Literature Report

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

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Checker: Wen-Jun Huang
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CV of Prof. Da-Gang Yu

Background:

- **2003 - 2007** B.S., Sichuan University
- **2007 - 2012** P.D., Peking University
- **2012 - 2014** Postdoc., University of Münster
- **2015 - now** Professor, Sichuan University

Research:

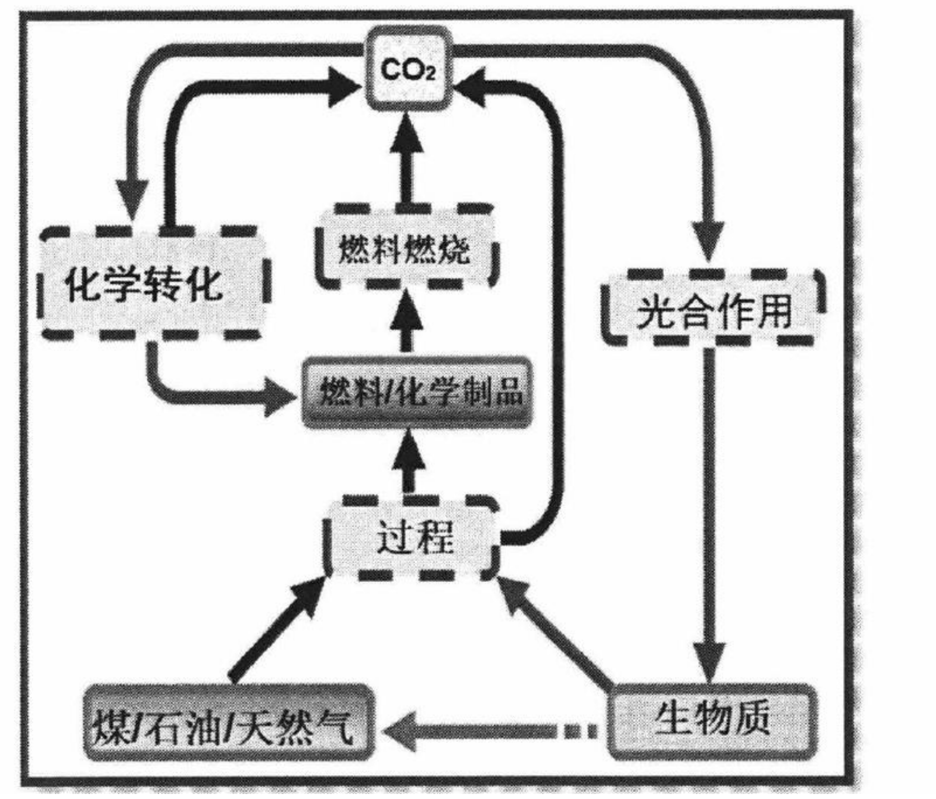
Green and Sustainable Organic Synthesis (CO_2 utilization, visible-light photocatalysis)

Novel Transition Metal-Catalysis (especially Cu- and Fe-catalysis).

Contents

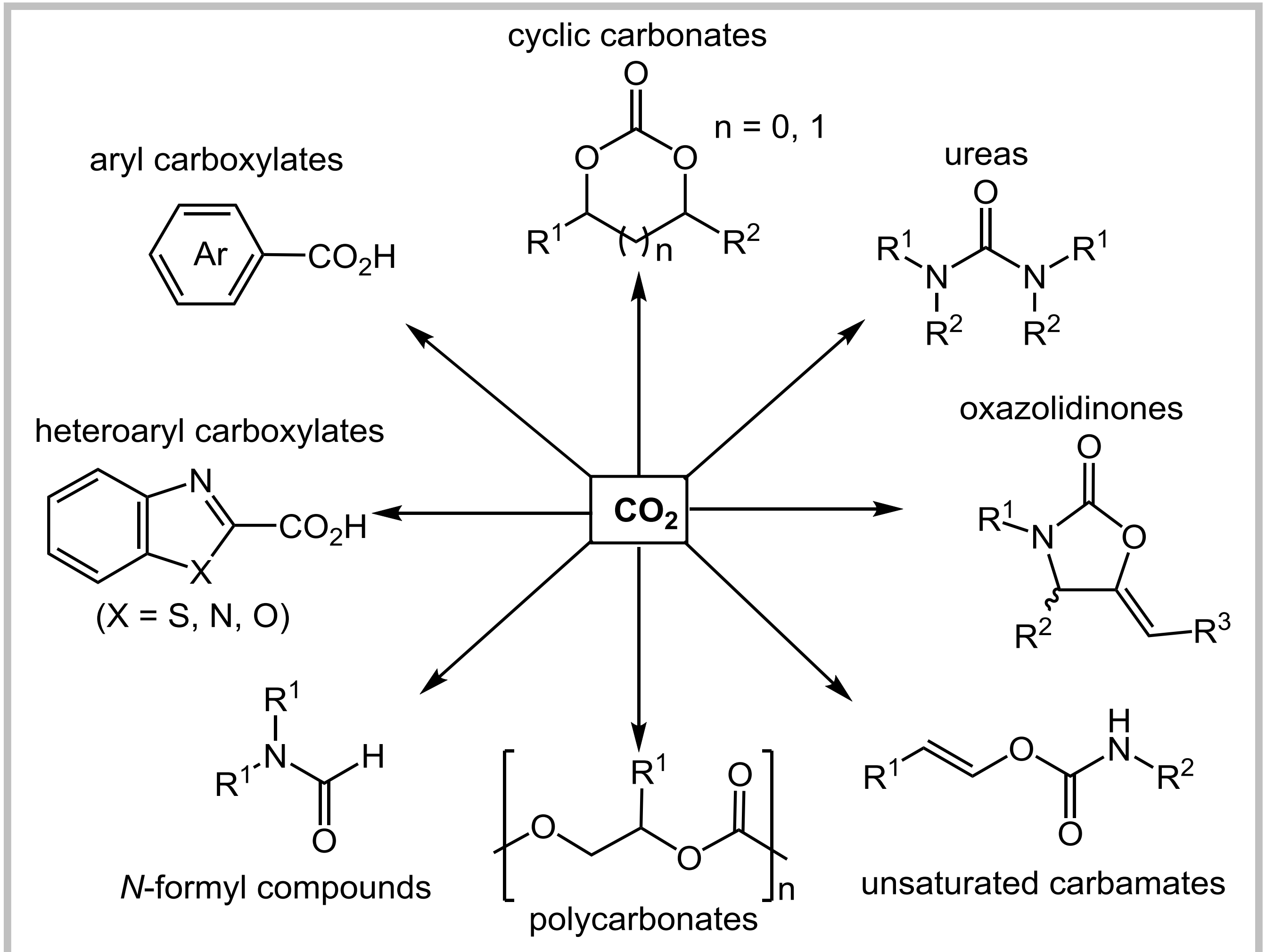
Introduction

二氧化碳（CO_2）既是空气中的重要组分，也是广泛存在、廉价易得、无毒、稳定和可再生循环使用的“碳一”（C1）资源。但是随着各国二氧化碳排放，温室气体猛增，对生命系统形成威胁。



