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Brønsted Acid Catalyzed [3 + 2]-Cycloaddition of Cyclic Enamides with *in Situ* Generated 2-Methide-2*H*-indoles: Enantioselective Synthesis of Indolo[1,2-*a*]indoles

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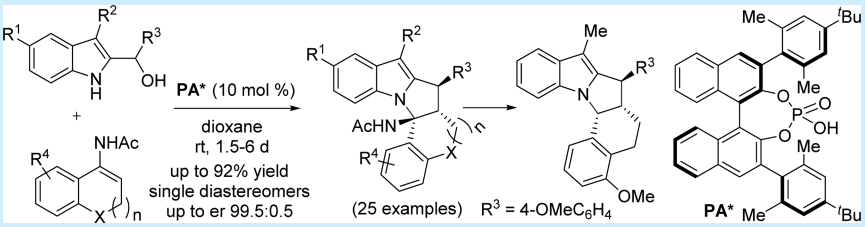
Supporting Information



ABSTRACT: An efficient formal [3 + 2]-cycloaddition toward the highly diastereo- and enantioselective synthesis of indolo[1,2-*a*]indoles is disclosed. A chiral BINOL-derived phosphoric acid catalyzed the highly enantioselective conjugate addition of cyclic enamides to *in situ* generated 2-methide-2*H*-indoles and subsequent aminalization to give rise to acetamide-substituted indolo[1,2-*a*]indoles carrying three contiguous stereogenic centers. Importantly, these products were formed as single diastereomers and with excellent yields and enantioselectivities. Mild reaction conditions at ambient temperatures, the facile removal of the acetamido group, and the possibility of a scale-up highlight the practicality of this methodology.

Indole-based nitrogen heterocycles have received considerable attention in synthetic and medicinal chemistry owing to their profound abundance as structural motifs in numerous alkaloids and biologically active synthetic molecules.[1] Indole fused-polycyclic frameworks, particularly pyrrolo- and indolo-[1,2-*a*]indoles have been found in various natural products and are also attractive skeleta for drug discovery due to their potentially diverse pharmacological properties.[2,3] For example, the flinderoles A−C which are part of an interesting dimeric alkaloid family display selective antimalarial activity (Figure 1).[4]

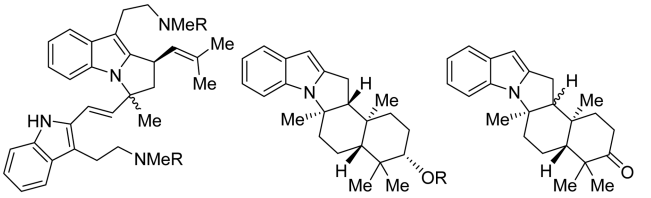


Figure 1. Representative natural products with a pyrrolo[1,2-*a*]indole and indolo[1,2-*a*]indole skeleton.

Indolo-sesquiterpene alkaloids such as polyavolensin, polyavolensinol, polyavolensinone, and polysin were isolated from the stem and stem bark of the medicinal plant *Polyathia suaveolens*, available in West Africa, and are of value for treating blackwater fever and stomach disorders (Figure 1).[3] Thus, an efficient and divergent enantioselective synthesis of such polycyclic indoles has become an important research area for synthetic organic chemistry.

In recent years, a few catalytic enantioselective syntheses of the pyrrolo[1,2-*a*]indole skeleta have been reported, most of which require multistep processes, however.[5] On the other hand, to the best of our knowledge, there is only one report available for the enantioselective synthesis of the indolo[1,2-*a*]indole skeleton, and this involved a chiral pool-based intramolecular nitrone cycloaddition toward the cyclohexene ring.[6] However, this method has a rather limited substrate scope. Thus, the development of a direct and broadly applicable synthetic method toward this important structural motif is highly desirable.

