Asymmetric Catalysis

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Enantioselective Michael/Mannich Polycyclization Cascade of Indolyl Enones Catalyzed by Quinine-Derived Primary Amines**

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Cascade reactions have become a subject of intense research in recent years,[1] as they often reduce labor and waste, and enables the use of more readily available starting materials to construct complex targets. Particularly with indole substrates, a cascade involving nucleophilic addition of C3 of an indole and subsequent intramolecular nucleophilic addition to the in situ formed indolenine[2] proved to be a very useful strategy in complex natural product synthesis.[3] In this regard, developing an enantioselective catalytic version of this synthetic strategy is in great demand. To our knowledge, however, there are only limited successful examples documented in the literature.[4] Both the tricyclic and tetracyclic core of **1** has drawn considerable attention because of its complexity and frequent appearance in natural products and pharmaceuticals (Figure 1).[5] An enantioselective cascade synthesis towards these scaffolds is highly desirable but poses a challenge given

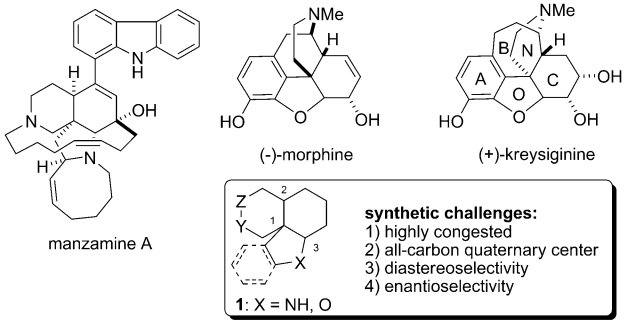
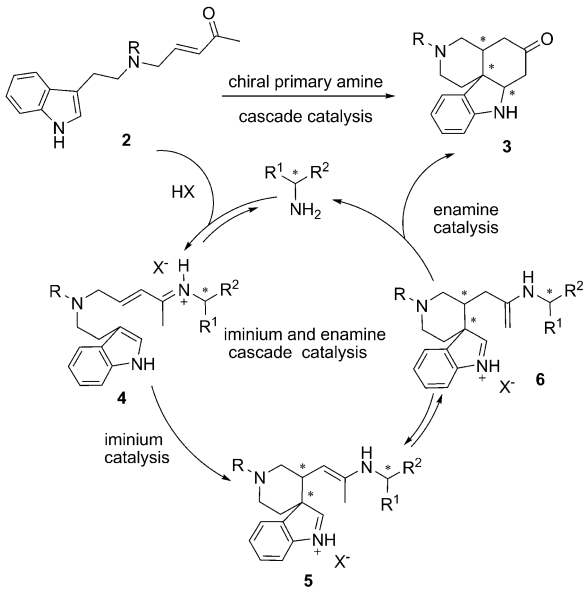


Figure 1. Representative natural products with tricyclic or tetracyclic core **1**.

the fact that three chiral centers including a quaternary all-carbon center need to be formed in a single process.

As part of our ongoing program targeting new asymmetric catalytic methods for the efficient construction of polycyclic indole frameworks,[6] we envisaged that the tetracyclic core **3** could be assembled through the nucleophilic polycyclization[7] of the indolyl methyl enone **2** in a cascade process with the proper choice of a chiral primary amine catalyst[8] (Scheme 1).



Scheme 1. Proposed catalytic cycle by a chiral primary amine.

The intramolecular Michael addition of the indolyl enone **2** generates the spirocyclic indolenine intermediate **5** through iminium catalysis[9] and the tetracylic product **3** is obtained through the intramolecular Mannich reaction by enamine catalysis.[10] Herein we report such a novel asymmetric intramolecular Michael/Mannich cascade reaction catalyzed by a quinine-derived primary amine, thereby providing an efficient synthesis of enantiopure tetracycles bearing multiple chiral centers.