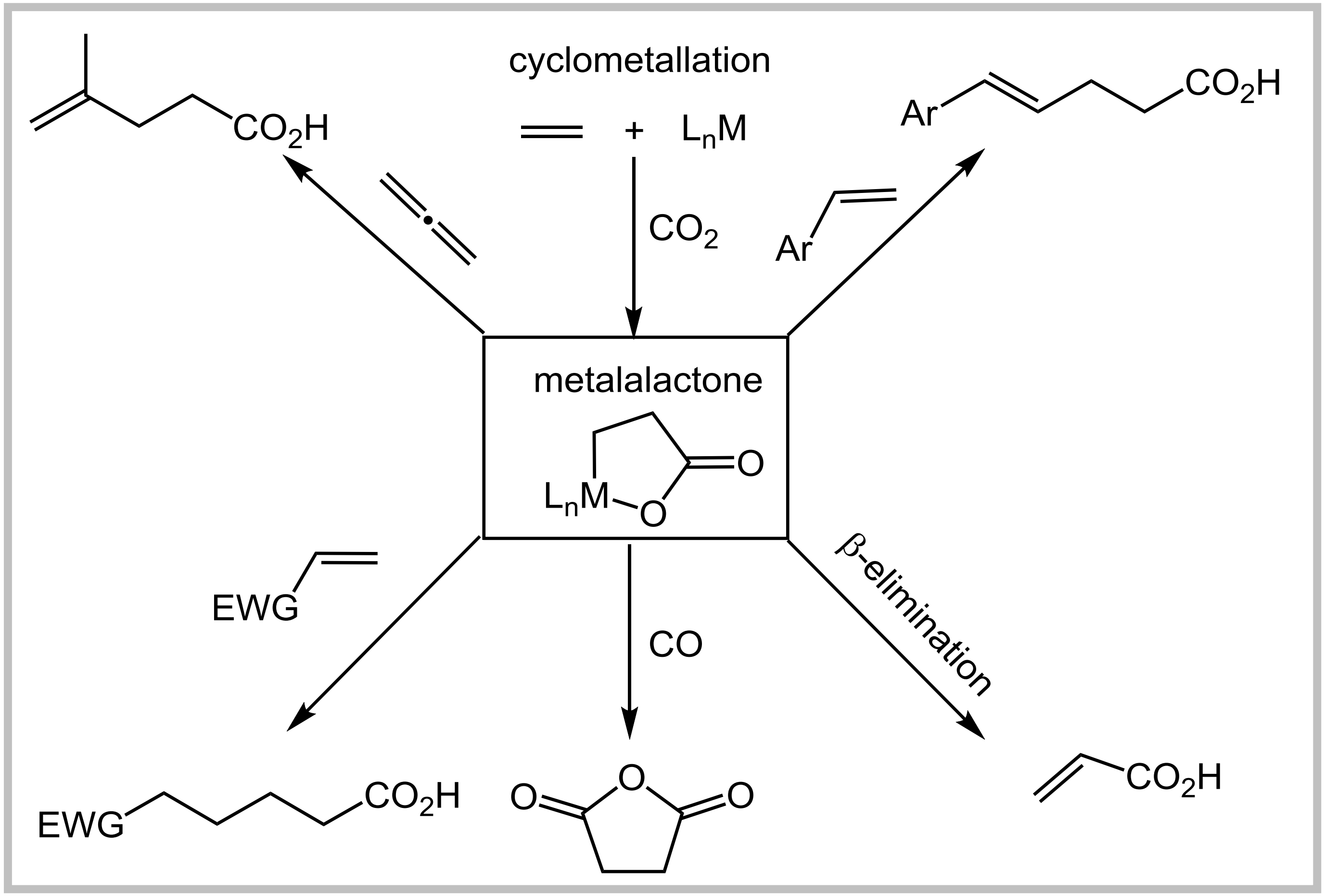
Introduction

Synthesis of various organic products from CO_2



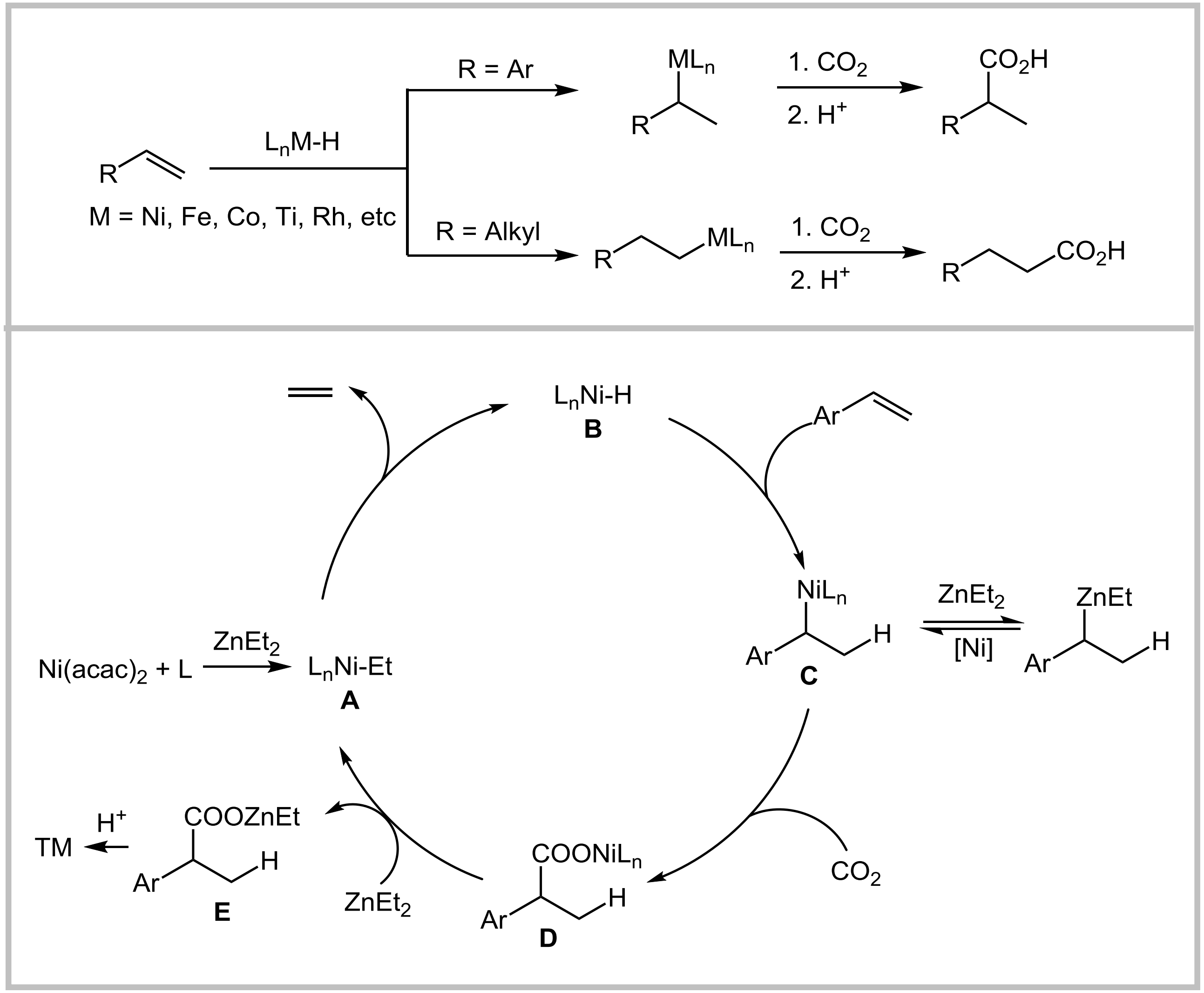
Introduction

Cyclometallation and the transformation of metalalactone



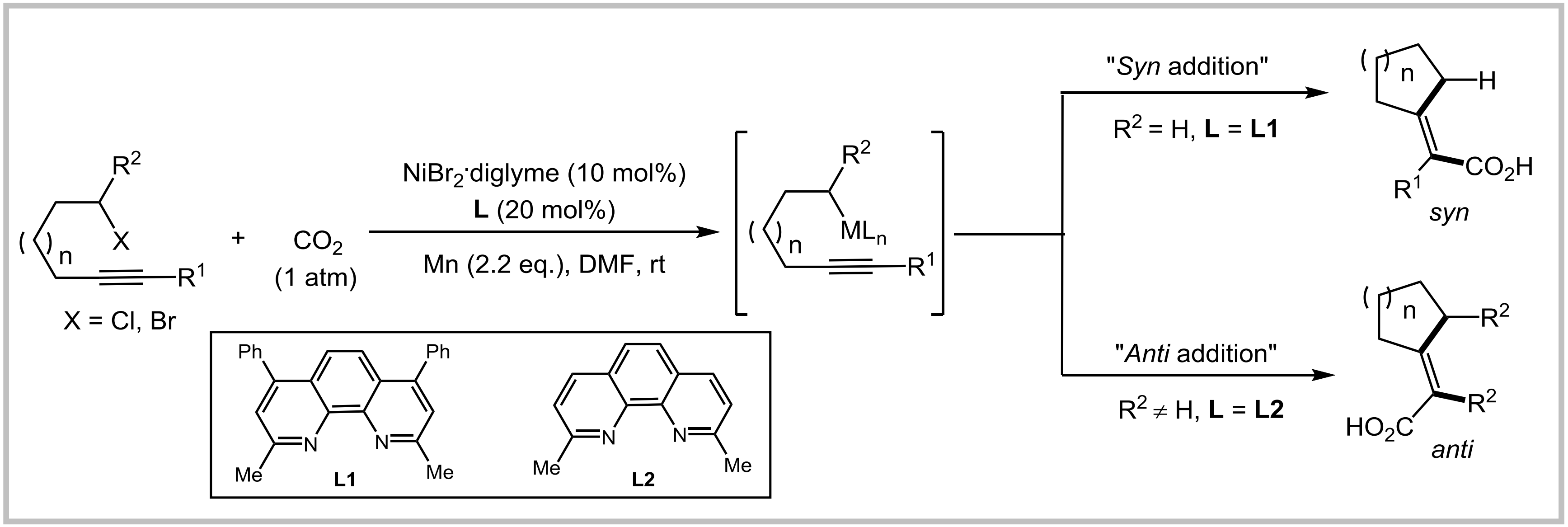
Introduction

Metal hydride



Introduction

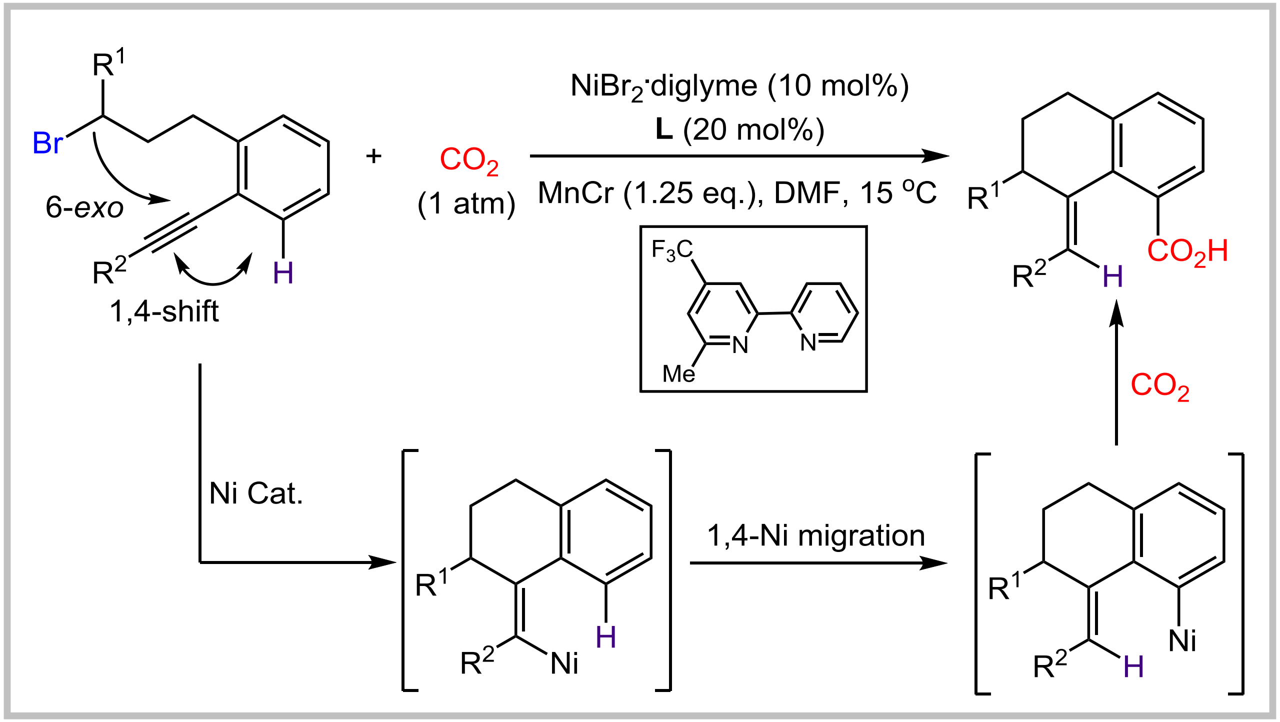
Ni-catalyzed cyclization/carboxylation of alkynes with CO_2



Martin, R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6476-6479.

