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Cobalt-Catalyzed Intermolecular Hydrofunctionalization of Alkenes: Evidence for a Bimetallic Pathway

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Supporting Information Placeholder

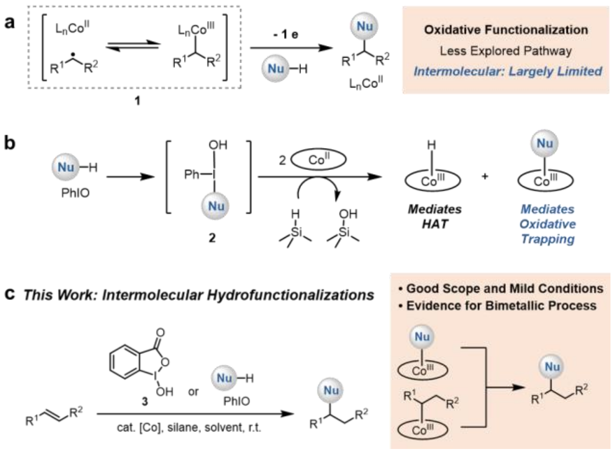
ABSTRACT: A functional group tolerant cobalt-catalyzed method for the intermolecular hydrofunctionalization of alkenes with oxygen- and nitrogen-based nucleophiles is reported. This protocol features a strategic use of hypervalent iodine(III) reagents that enables a mechanistic shift from conventional cobalt–hydride catalysis. Key evidence was found supporting a unique bimetallic-mediated rate-limiting step involving two distinct cobalt(III) species, from which a new carbon–heteroatom bond is formed.

Catalytic carbon–heteroatom bond formation is of central importance in modern organic chemistry practice.[1] To this, intercepting a carbon-centered radical or an equivalent intermediate represents a useful strategy that is complementary to conventional polar reactions.[2] Such transformation is typically achieved via reacting with a radicalophile.[3] Alternatively, coupling with a heteroatom-based nucleophile (NuH) can take place accompanied by a one-electron oxidation process.[4] Kochi pioneered study on the latter in metal-mediated oxidations, which provides key insights for developing catalytic transformations.[5]

Such divergent pathways can be found in the cobalt-catalyzed Markovnikov-selective hydrofunctionalizations. These reactions feature a hydrogen atom transfer (HAT) process, which generates an alkyl radical that can be reversibly captured to form an organocobalt species (Scheme 1a).[6] Originated from Mukaiyama's discovery, elegant chemistry was developed by Carreira through intercepting the HAT intermediate **1** with heteroatom-based radicalophiles.[7] More recently, work from various groups has reshaped this field.[8] On the other hand, the mechanistically distinct oxidative functionalization has historically received less attention in the context of catalysis.[9] A breakthrough was made by Shigehisa that *N*-fluoropyridinium salt as a unique oxidant was found to effect oxidative trapping process.[10] Guided by this discovery, intramolecular transformations were developed including cyclizations and rearrangements, where crucial observations for carbocation-like reactivity and catalyst-controlled selectivity were recently noted by Shigehisa, Diaconescu and Pronin.[11] Nevertheless, unlike the reactions with radicalophiles, intermolecular oxidative functionalization so far has achieved limited success other than solvolysis in alcohols.[12]

A new system enabling efficient intermolecular coupling of **1** with common oxygen- and nitrogen-based nucleophiles would offer great synthetic potential as a milder and more selective alternative to the acid- or heavy-metal-catalyzed Markovnikov-addition methods.[13] To this end, we sought to take advantage of cobalt's dual role (Scheme 1b). We envisioned that the addition of NuH to iodosobenzene would furnish a group-transferring two-electron oxidant **2**.[14] In the presence of a hydrosilane, the reaction of **2** with two molecules of Co(II) complex affords a Co(III)–H and a Co(III)–Nu intermediate, which are expected to promote the HAT and oxidative C–Nu bond formation processes, respectively.[15] Challenges are posed by numerous potential side reactions. These comprise not only radical-type reactions via **1**, but also competing processes outside the metal hydride cycle.[16] Here, we report the realization of this design with both preformed and *in situ* generated I(III) reagents (Scheme 1c). In addition to a kinetic dependence on the catalyst's enantiopurity, we observed that the hydrofunctionalization is second-order with respect to the catalyst and zero-order regarding the stoichiometric reactants. These findings are consistent with a mechanism involving a unique C–Nu coupling process mediated by two Co complexes.

