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Nickel-Catalyzed Asymmetric Reductive Carbo-Carboxylation of Alkenes with CO_2

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Dedicated to Professor Peter Kündig and Professor Gerhard Erker on the occasion of their 75th birthdays

Abstract: *Reductive carboxylation of organo (pseudo)halides with CO_2 is a powerful method to provide carboxylic acids quickly. Notably, the catalytic reductive carbo-carboxylation of unsaturated hydrocarbons via CO_2 fixation is a highly challenging but desirable approach for structurally diverse carboxylic acids. There are only a few reports and no examples of alkenes via transition metal catalysis. We report the first asymmetric reductive carbo-carboxylation of alkenes with CO_2 via nickel catalysis. A variety of aryl (pseudo)halides, such as aryl bromides, aryl triflates and inert aryl chlorides of particular note, undergo the reaction smoothly to give important oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter. This transformation features mild reaction conditions, wide substrate scope, facile scalability, good to excellent chemo-, regio- and enantioselectivities. The method highlights the formal synthesis of (−)-Esermethole, (−)-Physostigmine and (−)-Physovenine, and the total synthesis of (−)-Debromoflustramide B, (−)-Debromoflustramine B and (+)-Coixspirolactam A; thereby, opening an avenue for the total synthesis of chiral natural products with CO_2.*

Introduction

Carbon dioxide (CO_2) has been regarded as an ideal C1 synthon in organic synthesis because of its abundance, nontoxicity, and renewability.[1] In the past decades, CO_2 chemistry has rapidly developed for transferring waste to treasure.[2] As carboxylic acids are ubiquitous motifs that do not only exist widely in drug molecules and natural products but also act as bulk feedstocks in the synthesis of fine chemicals and materials,[3] the generation of carboxylic acids from CO_2 is particularly attractive and a variety of strategies have been developed.[4–7] Particularly, the transition metal-catalyzed reductive carboxylation of organo (pseudo)halides with CO_2 attracts much attention because of its high step economy, easy operation and good compatibility by avoiding pregeneration and handing moisture-sensitive organometallic reagents.[8,9] Besides the widely-investigated *ipso*-carboxylation of carbon-(pseudo)halides,[9,10] the transition metal-catalyzed reductive carbo-carboxylation of unsaturated hydrocarbons via remote CO_2 fixation has become a highly desirable approach to generate structurally diverse carboxylic acids with complex structure.[11,12] As it is much more challenging considering the rate competition in reactions of organometallic intermediates, which are generated via oxidative addition of carbon-(pseudo)halide to low-valent transition metals, with unsaturated bond and CO_2, the reported methods are still limited to the use of highly reactive alkynes or allenes.[11] For example, in 2015 Martin realized the first nickel-catalyzed divergent cyclization/carboxylation of alkyl halides-tethered alkynes with CO_2 to give tetrasubstituted acrylic acids with carbocyclic skeletons (Figure 1 A, top).[11a,b] More recently, the same group has also reported a highly selective remote carboxylation of $C(sp^2)$–H bonds via catalytic 1,4-Ni migration with alkynes (Figure 1 A, middle).[11d] Besides, Sato also realized an elegant palladium-catalyzed intramolecular arylative carboxylation of allenes with Et_2Zn as a reductant (Figure 1 A, bottom).[11c] However, there is no report on transition metal-catalyzed reductive carbo-carboxylation of alkenes with CO_2, which might arise from a more facile reaction of nucleophilic organometallic intermediate with CO_2 than alkenes. With our continuous interest in the carboxylation of unsaturated bonds with CO_2,[12b,13] we aim to resolve such a challenge by developing an efficient transition metal-catalytic system for reductive carbo-carboxylation of alkenes with CO_2. If suc-

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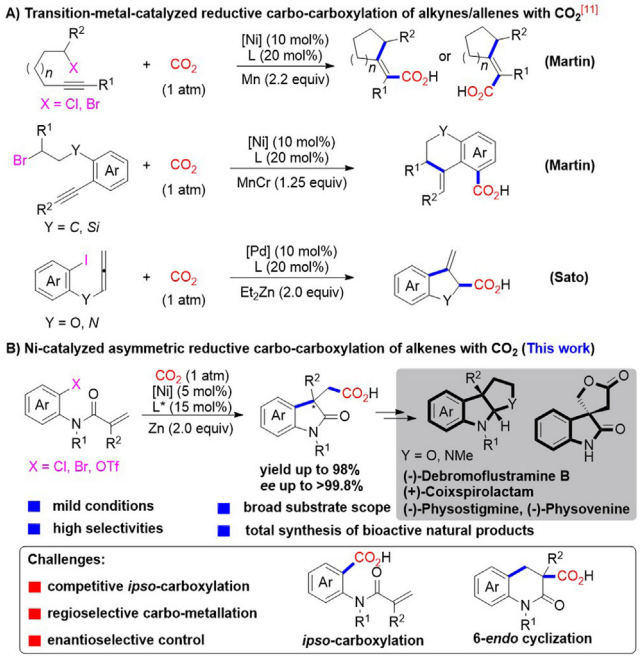


