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Molybdenum-Catalyzed Asymmetric Allylic Alkylation of 3-Alkyloxindoles: Reaction Development and Applications

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Abstract

We report a full account of our work towards the development of Mo-catalyzed asymmetric allylic alkylation reactions with 3-alkyloxindoles as nucleophiles. The reaction is complementary to the Pd-catalyzed reaction with regard to the scope of oxindole nucleophiles. A number of 3-alkyloxindoles were alkylated successfully under mild conditions to give products with excellent yields and good-to-excellent enantioselectivities. Applications of this method to the preparation of indoline alkaloids such as (–)-physostigmine, *ent*-(–)-debromoflustramine B, and the indolinoquinoline rings of communesin B are reported.

Keywords

Molybdenum; asymmetric allylic alkylation reactions; physostigmine; debromoflustramine; communesin B

Introduction

The 3, 3'-disubstituted oxindoles are important synthetic targets because they are found widely in alkaloid natural products and pharmaceutical candidates.^{1–2} Furthermore, the oxindole moiety can be easily elaborated to an indoline structure and, hence, they serve as valuable precursors to indoline compounds that bear a quaternary carbon stereocenter at the C-3 position.³ Development of a general and efficient method for the asymmetric preparation of this structural motif, however, has proven challenging due to the difficult installation of a quaternary carbon.⁴ While significant advances have been achieved involving resolution or diastereoselective method by the use of stoichiometric chiral auxiliaries or existing chirality, catalytic asymmetric synthesis of this class of molecules has not been reported until recently. In 1993, Wong first demonstrated that alkylation of a prochiral oxindole via phase transfer catalysis provided the chiral oxindoles with high yield and modest selectivity.⁵ Since then, a number of enantioselective approaches to 3, 3'-disubstituted oxindoles have appeared.^{6–12}

Transition metal catalyzed asymmetric allylic alkylation reactions (AAA reactions) of prochiral nucleophiles have been shown to be an effective method for the construction of quaternary carbon centers.¹³ The catalytic cycles is as follows (Figure 1): complexation of the alkene to the metal, ionization of the leaving group to generate the π -allyl complex, alkylation by the nucleophile, and finally decomplexation to regenerate the catalyst. The selectivity at the nucleophile is determined at the step where the nucleophile attacks the π -

allyl metal complex. Two types of mechanisms for this step are possible: an outer sphere mechanism involving direct attack of the nucleophile on the allyl moiety from the face opposite the metal and chiral ligand, or an inner sphere mechanism where the nucleophile pre-coordinates to the metal followed by reductive elimination. The inner sphere process positions the nucleophile and the chiral ligand in close proximity, and hence, should provide more opportunity for asymmetric induction. Pd-catalyzed allylic alkylation reactions generally follow the outer sphere mechanism and because the alkylation step occurs outside the coordination sphere of the metal, achieving high enantioselectivity has proven difficult under standard reaction conditions. Recently, both our group¹⁴ and the Stoltz group¹⁵ have reported Pd-catalyzed decarboxylative asymmetric allylic alkylation reactions, where a switch to inner sphere mechanism was proposed to explain the excellent level of selectivity at the nucleophile.

In 2004, our group reported that 3-aryloxindoles were efficiently allylated to form the quaternary stereocenters at the 3-position with Pd catalyst.^{11a} The same reaction with 3-alkyloxindoles as nucleophiles, however, generally proceeded with low selectivities, even under the decarboxylative conditions. Therefore, we turned our attention to the Mo-catalyzed AAA reaction,^{16–18} which had been shown to proceed via an inner sphere mechanism of coordination of nucleophile and reductive elimination. We conjectured that the Mo reaction would be more effective with 3-alkyloxindoles as nucleophiles in forming the desired quaternary centers with high selectivities. Herein, we describe in detail its successful implementation and application. A preliminary communication of a portion of this work was recently disclosed.^{11b}

Results and Discussion

Reaction optimization

Initial studies were focused on the optimization of the base and solvent for the allylation of oxindole **1** (Table 1). The counteraction of the base has the largest effects on the selectivity of the reaction. The reaction performed with cesium carbonate as the base gave no product (entry 1). The reactions with KHMDS and NaHMDS gave good reactivity but low selectivity (entry 2–3). The highest enantioselectivity was obtained when a silylazide base with lithium as the counteraction was used (entry 4). The reaction performed in THF afforded the best selectivity. Other organic solvent such as toluene, ether, DME, dioxane and dichloromethane were less effective compared to THF (entry 5–9).

