction of these electrophiles by the metal hydrides or the stoichiometric silane was observed, this could be minimized by using a slight excess of the olefin and Fe⁺³ salts as the catalyst.²⁸ Several feedstock alkenes served as competent nucleophilic components and delivered unnatural amino acids bearing β -quaternary carbons, and reactive groups like free-hydroxyls (**13**) or two-electron electrophiles such as esters, epoxides, or aldehydes (**8**, **15**, and **17**) are tolerated. Complex feedstock terpenes can engage the sulfinimines to deliver adducts **12**, **14**, and **15**, and even glycans deliver amino esters with good diastereocontrol (**16**). Comparison of the optical rotation obtained from our reaction to that of *t*-butyl glycine derivatives shows that sulfinimines with the (*S*)-configuration affords the (*S*)-amine whereas the (*R*)-sulfinimine affords the (*R*)-amine.²⁸ Better diastereoselectivity is obtained with the more hindered mesitylene or tri-isopropyl arene-derived sulfinamide, whereas the use of Ellman's *tert*-butyl sulfinamide was not compatible with these radical conditions.²⁸ Given the ease with which these compounds are made, requiring no prefunctionalization prior radical formation, we anticipate that this method will find application in the synthesis of unnatural amino acids.²⁹

Addition of the free radical to aldehydes, however, proved challenging (see Table 1), as may be expected due to

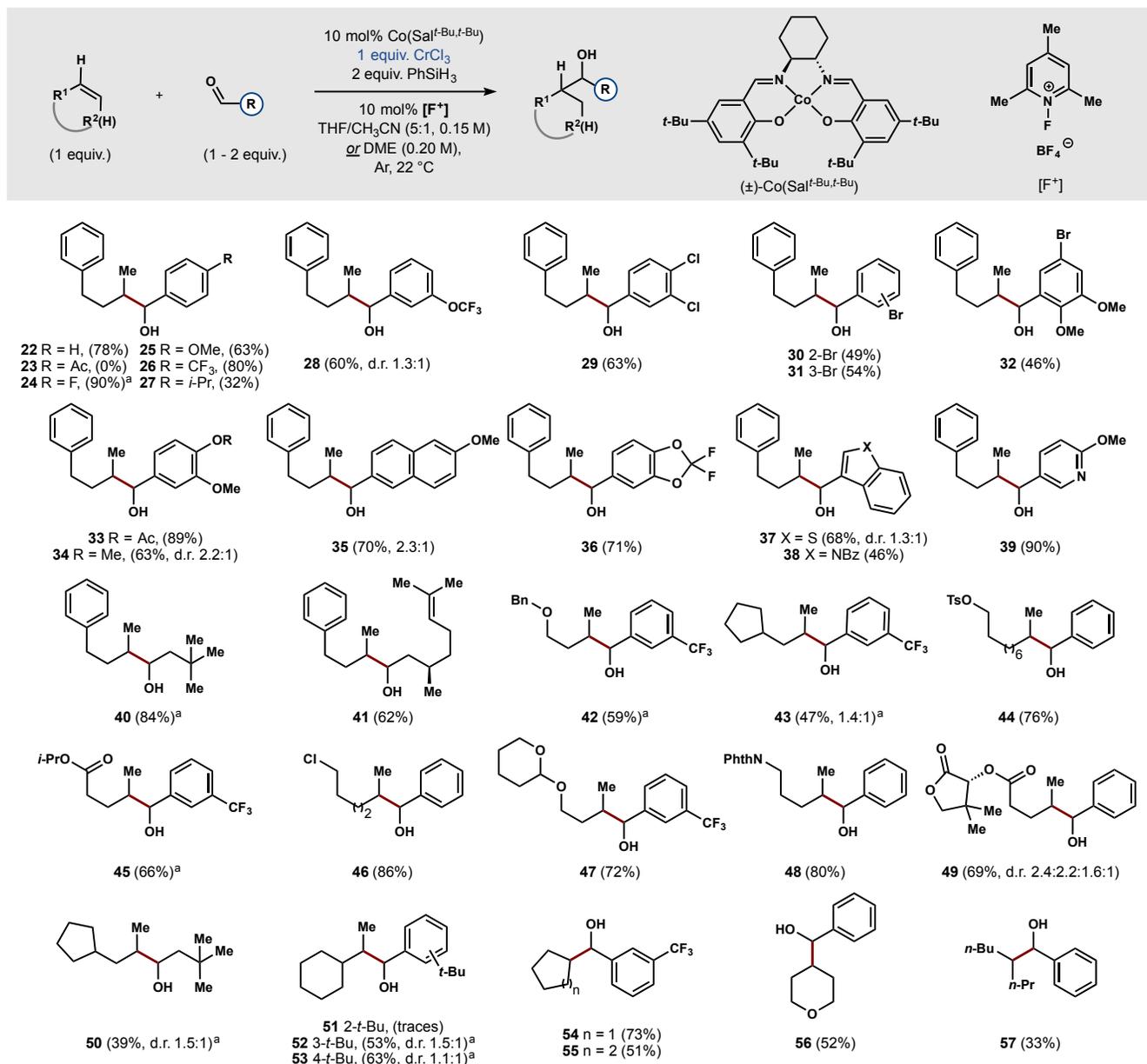
the higher instability of an *O*-centered radical relative to a *C*-centered radical, which is reflected by the more facile C–C bond scission than C–C bond formation.³⁰ Strategies to drive this energetically unfavorable addition include sequestering the unstable *O*-centered radical as an alkoxide (which

