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Enantioselective Construction of Oxindoles Bearing a Quaternary Carbon via Ni–Al Bimetal-Catalyzed Formyl C–H Alkylation

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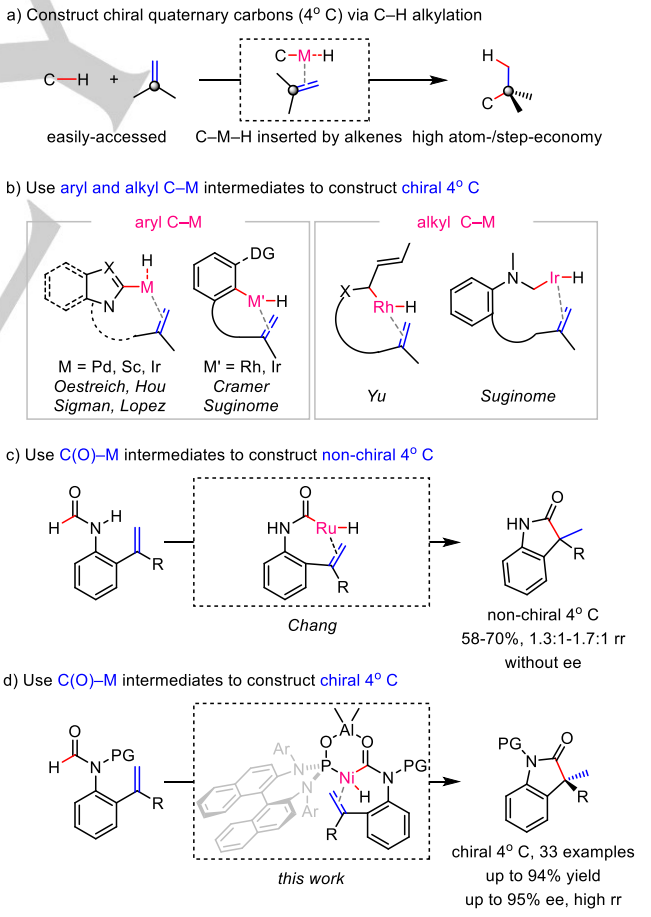
Abstract: Enantioselective transition metal-catalyzed C–H alkylation emerges as one of the most atom- and step-economical routes to chiral quaternary carbons, while big challenges still remain with acyl C–H alkylations. Herein, we use a Ni–Al bimetallic catalyst to facilitate a highly regioselective and highly enantioselective C–H alkylation of formamides with alkenes, constructing various oxindoles bearing a chiral quaternary carbon in up to 94% yield and up to 95% ee.

The construction of chiral quaternary carbons has received intensive attention in recent decades, because chiral quaternary carbons are prevalent structural units in numberous natural products, pharmaceuticals, and agrochemicals.[1] Among existing approaches,[2] enantioselective transition metal-catalyzed C–H alkylation represents one of the most atom- and step-economical routes to chiral quaternary carbons, owing to relatively easily-accessed starting materials and minimum loss of atoms during reactions (Scheme 1a).[3] Though appealing, this process often suffers from some big challenges such as low reactivity of inert C–H bond activation, difficult insertion of sterically-hindered 1,1-disubstituted alkenes into the formed C–M–H intermeidates, as well as tricky control of regioselectivity and enantioselectivity.[3b] To ease the process, the selection of C–H bonds and their activating method are critical. A big progress has been made for aryl C–H alkylations, in which relatively reactive heteroaryl C–H bonds or unreactive aryl C–H bonds are activated by Pd,[4] Rh,[5] Sc,[6] and Ir,[7] providing the corresponding aryl C–M intermediates that are stable and can be further inserted by 1,1-disubstituted alkenes to give final quaternary carbons with high ee (Scheme 1b, left). Another important advance is achieved by Yu[8] and Suginome,[9] who use allylic C–H bonds or C–H bonds adjacent to heteroatoms to generate alkyl C–M intermediates, which are also stable enough to be trapped by 1,1-disubstituted alkenes, furnishing chiral quaternary carbons with high ee (Scheme 1b, right). Nevertheless, the activation of acyl C–H bonds to form chiral quaternary carbons bearing easily-transformable carbonyl groups still remains an elusive challenge,[10] despite wide existence of such structral motifs in bioactive molecules.[11] A possible reason for this challenge is that unstable C(O)–M intermediates may undergo decarbonylation to release CO species, which will not only inhibit metal activity, but also hinder chiral ligands from coordinating with metals, resulting in low selectivity.[12] To address this issue, Chang and coworkers use a Ru catalyst to explore formyl C–H alkylation, achieving oxindoles bearing a sterically-hindered quaternary carbon as main products (Scheme 1c).[13] Despite a big breakthrough in acyl C–H alkylation, the lack of proper chiral ligands renders the control of regioselectivity and enantioselectivity quite difficult. Considering that oxindoles bearing a chiral quaternary carbon widely exist in bioactive molecules and their synthesis has received considerable interests during the past several decades,[14] herein, we use a phosphine oxide ligand-ligated Ni and Al bimetallic catalyst to realize a highly regioselective and highly enantioselective C–H alkylation of formamides with alkenes (Scheme 1d), constructing various oxindoles bearing a chiral quaternary carbon with up to 94% yield and up to 95% ee. Wide scope of substrates and versatile transformations of chiral carbonyl quaternary carbons demonstrate potential utilities of the current method.



