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Chiral Calcium VAPOL Phosphate Mediated Asymmetric Chlorination and Michael Reactions of 3-Substituted Oxindoles

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Abstract

We disclose a novel high yielding and highly enantioselective chiral calcium VAPOL phosphate-catalyzed chlorination of 3-substituted oxindoles with *N*-chlorosuccinimide (NCS). The reaction conditions are also shown to be effective for the catalytic enantioselective Michael addition of 3-aryloxindoles to methyl vinyl ketone.

Oxindoles bearing a tetrasubstituted chiral carbon center at the 3-position are important structural motifs found in alkaloid natural products and pharmaceuticals.[1] For this reason, methods for the stereoselective synthesis of chiral 3,3'-disubstituted oxindoles are of considerable interest.[1–3] Chiral oxindoles containing a heteroatom at the 3-position have found applications in medicinal chemistry.[4–6] Catalytic enantioselective methods for the synthesis of biologically important chiral 3-heteroatom substituted oxindoles such as 3-fluorooxindoles,[4] 3-hydroxyloxindoles[3a,5] and 3-aminooxindoles[3b,6] have been recently reported. In spite of these advancements, methods detailing the efficient enantioselective synthesis of 3-chlorooxindoles, which are potentially important in medicinal chemistry, are unavailable.[7–9]

Despite the fact that numerous important pharmaceutical agents contain chiral centers with chloro-substitution[10] there has been little corresponding progress in asymmetric chlorination. The examples of highly enantioselective chlorination are rare and often limited to 1,3-dicarbonyl compounds, such as β-keto esters[11] and aliphatic aldehydes.[12] Thus, the development of novel asymmetric chlorinations involving other substrate classes is of considerable importance.

Group 2 alkaline-earth metals, such as calcium, strontium and barium are abundant, inexpensive and relatively nontoxic, but their use in organic synthesis is fairly limited.[13] Applications of these metals as catalysts in asymmetric transformations is even more scarce.[14] Herein, we describe a novel enantioselective chlorination of oxindoles with *N*-chlorosuccinimide (NCS) catalyzed by a chiral calcium VAPOL phosphate to afford the product in quantitative yield with high enantioselectivity. Furthermore, we demonstrate that the methodology can be effectively extended to the catalytic enantioselective Michael addition of oxindoles to methyl vinyl ketone.

As part of our ongoing program toward the development of new chiral phosphoric acid-catalyzed asymmetric reactions,[15] we theorized that chiral phosphoric acids could activate NCS via protonation of the imide carbonyl. Following an initial screening of chiral phosphoric acids (purified by silica gel column chromatography),[16] we found VAPOL

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org

phosphoric acid (**PA1**) to be the best catalyst in terms of enantioselectivity. **PA1** also demonstrated the ability to dramatically accelerate the reaction (Table 1, entry 2 vs. entry 1). Solvent screening showed isopropyl acetate to be the most suitable solvent, allowing for 80% *ee* of **2** in just 1 h (Table 1, entries 2–6). When the concentration was decreased to 0.05 M, the *ee* increased to 90% (Table 1, entry 7).

Surprisingly, **PA1** washed with 6 *N* HCl, led to the formation of racemic product (Table 1, entry 8). Comparison of this result to a recent report by Ishihara and co-workers,[17] documenting the presence of chiral phosphate salts in the absence of a final HCl wash of the chiral phosphoric acid/salt mixture obtained by silica gel purification, led us to investigate different chiral VAPOL phosphate salts (Table 1, entries 9–14). Sodium and K derived VAPOL phosphates afforded racemic product (Table 1, entries 9 and 10). Magnesium, Ca, and Sr derived VAPOL phosphates allowed for the chlorination product with dramatically increased enantioselectivity (Table 1, entries 11–14). To our delight, the calcium derived VAPOL phosphate salt was able to yield the product with 99% yield and 91% *ee*. The enantioselectivity could be further increased to 94% through the slow addition of NCS.[18]

With the optimized conditions in hand, we turned our focus to the substrate scope and generality of the reaction. The introduction of electron-donating and electron-withdrawing groups on both the oxindole core and the 3-aryl group provided for products with excellent enantioselectivity with 10 minute reaction times. The enantioselectivity of products bearing electron-donating groups was found to be slightly lower than that of products bearing electron-withdrawing groups (Table 2, **2b** vs. **2c** and **2e** vs. **2f**). High yield and modest enantioselectivity can be obtained even with an alkyl substituent at the 3 position of the oxindole. With a 3-methyl substituted oxindole as a substrate, the reaction affords the product with 98% yield and 62% *ee* (Table 2, **2k**), although a longer reaction time is required. Variation of the carbamate protecting group afforded the product with high enantioselectivity (Table 2, **2l**), while lower *ee* or complete loss of reactivity was observed with other protecting groups on nitrogen.[19]

Although a detailed mechanism has yet to be elucidated, we propose a transition-state (Figure 1) that highlights the bifunctional nature of the chiral calcium VAPOL phosphate in activation of both the nucleophile and the electrophile.[14,17] Chelation of the carbonyl oxygens of the BOC group and the NCS to calcium creates a more compact reaction sphere. The increased Brønsted basicity of the chiral phosphate further activates the oxindole tautomer. Hydrogen bonding interactions between the oxindole tautomer and NCS coupled with the above mentioned interactions could allow for the high enantiocontrol observed.

