

Multicatalysis

Merging Gold and Organocatalysis: A Facile Asymmetric Synthesis of Annulated Pyrroles

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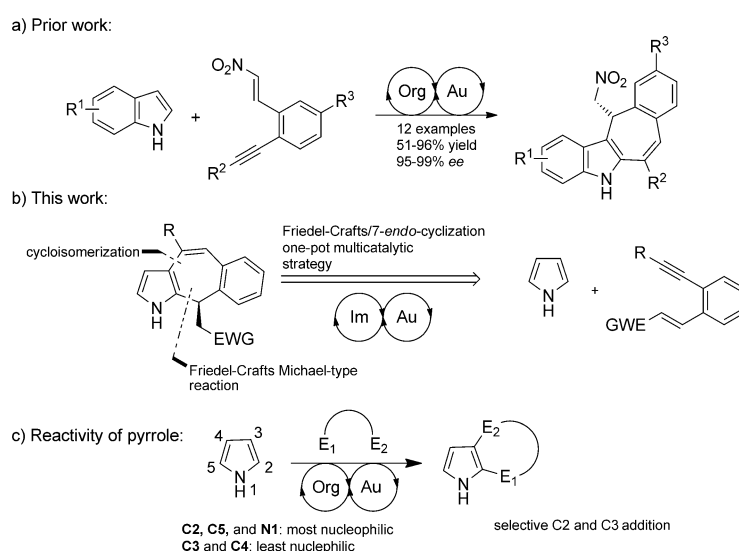
Abstract: The combination of cinchona-alkaloid-derived primary amine and Au^I-phosphine catalysts allowed the selective C–H functionalization of two adjacent carbon atoms of pyrroles under mild reaction conditions. This sequential dual activation provides seven-membered-ring-annulated pyrrole derivatives in excellent yields and enantioselectivities.

Although gold catalysis and organocatalysis have rapidly grown since the turn of the millennium and emerged as powerful tools in the general field of catalysis, examples of the combination of gold and organocatalysis in sequential and cooperative tandem reactions exploiting complementary activation modes are still scarce.^[1–3] Recently, we reported the asymmetric synthesis of tetracyclic indole derivatives containing seven-membered rings by the merger of a thioamide-based organocatalyst with a Au^I catalyst to effect two consecutive Friedel–Crafts-type reactions on unsubstituted indole substrates (Scheme 1a).^[4]

Due to the immense importance of the indole core, major emphasis has been given to the development of asymmetric Friedel–Crafts reactions involving indole derivatives. Pyrrole is another electron-rich heteroaromatic compound, core of which is found in many natural products.^[5,6] One attractive aspect of pyrrole chemistry that is unseen in indole substrates is the inherent nucleophilicity on the C2 position, which stands in contrast to indoles having a classical C3 nucleophilic site. Because Michael-type reactions of pyrroles usually gives 2,5-dialkylated products, it is difficult to monofunctionalize pyrrole substrates (Scheme 1c).^[7] To avoid this problem, we wanted to

selectively functionalize two adjacent sites on the pyrrolic heterocycle by using two different catalytic modes of activation to generate new annulated pyrrole derivatives in a one-pot reaction, which is quite difficult to achieve by using conventional methods.

Therefore, we report a new asymmetric one-pot dual catalytic protocol that uses primary amine and Au^I catalysis to access 2,3-annulated pyrroles containing a seven-membered ring (Scheme 1b). This method is intriguing, because medium-sized rings are difficult to synthesize by conventional organocatalytic methods.^[8] Moreover, a publication documenting a Au^I-catalyzed 7-*endo*-dig cyclization mode on pyrrole substrates is not known to date. Such cyclization modes have only been known



Scheme 1. Strategy comparison between current work and our recently reported annulations of indoles.

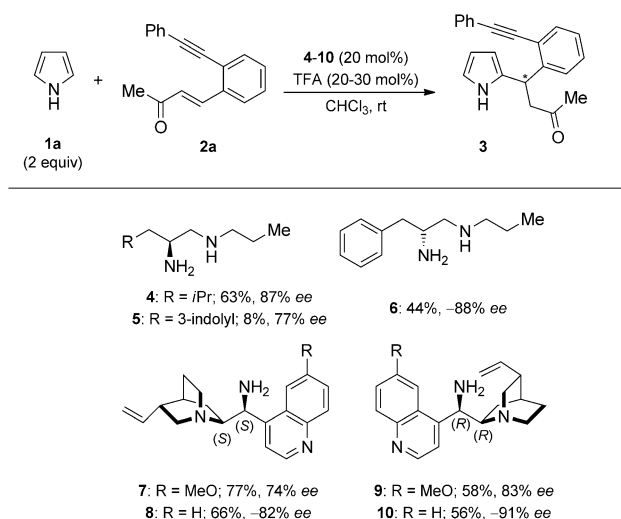
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to occur when platinum or Au^{III} catalysis was utilized.^[9] To the best of our knowledge, the method described herein is the first known example of an asymmetric one-pot operation, in which pyrroles act as a double nucleophile, hence augmenting the operational efficiency of this protocol.