Table 1. Conversion of *C*-centered radicals to 2-electron nucleophiles.



Entry	Deviations from above	Yield (%) ^a
1	Fe(dpm) ₃ , Fe(acac) ₃ , Co(acac) ₂ or Mn(dpm) ₃ instead of Co(Sal ^{<i>t</i>-Bu,<i>t</i>-Bu})	< 10%
2	CrCl ₂ instead of CrCl ₃	trace
3	with Zn ⁰ or Mn ⁰	11%
4	Co(salen)Cl and no [O]	45% ^c
5	no [O]	–
6	0.2 equiv. of CrCl ₃ instead of 1 equiv.	22%
7	0.2 equiv. of CrCl ₃ and TMSCl (1 equiv.)	–
8	in DMF instead of THF/CH ₃ CN	–
9	without CH ₃ CN	35%
10	under air	46%
11	with 1 equiv. of H ₂ O	–
12	No Co(Sal ^{<i>t</i>-Bu,<i>t</i>-Bu})	–
13	No CrCl ₃	– ^d

^ayield determined by GC/FID using a calibrated internal standard; ^b isolated yield with 20 mol % of Co(salen)Cl and CrCl₃(THF)₃; ^c1 equiv. of NaBF₄ added; ^disomerization and hydrogenation was observed; d.r. 1:1 in all cases.



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Figure 3. Conversion of alkenes into carbanion surrogates with branched-selectivity. d.r. at the formed bond is close to 1:1 unless otherwise noted. See Supporting Information for the d.r. of the isolated compounds. ^a20 mol% of [Co] and 20 mol% of [F⁺] were used.

cannot undergo homolytic β -scission) in an intramolecular setting³¹ or accessing excited-states via photochemistry.³² However, neither strategy may be used for intermolecular addition with alkyl-substituted olefins.³³ In light of the precedence for alkyl-cobalt complexes to transmetallate other metal species and the apparent facility with which organo-cobalt species can form from olefins,^{6,20} we wondered if a two-electron nucleophile equivalent could arise from unactivated olefins via sequential one-electron reductions via interception of organocobalt with chromium species.

