Synthetic Methods

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Complex Bioactive Alkaloid-Type Polycycles through Efficient Catalytic Asymmetric Multicomponent Aza-Diels–Alder Reaction of Indoles with Oxetane as Directing Group**

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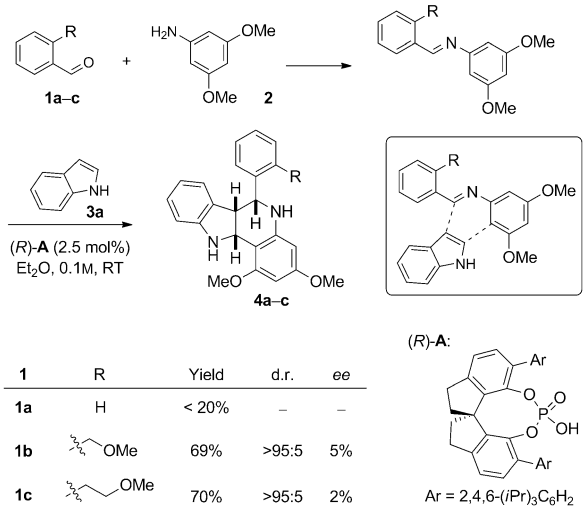
The biological activity of natural products has not only stimulated the development of efficient strategies for the assembly of complex structures, but also inspired the design of unnatural molecules with diverse structures and pharmaceutical applications.[1] Particularly intriguing are nitrogen-containing heterocyclic compounds. For example, indole/indoline, tetrahydroquinoline, and tetrahydroisoquinoline are key subunits found in a large number of complex molecules with significant biological activities.[2] Among the wide variety of synthetic approaches to access these heterocycles, multicomponent reactions (MCRs) have emerged as a particularly useful strategy, because of their bond-forming efficiency, atom economy, excellent stereoselectivity, product structure diversity/complexity, etc.[3] Nevertheless, despite these advantages and the significant efforts in developing practically useful MCRs, catalytic asymmetric MCRs to access enantioenriched complex molecules are underdeveloped.[3] Herein, we report an efficient catalytic asymmetric MCR for the efficient formation of multiple bonds in one pot with excellent stereocontrol over four new chiral centers, and thus provide facile access to a series of N-containing polycyclic molecules with anticancer activity.

The aza-Diels–Alder reaction represents one of the most powerful methods among the various strategies for the assembly of chiral N-containing heterocycles.[4] However, catalytic asymmetric multicomponent aza-Diels–Alder reactions are scarce.[5] Considering the fact that indole is a privileged structural unit found in numerous natural products and therapeutic agents,[6] we envisioned that the use of indole as the dienophile for the catalytic asymmetric aza-Diels–Alder reaction with inverse electron demand would provide a new method to access a broad range of indole-alkaloid-type polycycles. However, such intermolecular asymmetric aza-Diels–Alder reactions of indole remain unknown.[7]

We started our study with the reaction of indole (**3**) with the 2-azadiene generated in situ from benzaldehyde (**1a**) and 3,5-dimethoxyaniline (**2**). The use of chiral phosphoric acids as catalysts for imine formation and further activation toward nucleophilic addition is well-known.[8] However, in spite of our intensive efforts, the three-component reaction gave a mixture of various products in the presence of a chiral phosphoric acid, such as **A** (Scheme 1, R = H).[9] Indeed,



1	R	Yield	d.r.	*ee*
1a	H	< 20%	–	–
1b	OMe	69%	>95:5	5%
1c	OMe	70%	>95:5	2%

Scheme 1. Three-component aza-Diels–Alder reaction of indole.

a thorough literature survey showed that the above reaction may be complicated by the occurrence of several known side reactions, such as C–N bond cleavage and double additions of indole, etc.[10] Inspired by the wide success of the application of directing groups,[11] we hypothesized that the introduction of a hydrogen-bond acceptor on the aldehyde moiety may help to orient the transition state and lower the activation barrier for the desired process. Thus, we employed substrates with a simple ether group in proximity to the aldehyde moiety (**1b** and **1c**), and encouragingly, the desired aza-Diels–Alder reaction proceeded cleanly to form the desired products (**4b** and **4c**) with good yields and diastereoselectivities, but disappointing enantioselectivities.