Scheme 1. Intermolecular hydrofunctionalization via bimetallic-mediated coupling.

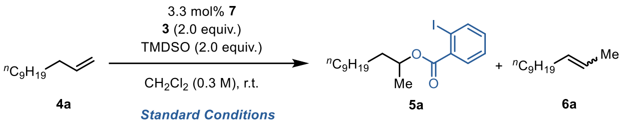


We commenced our study by examining the hydroacyloxylation reaction of 1-dodecene (**4a**) with a well-defined I(III) reagent **3** in the presence of a silane and a catalytic amount of Co(II)-salen complex at ambient temperature (Table 1). A set of optimal conditions was identified as shown in entry 1. A combination of chiral Co catalyst **7** and tetramethyldisiloxane (TMDSO) afforded the desired benzoate product (**5a**) in 84% yield. The rest of the mass balance was identified as isomerized alkenes (**6a**), which are likely produced by the competing reverse HAT.[8a] Minimal stereocontrol by this particular catalyst was noticed as **5a** was produced in nearly racemic form (ca. 5% ee).[17] Alternative solvents were employed and found to be inferior (entry 2). The choice of silane relies on a balance between the stability and reactivity (entry 3). For example, phenylsilane reacts instantly with **3** upon mixing, while triethylsilane is too stable. This protocol proved reasonably tolerant toward moisture and air inclusion (entries 4 and 5).

Key observations were made by evaluating the reaction concentration and catalyst. First, diluting the reaction was found to not only result in sluggish conversion, but also an increased share of **6a** (entry 6). Second, while identical yields were obtained using either **7** or its enantiomer as expected (entry 7 vs 1), their racemic mixture, however, displayed substantially attenuated catalytic activity toward hydroacyloxylation (entry 8). Nearly 50% of **4a** remained after 18 h. Interestingly, the isomerization process seems not affected. These findings prompted us to consider the potential involvement of a higher-order pathway, which is supported by subsequent kinetic studies as discussed *vide infra*. In addition to **7**, several achiral Co complexes were tested (entries 9-11). **8** is electronically similar to **7** and possesses additional steric bulk. This complex gave slower conversion, and a slight increase in **6a** was detected. Finally, Co complexes with either a less electron-rich (**9**) or more flexible (**10**) backbone did not promote the desired reaction.

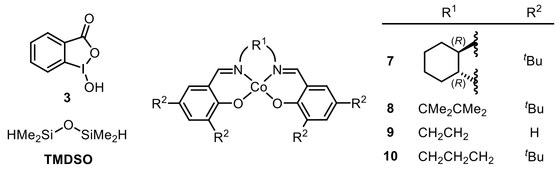
With the optimized protocol in hand, we first explored the reaction scope with respect to the alkenes by evaluating their reactions with **3** (Scheme 2a). A range of mono-substituted aliphatic alkenes and styrenes were found to undergo hydroacyloxylation smoothly at r.t., furnishing the corresponding benzoates **5** in medium to good yields. It is worth noting that the desired products were obtained with substrates that are incompatible with Brønsted or Lewis acid-catalyzed methods (**4e**-**g**). For an *ω*-unsaturated carboxylic acid (**4h**), intramolecular trapping was not detected. Decent yields were obtained for electron-rich and cyclic styrenes (**4i**-**l**) without modifying the protocol. For less electron-rich styrenes, substantial dimerization was observed, which is attributable to slower oxidative trapping and elevated free radical concentration. Shifting to catalyst **8** and increasing the loading was found to mitigate this problem (**4m**-**o**). Additionally, we demonstrate propargylic functionalization of a 1,3-enyne under similar conditions (**4p**). However, 1,1-disubtituted alkenes and 1,3-dienes are not viable substrates (**4q**-**s**).[18]