We were drawn to chromium chemistry for several reasons: 1) organochromium reagents are known to add into carbonyls in a 1,2-fashion 2) Cr⁺² salts are proposed to intercept alkyl-radicals to form organochromium species with bimolecular rate constants on the order of 10⁷ M⁻¹s⁻¹,³⁴ 3) alkyl-cobalamines and -cobaloximes can also be intercepted

by Cr⁺²,^{16,35,36} and 4) chromium salts are inexpensive and of low toxicity in the +2 and +3 oxidation states.³⁷ Furthermore, the weak Brønsted acidity of organochromium complexes allows for a high functional group tolerance and for their use in late-stage functionalization for complex molecule synthesis.³⁸

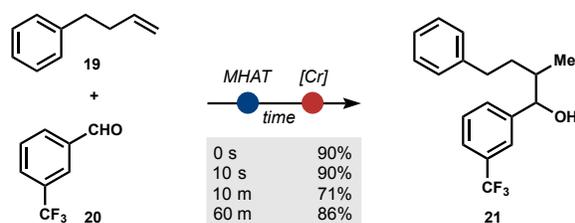
Initially, attempts to merge MHAT catalysis and chromium chemistry met with poor results. β -diketonate complexes of Co and Mn were not productive, although iron salts afforded the product in low yield (Table 1, Entry 1).³⁹ We discovered, however, that use of Co(Sal^{t-Bu,t-Bu}) and equimolar amounts of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate in the presence of phenylsilane and CrCl₃ could couple the terminal olefin in **19** to 3-trifluoromethyl benzaldehyde in good yields. Given that Cr⁺² is typically the active species in the addition of alkyl halides into carbonyls, we

initially explored the reaction using CrCl_2 or CrCl_3 alongside an external metal reductant only to discover that these conditions lead to less product formed than the amount of $[\text{Co}]$ pre-catalyst added (Entries 2 and 3). One explanation is that the external reductants impede the Co-cycle by unproductive reduction of Co^{+3} intermediates.⁴⁰ Our optimized conditions appear to circumvent this problem by reductive formation of Cr^{+2} *in situ* (see below). Although it is possible to perform this reaction with the pre-oxidized $\text{Co}(\text{Sal}^{\text{t-Bu,t-Bu}})\text{Cl}$, use of Co^{+2} and an external oxidant generally afforded higher yields (Entry 4), thereby allowing use of the more convenient +3 and +2 oxidation states of Cr and Co, respectively. Control experiments indicate that both metals are necessary for product formation (Entries 12-13).⁴¹

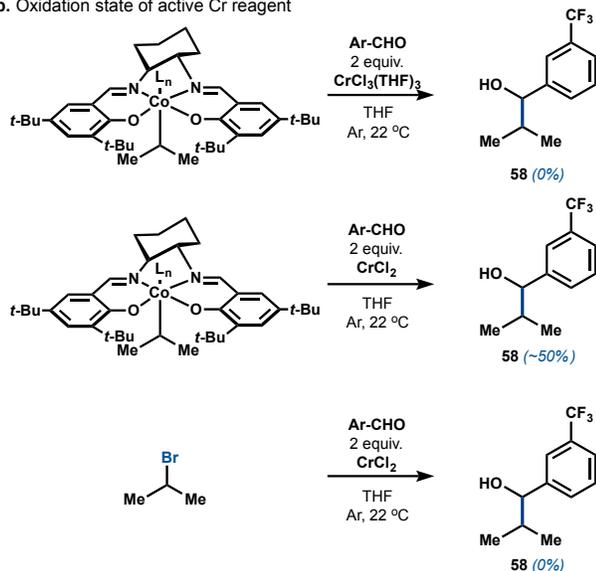
Evaluation of the scope (Figure 3) revealed that both aromatic and alkyl aldehydes are competent electrophiles, and a wide range of electronic variation is tolerated. In general, electron withdrawn substrates afford higher yields than electron-rich electrophiles, yet even vanillin-derived aldehydes such as **33** and **34** react in high yield. Various heteroaromatic aldehydes may be employed (**37** – **39**), as well as terpene-derived substrates (**41**). Esters (**45**), tosylates (**44**), and chlorides (**46**) are orthogonal electrophiles, but competitive reduction of bromides, and iodides was observed. A switch in solvent from THF to DME allows 1,2-disubstituted olefins to be engaged (**54** – **57**), although trisubstituted olefins are