We began the investigation by screening several readily available chiral primary amines (Figure 2) with **2a** as the model substrate. By using 9-amino-9-deoxyepiquinine[11] (**7a**; 20 mol%) and TFA (40 mol%) in 1,4-dioxane, we were delighted to find that the cascade reaction proceeded smoothly to afford the desired tetracyclic product in 60% yield with moderate selectivities (Table 1, entry 1). Fortunately, the use of nitrobenzoic acids served to increase the enantioselectivity significantly (Table 1, entries 8–11). After further examination of different solvents and acid additives, the optimal *ee* and d.r. values and yield were obtained with **7a** (20 mol%) and 2-nitrobenzoic acid (40 mol%) in EtOAc (Table 1, entry 16).

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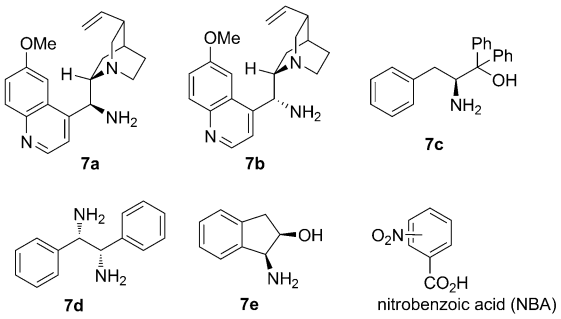
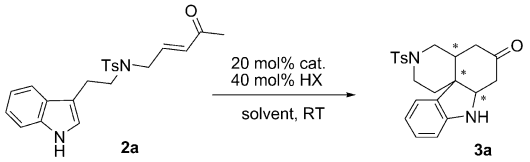


Figure 2. Readily available chiral primary amines.

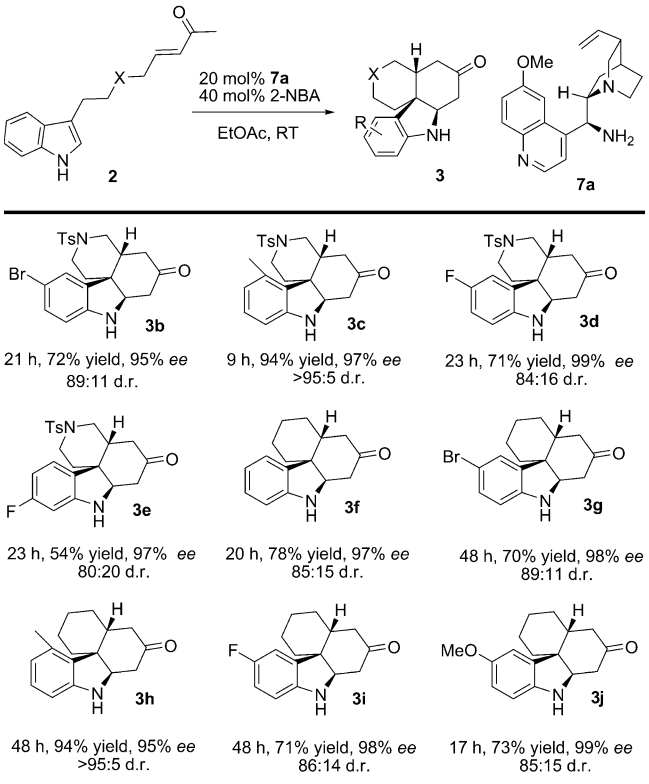
Table 1: Optimization of the reaction conditions for the cascade reaction.



Entry	Cat./HX	Solvent	*t* [h]	Yield [%][a]	*ee* [%][b]	d.r.[c]
1	**7a**/TFA	1,4-dioxane	13	60	44	82:18
2	**7b**/TFA	1,4-dioxane	38	33	28	64:36
3[d]	**7c**/TFA	1,4-dioxane	216	trace	n.d.	n.d.
4	**7d**/TFA	1,4-dioxane	144	37	−23	50:50
5[d]	**7e**/TFA	1,4-dioxane	192	complex	n.d.	n.d.
6	**7a**/ (D)-CSA	1,4-dioxane	168	54	−52	70:30
7	**7a**/TfOH	1,4-dioxane	48	trace	n.d.	n.d.
8	**7a**/3,5-DNBA	1,4-dioxane	5	84	95	78:22
9	**7a**/3-NBA	1,4-dioxane	24	53	94	85:15
10	**7a**/3,4-DNBA	1,4-dioxane	24	52	98	77:23
11	**7a**/2-NBA	1,4-dioxane	48	40	89	89:11
12	**7a**/3,5-DNBA	CH_2Cl_2	18	51	91	74:26
13	**7a**/3,5-DNBA	CH_3CN	24	27	48	49:51
14	**7a**/3,5-DNBA	MeOH	96	22	5	44:56
15	**7a**/3,5-DNBA	EtOAc	15	62	94	78:22
16	**7a**/2-NBA	EtOAc	2	78	98	89:11
17[d]	**7a**/2-NBA	EtOAc	12	73	98	86:14

