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Asymmetric *N*-Hydroxyalkylation of Indoles with Ethyl Glyoxalates Catalyzed by a Chiral Phosphoric Acid: Highly Enantioselective Synthesis of Chiral *N,O*-Aminal Indole Derivatives

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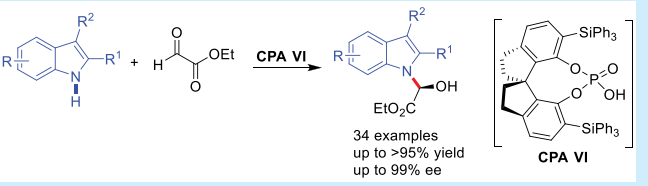
Supporting Information

ABSTRACT: A method of SPINOL-derived chiral phosphoric acid catalyzed asymmetric intermolecular *N*-hydroxyalkylation of multisubstituted indoles with ethyl glyoxalates is described in this report. This protocol provides an alternative, convenient, and direct strategy for efficient access to structurally unique α-chiral indole *N,O*-acyclic aminals with a broad substrate scope and good to excellent enantioselectivities. The synthetic utility of this methodology is illustrated by a gram-scale experiment and the subsequent efficient synthesis of more complex chiral *N,O*-aminal indole derivatives.



The framework for the asymmetric synthesis of chiral indoles is important and of interest because of their prevalence in bioactive natural products and pharmaceuticals.[1] Consequently, extensive efforts have been undertaken to explore the catalytic asymmetric reactions of indoles. In the past decades, significant advances have been made in the enantioselective functionalization of indoles at the C3- or C2-positions.[2] However, enantioselective functionalization of indole N−H was still a challenge due to the weak nucleophilicity.[3] In recent years, some successful examples of catalytic asymmetric *N*-alkylations of indoles were established, such as aza-Michael additions (Bandini and Umani-Ronchi,[4a,b] Wang,[4c] You,[4d] Trost,[4e] Lu,[4f] Shi[4g]), *N*-allylic alkylation (Trost,[5a] Chen,[5b] Hartwig,[5c] You,[5d,e] Xiao[5f]), and hydroamination of alkenes (Hartwig),[6a] alkynes (Dong),[6b] and allenes (Breit).[6c] More recently, Peters and Fu[7a] demonstrated asymmetric copper-catalyzed N−H functionalization of indoles induced by visible light. The Sun[7b] reported a novel *N*-alkylation of indoles via 1,6-conjugate addition of aza-*para*-quinone methides. Despite these advances, the development of more efficient and novel chiral indole *N*-functionalization formation methods continues to be extensively investigated in synthetic chemistry.

Chiral *N,O*-aminals of indoles, molecules bearing an *N,O*-substituted α-chiral carbon center on the N1-position of indoles, have been recognized as important structural motifs and are often critical to the biological activity in natural products and pharmaceutical drugs (Figure 1).[8,9] For example, vincamine[10] has cerebroprotective activity and functions in improving the global cerebral blood flow; Elbasvir,[11] an inhibitor of the HCV (hepatitis C virus) NS5A protein, has been clinically studied as a highly effition compound in the treatment of the HCV infection. In addition, compared to the corresponding imines,[12] *N,O*-aminals often display transformations in organic syntheses.[13] Therefore, the design and

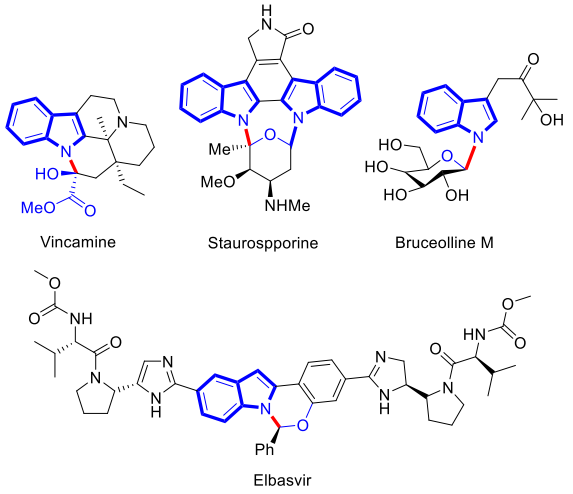


Figure 1. Important molecules containing chiral indole *N,O*-aminals skeletons.