To achieve the annulated pyrrole targets, we first focused on the optimization of the Friedel–Crafts–Michael-type reaction. For the 1,4-addition of pyrrole to enone **2a**, primary amines **4–6** derived from amino acids and cinchona-alkaloid-derived amines **7–10** together with trifluoroacetic acid (TFA) as additive were employed (Scheme 2).^[10,11] The primary amines **4–6**



Scheme 2. Catalyst screening for the Friedel-Crafts Michael-type reaction.

showed poor to good conversions with good enantioselectivity values, whereas the reactions with the primary amines 7–10 were finished within one day and provided comparable or better enantioselectivity values.

The catalyst 10 gave the highest enantioselectivity value, and further optimization was carried out by screening different solvents (Table 1). It turned out that the choice of the solvent did not have any crucial influence on the yield or the observed enantioselectivity values. However, we were able to obtain better yields and slightly improved enantioselectivities at higher dilution and lower temperature. Under these conditions, the amount of dialkylated pyrrole was low, and no other by-products could be observed. This fact is remarkable, because most known methods on 1,4-additions of pyrroles mainly give dialkylated products.^[5] We did not investigate the influence of

Table 1. Optimization of the reaction conditions for the Friedel-Crafts Michael-type reaction.^[a]

Entry	Solvent [mL]	t [h]	Yield [%] ^[b]	ee [%] ^[c]
1	CHCl ₃ (1.5)	16	56	91
2	CH ₂ Cl ₂ (1.5)	15	59	87
3	toluene (1.5)	21	60	88
4	PhCl (1.5)	21	61	87
5	toluene (3.0)	21	70	91
6	CH ₂ Cl ₂ (3.0)	24	68	91
7 ^[d]	CHCl ₃ (3.0)	65	89	93
8 ^[d]	toluene (3.0)	65	95	93

[a] General reaction conditions: **2a** (0.5 mmol), pyrrole **1a** (1.0 mmol), **10** (20 mol%), TFA (30 mol%), rt. [b] Yield of isolated **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at 0 °C.

different acids or different amounts of acid, because no beneficial effect was observed in related pyrrole 1,4-additions.^[12]

After having optimized the Michael addition, we directed our focus on the cyclization step by screening various gold(I) complexes (Figure 1). We observed that all gold catalysts promoted the cyclization reaction of the Friedel-Crafts product **3** in toluene, generally within 30 min and in excellent yields (Table 2). Only the triazole-gold complex **16** showed lower reactivity due to its higher stability and the strong coordination of the triazole ligand to the gold center (Table 2, entry 6).^[13] Although there was no huge difference in terms of yields, using the Echavarren-type catalysts **12–14** resulted in a cleaner isomerization without the formation of unwanted by-products (Table 2, Entry 2–4).^[14]

It is known from the literature that amines might deactivate gold(I) complexes by coordination to the vacant binding site.^[3e–g, k, 15] However, the active catalyst can be regenerated upon addition of acidic additives. As was expected, we did not observe any conversion of **3** under the reported conditions

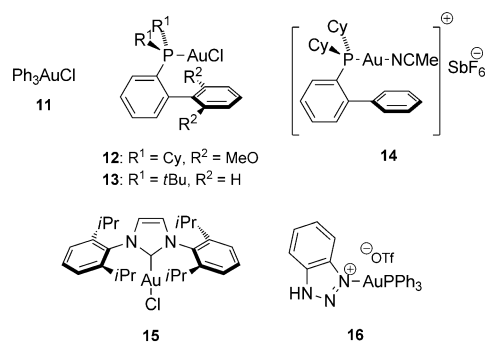


Figure 1. Au^I catalysts employed for the cyclization.

Table 2. Optimization studies for the gold-catalyzed cyclization.^[a]

Entry	Catalyst	Additive	t [h]	Yield [%] ^[b]
1	11 /AgNTf ₂	–	0.5	89
2	12 /AgNTf ₂	–	0.5	89
3	13 /AgNTf ₂	–	0.5	99
4	14	–	0.5	92
5	15 /AgNTf ₂	–	0.5	96
6	16	–	30	76
7	AgNTf ₂	–	>24	–
8	CuI	–	>24	–
9	Cu(OTf) ₂	–	>24	–
10	PtCl ₂	–	>24	–
11	–	30 mol % TFA	>24	–
12	13 /AgNTf ₂	20 mol % 10	>24	–
13	13 /AgNTf ₂	20 mol % 10 , 30 mol % TFA	0.5	96

[a] General reaction conditions: **2** (0.3 mmol), AgNTf₂ (10 mol%), toluene (1.7 mL), rt. [b] Yield of isolated **17a**.