Figure 1. Transition metal-catalyzed reductive carbo-carboxylation of unsaturated hydrocarbons with CO_2.

cessful, we could construct structurally diverse carbo/heterocyclic skeletons bearing carboxylic acids functional groups. More significantly, we might be able to synthesize high value-added enantiomerically pure carboxylic acids through chiral ligands-induced asymmetric reductive alkene carbo-carboxylation reaction, which has not been disclosed yet.[14,15]

Indoline- and oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter are not only widely found in bioactive molecules and natural products but also serve as key precursors to construct complex molecules (Figure 2).[16] Although some approaches,[17] such as Pd-catalyzed asymmetric carbonylation with CO as the carbonyl source,[17a,f,g] have been reported to obtain these core structures, it is highly desirable to seek more cost-efficient catalysts and user-friendly carbonyl source. Inspired by recent great progress on reductive cross couplings,[18–21] we hypothesized whether we could synthesize these structures via asymmetric reductive

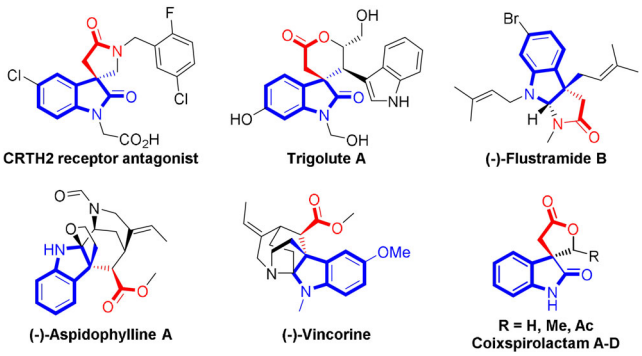


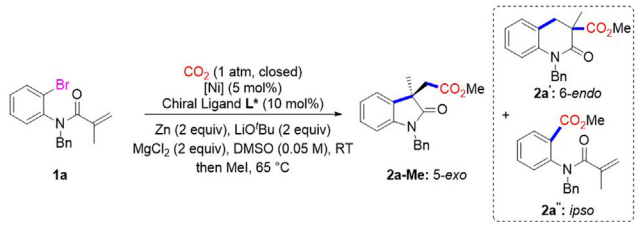
Figure 2. Bioactive indoline- and oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter.

carbo-carboxylation of aryl (pseudo)halides-tethered acrylamides using inexpensive transition-metal catalyst and non-toxic CO_2 as carboxyl source. To realize this transformation, several challenges need to be resolved. First, the transition metal-catalyzed reductive *ipso*-carboxylation of aryl halides has been widely studied in good efficiency,[8–10] which is highly competitive to the desired insertion of alkenes into reactive carbon-transition metal species, thus arising a chemoselectivity issue. Second, the insertion of alkenes into carbon–metal bonds must be achieved in high regio- and enantioselective fashion. Third, as CO_2 is a relatively inert electrophile, the final capture of the alkyl-metal species by CO_2 should be efficient to prevent side reactions,[20a,b] including protonation and homopolymerization. Herein, we report the first nickel-catalyzed asymmetric reductive carbo-carboxylation reaction of aryl halides-tethered alkenes and CO_2 under mild reaction conditions (Figure 1 B). Notably, as the oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter, which are generated in high chemo-, regio-, enantioselectivities, could transform into pyrroloindolines and spirolactam, privileged scaffolds widely existing in bioactive alkaloids, this strategy opens an avenue for the CO_2-involved enantioselective synthesis of biologically active natural products, including formal synthesis of (−)-Esermethole, (−)-Physostigmine and (−)-Physovenine, as well as the total synthesis of (−)-Debromoflustramide B, (−)-Debromoflustramine B and (+)-Coixspirolactam A.

