



Asymmetric Catalysis Hot Paper

Asymmetric Redox Allylic Alkylation to Access 3,3'-Disubstituted Oxindoles Enabled by Ni/NHC Cooperative Catalysis

Tao Fan, Jin Song,* and Liu-Zhu Gong*

Abstract: The feasibility of cooperative catalysis between chiral N-heterocyclic carbenes and nickel in asymmetric reactions has been demonstrated convincingly. The high efficiency of this catalytic system enables the asymmetric allylic alkylation of isatin-derived enals with allylic carbonates and [3+3] annulation with racemic vinyl epoxides to provide straightforward access to highly enantioenriched 3,3'-disubstituted oxindoles. The great practicality of this method in organic synthesis has been showcased by facile product modification and enantioselective synthesis of the key building block to access (–)-debromoflustramine B.

N-Heterocyclic carbene (NHC) catalysis, one of the most productive concepts in organocatalysis, has found enormous success in the creation of synthetic methods to construct structurally complex chiral molecules.^[1] In recent years, combined NHC and transition metal (TM) catalysis has gradually grown to be an emerging and exciting field, culminating in a numerous elegant organic transformations that are difficult to access by either of individual catalysts.^[2] The remarkable capacity for rejuvenated reactivity has made NHC/TM cooperative catalysis an invaluable platform^[3] for asymmetric organic synthesis.^[4–9] Since the inception of NHC/palladium cooperatively catalyzed transformations by Liu,^[4a,c] Scheidt,^[4b] and co-workers, considerable efforts have been directed toward expanding the repertoire of coupling partners in the TM-mediated reactions. Precious transition metals, such as ruthenium,^[5] palladium,^[6] iridium,^[7] and gold,^[8] in some cases tethered with an exogenous ligand, are most commonly competent with chiral NHC catalysts for enantioselective transformations with exception of a few cases involving copper as a co-catalyst^[9] (Scheme 1A). Nickel is an earth-abundant metal; its complexes exhibit unparalleled capacity in catalysis and

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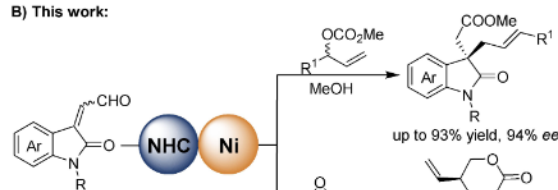
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A) Dual asymmetric catalytic systems of transition metals and NHCs



Transition metals
 Second & Third-row: Ru,^[5] Pd,^[6] Ir,^[7] Au^[8]
 First-row: Cu^[9] Ni

B) This work:

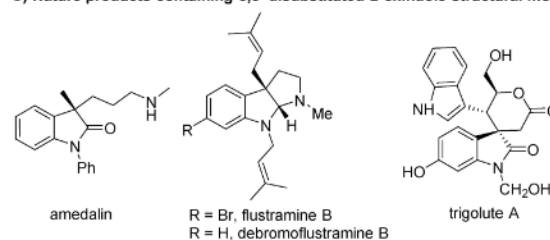


Challenges:

- NHC/Ni cooperative activation
- Homo-enolates with Ni-mediated electrophiles
- All-carbon quaternary stereocenters

up to 63% yield
 10:1 d.r., 99% ee

C) Nature products containing 3,3'-disubstituted 2-oxindole structural motifs



Scheme 1. Asymmetric allylic alkylation via NHC/Ni cooperative catalysis.

have exerted a historical impact on synthetic chemistry.^[10,11] The synergy and combined catalytic activity of NHC and nickel would provide room for the establishment of new asymmetric reactions. However, the adaptability of NHCs with this metal remains yet to be explored.

The asymmetric allylic alkylation (AAA) reaction,^[12] predominantly catalyzed by the second- and third-row transition metals (e.g. Pd, Rh, and Ir), represents one of the most important methods to assemble small molecules bearing quaternary carbon atoms bonded to four distinct carbon substituents.^[12e,13] Owing to the low cost and exceptional synthetic versatility of the first-row transition metals,^[10] great interest has been devoted to revealing the potential of nickel catalysts^[11] in catalyzing asymmetric allylic alkylation reactions to build up quaternary stereocenters.^[12e] However, only a limited number of “soft” nucleophiles, such as β-ketoesters,^[14a,c] α-carbonyl lactones,^[14b] and transient enamines^[14d] have been reported to participate in these transformations thus far. Cognizant of this, we considered NHC-bound homo-enolate equivalents as transient nucleophiles, which can engage in the enantioselective