Figure 4. Delayed addition and stoichiometric reactions suggest transmetalation of alkyl- Co^{+3} to alkyl- Cr^{+3} .

a. Effect of delayed addition of CrCl_3 ^a



b. Oxidation state of active Cr reagent



^areactions ran with 20 mol% of $[\text{Co}]$ and 20 mol% of $[\text{O}]$.

not yet competent. Modest diastereocontrol is imparted by a chiral directing group (**49**), and sterically bulky substrates (**35**, **43**, **50** and **52**).⁴²

Although we currently do not have a complete mechanistic model, several observations are worth noting. First, the yield of the product formed does not vary as a function of delayed Cr^{+3} addition, which is consistent with intermediate formation of a stable organocobalt species that is engaged by the Cr, and inconsistent with an alternative hypothesis that the cobalt cycle continuously generates a C-centered radical whose reactivity would favor formation of side products prior to addition of the CrCl_3 .⁴³ These observations draw analogy to our previously reported Ni/Co hydroarylation⁶ and the mechanistic studies of Espenson and coworkers.³⁵ Stoichiometric experiments support a transmetalation and suggest reaction with Cr^{+2} rather than the Cr^{+3} species. In these experiments, a *sec*-alkyl cobalt was formed in situ by displacement of 2-bromopropane by $\text{Co}(\text{Sal}^{\text{t-Bu,t-Bu}})(\text{py})_2$; addition of CrCl_3 and aldehyde **20** yields no product, whereas CrCl_2 produces around 50% of adduct **58** based on the yield of the alkyl-cobalt.²⁸ Control experiments with the alkyl-halide during the same period of time yields no product under these conditions. We suspect reduction of Cr^{+3} to Cr^{+2} occurs via the stoichiometric silane reductant necessary for the MHAT catalytic cycle.⁴⁴ By analogy to the proposal of Espenson and coworkers in similar systems,³⁵ a possible mechanism for the alkyl transfer could involve electron transfer from a Cr^{+2} to an alkyl- Co^{+3} intermediate to form an unstable alkyl- Co^{+2} species which is known to homolyze to afford an alkyl radical that could escape the solvent cage and capture a second Cr^{+2} species, a kinetically facile process ($k = 10^7 \text{ M}^{-1} \text{ s}^{-1}$).^{34,45,46}

In summary, we have discovered divergent reactivity available to alkenes that enables branch-selective (Markovnikov) addition to radicalophilic and non-radicalophilic electrophiles. First, carbon-centered radicals generated by MHAT are competent to add to chiral sulfinimines, which stabilize the incipient *N*-centered radical and impart stereocontrol. The products of these reactions are valuable, unnatural amino acid derivatives. Second and complementarily, although these same radicals do not productively add into aldehydes, the addition of Cr^{+3} salts allows coupling to occur. This latter method circumvents the poor reactivity of free radicals towards carbonyl intermediates while maintaining the Markovnikov reactivity and chemoselectivity of MHAT. Overall, this work enables cross-coupling of abundant chemical feedstocks (aldehydes and olefins) without the need for pre-functionalization. Mechanistic experiments and analogy to the literature is consistent with alkyl- Co^{+3} transmetalation to alkyl- Cr^{+3} , mediated by Cr^{+2} . This second example^{5,6} of catalytic MHAT organocobalt transmetalation calls attention to the potentially general use of these alkyl-cobalt complexes as catalytically-generated organometallic species capable of transferring their alkyl ligands to various other transition metals (including Ni and Cr) for previously inaccessible branch-selective bond-forming processes from olefins. This reactivity complements catalytically-generated organocuprate species which can also

engage in hydrometallation/ transmetallation, but do so with linear selectivity.⁴⁷

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, compound characterization and spectral data.