Further screening of a more extensive list of counteractions was carried out by using LiHMDS as the base in conjunction with one equivalence of Lewis acid additive (Table 2). Disappointingly, addition of Zn, Mg, Yb and Ho salts shut down the reaction (entry 1–4). Addition of tetra-*n*-hexylammonium salt, tri-*n*-butylborane, and BSA did not improve the reaction (entry 5–7). We also investigated whether hexamethyldisilazane, a by-product from deprotonation of oxindole with LiHMDS, affects the selectivity of the reaction. Although the effect was small, addition of excess amount of hexamethyldisilazane decreased the enantioselectivity of the reaction (entry 8–9). Addition of tetramethylenediamine (TMEDA), also lowered the selectivity of the reaction (entry 10). These results prompted us to investigate the use of lithium bases that would not generate amine byproduct (Table 3). Except for lithium methoxide, which gave no product (entry 2), reactions with lithium alkoxide bases all gave slightly better enantioselectivity than the reaction with LiHMDS (entry 3–6). Lithium *tert*-butoxide was selected as the optimal base as it is the most readily available. Finally, the best yield and enantioselectivity was achieved when the reaction was conducted with 2 equivalents of lithium *tert*-butoxide in THF at room temperature (entry 7).

The Merck group has reported an X-ray structure of a π -allyl molybdenum ligand complex and showed that the complex is not symmetrical: the ligand is coordinated to the metal via a three point binding, and it was postulated that the labile oxygen ligand dissociates to make room for the incoming nucleophile during the nucleophilic substitution step.^{18a} Several symmetrical and unsymmetrical ligands with different heterocyclic substitutions and amine linkages were examined to study whether variation of the electronic and steric properties of the chelating groups would provide enhanced selectivity. As shown in Table 4, all the ligands tested gave full conversion but with very different selectivities. Reactions performed with ligands that contain amide linkages and at least one pyridine ring afforded comparable enantioselectivities as the reaction with **L1** (entry 1–4). However, when both pyridine rings were substituted with other chelating heterocycles, the enantioselectivities dropped significantly (entry 5–6). Furthermore, reaction with ligand containing carbamate or sulfamide linkage gave much worse selectivity (entry 7–8). These results indicate the coordination of the pyridine ring and amide groups is important for the selectivity of the reaction.

To summarize, the optimized conditions for the synthesis of allylated 3-alkyloxindoles consisted of performing the reaction with ligand **L1** (15% mol), Mo(C₇H₈)(CO)₃ (10% mol), and LiO*t*Bu (2 equiv) in THF at room temperature.

Reaction scope-synthesis of substrates

A variety of 3-mono-substituted oxindole substrates were prepared by three different synthetic sequences (Scheme 1). 1,3-Dimethyloxindole was synthesized by oxidation of 1,3-dimethylindole with DMSO in the presence of concentrated hydrochloric acid (Eq.2).²⁰ This method, while straightforward, is limited by the availability of 3-substituted indoles. The use of concentrated hydrochloride acid also limits certain functional groups that can be tolerated. The majority of the substrates were prepared by mono-alkylation of unsubstituted oxindoles, many of which are commercially available or readily prepared by reduction of the corresponding isatins (Eq.3). Nakazawa reported that mono-alkylation of the un-substituted oxindole in the presence of HMPA minimizes the formation of bis-alkylation by-product and provides the desired 3-mono-substituted oxindoles in reasonable yield.²¹ Since the use of HMPA is undesirable, we also adopted a method reported by Overman for the mono-alkylation of oxindoles, which involves a Knoevenagel condensation between an oxindole and a non-enolizable aldehyde, followed by N-alkylation and lastly hydrogenation to reduce the double bond (Eq.4).²⁸ We found that the condensation step was most conveniently performed in a microwave reactor with a small amount of ethanol as solvent. The product is crystalline and was isolated by filtration. The subsequent *N*-alkylation and hydrogenation steps were both straightforward.

The optimized condition was then applied to examine the scope and limitations of the reaction (Table 5). Gratifyingly, in nearly all cases, excellent yields and good-to-excellent enantioselectivities were obtained and a variety of functional groups at the 3-position of the oxindoles were tolerated. The enantioselectivity of the reaction correlates with the size of the substituents on the oxindole. Increasing the size of the 3-alkyl group increased the enantioselectivity. However, increasing the size of the *N*-alkyl group was detrimental to the enantioselectivity. This is not unexpected as the oxindole enolate is likely coordinated to the bulky molybdenum catalyst during the reaction and would try to minimize the steric interaction by steering the large substituents away from the catalyst. We have previously reported that 3-aryl-substituted oxindoles are good substrates for Pd-catalyzed AAA reactions.^{11a} When we tested 3-phenyloxindole in the Mo-catalyzed AAA reaction under the optimized conditions, however, only moderate enantioselectivity was observed (**2p**). Thus,

the Mo reaction complements the Pd reaction with regard to the scope of the nucleophile in this case.