Scheme 1. Construct oxindoles bearing a chiral quaternary carbon via enantioselective transition metal-catalyzed C–H alkylation.

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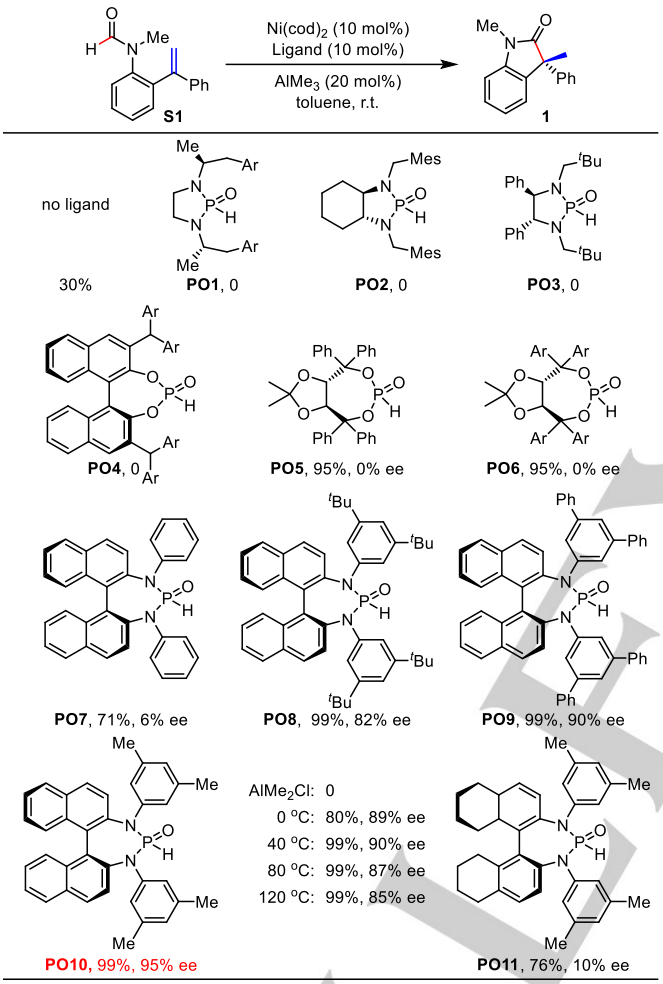
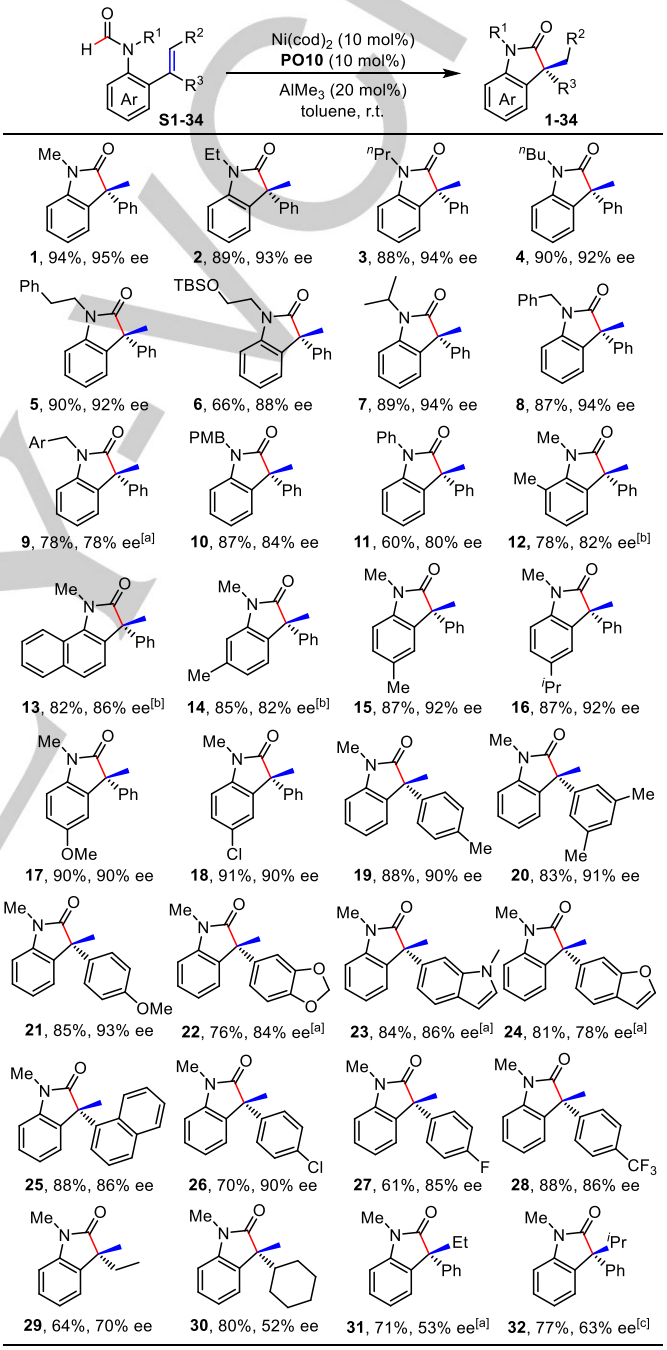
Inspired by Chang's work, we selected formamide **S1** as the model substrate for the investigation (Scheme 2). Without Al-Lewis acids, no cyclization occurred, while the addition of 20 mol% of $AlMe_3$ generated a sole *exo*-cyclization, providing chiral oxindole bearing a quaternary carbon in 30% yield. Encouraged by this result, we conducted a systematic survey on phosphine oxide (PO) ligands that can ligate Ni and Al metals for better synergistic catalysis.[15,16] The results revealed that chiral diamine-, and BINOL-derived POs were ineffective (**PO1**–**PO4**), while TADDOL-derived **PO5** and **PO6** greatly promoted the reactivity, both affording 95% yield but without ee.