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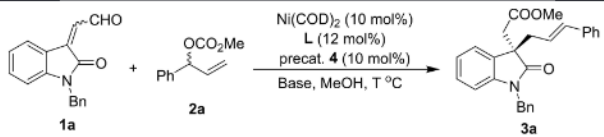
lective carbon–carbon bond formation event with electrophiles mediated by nickel catalysts.^[15] Herein, we report the NHC/Ni cooperatively catalyzed asymmetric redox allylation reaction of isatin-derived enals^[16] with allylic carbonates and [3+3] annulation reactions with racemic vinyl epoxides (Scheme 1B). Both reactions provide economical approaches to access highly enantioenriched 3,3'-disubstituted oxindoles and spirooxindole derivatives^[17] with structural diversity. More importantly, such structural motifs are important components of various biologically active natural products and pharmaceutical compounds (Scheme 1C).^[18]

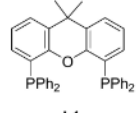
We commenced our study with the model reaction of an isatin-derived enal **1a** with allylic carbonate **2a** under NHC/Ni cooperative catalysis, and the key results are briefly summarized in Table 1 (see Supporting Information, Table S1 for more details). In the presence of 10 mol% Ni(COD)₂, 12 mol% Xantphos (**L1**), and 10 mol% NHC

precatalyst **4a** in MeOH at 50 °C, the linear allylation product **3a** was obtained exclusively in 60% yield and with 37% *ee* (Table 1, entry 1). The survey of diphosphine ligands (**L2** and **L3**) failed to improve the results (entries 2 and 3). Next, we focused on screening structurally different chiral N-heterocyclic carbenes **4b–4e** with Xantphos (**L1**) (entries 4–7) and identified **4e** to be a promising precatalyst (50% yield, 80% *ee*). Evaluation of other reaction parameters (entries 8–10) identified that lowering the temperature and using *N*-methylmorpholine (NMM) as a base further enhanced the yield to 73% and the enantioselectivity to 93% *ee* (entry 10). Interestingly, the reaction performance did not considerably change when the catalyst loading was decreased (entry 11). The best results were achieved when a higher concentration of the substrate (**2a**) was used (76% yield, 94% *ee*, entry 12). Control experiments revealed that no desired product was detected in the absence of NHC precatalyst **4e** (entry 13), exogenous ligand (**L1**) on nickel (entry 14), or the nickel-bisphosphine catalyst (entry 15).

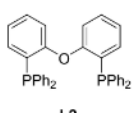
Under the optimized reaction conditions, the substrate scope of this process was evaluated (Table 2). Isatin-derived enals **1** possessing different *N*-substituents were all compatible (**3a–3c**, entries 1–3). A range of enals bearing either electron-donating or electron-withdrawing groups at the 5-

Table 1: Optimization of the reaction conditions.^[a]

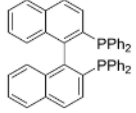




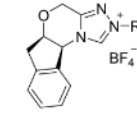
L1



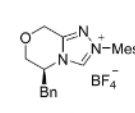
L2



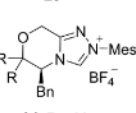
L3



4a, R = Mes
4b, R = C₆F₅



4c

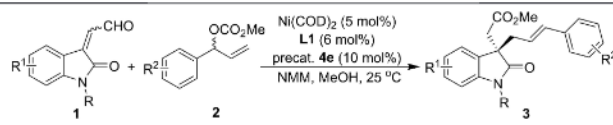


4d, R = Me
4e, R = Et

Entry	L	4	Base	T [°C]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	L1	4a	Et ₃ N	50	60	37
2	L2	4a	Et ₃ N	50	31	11
3	L3	4a	Et ₃ N	50	4	40
4	L1	4b	Et ₃ N	50	N.D.	
5	L1	4c	Et ₃ N	50	72	53
6	L1	4d	Et ₃ N	50	75	75
7	L1	4e	Et ₃ N	50	50	80
8	L1	4e	Et ₃ N	25	47	91
9	L1	4e	DIPEA	25	43	86
10	L1	4e	NMM	25	73	93
11 ^[d]	L1	4e	NMM	25	64	93
12 ^[d,e]	L1	4e	NMM	25	76(72)	94
13 ^[d,e]	–	–	NMM	25	N.D.	
14 ^[d,e]	–	4e	NMM	25	N.D.	
15 ^[d,e,f]	–	4e	NMM	25	N.D.	