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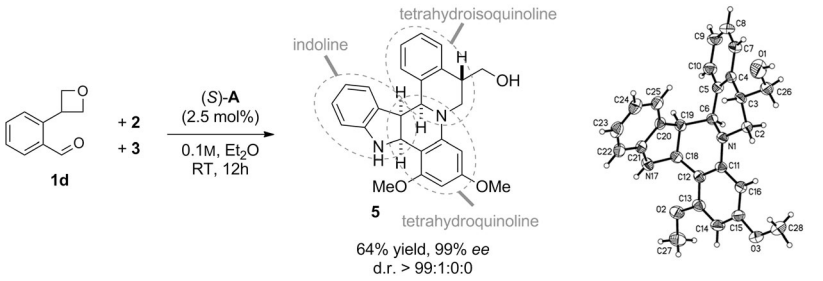
Further screening of different directing groups showed that the use of a relatively rigid oxetane[12] group can promote the three-component reaction, which proceeded smoothly to form polycyclic product **5** not only with good efficiency, but also with remarkable diastereoselectivity and enantioselectivity (99% *ee*, d.r. > 99:1, Scheme 2, see the Supporting Information for optimization of reaction conditions).[13] It is worth noting that in addition to the desired aza-Diels–Alder reaction, the process also involves an oxetane desymmetrization by the intramolecular nitrogen nucleophile.[14] It is also noteworthy that the reaction generates four new bonds (two C–C and two C–N bonds) and four new stereogenic centers in one pot from three achiral compounds.

Moreover, the polycyclic alkaloid-type product contains indoline, tetrahydroquinoline, and tetrahydroisoquinoline moieties, all of which are key elements found in numerous biologically active natural products and synthetic pharmaceuticals.[2] To the best of our knowledge, there have been no reports on such an efficient assembly of these three important structural units in one operation.

Next, we examined the substrate scope of this three-component polycyclization reaction. Differently substituted

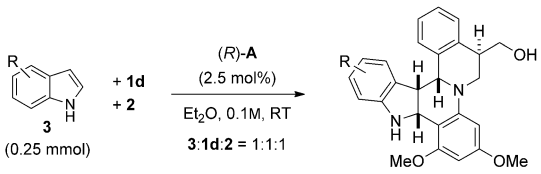


Scheme 2. Oxetane as the crucial directing group.

indoles participated smoothly in the reaction to form a range of polycyclic alkaloid-type molecules with excellent efficiency and stereoselectivity (Table 1). Electron-donating (entries 2–4 and 8–10) and electron-withdrawing groups (entries 5–7 and 11) all led to comparably good results. The method is also compatible with a diverse set of functional groups, such as halides (entries 5–7), ethers (entries 8 and 10), esters (entry 11), and the free hydroxy group (entry 9). It is noteworthy that the product purification is very easy. All the starting materials as well as the catalyst are soluble in diethyl ether, whereas the polycyclic products have low solubility and therefore precipitate out during the reaction. Thus, simple filtration (or centrifugation) followed by washing typically gave pure products.

The reaction scope in terms of the oxetane-tethered aldehydes and arylamines is shown in Scheme 4. Different aryl aldehydes could smoothly react to form the desired polycyclic products (**16**–**21**) efficiently. The reaction with other arylamines, such as 3,4,5-trimethoxyaniline, 3-methoxyaniline, and 3-hydroxyaniline proceeded to give the desired products (**22**–**24**) with moderate enantiomeric excess. A quaternary chiral center at position 4 of the tetrahydroisoquinoline moiety can also be generated (**25**), albeit with moderate enantiomeric excess. It is worth noting that the success of generating quaternary chiral centers by desymmetrization of 3-substituted oxetanes was limited.[14]

Table 1: Substrate scope of the reaction with regard to indoles.



Entry	R	*t* [h]	Product	Yield[a]	d.r.[b]	*ee*
1	H	12	**5**	85%	>99/1	98%
2	5-Me	12	**6**	89%	>99/1	92%
3	6-Me	12	**7**	96%	>99/1	93%
4	7-Me	12	**8**	92%	>99/1	94%
5	5-Br	36	**9**	76%	90/10	86%
6	6-Br	24	**10**	63%	>99/1	96%
7	6-F	24	**11**	74%	>99/1	94%
8	5-OMe	12	**12**	82%	>99/1	96%
9	5-OH	12	**13**	97%	>99/1	86%
10	6-OBn	12	**14**	78%	>99/1	98%
11	6-CO_2Me	24	**15**	74%	90/10	74%

[a] Yields of isolated purified products. [b] Ratio of the major diastereomer to the total of all other diastereomers.

