Indole Chemistry

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Highly Enantioselective Friedel–Crafts Alkylation/*N*-Hemiacetalization Cascade Reaction with Indoles**

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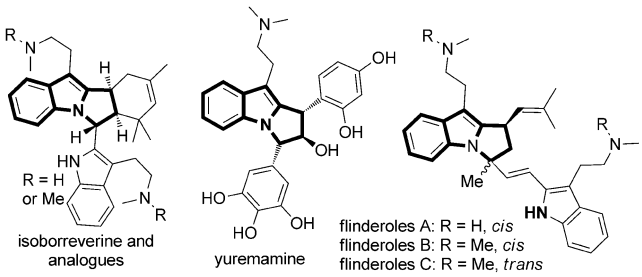
Chiral polycyclic indoles are ubiquitous and important ring systems found in many bioactive alkaloids and pharmaceuticals.[1] As a result, extensive effort has been devoted to the development of efficient methods for their synthesis. Most approaches developed to date are based on the direct functionalization of the "privileged" indole core.[2] Representative strategies include asymmetric intramolecular alkylation of the C3, C2, or N1 positions of indoles, these reactions are exemplified by allylic alkylation,[3] Friedel–Crafts alkylation,[4] the Pictet–Spengler reaction,[5] and *N*-alkylation.[6] Most of these processes are governed by the nucleophilic character of the C3, C2, or N1 positions in the indole ring and require the substrates to be carefully designed. The latter requirement often limits the substrate scope of these reactions. Recently, indole-based cascade reactions driven by the nucleophilicity of the indole C3 position and the electrophilicity of the iminium species generated in situ, have served as the basis for alternative and robust methods of polycyclic indole synthesis.[7] Despite these recent advances, the development of new approaches to the construction of polycyclic indole derivatives, which take advantage of the unique reactivity profile of indoles, remains an important goal.

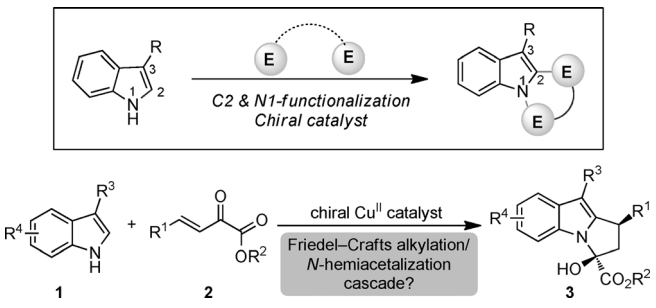
The [*a*]-annelated indole system, particularly the pyrrolo[1,2-*a*]indole scaffold, is present in a diverse family of structurally complex polycyclic indoles and has consequently become a primary target of synthetic efforts (Scheme 1).[8–10] In 2009, the groups of Chen[9c] and Hartwig[9b] uncovered regio and enantioselective *N*-allylation reactions of indoles that employed a cinchona alkaloid and an iridium/phosphoramidite complex, respectively. Routine elaboration of the products of these processes afforded highly substituted dihydropyrrolo[1,2-*a*]indoles in good overall yields. Recently,



Scheme 1. Representative natural products based on 1*H*-pyrrolo[1,2-*a*]indole.

You and co-workers described another highly enantioselective *N*-allylation reaction of indoles that involved an iridium-catalyzed allylic alkylation/oxidation cascade.[9a] The products of the reactions were also readily transformed, in this case into a diastereoisomer of naturally occurring methylyuremamine. Furthermore, Enders[6a] and Wang[6d] have also made significant contributions to the construction of these alkaloids by designing organocatalytic tandem *N*-alkylation/intramolecular cyclization reactions of modified indoles. However, to our knowledge, methods for the direct catalytic enantioselective assembly of structurally diverse and stereochemically complex pyrrolo[1,2-*a*]indole derivatives remain rare and, as a result, a challenging goal in the area of organic synthesis.

