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 (MHA T) catalysis to couple alkenes and competent radicalophilic electrophiles. Traditional two-electron electrophiles have remained unreactive. Herein we report the addition of electronically-unbiased alkenes into imines and aldehydes. Iron-catalysis allows addition of alkyl-substituted alkenes into imines through the intermediacy of free-radicals, whereas a combination of catalytic [Co(Salβ3Buβ3)] and chromium salts enable a branch-selective coupling of alkenes and aldehydes through the formation of a putative alkyl chromium intermediate.

Branch-selective reactions of alkyl-substituted alkenes via carbocationic or radical intermediates 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. In the absence of electronic bias, steric constraints dominate: canonical metal hydrides favor linear selectivity and linear hydrometallation is predominately observed. To obtain branch-selectivity with electronically-unbiased alkenes, we have investigated M—H hydrogen atom transfer (MHA T) catalysis and subsequent capture of the nascent intermediates by a second metal complex. For example, we recently established that nickel complexes intercept Co(Salβ3Buβ3)-catalyzed MHA T cycles in a direct organocobalt to organonickel transmetallation. Similar alkyl transmetallations have been reported in non-catalytic systems between alkyl—Co(dmglBF2):P2 and inorganic nickel, and proposed for bioorganometallic catalytic processes. This alkyl transfer does not appear limited to nickel: vitamin B12-mimetics (such as Co(salen) derivatives) can undergo alkyl transfer to palladium, rhodium, other cobalt, platinum, gold, chromium, and zinc 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.

The capacity to form cobalt organometallics via MHA T followed by cage-collapse 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 sp3—sp3 bonds. The former reaction with an activated electrophile occurs under standard MHA T catalysis, whereas the latter reaction requires interception of MHA T intermediates with chromium salts (Figure 1e). This transformation expands the current scope of olefins as carbanion surrogates 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, or undergo iron-catalyzed hydromagnesiation reactions to form linear nucleophiles.

We initially investigated the Markovnikov addition of alkenes into carbonyl derivatives by utilizing the intermediacy of the free radicals and noticed that productive reactions
were only obtained with standard radicalophiles, such as radical-stabilizing imines. Glyoxylinimes are preceded as radical acceptors, and chiral sulfanyl auxiliaries can be used to impart stereocontrol. Although the competitive reduction of these electrophiles by the metal hydrides and the stoichiometric silane was observed, this could be minimized by using a slight excess of the olefin and Fe$^{11}$ salts as the catalyst. 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 sulfanylimes to deliver adducts 12, 14, and 15, and even glycos deliver amino esters with good diasterecontrol (16). Comparison of the optical rotation obtained from our reaction to that of t-butyl glycine derivatives shows that sulfamnes with the (S)-configuration affords the (S)-amine whereas the (R)-sulfamine affords the (R)-amine. Better diastereoselectivity is obtained with the more hindered mesitylene or tri-isopropyl arene-derived sulfamidime. Given the ease with which these compounds are made (i.e. no pre-functionalization is necessary for radical formation) we anticipate that this method will find application in the synthesis of unnatural amino acids.

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviations from above</th>
<th>Yield (%)$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe(dpdm), Fe(acac)$_2$, Co(acac)$<em>2$, or Mn(dpdm) instead of Co(Sn$</em>{4Bu}$)$_2$</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>2</td>
<td>CrCl$_3$ instead of CrCl$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>with Zn or Mn$^&lt;$</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>Co(salen)Cl and no [O]</td>
<td>45%$^c$</td>
</tr>
<tr>
<td>5</td>
<td>no [O]</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>0.2 equiv. of CrCl$_3$ instead of 1 equiv.</td>
<td>22%</td>
</tr>
<tr>
<td>7</td>
<td>0.2 equiv. of CrCl$_3$ and TMSCl (1 equiv.)</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>in DMF instead of THF/CH$_3$CN</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>without CH$_3$CN</td>
<td>35%</td>
</tr>
<tr>
<td>10</td>
<td>under air</td>
<td>46%</td>
</tr>
<tr>
<td>11</td>
<td>with 1 equiv. of H$_2$O</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>No Co(Sn$_{4Bu}$)$_2$</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>No CrCl$_3$</td>
<td>–</td>
</tr>
</tbody>
</table>