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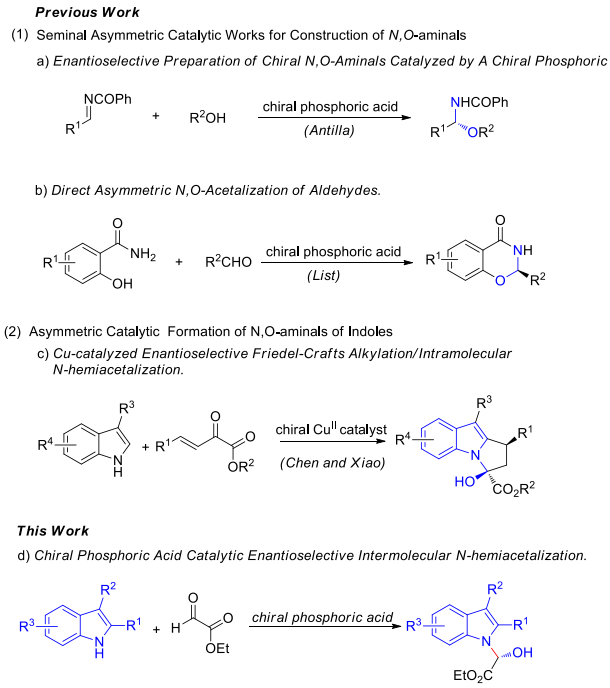
development of an efficient method for the direct catalytic enantioselective synthesis of chiral *N,O*-aminals of indoles is highly desirable. Over the past decades, the asymmetric construction of *N,N*-aminals[14] and *N,O*-aminals[15] has drawn considerable attention from synthetic chemists. In 2008, the seminal work of enantioselective synthetic *N,O*-aminals via addition of alcohols to imines catalyzed by a chiral phosphoric acid was reported by Antilla (Scheme 1A).[15a] In 2009, direct

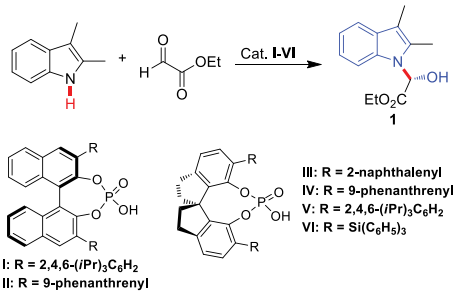
Scheme 1. Asymmetric Catalytic Works for Forming *N,O*-Aminals



asymmetric *N,O*-acetalization of aldehydes catalyzed by a chiral Brønsted acid was reported by List (Scheme 1B).[15b] However, to date, only a few examples of the asymmetric formation of *N,O*-aminals of indoles by the metal-catalyzed *N*-alkylaltion were reported; for example, the seminal work of Chen and Xiao reported a Cu-catalyzed highly enantioselective Friedel–Crafts C-2 alkylation/intramolecular *N*-hemiacetalization tandem reaction to efficiently construct 2,3-dihydro-1*H*-pyrrolo[1,2-α]indoles in 2013 (Scheme 1C).[15c] It is noted that the direct asymmetric organocatalytic *N*-functionalization of indoles to form chiral *N,O*-aminals has not been reported. Through our continuing interest and efforts to develop efficient and selective amination reactions with potential applications in the synthesis of natural products,[16] we developed and described in this report a novel methodology for the highly regioselective and enantioselective construction of *N,O*-aminal indoles catalyzed by chiral phosphoric acid. This protocol provides access to the structurally unique α-chiral *N,O*-acyclic aminals of indoles starting from commercially available materials.

Inspired by work by Terada in chiral phosphoric acid catalyis in which glyoxalates were successfully employed as electrophiles,[17] our investigation started with the reaction of 2,3-dimethylindole and ethyl glyoxalate in the presence of various chiral phosphoric acid catalyzed systems[18,19] (Table 1, entries 1–6). As shown in Table 1, the BINOL-derived chiral phosphoric acids promoted this reaction smoothly and

Table 1. Optimization of Asymmetric *N*-Hydroxyalkylaltion[a,f]



entry	cat.	solvent	t (°C)	yield (%)[b]	ee (%)[c]
1	**I**	Toluene (Tol)	−30	85	5
2	**II**	Tol	−30	90	7
3	**III**	Tol	−30	76	35
4	**IV**	Tol	−30	86	39
5	**V**	Tol	−30	43	68
6	**VI**	Tol	−30	56	82
7	**VI**	Tol/Et_2O (1:1)	−30	49	90
8	**VI**	Tol/Et_2O (1:1)	−20	80	91
9	**VI**	Tol/Et_2O (1:1)	−10	95	92
10	**VI**	Tol/Et_2O (1:1)	0	97	84
11[d]	**VI**	Tol/Et_2O (4:1)	−10	95	93
12[d,e]	VI	Tol/Et_2O (4:1)	−10	93	85