Based on the proposed transition-state, we envisioned this newly developed chlorination protocol could be applied to other reaction systems. Methyl vinyl ketone (MVK) is an exemplary electrophile for Michael additions.[3e,20] Application of our chlorination protocol to MVK afforded products bearing a quaternary carbon center with both high yield and high enantioselectivity (Table 3).[21]

In conclusion, we have developed a facile method for the highly efficient enantioselective chlorination of oxindoles catalyzed by a novel chiral calcium VAPOL phosphate salt. This method provides access to 3-chloro-oxindole products with high enantioselectivity. The aforementioned VAPOL phosphate salt was also found to be a highly effective promoter for the Michael reaction of 3-aryloxindoles with methyl vinyl ketone. Mechanistic investigations and extension of the asymmetric chlorination protocol to additional reaction systems is currently under investigation in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(16). For details on our initial catalyst/solvent screening, please see the supporting information.

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(18). When the reaction was run under identical conditions with NBS as the electrophile a 48% *ee* was found for the brominated product.

(19). 60% ee was observed for the Ac-protected oxindole, while no reactivity was seen for the Bn-protected oxindole. The Ts-protected product was unable to be separated by HPLC.

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(21). Examples of additional Michael acceptors that were tested can be found in the supporting information.

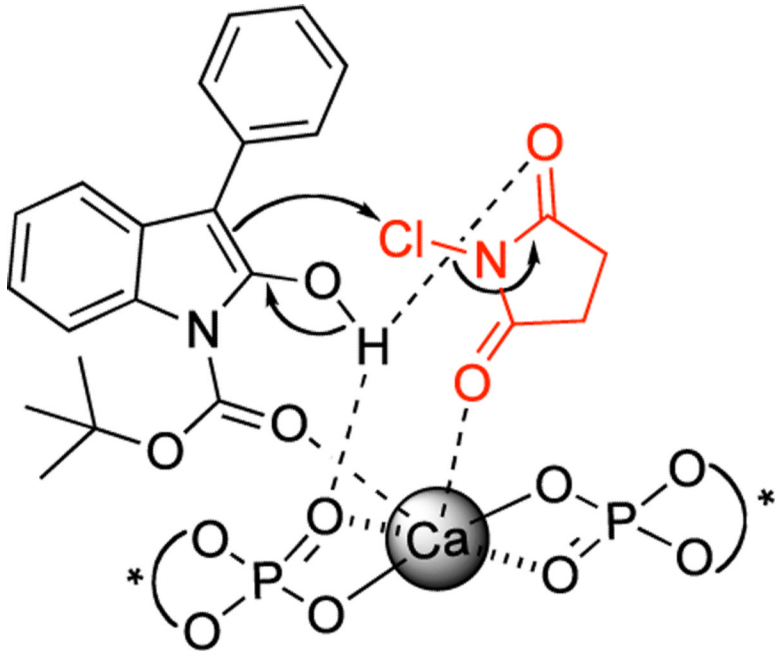
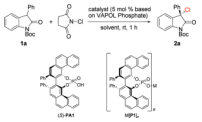


Figure 1.
Proposed transition-state for the asymmetric chlorination of oxindole **1a**.

Table 1

Catalyst Optimization for the Asymmetric Chlorination of 3-Phenyloxindole **1a**.[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1[d]	-	toluene	< 20	-
2	**PA1** purified on silica gel	toluene	99	51
3	**PA1** purified on silica gel	DCM	99	48
4	**PA1** purified on silica gel	EtOAc	99	50
5	**PA1** purified on silica gel	benzene	99	60
6	**PA1** purified on silica gel	*i*-PrOAc	99	80
7[e]	**PA1** purified on silica gel	*i*-PrOAc	99	90
7[e,f]	**PA1** washed with HCI	*i*-PrOAc	99	0
9[e]	Na[**P1**]	*i*-PrOAc	99	6
10[e]	K[**P1**]	*i*-PrOAc	99	0
11[e]	Mg[**P1**]$_2$	*i*-PrOAc	99	37
12[e]	Ca[**P1**]$_2$	*i*-PrOAc	99	91
13[e]	Sr[**P1**]$_2$	*i*-PrOAc	99	86
14[e]	Ba[**P1**]$_2$	*i*-PrOAc	99	9
15[g]	Ca[**P1**]$_2$	*i*-PrOAc	99	94

[a] Reaction conditions: **1a** (1.0 equiv), NCS (1.2 equiv), 5 mol % catalyst (based on VAPOL phosphate), with solvent indicated [0.10 M].

[b] Isolated yield.

[c] Enantiomeric excess determined by chiral HPLC analysis.

[d] Reaction time of 24 h.

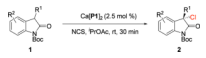
[e] Reaction performed at [0.050 M].