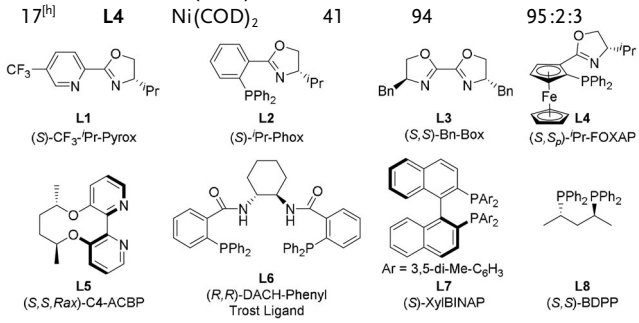
Results and Discussion

Our study was initiated by employing the *N*-benzyl-*N*-(2-bromophenyl)methacrylamide **1a** as the model substrate, $NiBr_2$·DME as nickel-precatalyst, zinc power as reductant, LiO^tBu as the base and $MgCl_2$ as Lewis acid to activate inert CO_2 (Table 1). We hypothesized that ligands might play an important role in achieving selective *cyclo* over *ipso* carboxylation. Several chiral ligands were first investigated at room temperature (entries 1–8). The reaction using electron-deficient (*S*)-CF_3-^{i}Pr-Pyrox (**L1**) gave the 5-*exo* product **2a-Me** in 27 % yield and 51 % *ee*; however, the ratio of 5-*exo*- (**2a-Me**), 6-*endo*- (**2a′**), to *ipso*-carboxylation (**2a″**) was low to 47:18:35 (entry 1). Replacing **L1** with relatively more electron-rich (*S*)-^{i}Pr-Phox (**L2**) could afford the product with higher enantioselectivity than **L1** (entry 2). Bisoxazoline ligand **L3** did not show any activity in this reaction (entry 3). Moreover, the reaction using bipyridyl ligand **L5** with central and axial chirality character afforded **2a** with 74 % *ee* and 73:7:20 ratio (entry 5). To our delight, when a chiral phosphine-oxazoline ligand linked with ferrocene scaffold **L4** was employed, the undesired *ipso* carboxylation and 6-*endo* cyclization were suppressed, the enantioselectivity dramatically elevated to 91 % and showed 95 % 5-*exo cyclo*-selectivity (entry 4). Other diphosphine ligands **L6–L8** also exhibited higher *cyclo*-selectivity than electron-deficient ligand **L1**, albeit with low enantioselectivity (entries 6–8). The investigation of nickel pre-catalysts showed that $Ni(COD)_2$ (entry 11) gave a slightly higher yield than $NiBr_2$·DME and $Ni(acac)_2$ (entry 10). When 15 mol % of **L4** was used, the desired product **2a** was isolated

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



Entry	L*	[Ni]	Yield[b] [%]	*ee*[c] [%]	2a-Me:2a′:2a″[d]
1	**L1**	$NiBr_2$·DME	27	51	47:18:35
2	**L2**	$NiBr_2$·DME	11	90	20:17:63
3	**L3**	$NiBr_2$·DME	trace	–	–
4	**L4**	$NiBr_2$·DME	83	91	95:2:3
5	**L5**	$NiBr_2$·DME	54	74	73:7:20
6	**L6**	$NiBr_2$·DME	< 5	–	67:20:13
7	**L7**	$NiBr_2$·DME	44	−2	92:2:6
8	**L8**	$NiBr_2$·DME	23	−39	85:2:13
9	**L4**	$NiCl_2$·DME	70	92	96:2:2
10	**L4**	$Ni(acac)_2$	78	92	96:2:2
11	**L4**	$Ni(COD)_2$	85	92	95:2:3
12[e]	**L4**	$Ni(COD)_2$	88	94	95:2:3
13	**L4**	w/o [Ni]	N.R.	–	–
14	–	$Ni(COD)_2$	trace	–	–
15[f]	**L4**	$Ni(COD)_2$	N.R.	–	–
16[g]	**L4**	$Ni(COD)_2$	60	94	94:4:2
17[h]	**L4**	$Ni(COD)_2$	41	94	95:2:3



[a] Conditions: **1a** (0.2 mmol), $NiBr_2$·DME (5 mol%), chiral ligand **L*** (10 mol%), Zn (2 equiv), LiO^{t}Bu (2 equiv), $MgCl_2$ (2 equiv) in solvent (4 mL) at room temperature (RT) for 48 h. [b] The isolated yields of **2a-Me** after column chromatography purification on silica gel. [c] Enantiomeric excess (*ee*) values were determined by chiral high performance liquid chromatography (HPLC) analysis. [d] Determined with gas chromatography (GC). [e] 15 mol% of **L4** was used. Isolated as acid after treating with 2 M HCl. [f] Without Zn. [g] Without LiO^{t}Bu. [h] Without $MgCl_2$. DME = Dimethoxyethane. COD = 1,5-cyclooctadiene. N.R. = No reaction. DMSO = Dimethyl Sulfoxide.

in 94% *ee* and 88% yield (entry 12). Further systematical investigation of bases and solvents failed to give superior results than entry 12 (see the Supporting Information for details). Control experiments showed that Ni-catalyst, ligand and Zn were all indispensable in this reductive transformation (entries 13–15). Furthermore, the basic LiO^{t}Bu and Lewis acidic $MgCl_2$ additive were also important for this transformation to achieve high yield (entries 16–17).

After establishing the optimal reaction conditions, we first examined several *N*-protecting groups of acrylamides. As shown in Table 2, various kinds of *N*-alkyl groups with different electronic properties could be well tolerated. Notably, acrylamides with *N*-allyl groups, such as 2-methyl propenyl (**1i**), prenyl (**1j**), cinnamyl (**1k**), which might undergo potential competitive 5-*exo* cyclization, also showed comparable reactivity and selectivity (55–89% yields, 84–94% *ee*).

