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Direct organocatalytic coupling of carboxylated piperazine-2,5-diones with indoles through conjugate addition of carbon nucleophiles to indolenine intermediates

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ABSTRACT

Organocatalytic conjugate addition of diketopiperazines to indoles was achieved in good to excellent yields through electrophilic indolenine intermediates generated under mild conditions. Screening of catalysts and solvents at different temperatures was performed in order to achieve high product yields.

The indole–diketopiperazine bridge is an important structural feature of many complex alkaloids of fungal origin that display a spectrum of interesting biological activity. Such alkaloids contain cyclotryptophan motifs of considerable structural diversity often fused to N-alkylated or sulfenylated diketopiperazine rings. Ditryptophenaline[1] (Fig. 1), extracted from several strains of *Aspergillus flavus*, incorporates 3a,3a′-bispyrrolidinoindoline core and shows cytotoxicity in several cell lines. Alkaloid (+)-WIN 64821,[2–6] also isolated from *Aspergillus* sp., is a potent competitive substance P antagonist against the human neurokinin 1[4–6] and cholecystokinin type B receptors.[7] Other indole alkaloids derived from tryptophan units and α-amino acids in diketopiperazine rings include (+)-asperazine[8] and (+)-gliocladin C.[9] Sporidesmins, toxic secondary metabolites produced by filamentous fungi of *Chaetomium* or *Pithomyces* sp., also contain cyclotryptophan motifs along with the disulfide or polysulfide bridges spanning diketopiperazine rings. Chaetocin and chetomin are two examples of dimeric epidithiodiketopiperazine (ETP) fungal metabolites[10,11] that incorporate an indole system fused to the ETP core (Fig. 1). The potent biological activity of these natural products is attributed to the redox properties of the disulfide bridges.[11,12] Apart from cytotoxic and immunomodulatory activities, chetomin also shows promising antiangiogenic action: it suppresses the neovascularization in solid tumors by disrupting the transcription of the vascular endothelial growth factor (*VEGF*) gene.[11,13]

Despite their striking architecture and interesting biological activity, many dimeric ETPs have remained elusive synthetic targets, with total synthesis of 11,11′-dideoxyverticillin A, a potent tyrosine kinase inhibitor, being the only reported example to date.[14] This highlights the challenges involved in the construction of such stereochemically complex, densely functionalized structures bearing high sensitivity to bases and reducing agents functional groups. Direct organocatalytic methods for the formation of the indole–diketopiperazine linkage could facilitate development of succinct routes for the efficient assembly of the key structural blocks of dimeric ETPs and bispyrrolidinoindoline alkaloids.

The lower reactivity of β-amido esters and diketopiperazines in α-alkylation reactions, as compared to aldehydes and ketones, remains the main challenge in the development of direct and effi-

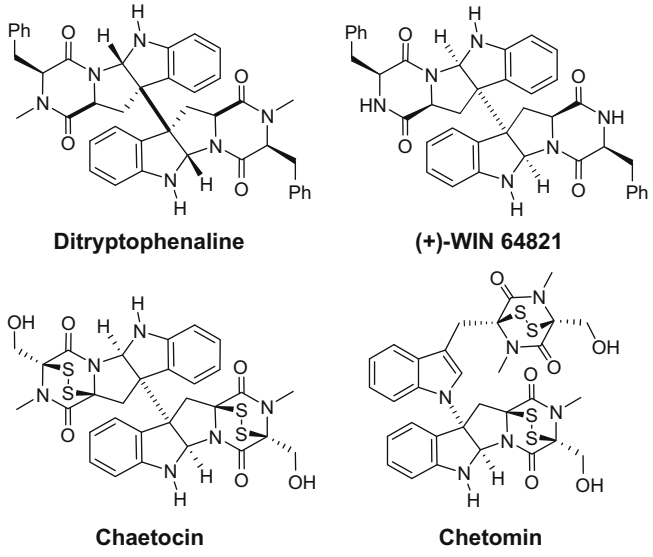

Figure 1. Natural products with cyclotryptophan motifs incorporating indole–diketopiperazine linkages.

