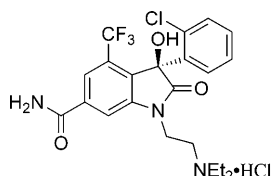


Highly Enantioselective Catalytic Benzoyloxylation of 3-Aryloxindoles Using Chiral VAPOL Calcium Phosphate**

Zuhui Zhang, Wenhua Zheng, and Jon C. Antilla*

3-Hydroxy-2-oxindoles are structural motifs present in a number of natural products and biologically active compounds.^[1,2] Among these molecules, 3-aryl-3-hydroxyoxindoles represent an important class of molecules that have found broad applications in medicinal chemistry. One such example is SM-130686 (Scheme 1), a compound exhibiting

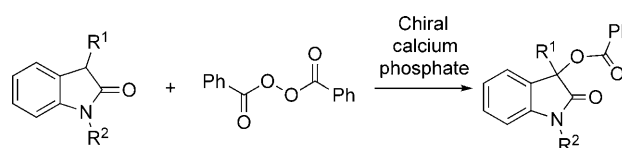


Scheme 1. Structure of SM-130686.

potent activity with respect to growth hormone release.^[2a] The absolute configuration of the hydroxy group at the C3 position was shown to further modulate the biological activity.^[2c] It is therefore of high importance to introduce asymmetry at the C3 position with high enantiocontrol. To date, only a limited number of approaches have been reported, which outline the preparation of chiral 3-hydroxy-2-oxindoles. One type of approach calls for the asymmetric nucleophilic addition of organometallic reagents^[3] or electron-rich reagents^[4–6] to isatins. The second approach entails asymmetric hydroxylation of 3-substituted 2-oxindoles.^[7] Despite these developments, the available methodologies are often limited and a new methodology is highly desirable, considering the importance of chiral 3-substituted oxindoles.

Since the independent reports by Akiyama and Terada in 2004,^[8] chiral phosphoric acids have proven to be versatile catalysts and have subsequently been applied to a variety of transformations with high stereocontrol.^[9] Moreover, the alkali or alkaline earth derived salts of chiral phosphoric acids have proven to be highly effective catalysts in several recent reports.^[10]

Benzoyl peroxide (BPO) is a readily available oxylation reagent, which has been known for decades.^[11] Nonetheless, asymmetric oxylation using BPO are very rare.^[12] Herein, we describe, to the best of our knowledge, the first example of a highly enantioselective benzoyloxylation of an oxindole with BPO catalyzed by a chiral calcium phosphate (Scheme 2).^[13] By comparison to published reports, this work provides access to 3-hydroxyoxindole derivatives with the highest stereoselectivity to date.



Scheme 2. Enantioselective benzoyloxylation of oxindoles.

We began our investigation with 3-phenyloxindole **1a** and BPO as substrates, and toluene as the solvent, as a starting point for optimization studies. Chiral phosphoric acids purified by silica gel column chromatography, were then screened. Catalysts H[P1], H[P4], and H[P6] (Table 1, entries 1, 4, and 6) imparted meagre stereoselectivity. H[P6], a VAPOL-derived phosphoric acid, proved to be the best catalyst when TBME was the solvent (Table 1, entries 7–9). The reverse selectivity was observed in DCM (Table 1, entry 10).^[14] To our delight, an upgrade to 99% *ee* was obtained using diethyl ether (Table 1, entry 11). Interestingly, H[P6] washed with 6 N HCl exhibited poor catalytic efficiency and enantioselectivity under the same conditions (Table 1, entry 12). Correlation of this result to that of a recent report by Ishihara and co-workers,^[10a] showing a high abundance of chiral phosphate salts in the absence of a final HCl wash of the chiral phosphoric acid/salt mixture obtained by silica gel purification, directed us to propose the active catalytic species to be that of a chiral phosphate salt.^[15] To identify the metal counterion, several variants of **P6** were prepared and evaluated. Na[P6] and K[P6] afforded the product with no selectivity (Table 1, entries 13 and 14). Ca[P6]₂ and Sr[P6]₂ both induced remarkably high selectivity (> 99%) (Table 1, entries 15 and 16). Ba[P6]₂ allowed for a significantly lower enantioselectivity (7%) (Table 1, entry 17). Mg[P6]₂ furnished the product with 60% *ee*, but with the opposite configuration (Table 1, entry 18), presumably due to a difference on coordination spheres compared to calcium.^[16] To our delight, excellent enantioselectivity (95%) is still observed with Ca[P6]₂, even when the catalyst loading is reduced to 0.10 mol% (Table 1, entry 22).