Introduction

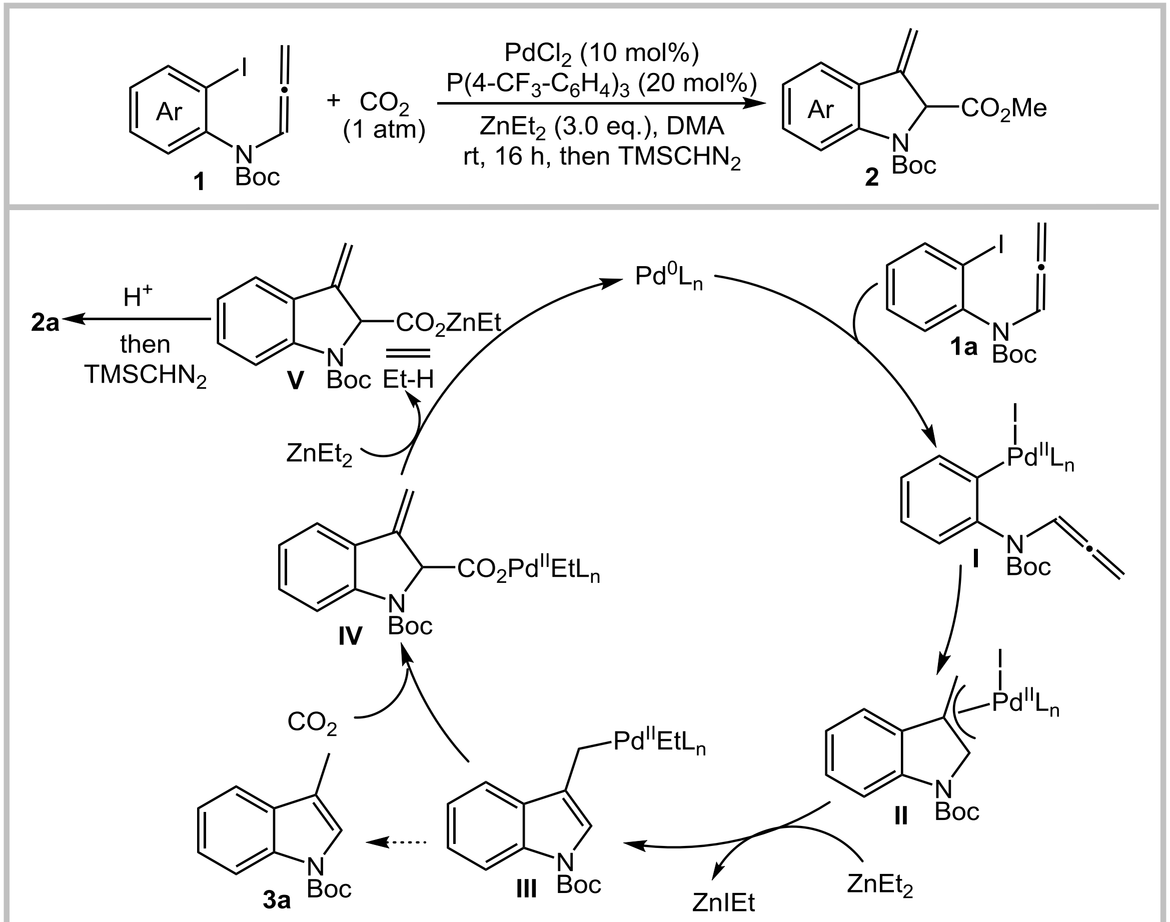
Ni-catalyzed cyclization/carboxylation of alkynes with CO_2



Martin, R. *et al*. *J. Am. Chem. Soc*. **2020**, *142*, 16234-16239.

Introduction

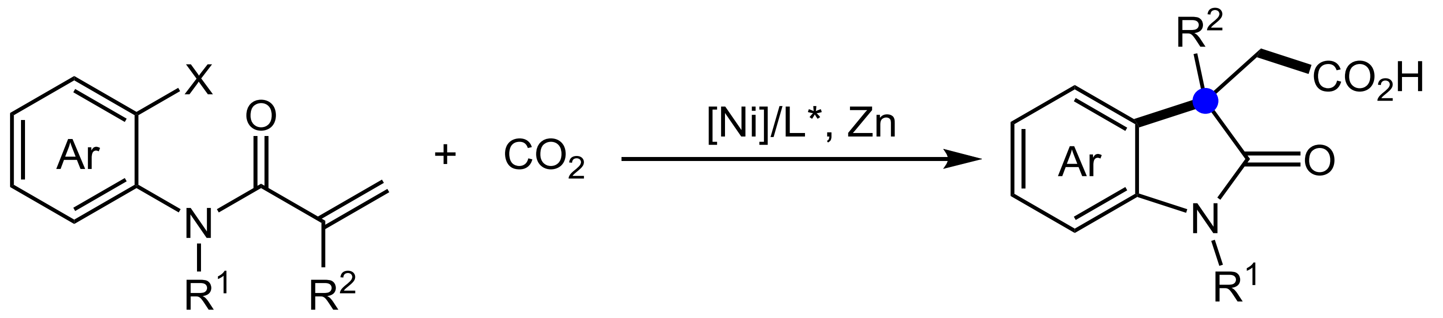
Pd-catalyzed cyclization/carboxylation of allenes with CO_2



Sato, Y. *et al. Org. Lett*. **2017**, *19*, 2710-2713.

Introduction

Ni-catalyzed cyclization/carboxylation of alkenes with CO_2

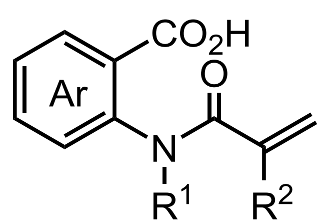


X = Cl, Br, OTf

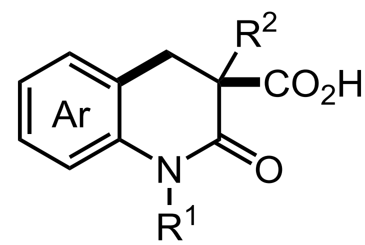
up to 98% yield, > 99.8% ee

Challanges:

- ♦competitive *ipso*-carboxylation
- ♦regioselective carbo-metallation
- ♦enantioselective control



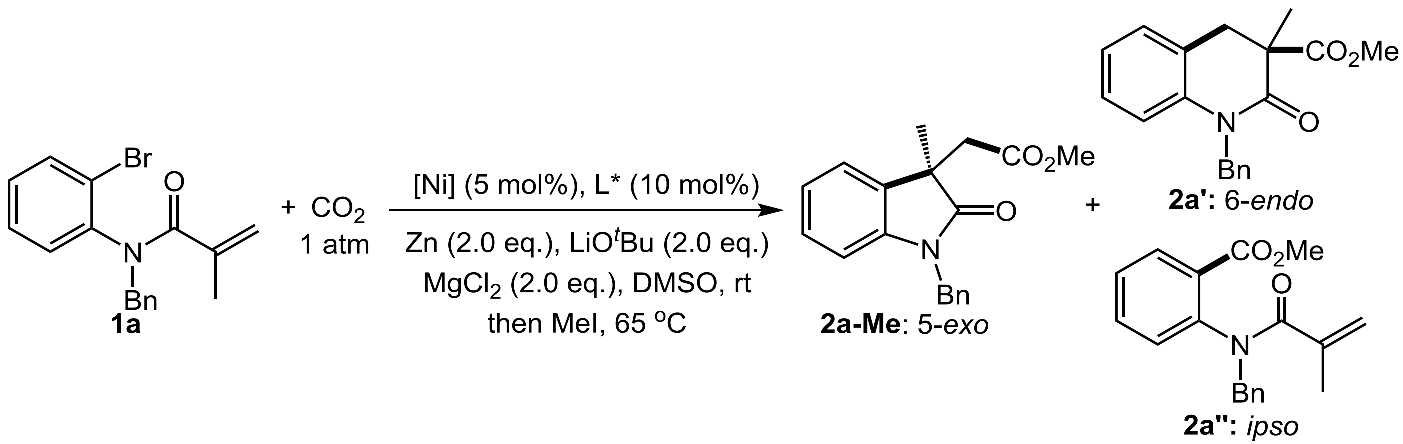
ipso-carboxylation



6-*endo* cyclization

Yu, D.-G. *et al*. *Angew. Chem. Int. Ed.* **2021**, *60*, ASAP.

