Hydroamination

How to cite:
International Edition: doi.org/10.1002/anie.202110178
German Edition: doi.org/10.1002/ange.202110178

Cobalt-Catalyzed Radical Hydroamination of Alkenes with *N*-Fluorobenzenesulfonimides

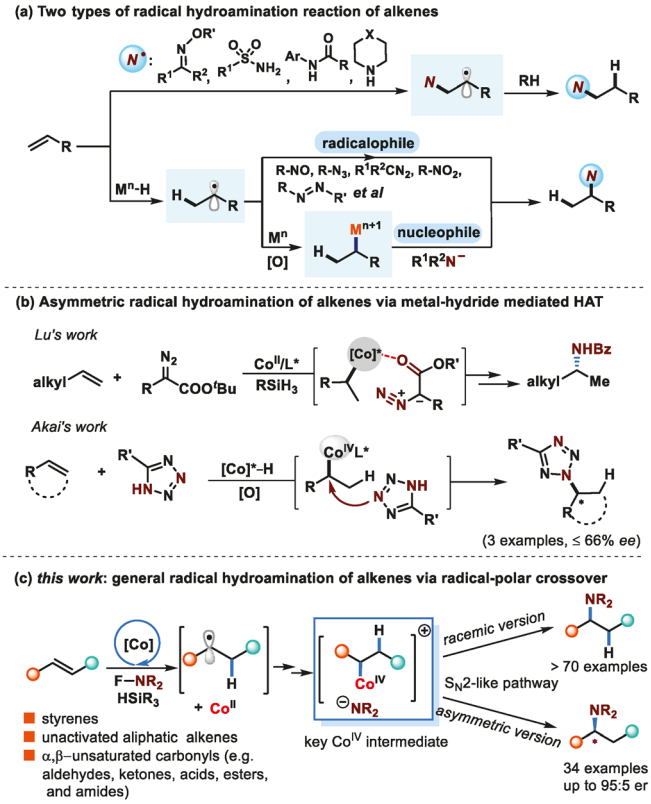
Tao Qin, Guowei Lv, Qi Meng, Ge Zhang, Tao Xiong,* and Qian Zhang**

Abstract: *An efficient and general radical hydroamination of alkenes using Co(salen) as catalyst, N-fluorobenzenesulfonimide (NFSI) and its analogues as both nitrogen source and oxidant was successfully disclosed. A variety of alkenes, including aliphatic alkenes, styrenes, α, β-unsaturated esters, amides, acids, as well as enones, were all compatible to provide desired amination products. Mechanistic experiments suggest that the reaction underwent a metal-hydride-mediated hydrogen atom transfer (HAT) with alkene, followed by a pivotal catalyst controlled S_N2-like pathway between in situ generated organocobalt(IV) species and nitrogen-based nucleophiles. Moreover, by virtue of modified chiral cobalt(II)-salen catalyst, an unprecedented asymmetric version was also achieved with good to excellent level of enantiocontrol. This novel asymmetric radical C–N bond construction opens a new door for the challenging asymmetric radical hydrofunctionalization.*

Introduction

Catalytic hydroamination of alkenes has been regarded as one of most convenient and rapid approaches to construct nitrogen-containing compounds, widespread in myriad biologically active natural products and pharmaceutical agents, and has therefore attracted considerable attention from the synthetic community in the past decades.[1] Among numerous approaches, transition-metal-catalyzed radical hydroamination of alkenes has proven to be a versatile and fascinating platform to forge the pivotal C–N bonds in recent years, owing to its high chemoselectivity, robust reactivity, excellent functional group tolerance, and easy-to-build congested carbon center.[2,3] In spite of impressive advances on this promising domain, the development of a highly general, efficient, and expedient radical hydroamination of alkenes under mild conditions, especially in an enantioselective fashion, to access the valuable chiral amines is extremely attractive but has proven to be a lasting formidable challenge.

From a mechanistic standpoint, transition-metal-catalyzed radical hydroamination can be classified into two types. As depicted in Scheme 1 a, one approach involved N-centered radical triggered addition to C–C double bonds, followed by a hydrogen atom transfer (HAT) process. In this context, Knowles,[4] Leonori[5] and Xiao[6] have independently developed an array of radical hydroamination reaction utilizing various N-centered radical precursors under mild conditions. The other pathway was denoted as metal-hydride mediated transformations (Scheme 1 a), wherein the in situ generated alkyl radicals, originated from the HAT between the metal-hydride catalysts and C–C double bonds, could typically fall into two scenarios: 1) directly reacting with a nitrogen-based radicalophiles, such as nitro compounds, azo compounds, azides and diazo compounds; 2) radical-polar crossover amination through the utilization of various nitrogen nucleophiles as the coupling partners. In the former subdomain, the groups of Carreira,[7] Boger,[8] Baran,[9] Lu,[10] and others[11] have demonstrated its efficiency and practicability by means



Scheme 1. Transition-metal-catalyzed radical hydroamination of alkenes.

[*] T. Qin, G. Lv, Q. Meng, G. Zhang, Prof. T. Xiong, Prof. Q. Zhang
Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University
Changchun 130024 (China)
E-mail: zhangg492@nenu.edu.cn
xiongt626@nenu.edu.cn
zhangq651@nenu.edu.cn
Prof. Q. Zhang
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.202110178.

of CoH, FeH and MnH catalysis. While only seldom nitrogen-based radicalophiles so far could be compatible with this metal-hydride-mediated radical hydroamination. Alternatively, some reports, by drawing upon $Co^{III}H$ catalyst in conjunction with the suitable oxidant, have been demonstrated that the in situ generated alkyl radicals can be further transformed to corresponding electrophilic intermediates, which then were captured with nitrogen nucleophiles to provide corresponding nitrogen-containing compounds in the latest years. Pioneered by Shigehisa[12] and with the contribution of Zhu,[13] and Akai,[14] this kind of radical-polar crossover reaction has emerged as a promising synthetic tool accessing these synthetically valuable alkyl amines, which is mainly due to a large number of readily available nucleophilic nitrogen sources.