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Ni(COD)₂ (10 mol%), ligand **L** (12 mol%), NHC precatalyst **4** (10 mol%), and base (0.2 mmol) in MeOH (1.0 mL) at T °C for 12 h under N₂. [b] The yield was determined by ¹H NMR spectroscopy (yield of isolated product in parentheses). [c] The enantiomeric excess (*ee*) was determined by HPLC. [d] Ni(COD)₂ (5 mol%), **L1** (6 mol%), and NHC precatalyst **4e** (10 mol%) were used. [e] **2a** (0.2 mmol) was used. [f] In the absence of Ni(COD)₂. DIPEA: *N,N*-diisopropylethylamine. NMM: *N*-methylmorpholine. N.D. = not detected.

Table 2: Substrate scope.^[a]



Entry	R	R ¹	R ²	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Bn	H	H	3a , 72	94
2	Me	H	H	3b , 58	90
3	Et	H	H	3c , 73	92
4	Bn	5-Me	H	3d , 70	90
5	Bn	5-OMe	H	3e , 59	92
6	Bn	5-F	H	3f , 41	87
7	Bn	5-Cl	H	3g , 40	84
8	Bn	6-OMe	H	3h , 90	92
9	Bn	6-OMe	4-F	3i , 93	92
10	Bn	6-OMe	4-Cl	3j , 93	92
11	Bn	6-OMe	4-Br	3k , 85	92
12	Bn	6-OMe	4-CF ₃	3l , 72	93
13	Bn	6-OMe	4-CN	3m , 90	93
14	Bn	6-OMe	4-Me	3n , 87	91
15	Bn	6-OMe	4-OMe	3o , 88	93
16	Bn	6-OMe	3-Cl	3p , 93	93
17	Bn	6-OMe	3-OMe	3q , 75	93
18	Bn	6-OMe	2-Me	3r , 86	91
19 ^[d]	Bn	6-OMe	R ²	3s , 75	91
20 ^[e]	Bn	6-OMe	R ²	3t , 41	94
21 ^[f]	Bn	H	R ²	3u , 58	83

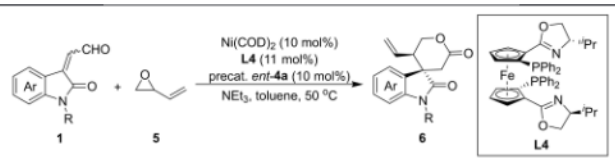
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Ni(COD)₂ (5 mol%), **L1** (6 mol%), NHC precatalyst **4e** (10 mol%), and NMM (0.2 mmol) in MeOH (1.0 mL) at 25 °C for 12 h under N₂. [b] Yield of isolated product **3**. [c] The *ee* value was determined by HPLC. [d] Methyl (1-(naphthalen-2-yl)allyl) carbonate was used. [e] Methyl (1-(1-tosyl-1*H*-indol-3-yl)allyl) carbonate was used. [f] Allyl methyl carbonate was used; reaction temperature: 50 °C.

position of the phenyl group all smoothly participated in the AAA reaction with allylic carbonate **2a** and the corresponding linear allylation products (**3d–3g**) were obtained with satisfactory results (entries 4–7). The 6-methoxy-substituted enal **1h** proved to be a reliable reaction partner, producing the 3,3'-disubstituted oxindole **3h** in 90% yield and 92% *ee* (entry 8). We next explored the scope of allylic carbonates for the allylation reaction (entries 9–21). Notably, in such umpolung reaction with 6-methoxy-substituted enal **1h**, a broad range of allylic carbonates bearing electron-withdrawing (F, Cl, Br, CF₃, CN) and electron-donating substituents (Me, OMe) on arene rings were all tolerated and gave the desired products **3i–3r** with excellent results (entries 9–18). Moreover, allyl carbonates with naphthyl and indole groups also worked well (entries 19 and 20). However, allyl methyl carbonate with the less bulky H-atom led to dropped enantioselectivity of 83% *ee* (**3u**, entry 21).