Optimization of the Reaction Conditions



Entry [a]	L*	[Ni]	Yield [b] (%)	Ee [c] (%)	**2a-Me:2a':2a''**[d]
1	**L1**	$NiBr_2{\cdot}DME$	27	51	47:18:35
2	**L2**	$NiBr_2{\cdot}DME$	11	90	20:17:63
3	**L3**	$NiBr_2{\cdot}DME$	trace	/	/
4	**L4**	**$NiBr_2{\cdot}DME$**	**83**	**91**	**95:2:3**
5	**L5**	$NiBr_2{\cdot}DME$	54	74	73:7:20

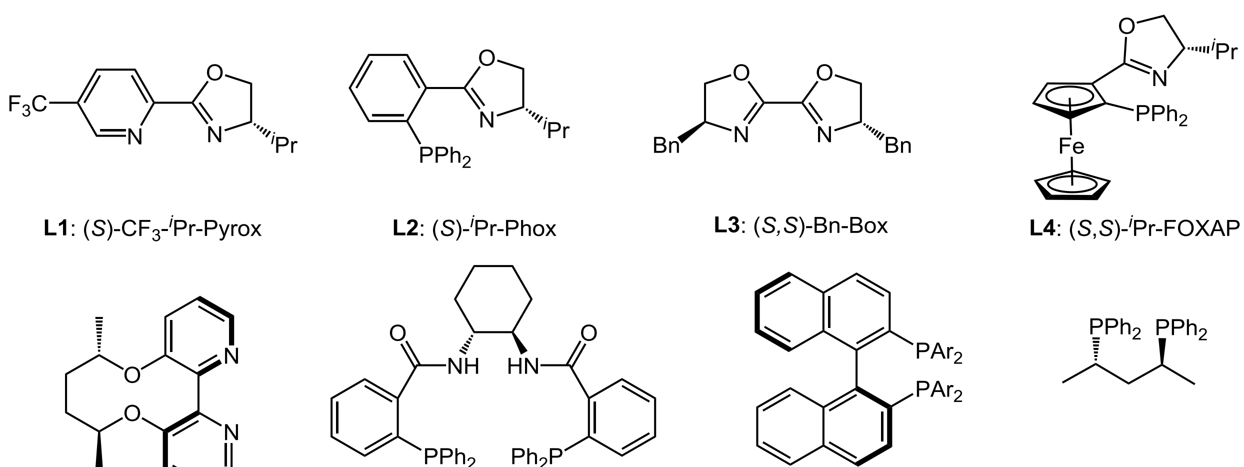
Optimization of the Reaction Conditions

Entry [a]	L*	[Ni]	Yield [b] (%)	Ee [c] (%)	**2a-Me: 2a':2a''**[d]
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[e]	**L4**	$Ni(COD)_2$	85	92	95:2:3
12	**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

Optimization of the Reaction Conditions

Entry [a]	L*	[Ni]	Yield [b] (%)	Ee [c] (%)	**2a-Me: 2a':2a''**[d]
17[h]	**L4**	$Ni(COD)_2$	41	94	95:2:3

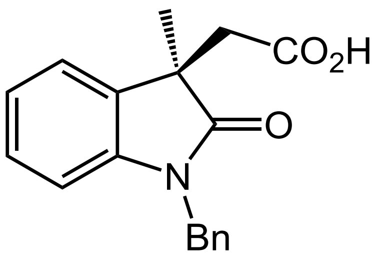
[a] Conditions: **1a** (0.2 mmol), $NiBr_2$·DME (5 mol%), chiral ligand **L*** (10 mol%), Zn (2 equiv), LiO^{t}Bu (2 equiv), $MgCl_2$ (2 equiv) in solvent (4 mL) at room temperature (rt) for 48 h. [b] The isolated yields of **2a-Me** after column chromatography purification on silica gel. [c] Enantiomeric 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 2M HCl. [f] Without Zn. [g] Without LiOtBu. [h] Without $MgCl_2$.



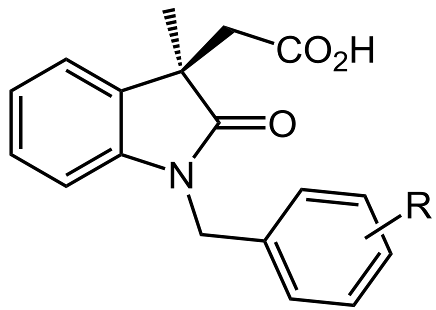
L1: (*S*)-CF_3-^{i}Pr-Pyrox **L2**: (*S*)-^{i}Pr-Phox **L3**: (*S*,*S*)-Bn-Box **L4**: (*S*,*S*)-^{i}Pr-FOXAP

L5:(*S*,*S*,*R*)-C4-ACBP **L6**: DACH-Phenyl Trost Ligand Ar = 3,5-di-Me-C_6H_3 **L7**: (*S*)-XylBINAP **L8**: (S,S)-BDPP

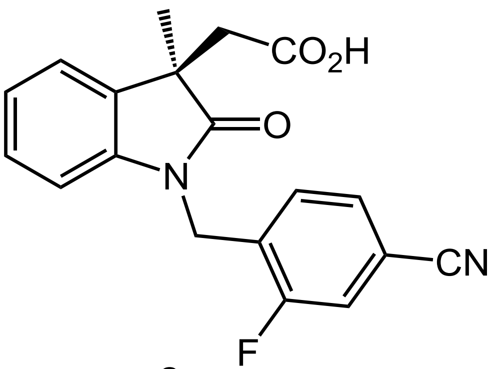
Substrate Scope of Aryl Bromides (*N*-PG)



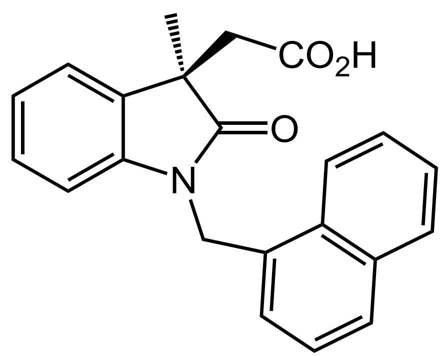
2a
88% yield, 94% ee



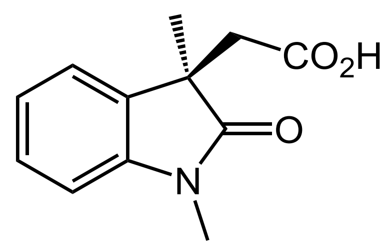
2b, R = *p*-MeO, 79% yield, 94% ee
2c, R = *p*-CF_3, 80% yield, 94% ee
2d, R = *m*-F, 69% yield, 93% ee



2e
42% yield, 92% ee

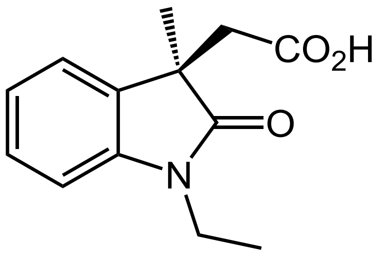


2f
87% yield, 94% ee



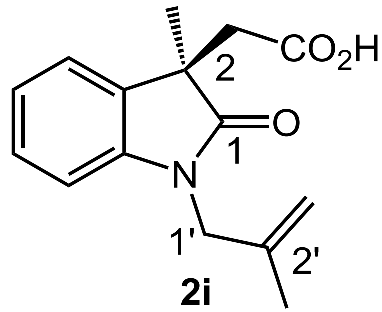
2g
68% yield, 95% ee

Substrate Scope of Aryl Bromides (*N*-PG)



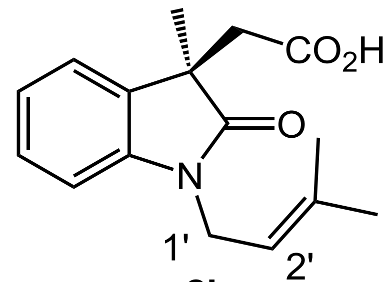
2h

71% yield, 93% ee



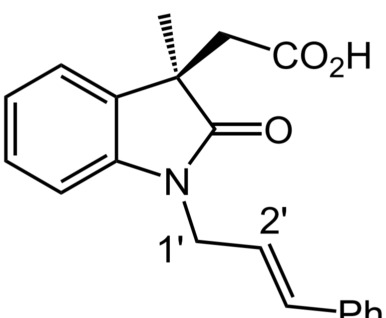
2i

73% yield, 94% ee



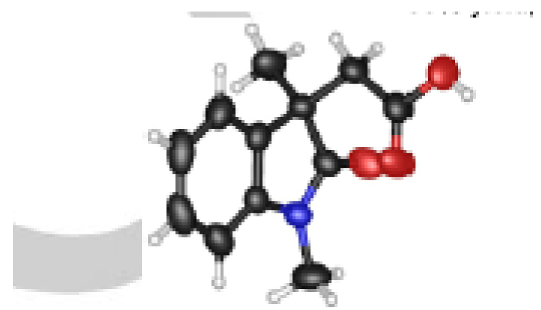
2j

89% yield, 91% ee



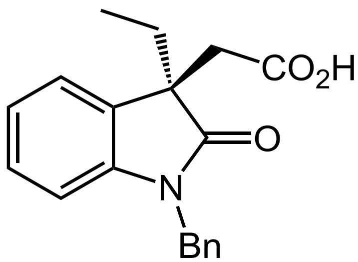
2k

55% yield, 84% ee

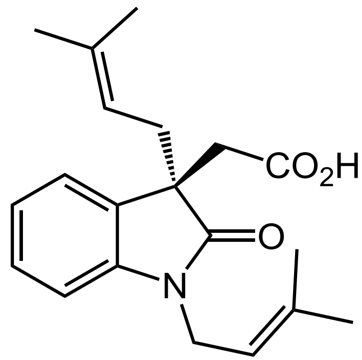


X-ray structure of **2g** CCDC: 2030840

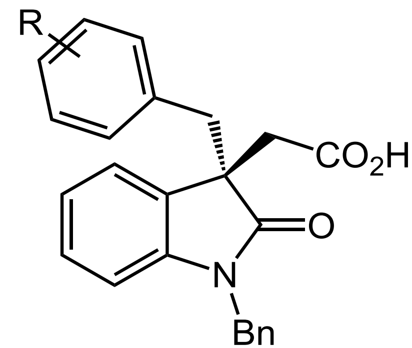
Substrate Scope of Aryl Bromides (Alkenes)



