Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes

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Supporting Information Placeholder

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 addition of electronically-unbiased olefins into imines and aldehydes. Iron-catalysis allows addition of alkyl-substituted olefins into imines through the intermediacy of free-radicals, whereas a combination of catalytic Co(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 carbocationic[1] or radical intermediates[2] 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[3]—all electronically biased systems that stabilize a developing carbon-metal bond.[4] In the absence of electronic bias, steric constraints dominate: canonical metal hydrides favor linear selectivity and linear hydrometallation is predominately observed.[5] 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.[6,7,8] For example, we recently established that nickel complexes intercept Co(Sal$^{t\text{-Bu},t\text{-Bu}}$)-catalyzed MHAT cycles in a direct organocobalt to organonickel transmetallation.[7,7] Similar alkyl transmetallations have been reported in non-catalytic systems between alkyl—$Co(dmgBF_2)_2Py_2$ and inorganic nickel,[9] and proposed for bioorganometallic[10] and catalytic processes.[11] This alkyl transfer does not appear limited to nickel: vitamin B12-mimetics (such as Co(salen) derivatives) can undergo alkyl transfer to palladium,[12] rhodium,[13] other cobalt,[14] platinum,[15] gold,[16] chromium,[17] and zinc[18] salts and organometallics species. Yet despite the apparent generality of this transformation, there is a paucity of preparative cross-coupling methods which leverage this reactivity.

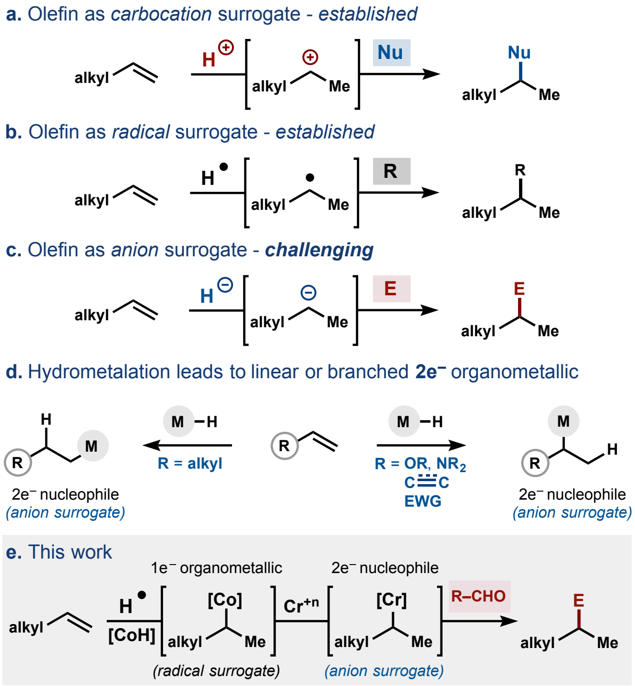


Figure 1: Transformation of olefins into carbanion equivalents by a radical/ polar crossover.

The capacity to form cobalt organometallics via MHAT followed by cage-collapse[7,19,20,21] prompted us to explore transmetallation partners that might lead to otherwise inaccessible branched products. Here we show that olefins can be added to imines and aldehydes to form sp^3–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 surrogates[22] 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,[23] or undergo iron-catalyzed hydromagnesiation reactions to form linear nucleophiles.[24,25,26]