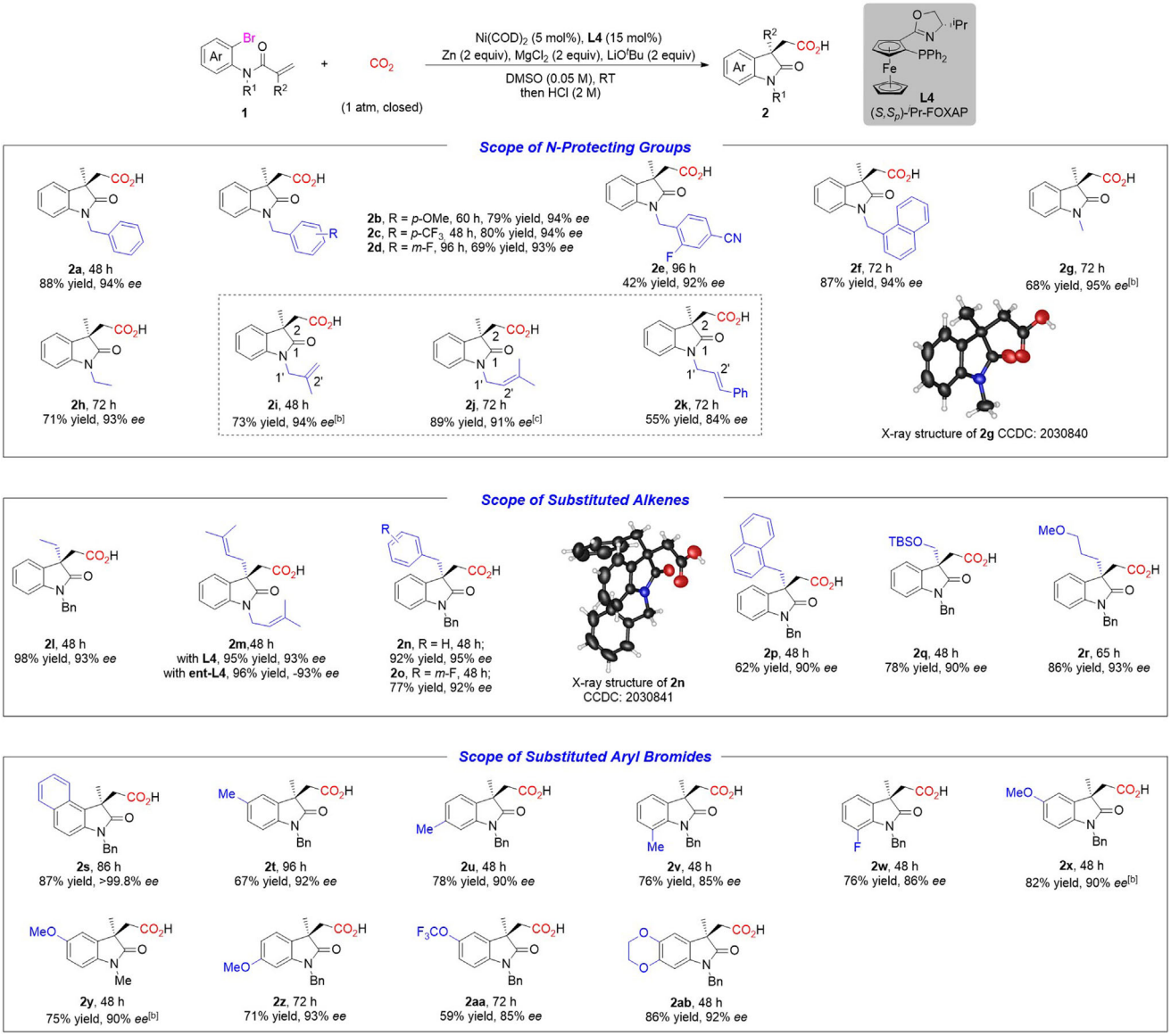
Next, the diversity of alkene motifs was also explored. Comparing with the alkenes bearing methyl group, those with more hindered alkyl groups, such as ethyl (**1l**), prenyl (**1m**), benzyl (**1n–1o**), 1-naphthalene methyl (**1p**), silyl ether (**1q**) and alkyl ether (**1r**) groups, could also react well to give desired products **2l–2q** in good yields (62–98%) and excellent enantioselectivities (90–96% *ee*). When the ***ent*-L4** was used as ligand, ***ent*-2m** can be obtained with a 96% yield and 93% *ee*. When the methyl group on the alkene moiety was replaced with phenyl group, only 6-*endo* product was detected.

Furthermore, we investigated the scope of aryl bromides. The substrate with 1-bromonaphthalene (**1s**) afforded the product **2s** in distinct yield (87%) and near optical purity (> 99.8% *ee*). The methyl group at *meta* and *para* position (**1t–1u**) did not affect the reaction. However, the methyl group (**1v**) and carbon−fluoro bond (**1w**) at *ortho* position induced slightly lower *ee* value (85–85.5% *ee*), which might arise from the steric hindrance. Besides, substrates bearing methoxy (**1x–1z**), trifluoromethoxy (**1aa**) groups and oxygenated heterocycles (**1ab**) reacted well to give good to excellent cyclo-selectivity and enantioselectivities. But the bromoarene bearing strong electron-withdrawing groups, such as CN, CO_2Me and CF_3 groups, led to poor selectivity. The chemical structure and absolute configuration of (*R*)-**2g** (CCDC 2030840) and (*R*)-**2n** (CCDC 2030841) were further assigned by single-crystal X-ray diffraction analysis.[22] The stereochemistry of other compounds was assigned by analogy.