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Table 1: Screening of catalysts and solvents.^[a]

$\text{1a} + \text{BPO} \xrightarrow[\text{solvent, RT, 20 h}]{\text{catalyst}} \text{2a}$

$\text{R} = 9\text{-anthryl, H[P1]}$
 $\text{R} = 9\text{-phenylanthryl, H[P2]}$
 $\text{R} = \alpha\text{-naphthyl, H[P3]}$
 $\text{R} = \text{SiPh}_3, \text{H[P4]}$
 $\text{R} = 3,5\text{-CF}_3\text{C}_6\text{H}_3, \text{H[P5]}$

M[P6]_n

	Solvent	Catalyst (mol %)	Yield [%] ^[b]	ee [%] ^[c]
1	toluene	H[P1] purified on silica gel (5)	77	50
2	toluene	H[P2] purified on silica gel (5)	65	0
3	toluene	H[P3] purified on silica gel (5)	79	30
4	toluene	H[P4] purified on silica gel (5)	80	40
5	toluene	H[P5] purified on silica gel (5)	84	0
6	toluene	H[P6] purified on silica gel (5)	81	45
7	TBME	H[P1] purified on silica gel (5)	80	72
8	TBME	H[P4] purified on silica gel (5)	78	36
9	TBME	H[P6] purified on silica gel (5)	80	96
10	DCM	H[P6] purified on silica gel (5)	56	–36
11	ether ^[d]	H[P6] purified on silica gel (5)	81	99
12	ether	H[P6] washed with HCl (5)	11	15
13	ether	Na[P6] (5)	62	2
14	ether	K[P6] (5)	18	2
15	ether	Ca[P6] ₂ (2.5)	83	> 99
16	ether	Sr[P6] ₂ (2.5)	82	> 99
17	ether	Ba[P6] ₂ (2.5)	51	7
18	ether	Mg[P6] ₂ (2.5)	80	–60
19	ether	Ca[P6] ₂ (1.0)	82	99
20	ether	Ca[P6] ₂ (0.5)	81	98
21	ether	Ca[P6] ₂ (0.25)	81	97
22	ether	Ca[P6] ₂ (0.10)	80	95

[a] Reaction conditions: **1a** (1.0 equiv), BPO (1.1 equiv), catalyst (*x* mol %), solvent (0.1 M) under argon. [b] Yield of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. TBME: *tert*-butyl methyl ether. [d] Ether in entries 11–22 means diethyl ether.

With the optimized reaction conditions in hand, we turned our attention to the scope of the asymmetric benzoyloxylolation of 3-aryloxindoles with Ca[P6]₂. As shown in Table 2, introduction of either electron-donating or electron-withdrawing groups on the 3-aryl ring or the arene ring of the oxindole have little effect on the enantioselectivity (**2a–2m**). The majority of products were obtained with 99% *ee* and good yield. It is worthy of note that 3-aryloxindoles bearing a heteroatom can provide the desired product with excellent enantioselectivity (**2n**). Unfortunately, no product was detected using 3-benzoyloxindole due to lower reactivity.