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

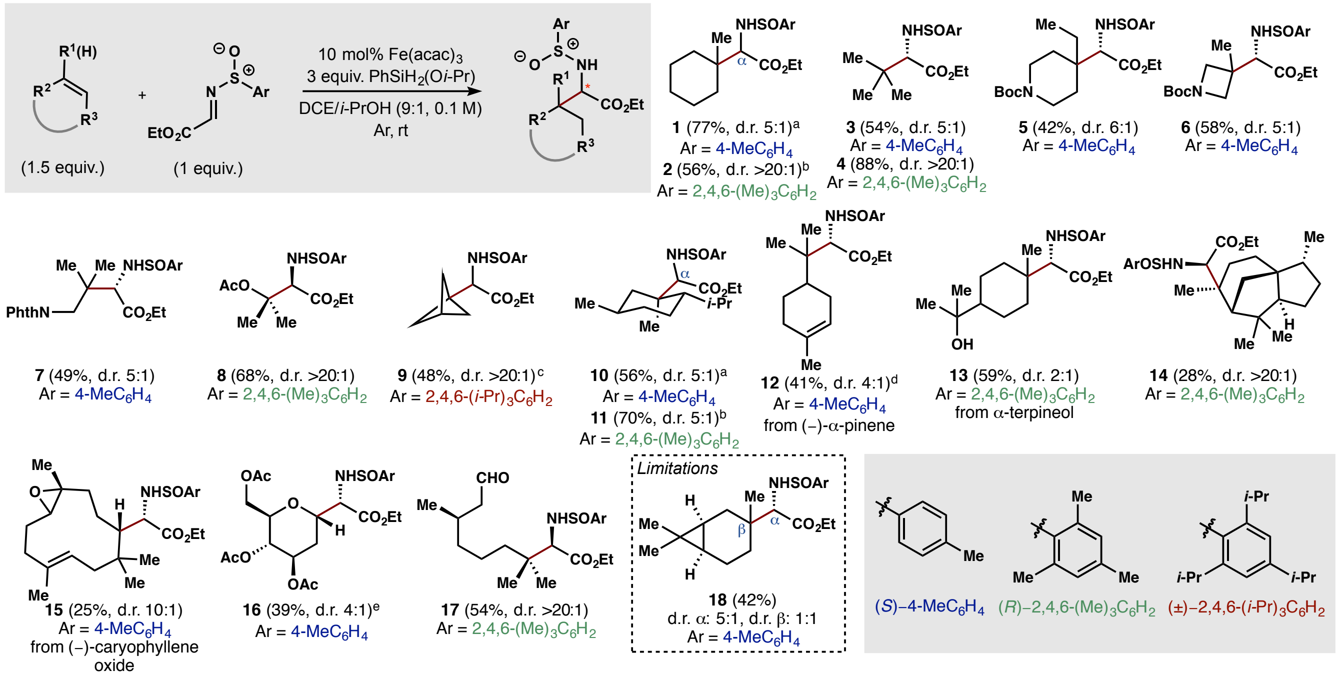
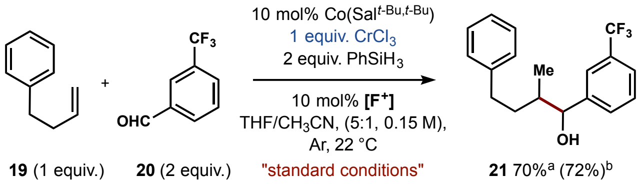


Figure 2. Alkyl radicals generated by MHAT add to chiral sulfinimines. d.r. of two major diastereomers reported. [a]stereochemistry at the α-carbon is (*S*). [b]stereochemistry in the α-carbon is (*R*). [c]$Mn(dpm)_3$ instead of $Fe(acac)_3$ was used. [d]contains 15% unrearranged pinene product and its diastereomer. [e]3 equiv. of olefin used.

were only obtained with standard radicalophiles, such as radical-stabilizing imines. Glyoxylimines are precedented as radical acceptors,[27,28] 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.[29] Several feedstock alkenes served as competent nucleophilic components and delivered unnatural amino acids derivatives with good to excellent diastereoselectivities. (Figure 2). The early transition state of radical reactions allows facile formation of sterically hindered unnatural α-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 sulfinylimines 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 sulfinimes with the (*S*)-configuration affords the (*S*)-amine whereas the (*R*)-sulfinime affords the (*R*)- amine.[29] Better diastereoselectivity is obtained with the more hindered mesitylene or tri-isopropyl arene-derived sulfinamide. Given the ease with which these compounds are made (i.e. no prefunctionalization is necessary for radical formation) we anticipate that this method will find application in the synthesis of unnatural amino acids.[30]

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.[31] Strategies to drive this energetically disfavorable addition include sequestering the unstable *O*-centered radical as an alkoxide (which cannot undergo homolytic *β*-scission) in an intramolecular setting[32] or accessing excited-states via photochemistry.[33] However, neither strategy may be used for intermolecular