We recently reported a highly diastereo- and enantioselective synthesis of pyrrolo[1,2-*a*]indoles through a phosphoric acid catalyzed [3 + 2]-cycloaddition of 2-vinylindoles with 2-methide-2*H*-indoles, which were obtained *in situ* from the corresponding 1*H*-indol-2-yl carbinols by dehydration.[7] We anticipated that enamides[8] **3** could be employed, as well as dienophiles, in a [3 + 2]-cycloaddition with 1*H*-indol-2-yl carbinols **1** in the presence of a chiral phosphoric acid[9] which would give rise to an indolo[1,2-*a*]indole **4** as the primary reaction product (Scheme 1). We envisioned that a chiral phosphoric acid could activate both the *in situ* generated 2-methide-2*H*-indole **2** and the enamide **3** through double hydrogen bonding and thus promote the ensuing [3 + 2]-cycloaddition. Han et al. have recently shown that enamides can

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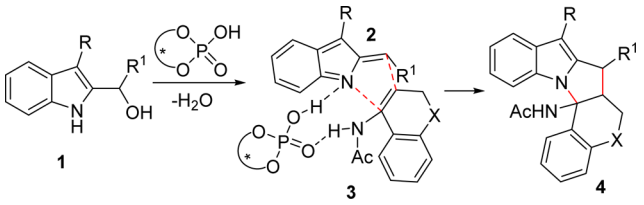
Scheme 1. Conceptualization of the Synthesis of Indolo[1,2-*a*]indoles 4



add to *N*-protected indol-2-yl carbinols under Brønsted acid catalysis, resulting in the formation of a single new C−C bond with good-to-excellent enantioselectivity.[10]

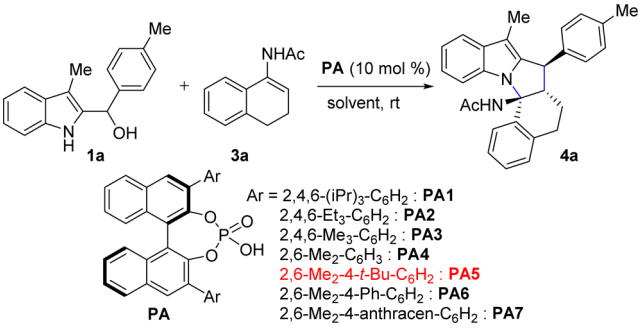
Herein we report the successful execution of this strategy, which has furnished indolo[1,2-*a*]indoles **4** in a one-step process with excellent yields. Single diastereomers were obtained with very high enantioselectivity in almost all cases studied.

To identify suitable reaction conditions, various BINOL-derived phosphoric acids **PA1**−**7** (10 mol %) were examined in the reaction between indol-2-yl carbinol **1a** and the cyclic enamide **3a** in CH_2Cl_2 at rt (Table 1). In all cases, the desired product indolo[1,2-*a*]indole **4a** was obtained as a single diastereomer and in good-to-excellent yield, although the enantioselectivity was found to be highly dependent on the steric bulk of the aryl groups at the 3,3′-position of the BINOL-backbone. For example, phosphoric acids **PA1**−**PA4**, which have routinely been employed by ourselves and other groups with great success before, gave rise to only low selectivity (entries 1−4). Eventually, we found the catalyst **PA5**, with 2,6-dimethyl-4-*tert*-butyl phenyl groups, to be optimal for our process. It provided indolo[1,2-*a*]indole **4a** as a single diastereomer in 83% isolated yield and with 88.5:11.5 er (entry 5). Other bulky *para*-substituents within the 3,3′-aryl groups did not further improve this selectivity (entries 6−7). However, additional improvement of enantioselectivity was achieved through solvent modification (entries 8−13). Though the reaction time proved to be longer in the case of ethereal solvents, this change provided better enantioselectivity compared to hydrocarbon and chlorinated solvents (entries 8−13). Finally, we found 1,4-dioxane optimal for this reaction, which gave rise to indolo[1,2-*a*]indole **4a** in 86% yield and 95:5 er within 48 h at rt, in the presence of 10 mol % of **PA5** (entry 13).

These optimized reaction conditions were broadly applicable to a range of enamides **3a**−**h** (Scheme 2). Various substituents such as methoxy, methyl, and bromo on the aryl ring of the benzannulated enamides were well tolerated and provided the desired products **4b**−**f** as single diastereomers with excellent yields and enantioselectivities. The 7-membered cycloalkyl enamide **3g** also reacted smoothly with indol-2-yl carbinol **1a** to give rise to product **4g** in moderate yield and enantioselectivity. To our delight, this process was also efficient for a partial kinetic resolution of racemic chiral enamide. Thus, reaction of indolyl-2-carbinol **1a** with enamide **3h** (3 equiv) furnished cycloadduct **4h** as a 4:1 mixture of diastereomers in 85% yield and excellent enantioselectivity.

