Asymmetric Catalysis

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Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles: Facile Access to Oxindoles with C3 All-Carbon Quaternary Stereocenters**

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The construction of all-carbon quaternary stereocenters remains one of the most challenging problems in asymmetric catalysis and has been an area of great interest in our laboratories.[1,2] Over the past several years, significant effort from many research groups has been directed toward the enantioselective synthesis of 3,3-disubstituted oxindoles and derivatives thereof, given the prevalence of this structural motif in biologically active molecules and their interesting molecular architectures (Figure 1).[3–5] Although a number of catalytic enantioselective approaches to this motif have been developed (Heck reaction,[6] cyanoamidation,[7] cycloadditions,[8] arylation,[9] alkylation,[10,11] acyl migration,[12] Claisen rearrangement,[13] aldol,[14] Mannich,[15] and conjugate addition reactions[15b]), we pursued an alternative tactic.[16–18] In all of the reported systems that rely on stereoselective functionalization of an existing oxindole,[9–15] this unit serves as a nucleophile. In contrast, we present herein an unusual strategy for the enantioselective synthesis of substituted oxindoles with C3 quaternary stereocenters that employs the oxindole moiety as the electrophilic partner for the facile and rapid coupling to malonate nucleophiles.

Despite an early report from Hinman and Bauman in 1964,[19] the use of 3-halooxindoles as electrophiles in substitution chemistry has been limited. Although the addition of carbon-based π- and heteroatom-nucleophiles to the C3 position of oxindoles has been reported, no enantioselective methods exist.[20] We recently reported the base-promoted addition of malonate esters to 3-halooxindoles by the in situ formation of a putative *o*-azaxylylene (Scheme 1a).[21] In light of these results and our general interest in stereoablative reactions,[22] we sought to develop a catalytic enantioselective system (Scheme 1b).[23] We hypothesized that a Lewis acid could facilitate the base-mediated reaction by lowering the pK_a of the N–H proton of the halooxindole and/or the C_α–H proton of the malonate. Through either pathway, complexation by a chiral Lewis acid could potentially lead to asymmetric induction.

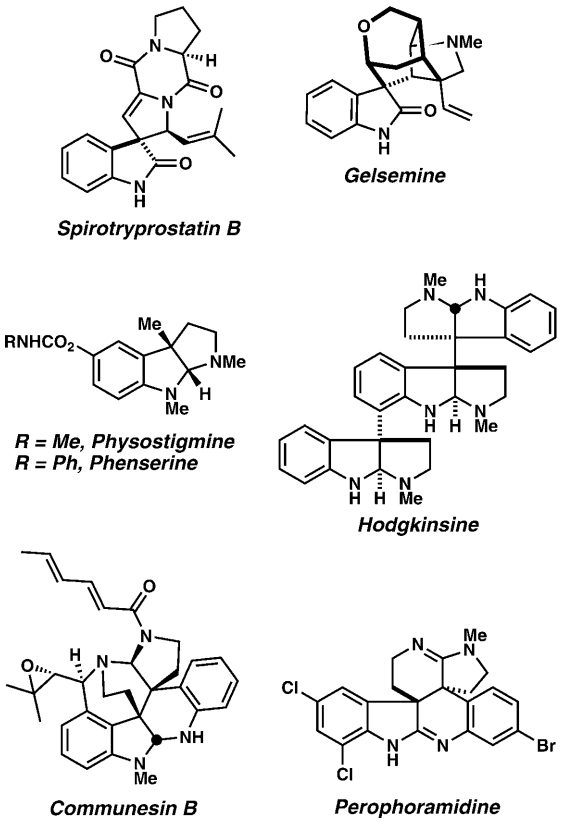

Figure 1. Naturally occurring 3,3-disubstituted oxindoles and indolines bearing all-carbon quaternary stereocenters.

We reasoned that the key to implementing a catalytic enantioselective system would be to identify a base that did not promote competitive background reactions in the absence of catalyst. In our initial experiments, we found that exposure of racemic bromooxindole (±)-**1** to *N*,*N*-diisopropylethyl-