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



19 (1 equiv.) **20** (2 equiv.) "standard conditions" **21** 70%[a] (72%)[b]

Entry	Deviations from above	Yield (%)[a]
1	$Fe(dpm)_3$, $Fe(acac)_3$, $Co(acac)_2$ or $Mn(dpm)_3$ instead of $Co(Sal^{t\text{-}Bu,t\text{-}Bu})$	< 10%
2	$CrCl_2$ instead of $CrCl_3$	trace
3	with Zn° or Mn°	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_3CN	–
9	without CH_3CN	35%
10	under air	46%
11	with 1 equiv. of H_2O	–
12	No $Co(Sal^{t\text{-}Bu,t\text{-}Bu})$	–
13	No $CrCl_3$	–[d]

[a]yield determined by GC/FID using a calibrated internal standard; [b] isolated yield with 20 mol % of Co(salen)Cl and $CrCl_3(THF)_3$; [c]1 equiv. of $NaBF_4$ added; [d]isomerization and hydrogenation was observed; d.r. 1:1 in all cases.

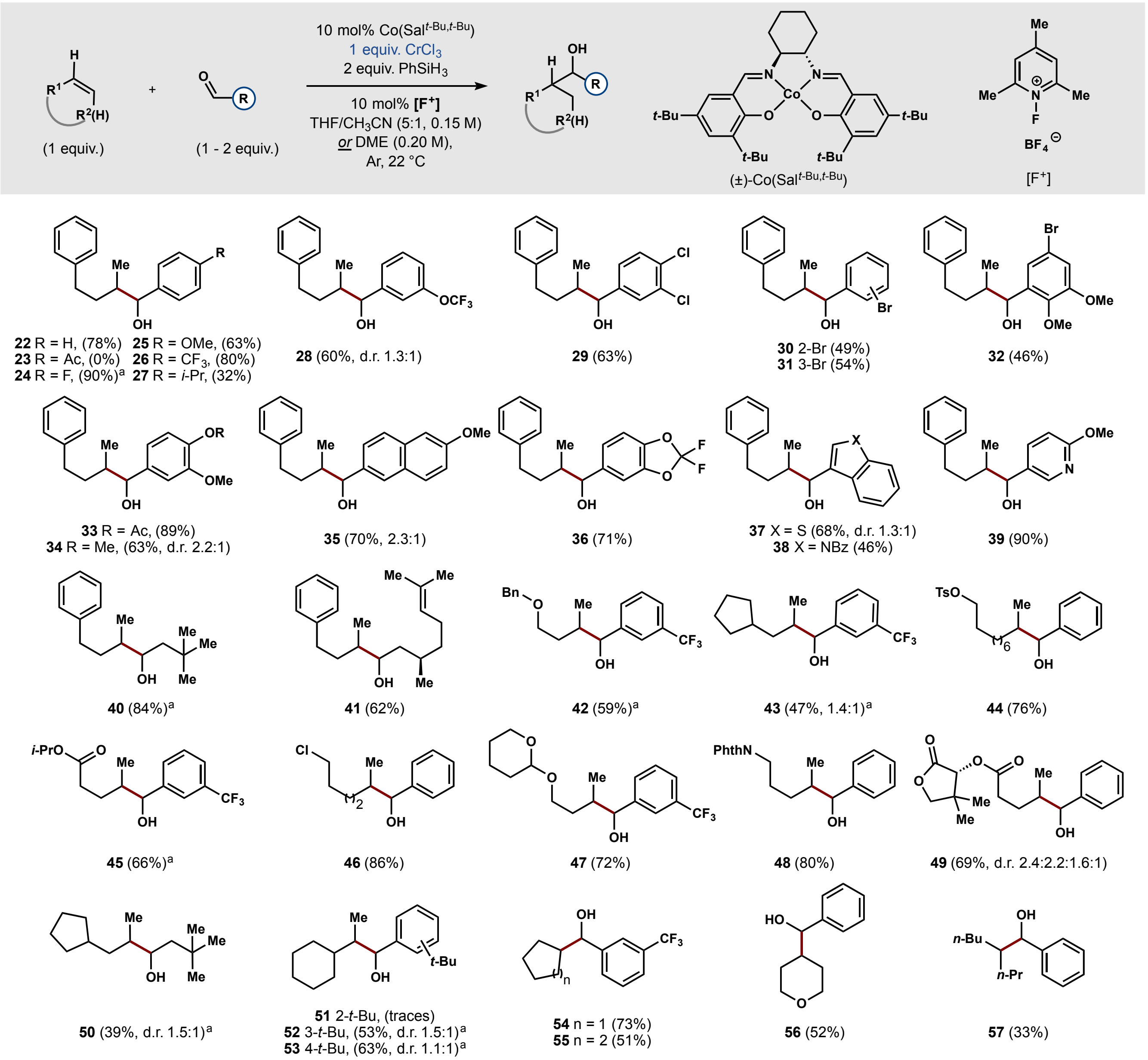


Figure 3. Conversion of alkenes into carbanion surrogates with branched-selectivity. d.r. at the formed bond is close to 1:1 unless otherwise noted. See Supporting Information for the d.r. of the isolated compounds. ^{a}20 mol% of [Co] and 20 mol% of [F$^+$] were used.

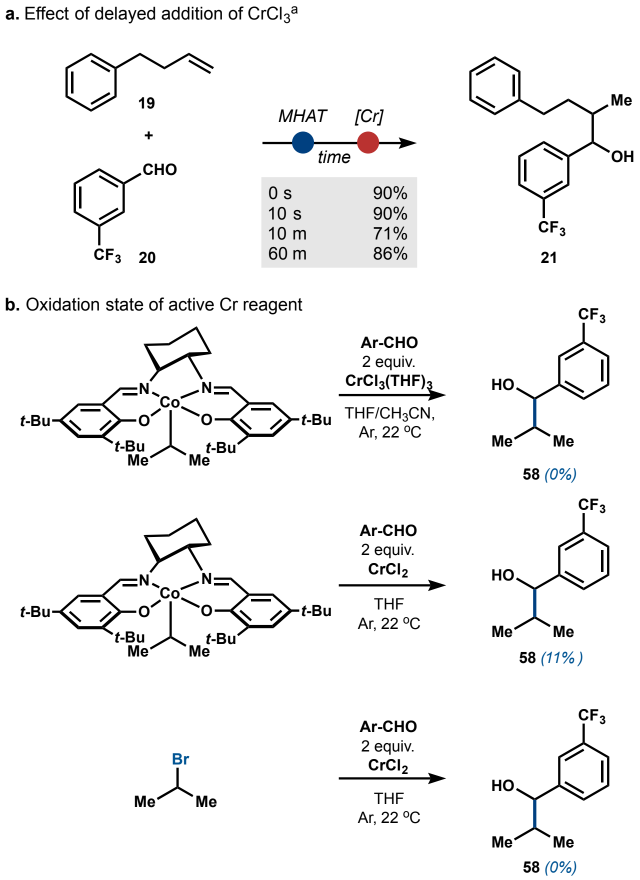
addition with alkyl-substituted olefins.[34] In light of the precedence for alkyl-cobalt complexes to transmetallate other metal species and the apparent facility with which organocobalt species can form from olefins,[7,19] we wondered if a two-electron nucleophile equivalent could arise from unactivated 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 10^7 M^{-1}s^{-1},[35] 3) alkyl-cobalamines and -cobaloximes can also be intercepted by Cr^{+2},[17,36,37] and 4) chromium salts are inexpensive and of low toxicity in the +2 and +3 oxidation states.[38] 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.[39]

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).[40] We discovered, however, that use of Co(Sal$^{t\text{-Bu},t\text{-Bu}}$) and equimolar amounts of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate in the presence of phenylsilane and CrCl$_3$ 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 [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.[41] 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 Co(Sal$^{t\text{-Bu},t\text{-Bu}}$)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).[42]

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 not yet competent. Modest diastereocontrol is imparted by a chiral directing group (**49**),[43] and sterically bulky substrates (**35**, **43**, **50** and **52**).[44]

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


a. Effect of delayed addition of $CrCl_3$^{a}

b. Oxidation state of active Cr reagent

^{a}reactions ran with 20 mol% of [Co] and 20 mol% of [O].