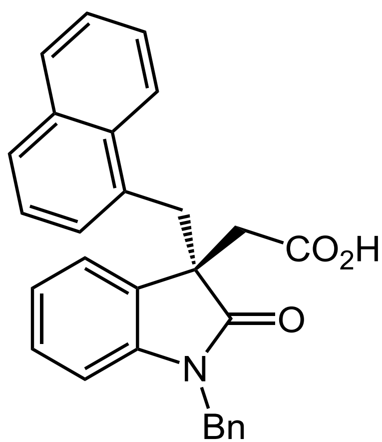
2l
98% yield, 93% ee



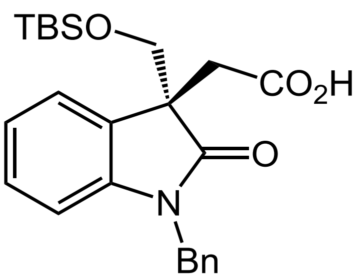
2m
95% yield, 93% ee



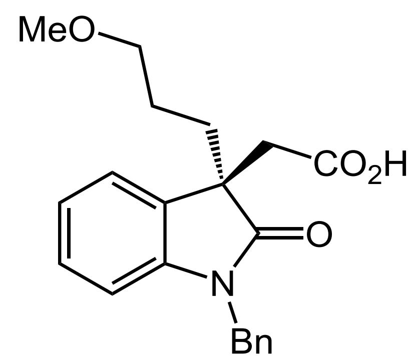
2n, R = H, 92% yield, 95% ee
2o, R = *m*-F, 77% yield, 92% ee



2p
62% yield, 90% ee

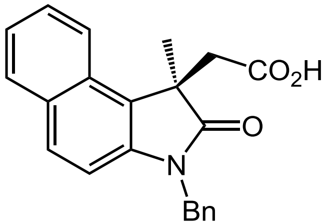


2q
78% yield, 90% ee

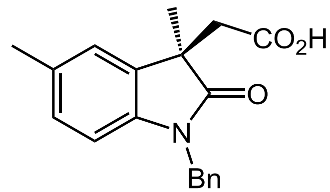


2r
86% yield, 93% ee

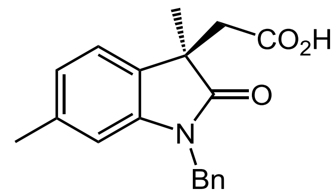
Substrate Scope of Aryl Bromides (Aryl bromides)