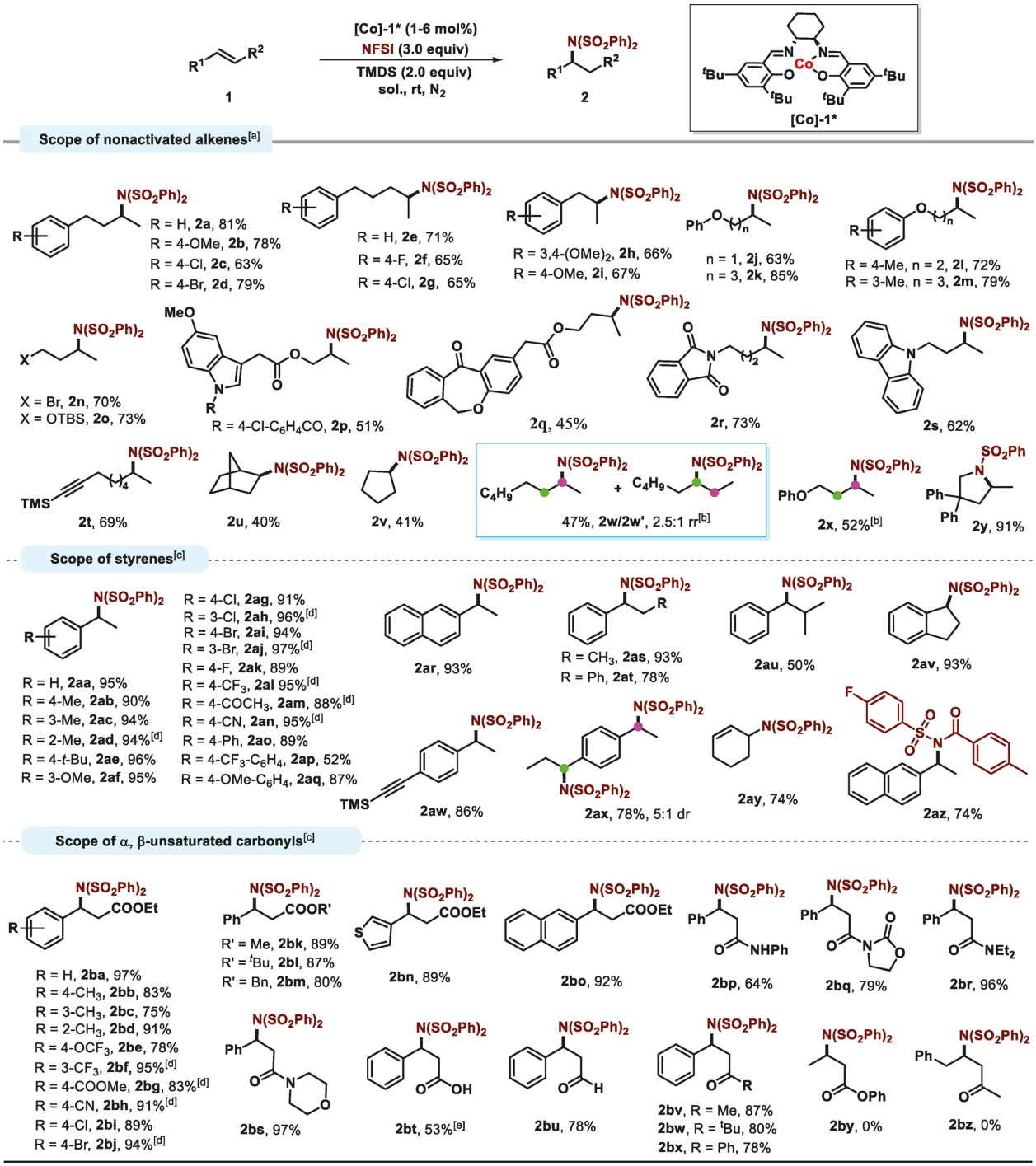
Although numerous approaches primarily focusing on transition-metal-catalyzed asymmetric ionic hydroamination of C=C bonds, including chiral Ir,[15,16] Rh,[17] Pd,[18] rare earth metal catalysis,[19] and recent CuH catalysis,[1d,20] have been well established to prepare chiral amines in the latest decades, the enantioselective incorporation of a nitrogen-containing functionality into an alkene involving open-shell radicals remains a significantly less explored. The major difficulty might rest on the lack of a catalytic system that can be capable of competent interactions between the chiral catalyst with the open-shell N-centered or prochiral alkyl radicals to implement the high enantiodifferentiation. In this aspect, to the best of our knowledge, only sporadic examples have been disclosed to successfully override this arduous challenge until recently. For instance, the group of Lu successfully showcased an Co-catalyzed asymmetric intermolecular hydroamination of nonactivated alkenes using tertiary butyl 2-diazo-phenylacetate as nitrogen source (Scheme 1b, top).[21] Meanwhile, Akai et al. realized a Co-catalyzed asymmetric radical hydroamination of alkenes with 5-substituted tetrazoles for furnishing chiral amines (3 examples, no more than 66% *ee*) (Scheme 1b, bottom).[22] Besides, utilizing visible light induced proton-coupled electron transfer (PCET) process, Knowles[23] and Meggers[24] developed enantioselective radical hydroamination of alkenes, adopting sulfonamides and *N*-aryl carbamates as nitrogen-based radical precursors, respectively. As our continuing interest in radical amination,[25] we herein reported the discovery of a highly general and efficient Co-catalyzed radical hydroamination of various alkenes, including styrenes, alkyl substituted alkenes, strained alkene, as well as α, β-unsaturated carbonyls (e.g. aldehydes, ketones, acids, esters, and amides) with *N*-fluorobenzenesulfonimide (NFSI) and its analogues, furnishing a wide range of valuable amines in general good to excellent yields with exclusive Markovnikov selectivity (Scheme 1c). More strikingly, the corresponding asymmetric version has been resoundingly enforced through the modified chiral cobalt(II)-salen catalyst in good to excellent level of enantiocontrol.

Results and Discussion

We initiated our investigation by subjecting simple 4-phenylbutene (**1a**) as a model substrate with NFSI as a nitrogen source. After a serial of reaction conditions screening, we disclosed that the reaction was best conducted with Co(salen) catalyst ([Co]-**1***) (4.0 mol%) in the presence of 1,1,3,3-tetramethyldisiloxane (TMDS) as hydrogen donor in dry 1,4-dioxane at room temperature, providing regiospecific Markovnikov product **2a** in 81% yield. Examining other commercially available hydrosilanes and solvents were also performed and slightly inferior yields under the otherwise optimal reaction conditions were observed (See Supplementary Information for details). Moreover, control experiments clearly indicated that the Co catalyst and the oxidative nitrogen source were both necessity for this reaction occurring.

To assess the generality of this method, we investigated the substrate scope of this cobalt-catalyzed radical hydroamination reaction (Scheme 2). We first explored a variety of aliphatic alkenes. Gratifyingly, these simple alkenes bearing electron-rich or electron-withdrawing groups on aromatic rings, participated in this regiospecific hydroamination reaction to provide **2a**–**2i** in moderate to good yields. For more broad synthetic interests, various functional groups, including ethers (**2j**–**2m**), bromo (**2n**), fluoroanion-sensitive silyl ether (**2o**), ester (**2p** and **2q**), amide (**2r**), nitrogen containing heterocycle (**2s**) as well as alkyne (**2t**), were well tolerated, proceeding with moderate to good yields and remarkable Markovnikov selectivity. In addition to these terminal alkenes, the internal alkenes, including strained norbornene (**1u**), the non-strained cyclopentene (**1v**), and 2-octylene (**1w**) were all valid substrates for this radical hydroamination, furnishing corresponding branched amines **2u**-**2w** in moderate yields and the regioisomers of **2w** and **2w′** in approximate 2.5:1 ratio. In addition, internal alkenes (*E*)-(but-2-en-1-yloxy)benzene **1x** proceeded to give the single regioselective product **2x** in 52% yield, probably due to the coordination of heteroatom to the cobalt center. Interestingly, unactivated alkene **1y** tethered a benzensulfonimide unit was subjected to the reaction conditions with NFSI as the oxidant, affording pyrrolidine **2y** in 91% yield and without observation of intermolecular hydroamination product.