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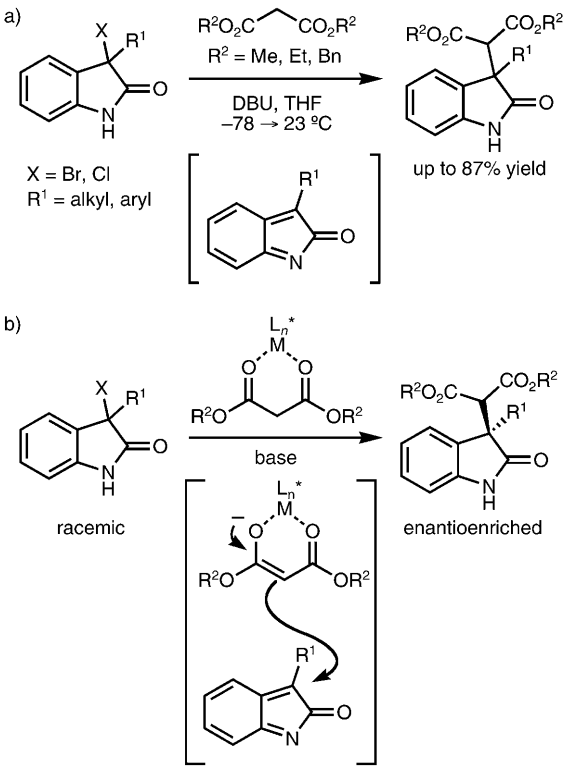
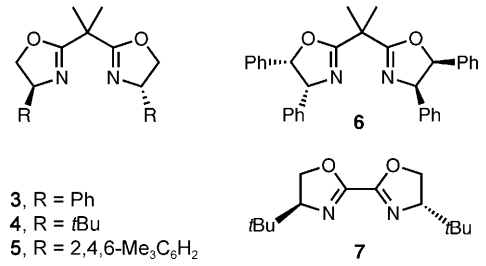


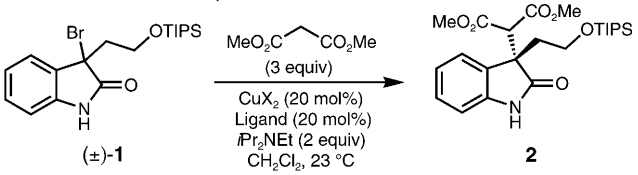
Scheme 1. a) Base-mediated addition of malonates to halooxindoles via a reactive *o*-azaxylylene intermediate.[21] b) Proposed Lewis acid catalyzed enantioselective alkylation of 3-halooxindoles. Only the malonate activated pathway is shown. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

amine (iPr$_2$NEt) and dimethyl malonate in the absence of a Lewis acid did not result in formation of adduct **2**.[24] Encouraged by this finding, we then surveyed a variety of chiral Lewis acids (e.g., Cu^{II}, Mg^{II}, La^{III}, and Ni^{II} complexes) that could potentially promote the asymmetric alkylation. The combination of copper(II) triflate and (*S*)-Ph-box (**3**)



gave the most promising result, producing **2** in 63 % yield and 77 % *ee* (Table 1, entry 1).[25,26] Related bis(oxazoline) ligands **4**–**7** resulted in diminished yields and enantioselectivity (Table 1, entries 2–5). Given the strong electronic effects observed in related Lewis acid catalyzed processes, we investigated the effect of less coordinating counterions.[27] Although imparting only a moderate influence on chemical yield, a more pronounced counterion effect was observed for enantioselectivity. For example, with the hexafluoroantimonate (SbF_6^-) complex, malonate adduct **2** was produced in 72 % yield and 84 % *ee* in less than 10 min (Table 1, entry 9). Ultimately, we found that employing the preformed [Cu(**3**)] $(SbF_6)_2$ complex at low temperature (i.e., −40 °C) in the presence of 3 Å molecular sieves[28] produced oxindole **2** in 77 % yield and 88 % *ee* (Table 2, entry 1).

Table 1: Reaction development.



Entry	X	Ligand	Yield[b] [%]	*ee*[c] [%]
1	OTf	**3**	63	77
2	OTf	**4**	45	6
3	OTf	*ent*-**5**	24	−42
4	OTf	**6**	37	−64
5	OTf	**7**	49	13
6[a]	PF_6[d]	**3**	65	81
7	NTf_2[d]	**3**	65	79
8[a]	BF_4[d]	**3**	61	76
9	SbF_6[d]	**3**	72	84

[a] Performed at −78→23 °C. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] The catalyst was generated by in situ metathesis of [Cu(**3**)Cl_2] with the corresponding AgX salt.[24]

On examining the scope of the transformation, we found that malonate esters could be alkylated with various 3-alkyl and 3-aryl halooxindoles in good yields and high enantioselectivities (Tables 2 and 3).[29] Methyl, ethyl, and benzyl malonates each added to bromide (±)-**1**, via the putative *o*-azaxylylene, with similar levels of selectivity and yield (Table 2, entries 1–3). Silyl ethers (entries 1–5), benzoate esters (entry 6), and phthalimides (entries 8–10) were all tolerated as substituents on the C3 alkyl chain. Additionally, substituted alkyl chains of various lengths led to alkylation products in high enantioselectivities (entries 1 and 5). Finally, substitution of the bromooxindole core at C5 with a methoxy group produced the malonate addition product in 51 % yield and 91 % *ee* (entry 10).