In our recent research into the efficient asymmetric functionalization of indoles,[11] we envisaged that simple 3-substituted 1*H*-indoles might serve as N1 and C2 dinucleophiles in cascade reactions with suitable dielectrophiles to generate polycyclic indoles (Scheme 2). In elaborating this scenario, several issues had to be considered, including: 1) the possibility of competitive single reactions at either N1, C2, or C3, 2) the occurrence of tandem reactions involving the C3 and C2 positions, and 3) the control of diastereo- and



Scheme 2. Conceptual basis for the enantioselective Friedel–Crafts alkylation/*N*-hemiacetalization cascade reaction with indoles.

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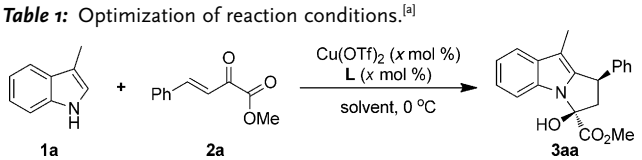
enantioselectivity. The ensuing effort to probe these issues led to the development of an unprecedented, copper-catalyzed C2 Friedel–Crafts alkylation/*N*-hemiacetalization cascade process that transformed 3-substituted indoles and β,γ-unsaturated α-ketoesters[12] into a wide range of functionally diverse, enantioenriched 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indoles in a single step.

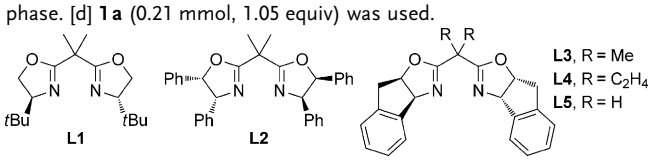
In an initial investigation aimed at examining the feasibility of the strategy described above, we observed that treatment of 3-methylindole **1a** with the β,γ-unsaturated α-ketoester **2a** in the presence of copper(II) triflate (10 mol%) promoted a cascade reaction that afforded the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **3aa** in 85% yield and 3:2 d.r. (Table 1, entry 1). Next, a series of commercially available

Table 1: Optimization of reaction conditions.[a]



Entry	L	*x* [mol%]	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	–	10	Et_2O	36	85	3:2	–
2	**L1**	10	Et_2O	36	95	70:30	46
3	**L2**	10	Et_2O	12	95	80:20	91
4	**L3**	10	Et_2O	12	92	80:20	96
5	**L4**	10	Et_2O	12	96	85:15	97
6	**L5**	10	Et_2O	12	94	91:9	98
7	**L5**	10	THF	48	70	75:25	88
8	**L5**	10	CH_2Cl_2	12	93	83:17	93
9	**L5**	10	toluene	12	95	94:6	>99
10[d]	**L5**	10	toluene	12	96	95:5	>99
11[d]	**L5**	5	toluene	12	95	95:5	>99
12[d]	**L5**	1	toluene	32	94	94:6	>99

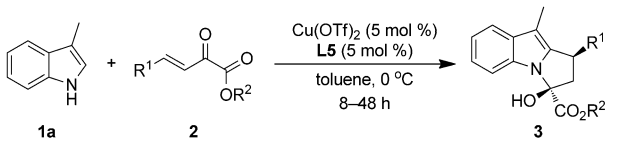
[a] Reaction conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv) in 2.0 mL solvent at 0°C. [b] Yield of the isolated diastereomeric mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **1a** (0.21 mmol, 1.05 equiv) was used.



chiral bis(oxazoline) ligands[13] were screened to uncover an asymmetric variant of this process. As the data summarized in Table 1 show, reactions with most of the ligands probed produced **3aa** with modest to high levels of enantioselectivity, with ligand **L5** providing the highest yield (94%) and most stereoselective (91:9 d.r. and 98% *ee*) results (Table 1, entry 6). A simple survey of solvents showed that toluene was optimal in terms of diastereo- and enantioselectivity (Table 1, entries 6–9). Further investigations, such as probing substrate ratios and catalyst loadings, led to the optimized conditions (**3aa**, 95%, 95:5 d.r., >99% *ee*, Table 1, entry 11): $Cu(OTf)_2$/**L5** (5 mol%) at 0°C in 2.0 mL of toluene.