To our delight, this catalytic system could be successfully extended to a broad range of vinylarenes and showcased generally high catalytic efficiency, providing Markovnikov-hydroamination products **2aa**–**2aq** in more than 90% yields in most cases within 30 min even using 1 mol% catalyst [Co]-**1***. The position of the substituent on the phenyl ring almost did not alter the reaction efficiency as demonstrated with the methyl substituent (**2ab**–**2ad**). Various functional groups such as tertiary butyl (**2ae**), methoxyl (**2af**), halogens (**2ag**–**2ak**), trifluoromethyl (**2al**), acetyl (**2am**), and cyan (**2an**) as well as aryl (**2ao**–**2aq**) were all compatible, affording the expected products in excellent yields except **2ap**. The tolerance of aryl halides units could offer an opportunity for further manipulation. 2-Vinylnaphthalene was compatible to deliver **2ar** in 93% yield. Some β-substituted styrenes were also examined whether these substrates are suitable for this hydroamination. Indeed, β-methyl, phenyl, β, β-dimethyl substituted styrenes, as well as indene, all of which can be transformed into corresponding amines in good to excellent yields, albeit moderate yield for **2au**. The C=C bond in 4-alkynyl sub-



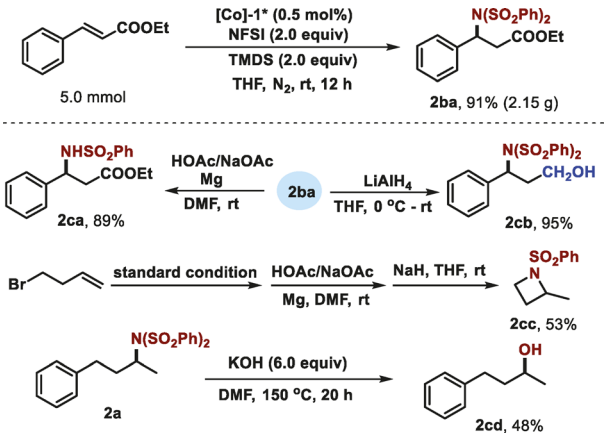
Scheme 2. Substrate scope of racemic radical hydroamination. [a] Reaction conditions: alkenes (0.20 mmol), NFSI (3.0 equiv), TMDS (2.0 equiv) and [Co]-**1*** (4 mol%) in dry 1,4-dioxane (1.0 mL) at room temperature for 10 hours. Isolated yields are shown. [b] Using 6 mol% catalyst [Co]-**1***. [c] Reaction conditions: alkenes (0.20 mmol), NFSI (3.0 equiv), TMDS (2.0 equiv) and [Co]-**1*** (1 mol%) in THF (1.0 mL) at room temperature for 30 min. Isolated yields are shown. [d] Using 1,4-dioxane instead of THF and the reaction was conducted at room temperature for 3 h. [e] The reaction was conducted with catalyst [Co]-**1*** (3 mol%), cinnamic acid (0.2 mmol), NFSI (3.0 equiv), TMDS (2.0 equiv) in THF at −40°C.

stituted styrene **1aw** can be selectively hydroaminated while simultaneous the C−C triple bond maintaining inert, providing product **2aw** in 86% yield. By contrast, no chemoselectivity was observed under the present reaction conditions for internal and terminal C=C bond as demonstrated by **1ax**, and hence double hydroamination occurred, providing product **2ax** in 78% yield with 5:1 diastereomeric ratio. 1,3-Cyclohexadiene was also viable for constructing allylic amination product **2ay** in 74% yield. With respect to nitrogen supplier, we found that *N*-fluoro-*N*-acylarylsulfonamide was also assessed and enabled the nitrogen-containing substructure to integrate into the expected product **2az** in good yield,

while *N*-fluoro-*N*-alkylarylsulfonamides are not viable nitrogen suppliers.

These exciting results stimulate us to evaluate whether more wide scope of alkenes such as α, β-unsaturated carbonyls are also amenable to this radical hydroamination. Delightedly, an array of α, β-unsaturated esters bearing either electron-donating functional groups or electron-withdrawing functional groups on the aromatic rings can be converted smoothly into the desired β-aminated products **2ba**–**2bj** in generally excellent yields, and the structure of **2ba** was unequivocally determined by single-crystal X-ray diffraction. Besides, α, β-unsaturated amides and acid[26] were also suitable for this hydroamination, furnishing corresponding amination products **2bp**–**2bt** in a range of 53–97% yields. In addition to α, β-unsaturated esters, amide and acid, we also evaluate the feasibility with enone and enal as the coupling partners. Gratifyingly, the C=C bond in these compounds can also be selectively hydroaminated under this CoH catalysis, unlike previous reports on CuH chemistry,[27] delivering β-sulfonimideyl substituted products **2bu**–**2bx** in good yields. While β-alkyl substituted α, β-unsaturated carbonyls, for example **1by** and **1bz**, were not suitable for this radical hydroamination, and only chemoselective reduction of C=C bond was observed (see Supporting Information).

With the aim of further extending synthetic utility of this methodology, a gram-scale synthesis was conducted to demonstrate the practicability of this method, the target β-amino ester **2ba** was obtained in good yield with 0.5 mol% cobalt catalyst (Scheme 3, top). Meanwhile, **2ba** would undergo a selective mono-desulfonylation or reduction process, offering β-amino ester **2ca** and important γ-amino alcohol **2cb** in 89% and 95% yields, respectively. A three-step reaction consisting of alkene hydroamination, magnesium promoted mono-desulfonylation, and ring-closure could be realized smoothly without any purification of the intermediates to deliver the corresponding benzenesulfonylazetidine **2cc** with overall 53% yield, which is prevalent in both naturally occurring products and clinical candidates.[28] In addition, the alkyl substituted branched dibenzenesulfonimide **2a** would be converted to corresponding secondary alcohol **2cd** in moderate yield.

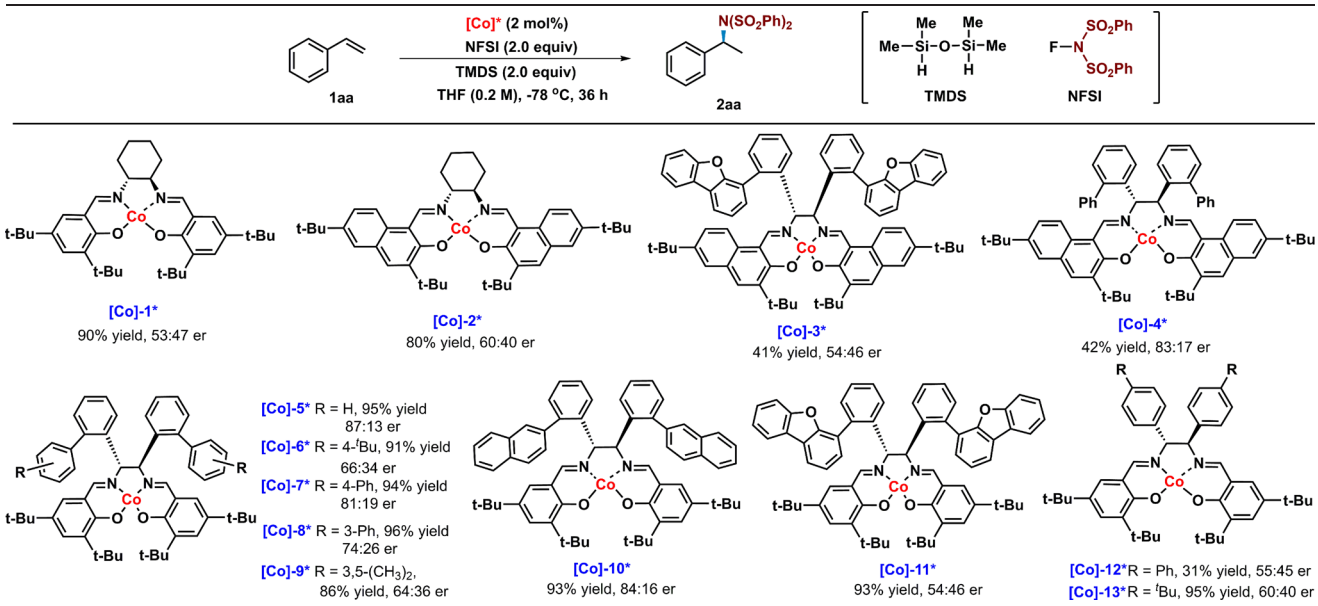


Scheme 3. Gram-scale synthesis and synthetic applications.