[a] Yield of the isolated major isomer. [b] Determined by HPLC analysis (Chiralpak AD-H). [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] 20 mol% of the acid (HX) was added. n.d. = not determined. D-CSA = D-camphorsulfonic acid, DNBA = dinitrobenzoic acid, NBA = nitrobenzoic acid, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

Under the optimal reaction conditions, various indolyl enones were tested to examine the generality of this reaction. Substrates bearing either an electron-withdrawing group (Br or F) or an electron-donating group (Me) on the indole ring all led the formation of tetracyclic products with excellent *ee* values (**3b**–**3e**, Scheme 2). A slight decrease of yield and diastereoselectivity was observed for the F-substituted indole substrate **3e**. The carbon-tethered indolyl enone substrates were also well tolerated, thus affording the tetracyclic products **3f**–**3j** with excellent yields and d.r. and *ee* values. It should be pointed out that the substrates having a methyl group on C4 of the indole led to the corresponding cyclization

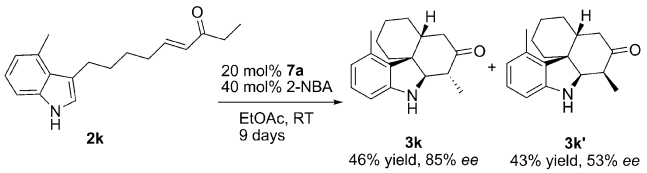


Scheme 2. Substrate scope of the cascade reaction. The yields are those of the isolated major isomers and the *ee* values were determined by HPLC analysis. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The absolute configuration was determined by the X-ray analysis of **3b**.[12]

products with improved diastereoselectivities (**3c** and **3h**). Notably, the two product diastereoisomers (in all cases) were easily separated by silica gel column chromatography.[13] In addition, the reaction proceeded very slowly when the indole nitrogen atom was protected with a methyl group.

Further exploration of the substrate scope revealed that the ethyl ketone **2k** was also suitable for the casacade reaction (Scheme 3). The reaction went smoothly under the optimized reaction conditions to afford a pair of diasteroisomers, **3k** and **3k′**, each bearing four chiral centers in good yield (89% yield) and with good *ee* values, abeit with unsatisfactory diastereoselectivity.[14]

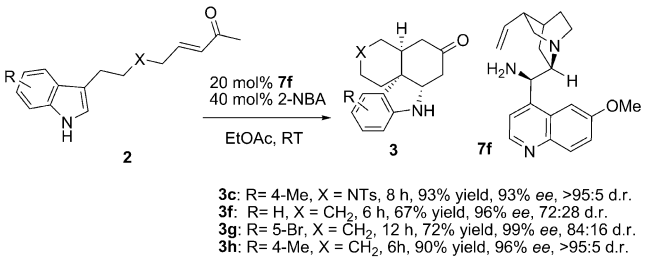
We then extended our efforts to obtain the enantiomers of the polycyclic products. Fortunately, using 20 mol% of 9-amino 9-deoxy epiquinidine (**7f**), the pseudoenantiomer of **7a**, under the optimal reaction conditions, the enantiomers of **3c**, **3f**, **3g**, and **3h** were accessed with excellent enantiose-



Scheme 3. The cascade reaction of **2k**.[14]

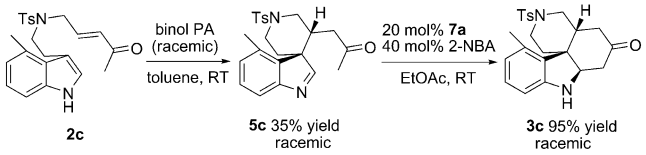
lectivities and moderate to high diastereoselectivities (Scheme 4).