The scope of β,γ-unsaturated α-ketoesters **2** that participate in the cascade reaction carried out under the optimized conditions was explored next (Table 2). Changing the ester group in **2** from methyl to ethyl, benzyl, or *iso*-propyl had no

Table 2: Scope of the β,γ-unsaturated α-ketoesters.[a]



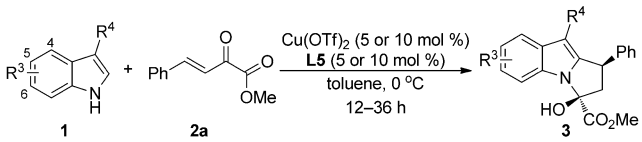
Entry	R^1, R^2	3	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	Ph, Me (**2a**)	**3aa**	95	95:5	>99
2	Ph, Et (**2b**)	**3ab**	93	96:4	>99
3	Ph, Bn (**2c**)	**3ac**	92	95:5	>99
4	Ph, *i*Pr (**2d**)	**3ad**	93	96:4	>99
5	4-MeC_6H_4, Me (**2e**)	**3ae**	96	95:5	>99
6	4-$MeOC_6H_4$, Me (**2f**)	**3af**	95	96:4	>99
7	4-FC_6H_4, Me (**2g**)	**3ag**	95	95:5	>99
8	4-ClC_6H_4, Me (**2h**)	**3ah**	94	93:7	98
9	4-BrC_6H_4, Me (**2i**)	**3ai**	93	92:8	96
10	3-BrC_6H_4, Me (**2j**)	**3aj**	93	92:8	97
11	2-FC_6H_4, Me (**2k**)	**3ak**	96	88:12	94
12	2-thiophenyl, Me (**2l**)	**3al**	92	95:5	>99
13	PhCH=CH, Me (**2m**)	**3am**	90	89:11	99
14[d]	CO_2Et, Me (**2n**)	**3an**	92	85:15	98
15[e]	Cy, Et (**2o**)	**3ao**	90	97:3	91
16[f]	$(MeO)_2CH$, Et (**2p**)	**3rp**	91	56:44	73 (98)
17[e]	propyl, Et (**2q**)	**3aq**	67	67:33	27 (76)

[a] Reaction conditions: **1a** (0.42 mmol, 1.05 equiv), **2** (0.4 mmol, 1.0 equiv) in 4.0 mL toluene at 0°C. [b] Yield of the isolated diastereomeric mixture. [c] Determined by HPLC analysis on a chiral stationary phase. Data in parentheses are the *ee* values of the minor diastereomers. [d] Performed at −20°C. [e] **1a** (0.48 mmol, 1.2 equiv) was used. [f] **1r** (0.48 mmol, 1.2 equiv) was used.

obvious effect on the reaction (Table 2, entries 1–4). Moreover, substrates containing a range of electron-donating and -withdrawing substituents on the γ-aryl ring react with 3-methylindole **1a** to afford the corresponding 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **3ae**–**3ak** in high yields (93–96%) and with high diastereo- and enantioselectivities (up to 96:4 d.r. and >99% *ee*; Table 2, entries 5–11). Heteroaromatic and vinyl-substituted β,γ-unsaturated α-ketoesters, such as **2l** and **2m**, also participate in this transformation (Table 2, entries 12 and 13). Moreover, reactions of **1a** with γ-ester- and γ-alkyl-substituted β,γ-unsaturated α-ketoesters (**2n** and **2o**) also proceed smoothly to give the corresponding products (**3an** and **3ao**) in a highly enantioselective manner (Table 2, entries 14 and 15). Note that the straight-chain aliphatic substrates (**2p** and **2q**) could also participate in the reaction to afford the corresponding products **3rp** and **3aq** in good yields, albeit with decreased diastereoselectivities (Table 2, entries 16 and 17).