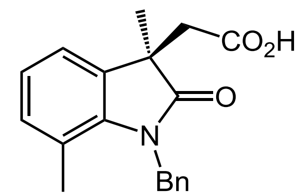
2s
87% yield, >99.8% ee



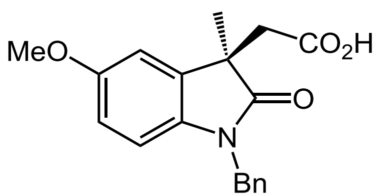
2t
67% yield, 92% ee



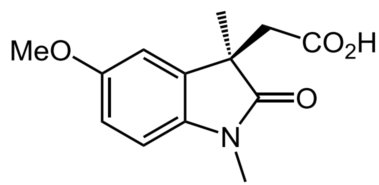
2u
78% yield, 90% ee



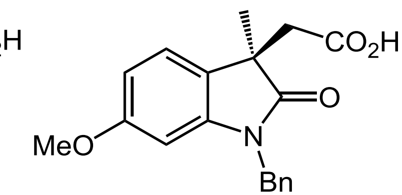
2v
76% yield, 85% ee



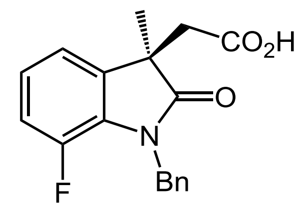
2w
82% yield, 90% ee



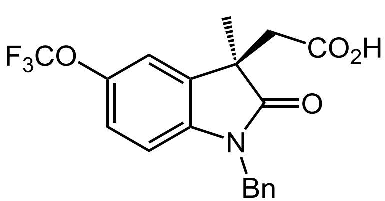
2x
75% yield, 90% ee



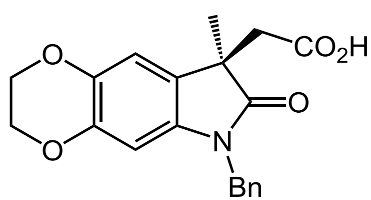
2y
71% yield, 93% ee



2z
76% yield, 86% ee

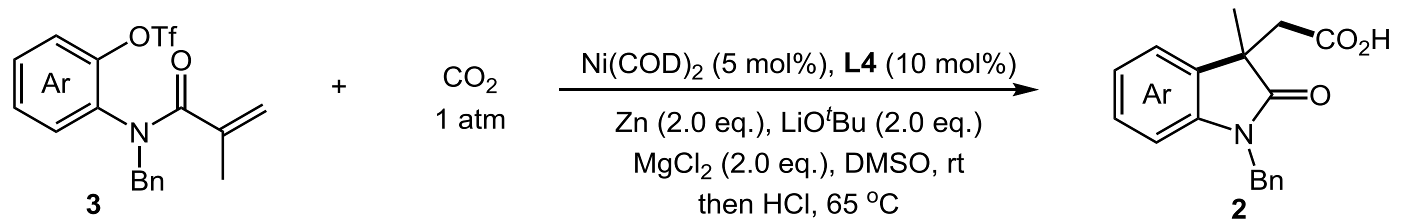


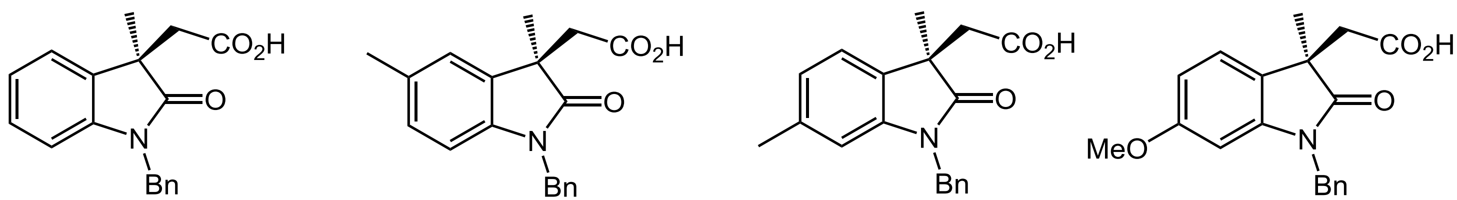
2aa
59% yield, 85% ee



2ab
86% yield, 92% ee

Substrate Scope of Aryl Triflates





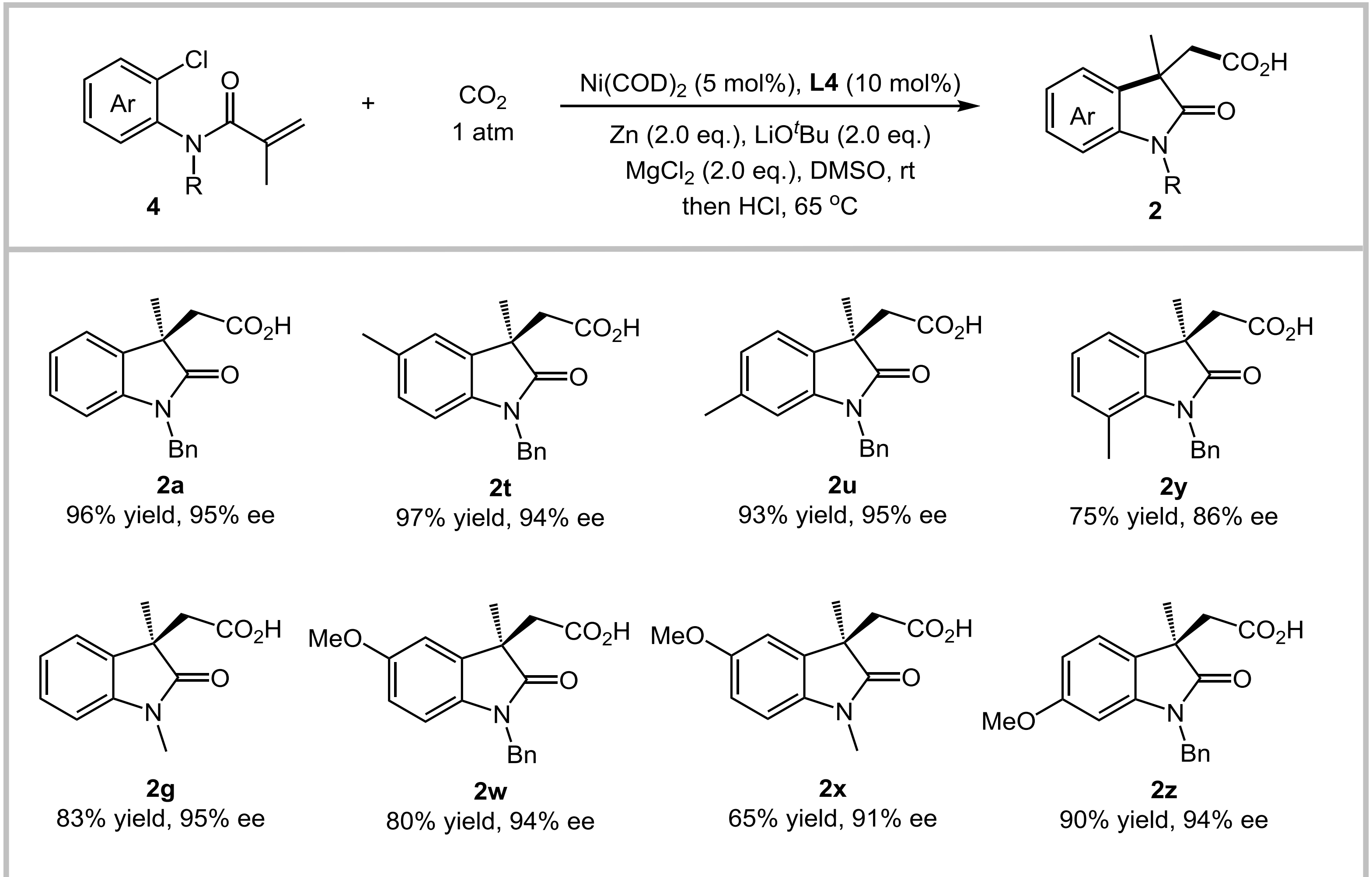
2a
57% yield, 93% ee

2t
46% yield, 93% ee

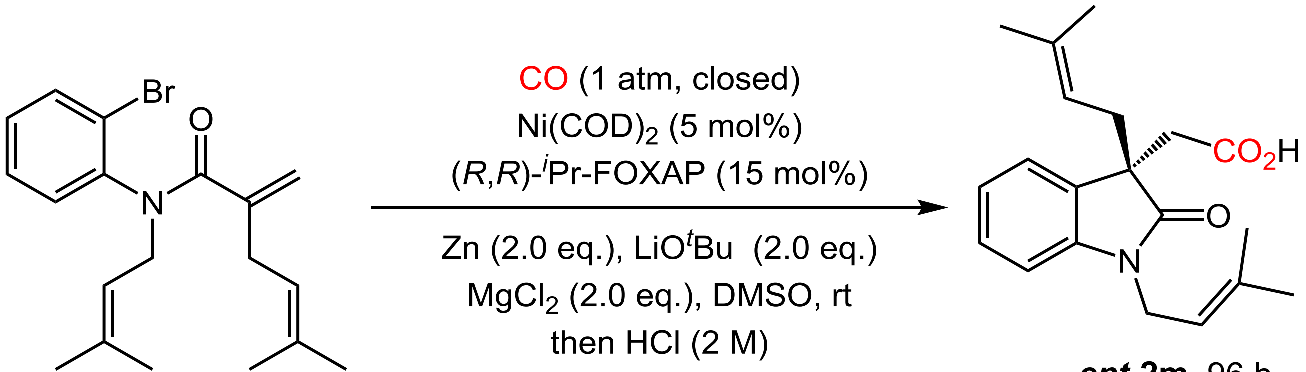
2u
53% yield, 90% ee

2y
43% yield, 92% ee

Substrate Scope of Aryl Chlorides



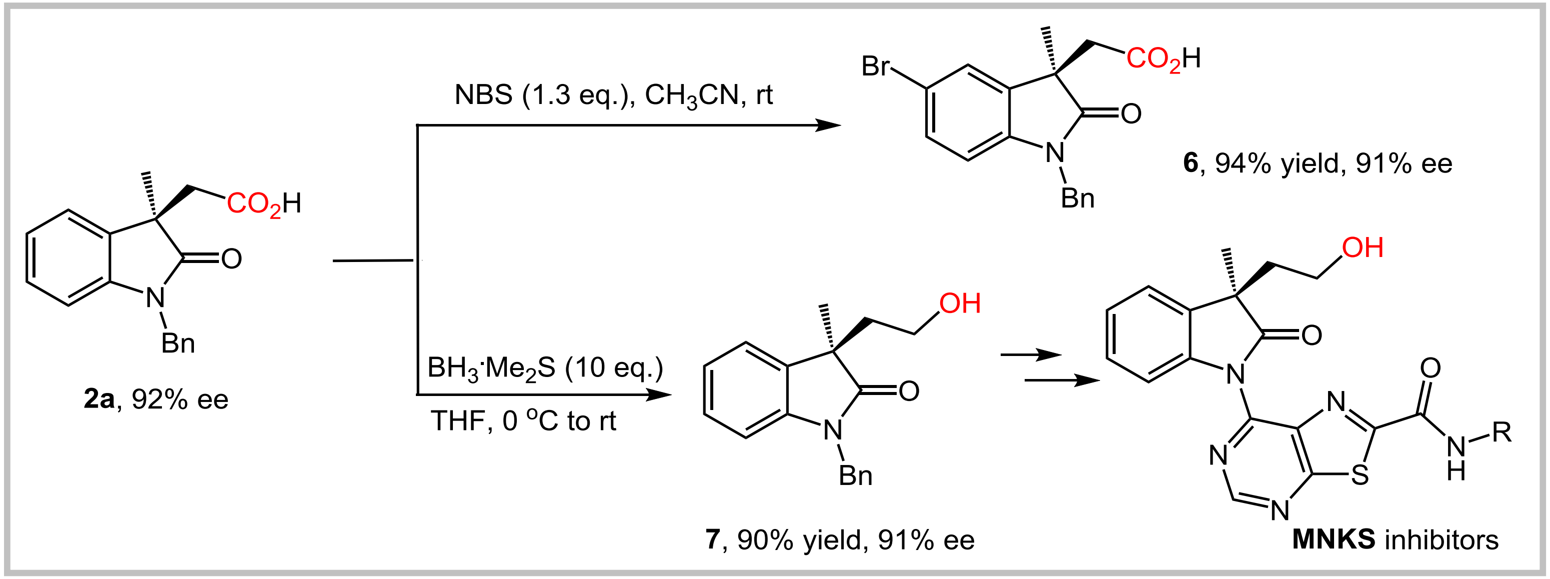
Scale-up Reaction of 1m



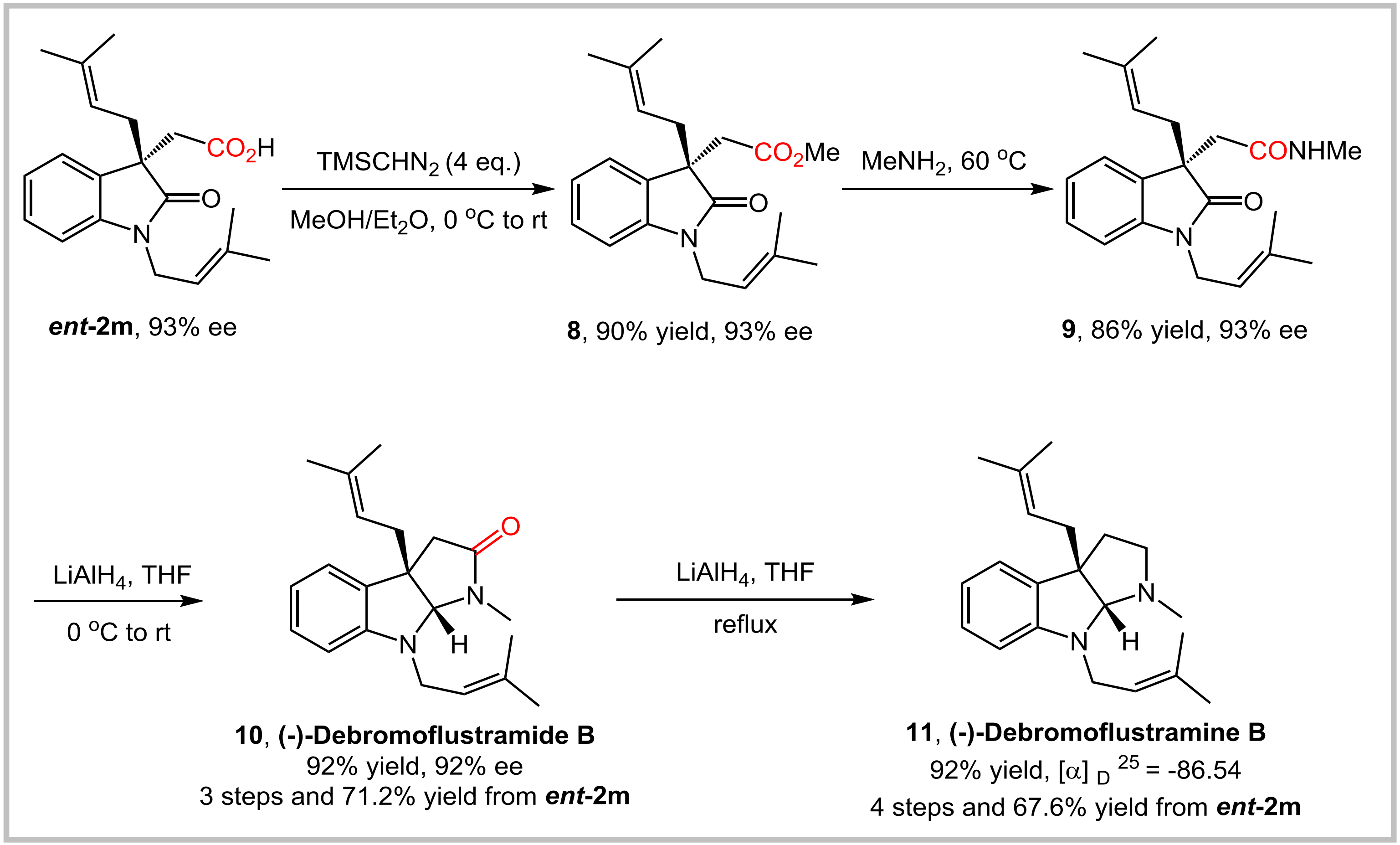
1m, 3 mmol

***ent*-2m**, 96 h
706 mg, 72% yield, 93% ee
18% R.S.M

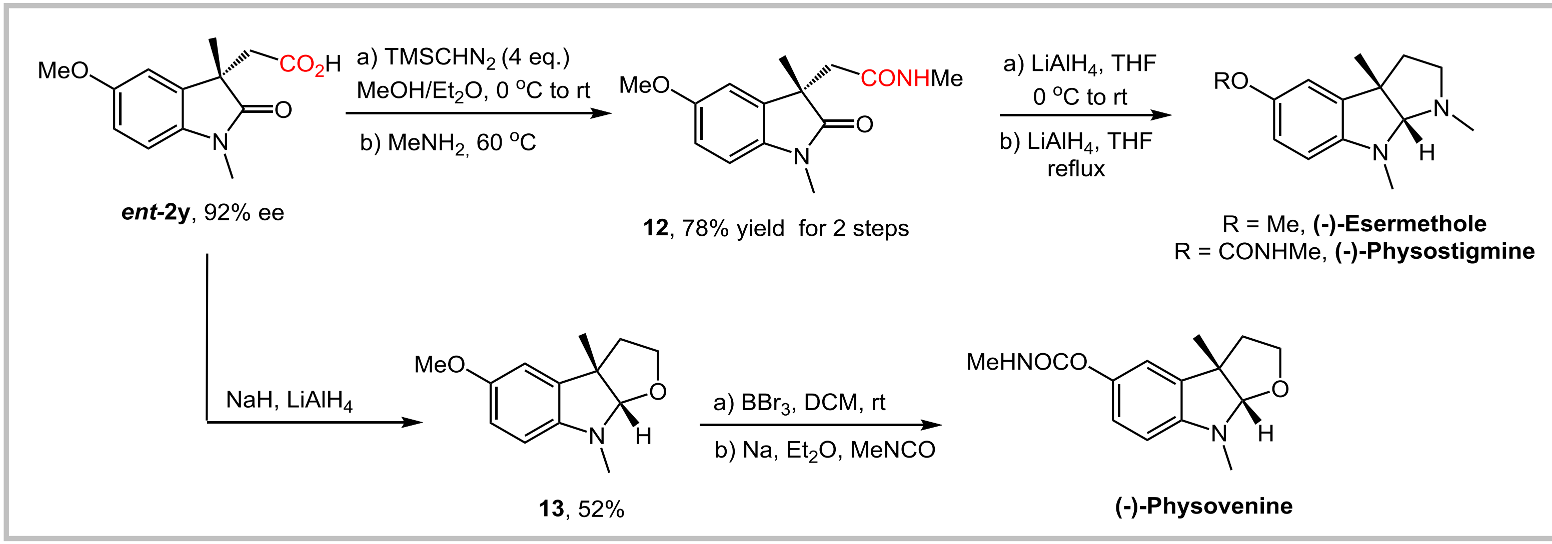
FacIle Transformations of 2a

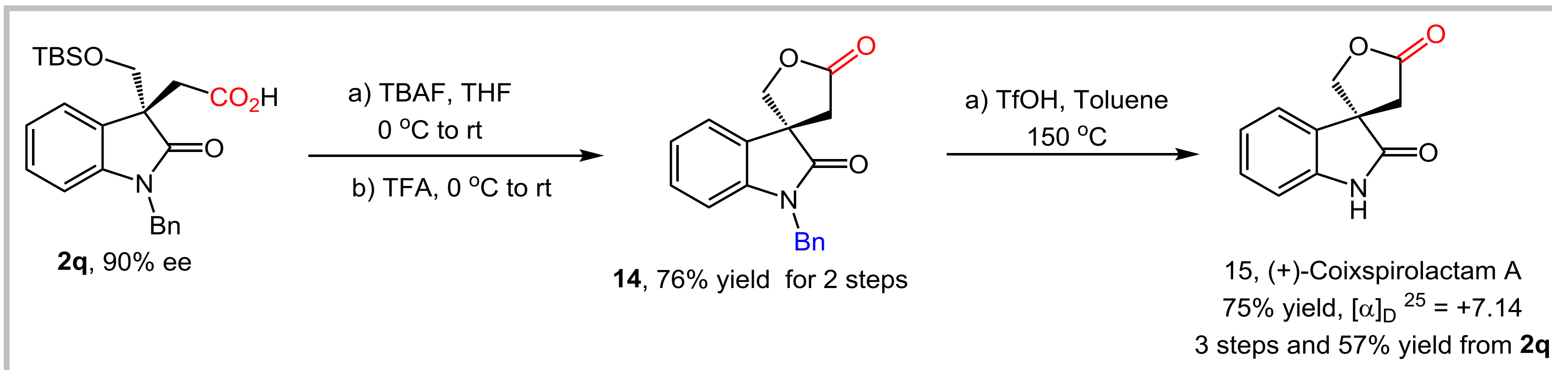


Synthesis of (-)-Debromoflustramide/amine B

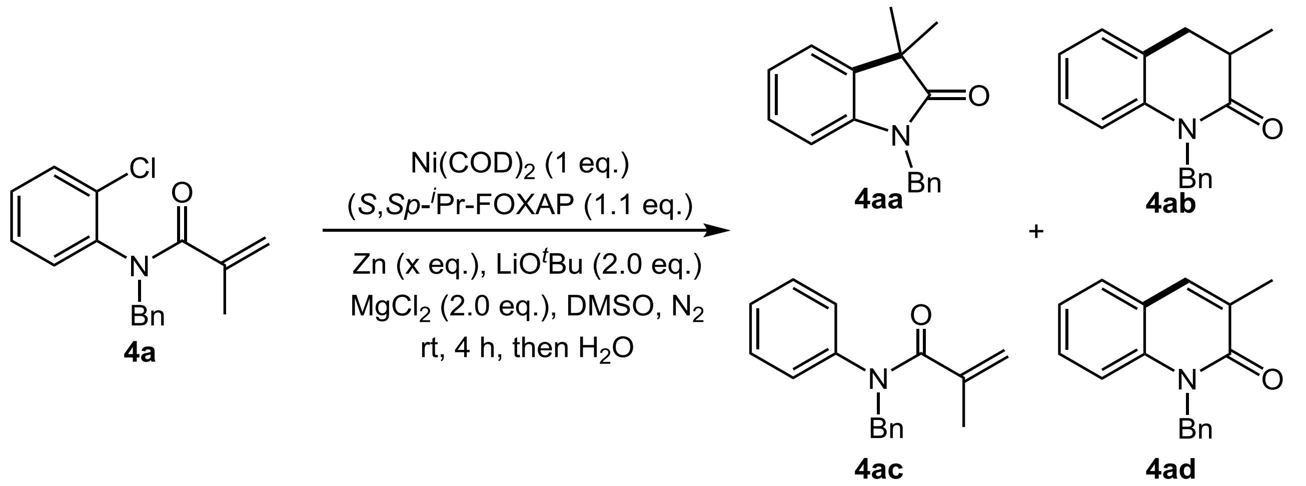


Synthesis of Bioactive Compounds



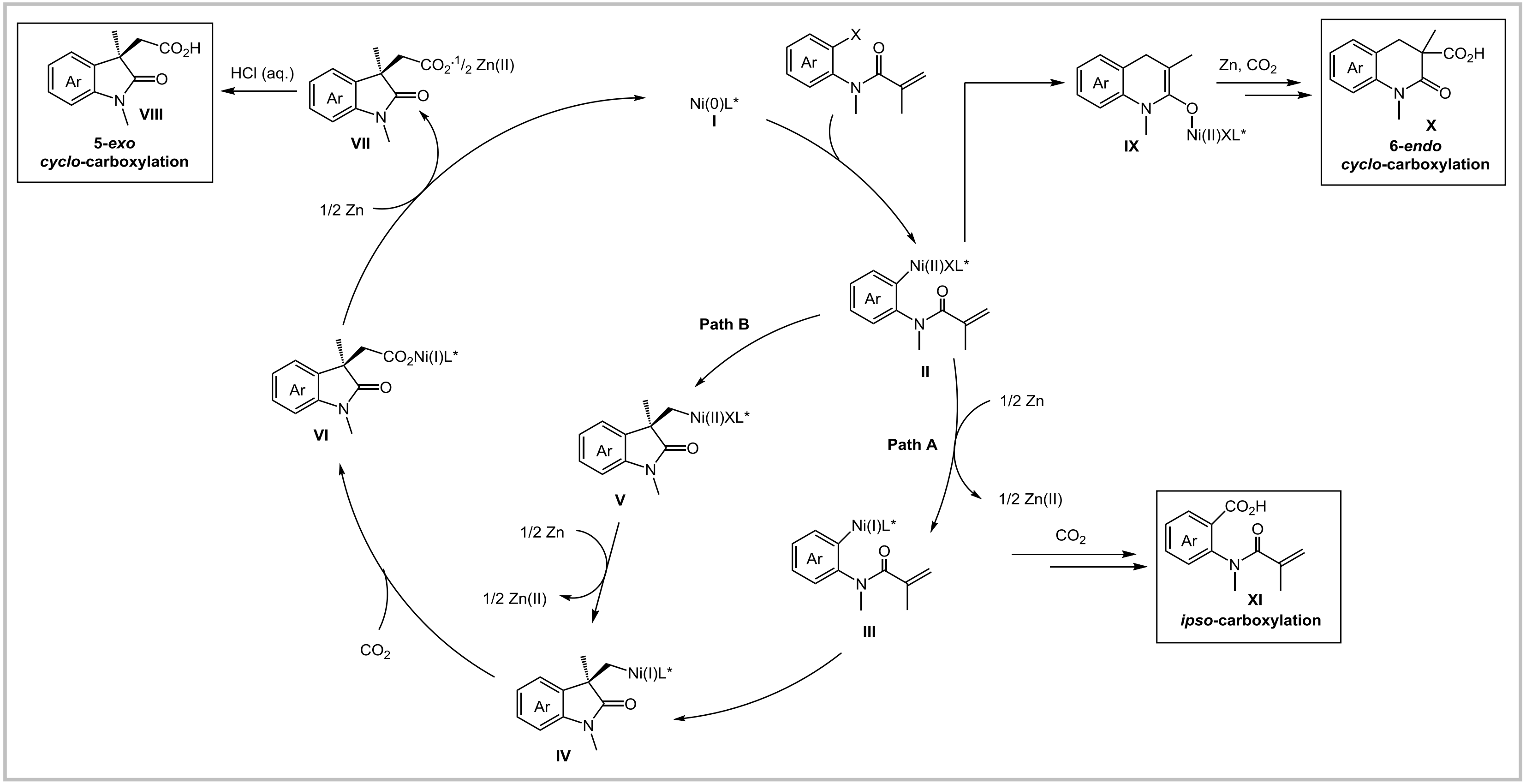


Control Experiments



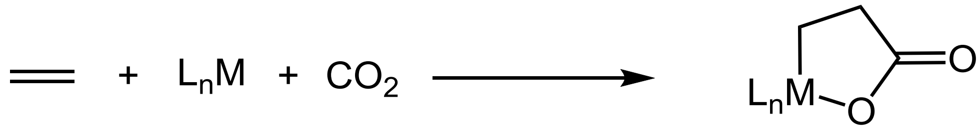
Entry	x	**4aa**	**4ab**	**4ac**	**4ad**
1	0	6%	36%	<5%	17%
2	2	8%	38%	<5%	<5%
3	3	13%	34%	<5%	<5%