Scheme 2. Reaction optimization. Reaction conditions: **S1** (0.2 mmol) in toluene (1.0 mL) under N_2 for 12 h; yield was determined by ^1H NMR with $C_2H_2Cl_4$ as the internal standard; ee was determined by HPLC on a chiral stationary phase. Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$.

Until the appearance of BINAM-derived **PO7**, low ee was then observed with nearly quantitative yield. Therefore, a series of BINAM-derived PO ligands were synthesized and examined. Surprisingly, the modification of N-phenyl group with proper substituents at 3,5-positions proved critical to ee. For example, *tert*-butyl (**PO8**) and phenyl groups (**PO9**) at 3,5-positions significantly improved ee to 82% and 90%, respectively. Finally, methyl group proved to be the optimal one (**PO10**), providing 99% yield and 95% ee. Further tuning steric hindrance and electronic property by introducing partially-hydrogenated binaphthyl rings (**PO11**) decreases ee to 10%. With the optimal ligand in hand, other conditions were investigated: control experiments showed that the acidity of Al-Lewis acids has a strong influence to the reactivity, and a little weaker Lewis acid such as $AlMe_2Cl$ were completely ineffective. In addition, room temperature was found to be optimal, and lower or higher temperature led to a slightly decreasing ee. Impressively, the reaction still proceeded well even at 0 °C, displaying high reactivity of the current method.



Scheme 3. Scope of substrates. Reaction conditions: **S1–32** (0.2 mmol) in toluene (1.0 mL) under N_2 for 12 h at room temperature; yield of isolated products; ee was determined by HPLC on a chiral stationary phase. [a] 40 mol% $AlMe_3$ at 80 °C. [b] 80 °C. [c] 40 mol% $AlMe_3$ at 120 °C. ^{n}Pr = *n*-propyl. ^{n}Bu = *n*-butyl. Et = ethyl. OTBS = (*tert*-butyldimethylsilyl)oxy. Ar = 4-$CF_3OC_6H_4$. PMB = 4-methoxybenzyl. ^{i}Pr = *i*-propyl.