Having successfully established the racemic radical hydroamination of alkenes, we then particularly interested in whether the more intriguing asymmetric version can be executed in a high level of enantiocontrol fashion. When we commenced on the asymmetric transformation, we are aware of Pronin's seminal report, in which intramolecular C–O bond has been constructed enantioselectively to prepare chiral epoxides from tertiary allylic alcohols via chiral cobalt salen-catalyzed HAT and radical-polar crossover process.[29] Shortly after this, Shigehisa et al. also disclosed an impressive hydroalkoxylation of unactivated alkenes to yield enantioenriched tetrahydrofurans through both chiral cobalt-salen catalyst and silane-controlled enantioselectivity.[30] These reports inspired us to envisage that this challenging intermolecular asymmetric radical hydroamination of alkenes might be achieved by virtue of the similar chiral cobalt-salen catalysis platform.

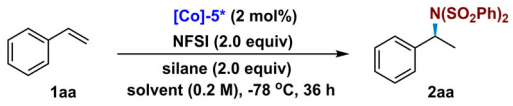
With this in mind, preliminary investigation of this proposed asymmetric version began with styrene **1aa** and NFSI with 2 mol% chiral cyclohexanediamine-derived [Co]-**1*** as the catalyst. As illustrated in Table 1, the expected hydroamination product **2aa** was observed in 90% yield with very low enantioinduction in the presence of TMDS as hydrogen supplier at −78 °C in THF. In spite of low enantiodifferentiation, this outcome implied that this challenging radical hydroamination might be implemented through further modified the chiral salen ligand. Increasing the steric hinderance of salicylaldehyde substructure in chiral cobalt-salen catalyst ([Co]-**2***) led to improve the enantioselectivity to 20%, while [Co]-**3***, the optimal catalyst in Pronin's report,[29] showed moderate reactivity but resulting in sharply decline in the enantiocontrol. To our delight, switching dibenzofuran motif to less steric phenyl at the *ortho*-position of diamine substructure ([Co]-**4***)[29] allowed for significant enhancement of the enantioselectivity with moderate reactivity. Surprisingly, excellent reactivity with slightly increased enantiocontrol was observed via altering the salicylaldehyde fragment ([Co]-**4*** vs. [Co]-**5***). Extensive experimentation with modifications in the salicylaldehyde- and diamine-derived fragments, disappointingly, showed no positive effect on either enantiodifferentiation or reactivity ([Co]-**6***–[Co]-**25***) (see Table 1 and Supplementary Table S4). In addition, other chiral cobalt complexes, such as Katsuki' catalyst,[31] β-ketoiminate ligand,[32] and chiral N,N,N-tridentate ligands[23,33] were also explored but resulting unsatisfactory results (see Supplementary Table S6). In addition to assessment of various chiral cobalt-salen catalysts, an array of hydrosilanes were also investigated, owing to the potential effect on enantiocontrol in Shigehisa's work.[30] Experimental results showed that TMDS is the best hydrogen supplier in terms of both reactivity and enantiocontrol (Table 2, entries 1–7). Moreover, other conventional solvents, such as EtOAc, DCM, Et_2O, and MTBE were also examined, giving moderate to excellent yields but detrimental effect on enantioselectivity (Table 2, entries 8–11). Collectively, after extensive evaluation of a range of reaction parameters (> 200 runs, > 36 cobalt catalysts, > 10 silanes), the reaction was conducted in THF at −78 °C with [Co]-**5*** as catalyst and TMDS as hydrogen source, giving chiral amine **2aa** in

Table 1: Screening of cobalt catalysts.[a]



[a] Unless otherwise noted, the reactions were carried out using **1aa** (0.20 mmol), NFSI (2.0 equiv), TMDS (2.0 equiv) and [Co] catalyst (2 mol%) in THF (1.0 mL) at −78 °C for 36 h. Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. The er values were determined by HPLC on a chiral stationary phase.

Table 2: Optimization of silanes and solvents.[a]

