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Organocatalyzed Enantioselective Formal [4 + 2] Cycloaddition of 2,3-Disubstituted Indole and Methyl Vinyl Ketone

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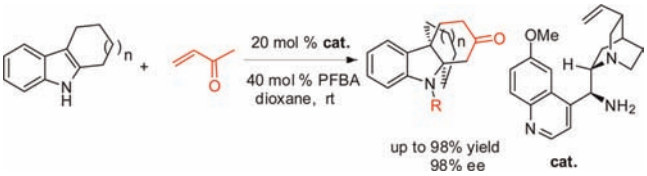
ABSTRACT



A formal [4 + 2] cycloaddition of 2,3-disubstituted indoles with vinyl methyl ketone was realized in the presence of a catalytic amount of quinine-derived primary amine and pentafluorobenzoic acid. This method provides bridged-ring indoline scaffolds containing two quaternary carbon centers with excellent yields and enantioselectivity (up to 98% yield and 98% ee).

The indoline ring is an important scaffold due to its frequent occurrence in natural products and pharmaceuticals.[1] As a result, various methods have been developed for efficient synthesis of indoline derivatives.[2] Among them, the cascade annulation of indoles through the indolenine intermediate has drawn much attention due to the ready availability of indole derivatives.[3] The asymmetric catalytic version of this strategy has also been realized and documented in the literature.[4] Notably, most of the successful examples employed the substrate bearing a pendant nucleophile, tethered on the indole core such as tryptamine or tryptanol derivatives,[4a−h] which captures the *in situ* formed iminium intermediate (eq 1). A cascade approach allows the utilization of simple substituted indoles, and thus facile construction of complex ring structures will be highly feasible (eq 2). This strategy will enable the synthesis of more diversified ring structures given the rich combination of indoles and dipoles. However, to our knowledge,

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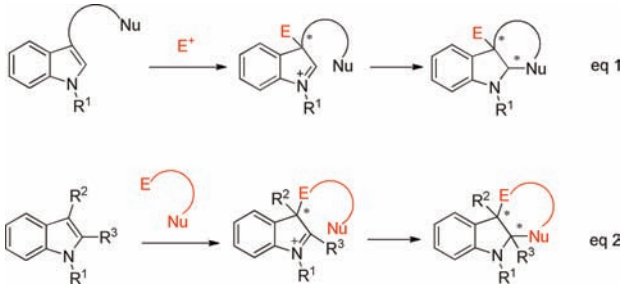
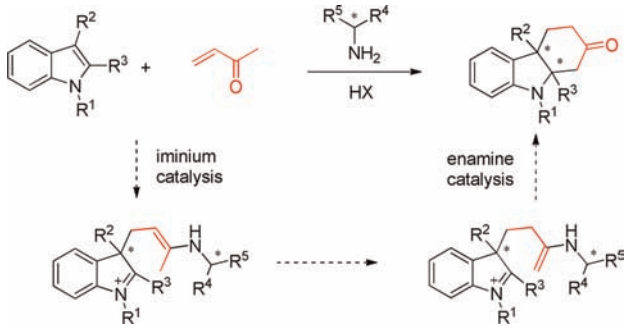
there are only limited catalytically asymmetric examples by either Lewis acid or transition-metal complexes.[5]



Recently, we have developed an intramolecular Michael–Mannich cascade reaction of indolyl methyl enones catalyzed by the quinine-derived primary amine, affording a series of highly enantioenriched tetracyclic compounds in high yields with excellent enantioselectivity.[4j] Meanwhile, methyl vinyl ketone (MVK) was a well-known annulated substrate by reacting as an electrophile and a nucleophile in a sequence.[6] We envisaged that the combination of MVK and 2,3-disubstituted indole will constitute a formal [4 + 2] cycloaddition through a Michael and Mannich cascade process. As shown in Scheme 1, in the presence of a chiral primary amine,[7] a Michael reaction provides an indolenine intermediate bearing an all-carbon quaternary chiral center *via* iminium catalysis.[8] Subsequently, the methyl ketone group of MVK would trap the iminium electrophile *via* enamine catalysis.[6c,9] Herein, we describe such a novel organocatalyzed, enantioselective [4 + 2] annulation of indoles to construct a bridged indoline ring structure bearing two quaternary carbon centers.