To further expand the scope of this cycloaddition we subjected various indol-2-yl carbinols **1b**−**m** carrying different aryl and alkyl groups at the carbinol center to the reaction with enamides **3b**−**c** (Scheme 3). Irrespective of the electronic and

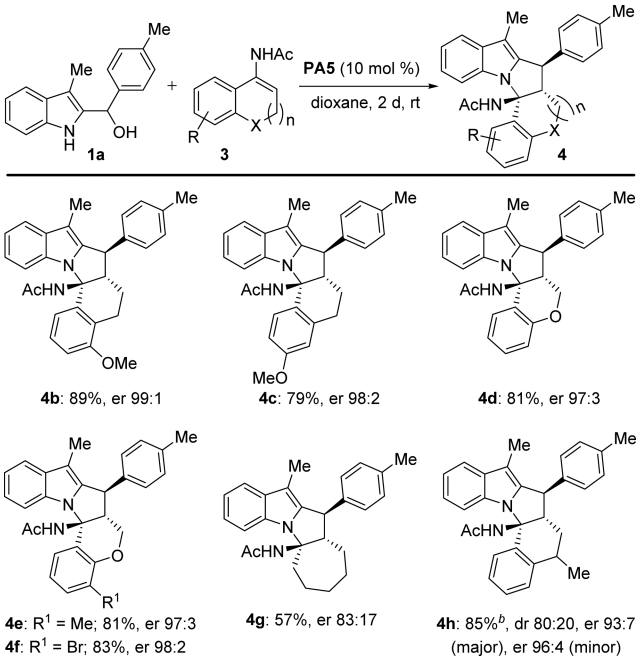
Table 1. Catalyst Screening and Reaction Optimization[a]



entry	PA	solvent	*t* (h)	yield (%)[b]	er[c]
1	**1**	CH_2Cl_2	3	72	47:53[d]
2	**2**	CH_2Cl_2	3	88	55:45
3	**3**	CH_2Cl_2	3	62	34:66[d]
4	**4**	CH_2Cl_2	3	92	37:63[d]
5	**5**	CH_2Cl_2	3	90 (83)	88.5:11.5
6	**6**	CH_2Cl_2	3	83	47:53[d]
7	7	CH_2Cl_2	3	66	78:22
8	**5**	chloroform	3	82	82.5:17.5
9	**5**	toluene	3	83	89:11
10	**5**	THF	48	75	93:7
11	**5**	diethyl ether	48	85	90:10
12	**5**	tetrahydropyran	48	81	94:6
13[e]	**5**	**dioxane**	**48**	**92 (86)**	**95:5**

[a]Conditions: Catalyst **PA** (0.01 mmol, 0.1 equiv), **3a** (0.15 mmol, 1.5 equiv), and **1a** (0.1 mmol, 1 equiv) in 0.5 mL solvent at rt. [b]NMR yield with anisole as an internal standard; in parentheses, isolated yield after silica gel column chromatography. [c]Determined by chiral HPLC. [d]Opposite enantiomer. [e]Reaction was performed on 0.3 mmol scale with 1.5 mL of solvent.

Scheme 2. Substrate Scope of Enamides 3[a]



[a]Conditions: Catalyst **PA5** (0.03 mmol, 0.1 equiv), **3** (0.45 mmol, 1.5 equiv), and **1a** (0.3 mmol, 1 equiv) in 1.5 mL of dioxane at rt; isolated yields after silica gel column chromatography. [b]0.9 mmol of enamides **3h** was employed.

