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Cobalt-Catalyzed Asymmetric Alkylation of (Hetero)Arenes with Styrenes

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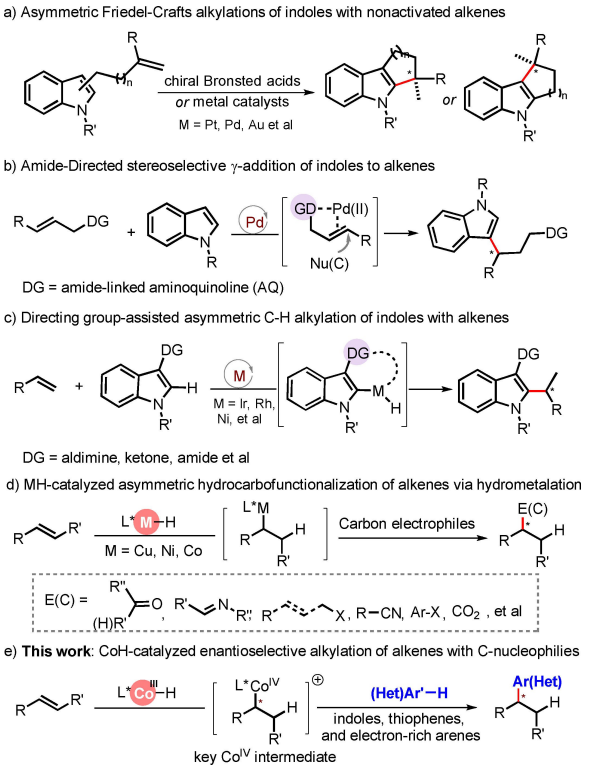
Abstract: An efficient and general intermolecular Cobalt(II)-catalyzed asymmetric alkylation of styrenes with (hetero)arenes including indoles, thiophene and electron rich arenes has been developed, providing straightforward access to enantioenriched alkyl(hetero)-arenes with high enantioselectivity. Mechanistic studies suggest that the reaction underwent a CoH-mediated hydrogen atom transfer (HAT) with alkenes, followed by a pivotal catalyst-controlled S_N2-like pathway between in situ generated organocobalt(IV) species and aromatic nucleophiles. This is the first CoH-catalyzed asymmetric hydrofunctionalization using carbon nucleophiles, providing a new strategy for asymmetric Friedel–Crafts type alkylation.

Alkenes and (hetero)arenes are fundamental and ubiquitous feedstocks that can be obtained from petroleum directly or by single operation. Asymmetric alkylation of (hetero)arenes with alkenes, one of the representative approaches that allows for directly merging of the two abundant and structurally diverse raw materials in a catalytic enantioselective fashion, can greatly augment the synthetic toolbox for the construction of complex carbon skeletons.[1,2] In particular, the asymmetric alkylation of indoles using alkenes as alkylating reagents has received extensive attention, owning to the important chemical and medicinal utility of indole framework.[3] In this realm, significant advances have been achieved using highly reactive Michael acceptors, such as α,β-unsaturated carbonyl compounds[4] and nitroolefins,[5] wherein the EWG group and the chiral catalyst could produce a network of interactions for chiral recognition. On the other hand, asymmetric alkylation of non-activated alkenes with indoles were usually achieved in an intramolecular manner to form enantioenriched 5- or 6-membered rings under chiral Brønsted[6] or Lewis acid[7] catalysis (Scheme 1a). In addition, the directing groups (DG) strategy has emerged as an alternative approach for enantioselective alkylation of indoles and other (hetero)-arenes, which rely on the coordination of metal complex with directing group in either alkenes or indoles (arenes) for facilitating reactivity and efficient control of enantioselectivity through intramolecular delivery (Scheme 1b and c).[8–10] In sharp contrast, intermolecular asymmetric alkylation of indoles with alkenes without the assistance of DG is very rare.[11] Therefore, the development of mechanistically distinct method for enantioselective alkylation of indoles and other (hetero)arenes with alkenes is highly challenging and appealing.

Over the past few years, transition-metal-catalyzed asymmetric hydrometalation reaction, represented by CuH,



Scheme 1. Approaches for asymmetric alkylation of indoles with alkenes and MH-catalyzed enantioselective hydrocarbofunctionalization of alkenes.