Considering the similar reactivity of aryl sulfonates to halides, we further tested aryl triflates in this transformation (Table 3). Indeed, the desired products **2** could be obtained with high enantiopurities. The moderate yields arise from competitive protonation.

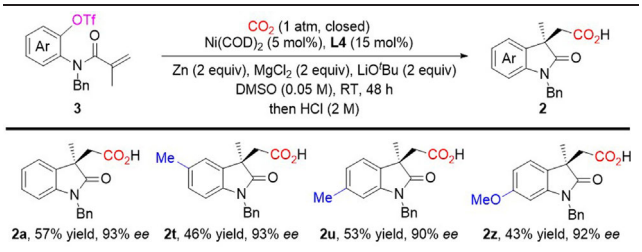
Encouraged by these results, we further explored more accessible but challenging aryl chlorides, which show lower reactivity and have been rarely investigated in asymmetric reductive difunctionalization of unsaturated bonds.[20a,g] To our delight, these aryl chlorides-tethered acrylamides reacted smoothly with CO_2 under the same reaction conditions (Table 4). Moreover, the reaction of aryl chloride **4a** gave **2a** in a higher yield of 96% and a slightly better *ee* value of 95% than the result (88% yield, 94% *ee*) of corresponding bromide **1a**. Changing the *N*-protecting group with methyl (**4b**) and geranyl (**4c**) also gave the product with high yields and enantioselectivities. An array of aryl chlorides with different functional groups, such as methyl (**4d–4f**), methoxy (**4g–4h**), fluoro (**4i**), trifluoromethyl (**4j**) reacted well to generate the desired products in good to excellent yields and enantioselectivities (85–95% *ee*). Swapping the methyl group on the alkene motif with the benzyl group (**4l**, **4m**) provided the carbo-carboxylation products with commendable yields and enantioselectivities (90% yield, 94–95% *ee*). A challenging substrate **4k**, in which the C−Cl bond is deactivated with electron-donating methoxyl group at the *ortho* position, could

Table 2: Substrate scope of aryl bromides.[a]



[a] Conditions: substrate **1** (0.3 mmol), $Ni(COD)_2$ (5 mol%), **L4** (15 mol%), Zn (2 equiv), LiO^tBu (2 equiv), $MgCl_2$ (2 equiv) in 6 mL DMSO at RT. Isolated yields are given and *ee* values were determined by chiral HPLC analysis. [b] $Ni(COD)_2$ (10 mol%), **L4** (30 mol%). [c] $NiBr_2$·DME (10 mol%), **L4** (30 mol%).

Table 3: Substrate scope of aryl triflates.[a]



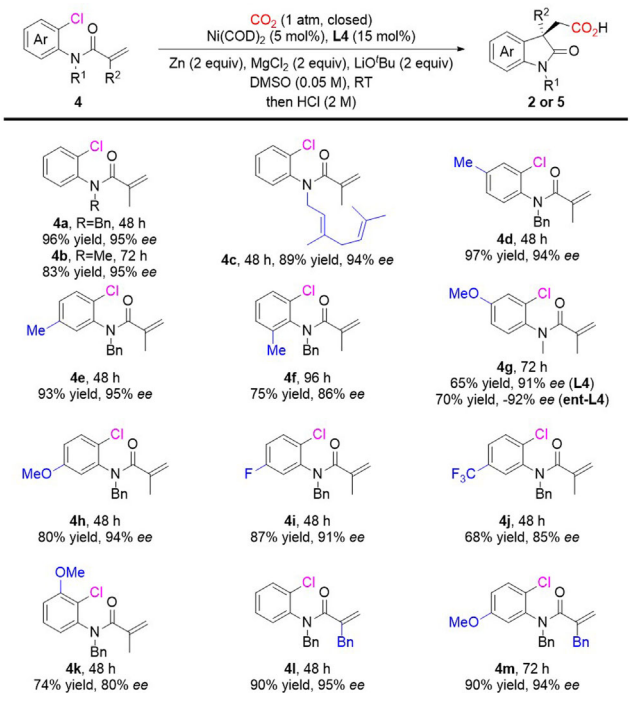
[a] Conditions: substrate **3** (0.3 mmol), $Ni(COD)_2$ (5 mol%), **L4** (15 mol%), Zn (2 equiv), LiO^tBu (2 equiv), $MgCl_2$ (2 equiv) in 6 mL DMSO at RT. Isolated yields are given and *ee* values were determined by chiral HPLC analysis.

also react well to give the desired product in 74% yield albeit with 80% *ee*.