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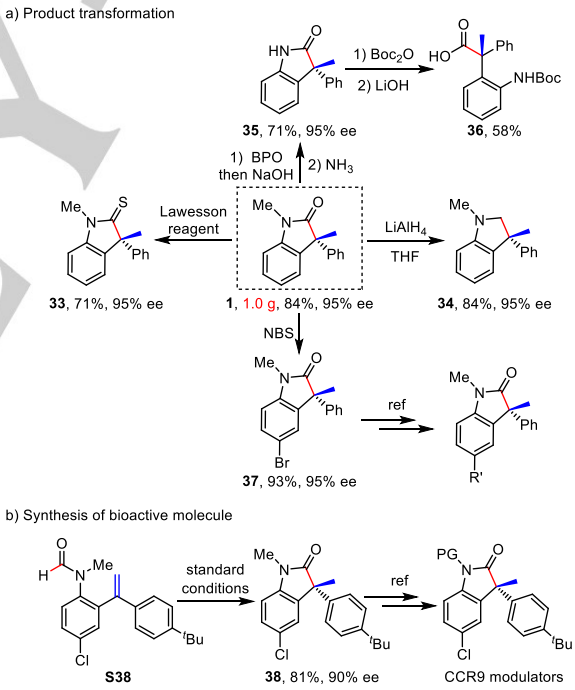
With the optimal conditions in hand, we first explored the effect of formamide moiety. As shown in Scheme 3, various linear or branched alkyl substituents on the nitrogen atom of formamide were all well tolerated (**1**–**10**), providing the corresponding product in 66%–94% yield and 78%–95% ee. Notably, the presence of oxygen-containing functional group resulted in a slightly lower yield and ee (**6** and **9**), which was probably attributed to the coordination of O atom with Al-Lewis acid. Compared with good performance of alkyl substituents, aryl substituents gave decreasing yield and ee (**11**). We reasoned that aryl substituents may reduce electronic density of carbonyl group, further inhibiting the coordination of carbonyl group with Al-Lewis acid. Based on the crystal structure of product **11**, the absolute configuration of chiral quaternary carbon was assigned as *R* (see the supporting information).[17] In addition, the position of substituents on the aryl ring of formamide moiety also proved crucial. Substituents at *ortho*- and *meta*-position of the N atom led to a decreasing ee (**12**–**14**), while various *para*-substituents including both electron-donating (**15**–**17**) and electron-withdrawing group (**18**) were well compatible, offering 87%–91% yield and 90%–92% ee. Next, the effect of alkene moiety was investigated. Aryl substituents bearing electron-donating groups such as methyl group (**19** and **20**) and alkoxy groups (**21** and **22**) and fused (hetero)aryl rings (**23–25**) were all well tolerated, yielding the corresponding products in 76%**–**88% yield and 78%**–**93% ee. Notably, the presence of heteroaryl rings often required more loadings of $AlMe_3$ and higher temperature (**23–25**), probably because the coordination of hetero atoms reduced Lewis acidity of $AlMe_3$. Similarly, electron-withdrawing groups such as Cl (**26**), F (**27**) and CF_3 (**28**) group were also well compatible in the reaction, affording 61%**–**88% yield and 85%**–**90% ee. In comparison with aryl substituents, alkyl substituents (**29** and **30**) still gave good yield but with decreasing ee (64%**–**80% yield and 52%**–**70% ee). We presumed that more flexible structure of alkyl substituents may diminish enantioselective control. Surprisingly, highly sterically-hindered tri-substituted (**31**) and even tetra-substituted alkenes (**32**) still worked well at elevated temperatures, providing the corresponding product in 71%**–**77% yield and 53%**–**63% ee.

To demonstrate the utility of the current reaction, product transformations and the synthesis of bioactive molecule were conducted. The model reaction was run at gram scale, smoothly affording product **1** in a little decreasing yield but without loss of ee (Scheme 4a). When treated with Lawesson reagent or $LiAlH_4$, compound **1** can be transformed into thioamide (**33**) in 71% yield and amine (**34**) in 84% yield. In addition, methyl protecting group can be removed from the N atom through sequential oxidation and hydrolysis, providing product **35** in 71% yield. The followed ring-opening process delivered a synthetically useful amino acid bearing a chiral quaternary carbon (**36**). In addition, electron-rich anilide can be easily brominated, offering compound **37** that allows more versatile elaboration at the position of Br group.[18] In light of wide existence of oxindoles with a chiral quaternary carbon in bioactive molecules, compound **38** that is a key precursor of a series of antagonists or modulators of CCR9 chemokine receptors,[19] was successfully synthesized in 81% yield and 90% ee under the standard conditions (Scheme 4b), suggesting possible wide applications of the current approach.