4	5	52%	23%	<5%	<5%
5	10	56%	31%	<5%	<5%

Proposed Mechanism



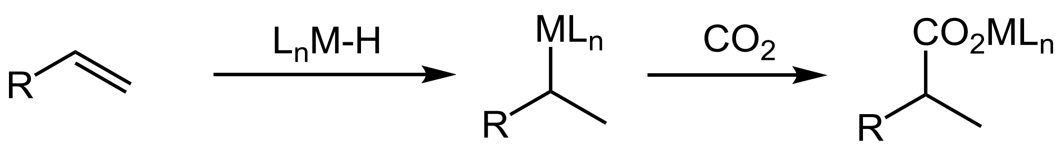
Summary

Cyclometallation

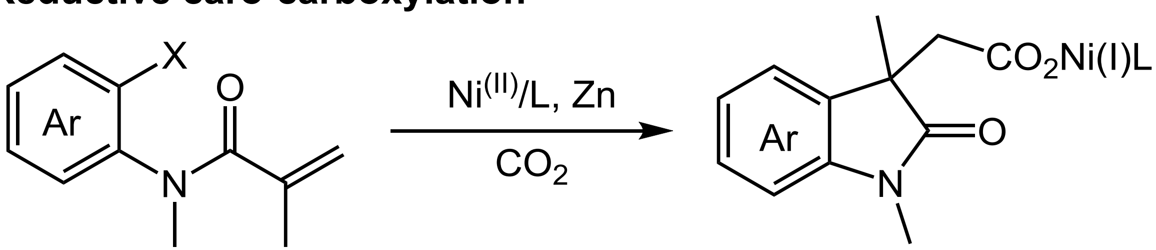


metalalactone

Metal hydride



Reductive caro-carboxylation



The First Paragraph

Writing Strategy

二氧化碳作为C1合成子的重要性

↓

过渡金属催化二氧化碳的羧基化

The First Paragraph

Carbon dioxide (CO_2) has been regarded as an ideal C1 synthon in organic synthesis because of its abundance, nontoxicity, and renewability. In the past decades, CO_2 chemistry has rapidly developed for transferring waste to treasure. 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, the generation of carboxylic acids from CO_2 is particularly attractive and a variety of strategies have been developed. 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. Besides the widely-investigated *ipso*-carboxylation,

The First Paragraph

of carbon-(pseudo)halides, 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. 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. 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. More recently, the same group has also reported a highly selective remote carboxylation of $C(sp^2)-H$ bonds via catalytic 1,4−Ni

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migration with alkynes. Besides, Sato also realized an elegant palladium-catalyzed intramolecular arylative carboxylation of allenes with Et_2Zn as a reductant. 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, 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 successful, 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.