To shed light on the reaction mechanism, we tried to isolate the indolenine intermediate **5**. The intermediate is



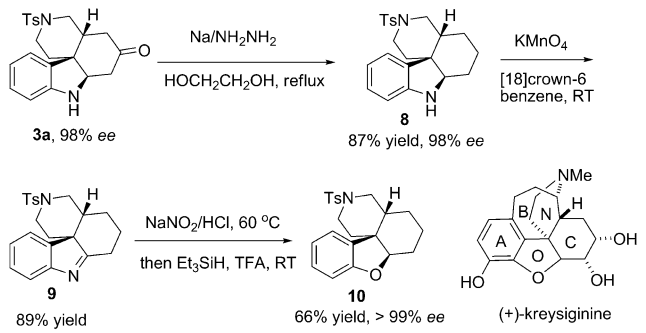
Scheme 4. Synthesis of the enantiomers of **3c**, **3f**, **3g**, and **3h**.

very reactive and inseparable under the optimal reaction conditions. To our delight, **5c** could be obtained in 35% yield from **2c** when catalyzed by a binol-derived phosphoric acid. In the presence of catalytic amount of **7a** and 2-NBA, **5c** was smoothly converted into product **3c** in 95% yield (Scheme 5). This result suggests that the cascade reaction likely proceeds by a tandem Michael addition and Mannich reaction.



Scheme 5. Preparation of **5c** and investigations into the mechanism. binol = 2,2′-dihydroxy-1,1′-binaphthyl, PA = phosphoric acid.

To demonstrate the synthetic utility of this methodology, we undertook the synthesis of an ACNO analogue of the natural product (+)-kreysiginine (Scheme 6).[15] The deoxygenation of ketone **3a** by the Huang Minlon reduction proceeded very well without any loss of the enantiomeric purity.[7c] The reduced compound **8** was oxidized to imine **9** in 89% yield by $KMnO_4$ in the presence of [18]crown-6. Compound **10** was then accessed in 66% yield through the oxidation of **9** by $NaNO_2$ under acidic conditions and subsequent Et_3SiH reduction.[16] The (+)-kreysiginine analogue (**10**) was obtained in 99% *ee* and the absolute configuration was in accordance with that of the natural product.



Scheme 6. Synthesis of the ACNO analogue of (+)-kreysiginine.

In conclusion, we have developed an intramolecular Michael/Mannich cascade reaction of indolyl methyl enones catalyzed by a quinine-derived primary amine, thus affording a series of highly enantioenriched tetracyclic compounds in high yields with good diastereoselectivities and excellent enantioselectivities. With this methodology, an analogue of (+)-kreysiginine could be synthesized in a short and efficient manner. Further application of this methodology to the total synthesis of complex natural products is currently underway in our lab.

Experimental Section

General procedure for polycyclization cascade of indolyl enones: A round bottom flask was charged with 9-*epi*-quinine amine **7a** (6.4 mg, 0.02 mmol) and ethyl acetate (2 mL). Then 2-nitrobenzoic acid (6.7 mg, 0.04 mmol) was added. After the salt was dissolved, substrate **2** (0.1 mmol) was added. After the reaction was complete (monitored by TLC or ^{1}H NMR spectroscopy), the solvent was removed under reduced pressure. The diastereoselective ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The residue was then purified by silica gel column chromatography (hexanes/EtOAc 1:1) to afford the product.

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[13] Since only two diastereoisomers were isolated, the origin of the diastereoselectivity was studied by computational method. The DFT calculations suggested that the Mannich reaction is stereospecific because of the rigid polycylic skeleton. The *cis*-fused [4.3.0] bicyclic structure is the only accessible product of the cyclization process. See the Supporting Information for details.

[14] The relative configurations of **3k** and **3k′** were determined by the X-ray diffraction. CCDC 828201 and 828107 contain 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.

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