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Organocatalytic Asymmetric Synthesis of 3-Chlorooxindoles Bearing Adjacent Quaternary–Tertiary Centers

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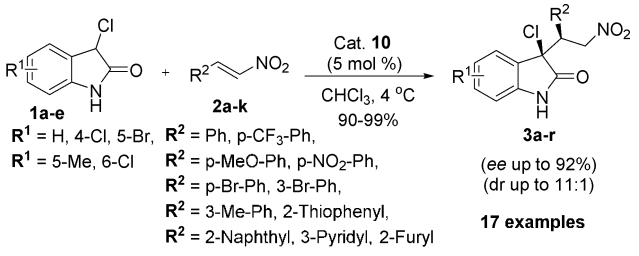
ABSTRACT



A new methodology was developed for the synthesis of enantiomerically enriched 3,3-disubstituted 3-chlorooxindoles 3 via a Michael addition of 3-chloroxindoles to nitroolefins 2, catalyzed by chiral squaramide 10. Products with adjacent quaternary–tertiary centers were isolated in excellent yields (up to 99%), high diastereoselectivities (up to 11:1), and enantiomeric purities (up to 92%). This is the first example where 3-chloroxoindoles 1 have been used as nucleophiles in a highly stereoselective organocatalytic reaction.

Oxindoles bearing a chiral quaternary center at C3 make up the core of many natural products and pharmaceuticals.[1] These compounds are used as building blocks in alkaloid synthesis[2] and, in many cases, as starting materials in medicinal chemistry.[3]

The syntheses of biologically important chiral 3-fluorooxindoles, 3-hydroxyoxindoles,[4] and 3-aminooxindoles have been described;[5] however, the 3,3-disubstituted 3-chlorooxindoles have been synthesized only via asymmetric chlorination of Boc-protected 3-substituted oxindoles.[6] From a synthetic point of view, use of unprotected NH oxindole would be advantageous.[7] However, for oxindoles this is not straightforward due to the high pK_a value of the C–H bond at C3 (pK_a 18.2 in DMSO)[8] and only a small number of successful transformations have been reported.[9] This limitation is usually tackled by introducing an electron-withdrawing protective group (e.g., Boc or acetyl) to the nitrogen atom, thus reducing the pK_a value of the substrate.[10] Alternatively, the same effect can be achieved by placing an electronegative

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atom at the 3-position of the oxindole ring. This is a case of 3-chlorooxindoles where the electronegativity of chlorine will increase the acidity of the C3 proton. This approach not only makes the use of unprotected 3-substituted oxindoles as nucleophiles possible but also presents an opportunity to introduce a chlorine atom at a quaternary center.

To the best of our knowledge, no examples of using 3-chlorooxindoles as nucleophiles in asymmetric 1,4-Michael addition reactions have been reported. This chemistry will provide unconventional access to 3-chlorooxindoles with a chiral quaternary center. A number of successful examples of conjugated addition reactions to nitroolefins using both protected and unprotected 3-aryl- and 3-alkyl-oxindoles have been described previously by Barbas III,[11] Shibasaki,[10a] Maruoka,[12] Zhou,[9b] Enders,[10b] and others. More recently, Melchiorre and co-workers reported a similar transformation of 3-hydroxyoxindoles.[13]

The addition of oxindoles to nitroolefins serves as a potent source of precursors in the synthesis of alkaloids and their derivatives. Also, a number of pharmaceutical agents contain chiral centers with chloro-substitution.[14]

Chiral thioureas[15,16] and, more recently, squaramides[17] are widely used as catalysts to activate nitroolefins for Michael addition reactions. In the conjugated addition reaction described in the present work, the reactivity of both substrates, 3-chlorooxindole **1** and nitroolefin **2**, can be tuned by the appropriate catalyst.