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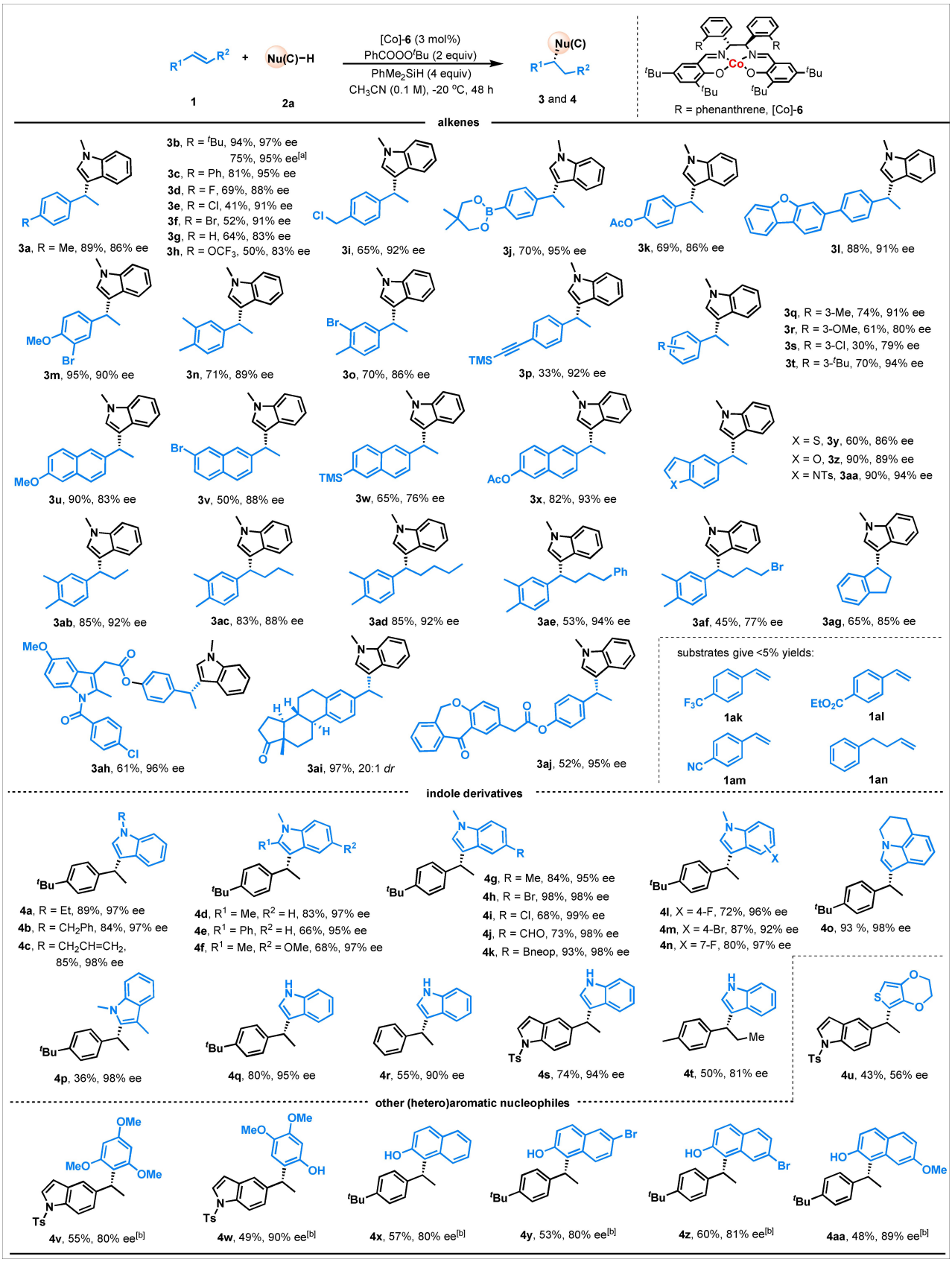
NiH and CoH catalysis, has emerged as a robust and practical synthetic platform for construction of enantioenriched C–C and carbon-heteroatom bonds.[12] Such transformation is typically achieved via in situ generated chiral alkyl metal intermediates, originated from MH migratory insertion into alkenes, serving as surrogates of pre-prepared organometallics to be intercepted by various electrophiles (Scheme 1d). A diverse range of carbon electrophiles including aldehydes,[13] ketones,[14] imines,[15] allyl/alkyl electrophiles,[16] etc[17] have been implemented to enantioselective hydrocarbofunctionalization for chiral C–C bond formation. In contrast, metal-hydride-catalyzed enantioselective hydrocarbonation of alkenes using nucleophilic indoles as carbon-based partner is rare.[18] More recently, by utilizing Co^{III}-H catalyst, intramolecular asymmetric hydroalkoxylation for the synthesis of important chiral epoxides and tetrahydrofurans products was reported by the group of Pronin[19] and Shigehisa,[20] respectively. We have discovered that CoH-catalyzed intermolecular asymmetric hydroamination of alkenes can be realized by virtue of *N*-fluorobenzenesulfonimides as both nucleophilic nitrogen source and oxidant.[21] Inspired by these works and CoH-initiated HAT reaction,[22] we designed a blueprint to achieve enantioselective hydrocarbonation using carbon-based nucleophile through an HAT strategy. Herein, we report an efficient intermolecular asymmetric alkylation of indole derivatives with alkenes via CoH-mediated HAT pathway. In addition to indole derivatives, this method is capable of extending to other (hetero)aromatic nucleophiles, and therefore, provides a mechanically distinct, alternative route to synthetically valuable chiral indoles and heteroaromatic scaffolds in a high efficiency, excellent level of regio- and enantioselectivity fashion (Scheme 1e). To the best of our knowledge, this is the first case of enantioselective C–C bond formation reaction in the realm of CoH-catalyzed hydrofunctionalization of alkenes.