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cient procedures of their alkylation. Although many examples of organocatalytic alkylations of aldehydes and ketones can be found in the recent literature,[15] none have been reported so far for substituted β-amido esters and diketopiperazines. Organocatalytic transformations of the piperazine-2,5-dione ring system are known to be more challenging as compared to those of aldehydes, ketones, and esters due to its lower reactivity toward electrophiles and greater steric bulk.[16] In this Letter, we report the first direct, organocatalytic coupling of substituted diketopiperazines and indoles.

Only a few strategies for the direct construction of the indole–diketopiperazine bridge are known to date. The most commonly used is the method pioneered by the groups of Kametani and Somei (Fig. 2).[17,18] This remarkable reaction involves coupling of the nucleophilic substrate with gramine in refluxing acetonitrile in the presence of trialkylphosphine. This reaction has received a number of applications, for example, in the synthesis of paraherquamides A[19] and B,[20,21] by Williams and co-workers as well as in the mechanistic study of the Morin rearrangement,[22] although it uses toxic trialkylphosphine and generally gives the product in moderate yields (40–70%). An interesting modification of this reaction has been reported by Hart and Magomedov, where treatment of substituted diketopiperazine with Li_2CuCl_4 followed by the addition of gramine methosulfate gave coupling product in 54% yield.[23]

Our first goal was to improve the efficiency and increase product yields in the coupling of gramine with substituted diketopiperazines. Hence, we directed our initial efforts to exploration of the feasibility of the reaction between gramine **1a** and ethyl ester **2a** using inexpensive, readily available quinine as a Lewis base (Fig. 2). The results were encouraging as higher yields were obtained when quinine was used in place of tributylphosphine. To further explore the scope of this transformation, three substrates **2a**–**c** were tested at temperatures ranging from ambient to the reflux of acetonitrile (Table 1). No reaction was taking place at room temperature, and low yields were obtained at 50 °C (Table 1, Entries 1–4), presumably due to the low rate of formation of 3-methylene indolenine intermediate from gramine. However, further increase of the temperature to 82 °C dramatically improved the reaction. The products **3a**–**3c** formed in good to excellent yields, although as expected, the reaction showed decrease in yields with the increase in the steric bulk of the ester groups in substrates **2a**–**2c** (Table 1, Entries 5–7). To compensate for such a decrease, longer reaction time and larger excess of **1a** were used. The use of chiral quinine opened a possibility for an asymmetric induction during the catalytic cycle. Unfortunately, the observed enantioselectivity was rather low, with ee ranging from 10 to 25%. The use of gramine-*N*-oxide **1b**[24] or 1-Boc-gramine **1c**[25] (Fig. 3) did not improve product yield or enantioselectivity.

In a search for donors that generate indolenine intermediates at ambient temperature and tolerating indole ring and methylene bridge substituents, we turned to arylsulfonyl indoles that have been recently reported to promote proline-catalyzed α-alkylation of aldehydes.[15,26,27] Two types of arylsulfonyl indoles were chosen: one with the phenyl group at the indolyl position, which could facilitate determination of the diastereomeric ratio of the products, and the substrate **5c** with unsubstituted methylene bridge[28] (vide infra). The sulfonyl group at the benzylic position of 3-substituted

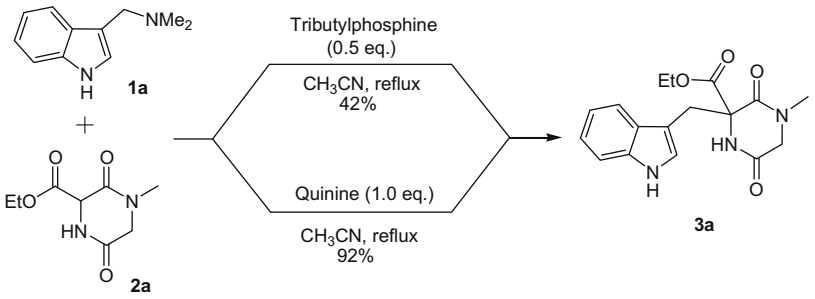
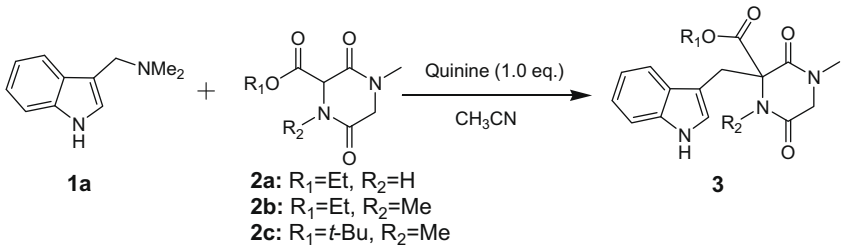