Having established a general and modular protocol for the synthesis of linear allylic oxindoles, we sought to investigate the branch-coupling reaction with control over diastereoselectivity. The use of readily available vinyl epoxides^[19] as 1,3-dipoles with unsaturated systems has proven to be highly valuable in TM-catalyzed asymmetric annulation reactions.^[20] Nickel complexes, however, have obtained less attention.^[21] The current cooperative NHC/Ni catalytic system could be successfully expanded to the [3+3] annulation reaction between NHC-bound homoenolates with π -allyl-Ni species, and the synthesis of spirooxindole tetrahydropyranone derivatives was achieved by using isatin-derived enals **1** and vinyl epoxides **5** as substrates (Table 3). Employing ferrocene bis(oxazoline-phosphine) ligand **L4**^[22] with Ni(COD)₂ in combination with the NHC precatalyst *ent-4a*, the desired product **6a** was obtained in 61% yield, 8:1 d.r., and 97% *ee* (Table 3A, entry 1, see Supporting Information, Table S2 for more details). A series of control experiments exhibiting significant variations in the yield and diastereo- and enantioselectivity verified the necessity of each catalyst component (entries 2–5). Notably, with the use of the opposite enantiomer of the NHC catalyst (entry 2), a reverse diastereoselectivity was observed (entry 2 vs entry 1), thus clearly suggesting that the chiral NHC catalyst and the nickel complex work cooperatively in the annulation process. The substrate scope for substituted isatin-derived enals **1** is shown in Table 3B. A variety of substituents and substitution patterns of enals **1** was tolerated, and the corresponding products **6a–6l** were obtained in moderate yields, but with good diastereoselectivity and excellent enantioselectivity (up to 99% *ee*). The absolute configuration of **6a** was assigned by X-ray analysis, and all the other adducts were tentatively assigned by analogy.^[23]

The synthetic application of this method was demonstrated in several transformations on the highly functionalized 3,3'-disubstituted oxindole derivatives (Scheme 2). The oxidative cleavage of compound **3a** with ozone led to aldehyde **7** in 77% yield and with maintained *ee* (Scheme 2A). The transformation of **3a** to a precursor for the synthesis of (–)-debromoflustramine B^[18d] is illustrated in Scheme 2B. In the presence of the Grubbs second-gener-

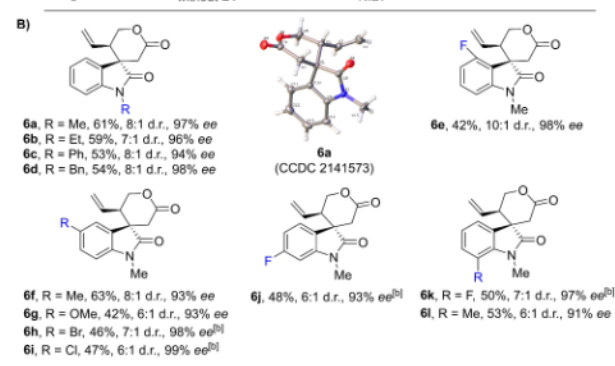
Table 3: NHC/Ni cooperatively catalyzed [3+3] annulation reaction.^[a]



A)

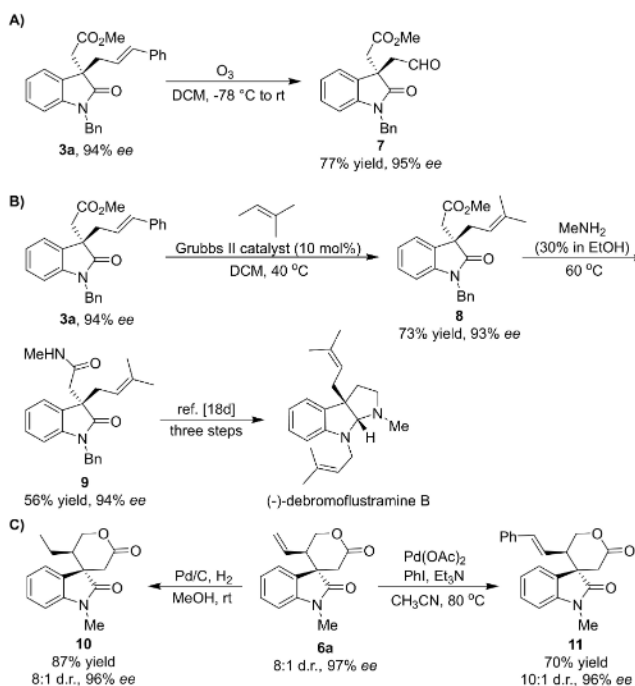
Entry	Variation from the standard conditions	Yield [%] of 6a	d.r. of 6a	<i>ee</i> [%] of 6a
1	none	61	8:1	97
2	with precatalyst 4a	60	1:2	92
3	without precatalyst <i>ent-4a</i>	N.D.	-	-
4	without Ni(COD) ₂	N.D.	-	-
5	without L4	N.D.	-	-

B)