We also conducted some control experiments to probe the reaction mechanism. The reaction of *N*-methyl-6-bromoindole resulted in the formation of a mixture of products, and the desired N-methylated analogue of product **10** was obtained in less than 20% yield (compare with entry 6 in Table 1), thus suggesting that the indole N–H moiety is presumably involved in hydrogen bonding. In addition, we found that the reaction exhibits a small positive nonlinear effect (NLE, Figure 1). In addition, the reaction with racemic catalyst **A** proceeded significantly slower that that with enantiopure catalyst under otherwise identical conditions. Since we did not observe a solubility difference between enantiopure and racemic catalyst **A** in diethyl ether,[15] the observed NLE may result from the

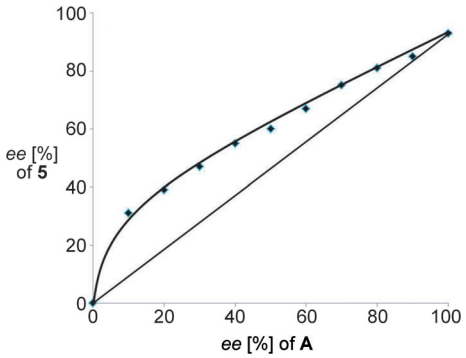
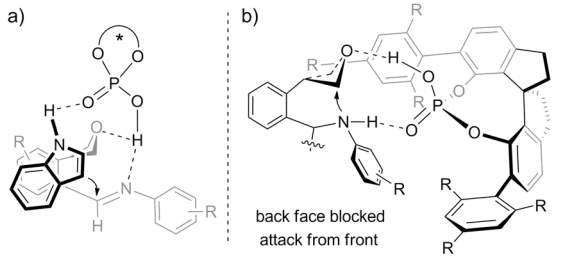


Figure 1. Nonlinear correlation between the enantiomeric excess of **A** and that of product **5**.

involvement of multiple catalyst components or higher-order interactions that are not involved in the catalysis.[16] Moreover, in some cases, we observed a by-product in which the C–C bond between C2 of the indole and C2 of the aniline is not formed, thus suggesting that the aza-Diels–Alder reaction is stepwise.

We propose possible transition states to rationalize the observed absolute stereochemical outcome (Scheme 3). The transition state shown in Scheme 3a determines the stereochemistry of the aza-Diels–Alder cycloaddition step, in which the chiral catalyst is involved in multiple hydrogen bonds. The rigid oxetane moiety may also serve as a hydrogen-bond



Scheme 3. Proposed transition states for rationalization of absolute stereochemistry: a) indole addition, b) oxetane desymmetrization.

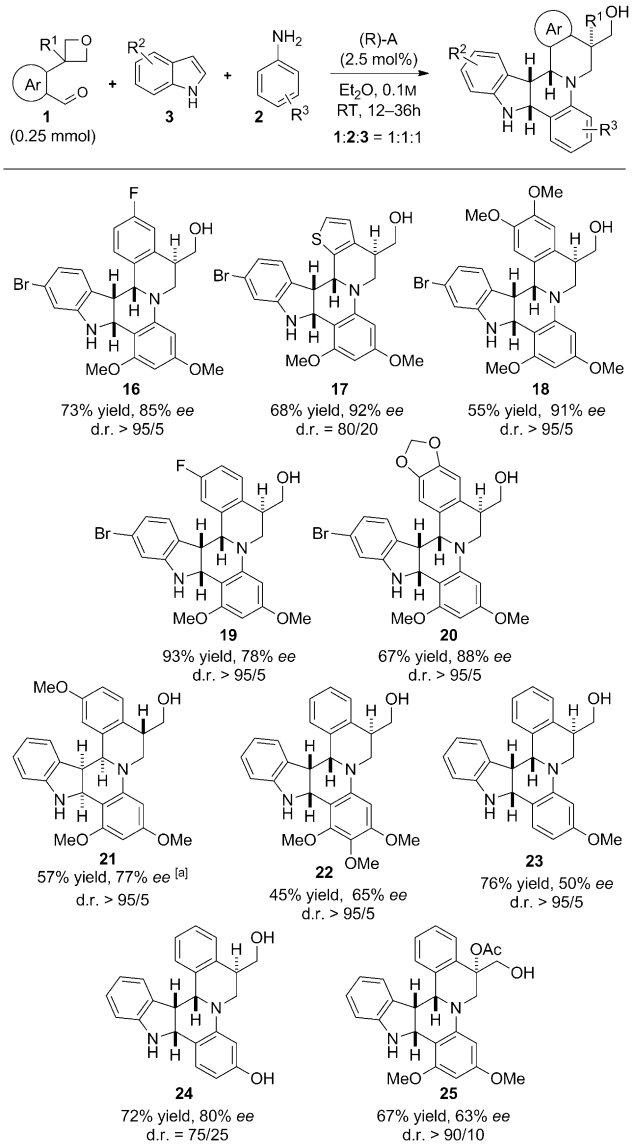
acceptor.[17] A possible transition state for the oxetane desymmetrization is shown in Scheme 3b. The nitrogen nucleophile is oriented to approach the oxetane moiety from the front face, because the back face is blocked by the chiral backbone of the catalyst, which is consistent with the observed product stereochemistry.