We initiated our investigation by subjecting simple 4-methyl styrene (**1a**) and *N*-methyl indole (**2a**) as model substrates. Reaction conditions screening disclosed that the reaction was best conducted with Co(salen) complex [Co]-**6** (3.0 mol %) in the presence of $PhMe_2SiH$ as hydrogen supplies and *tert*-butyl peroxybenzoate (TBPB) as oxidant in a solution of CH_3CN at −20 °C, generating the expected product **3a** in 89 % yield and 86 % enantiomer excess. Examining other cobalt catalysts, commercially available silanes, solvents and oxidants were also performed and slightly inferior yield under otherwise optimal reaction conditions were observed (for details see Supporting Information Table S1–S4).

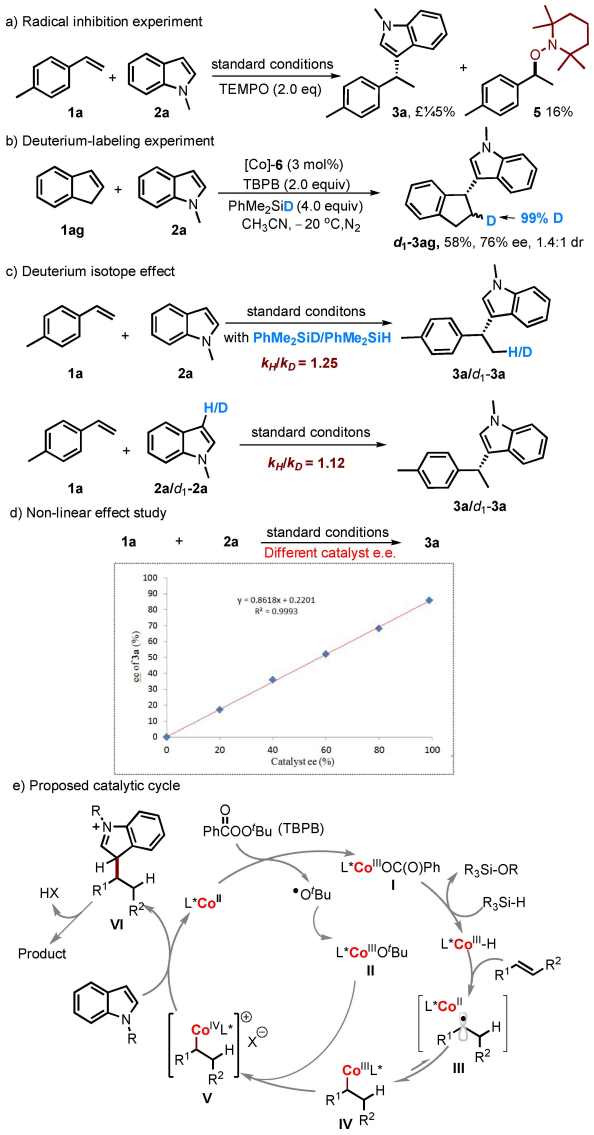
In assessing the scope of the catalytic reaction (Scheme 2), we found that an array of styrenes **1** could be efficiently reacted with *N*-methyl indole **2a** to deliver the desired chiral 1,1-di(hetero)aryl alkanes **3** in generally good yields with good to excellent enantioselectivities. Various substituents including alkyl, phenyl, halogens, trifluoromethoxy, chloromethyl, boronic acid pinacol ester, acetoxyl, methoxyl and dibenzofuran as well as reactive alkyne moieties at either *para*- or *meta*-position on the aromatic rings of styrenes were all compatible, and all of the reactions proceeded smoothly to afford the corresponding products **3a**–**3t** with high level of enantiocontrol (80–97 % ee). The tolerance of aryl halides and boronic acid pinacol ester as well as alkyne units also offered an opportunity for further manipulation. While *ortho*-substituted styrene could not be converted to the targeted product, likely due to the steric hindrance. In addition, a broad spectrum of vinylnaphthalene (**3u**–**3x**) and heteroaryl substituted alkenes, such as 5-vinylbenzo[*b*]thiophene (**3y**), 5-vinylbenzofuran (**3z**) as well as tosyl-protected 5-vinylindoles (**3aa**), were viable alkylating reagents, furnishing the corresponding chiral alkylated heteroarenes in good to excellent yields with a range of 76 % to 94 % ee. Additionally, β-substituted internal alkenes as well as indene could undergo this transformation to afford the corresponding products **3ab**–**3ag** in moderate to good yields and acceptable enantiocontrol. Structurally more complicated indomethacin, estrone, isoxepac derivated alkenes could also be transformed into the corresponding products **3ah**–**3aj** smoothly in good yields with excellent diastereo- and enantiocontrol. Gratifyingly, a reaction scaled up to 4 mmol was successful and comparable results of **1b** (75 % yield and 95 % ee) were obtained with a lower catalyst loading. However, electron-poor styrenes and aliphatic alkenes were not viable substrates (**1ak**–**1an**).[23]