6a, R = Me, 61%, 8:1 d.r., 97% *ee*
6b, R = Et, 59%, 7:1 d.r., 96% *ee*
6c, R = Ph, 53%, 8:1 d.r., 94% *ee*
6d, R = Bn, 54%, 8:1 d.r., 98% *ee*
6e, R = Me, 42%, 6:1 d.r., 93% *ee*^[b]
6f, R = Me, 63%, 8:1 d.r., 93% *ee*
6g, R = OMe, 42%, 6:1 d.r., 93% *ee*
6h, R = Br, 46%, 7:1 d.r., 98% *ee*^[b]
6i, R = Cl, 47%, 6:1 d.r., 99% *ee*^[b]
6j, R = Me, 48%, 6:1 d.r., 93% *ee*^[b]
6k, R = F, 50%, 7:1 d.r., 97% *ee*^[b]
6l, R = Me, 53%, 6:1 d.r., 91% *ee*

[a] Reaction conditions: **1** (0.1 mmol), **5** (0.2 mmol), Ni(COD)₂ (10 mol%), **L4** (11 mol%), NHC precatalyst *ent-4a* (10 mol%), and NEt₃ (0.05 mmol) in toluene (1.0 mL) at 50 °C for 12 h under N₂. Yield of isolated product **6**. The diastereomeric ratio was determined by ¹H NMR spectroscopic analysis. The *ee* value was determined by HPLC. [b] Ni(COD)₂ (15 mol%) and **L4** (16 mol%) were used. N.D. = not detected.



Scheme 2. Synthetic transformations of products **3a** and **6a**.

ation catalyst, the olefin cross-metathesis reaction of compound **3a** and 2-methyl-2-butene took place smoothly, and the cinnamyl group was converted to the requisite alkene group in high efficiency (**8**, 73% yield, 93% *ee*). The amidation reaction of **8** with methylamine successfully produced the methyl amide **9**, which is the key intermediate for the total synthesis of (–)-debromoflustramine B. The absolute configuration of **3a** was determined by comparison of the optical rotation of amide **9** with that reported in the literature,^[18d] and all the other adducts **3** were tentatively assigned. As shown in Scheme 2C, the spirooxindole tetrahydropyranone product **6a** generated from the [3+3] annulation reaction was readily elaborated under mild conditions. Hydrogenation of **6a** over Pd/C catalyst led to the reduction of the olefin moiety (**10**, 87% yield, 8:1 d.r., 96% *ee*). A Heck coupling reaction installed an aryl group onto **6a**, generating compound **11** with satisfactory results.

To gain insight into the reaction mechanism, we carried out some preliminary mechanistic studies (Figure 1). Reactions of enal **1a** with 1.5 equivalent of allylic carbonate **2a** were carried out with the cooperative catalytic system consisting of 10 mol % nickel catalyst and 12 mol % diphosphine ligand (**L1**), along with 2.5 mol % to 20 mol % NHC precatalyst **4e** (Figure 1A). To our surprise, the combination of 2.5 mol % NHC precatalyst **4e** with 10 mol % Ni(COD)₂ and 12 mol % **L1** still made the reaction work, enabling **3a** to be formed in 24% yield and with 90% *ee* (entry 1). The amount of the NHC precatalyst **4e** had a considerable effect on the reaction conversion, but the enantioselectivity was almost maintained in all cases (entries 1–4). Next, we searched for nonlinear effects using achiral diphosphine ligand **L1** and chiral NHC precatalyst **4e** with different optical purities (see Supporting Information, Table S3 for

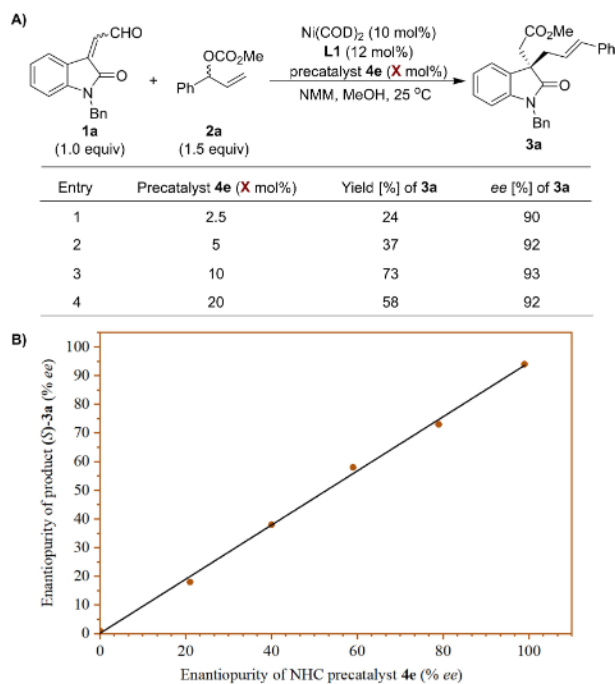


Figure 1. Mechanistic studies.