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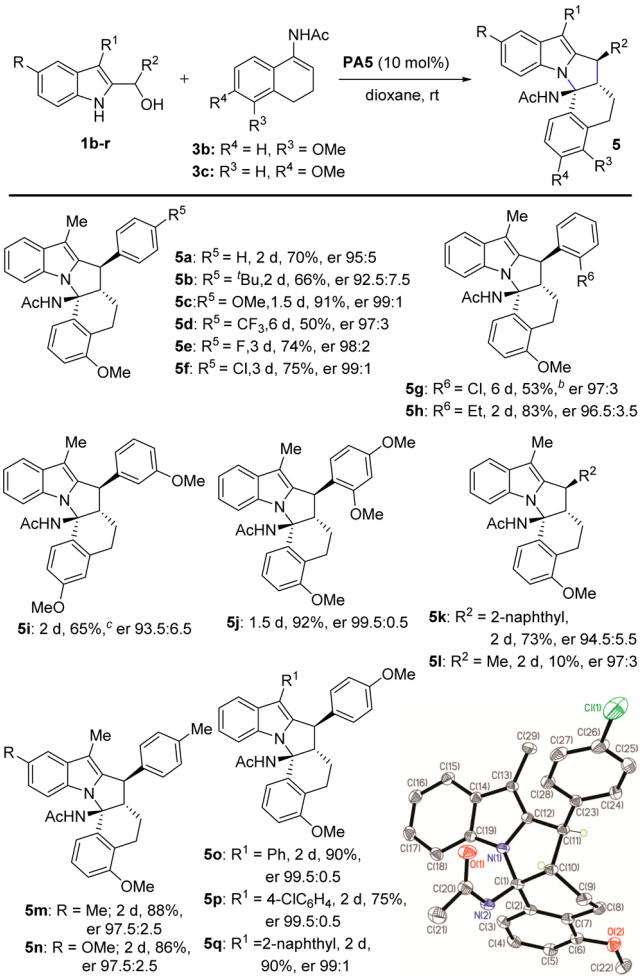
Scheme 3. Substrate Scope[a,b,c]



[a]Conditions: Catalyst **PA5** (0.03 mmol, 0.1 equiv), **3** (0.45 mmol, 1.5 equiv) and **1** (0.3 mmol, 1 equiv) in 1.5 mL dioxane at rt; isolated yields after silica gel column chromatography. [b]dr 98:2. [c]dr >95:5.

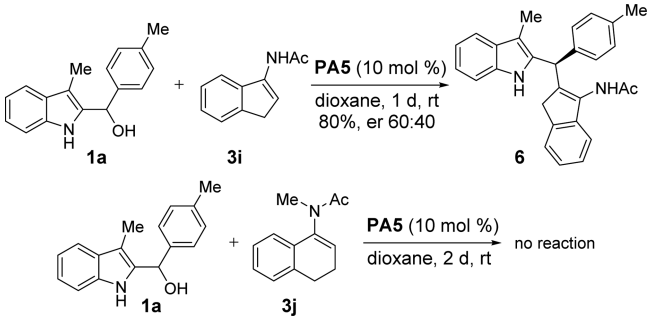
steric properties and the position of additional substituents on the aryl ring of **1b–l**, the indolo[1,2-*a*]indoles **5a–k** were obtained as single diastereomers (except for **5g** and **5i** where dr was 98:2 and >95:5 respectively) with good-to-excellent yields and enantioselectivities of up to er >99:1. However, the reaction rate was highly dependent on the electronic nature of the substituents. With electron-donating substituents such as alkoxy and alkyl groups (**5a–c** and **5h–k**), the reaction proceeded faster compared to substrates carrying electron-withdrawing groups such as halogens and the trifluoromethyl group (**5d–g**). The lower yield for the alkyl-substituted cycloadduct **5l** was presumably a result of a faster decomposition of the starting 2-methide-2*H*-indole intermediate **2m** in an undesired pathway caused by the lack of extra π-conjugation.

Finally, structurally more diverse cycloadducts were obtained by subjecting more highly substituted and functionalized 1*H*-indol-2-yl carbinols to the [3 + 2]-cycloaddition (Scheme 3). For example, cycloadducts **5m** and **5n** bearing methyl and methoxy groups at the 5-position of the indole, respectively, were obtained from enamide **3b**, as single diastereomers in excellent yields and enantioselectivities. Also, various substituted aryl groups, such as phenyl, 4-chlorophenyl, and 2-naphthyl at the 3- position of indole, were well tolerated under the reaction conditions and afforded the cycloadducts **5o–q** as single diastereomers in excellent yields and enantioselectivities of >99:1 er.