In addition to the reactions of bromooxindoles, dimethyl malonate reacted smoothly with racemic 3-aryl chlorooxindoles to produce the C3-malonate adducts in good yields and enantioselectivities (Table 3). In these reactions, Et_3N proved to be a better base than iPr$_2$NEt in both yield and enantioselectivity. Products with phenyl (entry 1), bromophenyl (entry 2), 3,5-dimethylphenyl (entry 3), and naphthyl substitution at C3 (entry 4) were stereoselectively formed with this method. Additionally, methoxy substitution on the oxindole framework at C5 was well tolerated (entry 5).

We proceeded to apply the new method for enantioselective generation of C3-quaternary oxindoles to the synthesis of natural product scaffolds. To construct the pyrrolidinyl-spirooxindole core prevalent in a large family of biologically active alkaloids,[3] we began with malonate adduct **8** (Table 2, entry 10), which could be recrystallized to 99 % *ee* (Scheme 2). Oxindole malonate **8** was converted to phthali-

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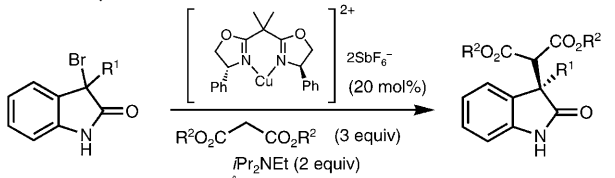
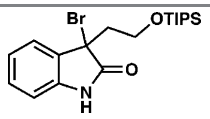
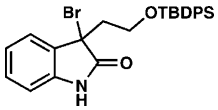
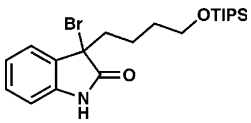
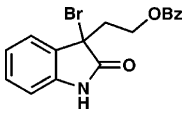
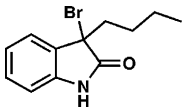
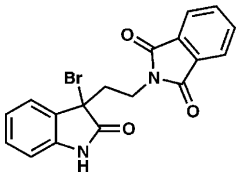
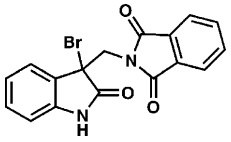
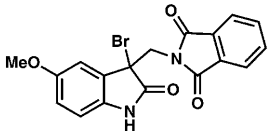
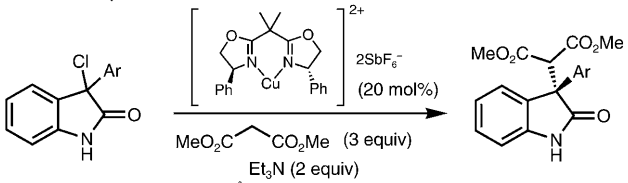
Table 2: Alkyl-substituted oxindoles as substrates in the enantioselective malonate alkylation.

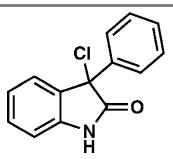
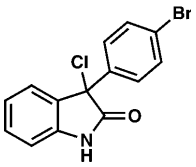
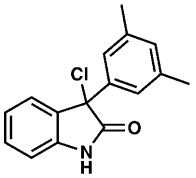
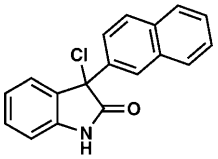
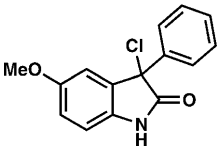


Entry	Racemic substrate	R^2	T [°C]	Yield[a] [%]	*ee*[b] [%]
1		Me	−40	77	88
2		Et	−40	73	84
3		Bn	−40	78	88
4		Me	−40	78	88
5		Me	−20	47	86
6		Me	−20	51	83
7		Me	−40	44	84
8		Me	−20	63	94
9		Me	−20	42	81
10		Me	−20	51	91

[a] Yield of isolated product. [b] Determined by chiral-phase HPLC.

Table 3: Aryl-substituted oxindoles as substrates in the enantioselective malonate alkylation.