Figure 2. Alkylation of piperazine-2,5-dione **2a** with gramine **1a.**

Table 1
Effect of substrate and temperature on the quinine-promoted alkylation of substituted diketopiperazines with gramine



Entry	Substrate	Equiv of **1a**	Time (h)	Temp. (°C)	Yield[a] (%)
1	**2a**	2.0	24	rt	NR
2	**2b**	2.0	24	rt	NR
3	**2a**	2.0	24	50	10
4	**2b**	2.0	24	50	<5
5	**2a**	2.0	24	82	92
6	**2b**	3.5	48	82	81
7	**2c**	4.0	48	82	72

[a] Yield of purified product after chromatographic separation.

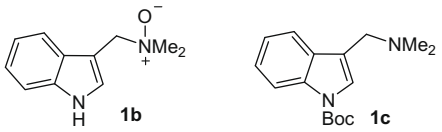
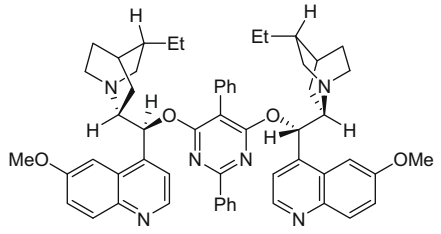
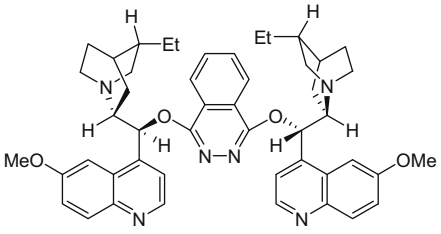


Figure 3. Gramine-*N*-oxide **1b** and 1-Boc-protected gramine **1c** as substrates for organocatalytic α-alkylation of diketopiperazines.





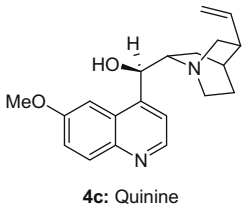
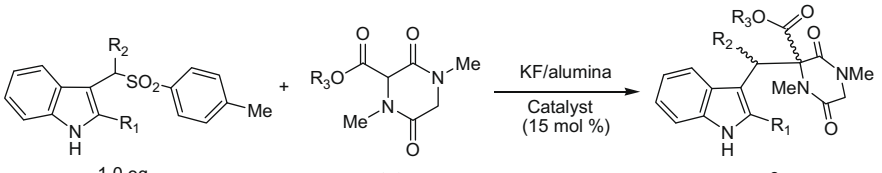


Figure 4. Cinchona alkaloid Lewis bases used in this study.

indoles constitutes a good leaving group, which under basic or acidic conditions allows for a facile generation of an electrophilic indolenine intermediate. To generate such intermediates from the arylsulfonyl indoles, a method that involves treatment with KF on basic alumina[29] is often used. Because β-amido esters are usually compatible with such bases, we sought to develop a simple and general protocol for the alkylation of substituted diketopiperazines with arylsulfonyl indoles using cinchona alkaloids as catalysts.