Determination of the absolute configuration of the products, as well as potential synthetic utility of this methodology is shown in Scheme 3. Boc-deprotection followed by reduction of the benzoyl group of **2a** yielded known compound **4a** in two steps with good overall yield and excellent retention of chirality.^[17]

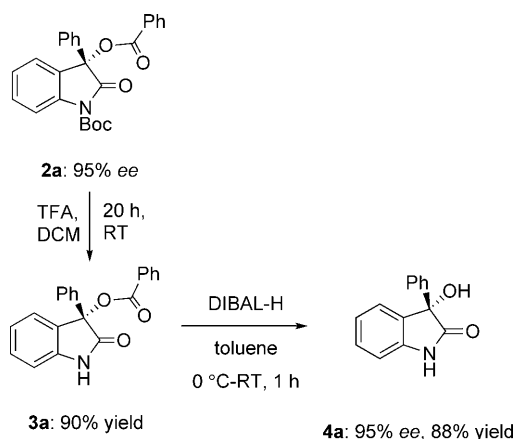
Table 2: Substrate scope for the asymmetric benzoyloxylolation of oxindoles.^[a]

$\text{1a-n} + \text{BPO} \xrightarrow[\text{diethyl ether, RT, 20 h}]{\text{Ca[P6]}_2 (2.5 \text{ mol \%})} \text{2a-n}$

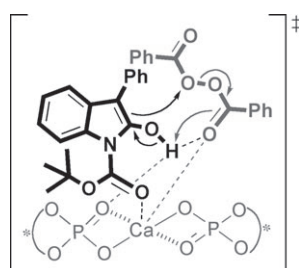
 2a : 99.7% <i>ee</i> , 83% yield	 2b : 99% <i>ee</i> , 92% yield	 2c : 99% <i>ee</i> , 96% yield
 2d : 99% <i>ee</i> , 78% yield	 2e : 99% <i>ee</i> , 87% yield	 2f : 91% <i>ee</i> , 63% yield ^[b]
 2g : 99% <i>ee</i> , 94% yield	 2h : 99% <i>ee</i> , 90% yield	 2i : >99% <i>ee</i> , 96% yield
 2j : 99% <i>ee</i> , 90% yield	 2k : 99% <i>ee</i> , 88% yield	 2l : 99% <i>ee</i> , 92% yield
 2m : 99% <i>ee</i> , 96% yield	 2n : 97% <i>ee</i> , 60% yield	

[a] Reaction conditions: **1a–n** (1.0 equiv), BPO (1.1 equiv), Ca[P6]₂ (2.5 mol %), diethyl ether (0.1 M) at room temperature under argon. Yields refer to isolated product. Enantiomeric excess was determined by HPLC analysis using either a chiral AD-H or OD-H column. [b] (R)-Ca[P6]₂ was used as the catalyst.

While a detailed mechanism for this novel transformation is unknown, we propose that the bifunctional nature of the chiral calcium phosphate salt allows for activation of both the nucleophile and the electrophile, as shown in Scheme 4. Two characteristics of calcium were considered in developing this plausible transition state. First, the low electronegativity of calcium should lead to a significant increase in the Brønsted basicity of the chiral phosphate counteranion. Second, calcium's various coordination sites presumably allow for a greater number of favorable electrostatic interactions.^[18] The coordination between calcium and the carbonyl oxygens of both BPO and the Boc-group of the oxindole serve not only to activate the electrophile but also force the two substrates to be in closer proximity to one another, in the chiral environment. These interactions coupled with the hydrogen-bonding



Scheme 3. Transformation of **2a** to known hydroxyoxindole **4a**. TFA = trifluoroacetic acid, DIBAL-H = diisobutylaluminum hydride.



Scheme 4. Proposed transition state for the $\text{Ca}[\text{P6}]_2$ -catalyzed benzoyloxylation of oxindole **1a**.

interactions between the hydroxy group of the oxindole tautomer and the $\text{P}=\text{O}$ moiety of the catalyst can be used to rationalize the unprecedented enantioselectivity observed.