The Last Paragraph

Writing Strategy

概括本文工作

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该工作的优点，以及在合成应用

The Last Paragraph

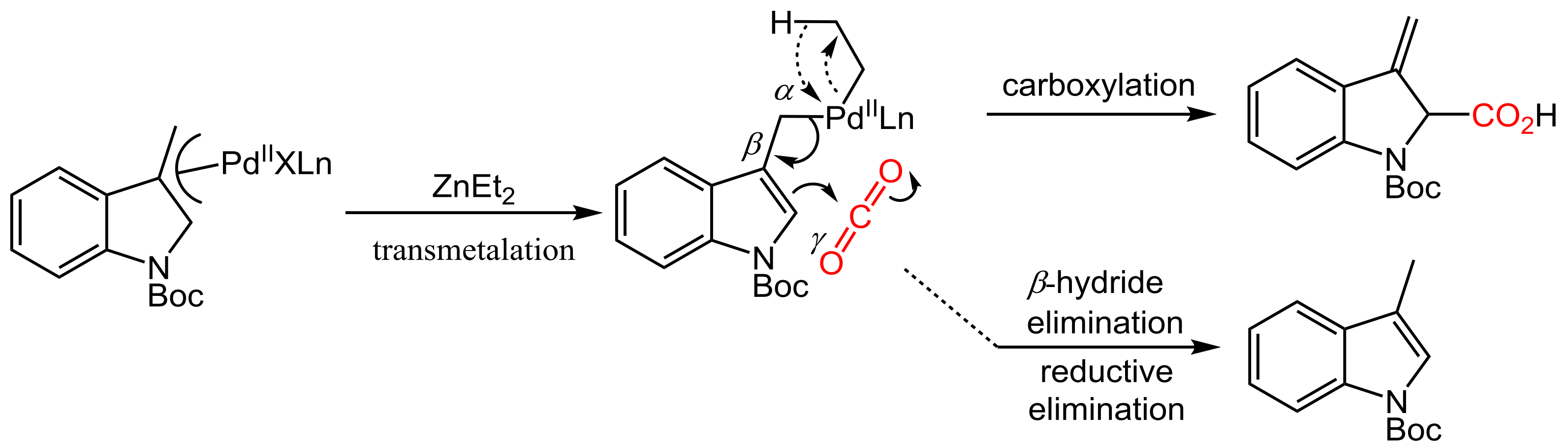
In conclusion, we have developed the first nickel-catalyzed asymmetric reductive carbo-carboxylation of alkenes using sustainable CO_2 as the carboxyl source, which provides an efficient approach to the synthesis of versatile oxindole-3-acetic acid derivatives bearing a C3-quaternary stereocenter. Aside 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 enantio-selectivity. 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.

Representative Examples

Considering the similar reactivity of aryl sulfonates to halides, we further tested aryl triflates in this transformation. (考虑到反应活性相似)

We aim to resolve such a challenge by developing an efficient transition metal-catalytic system for reductive carbo-carboxylation of alkenes with CO_2. (我们旨在解决这一挑战)

To highlight the utility of this methodology, we sought to employ it in the synthesis of bioactive natural products. (该方法学的应用）



H
α
β
γ
Pd^{II}XLn
N
Boc
ZnEt$_2$
transmetalation
Pd^{II}Ln
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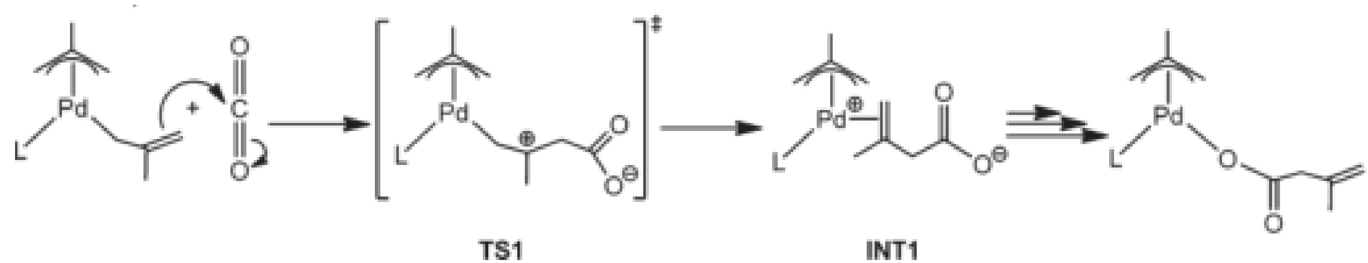
O
carboxylation
CO_2H
β-hydride
elimination
reductive
elimination



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