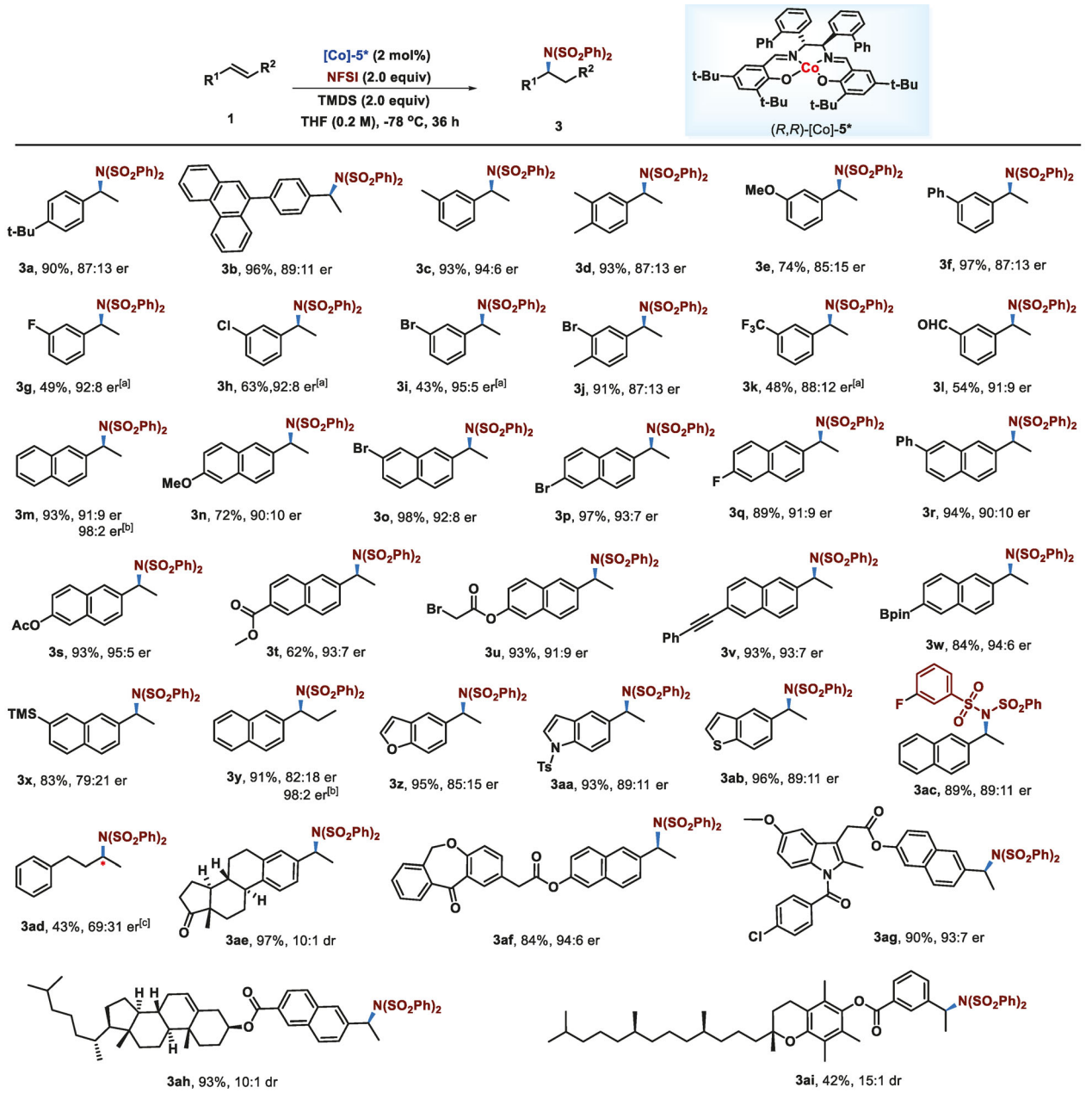


Entry	Silane	Solvent	Yield [%][b]	E.r.[c]
1	TMDS	THF	95	87:13
2	Ph_2SiH_2	THF	91	80:20
3	$PhMeSiH_2$	THF	78	79:21
4	Et_2SiH_2	THF	67	77:23
5	$PhMe_2SiH$	THF	48	83:17
6	DMMS	THF	33	74:26
7	$PhSiH_3$	THF	73	82:18
8	TMDS	EtOAc	90	51:49
9	TMDS	DCM	89	52:48
10	TMDS	Et_2O	76	52:48
11	TMDS	toluene	65	64:36

[a] Standard conditions: styrene **1aa** (0.2 mmol), NFSI (2.0 equiv), silane (2.0 equiv) and [Co]-**5*** (2 mol%) in various solvent (1.0 mL) at −78 °C for 36 h. [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] The e.r. values were determined by HPLC on a chiral stationary phase. DMMS = methyldimethoxysilane.

excellent yield with good enantioselectivity. It is worth noting that the level of enantiocontrol can be further enhanced (91:9 er) with 2-vinylnaphthalene derivatives as feedstocks (vide infra). In addition, we are aware of a Pd-catalyzed hydroamination of styrenes with NFSI, underwent a reductive elimination pathway of Pd^{IV} intermediate to yield chiral amines with comparable level of enantioselectivity, was disclosed by Cheng and Liu in 2015.[18] However, a mechanically distinct asymmetric radical hy-droamination remains elusive to date.

We next assessed the generality of our established conditions with a variety of alkenes (Scheme 4). Brief exploration of the styrene substrate scope revealed that the substituent on the *meta*-position of the aromatic ring in styrenes was beneficial to improve the enantiocontrol than these of *ortho*- or *para*-substituted styrenes, despite showing comparable reactivity (see Supplementary Table S7). Hence, several styrenes bearing various substituents (e.g., $-CH_3$, $-OCH_3$, -aryl, -F, -Cl, -Br, $-CF_3$, and -CHO) at the *meta*-position were examined and these substrates can be converted into corresponding chiral amines **3a**–**3l** smoothly with moderate to excellent yields and good level of enantioselectivities. The absolute configuration of the product **3c** was unequivocally determined by single-crystal X-ray diffraction. In addition, a broad spectrum of vinylnaphthalene derivatives were also viable coupling partners, delivering a variety of chiral amines in good to excellent yields with a range of 79:21 to 95:5 er. Due to the mild reaction conditions, aryl alkyne, boronate and silane were well accommodated under this CoH catalytic system and therefore furnished opportunities for further elaborations. Additionally, internal alkene could undergo this transformation to afford corresponding chiral amine **3y** in 91% yield and 82:18 er (98:2 er after recrystallization). Various heteroaryl substituted alkenes, such as 5-vinylbenzofuran, tosyl-protected 5-vinylindoles, as well as 5-vinylbenzo[*b*]-thiophene, all of which can be hydroaminated smoothly in excellent yields with good enantiocontrols (**3z**–**3ab**). Fluorine-substituted NFSI derivative was also competent to furnish the corresponding product **3ac** with consistent yield and enantioselectivity. Simple aliphatic alkenes were also viable for this asymmetric radical transformation. For instance, 4-phenylbutene was subjected to modified reaction conditions, providing the corresponding



Scheme 4. Substrate scope of asymmetric hydroamination. Unless otherwise noted, the reactions were carried out using alkenes (0.20 mmol), NFSI (2.0 equiv), TMDS (2.0 equiv) and catalyst [Co]-**5*** (2 mol%) in THF (1.0 mL) at −78 °C for 36 h, isolated yield. The er values were determined by HPLC on a chiral stationary phase. [a] Using 4 mol% catalyst [Co]-**5***. [b] HPLC analysis after recrystallization. [c] The reaction was carried out using nonactivated alkene **1a** (0.20 mmol), NFSI (2.0 equiv), $PhMeSiH_2$ (2.0 equiv) and catalyst [Co]-**10*** (3 mol%) in THF (1.0 mL) at −60 °C for 36 h.

chiral alkyl amine **3ad** in 43% yield with 69:31 er. Moreover, some bioactive molecules, such as estrone, isoxepac, indomethacin, and structurally more complicated cholesterol and Vitamin E-derivated alkenes were conveniently transformed to the corresponding chiral amines **3ae**–**3ai** in 42–97% yields with excellent diastereo- and enantiocontrol, which demonstrated that this method would be suitable for late-stage functionalization of complicated molecules.

To gain some insights into the mechanism of this transformation, several control experiments were performed. Upon the addition of radical inhibitors such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) into the model reaction, the formation of **2a** was almost inhibited (Figure 1a). In particular, the TEMPO-trapped product **4** was detected by High-resolution mass spectrometry (HRMS) analysis. In addition, the radical-clock experiment with (2-vinylcyclopropyl)-benzene **1y** led to the ring opening/amination product **5** in 53% yield (Figure 1b). These phenomena suggest that an alkyl radical intermediate is probably involved in this transformation, in line with the speculated CoH-mediated HAT process. Performing the reaction with $PhMeSiD_2$ as the hydrogen supplier