The 3-substituted indole substrate scope of the cascade reactions was also investigated. As seen by inspection of the data displayed in Table 3, a variety of substituted indoles participate in reactions that produce 2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]indoles in high yields (89–97%) and excellent levels of stereoselectivity (92:8–96:4 d.r., 98–>99% *ee*; Table 3, entries 1–11). The 3-substituted indoles containing C3 ethyl, *iso*-propyl, cyclohexyl, and benzyl groups were also observed to react with β,γ-unsaturated α-ketoester **2a** to afford the expected products **3la**–**3oa** in good yields (85–94%) and with excellent diastereo- and enantioselectivities (Table 3,

Table 3: Scope of the 3-substituted indoles.[a]

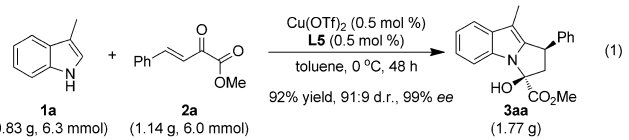


Entry	R^3, R^4	3	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	H, Me (**1a**)	**3aa**	95	95:5	>99
2	4-Me, Me (**1b**)	**3ba**	93	93:7	98
3	5-Me, Me (**1c**)	**3ca**	96	95:5	>99
4	6-Me, Me (**1d**)	**3da**	97	96:4	>99
5	5-MeO, Me (**1e**)	**3ea**	93	92:8	99
6	5-BnO, Me (**1f**)	**3fa**	96	95:5	>99
7	5-F, Me (**1g**)	**3ga**	91	94:6	99
8	5-Cl, Me (**1h**)	**3ha**	96	96:4	98
9	5-Br, Me (**1i**)	**3ia**	89	96:4	99
10	6-Cl, Me (**1j**)	**3ja**	93	96:4	>99
11	6-F, Me (**1k**)	**3ka**	95	96:4	>99
12	H, Et (**1l**)	**3la**	85	95:5	99
13	H, *i*Pr (**1m**)	**3ma**	89	95:5	98
14	H, Cy (**1n**)	**3na**	92	93:7	96
15	H, Bn (**1o**)	**3oa**	94	91:9	98
16	H, Ph (**1p**)	**3pa**	90	86:14	80 (93)
17	H, $CH_2CO_2CH_3$ (**1q**)	**3qa**	92	90:10	98
18	H, $(CH_2)_2$OTBS (**1r**)	**3ra**	95	94:6	>99
19	H, $(CH_2)_2$NPhth (**1s**)	**3sa**	90	92:8	98

[a] Reaction conditions: **1** (0.42–0.60 mmol, 1.05–1.50 equiv), **2a** (0.4 mmol, 1.0 equiv) in 4 mL toluene at 0°C; $Cu(OTf)_2$/**L5** (5 mol%) was used for entries 1–12 and 10 mol% for entries 13–19. [b] Yield of the isolated diastereomeric mixture. [c] Determined by HPLC analysis on a chiral stationary phase. Data in parentheses are the *ee* values of minor diastereomers. TBS = *tert*-butyldimethylsilyl; NPhth = phthalimide.

entries 12–15, 91:9–95:5 d.r., 96–99% *ee*). In the reaction of 3-phenylindole **1p** with **2a**, the product was formed in high yield, but with a somewhat decreased level of stereoselectivity (Table 3, entry 16). Notably, indoles bearing ester (**1q**), *tert*-butyldimethylsiloxyethyl (**1r**), and protected aminoethyl (**1s**) substituents also undergo reaction with **2a** to produce the corresponding products with high enantioselectivities (Table 3, entries 17–19). These products are deserving of special note, because such functional groups at the 3-position of indole would facilitate further modification.