The synthetic utility of this protocol was first demonstrated by the scale-up reaction of **1m** in a 3 mmol scale. With (R,R_p)-^{i}Pr-FOXAP as the ligand, the desired product ***ent*-2m** could be obtained in 72% yield and 93% *ee* along with 18% starting material recovery (Scheme 1A). Additionally, selective C5- bromination of **2a** took place smoothly to give **6** in 94% yield and 91% *ee*. Moreover, **2a** could be reduced by BH_3·SMe_2 in high efficiency to generate useful chiral indoline **7** with a C3 quaternary stereocenter, which is a key intermediate for MNKS inhibitors synthesis (Scheme 1B).[23]

To highlight the utility of this methodology, we sought to employ it in the synthesis of bioactive natural products. As (−)-Debromoflustramine B, (−)-Esermethole, (−)-Phys-

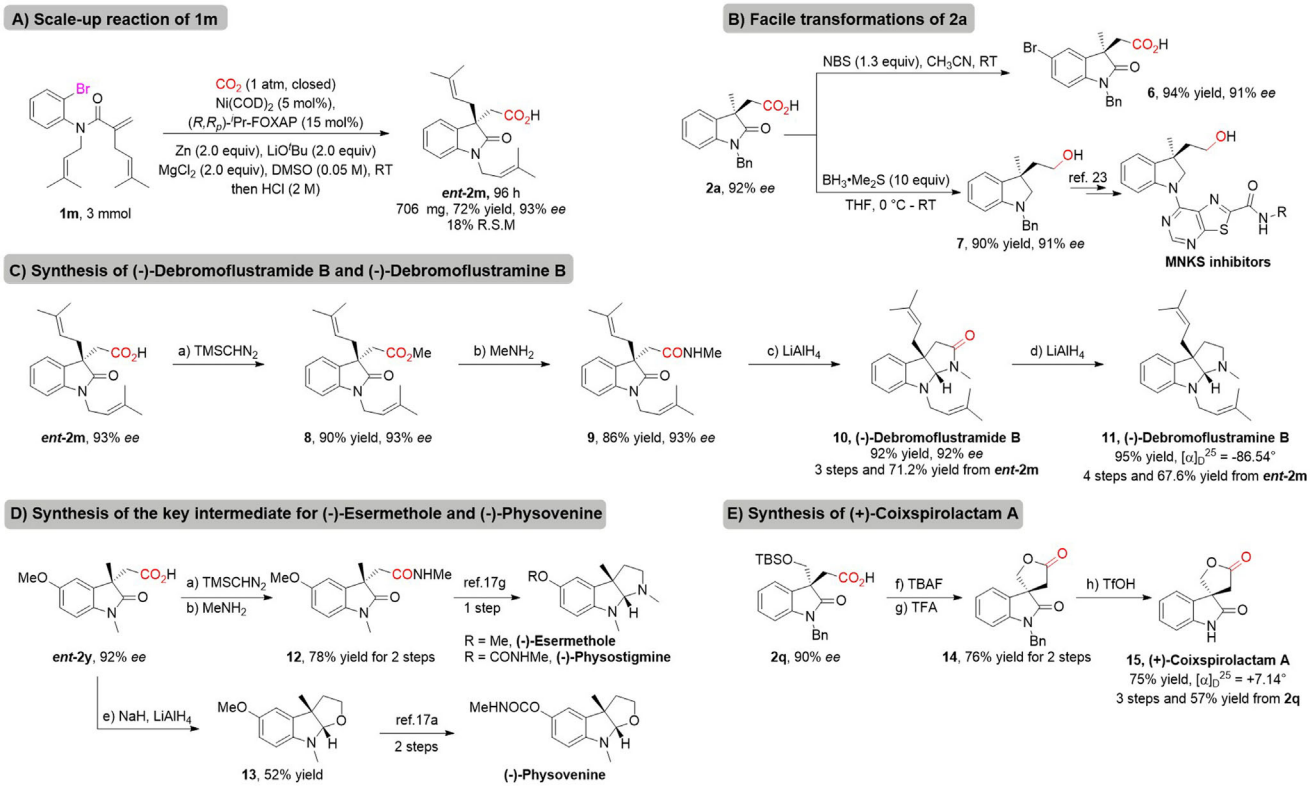
Table 4: Substrate scope of aryl chlorides.[a]



[a] Conditions: substrate **3** (0.3 mmol), $Ni(COD)_2$ (5 mol%), **L4** (15 mol%), Zn (2 equiv), LiO^tBu (2 equiv), $MgCl_2$ (2 equiv) in 6 mL DMSO at RT. Isolated yields are given and *ee* values were determined by chiral HPLC analysis.