The indole-alkaloid-type polycyclic products of our multicomponent reactions share the same core structure with some natural products and biologically active compounds, such as melonine (**26**) and an MCH-I receptor antagonist (**27**; Scheme 5).[18] The structure resemblance prompted us to evaluate the biological activity of our products. The cytotoxicities of randomly selected compounds (**6**, **7**, and **9**) in human lung carcinoma (A549) and human cervical carcinoma (HeLa) cells were tested using the MTT assay (Table 2). For both of the cancer cell lines, these alkaloid-type molecules exhibit inhibitory effects against cell proliferation with IC_{50} values in the range of 15.0–27.5 μM. These initial results demonstrate that our polycyclic alkaloid-type products are

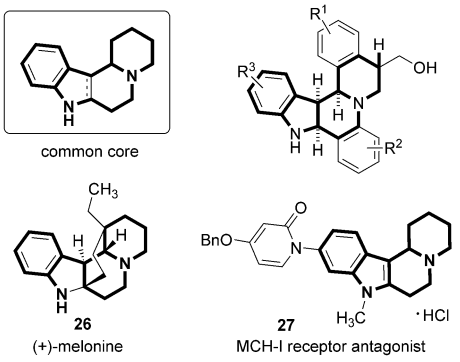
Table 2: Cytotoxicities of **6**, **7**, and **9** in A549 and HeLa cells.

Compound	IC_{50} [μM][a]	
	A549	HeLa
6	23.9±1.0	17.3±2.4
7	23.2±3.1	27.5±3.4
9	22.9±1.7	15.0±1.6
paclitaxel [nM][b]	11.3±4.6	4.7±1.4

[a] IC_{50} values were measured by an MTT assay following a 72 h exposure. Values were obtained through independent measurements of cell viability. [b] Paclitaxel was used as a positive control.



Scheme 4. Substrate scope of the reaction with regard to arylamines and aldehydes. Given yields are those of isolated purified products. d.r. represents the ratio of the major diastereomer to the total of all other diastereomers. [a] Catalyst (*S*)-**A** was used.



Scheme 5. Structure resemblance of products of aza-Diels–Alder reaction with natural products and bioactive compounds.

promising candidates for further development into potential anticancer drugs.

In summary, we have developed the first catalytic asymmetric three-component aza-Diels–Alder reaction using indole as the dienophile. In this reaction, oxetane was shown to be a superb directing group that played a crucial role in achieving both high yields and high enantioselectivities. Thus, in the presence of a chiral phosphoric acid catalyst, a range of complex polycyclic alkaloid-type molecules that contain indoline, tetrahydroquinoline, and tetrahydroisoquinoline moieties were rapidly assembled from simple achiral starting materials. The process features efficient formation of multiple bonds (two C–C and two C–N bonds) and multiple (four) chiral centers, rapid installation of molecular complexity, excellent chemical efficiency and stereoselectivity, easy product purification, and proven biological activity of the products. This new catalytic asymmetric multicomponent reaction should be attractive for diversity-oriented synthesis and drug discovery. Further investigations on the reaction mechanism and biological properties of the polycyclic alkaloid-type products are underway.

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