To demonstrate the synthetic potential of this new cascade process, we explored a gram scale reaction of 3-methylindole **1a** and β,γ-unsaturated α-ketoester **2a**. As shown in Equation (1), the use of only 0.5 mol% $Cu(OTf)_2$/**L5** promotes the



(1)

formation of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **3aa** in 92% yield with 91:9 d.r. and 99% *ee*. The absolute configuration of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **3ah** was determined to be 1*R*, 3*S* through X-ray crystallographic analysis (Figure 1).[14]

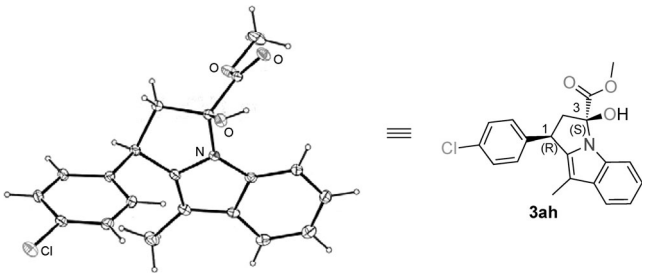
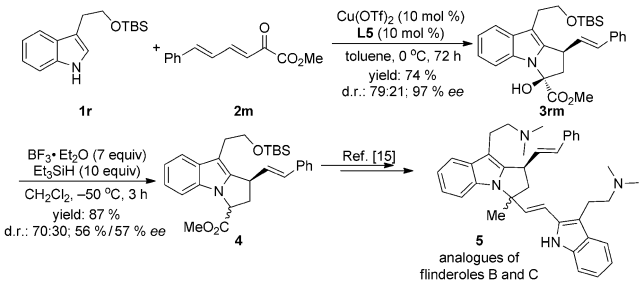


Figure 1. X-ray crystal structure of compound **3ah**.[14] Thermal ellipsoids set at 30% probability.

This method can be applied in the formal total synthesis of natural products, such as flinderoles B and C, which have been found to exhibit impressive selective antimalarial activities.[8a] As shown in Scheme 3, indole **1r** reacted well



Scheme 3. Formal total synthesis of analogues of flinderoles B and C.

with vinyl-substituted β,γ-unsaturated α-ketoester **2m** under the standard reaction conditions to give the corresponding product **3rm** in 74% yield with 97% *ee* and 79:21 d.r. Next, reduction of **3rm** with Et_3SiH–$BF_3{\cdot}Et_2O$ at −50°C provided key intermediate **4** in good yield. Further transformations of **4**, according to the procedure reported by the groups of Dethe[15a] and Toste,[15b] could give the analogues **5** of flinderoles B and C.

In conclusion, the studies described above have led to the development of a new copper-catalyzed, enantioselective Friedel–Crafts alkylation/*N*-hemiacetalization cascade reaction between substituted indoles and β,γ-unsaturated α-ketoesters. The process enables the efficient construction of diversely functionalized 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indoles in a highly enantioselective manner. We expect that this and related strategies will have broad application in the synthesis of bioactive natural alkaloids, such as those highlighted in Scheme 1, a proposal that is currently being explored in our laboratory.

Experimental Section

Representative procedure: The metal catalyst $Cu(OTf)_2$ (7.23 mg, 0.02 mmol; 5 mol%) and ligand **L5** (6.61 mg, 0.02 mmol; 5 mol%) were stirred in 4.0 mL of toluene at room temperature for 1 h in a 10 mL schlenk tube under Ar. Then, β,γ-unsaturated α-ketoester **2a** (76 mg, 0.40 mmol) was added and the reaction mixture was stirred for a further 10 min. The mixture was placed in a 0°C cooling bath

and stirred for 20 min. Then, 3-methyl indole **1a** (55 mg, 0.42 mmol) was added quickly to the mixture. Upon reaction completion (determined by TLC), the crude reaction mixture was directly subjected to column chromatograpy (petroleum ether/ethyl acetate = 15:1 to 7:1) to afford the desired product **3aa** as a yellowish solid in 95% yield with 95:5 d.r. and > 99% *ee*.

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