Although we currently do not have a complete mechanistic understanding, 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 an organocobalt species that is engaged by the Cr, and inconsistent with an alternative hypothesis of Cr capture by a freely-diffusing *C*-centered radical;[45] analogy can be drawn to our previously reported Ni/Co hydroarylation[7] and the mechanistic studies of Espenson and coworkers.[36] Stoichiometric experiments support a transmetallation 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 Co^I(Sal$^{t\text{-Bu}, t\text{-Bu}}$); addition of $CrCl_3$ and aldehyde **20** yields no product, whereas $CrCl_2$ produces 11% of adduct **58**.[46] We suspect reduction of Cr^{+3} to Cr^{+2} occurs via the stoichiometric silane reductant necessary for the MHAT catalytic cycle.[47,48] By analogy to the proposal of Espenson and coworkers in similar systems,[36] 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 ($k = 10^7\ M^{-1}s^{-1}$).[35,49,50]

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} transmetallation to alkyl–Cr^{+3}, mediated by Cr^{+2}. This second example[7,7] of catalytic MHAT organocobalt transmetallation 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.[51]

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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38. (a) Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P. Efficient chromium(II)-catalyzed cross-coupling reactions between Csp2 centers. *J. Am. Chem. Soc*. **2013**, *135*, 15346. (b) Oral-rat LD 50 for Cr_2O_3 > 2700 mg/kg. Chromium(III) and its Inorganic Compounds. **2014**, The MAK-Collection for Occupational Health and Safety. doi:10.1002/3527600418.mb1606583vee4614.
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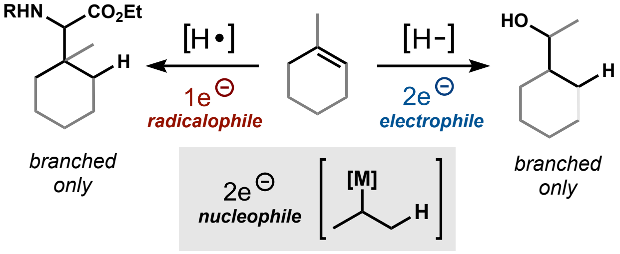
40. Kurosu, M.; Lin, M. H.; Kishi, Y. Fe/Cr- and Co/Cr-mediated catalytic asymmetric 2-haloallylations of aldehydes. J. *Am. Chem. Soc*. **2004**, *126*, 12248.
41. Co^{+3} is the oxidation state necessary for formation of the Co–H with the silane. Use of external metal reductants typically lead to formation of an inactive Co^{+2}.
42. 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.; Schafers, 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.)
43. The chiral lactone auxiliary has been used in Ref. 21d.
44. Addition of Lewis basic ligands did not change diastereoselectivity and tended to suppress reactivity.
45. A mechanism in which subsequent alkyl transfer occurs via a free radical intermediate cannot be ruled out (see Ref. 36). 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**.
46. Control experiments with the akyl-halide during the same period of time yields no product under these conditions.
47. 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.
48. The low yield might be suggestive of possible decomposition of the ligand under these conditions. See Andrez, J.; Guidal, V.; Scopelliti, R.; Pécaut, J.; Gambarelli, S.; Mazzanti, M. Ligand and Metal Based Multielectron Redox Chemistry of Cobalt Supported by Tetradentate Schiff Bases. *J. Am. Chem. Soc.,* **2017**, *139*, 8628.
49. 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.
50. An alternative mechanism of S_H2, as finally proposed in Ref. 36a, 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. 7) is also unlikely given that control experiments indicate there is no reactivity with Cr^{+3} (Figure 4).
51. Pyea, D. R.; Mankad, N. P. Bimetallic catalysis for C–C and C–X coupling reactions. *Chem. Sci.* **2017**, *8*, 1705.

TOC GRAPHIC



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