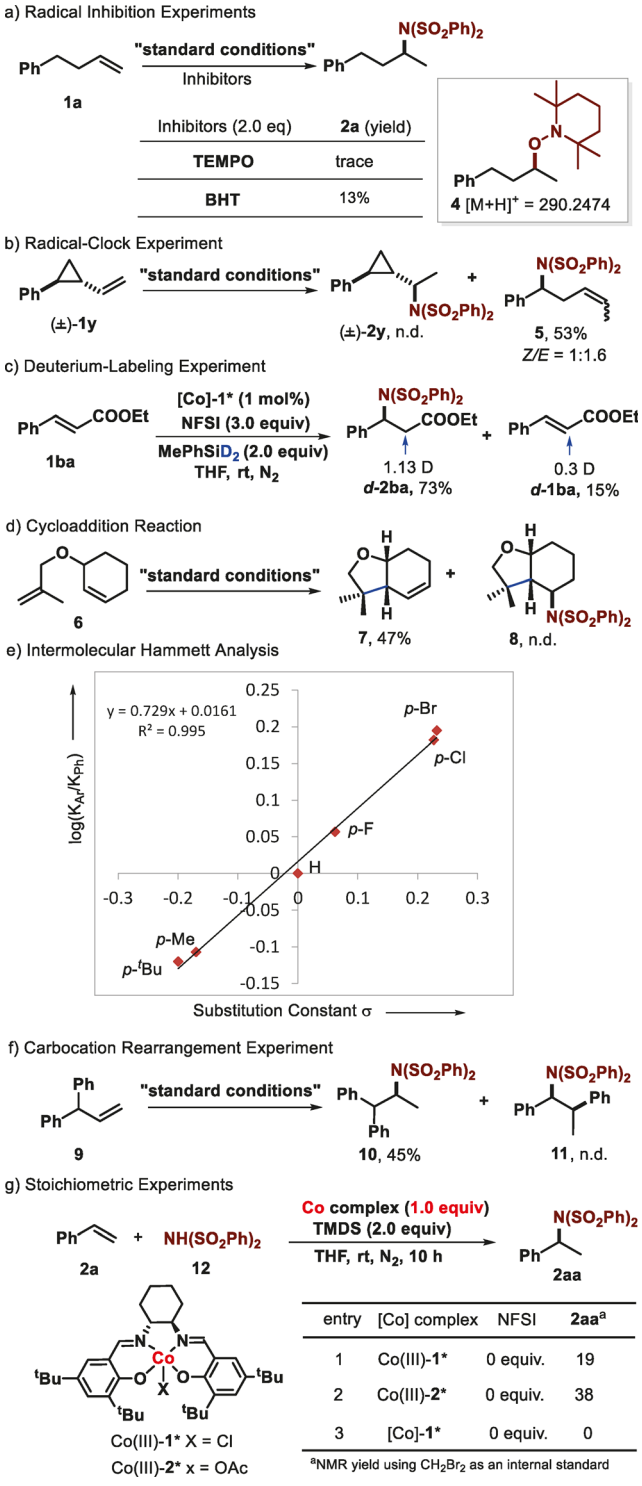
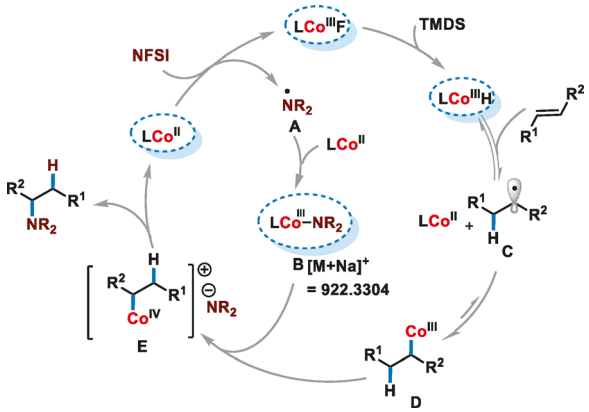


Figure 1. Mechanistic investigation. a) Radical inhibition experiments. b) Radical-clock experiment. c) Deuterium-labeling experiment. d) Cycloaddition reaction. e) Hammett plot for the hydroamination of styrenes: relative rates for the formation of **2** versus σ. f) Carbocation rearrangement experiment. g) Preliminary stoichiometric experiments.

under otherwise identical conditions, *d*-**2ba** bearing 1.13 D at the α-position of the ester group and α-deuterated *d*-**1ba** were observed, suggesting the reversibility of $Co^{III}H$-mediated HAT process (Figure 1c). In addition, diene **6** was subjected to standard reaction conditions, affording only cyclization product **7** in 47% yield, without hydroamination product **8**. This observation might mean that CoH-mediated HAT should be prior to the C–N bond formation under the present catalytic conditions (Figure 1d). The Hammett analysis with a series of competition experiments between styrene and its derivatives was performed to experimentally observe substituent effects of this reaction, and a linear relationship between $\log(k_{Ar}/k_{Ph})$ and σ yields a small ρ value of 0.73 with an R^2 of 0.99 (Figure 1e). This result implicated a slight buildup of negative charge at the benzylic position during the formation of the transition state.[34] Therefore, the possibility of further oxidizing the resulting alkyl radical intermediate to corresponding carbocation species,[35] in contrast to recent Ye's report,[36] might be unlikely. In addition, the reaction using 3,3-diphenyl-1-propene **9** as the substrate was conducted under the optimal reaction conditions, and 1,2-phenyl shift product was not observed, which means that the carbocation intermediate is not likely involved in this transformation (Figure 1f).[37] To further shed light on the mechanism, some stoichiometric experiments were carried out. As illustrated in Figure 1g, employing the combination of $HN(SO_2Ph)_2$ and easily prepared 1.0 equivalent of Co^{III}-**1*** or Co^{III}-**2*** as the alternatives for superstoichiometric NFSI and catalytic amount of cobalt(II)-salen catalyst, the expected hydroamination **2aa** can be obtained in 19% and 38% yield, respectively. These results, in line with Shigehisa's observation,[30] clearly demonstrated that the Co^{III}-salen catalyst could serve as the single electron oxidant enabling the hydroamination (vide infra).

Based on these experiment results and literature precedents,[7a,c–e] a possible $Co^{III}H$-catalyzed radical hydroamination pathway was shown in Scheme 5.[12–14] The catalytic cycle begins with the oxidation of LCo^{II} species by NFSI to deliver the $LCo^{III}F$ species and benzenesulfonimide radical **A**,[2,36,38,39] followed by the transmetalation of $LCo^{III}F$ with TMDS forming the $LCo^{III}H$ species.[40,41] The resulting radical **A** might be trapped by Co^{II} species to form the LCo^{III}-NR_2 species **B**, which has been detected by high-resolution mass spectrometry (HRMS) (see supplementary materials). Then, a $LCo^{III}H$-mediated reversible HAT[42] with alkene would furnish the alkylcobalt(III) species **D**[43] through the interme-



Scheme 5. Proposed mechanism.

diacy of **C**. Subsequently, a SET between the resulted alkylcobalt(III) complex **D** and Co^{III}-NR_2 species **B**, illustrated as Figure 1 g, would occur to form the pivotal radical cationic alkyl Co^{IV} intermediate **E**, i.e., with counter anion $^{-}NR_2$.[44] According to early Halpern and recent Pronin, Shigehisa and other's investigations,[29,30,44,45] this radical cationic Co^{IV} species, formally as $[Co^{IV}R^{-}]$, has been found to enable undergoing a stereochemical inversed displacement with various nucleophiles.[44d,e,f] On the basis of these reports, a similar S_N2-like pathway, which is consistent with the Hammett analysis but unlike the actions of free carbon cation,[36] between this cationic alkyl Co^{IV} species with nitrogen nucleophile could occur, affording the expected amination product with simultaneous release of the Co^{II} for the next catalytic cycle. In addition, the possibility of direct combination of alkylcobalt(III) complex **D** and benzenesulfonimide radical **A** to yield alkyl Co^{IV} intermediate **E**, followed by a S_N2-like pathway to deliver desired hydroamination product is not excluded under the present catalytic conditions.