Table 1. Evaluation of reaction conditions.[a]

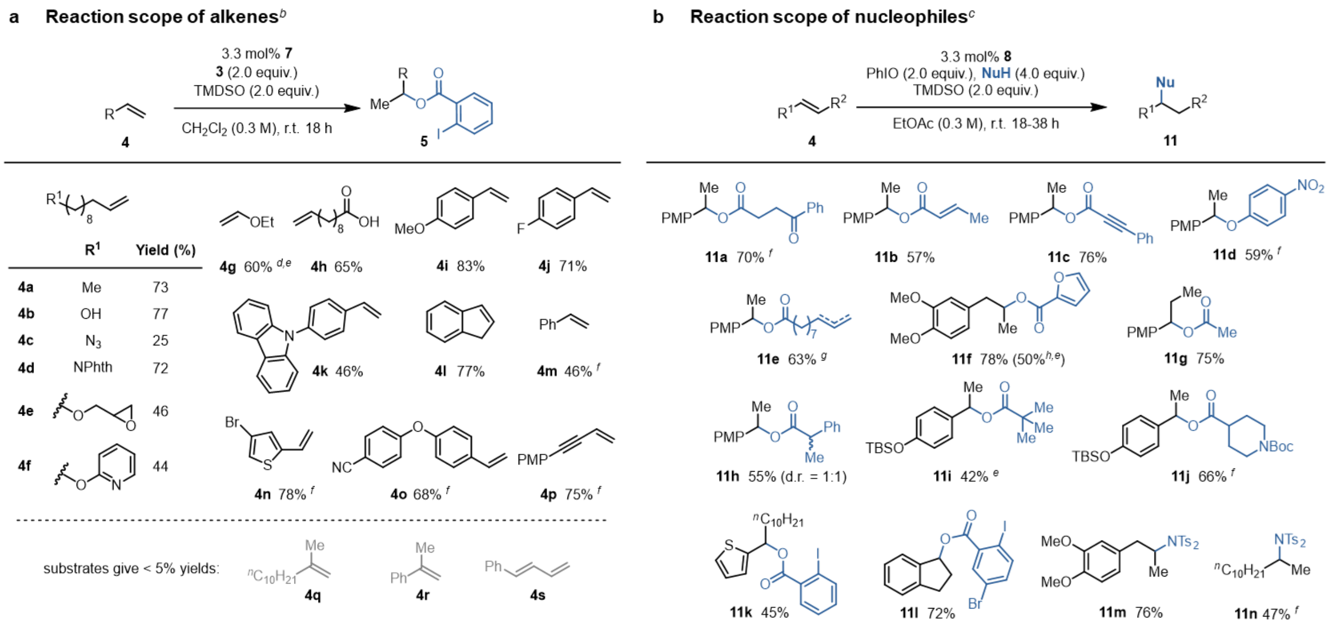


Entry	Changes from "Standard Conditions"	**5a** (%)[b]	**6a** (%)[b]
1	None	84	16
2	In THF, EtOAc, EtOH or toluene instead of CH_2Cl_2	< 10	8 ~ 21
3	$PhSiH_3$ or Et_3SiH instead of TMDSO	< 5	< 5
4	With H_2O (1.0 equiv.)	69	21
5	Open to air	63	21
6	0.1 M instead of 0.3 M	24	10
7	***ent*-7** instead of **7**	81	17
8	***rac*-7** instead of **7**	36	15
9	**8** instead of **7**	67	19
10	**9** instead of **7**	< 5	14
11	**10** instead of **7**	5	5

[a] Standard conditions: **4a** (0.3 mmol, 1.0 equiv.), **3** (2.0 equiv.), TMDSO (2.0 equiv.), **7** (3.3 mol%) in 1.0 mL dichloromethane at r.t. for 18 h. [b] Determined by ¹H NMR analysis of the crude reaction mixture.