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Funding Sources

Generous support was provided by the National Institutes of Health (R35 GM122606), the NSF (GRFP to J. L. M. M.), and Shionogi & Co., Ltd. (funding for T.O.). We thank Dr. L. Pasternack and Dr. D.-H. Huang for NMR assistance, Dr. J. Chen and Brittany Sánchez for HRMS measurements, Dr. R. Gianatassio for providing the starting material for **9**, and Dr. S. Crossley, B. Huffman, R. Demoret, S. Shevick, and M. Baker for constructive feedback during preparation of the manuscript.

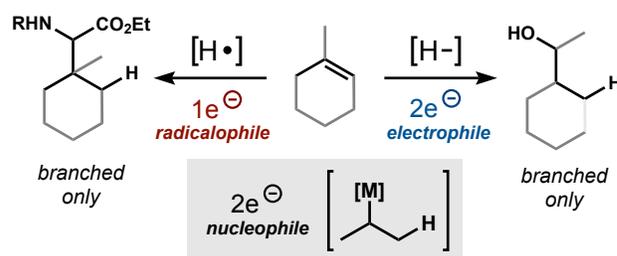
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- K.; Nitta, K.; Fujimura, O.; Utimoto, K. Preparation of alkylchromium reagents by reduction of alkyl halides with chromium(II) chloride under cobalt catalysis. *J. Org. Chem.*, **1989**, *54*, 4732.; as well as the coupling of dienes with aldehydes: Takai, K.; Toratsu, C. B12-Catalyzed Generation of Allylic Chromium Reagents from 1,3-Dienes, CrCl₂, and Water. *J. Org. Chem.* **1998**, *63*, 6450. In more recent examples, combination of Co/Cr have been used in: Xiong, Y.; Zhang, G. Enantioselective 1,2-Difunctionalization of 1,3-Butadiene by Sequential Alkylation and Carbonyl Allylation. *J. Am. Chem. Soc.* **2018**, *140*, 2735.
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40. Co⁺³ is the oxidation state necessary for formation of the Co–H with the silane. Use of external metal reductants typically lead to formation of an inactive Co⁺².
41. Different attempts to make the chromium catalytic have been so far unsuccessful; presumably the additives necessary to dissociate the Cr–O bond, as proposed in standard Cr-catalyzed reactions, can also react with the salen ligand from the cobalt (see: Namba, K.; Kishi Y. New catalytic cycle for couplings of aldehydes with organochromium reagents. *Org. Lett.* **2004**, *6*, 5031.) Recent examples of combining Ir-photocatalysis with Cr where dissociation of the putative Cr–O bond seems to occur without an external agent, could in a future be explored for these endeavors (see: Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F.; Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 12705.)
42. Addition of Lewis basic ligands did not change diastereoselectivity and tended to suppress reactivity.
43. Formation of an intermediate alkyl-chloride that leads to formation of product is unlikely, given that we do not see reaction through the alkyl-chloride in **46**.
44. Aluminum- and borohydrides are known to reduce Cr⁺³ into Cr⁺², perhaps reduction by the silane or a derivative could occur through a similar mechanism. See: Fürstner, A. Carbon–Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.*, **1999**, *99*, 991.
45. Outer sphere electron transfer from Cr to Co: Candlin, J. P.; Halpern, J.; Trimm, D. L. Kinetics of the Reduction of Some Cobalt(III) Complexes by Chromium(II), Vanadium (II), and Europium (II). *J. Am. Chem. Soc.*, **1964**, *86*, 1019.
46. An alternative mechanism of SH₂, as finally proposed in Ref. 35a, is not likely operative given that Co⁺² is not catalytically active in our system (Table 1, entry 5). A mechanism similar to our previously reported Co/Ni dual catalysis involving oxidation of the alkyl–Co⁺³ to an alkyl–Co⁺⁴ prior to homolysis and concomitant reduction of the Cr⁺³ to Cr⁺² (see Ref. 6) is also unlikely given that control experiments indicate there is no reactivity with Cr⁺³ (Figure 4).
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TOC GRAPHIC



Hydrometallation of unbiased alkenes with high branched selectivity by radical–anion crossover