Conclusion

We have reported an efficient and general HAT-initiated radical hydroamination reaction catalyzed by a cobalt(II)-salen complex. A broad variety of alkenes, including styrenes, alkyl substituted alkenes, strained alkene, as well as α, β-unsaturated carbonyls (e.g. aldehydes, ketones, acids, esters, amides) were all applicable. This transformation features mild reaction conditions, broad functional group tolerance, and highly chemo- and regioselectivity. More importantly, the asymmetric radical hydroamination of alkenes has also been successfully achieved by using a modified chiral Co^{II}-salen catalyst, affording chiral amine derivatives with good yields and enantioselectivities. Furthermore, the last-stage hydroamination reaction of valuable drug-like molecules and gram-scale synthesis also demonstrate the potential applications in the preparation of complicated molecules. Mechanism studies suggest that this hydroamination reaction involves a key carbon radical intermediate derived from metal-hydride-catalyzed HAT and subsequent catalyst controlled S_N2-like pathway between the resulting pivotal organocobalt(IV) species and nitrogen-based nucleophiles. This method provides an alternative and unique platform for access to important nitrogen-containing compounds, particularly for chiral amines.

Acknowledgements

We thank the NSFC (Grants 21831002, 21801039), the Fundamental Research Funds for the Central Universities, and the Ten Thousand Talents Program for generous financial support.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · cobalt catalysis · hydrogen atom transfer · radical hydroamination

[1] For selected reviews, see: a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795 – 3892; b) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596 – 2697; c) J. Hannedouche, E. Schulz, *Organometallics* **2018**, *37*, 4313 – 4326; d) M. T. Pirnot, Y.-M. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 48 – 57; *Angew. Chem.* **2016**, *128*, 48 – 57; e) A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev.* **2020**, *120*, 2613 – 2692; f) P. Colonna, S. Bezzenine, R. Gil, J. Hannedouche, *Adv. Synth. Catal.* **2020**, *362*, 1550 – 1563.
[2] T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069 – 3087.
[3] C. P. Jasperse, *Chem. Rev.* **1991**, *91*, 1237 – 1286.
[4] a) Q. Zhu, D. E. Graff, R. R. Knowles, *J. Am. Chem. Soc.* **2018**, *140*, 741 – 747; b) D. C. Miller, G. J. Choi, H. S. Orbe, R. R. Knowles, *J. Am. Chem. Soc.* **2015**, *137*, 13492 – 13495; c) A. J. Musacchio, L. Q. Nguyen, G. H. Beard, R. R. Knowles, *J. Am. Chem. Soc.* **2014**, *136*, 12217 – 12220; d) A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727 – 730.
[5] a) J. Davies, S. G. Booth, S. Essafi, R. A. W. Dryfe, D. Leonori, *Angew. Chem. Int. Ed.* **2015**, *54*, 14017 – 14021; *Angew. Chem.* **2015**, *127*, 14223 – 14227; b) J. Davies, T. D. Svejstrup, D. F. Reina, N. S. Sheikh, D. Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092 – 8095.
[6] a) X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. M. Beauchemin, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 12163 – 12167; *Angew. Chem.* **2014**, *126*, 12359 – 12363; b) J. Chen, H.-M. Cuo, Q.-Q. Zhao, J.-R. Chen, W.-J. Xiao, *Chem. Commun.* **2018**, *54*, 6780 – 6783.
[7] a) J. Waser, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 4099 – 4102; *Angew. Chem.* **2004**, *116*, 4191 – 4194; b) J. Waser, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 5676 – 5677; c) J. Waser, J. C. González-Gómez, H. Nambu, P. Huber, E. M. Carreira, *Org. Lett.* **2005**, *7*, 4249 – 4252; d) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693 – 11712; e) J. Waser, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 8294 – 8295.
[8] E. K. Leggans, T. J. Barker, K. K. Duncan, D. L. Boger, *Org. Lett.* **2012**, *14*, 1428 – 1431.
[9] J. Gui, C. M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E. Mertzman, W. J. Pitts, T. E. LaCruz, M. A. Schmidt, N. Darvatkar, S. R. Natarajan, P. S. Baran, *Science* **2015**, *348*, 886 – 891.
[10] J. Chen, X. Shen, Z. Lu, *J. Am. Chem. Soc.* **2020**, *142*, 14455 – 14460.
[11] a) J. Zheng, J.-F. Qi, S.-L. Cui, *Org. Lett.* **2016**, *18*, 128 – 131; b) K.-L. Zhu, M. P. Shaver, S. P. Thomas, *Chem. Asian J.* **2016**, *11*, 977 – 980; c) Y. Zhang, C. Huang, X. Lin, Q. Hu, B. Hu, Y. Zhou, G. Zhu, *Org. Lett.* **2019**, *21*, 2261 – 2264.
[12] a) H. Shigehisa, N. Koseki, N. Shimizu, M. Fujisawa, M. Niitsu, K. Hiroya, *J. Am. Chem. Soc.* **2014**, *136*, 13534 – 13537; b) T. Nagai, N. Mimata, Y. Terada, C. Sebe, H. Shigehisa, *Org. Lett.* **2020**, *22*, 5522 – 5527; c) S. Ohuchi, H. Koyama, H. Shigehisa, *ACS Catal.* **2021**, *11*, 900 – 906.
[13] a) X.-L. Zhou, F. Yang, H.-L. Sun, Y.-N. Yin, W.-T. Ye, R. Zhu, *J. Am. Chem. Soc.* **2019**, *141*, 7250 – 7255; b) H.-L. Sun, F. Yang, W.-T. Ye, J.-J. Wang, R. Zhu, *ACS Catal.* **2020**, *10*, 4983 – 4989.
[14] K. Yahata, Y. Kaneko, S. Akai, *Org. Lett.* **2020**, *22*, 598 – 603.
[15] Y. Xi, S. Ma, J. F. Hartwig, *Nature* **2020**, *588*, 254 – 260.