Scheme 2. Evaluation of the reaction scope.[a]



[a] Unless noted otherwise, yields correspond to isolated, analytically pure material. [b] **4** (0.30 mmol, 1.0 equiv.), **3** (2.0 equiv.), TMDSO (2.0 equiv.), **7** (3.3 mol%) in 1.0 mL dichloromethane at r.t. [c] **4** (0.30 mmol, 1.0 equiv.), NuH (4.0 equiv.), PhIO (2.0 equiv.), TMDSO (2.0 equiv.), **8** (3.3 mol%) in 1.0 mL ethyl acetate at r.t. [d] With additional 2,6-lutidine (1.0 equiv.). [e] Determined by ¹H NMR analysis of the crude reaction mixture. [f] With **8** (10 mol%) in 3.0 mL solvent. [g] Obtained as inseparable isomers (terminal/internal = 7/3). [h] With 2-furoic acid (1.0 equiv.) and PhIO (1.0 equiv.).

Next, the scope of nucleophiles was studied using *in situ* formed I(III) reagents from PhIO (Scheme 2b). Both **7** and **8** catalyzed the transformation, and slightly better yields were obtained with the latter. We were particularly interested in testing the compatibility of our system with potential hydride-acceptors.[19] It was found that carboxylic acids and phenols containing ketones (**11a**), nitro groups (**11d**), or Michael-acceptors (**11b**, **c**) were efficiently added to alkenes without noticeable reduction. The chemoselectivity was further illustrated by the selective functionalization of styrene in the presence of an aliphatic alkene (**11e**). Increasing steric bulk in the nucleophile attenuates the yield (**11g**-**i**). When the reaction was carried out using stoichiometric amounts of PhIO and the carboxylic acid, a useful yield (50%) was still obtained (**11f**). The mild conditions preserve acid-sensitive groups such as a *tert*-butyldimethylsilyl protected phenol and a *tert*-butyloxycarbonyl protected secondary amine (**11j**). Additional examples involving *β*-substituted alkenes were shown (**11k**, **l**). Finally, we demonstrate that amine derivatives could be accessed from a sulfonimide (**11m**, **n**).

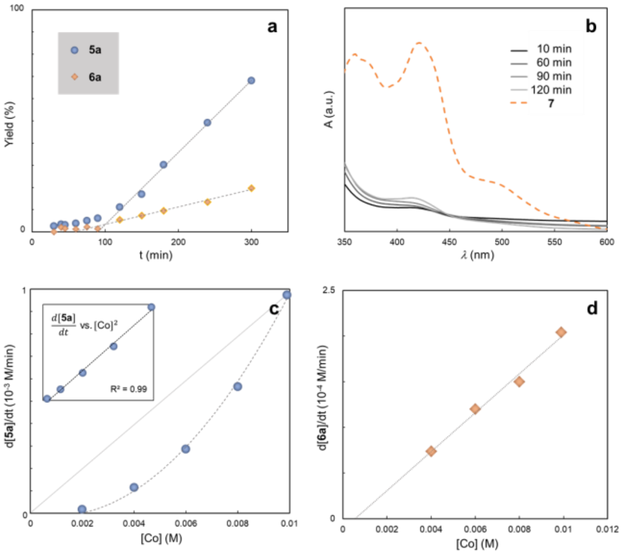
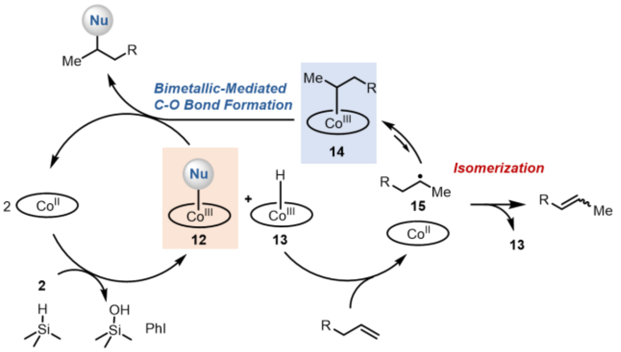


Figure 1. Kinetic studies. a) b) Reaction profiles of **4a** under standard conditions (see Table 1) obtained by ^{1}H NMR and UV-Vis spectroscopy; c) Steady state rate of **5a** formation as a function of [Co] (lines added for a visual aid) and [Co]^2 (inset); d) Steady state rate of **6a** formation as a function of [Co].