[a]Reaction conditions: 2,3-dimethylindole (0.1 mmol, 1.0 equiv), ethyl glyoxalate (3.0 equiv), and catalyst (10 mol %) in solvent (0.5 mL) at the indicated temperature for 48 h. [b]Isolated yield. [c]ee was determined by HPLC analysis. [d]Performed for 60 h. [e]5 mol % catalyst loading. [f]Chiral metal-phosphates catalyzed addition data were shown in the Supportting Information.

produced the desired product **1** in 85–90% yield with a low level (5–7%) of ee (entries 1–2). Interestingly, when the SPINOL-derived chiral phosphoric acids **III**–**V** served as catalysts in our reaction system, we found that the conversion was controlled efficiently and the enantioselectivity of the desired product was notably improved to 35–68% ee (entries 3–5). Significantly, the use of the hindered Ph_3Si-substituted SPINOL-derived chiral phosphoric acid **VI**[20] in the reaction system gave the best result, generating 82% ee with a 56% isolated yield (entry 6). Encouraged by this impressive result, we further extensively screened various solvents and temperatures; finally, the toluene/Et_2O (4:1) mixture stood out as the best-performing solvent at −10 °C, producing the best isolated yield of 95% with 93% ee (entry 11). Additionally, reducing the catalyst loading from 10 to 5 mol % resulted in a slight decrease of the ee value (85%) (Table 1, entry 12).

With the optimized conditions, we next examined the substrate scope and limitations of this asymmetric *N*-hydroxyalkylation reaction. As shown in Scheme 2, a broad range of indoles were well tolerated in the reaction and smoothly provided the corresponding *N,O*-aminal products. For the C2- and C3-position substituted indoles (**2**–**11**), the results indicated that a variety of substituted functional groups such as alkyl, aryl, and halogens were well tolerated under the optimal reaction conditions and produced the *N,O*-acyclic aminal indoles in good to excellent yield with up to 99% ee. Interestingly, the *N,O*-aminal products substituted by methoxycarbonylmethyl (**7**), cyanomethyl (**10**), and bromine (**11**) could provide a convenient and potential method for the further synthesis of a variety of indole derivatives. Sub-

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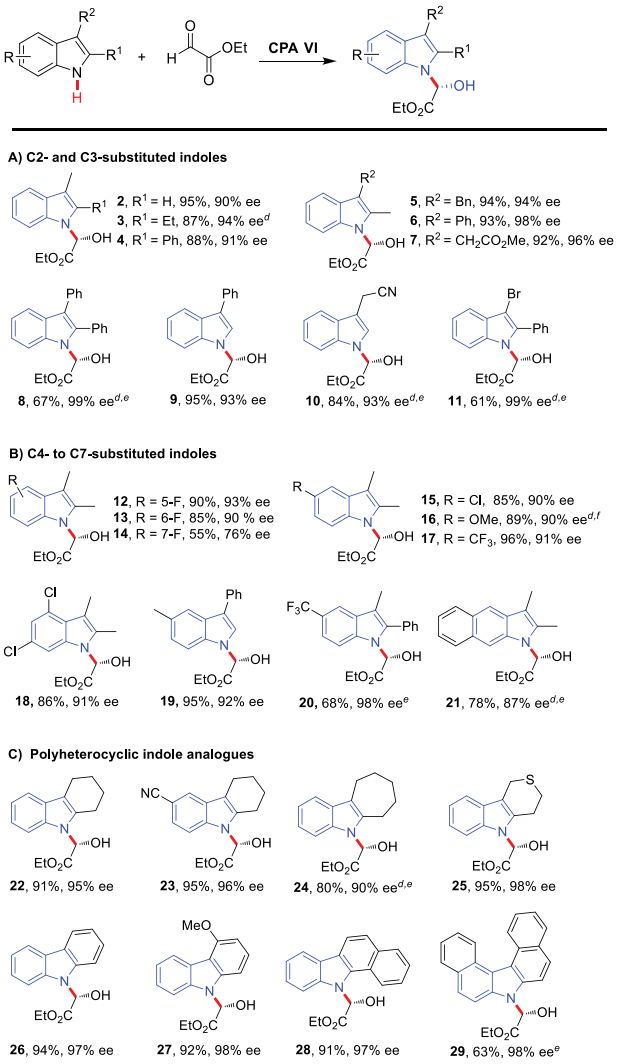
Scheme 2. Substrate Scope[a,b,c]