[16] S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2012**, *14*, 780 – 783.
[17] E. P. Vanable, J. L. Kennemur, L. A. Joyce, R. T. Ruck, D. M. Schultz, K. L. Hull, *J. Am. Chem. Soc.* **2019**, *141*, 739 – 742.
[18] F. Yu, P. Chen, G. Liu, *Org. Chem. Front.* **2015**, *2*, 819 – 822.
[19] D. V. Gribkov, K. C. Hultzsch, F. Hampel, *J. Am. Chem. Soc.* **2006**, *128*, 3748 – 3759.
[20] a) S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746 – 15749; b) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 10830 – 10834; *Angew. Chem.* **2013**, *125*, 11030 – 11034. For recent review on CuH catalysis, see: R. Y. Liu, S. L. Buchwald, *Acc. Chem. Res.* **2020**, *53*, 1229 – 1243.
[21] X. Shen, X. Chen, J. Chen, Y. Sun, Z. Cheng, Z. Lu, *Nat. Commun.* **2020**, *11*, 783 – 790.
[22] K. Yahata, Y. Kaneko, S. Akai, *Chem. Pharm. Bull.* **2020**, *68*, 332 – 335.
[23] C. B. Roos, J. Demaerel, D. E. Graff, R. R. Knowles, *J. Am. Chem. Soc.* **2020**, *142*, 5974 – 5979.
[24] Z. Zhou, Y. Li, B. Han, L. Gong, E. Meggers, *Chem. Sci.* **2017**, *8*, 5757 – 5763.
[25] a) G. Zhang, Y. Liang, T. Qin, T. Xiong, W. Guan, Q. Zhang, *CCS Chem.* **2020**, *2*, 1737 – 1745; b) Z. Li, J. Zhao, B. Sun, T. Zhou, M. Liu, S. Liu, M. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 11702 – 11705; c) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2529 – 2533; *Angew. Chem.* **2013**, *125*, 2589 – 2593; d) H. Zhang, Y. Song, J. Zhao, J. Zhang, Q. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 11079 – 11083; *Angew. Chem.* **2014**, *126*, 11259 – 11263; e) G. Zhang, T. Xiong, Z. Wang, G. Xu, X. Wang, Q. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 12649 – 12653; *Angew. Chem.* **2015**, *127*, 12840 – 12844; f) G. Zheng, Y. Li, J. Han, T. Xiong, Q. Zhang, *Nat. Commun.* **2015**, *6*, 7011; g) S. Yang, L. Wang, H. Zhang, C. Liu, L. Zhang, X. Wang, G. Zhang, Y. Li, Q. Zhang, *ACS Catal.* **2019**, *9*, 716 – 721.
[26] When the reaction was conducted with α,β-unsaturated acid **1bt** under standard condition, a benzyl amination product **2aa** was obtained in 58% yield, which possibly generated via a cobalt-catalyzed HAT/decarboxylation/hydroamination cascade, see: J. Ma, W. Yi, G. Lu, C. Cai, *Adv. Synth. Catal.* **2015**, *357*, 3447 – 3452.
[27] S.-L. Shi, Z. L. Wong, S. L. Buchwald, *Nature* **2016**, *532*, 353 – 356.
[28] J. Frigola, A. Torrens, J. A. Castrillo, J. Mas, D. Vaňó, J. M. Berrocal, C. Calvet, L. Salgado, J. Redondo, S. García-Granda, E. Valentí, J. R. Quintana, *J. Med. Chem.* **1994**, *37*, 4195 – 4210, and references therein.
[29] C. A. Discolo, E. E. Touney, S. V. Pronin, *J. Am. Chem. Soc.* **2019**, *141*, 17527 – 17532.
[30] K. Ebisawa, K. Izumi, Y. Ooka, H. Kato, S. Kanazawa, S. Komatsu, E. Nishi, H. Shigehisa, *J. Am. Chem. Soc.* **2020**, *142*, 13481 – 13490.
[31] T. Niimi, T. Uchida, R. Irie, T. Katsuki, *Adv. Synth. Catal.* **2001**, *343*, 79 – 88.
[32] T. Nagata, K. Yorozu, T. Yamada, T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2145 – 2147; *Angew. Chem.* **1995**, *107*, 2309 – 2311.
[33] T. Inagaki, L. T. Phong, A. Furuta, J. Ito, H. Nishiyama, *Chem. Eur. J.* **2010**, *16*, 3090 – 3096.
[34] X. Zhang, J. Ren, S. M. Tan, D. Tan, R. Lee, C.-H. Tan, *Science* **2019**, *363*, 400 – 404.
[35] S. Banerjee, S. Sathyamoorthi, J. D. Bois, R. N. Zare, *Chem. Sci.* **2017**, *8*, 7003 – 7008.
[36] P. Guo, J.-F. Han, G.-C. Yuan, L. Chen, J.-B. Liao, K.-Y. Ye, *Org. Lett.* **2021**, *23*, 4067 – 4071.
[37] M. Yasuda, S. Yamasaki, Y. Onishi, A. Baba, *J. Am. Chem. Soc.* **2004**, *126*, 7186 – 7187.
[38] P. Guo, Y. Li, X.-G. Zhang, J.-F. Han, Y. Yu, J. Zhu, K.-Y. Ye, *Org. Lett.* **2020**, *22*, 3601 – 3606.
[39] The THF or 1,4-dioxane solution of Co(salen) complex I is bright red. The solution becomes olive green upon addition of NFSI.
[40] K. Ding, T. R. Dugan, W. W. Brennessel, E. Bill, P. L. Holland, *Organometallics* **2009**, *28*, 6650 – 6656.
[41] The mechanism involved a FCo^{IV}-$N(SO_2Ph)_2$ species, derived from direct oxidative addition of Co^{II}-salen catalyst with NFSI, followed by an in turn ligand exchange with silane yielding HCo^{IV}-$N(SO_2Ph)_2$ and a HAT process to yield intermediates **B** and **C**. Then, the combination of **B** and **C** also provided the key radical cationic Co^{IV} intermediate **D**. This pathway can not be ruled out, however, the state-of-the-art radical reactions involving cobalt hydride catalysis HAT are favorable to $Co^{III}H$ species rather than $Co^{IV}H$.
[42] Y.-N. Yin, R.-Q. Ding, D.-C. Ouyang, Q. Zhang, R. Zhu, *Nat. Commun.* **2021**, *12*, 2552.
[43] The existence of proposed alkylcobalt(III) intermediate has been investigated by the group of Shenvi in the recently reported cobalt-catalyzed hydroarylation reactions of alkenes, see: S. L. Shevick, C. Obradors, R. A. Shenvi, *J. Am. Chem. Soc.* **2018**, *140*, 12056 – 12068.
[44] a) J. Topich, J. Halpern, *Inorg. Chem.* **1979**, *18*, 1339 – 1343; b) J. Halpern, M. S. Chan, J. Hanson, T. S. Roche, J. A. Topich, *J. Am. Chem. Soc.* **1975**, *97*, 1606 – 1608; c) P. Abley, E. R. Dockal, J. Halpern, *J. Am. Chem. Soc.* **1972**, *94*, 659 – 660; d) M. E. Vol'pin, I. Y. Levitin, A. L. Sigan, J. Halpern, G. M. Tom, *Inorg. Chim. Acta* **1980**, *41*, 271 – 277; e) R. H. Magnuson, J. Halpern, I. Y. Levitin, M. E. Vol′pin, *J. Chem. Soc. Chem. Commun.* **1978**, 44 – 46; f) S. N. Anderson, D. H. Ballard, J. Z. Chrzastowski, D. Dodd, M. D. Johnson, *J. Chem. Soc. Chem. Commun.* **1972**, 685 – 686.
[45] E. R. Touney, N. J. Foy, S. V. Pronin, *J. Am. Chem. Soc.* **2018**, *140*, 16982 – 16987.

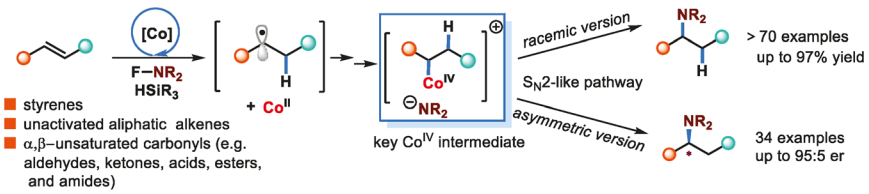
Manuscript received: July 29, 2021
Revised manuscript received: September 11, 2021
Accepted manuscript online: September 25, 2021
Version of record online: ■■ ■■, ■■■■

Research Articles

Hydroamination

T. Qin, G. Lv, Q. Meng, G. Zhang,*
T. Xiong,* Q. Zhang* ——— ■■■■–■■■■

Cobalt-Catalyzed Radical Hydroamination of Alkenes with *N*-Fluorobenzenesulfonimides



A highly general and efficient Co-catalyzed radical hydroamination of alkenes with *N*-fluorobenzenesulfonimide and its analogues has been developed. The corresponding asymmetric version has also been achieved by using a chiral cobalt(II)-salen catalyst in good to excellent level of enantiocontrol.