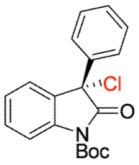
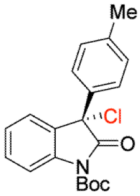
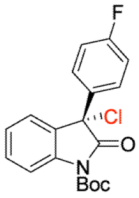
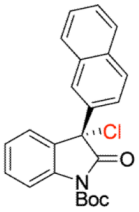
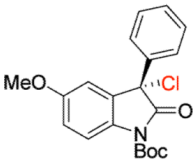
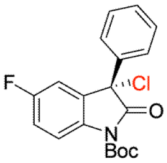
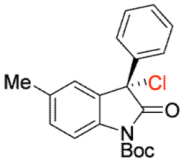
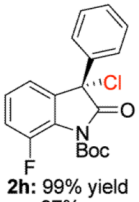
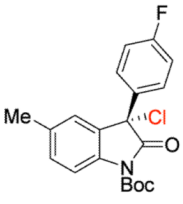
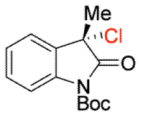
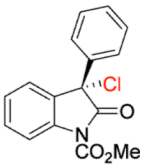
[f] Reaction time of 3 h.

[g] NCS was added as a [0.12 M] solution in *i*-PrOAc.

Table 2

Substrate Scope for the Ca[**P1**]$_2$ Catalyzed Asymmetric Chlorination.[a]



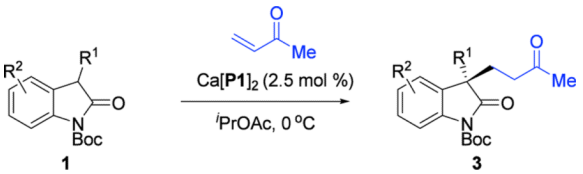
 **2a:** 99% yield 94% *ee*	 **2b:** 99% yield 93% *ee*	 **2c:** 99% yield 96% *ee*	 **2d:** 99% yield >99% *ee*
 **2e:** 99% yield 90% *ee*	 **2f:** 99% yield 93% *ee*	 **2g:** 99% yield 87% *ee*	 **2h:** 99% yield 97% *ee*
 **2i:** 99% yield 92% *ee*	 **2j:** 99% yield 98% *ee*	 **2k**[b]: 98% yield 62% *ee*	 **2l:** 99% yield 97% *ee*

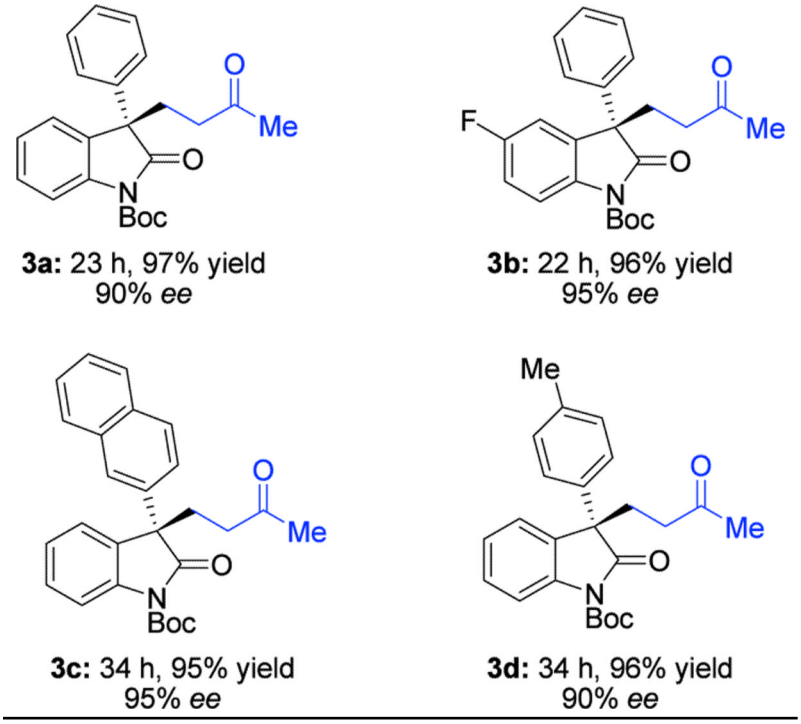
[a]Reaction conditions: **1** (1.0 equiv), Ca[**P1**]$_2$ (2.5 mol %), and NCS (1.2 equiv) is added as a 0.12 M solution in *i*-PrOAc over 20 min. The (*S*)-VAPOL derived salt was used in each example.

[b]Reaction time of 80 min.

Table 3

Asymmetric Michael Reaction of Oxindoles and Methyl Vinyl Ketone Catalyzed by Ca[**P1**]$_2$[a]





[a]Reaction conditions: **1** (1.0 equiv), methyl vinyl ketone (3.0 equiv), and 2.5 mol % catalyst at 0 °C. Yields reported are isolated. Enantiomeric excess was determined by Chiral HPLC Analysis. The (*R*)-VAPOL derived salt was used in each example.