The relative as well as absolute configuration of the products **4** and **5** was unambigously determined by single crystal X-ray analysis of indolo[1,2-*a*]indole **5f** which was assigned to all other products by analogy (Scheme 3).[11]

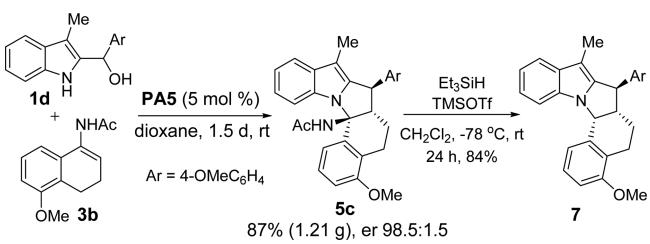
To shed some light on the mechanism of this formal [3 + 2]-cycloaddition we carried out few control experiments (Scheme 4). The 1-indanone-derived enamide **3i** reacted smoothly with indolyl carbinol **1a** and afforded the uncyclized product **6** exclusively in an interrupted cycloaddition. This result suggests that the title reaction proceeded through a stepwise process initiated by a conjugate addition and subsequent cyclization to the aminal. When we submitted **6** to a reaction with tetralone-derived enamide **3b**, under otherwise identical reaction conditions, only unreacted indole **6** could be quantitatively recovered. This finding rules out the possibility of a reversible first step in the sequence and suggests that step to be the enantioselectivity-determining part of the process. Further, the reaction using the *N*-methylated enamide **3j** and carbinol **4a** as substrates failed to provide the desired cycloadduct at all. This observation indicates that the free N–H moiety within the enamide **3** plays a pivotal role in the successful activation and preorganization of the substrates as outlined above.

Scheme 4. Control Experiments



In order to demonstrate the synthetic utility of our method, a representative cycloaddition was carried out on gram-scale. Only 5 mol % of Brønsted acid catalyst PA5 was sufficient to catalyze the reaction of carbinol **1d** (3.00 mmol, 0.80 g) with enamide **3b** (4.50 mmol, 0.98 g) which furnished acetamide-substituted indolo[1,2-*a*]indole **5c** in 87% yield (1.21 g), with complete diastereoselectivity and 98.5:1.5 er over a period of 1.5 day at rt (Scheme 5). The reaction products could be further functionalized via iminium ion generation followed by the addition of nucleophiles. Thus, in a representative process the above prepared cycloadduct **5c** was subjected to Lewis acid assisted hydrogenation conditions using TMSOTf and

Scheme 5. Scale-up Reaction and Synthetic Application



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triethylsilane to furnish the indolo[1,2-*a*]indole **7** in 84% yield and with full retention of diastereoselectivity (Scheme 5). The relative configuration of **7** was unambiguously determined through an X-ray crystal structure analysis (for details see the Supporting Information).[11]

In conclusion, we have developed a chiral phosphoric acid catalyzed, asymmetric, formal [3 + 2]-cycloaddition of cyclic enamides **3** with 2-methide-2*H*-indoles **2** obtained via dehydration *in situ* from 1*H*-indol-2-yl carbinols **1**. The products were typically obtained as single diastereomers in excellent yields and enantioselectivities. This cycloaddition was shown to proceed via a stepwise process initiated by a conjugate addition and subsequent cyclization of the indole to the aminal. A large-scale reaction demonstrated the practicality of this process which furnished the product in identical yield and enantioselectivity. In addition, further synthetic transformation of final adduct was possible. Further extension of this process with respect to other nucleophiles and the application of this method to the synthesis of natural products and biologically active molecules is currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02898.

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data for **5f** and **7** (PDF)

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Notes

The authors declare no competing financial interest.

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We dedicate this manuscript with great respect and affection to our friend and colleague Professor Gerhard Bringmann (University of Würzburg) on the occasion of his 65th anniversary. We thank the DFG for generous financial support and Prof. J. Sieler and Dr. P. Lönnecke (University of Leipzig) for the crystal structure analysis. We are grateful to BASF and Evonik for the donation of chemicals.

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(11) CCDC 1500399 and CCDC 1500401 contain the supplementary crystallographic data for this paper. For details concerning the crystal structure of **5f** and **7**, see the Supporting Information as well.

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