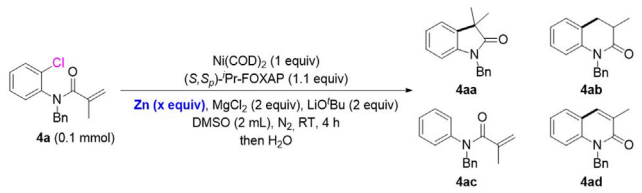
ovenine show remarkable bioactivity, such as cholinesterase inhibition.[24] Several groups have realized the asymmetric total synthesis.[17] However, many methods suffer from the use of precious metal catalysts or toxic reagents. Therefore, we aimed to develop a concise route to the valuable nature product by using the nickel-catalyzed asymmetric carbo-carboxylation as a key step. First, ***ent*-2m** could undergo efficient esterification to give compound **8** in 90% yield with $TMSCHN_2$. Second, the ammonolysis of ester **8** in the presence of methylamine afforded amide **9** with 86% yield, which took part in the reductive cyclization in the presence of $LiAlH_4$ to give (−)-Debromoflustramide B **10**. Moreover, further reduction of **10** yielded bioactive (−)-Debromoflustramine B **11**, which showed 7500 times more potent than its *dextro*-enantiomer in biological testing.[24c] This process went through four steps with 68% total yield and the enantioselectivity maintained well (Scheme 1C). Similarly, the product ***ent*-2y** can be easily transformed to amide **12**, which is a key intermediate in the facile synthesis of (−)-Esermethole and (−)-Physostigmine.[17g] Besides, ***ent*-2y** can also be transformed to furoindoline scaffold **13**, which is a key intermediate to the synthesis of (−)-Physovenine (Scheme 1D).[17a] Furthermore, successively treating **2q** with TBAF and TFA yielded spironolactone **14**. The following debenzylation of **14** gave the natural product (+)-Coixspirolactam A **15** with 57% total yield from **2q** in 3 steps (Scheme 1E).

To gain more insight into this selective reductive carbo-carboxylation, stoichiometric reactions using equivalent



Scheme 1. Synthetic utility. A) Scale-up reaction of **1m**. B) Facile transformations of **2a**. C) Synthesis of (−)-Debromoflustramide B and (−)-Debromoflustramine B. D) Synthesis of the key intermediate for (−)-Esermethole and (−)-Physovenine. E) Synthesis of (+)-Coixspirolactam A. a) $TMSCHN_2$ (4 equiv), MeOH/Et_2O, 0 °C–RT; b) $MeNH_2$ (33 wt% in EtOH), 60 °C; c) $LiAlH_4$ (10 equiv), THF, 0 °C–RT; d) $LiAlH_4$ (10 equiv), THF, reflux. e) NaH (2.5 equiv), THF, 0 °C–RT; then $LiAlH_4$ (4 equiv), 0 °C–RT. f) TBAF (4 equiv), THF, 0 °C–RT. g) TFA (1 drop), DCM, 0 °C–RT. h) TfOH (15 equiv), toluene, 120 °C.

Table 5: Control experiments.[a]



Entry	*x*	**4aa** [%]	**4ab** [%]	**4ac** [%]	**4ad** [%]
1	0	6	36	<5	17
2	2	8	38	<5	<5
3	3	13	34	<5	<5
4	5	52	23	<5	<5
5	10	56	31	<5	<5

[a] GC yields.

$Ni(COD)_2$ were conducted under N_2 to determine the possible intermediates (Table 5). In the absence of Zn, 36% of 6-*endo* product **4ab** was obtained along with 17% of β-H elimination product **4ad** and <5% of **4ac** formation. Interestingly, the expected 5-*exo* product **4aa** was formed in just only 6% yield. By increasing the loading of Zn reductant from 0 to 10 equivalents, we observed the yield of 5-*exo* product **4aa** improved a lot. These control experiments indicated that Ar-Ni^{II}L* generated from oxidative addition might favor 6-*endo* cyclization but the Ar-Ni^{I}L*, which is formed in situ through single-electron reduction of Ar-Ni^{II}L* by Zn, might favor a 5-*exo* cyclization. This investigation provides new insight into the Ni-catalyzed reductive cyclization.

Based on the experimental observation and previous reports, the possible mechanism was proposed in Figure 3. First, the oxidative addition of carbon–(pseudo)halides bonds to Ni^{0}L* **I** gave Ar-Ni^{II}L* species **II**, which might undergo a Zn-mediated single electron reduction to give a Ar-Ni^{I}L* species **III** (path A). The following enantioselective 5-*exo* cyclization would afford an alkyl-Ni^{I}L* intermediate **IV**.[20d] Meanwhile, Ar-Ni^{II}L* species **II** might also go through 5-*exo* cyclization to afford alkyl-Ni^{II}L* intermediate **V**, which could be reduced by Zn to yield the intermediate **IV** (path B). Subsequent nucleophilic attack of **IV** to CO_2 gave Ni^{I}-carboxylate **VI**. Further reduction and transmetalation could yield the carboxylate **VII** and regenerate reactive Ni^{0}L* **I**. Final workup of the reaction with hydrolysis of **VII** gave the desired product **VIII**. Additionally, Ar-Ni^{II}L* species **II** might proceed 6-*endo* cyclization to form relative stable Ni^{II}L* enolate species **IX**, which could form the byproduct **X**. The *ipso*-carboxylation byproduct **XI** might result from the nucleophilic attack of Ar-Ni^{I}L* species **III** to CO_2 according to previous reports.[9b,10b]