details). As depicted in Figure 1B, the linear relationship between the *ee* values of **4e** and those of the oxindole product (*S*)-**3a** indicated that one molecule of NHC catalyst is involved in the stereochemical control event. Based on the preliminary mechanistic investigations and the control experiment shown in Table 1 (entry 14), we propose that the coordinating event between NHC and the nickel center^[24] may be inhibited by the strong coordination of the bidentate phosphine ligand.^[6c] The [Ni-**L1**] complex^[25] is likely to be the active metal catalyst and NHC **4e** serves as an organo-catalyst to activate the enal. A plausible mechanism is proposed in Figure 2. The nickel complex coordinates with allylic carbonate **2a** to afford an intermediate **I**, which then undergoes oxidative addition to deliver electrophile **II**. Meanwhile, the Breslow intermediate **III** or azolium homo-enolate species **IV** is generated from the enal **1a** and NHC. The two catalytic cycles intersect when the homo-enolate species **IV** (or **III**) attacks the electrophilic allylnickel intermediate **II** from the bottom face unblocked by the substituents on NHC in a linear selective fashion, and affords the keto azolium intermediate **V**. The subsequent methanolysis leads to catalyst turnover and finally delivers product **3a**.

In conclusion, we have proved that chiral N-heterocyclic carbene and nickel complexes are highly compatible and can synergistically catalyze the enantioselective allylic alkylation reactions of isatin-derived enals with allylic carbonates and vinyl epoxides, respectively. The NHC-bound homo-enolate equivalents are excellent nucleophiles and undergo allylic

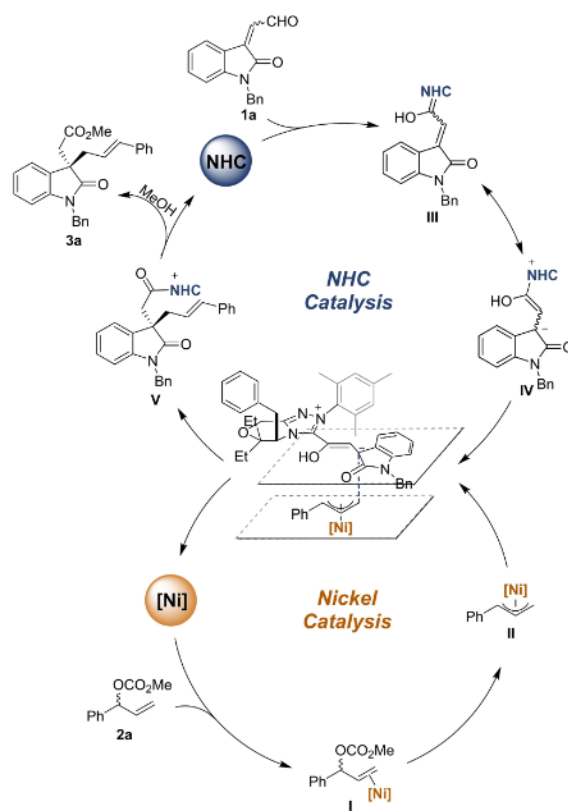


Figure 2. Proposed catalytic cycles.

substitution with π -allyl-Ni species, leading to chiral quaternary carbon stereogenic centers in high stereoselectivity. More importantly, the method has practical applications, as showcased by its application to the synthesis of privileged heterocycles and a key building block to access (–)-debromoflustramine B. We expect that this study will inspire further exploration and provide a general platform for the development of unforeseen asymmetric transformations.

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 supplementary material of this article.

Keywords: All-Carbon Quaternary Stereocenters · Cooperative Catalysis · N-Heterocyclic Carbene · Nickel · Oxindoles

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Communications

Asymmetric Catalysis

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Asymmetric Redox Allylic Alkylation to
Access 3,3'-Disubstituted Oxindoles En-
abled by Ni/NHC Cooperative Catalysis



Chiral N-heterocyclic carbene and nickel cooperative catalysis enables asymmetric redox allylic alkylation to access 3,3'-disubstituted oxindoles with high enantioselectivity.