We first performed the reaction with substrates **2c** and **5a** in dichloromethane as the solvent. The presence of a phenyl group at the indolyl position produces diastereomeric products whose dr could be readily determined by ^{1}H NMR spectroscopy. This would provide an opportunity to study the effect of different organocatalysts (Fig. 4) on the diastereoselectivity of the reaction. Gratifyingly, the reaction proceeded in moderate to high yields with moderate amounts of cinchona alkaloids (Table 2, Entries 1–11). After the successful reaction of the arylsulfonyl indole **5a** with the diketopiperazine **2a** we focused on optimizing the reaction conditions by varying solvents, temperatures, and substituents on aryl indoles and diketopiperazine. Substituents at the indole ring (C-2 position) and at the bridging carbon are well tolerated, suggesting wide scope of the reaction (Table 2, Entries 10-11). We found that 80 mg of KF/alumina per 0.1 mmol of sulfone was needed to obtain good yields. Next, the effects of catalyst loading, temperature, and solvents were studied in the reactions with substrate **2c**. The catalyst **4b** gave the best yields with good diastereomeric ratios at room temperature. Lowering the reaction temperature to 0 °C resulted in a decrease of product yield but did not improve stereoselectivity of the reaction. Even with the relatively bulky substrate **2c**, high yields were obtained after increasing its stoichiometric amount from three to five equivalents (Table 2, Entry 7). Finally, arylsulfonyl indole **5c**, with methylene group at the indolyl position in the reactions with substrate **2c,** gave product in 90% yield (Table 2, Entry 12), illustrating that this transformation could be readily used in the synthesis of natural products containing cyclotryptophan motifs.

Table 2
Scope of α-alkylation of diketopiperazines **2b**–**2c** with arylsulfonyl indoles **5a**–**5c** catalyzed by cinchona alkaloids **4a**–**4c**



1.0 eq. 3.0 eq. **6**

5a: R_1 = Me, R_2 = Ph
5b: R_1 = H, R_2 = Ph
5c: R_1 = H, R_2 = H

2b: R_3 = Et
2c: R_3 = *t*-Bu

Entry	Indole	DKP	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield[a] (%)	dr
1	**5a**	**2c**	CH_2Cl_2	**4a**	rt	48	55	5:1
2	**5b**	**2c**	CH_2Cl_2	**4a**	rt	72	70	2.6:1
3	**5a**	**2c**	CH_2Cl_2	**4b**	rt	48	72	4.5:1
4	**5a**	**2c**	Toluene	**4b**	0	120	NR	—
5	**5a**	**2c**	Toluene	**4b**	rt	120	46	3.8:1
6	**5b**	**2c**	CH_2Cl_2	**4b**	rt	72	75	3:1
7	**5a**	**2c**	CH_2Cl_2	**4b**	rt	72	89[b]	4.5:1
8	**5a**	**2b**	CH_2Cl_2	**4c**	rt	48	71	1:1
9	**5a**	**2b**	Toluene	**4c**	rt	48	54	1:1
10	**5a**	**2c**	CH_2Cl_2	**4c**	rt	48	70	2.7:1
11	**5b**	**2c**	CH_2Cl_2	**4c**	rt	72	70	2.5:1
12	**5c**	**2c**	CH_2Cl_2	**4b**	rt	48	90	N/A

[a] Yield of purified product after chromatographic separation.
[b] 5 equiv of **2c** was used.

We also performed the reactions using different stoichiometries of diketopiperazine and arylsulfonyl indole in order to determine the best ratio of reactants. Interestingly, it was found that the best yields were obtained when the arylsulfonyl indole, as opposed to carboxylated diketopiperazine, was used as the limiting reagent.

In conclusion, a new strategy for the direct organocatalytic coupling of substituted diketopiperazines with indoles has been developed through the use of 3-(-1-arylsulfonylalkyl)indoles as convenient precursors to indolenine intermediates and cinchona alkaloids as organocatalysts. This method could provide an efficient means for rapid construction of bispyrrolidinoindoline scaffolds of alkaloids and epidithiodiketopiperazine fungal metabolites. Further exploration of the mechanism of this reaction and development of its enantioselective variant are under investigation.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures, characterization, and NMR spectra of compounds **3a–c** and **6a–c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.068.

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