To gain more insights into the mechanism, relevant mechanistic experiments were conducted. The deuterium-labeling experiment showed that formyl H was completely transferred to the alkene terminus (scheme 5a). No significant kinetic isotopic effect was observed in parallel experiments (k_H/k_D = 1.04) (Scheme 5b), indicating that the cleavage of formyl C–H would not be involved in the rate-determining step. In addition, anomalous kinetic behavior with respect to Ni, PO, and the substrate was observed, suggesting that the formation of bimetallic catalyst and the cyclization could be very complicated (see Supporting Information for details). When oct-4-yne was added to the reaction under the standard conditions but at 80 °C, the original cyclization product **1** was isolated in 34% yield and 85% ee, accompanying by new product **39** in 54% yield and 54% ee (scheme 5c). Different ees achieved for product **1** and **39** suggested that these two products could be formed through different intermediates. On the basis of these results and previous studies,[20] a plausible mechanism was then proposed in Scheme 5d: the coordination of **S1** with PO–Ni–Al bimetallic catalyst affords intermediate **A**, which undergoes direct intramolecular ligand-to-ligand H transfer (LLHT) with alkene motif to provide intermediate **B**,[21] followed by reductive elimination to give product **1**; However, in the presence of oct-4-yne, intermediate **A** may undergo intermolecular ligand-to-ligand H transfer with alkyne to afford intermediate **C**. Subsequent insertion of alkene motif into C(O)–Ni bond or Ni–C bond gives intermediate **D** or **D'**, followed by reductive elimination to give product **39**.



Scheme 4. Synthetic utility.

In conclusion, chiral quaternary carbons bearing a formyl group were successfully constructed via a highly regioselective and highly enantioselective bimetal-catalyzed C–H alkylation of formamides with alkenes under mild conditions. A naphthylamine-derived phosphine oxide-ligated Ni and Al bimetallic catalyst was identified as the optimal catalyst. A wide range of di-, tri- and even tetra-substituted alkenes were compatible with the reaction, affording oxindoles bearing a quaternary carbon in up to 94% yield and up to 95% ee. Versatile transformations of amide group, oxindole and aryl ring demonstrates potential utility of the method.

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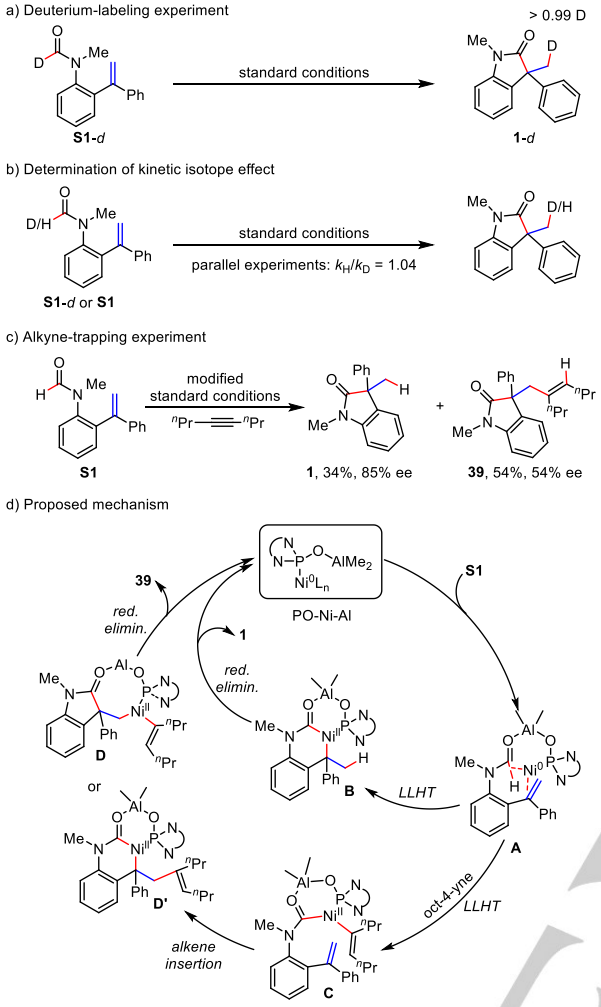

Scheme 5. Mechanistic experiments and proposed mechanism.

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[17] Deposition number 2343818 (for **11**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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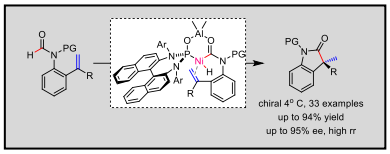

Enantioselective transition metal-catalyzed C–H alkylation emerges as one of the most atom- and step-economical routes to chiral quaternary carbons, while big challenges still remain with acyl C–H alkylations. Herein, we use a Ni–Al bimetallic catalyst to facilitate a highly regioselective and highly enantioselective C–H alkylation of formamides with alkenes, constructing various oxindoles bearing a chiral quaternary carbon in up to 94% yield and up to 95% ee.