In conclusion, we report a novel asymmetric benzoyloxylation of 3-aryl-2-oxindoles catalyzed by a chiral VAPOL calcium phosphate salt. This transformation utilizes readily available benzoyl peroxide as a benzoyloxylation reagent. A series of 3-aryl-3-benzoyloxindoles are obtained with good yields and excellent enantioselectivities. Further studies of the benzoyloxylation of additional nucleophiles are currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General procedure: Oxindole **1** (0.10 mmol, 1.0 equiv), benzoyl peroxide (0.11 mmol, 26.6 mg, 1.1 equiv), and $\text{Ca}[\text{P6}]_2$ (2.5 mol %, 3.2 mg) were added to a flame-dried test tube. The vessel was placed under vacuum and the atmosphere exchanged with argon three times before the addition of ether (1.0 mL). The reaction was stirred at room temperature for 20 h and the reaction mixture then purified directly by silica gel column chromatography (eluent: hexanes/ethyl acetate 15:1 to 2:1) to afford pure product **2**.

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- [1] a) Y.-Q. Tang, I. Sattler, R. Thiericke, S. Grabley, X.-Z. Feng, *Eur. J. Org. Chem.* **2001**, 261–267; b) C.-Y. Gan, T.-S. Kam, *Tetrahedron Lett.* **2009**, 50, 1059–1061; c) H. Suzuki, H. Morita, M. Shiro, J. Kobayashi, *Tetrahedron* **2004**, 60, 2489–2495; d) J. Kohno, Y. Koguchi, M. Nishio, K. Nakao, M. Kuroda, R. Shimizu, T. Ohnuki, S. Komatsubara, *J. Org. Chem.* **2000**, 65, 990–995.
- [2] a) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi, R. Nagata, *J. Med. Chem.* **2001**, 44, 4641–4649; b) T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji, R. Nagata, *Bioorg. Med. Chem. Lett.* **2005**, 15, 1789–1792; c) P. Hewawasam, M. Erway, S. L. Moon, J. Niipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang, V. K. Gribkoff, N. A. Meanwell, *J. Med. Chem.* **2002**, 45, 1487–1499.
- [3] a) D. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, 131, 6946–6948; b) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem.* **2006**, 118, 3431–3434; *Angew. Chem. Int. Ed.* **2006**, 45, 3353–3356; c) J. Itoh, S. B. Han, M. J. Krische, *Angew. Chem.* **2009**, 121, 6431–6434; *Angew. Chem. Int. Ed.* **2009**, 48, 6313–6316; d) C. D. Grant, M. J. Krische, *Org. Lett.* **2009**, 11, 4485–4487; e) K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem.* **2003**, 115, 5647–5650; *Angew. Chem. Int. Ed.* **2003**, 42, 5489–5492; f) P. Y. Toullec, R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. L. Minnaard, *Org. Lett.* **2006**, 8, 2715–2718; g) H. Lai, Z. Huang, Q. Wu, Y. Qin, *J. Org. Chem.* **2009**, 74, 283–288.
- [4] For examples using electron-rich nucleophiles, see: a) N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fetting, A. K. Franz, *Angew. Chem.* **2010**, 122, 756–759; *Angew. Chem. Int. Ed.* **2010**, 49, 744–747; b) P. Chauhan, S. S. Chimni, *Chem. Eur. J.* **2010**, 16, 7709–7713; c) T. Nakamura, S. Shirokawa, S. Hosokawa, A. Nakazaki, S. Kobayashi, *Org. Lett.* **2006**, 8, 677–679.
- [5] For aldol-type reactions catalyzed by secondary amines, see: a) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman, C. Tomasini, *J. Org. Chem.* **2005**, 70, 7418–7421; b) T. Itoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2009**, 11, 3854–3857; c) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková, P. Kočovský, *Org. Lett.* **2007**, 9, 5473–5476; d) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, 14, 8079–8081; e) N. Hara, S. Nakamura, N. Shibata, T. Toru, *Chem. Eur. J.* **2009**, 15, 6790–6993; f) G. Luppi, M. Monari, R. J. Correa, F. A. Violante, A. C. Pinto, B. Kaptein, Q. B. Broxterman, S. J. Garden, C. Tomasini, *Tetrahedron* **2006**, 62, 12017–12024; g) J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang, W.-J. Xiao, *Tetrahedron* **2007**, 63, 10437–10444.
- [6] For an MBH reaction catalyzed by an alkaloid, see: Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang, J. Zhou, *J. Am. Chem. Soc.* **2010**, 132, 15176–15178.
- [7] a) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *J. Am. Chem. Soc.* **2006**, 128, 16488–16489; b) D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, 10, 1593–1595; c) T. Bui, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2010**, 132, 5574–5575.
- [8] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, 116, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, 43, 1566–1568; b) D. Uruguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356–5357.
- [9] For reviews, see: a) T. Akiyama, *Chem. Rev.* **2007**, 107, 5744–5758; b) M. Terada, *Synthesis* **2010**, 1929–1982; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) A. D. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, 107, 5713–5743.
- [10] a) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, 122, 3911–3914; *Angew. Chem. Int. Ed.* **2010**, 49, 3823–3826; b) M. Klusmann, L. Ratjen, S. Hoffmann, V. Wakchaure,