*Yield determined by GC/FID using a calibrated internal standard; $^b$ indicates yield with 20 mol % of Co(salen)Cl and CrCl$_3$(THF)$_2$; $^c$ equiv. of NaBF$_4$ added; $^d$ isomerization and hydrogenation was observed; d.r. 1:1 in all cases.
addition with alkyl-substituted olefins.\textsuperscript{24} 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,\textsuperscript{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\textsuperscript{2} 2) Cr\textsuperscript{2+} salts are proposed to intercept alkyl-radicals to form organochromium species with bi-molecular rate constants on the order of 10\textsuperscript{7} M\textsuperscript{-1}s\textsuperscript{-1};\textsuperscript{3,5} 3) alkyl-cobalamines and -cobaloximes can also be intercepted by Cr\textsuperscript{2+}\textsuperscript{17,36,37} and 4) chromium salts are inexpensive and of low toxicity in the +2 and +3 oxidation states.\textsuperscript{\textasteriskcentered} Furthermore, the weak Bronsted acidity of organochromium complexes allows for a high functional group tolerance and for their use in late-stage functionalization for complex molecule synthesis.\textsuperscript{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).\textsuperscript{10} We discovered, however, that use of Co(Sal\textsuperscript{-Bu}{\textsubscript{3}}-Bu\textsubscript{3}) and equimolar amounts of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate in the presence of phenylsilane and CrCl\textsubscript{3} could couple the terminal olefin in 19 to 3-trifluoromethyl benzaldehyde in good yields. Given that Cr\textsuperscript{2+} is typically the active species in the addition of alkyl halides into carbonyls, we initially explored the reaction using CrCl\textsubscript{3} or CrCl\textsubscript{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.$^{51}$ 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$^t$-Bu$_2$-r-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 terpenederived 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 diastereorecontrol 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$_2$.$^a$

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90%</td>
</tr>
<tr>
<td>10</td>
<td>90%</td>
</tr>
<tr>
<td>10</td>
<td>71%</td>
</tr>
<tr>
<td>60</td>
<td>86%</td>
</tr>
</tbody>
</table>

b. Oxidation state of active Cr reagent.

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 Co capture by a freely-diffusing C-centered radical.$^{45}$ analogy can be drawn to our previously reported Ni/Co hydroarylation$^t$ 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 transmetallation and produced 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 sulfonimines, which stabilize the incipient N-centered radical, and impart stereosecontrol. 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$^{3,7}$ 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
Funding Sources

REFERENCES


25. α-olefins have also been added to activated α-hydroxy ketones or diols via cyclometallation (a) Yamaguchi, E.; Mowat, J.; Luong, T.; Krische, M. J. Regio- and Diastereoselective C-C Coupling of α-Olefins and Sterenes to 3-Hydroxy-2-oxindoles by Ru-Catalyzed Hydroxyalkylation. Angew. Chem. Int. Ed. 2013, 52, 8428. (b) Park, B. Y.; Luong, T.; Sato, H.; Krische, M. J. Osmium(0)-Catalyzed C-C Coupling of Ethylene and α-Olefins with Diols, Ketols, or Hydroxy Esters via Transfer Hydrogenation. J. Org. Chem., 2016, 81, 8585.


29. See Supporting Information


34. Reference 33 has a single example.


37. This reactivity has also been used for the coupling of unactivated alkyl halides and aldehydes using Cr2+: Takai, 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, CrCl3, 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...
Addition of Lewis basic ligands did not change diastereoselectivity and tended to suppress reactivity. The control experiments indicate there is no reaction through the alkyl-chloride in 46. Control experiments with the alkyl-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.


50. An alternative mechanism of Sn2, 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).


**TOC GRAPHIC**

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