Formal synthesis of (–)-physostigmine and (–)-phenserine

Physostigmine, originally isolated from the seeds of the African Calabar bean, is a potent reversible inhibitor for cholinesterase and has been used clinically to treat a myriad of conditions including glaucoma and *gamma*-hydroxybutyric acid overdose.^{22–24} Phenserine is a synthetic analog of physostigmine with more favourable pharmacological properties. Phenserine had also been examined for the treatment of Alzheimer's disease.^{25–26}

Physostigmine and phenserine share the same pyrrolidinoindoline ring system and differ only by carbamate substitutions. It has been shown that phenserine can be prepared from physostigmine via a two-step sequence of hydrolysis and re-protection.²⁷ Due to their biological importance, a number of asymmetric syntheses of these molecules have been reported.^{6a, 9b, 12c, 28} Our synthesis commenced from prochiral oxindole **1a** readily prepared from 4-methoxy-*N*-methylaniline and chloroacetone in two steps.²⁹ Allylation of **1a** under the optimized conditions proceeded with 95% yield and 82% ee. Oxidation of the allylated product **2a** (OsO₄, NMO, and then NaIO₄) provided the aldehyde **3** in 92% yield. Two recrystallizations from isopropyl alcohol and cyclohexane upgraded the enantiopurity of **3** to 99%. Reductive cyclization of **3** using conditions optimized by Overman and coworkers afforded (–)-esermethole,^{6a} which had been transformed to (–)-physostigmine and (–)-phenserine in two steps. Thus our work constitutes a formal synthesis of (–)-physostigmine and (–)-phenserine, in seven steps from commercially available starting materials.

Synthesis of *ent*- (–)-debromoflustramine B

The flustramines are a family of prenylated or “reverse” prenylated pyrrolidinoindoline marine alkaloids isolated from the marine bryozoan *Flustra foliacea*.^{30–31} Flustramine B was shown to be effective blockers for voltage-activated potassium channels and exhibit both skeletal and smooth muscle relaxant activities.³¹ Synthetic interests in this family of natural products were stimulated primarily by their deceptively simple yet unique structures. A number of racemic syntheses of various members of this family have been developed since their isolations.³² The only asymmetric synthesis of flustramines using catalytic enantioselective methods was reported in 2004 by MacMillan and coworkers.³³

We envisioned that the C-3 stereocenter of debromoflustramine B can be constructed using the Mo-AAA reaction and we chose a cyano group as a methylamine surrogate. Disappointingly, oxindole **5b** bearing a prenyl group on the nitrogen gave only 74% ee for the allylation reaction. This is in line with our observations from the earlier studies that a large *N*-substituent is detrimental to the enantioselectivity of the reaction. Switching to a smaller *N*-allyl group improved the enantioselectivity of the reaction to 93%. A double cross-metathesis reaction with 2-methylbutene and the Grubbs' second-generation catalyst then yielded the required bis-prenyl functionality.³⁴ Reductive cyclization and *N*-methylation under previous reported conditions afforded debromoflustramine B in 55% yield.^{32a} Comparison of optical rotation with literature reports revealed that the enantiomer of the natural product was synthesized (Scheme 3).^{31b}

Synthesis of the dihydro-indolinoquinoline core of Communesin B and Perophoramidine

Closely related polycyclic indoline compounds communesin B and perophoramidine were isolated respectively from marine alga *Enteromorpha intestinalis*³⁵ and the Philippine ascidian *Perophora namei*.³⁶ Synthetic interests in these two and other related structures have been fueled by a desire to understand their structure-activity relationships as both compounds contain unusual structural features and exhibit significant biological

activities.^{37–38} Communesin B, in particular, shows both potent cytotoxicity against P-388 leukemia ($ED_{50} = 0.45 \mu\text{g/mL}$) and insecticidal activity against silk worms ($LD_{50} 5 \mu\text{g/mL}$).³⁹ Perophoramidine is cytotoxic against the HCT-116 colon carcinoma cell line ($IC_{50} 60 \mu\text{M}$) and induces apoptosis via PARP cleavage.⁴⁰

Given our success with the Mo reactions at forming C-3 quaternary centers of oxindoles, we anticipated that the quaternary centers in communesin B can be formed by alkylation of oxindole **8** (Scheme 4). Reductive cyclization of the aniline nitrogen with the oxindole amide in **9** should provide the indolinoquinoline ring system of communesin B. The second quaternary center would be then constructed via a diastereoselective nitrile alkylation.