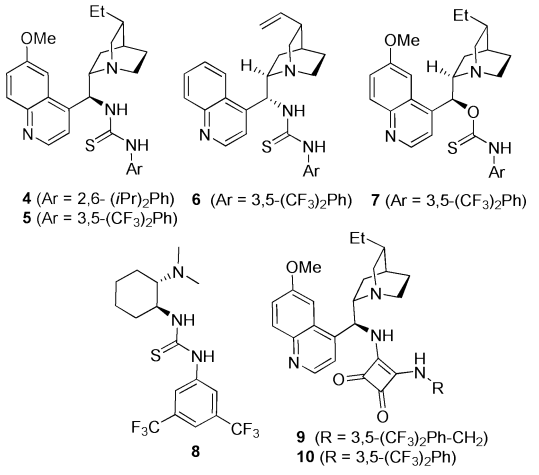
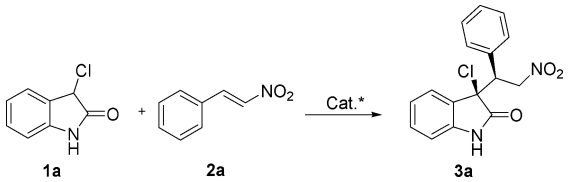


Figure 1. Catalysts used.

It was conjured that bifunctional thioureas or squaramides represent an ideal choice for this role, where the H-bond donor part of the catalyst would serve as an activator to nitroolefin **2**, whereas the tertiary amine subunit, as a chiral base, would facilitate deprotonation/enolization of the 3-chlorooxindole **1**, thus holding both reactants together and promoting the C–C bond formation.

Scheme 1. Model Reaction between 3-Chloroxoindole **1a** and β-Nitrostyrene **2a**[a]



[a] Reaction conditions: 0.1 mmol (1 equiv) of **1a**, 0.12 mmol (1.2 equiv) of **2a**, and 0.05 or 0.1 mmol (5 or 10 mol %) of catalyst.

Our initial studies were focused on the reaction of 3-chlorooxindole **1a** with β-nitrostyrene **2a** (Scheme 1), catalyzed by a thiourea or squaramide catalyst (Figure 1).

Preliminary screening of the catalysts was conducted in chloroform at ambient temperature using 10 mol % of the appropriate catalyst (**4**–**10**, Figure 1) (for details see Supporting Information (SI)). This revealed that, although thioureas **5** and **8** (introduced by Soós[18] and Takemoto[19] respectively) provide high levels of diastereo- and enantiocontrol, squaramides **9** and **10** proved superior in every respect. Catalysts **9** and **10** yielded products with similar enantioselectivities (93% and 90% *ee* respectively); however, the latter provided a slightly better diastereocontrol (3:1 to 6:1, respectively) and was therefore chosen for optimization studies. Screening of the temperature, catalyst loading, and solvent identified the optimal conditions for the reaction as follows: chloroform as a solvent (0.5 M), 1 equiv of **1**, 1.2 equiv of **2**, and 5 mol % of catalyst **10** at 4 °C. Under these conditions, **3a** was obtained in 95% yield, 91% *ee*, and 10:1 dr (Table 1).

With optimal reaction conditions in hand, the substrate scope was explored by reacting 3-chlorooxindole **1a** with different nitroolefins (Table 1). All the reactions were complete within 24 h (Table 1). The substitution pattern in the aromatic ring of the starting nitroolefin **2a**–**j** did not affect the efficacy of the process: the 3-chlorooxindoles **3a**–**j** were uniformly obtained in high yields (90–96%) and high enantio- or diastereoselectivities (*ee* up to 91% and dr up to 11:1).

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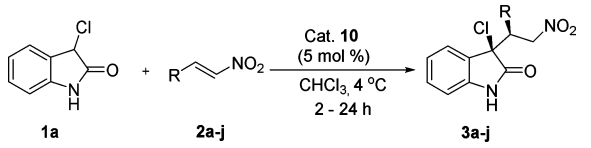
Table 1. Substrate Scope for the Reaction of 3-Chlorooxindole **1a** with Different Nitroolefins[a]



2	3	R	time (h)	yield (%)	dr[b]	*ee* (%)[b]
2a	**3a**	Ph	15	95	10:1	91
2b	**3b**	4-Br-Ph	24	96	11:1	90
2c	**3c**	4-CF_3O-Ph	5	90	7.7:1	86
2d	**3d**	4-NO_2-Ph	23	91	6.7:1	87
2e	**3e**	2-thiophenyl	3	96	10:1	90
2f	**3f**	2-naphthyl	18	95	10:1	90
2g	**3g**	3-pyridyl	7	91	9.1:1	90
2h	**3h**	3-Br-Ph	5	96	11:1	90
2i	**3i**	3-Me-Ph	24	91	11:1	91
2j	**3j**	2-furyl	2	95	5.6:1	88

[a] Reaction conditions: 0.1 mmol (1equiv) of **1a**, 0.12 mmol (1.2 equiv) of **2**, and 0.05 mmol (5 mol %) of squaramide **10** were stirred at ambient temperature in chloroform (0.5 mL); the reaction was monitored by TLC. [b] dr was determined by ^{1}H NMR, and *ee* by chiral HPLC analysis.