Next, we investigated the scope of indole derivatives. It was found that various *N*-alkyl-protected indoles including ethyl, benzyl and allyl were well-tolerated (**4a**–**4c**). A series of indoles bearing various functional groups at different positions were also surveyed, affording the corresponding products (**4d**–**4o**) in good yields with excellent enantioselectivities (92–99 % ee). Several substituents, such as 2-Ph, 5-Me, 5-CHO, 5-Bpin, 5-Cl, 6-Br, and 7-F, on the indole core were perfectly tolerated. Clearly, the enantioselectivity is not sensitive to both steric and electronic effects for the indole substituents. When using the 3-substituted indole, alkylation occurred at the C2-position (**4p**) with 98 % ee, albeit with a relative low yield. It is worth noting that *N*-protection is not required for the indoles, indoles with free N–H could be efficiently transformed to the corresponding products **4q**–**4s** in moderate yields in 90 % to 95 % ee. Decent yield and enantioselectivity were also obtained for the reaction of free N–H indole with internal alkene (see **4t**). The success of this asymmetric HAT strategy for indoles derivatives encouraged us to continue examining other (hetero)aromatic nucleophiles. To our delight, 3,4-ethylenedioxythiophene and a range of electron-rich arenes, such as anisoles and 2-naphthol derivatives, were also viable substrates, giving the corresponding chiral alkylated (hetero)arenes **4u**–**4aa**, despite showing relatively low enantiocontrol compared with that of indole derivatives.

Control experiments were performed to illustrate the possible mechanism (Scheme 3). Upon the addition of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the formation of **3a** was inhibited and TEMPO-trapped product **5** was obtained (Scheme 3a). This result suggests that an alkyl radical intermediate is probably involved in this transformation, in line with the proposed Co^{III}-H mediated HAT process. A deuterium-labeling experiment of indene using $PhMe_2SiD$ was conducted to afford



Scheme 2. Scope of the reaction with alkenes and (hetero)arene nucleophiles. Reaction conditions: alkenes (0.2 mmol), (hetero)arene nucleophiles (1.2 equiv), TBPB (2.0 equiv), $PhSiMe_2H$ (4.0 equiv) and [Co]-**6** (3 mol%) in CH_3CN (2.0 mL) at −20 °C, isolated yield. The ee values were determined by HPLC on a chiral stationary phase. [a] Gram-scale using alkene (4.0 mmol), nucleophiles (1.2 equiv), TBPB (1.5 equiv), $PhSiMe_2H$ (3.0 equiv) and [Co]-**6** (2.0 mol%) in CH_3CN (30 mL) at −20 °C, isolated yield. [b] Using 1.5 equiv aryl nucleophiles.