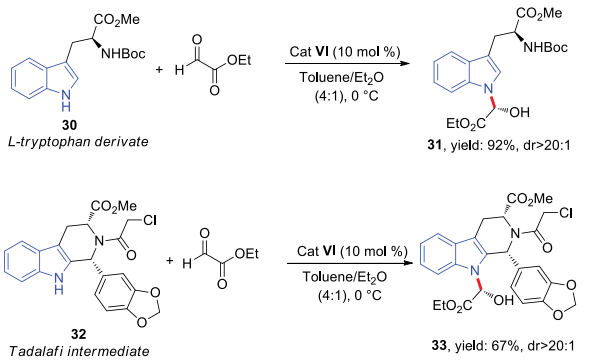


[a]Reaction conditions: indole derivative (0.1 mmol, 1.0 equiv), ethyl glyoxalate (3.0 equiv), and **VI** (10 mol %) in solvent (0.5 mL) at −10 °C for 48 h. [b]Isolated yield. [c]Ee was determined by HPLC analysis. [d]Performed at −30 °C. [e]Performed for 60 h. [f]Performed for 24 h.

sequently, the C4- to C7-substituted indole substrates were used to examine the effects of steric hindrance and electrons on the benzene ring of the indoles (**12**−**21**). The results clearly indicate that the lower steric hindrance of the C4- (**18**), C5- (**12**), and C6 (**13**)-substituted substrates produced excellent yields with 90−93% ee. The steric hindrance of the C7-position slowly depresses the reaction activity which gave a 55% yield with 76% ee (**14**). Moreover, the effects of both the electron-withdrawing and -donating groups on the benzene ring of the indoles were found to be well-accommodated (**15**−**17**), affording satisfactory product yields and high levels of stereocontrol. Furthermore, multisubstituted indoles also reacted efficiently to produce *N*-hydroxyalkylation with high enantioselectivity and good to excellent yield (**18**−**21**). Encouraged by these results, we turned our attention to complicated polyheterocyclic indole analogies. As expected, a series of polyheterocyclic indoles reacted predictably under the optimal reaction conditions (**22**−**29**). For instance, carbazole and 4-methoxycarbazole generated the desired *N,O*-aminal products **26** in 94% yield with 97% ee and **27** in 92% yield with 98% ee. The dibenzocarbazole produced **29** in 63% yield with 98% ee. In addition, the absolute stereochemistry of product **23** was unambiguously determined to be (*R*) by X-ray crystallographic analysis, and those of other products were assigned by analogy.

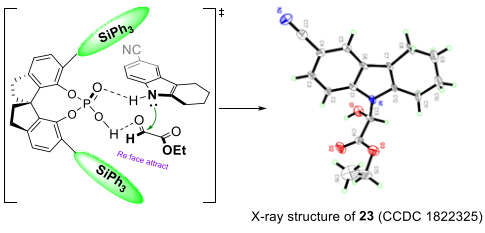
To investigate and enhance the scalability and application of our strategy in enantioselective *N*-hydroxyalkylaltion chemistry for the synthesis of bioactive molecules, we applied our process to the late-stage modification of the L-tryptophan derivative **30** and the tadalafil[21] intermediate **32** (Scheme 3). The desired *N*-

Scheme 3. Synthetic Applicability



hydroxyalkylation products **31** (92% yield, dr >20:1) and **33** (67% yield, dr >20:1) were obtained with good functional group tolerance, demonstrating the value of this asymmetric transformation in synthetic chemistry. Furthermore, applications of the chiral *N,O*-aminals of indoles in the synthesis of natural indole alkaloids are currently under investigation. In addition, the proposed transition state for the enantioselective *N*-hydroxyalkylation is shown in Scheme 4. The indole and the

Scheme 4. Proposed Transition State



ethyl glyoxalate are both activated by the phosphoric acid; then, the indole attacks the ethyl glyoxalate from the *Re*-face preferentially, affording the (*R*)-isomer of the product with high enantioselectivity and good to excellent yield.

In conclusion, we have successfully developed a method for the SPINOL-derived chiral phosphoric acid catalyzed asymmetric *N*-hydroxyalkylation of indoles. This protocol provides an alternative, convenient, and direct strategy to efficiently access the structurally unique *α*-chiral *N,O*-acyclic hemiaminals of indoles, and this method uses a broad substrate scope and has excellent functional group compatibility. Further, this reaction proceeds with high efficiency (up to >95% yield, 99% ee) and starts from commercially available materials. The applications of this N−H hydroxyalkylation methodology for indoles in the synthesis of complex, natural alkaloids containing various *α*-chiral *N,O*-acyclic hemiaminals, such as vincamine, are currently under investigation.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00757.

Experimental procedures, NMR spectra, and X-ray and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1892289 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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