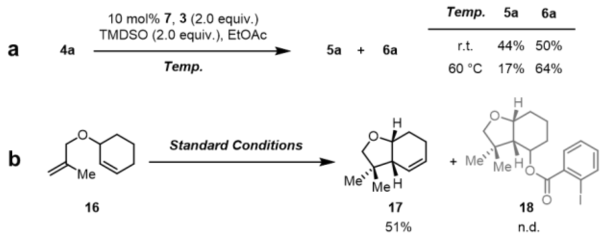
To shed light on the mechanistic origin of the concentration and catalyst effects, we monitored the reaction of **4a** and **3** under standard conditions by ^{1}H NMR and UV-Vis spectroscopy (Figure 1a, b). No characteristic absorption bands of Co(II) were observable in the UV-Vis spectrum after a few minutes upon mixing.[20] Following an induction period that is typical for Co-catalyzed HAT-type reactions, it appears that the formation of both **5a** and **6a** followed zero-order kinetics until high conversion, indicating that the stoichiometric reactants are likely not involved in the rate-determining step (r.d.s.). Next, we performed the reaction with various concentrations of **7** ([Co]) and measured the steady state rates respectively (Figure 1c, d). It was found that the rate at which **5a** is produced is proportional to the square of [Co], while that of the competing isomerization is proportional to [Co].[21] Therefore, the observed decrease in the ratio of **5a**/**6a** upon dilution is attributable to the different reaction orders.

The rate law, in conjuction with the kinetic dependence on the catalyst's enantiopurity, points to a mechanistic hypothesis involving a key interplay between two Co(III) species (Scheme 3). The catalytic cycle begins with the formation of a Co–Nu (**12**) and a Co–H (**13**) complexes, followed by HAT that generates a secondary alkyl radical **15** in equilibrium with an organocobalt complex **14**. The reverse HAT would give either the starting alkene or its isomers.[22] Most importantly, our kinetics data suggests that the r.d.s. for the desired transformation is attributable to a bimetallic process, presumably between **12** and **14**, which leads to final C–Nu bond formation.[23] Such pathway has few precedents in catalytic oxidative carbon–heteroatom forming reactions.[24] Nonetheless, it is worth noting that the concept of bimetallic synergy has achieved phenomenal success in the metal-salen-catalyzed epoxide opening reactions.[25] Based on this hypothesis, the discrepancy between the activities of *rac*-**7** and those of **7**/*ent*-**7** (Table 1) could imply higher barriers via statistically formed heterochiral transition-state complexes.[26] The stereoselectivity obtained with **7**/*ent*-**7**, though very moderate, also strongly supports an inner-sphere mechanism.[27]

Scheme 3. Proposed catalytic cycle.



Scheme 4. Interrupting putative organocobalt(III).



To gain additional insight into the proposed intervention of the organocobalt intermediate **14** in the C–Nu coupling process, we performed experiments where the formation of **14** was interrupted (Scheme 4). First, elevated temperature, which promotes the homolysis of the organocobalt intermediate, led to significant increase in isomerization and decrease in hydrofunctionalization (Scheme 4a). Second, we tested a substrate (**16**) that upon HAT would cyclize and produce a hindered secondary radical, which sterically discourages a Co–C bond (Scheme 4b).[8a] As a result, the isomerized alkene was obtained as the sole product. This corroborates the observation that 1,1-disubstituted alkenes (**4q**, **r**) failed in the hydroacyloxyaltion reaction despite the lower oxidation potential of a tertiary alkyl radical than that of a secondary one, since a tertiary alkylcobalt is disfavored.[28] Collectively, these results are in accordance with our hypothesis that the two competing pathways, namely oxidative functionalization and isomerization, are operating in parallel from **14** and **15**, respectively.