Synthesis of a model substrate, oxindole **14**, was initiated with condensation of oxindole **11** with aldehyde **12** under microwave heating to give **13** as a mixture of alkene isomers. N-Methylation and hydrogenation of **13** then provided **14** in 95% yield. The Mo-catalyzed AAA reaction proceeded well and the allylated product **15** was isolated in 96% yield and 95% ee. Deprotection of the Boc group with TFA and dehydrative cyclization with titanium tetrakisopropoxide then provided the dihydro-indolinoquinoline **16** (Scheme 5).

With the establishment of the core ring system asymmetrically, we turned our attention to installing a substituent to in the benzylic position of the 6-membered ring to facilitate formation of the spiro fused ring. Thus, a separate model system, it was demonstrated that a benzylic cyano group in **17a** was tolerated and gave the desired allylated product in high ee. The stereochemistry of the cyano group was irrelevant since we would be subsequently deprotonating it to effect a diastereoselective alkylation (Scheme 6). However, in the presence of the *ortho*-NHBoc group that is required for the formation of the dihydroquinoline ring, oxindole **17b** underwent an unexpected fragmentation reaction to generate the allylated product **19**.⁴¹

Determination of the absolute chemistry of the product and proposed mechanism of the reaction

The formal synthesis of (–)-physostigmine and synthesis of *ent*-(–)-debromoflustramine allowed us to establish the absolute stereochemistry of the products of the Mo reactions. The selectivity is in agreement with the transition state depicted in Figure 2. The facial approach in A is favored because it lessens the steric congestion between the ligand and the enolate of the oxindole as the C-terminus of the enolate moves towards the π -allyl. In the alternative approach in B, the steric interaction becomes more severe as the bulk of the oxindole is pushed towards the ligand during the bond formation.

Conclusion

Transition metal catalyzed AAA reactions are powerful methods for the generation of quaternary carbon centers. Exploration of metals other than palladium has led to discovery of many new selective transformations. In this instance, we have developed the first enantioselective Mo-catalyzed AAA reaction for the generation of quaternary stereocenters at a prochiral nucleophile, in this case the 3-position of 3-alkyl oxindoles. The reaction is successful with a variety of alkyl substitutions, and its utility is demonstrated in the synthesis of (–)-physostigmine, *ent*-(–)-debromoflustramine, and the indolinoquinoline core of communesin B and perophoramidine.

Experimental Section

Representative procedure for Mo catalyzed AAA reactions

In a sealed pyrex test tube, a solution of (*R,R*) ligand **L1** (2.4 mg, 0.015 mmol) and $[(\eta^3\text{-C}_7\text{H}_8)\text{Mo}(\text{CO})_3]$ (1.4mg, 0.01 mmol) in THF (freshly distilled and degassed, 0.3 mL) was stirred at 60 °C for 5 min under Ar atmosphere. A second pyrex test tube containing 0.1 mmol of oxindole **1a** was transferred to the dry box and to it LiOtBu (0.2 mmo) was added. The test tube was sealed, taken out of the dry box, and to it was added THF (0.7 mL). The resulting solution was stirred for 5 min at room temperature before the solution of the active catalyst solution was added via cannula, followed by the addition of allyl *tert*-butyl carbonate (0.12 mmol) via syringe. The reaction was stirred at room temperature for 3–6 h until TLC indicates complete consumption of **1a**. The reaction mixture was then concentrated and purified through silica gel to give the desired product **2a** (22 mg, 95% yield, 82% ee).

Chiral HPLC, OJ-column, flow rate 1.0 mL/min, 90/10 heptane / *i*-PrOH, t_A (major) = 9.70 min, t_B (minor) = 10.90min; IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3077, 2929, 2835, 1715, 1643, 1600, 1504, 1470, 1373, 1291, 1235, 1204, 1177, 1122, 1037, 920, 741; ^1H NMR (400 MHz, CDCl_3): δ = 6.92 – 6.72 (m, 3H), 5.50 – 5.40 (m, 1H), 5.02 – 4.91 (m, 2H), 3.80 (s, 3H), 3.17 (s, 3H), 2.54 – 2.44 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ = 180.1, 156.2, 136.9, 135.2, 132.8, 118.9, 111.8, 110.9, 108.3, 56.0, 48.9, 42.6, 26.4, 23.0.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2.
Model for enantiodiscrimination