Scheme 3. Mechanistic studies. a) Radical inhibition experiments. b) Deuterium-labeling experiment. c) Kinetic isotope effects. d) Non-linear effect study. e) Proposed catalytic cycle.

***d*-3ag** in 58 % yield with 99 % D and 1.4:1 dr (Scheme 3b), which demonstrated that the hydrogen came from silanes and deuterium incorporation of no more than 99 % suggested the irreversibility of Co^{III}-H-mediated HAT process. In addition, intermolecular competitive kinetic isotope effects (KIEs) experiments were conducted under standard conditions (Scheme 3c). The k_H/k_D value for $PhMe_2SiH$ and $PhMe_2SiD$ was found to be 1.25. Similar intermolecular KIE value ($k_H/k_D = 1.12$) was obtained by comparing the initial rates with substrates **2a** versus ***d*$_1$-2a**.[24] These results indicated that the cleavage of Si–H and C–H might not be involved in the turnover-limiting step.

To gain more insights into the cobalt-catalyzed asymmetric alkylation of heteroarenes, detailed kinetic analysis experiments for styrene were conducted under optimal reaction conditions. The rate data indicated a first-order dependence on the concentration of cobalt catalyst, alkene and TBPB oxidant, while a zeroth-order for the silane and indole nucleophile concentration (Supplementary Figures S16–S25). These results revealed that the oxidation of cobalt(III) might be the turnover-limiting step. Additionally, a linear correlation between the catalyst enantiomeric composition and that of the product **3a** suggested that only a single, monomeric chiral catalyst may be involved in the enantiodetermining transition state (Scheme 3d). To gain some insights into the enantiodetermining step of this reaction, we investigated the thermal dependence of the enantioselectivity (Figure S27). We found that the ee variation was not monotonic with temperature, and slightly convex Eyring plot is characterized by two lines with an inversion point ($T_{inv} = -20\,^{\circ}C$).[25] This nonlinearity indicated that our enantioselective catalysis may include no fewer than two enantiodetermining steps.

Based on these experiments and related literature,[19–22] we proposed a catalytic cycle as depicted in Scheme 3e. The catalytic cycle begins with the formation of Co^{III}-H species and cobalt(III) complexes **II**. The Co^{III}-H mediated HAT process is known to produce a metallo-/alkyl radical pair **III**.[26] Subsequently, cage collapse would generate an alkylcobaly(III) intermediate **IV**.[27] According to early investigations by Halpern[28] and recent reports by Pronin,[19] Shigehisa[20] and our group,[21] a SET oxidation of the resulted alkylcobalt complex **IV** would generate a cationic alkyl Co^{IV} intermediate **V**.[29] Finally, C–C bond would formed by nucleophilic displacement[19–21,30] to afford the product and simultaneous release of the Co^{II} for the next catalytic cycle. Based on the preliminary mechanistic studies and related literatures,[19,20] we suspect that both nucleophilic displacement of cationic alkylcobalt(IV) complex with nucleophiles (**V**→**VI**) and the formation of alkylcobalt(III) through cage collapse (**III**→**IV**) may be involved in enantiodetermining step. Detailed enantiocontrol and influencing factors still need further experimental evidence and theoretical calculation, relevant research was undergoing in our lab.

In conclusion, we have developed an efficient Co-catalyzed asymmetric alkylation reaction of alkenes with indoles, thiophenes and electron rich arenes. It represents not only a new Friedel–Crafts type alkylation with general scope, but also the first of CoH-catalyzed asymmetric hydrocarbonfunctionalization using carbon nucleophiles. Further expansion of the substrate scope of this enantioselective hydrofunctionalization and detailed mechanistic studies are currently ongoing in our group.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: (Hetero)Aryl Nucleophiles · Alkylation · Asymmetric · Cobalt Catalysis · Hydrogen Atom Transfer

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Communications

Cobalt Catalysis

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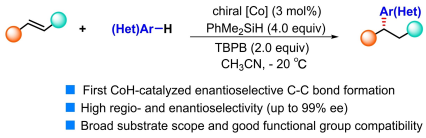
Cobalt-Catalyzed Asymmetric Alkylation of (Hetero)Arenes with Styrenes



A highly efficient Co-catalyzed enantioselective alkylation of alkenes with indoles, thiophenes and electron rich arenes has been developed. This is the first CoH-catalyzed asymmetric hydrofunctionalization using carbon nucleophiles via hydrogen atom transfer.