The mechanistic detail of the intriguing bimetallic-mediated coupling remains unclear at this stage and will be a topic of future investigation. Nevertheless, C–Nu bond formation accompanied by a single-electron transfer (SET) between two Co(III) centers could be possibly involved based on reports of electro- and chemical oxidations.[9c, 11f] In addition, a Co/Ni transmetalation process via a Co(IV) intermediate was proposed by Shenvi for arylative HAT-type reaction.[29,30]

In conclusion, we have developed a Co-catalyzed intermolecular hydrofunctionalization reaction through the oxidative coupling between a non-solvent oxygen- or nitrogen-based nucleophile and an HAT intermediate derived from either an unactived alkene, styrene or 1,3-enyne. Synthesis of a broad spectrum of esters, aromatic ethers, and sulfonimides are achieved. Notably, experimental evidence for a unique rate-limiting bimetallic-mediated coupling process was obtained. Specifically, C–Nu coupling via an organocobalt(III) and a Co(III)–Nu complex is proposed to account for the observed rate law and heterochiral effect. The identification of such pathway provides a potentially valuable handle for expanding the scope of Co–H chemistry through catalyst tuning. In a broader sense, these results represent an emerging mechanistically distinct mode for carbon–heteroatom bond formation in catalytic reactions. We anticipate new design principles stem from this finding, for instance, dimeric catalysts, would likely offer further increased efficiency and potentially stereoselectivity, as seen in the classic Jacobsen epoxide-opening reactions.[25b] These possibilities are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization, spectra and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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14. Yoshimura, A.; Zhdankin, V. V., Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016,** *116*, 3328. Other I(III) species containing Nu as ligands might also be produced in addition to **2**, which would lead to similar reactions affording Co–H and Co–Nu complexes. It is worth mentioning that using I(III) reagents can avoid the undesired fluorination side reaction observed with *N*-fluoropyridinium salt. See reference 8i.

15. For Co(III) carboxylate-mediated oxidative trapping: Lande, S. S.; Kochi, J. K., Formation and oxidation of alkyl radicals by cobalt(III) complexes. *J. Am. Chem. Soc.* **1968,** *90*, 5196.

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17. For comparison, -7% ee was obtained using *ent*-**7** (entry 7). See Table S1 for details.

18. See supporting information (S14) for details.

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20. (a) Liao, C.-M.; Hsu, C.-C.; Wang, F.-S.; Wayland, B. B.; Peng, C.-H., Living radical polymerization of vinyl acetate and methyl acrylate mediated by Co(Salen*) complexes. *Polym. Chem.* **2013,** *4*, 3098; (b) Clarke, R. M.; Herasymchuk, K.; Storr, T., Electronic structure elucidation in oxidized metal–salen complexes. *Coord. Chem. Rev.* **2017,** *352*, 67. For a discussion, see supporting information (S22).

21. For data from individual experiments, see supporting information.

22. Organocobalt has been proposed to be an off-cycle species in catalytic isomerization. See reference 8a.

23. The absence of substantial enantiomeric excess prevented detection or exclusion of a potential non-linear effect at this point.

24. For important precedents of binuclear Pd intermediates in oxidative catalysis, see: (a) Powers, D. C.; Ritter, T., Bimetallic redox synergy in oxidative palladium catalysis. *Acc. Chem. Res.* **2012**, *45*, 840; (b) Powers, D. C.; Ritter, T., Bimetallic Pd(III) complexes in palladium-catalysed carbon–heteroatom bond formation. *Nat. Chem.* **2009**, *1*, 302.; For a recent review: (c) Pye, D. R.; Mankad, N. P., Bimetallic catalysis for C-C and C-X coupling reactions. *Chem. Sci.* **2017,** *8*, 1705.

25. (a) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N., On the mechanism of asymmetric nucleophilic ring-opening of epoxides catalyzed by (salen)Cr$^{\text{III}}$Complexes. *J. Am. Chem. Soc.* **1996**, *118*, 10924; (b) Ford, D. D.; Nielsen, L. P.; Zuend, S. J.; Musgrave, C. B.; Jacobsen, E. N., Mechanistic basis for high stereoselectivity and broad substrate scope in the (salen)Co(III)-catalyzed hydrolytic kinetic resolution. *J. Am. Chem. Soc.* **2013,** *135*, 15595; (c) Mulzer, M.; Whiting, B. T.; Coates, G. W., Regioselective carbonylation of *trans*-disubstituted epoxides to β-lactones: a viable entry into syn-aldol-type products. *J. Am. Chem. Soc.* **2013,** *135*, 10930.