- R. Goddard, B. List, *Synlett* **2010**, 2189–2192; c) M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776–1780; d) K. Shen, X. Liu, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2009**, *15*, 6008–6014.
- [11] For representative examples, see: a) R. L. Augustine, *J. Org. Chem.* **1963**, *28*, 581–582; b) S. J. Hecker, K. M. Werner, *J. Org. Chem.* **1993**, *58*, 1762–1765.
- [12] a) T. Kano, H. Mii, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 3450–3451; b) M. J. P. Vaismaa, S. C. Y. Yau, N. C. O. Tomkinson, *Tetrahedron Lett.* **2009**, *50*, 3625–3627; c) H. Gotoh, Y. Hayashi, *Chem. Commun.* **2009**, 3083–3085.
- [13] Selected examples of enantioselective reactions with chiral Ca catalysts: a) T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki, R. Noyori, *Tetrahedron Lett.* **2001**, *42*, 4669–4671; b) G. Kumaraswamy, M. N. V. Sastry, N. Jena, *Tetrahedron Lett.* **2001**, *42*, 8515–8517; c) G. Kumaraswamy, N. Jena, M. N. V. Sastry, M. Padmaja, B. Markondaiah, *Adv. Synth. Catal.* **2005**, *347*, 867–871; d) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364–5365; e) T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332; f) S. Kobayashi, T. Tsubogo, S. Saito, Y. Yamashita, *Org. Lett.* **2008**, *10*, 807–809; g) T. Poisson, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7890–7892; h) T. Poisson, T. Tsubogo, Y. Yamashita, S. Kobayashi, *J. Org. Chem.* **2010**, *75*, 963–965. Sr catalysts: i) M. Agostinho, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2430–2431; j) S. Kobayashi, M. Yamaguchi, M. Agostinho, U. Schneider, *Chem. Lett.* **2009**, *38*, 296–297.
- [14] For a similar solvent effect, see: J. Zhou, M.-C. Ye, Z.-Z. Huang, Y. Tang, *J. Org. Chem.* **2004**, *69*, 1309–1320.
- [15] For a recent report demonstrating the importance of reacidification, see: M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903–6906; *Angew. Chem. Int. Ed.* **2008**, *47*, 6798–6801.
- [16] For a review, see: M. Bartók, *Chem. Rev.* **2010**, *110*, 1663–1705.
- [17] For details, see the Supporting Information.
- [18] *Basic Inorganic Chemistry*, 3rd ed. (Eds.: F. A. Cotton, G. Wilkinson, P. L. Gaus), Wiley, New York, **1995**.