Conclusion

In conclusion, we have developed the first nickel-catalyzed asymmetric reductive carbo-carboxylation of alkenes using sustainable CO_2 as the carboxyl source, which provides an efficient approach to the synthesis of versatile oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter. Aside from aryl bromides, other aryl electrophiles, such as triflates and chlorides, are also amenable in this reaction. This transformation features mild reaction conditions, wide substrate scope, facile scalability, with good chemo-, regio- and enantioselectivity. The utility of this methodology is highlighted by the formal synthesis of (−)-Esermethole, (−)-Physostigmine and (−)-Physovenine, as well as the total synthesis of (−)-Debromoflustramide B, (−)-Debromoflustramine B and (+)-Coixspirolactam A, opening an avenue for the total synthesis of chiral natural products with CO_2.

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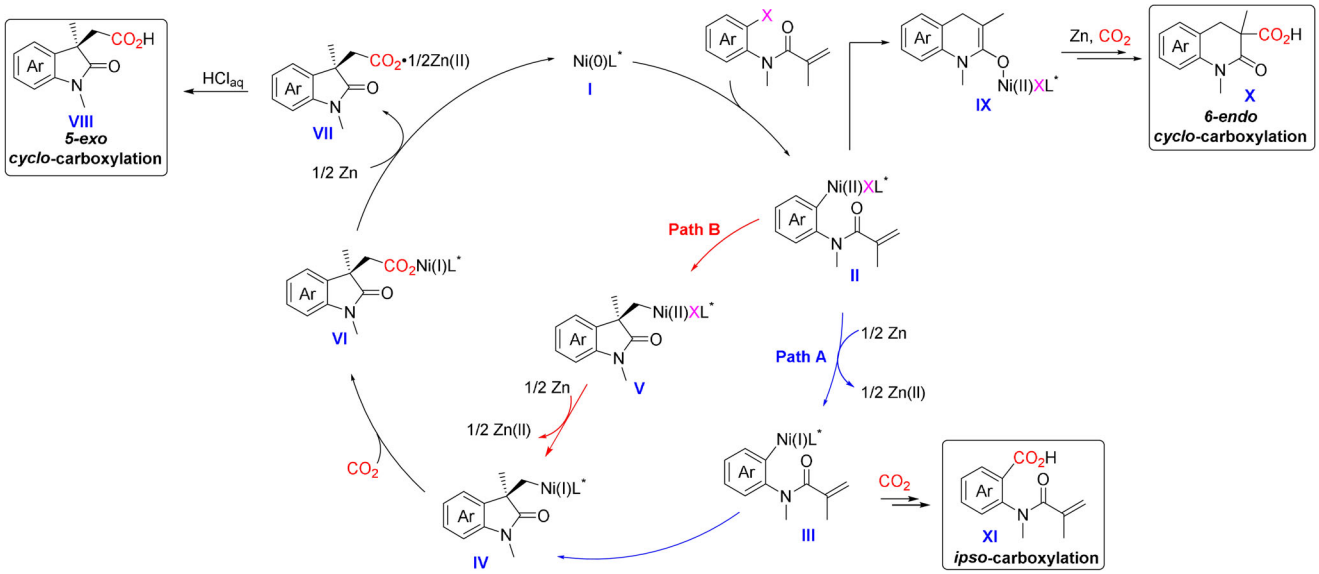

Figure 3. Proposed mechanism.

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Conflict of interest

On March 29, 2021, a Chinese Patent on this work was applied for with the number (202110330170.6).

Keywords: alkenes · carbo-carboxylation · carbon dioxide · nickel

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[22] Deposition Numbers 2030840 (for **2g**), and 2030841 (for **2n**) contain 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 www.ccdc.cam.ac.uk/structures.

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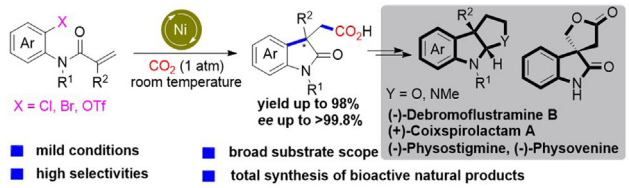
Research Articles

Asymmetric Synthesis

X.-W. Chen, J.-P. Yue, K. Wang, Y.-Y. Gui, Y.-N. Niu, J. Liu, C.-K. Ran, W. Kong,* W.-J. Zhou, D.-G. Yu* ____ ▮▮▮▮–▮▮▮▮

Nickel-Catalyzed Asymmetric Reductive Carbo-Carboxylation of Alkenes with CO_2



A strategy is presented for nickel-catalyzed asymmetric reductive carbo-carboxylation of alkenes with CO_2. A variety of aryl (pseudo)halides react to produce oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter. Notably, synthesis of a range of bioactive pyrroloindolines was achieved.