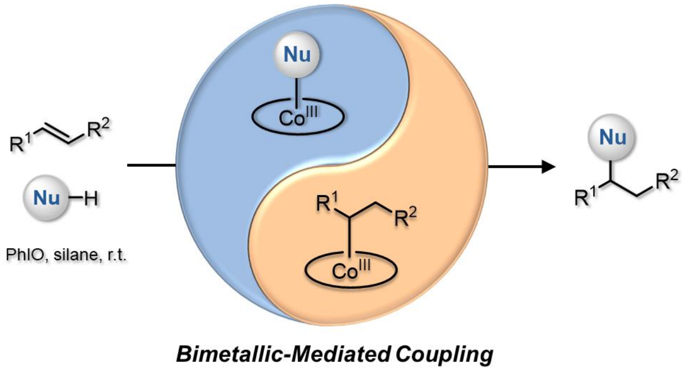
26. The stereogenic carbon atom bound to Co in **14** complicates a strictly accurate description. In spite of this, considering the fast equilibrium between **14** and **15**, such kinetic effect, if not predominantly, could be at least partially derived from the stereochemical heterogeneity in the salen ligand. It should be also noted that the current data does not exclude the effect of potential persistent off-cycle multinuclear species.

27. A few alternative monometallic pathways were considered, including: 1) oxidation of **15** by **12** or **2**; 2) oxidation of **14** by **2**. However, they are ruled out due to inconsistent kinetics and failure to account for the enantiopurity effect.

28. Wayner, D. D. M.; McPhee, D. J.; Griller, D., Oxidation and reduction potentials of transient free radicals. *J. Am. Chem. Soc.* **1988,** *110*, 132. Our observations underline the mechanistic difference between intra- and intermolecular reactions. While mono-cobalt mediated radical oxidation is proposed in the former (reference 10), the latter seems to necessitate a bimetallic pathway.

29. (a) For an excellent discussion on bimetallic-mediated C–C bond formation process, see: Shevick, S. L.; Obradors, C.; Shenvi, R. A., Mechanistic interrogation of Co/Ni-dual catalyzed hydroarylation. *J. Am. Chem. Soc.* **2018,** *140*, 12056. (b) For a dimeric iron species in FeH-catalyzed olefin coupling reactions, see: Lo, J. C.; Kim, D.; Pan, C. M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S., Fe-Catalyzed C-C bond construction from olefins via radicals. *J. Am. Chem. Soc.* **2017,** *139*, 2484.

30. Although the oxidation potential of a secondary alkyl Co(III) salen complex is estimated to be slightly higher than the reduction potential of a Co(III)–X complex by ca. 0.1 V, this gap is small and subjected to change as the coordination environment varies, thereby possibly allowing SET during catalytic reactions. See supporting information (S25) for further discussion. (a) Chiang, L.; Allan, L. E.; Alcantara, J.; Wang, M. C.; Storr, T.; Shaver, M. P., Tuning ligand electronics and peripheral substitution on cobalt salen complexes: structure and polymerisation activity. *Dalton Trans* **2014,** *43*, 4295; (b) Kurahashi, T.; Fujii, H., Unique ligand-radical character of an activated cobalt salen catalyst that is generated by aerobic oxidation of a cobalt(II) salen complex. *Inorg. Chem.* **2013,** *52*, 3908; (c) Levitin, I.; Sigan, A. L.; Vol'pin, M. E., Electrochemical generation and reactivity of organo-cobalt(IV) and -rhodium(IV) chelates. *J. Chem. Soc., Chem. Commun.* **1975,** 469.


R1
R2
Nu
H
PhIO, silane, r.t.
Nu
CoIII
R1
R2
CoIII
Nu
R1
R2
Bimetallic-Mediated Coupling