To further expand the substrate scope, a series of substituted 3-chlorooxindoles **1a**–**e** were synthesized (for details, see SI). Electronegative substituents at the C5 and C6 of the oxindole core were well tolerated (Table 2, **3k**, **3l**, **3n**, and **3o**), yielding products with nearly quantitative yields, high enantioselectivities (up to 92%), and dr's ranging from 5:1 to 9.1:1 (isomers were inseparable by column chromatography). 5-Methyl substituted 3-chlorooxindole **1d** provided the products (Table 2, **3p** and **3r**) with *ee*'s of 91% and 92%, respectively, and excellent diastereocontrol. 3,4-Dichlorooxindole **1b** proved to be a more challenging substrate, as the product was isolated with high dr but slightly lower *ee* (Table 2, **3m**). This can be explained by the close proximity of chlorine at the 4-position, which may have influenced the formation of the transition state complex.

As a limitation to the method, aliphatic nitroolefin **2l** failed to react with 3-chlorooxindole **1a** under the reaction conditions, even at elevated temperatures (Table 2, **3s**).

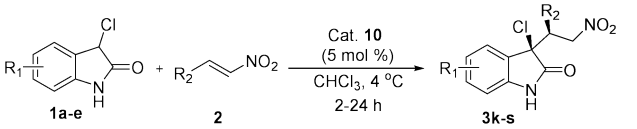
The relative and absolute stereochemistry of 3-chlorooxindole **3m** was unambiguously assigned by single crystal X-ray diffraction (Figure 2).

Other compounds in the series were assigned based on the analogy. According to the observed *syn* geometry of the product, the following transition state for the 1,4-addition to nitroolefins was proposed (Figure 3).

It can be assumed that nitroalkene **2** was activated by the H-bonding to squaramide **10** whereas deprotonation/enolization of 3-chorooxindole **1** was facilitated by the tertiary amine moiety of the catalyst. The *re-face* attack of enolate to the *re-face* of nitroolefin led to the formation of the product with adjacent quaternary–tertiary centers.

These results are in agreement with the literature observations, where 3-alkyloxindoles or 3-aryloxindoles have been used as nucleophiles in a conjugated addition to nitroalkenes under H-bond catalysis.[9a,b,10b,11]

Table 2. Expanding the Substrate Scope[a]



1a (R^1=H); **1b** (R^1=4-Cl)
1c (R^1=5-Br); **1d** (R^1=5-Me)
1e (R^1=6-Cl)

2	3	R^1	R^2	yield (%)	dr[b]	*ee* (%)[b]
2a	**3k**	6-Cl	Ph	97	5:1	90
2k	**3l**	6-Cl	4-MeO-Ph	99	6.3:1	90
2a	**3m**	4-Cl	Ph	99	8.3:1	76
2a	**3n**	5-Br	Ph	99[c]	9.1:1	92
2e	**3o**	5-Br	2-thiophenyl	97[c]	7.1:1	87
2a	**3p**	5-Me	Ph	94	10:1	92
2g	**3r**	5-Me	3-pyridyl	90	8.3:1	91
2l	**3s**	6-Cl	*c*-hexyl	–[d]	–	–

[a] Reaction conditions: 0.1 mmol (1equiv) of **1a**–**e**, 0.12 mmol (1.2 equiv) of **2**, and 0.05 mmol (5 mol %) of squaramide **10** were stirred at ambient temperature in chloroform (0.5 mL); the reaction was monitored by TLC. [b] dr was determined by ^{1}H NMR, and *ee* by chiral HPLC analysis. [c] Reaction conducted at ambient temperature. [d] Temperature was increased from 4 °C to up to 60 °C, but no reaction occurred.

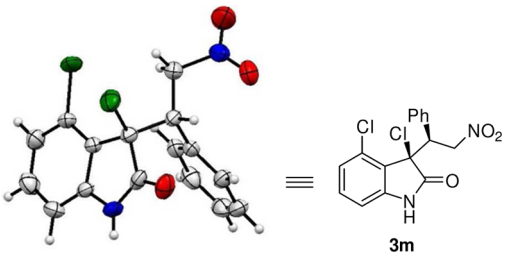


Figure 2. Molecular moiety in the crystal structure of oxindole **3m**. For clarity, only one formula unit is shown ($Z' = 3$). Displacement ellipsoids are drawn at the 50% probability level.