Scheme 1. Proposed Annulation of 2,3-Disubstituted Indole with MVK Catalyzed by Chiral Primary Amine



We began our studies by testing several readily available chiral primary amines (**3a**–**3d**) as the catalyst in the reaction of the unprotected tetrahydrocarbazole **1a** with MVK (entries 1–4, Table 1). To our delight, with 9-amino-9-deoxyepiquinine[10–15] (**3a**, 20 mol %) and 3,5-dinitrobenzoic acid (40 mol %) in THF, the cascade reaction proceeded smoothly to afford the bridged ring product **2a** in 52% yield and 97% *ee* (entry 1, Table 1). Notably, the dearomatization of indole generated a secondary amine that occurred *via* an aza-Michael reaction with MVK under the reaction conditions. Decreasing the amount of MVK to 1 equiv also led to product **2a**, albeit in a lower yield (entry 16, Table 1). No reaction occurred when *N*-protected indoles were employed. Further screening of acid additives (entries 5–8, Table 1) revealed that pentafluorobenzoic acid

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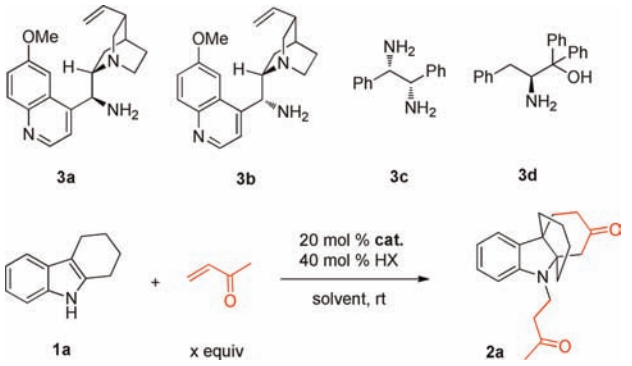
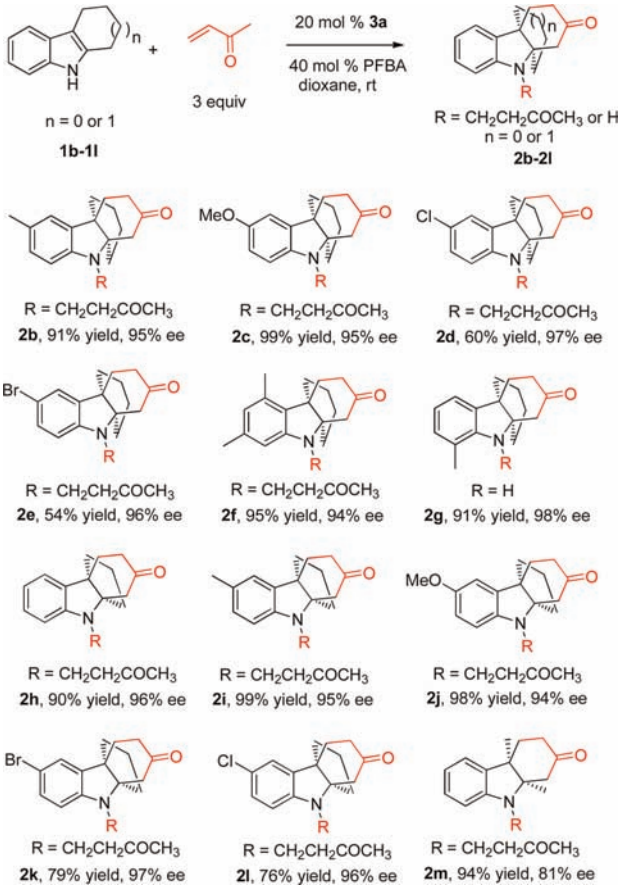
Table 1. Optimization of the Reaction Conditions for the [4 + 2] Annulation



entry[a]	cat./HX	solvent	x	t (h)	yield (%)[b]	ee (%)[c]
1	**3a**/3,5-DNBA	THF	5	36	52	97
2	**3b**/3,5-DNBA	THF	5	312	13	−77
3	**3c**/3,5-DNBA	THF	5	312	6	75
4	**3d**/3,5-DNBA	THF	5	312	trace	2
5	**3a**/TFA	THF	5	36	93	67
6	**3a**/2-NBA	THF	5	36	36	>99
7	**3a**/3,4-DNBA	THF	5	36	36	97
8	**3a**/PFBA	THF	5	36	59	97
9	**3a**/PFBA	CH_2Cl_2	5	36	quant.	83
10	**3a**/PFBA	$ClCH_2$-CH_2Cl	5	36	86	80
11	**3a**/PFBA	EtOAc	5	36	quant.	92
12	**3a**/PFBA	dioxane	5	36	87	97
13	**3a**/PFBA	dioxane	4	36	71	97
14	**3a**/PFBA	dioxane	3	72	97	97
15	**3a**/PFBA	dioxane	2	36	91	97
16	**3a**/PFBA	dioxane	1	48	27	97

[a] Reaction conditions: 20 mol % **cat.**, 40 mol % HX, rt, 0.1 mol/L of **1a** in 1,4-dioxane. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H). DNBA = dinitrobenzoic acid, NBA = nitrobenzoic acid, TFA = trifluoroacetic acid, PFBA = pentafluorobenzoic acid.