Entry	Substrate	T [°C]	Yield[a] [%]	*ee*[b] [%]
1		−20	76	−76[c]
2		0	84	81
3		−40	69	84
4		0	74	74
5		−20	76	84

[a] Yield of isolated product. [b] Determined by chiral-phase HPLC. [c] (*R*,*R*)-**3** was employed as ligand.

midoester **9** by Krapcho decarboxylation.[30] Cleavage of phthalimide **9** with hydrazine resulted in rapid formation of spirocyclic bis(lactam) **10**. Double alkylation of oxindole **10** produced bis(*p*-bromobenzyl)lactam **11**, a crystalline compound amenable to single crystal X-ray analysis and determination of absolute configuration.[31]

In addition to spirocyclic motifs, fused pyrrolidinoindolines are also a key moiety found in many natural products. To access this family, quaternary C3-aryl oxindole malonate adduct **12** was subjected to Krapcho decarboxylation[30] and N-alkylation to give methyl ester **13** (Scheme 3). Finally, ester **13** was converted to methyl amide **14** and reduced with $LiAlH_4$, providing lactam **15** with the pyrrolidinoindoline core.

In summary, we have discovered a unique copper-catalyzed enantioselective synthesis of C3-quaternary oxindoles. This stereoablative transformation most likely involves the in situ formation of a highly reactive *o*-azaxylylene from C3-halooxindoles followed by enantioselective malonate addition. Finally, we have demonstrated that our method is

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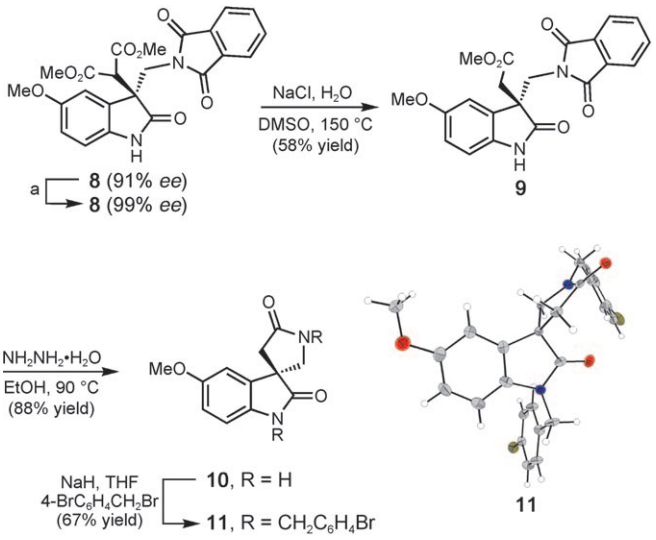
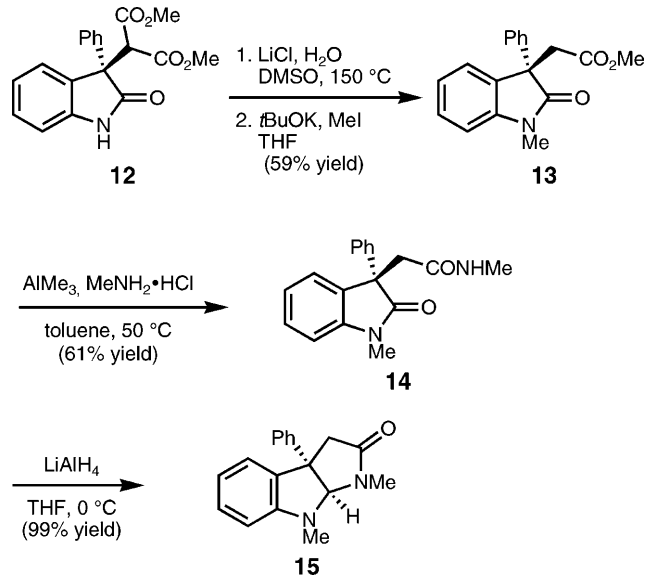


Scheme 2. The synthesis of a pyrrolidinone-spirooxindole. a) Recrystallization from CH_2Cl_2/hexanes (3.5:1), 92% yield.[24]



Scheme 3. The synthesis of a fused indolinopyrrolidinone.

useful for the rapid and stereoselective construction of the core structures of important biologically active alkaloids. Mechanistic studies and further synthetic applications of our method are underway.

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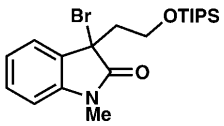
[29] Consistent with our proposal of an *o*-azaxylylene intermediate, exposure of *N*-methyl bromooxindole **16** to our reaction conditions (see Table 2) failed to give any detectable amount of the malonate adduct.



16

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