The introduction of a chlorine atom at the quaternary center of oxindole presents a distinctive advantage, as chlorine can serve as a leaving group in nucleophilic substitution reactions. Indeed, it has been shown that in similar 3-chlorooxindoles the chlorine can be substituted by a number of *C*-nucleophiles, as well as being dehalogenated stereospecifically.[20]

Although under the catalysis of squaramide **10** no cyclopropanation or formation of a five-membered ring by the attack of nitronate oxygen was observed, we envisioned that the utility of 3-chlorooxindoles could be expanded by using them as starting materials in a novel cascade reaction, resulting in the formation of spiro-bisoxindoles **12** (Scheme 2).

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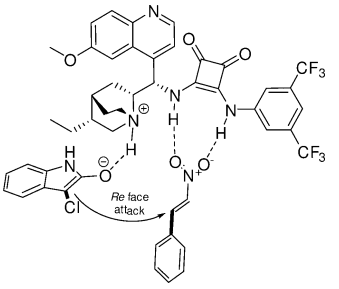
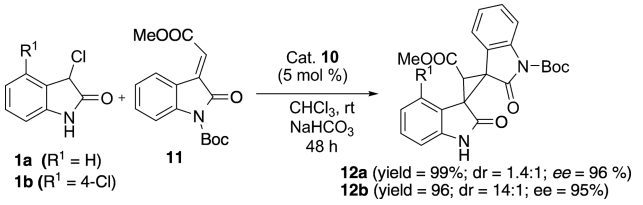


Figure 3. Proposed transition state for the conjugated addition of 3-chlorooxindoles to nitroolefins.

Scheme 2. Synthesis of Spiro-bisoxindoles **10**



To investigate the proposed cascade outlined in Scheme 2, a model reaction between oxindole **11** and 3-chlorooxindole **1a** was chosen. Much to our delight, a high level of enantiocontrol (*ee* 96% for both isomers) was observed with a moderate level of diastereoselectivity (Scheme 2, **12a**).

As a likely scenario of the process, oxindole **11** is activated by the H-bonding to catalyst **10**, whereas 3-chlorooxindole **1** is coordinated by the tertiary amine, resulting in a stereospecific Michael addition followed by the intramolecular cyclization, where chlorine acts as the leaving group. As a result of this cascade of reactions, three contiguous stereogenic centers are formed, two of them being quaternary. From a practical viewpoint, sodium hydrogen carbonate was used as a scavenging agent to neutralize the hydrogen chloride released during the reaction, as excess HCl could render the catalyst inactive.

Of eight possible stereoisomers, only two were formed. The observed similar levels of enantiomeric purity of both diastereoisomers lead us to speculate that, as a likely scenario, diastereoselectivity could be determined by the first Michael addition step, although without knowing the relative stereochemisty of both isomers we cannot really unambiguously determine where the diastereoselectivity is derived. Further support of this hypothesis, however, was received when a sterically bulky substituent within 3-chlorooxindole **1b** caused a remarkable increase in diastereoselectivity (Scheme 2, **12b**). These results present an important avenue for further studies. The substrate scope, as well as the stereochemistry of the reaction, will be further investigated by our group and reported in due course.

In conclusion, we have developed a novel methodology for the synthesis of 3,3-disubstituted 3-chlorooxindoles **3a**–**r** *via* a conjugated addition of 3-chlorooxindoles to nitroolefins under organocatalytic conditions. High levels of diastereoselectivity (dr up to 11:1) and enantioselectivity (*ee* up to 92%) were observed, with the yields ranging from 90 to 99%. Both electron-donating and -withdrawing groups were well tolerated at the aromatic ring of nitroalkenes as well as the heteroaromatic substituents. To the best of our knowledge, this represents the first catalytic asymmetric reaction where 3-chlorooxindoles **1** have been used as nucleophiles to yield products with adjacent quaternary–tertiary stereocenters. It was further demonstrated that, under similar reaction conditions, oxindoles **11** could be also used as Michael acceptors resulting in the formation of spiro-bisoxindoles **12** with high levels of diastereo- and enantiocontrol. Elaboration of this method will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, ^{1}H, ^{13}C NMR spectra, chiral HPLC chromatograms, and X-ray data of **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.