Scheme 2. Substrate Scope of the Cascade Reaction[a]



[a] The yields refer to isolated yields, and the *ee* values were determined by HPLC analysis. The absolute configuration was determined by the X-ray analysis of enantiopure (*R,R*)-**2e**.[16]

(PFBA) was the best one (59% yield, 97% *ee*, entry 8, Table 1). With 1,4-dioxane as the solvent, the yield could be increased significantly to 87% without affecting the enantioselectivity (entry 12, Table 1). The optimal yield (97%) and enantioselectivity (97% *ee*) were obtained with 3 equiv of methyl vinyl ketone (entry 14, Table 1).

Under the optimal reaction conditions, the substrate scope has been examined to test the generality of the current method. In general, tetrahydrocarbazoles bearing an electron-withdrawing group (Cl or Br) or electron-donating

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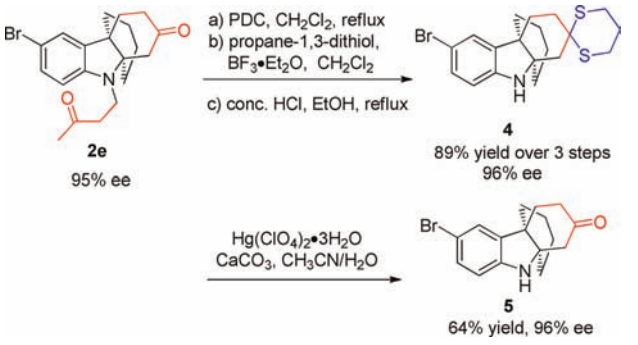
(16) The absolute configuration was determined by the X-ray diffraction of enantiopure (*R,R*)-**2e**. CCDC 863418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Scheme 3. Proposed Annulation of 2,3-Disubstituted Indole with MVK Catalyzed by Chiral Primary Amine



group (Me or MeO) on the indole core were all tolerated to afford the corresponding indolines with excellent enantioselectivity (94−98% *ee*, **2b**−**2g**, Scheme 2). Slightly decreased yields were observed for the electron-withdrawing group substituted substrates (**2d**−**e**). It should be noted that when 8-methyl-2,3,4,9-tetrahydro-1*H*-carbazole was used, product **2g** without the aza-Michael addition reaction was obtained in 91% yield and 98% *ee*. It is reasoned that the steric effect of the methyl group near the nitrogen hindered the second aza-Michael addition. The substituted 1,2,3,4-tetrahydrocyclopenta[*b*]indoles were also well tolerated, affording the corresponding products **2h**−**2l** with good yields and excellent enantioselectivity (76−99% yields, 94−97% *ee*). Remarkably, the utilization of 2,3-dimethyl indole also provided the hexahydrocarbazole **2m** in 94% yield and 81% *ee*.

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Removal of the alkyl group on the nitrogen of the product was also explored, as shown in Scheme 3. The oxidation of **2e** (95% *ee*) with pyridium dichromate (PDC) led to the corresponding amide. The two carbonyl groups of the amide were protected by propane-1,3-dithiol. Then the amide was hydrolyzed under acidic conditions to afford **4** in 89% yield over three steps in a one-pot fashion. Compound **5** was obtained in 64% yield without loss of the enantiomeric purity by treating cyclic dithiol ketal **4** with mercury(II) perchlorate trihydrate.[17]

In conclusion, a novel asymmetric formal [4 + 2] cycloaddition of 2,3-disubstituted indole derivatives with methyl vinyl ketone has been developed. This iminium-enamine catalysis cascade reaction allows the synthesis of bridged ring indoline products containing two quaternary carbon centers in excellent yields and enantioselectivities. The method features a readily available catalyst and substrates, mild conditions, and synthetically challenging products. Further application of this method to the synthesis of complex molecules is currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of (*R,R*)-**2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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