Scheme 1. Representative synthesis of oxindole substrates

Scheme 2. Formal synthesis of (-)-Physostigmine

Scheme 3. Synthesis of debromoflustramine

Scheme 4. Retrosynthetic analysis of communesin B

Scheme 5. Preparation of indolinoquinoline 14

Scheme 6. Mo-AAA reaction with oxindole **17a** and **17b**

Table 1

Screening of base and solvent Equation (1)^a

Entry	Base	Solvent	Temperature	ee(%)	Yield(%) ^b
1	Cs ₂ CO ₃	THF	67 °C	--	NR
2	KHMDS	THF	67 °C	38	ND
3	NaHMDS	THF	67 °C	60	ND
4	LiHMDS	THF	67 °C	75	75–92%
5	LiHMDS	Toluene	67 °C	20	60%
6	LiHMDS	Ether	40 °C	--	NR
7	LiHMDS	DME	67 °C	63	80%
8	LiHMDS	Dioxane	67 °C	55%	80%
9	LiHMDS	DCM	40 °C	--	0

^[a]The reaction was performed with 0.1 mmol of oxindole **1a**, 0.12 mmol of allyl *tert*-butyl carbonate, 10% Mo(C₇H₈)(CO)₃, 15% **L1**, 0.12 mmol of base in THF(1mL).

^[b]Isolated Yield.

Table 2

Screening of additive for Equation (1).^a

Entry	Base (1.2 eq.)	Additive (1.0 eq.)	ee(%)	Yield (%) ^b
1	LiHMDS	ZnCl ₂	--	NR
2	LiHMDS	MgBr ₂	--	NR
3	LiHMDS	HoCl ₃	--	NR
4	LiHMDS	YbCl ₃	--	NR
5	LiHMDS	Bu ₃ B	75	ND
6	LiHMDS	<i>n</i> -Hexyl ₄ NCl	75	ND
7	LiHMDS	BSA	72	20
8	LiHMDS	HMDS(2 eq.)	73	80
9	LiHMDS	HMDS (4 eq.)	70	80
10	LiHMDS	TMDEA	69	80

[a] The reaction was performed with 0.1 mmol of oxindole **1a**, 0.12 mmol of allyl *tert*-butyl carbonate, 10% Mo(C₇H₈)(CO)₃, 15% **L1**, 0.12 mmol of LiHMDS in THF(1mL).

[b] Isolated Yield.

Table 3

Screening of base and temperature for Equation (1).^a

Entry	Base (1eq.)	Temperature	ee (%)	Yield (%) ^b
1	<i>s</i> -BuLi	67 °C	71	ND
2	LiOMe	67 °C	--	NR
3	LiOtBu	67 °C	79	80%
4	LiOtBu	rt	82	70–90%
5	LiOtAmyl	rt	81	70
6	LiOtHept	rt	81	70
7	LiOtBu (2 eq.)	rt	82	95–98
8	LiOtBu (2 eq.)	4 °C	83	95
9	LiOtBu (2 eq.)	-10 °C	73	90

[a] The reaction was performed with 0.1 mmol of oxindole **1a**, 0.12 mmol of allyl *tert*-butyl carbonate, 10% Mo(C₇H₈)(CO)₃, 15% **L1**, 0.12 mmol of base in THF(1mL).

[b] Isolated Yield.

Table 4

Screening of chiral ligands for Equation (1).^a

Entry	Ligand	ee %	Conversion (%)
1	L2	72	>95
2	L3	75	>95
3	L4	72	>95
4	L5	75	>95
5	L6	61	>95
6	L7	64	>95
7	L8	24	>95
8	L9	10	>95

[a] The reaction was performed with 0.1 mmol of oxindole **1a**, 0.12 mmol of allyl *tert*-butyl carbonate, 10% Mo(C₇H₈)(CO)₃, 15% ligand 0.2 mmol of LiOtBu in THF(1mL) at 67 °C.

Table 5

Scope of the reaction

2a	2b	2c	2d
95% yield, 82% ee	99% yield, 81% ee	93% yield, 75% ee	95% yield, 93% ee
2e	2f	2g	2h
95% yield, 87% ee	92% yield, 87% ee	99% yield, 88% ee	96% yield, 91% ee
2i	2j	2k	2l
98% yield, 85% ee	99% yield, 93% ee	95% yield, 80% ee	94% yield, 75% ee
2m	2n	2o	2p
95% yield, 80% ee	95% yield, 75% ee	96% yield, 88% ee	88% yield, 25% ee

[a] The reaction was performed with 0.1 mmol of oxindole **1**, 0.12 mmol of allyl *tert*-butyl carbonate, 10% Mo(C₇H₈)(CO)₃, 15% **L1**, 0.2 mmol of LiOtBu in THF (1mL) at room temperature.