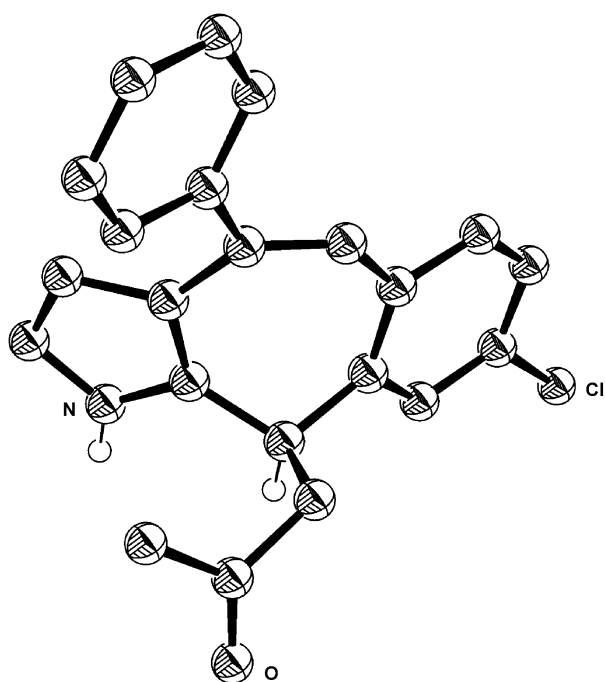


Figure 2. X-ray crystal structure of (*R*)-17b.

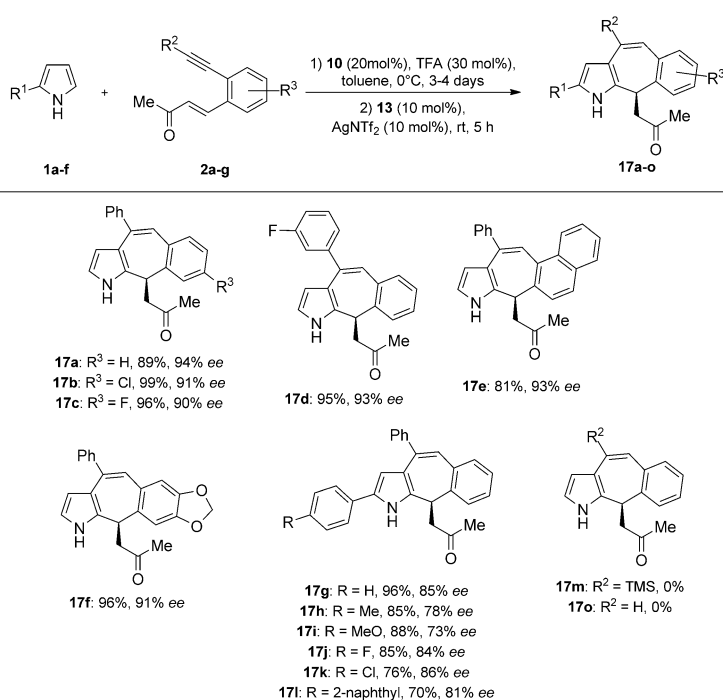
when only organocatalyst **10** was present (Table 2, entry 12). On the contrary, the reaction was completed within 30 min, if 30 mol% TFA was also present, and the product **17a** was obtained in excellent yields (Table 2, entry 13).

Thus, it was not necessary to add any further additives, because the same amount of TFA had to be already added in the Michael addition. In an additional control experiment, we could show that TFA does not catalyze the cycloisomerization, because no product could be observed after 24 h (Table 2, entry 11). In addition, other metal catalysts containing platinum or copper also failed to promote this reaction, although those metals are strongly associated with the activation of alkynes (Table 2, entries 8–10).

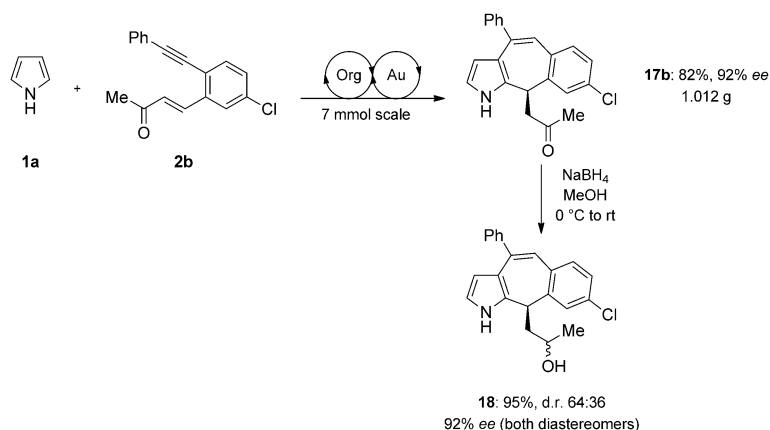
With the optimized conditions in hand, a variety of substituted enones and pyrroles were used to demonstrate the flexibility of the reported method (Scheme 3). To our delight, we obtained good to excellent yields and enantioselectivity values for all enones tested, tolerating electron-withdrawing, as well as electron-donating, groups (EWG and EDG, respectively; **17a–f**). Likewise, 2-arylpyrroles can also be used for this reaction, albeit with slightly lower yields and enantioselectivity values (**17g–l**). Apparently, the increased steric bulk introduced by the additional aryl group on pyrrole seems to hamper the transition state in the enantioselective step. In ad-

dition, we observed that the products are less stable to acid and heat than the products, which are derived from unsubstituted pyrrole, thus leading to lower yields. Further, we investigated if the method could be extended to enones with terminal alkynes and trimethylsilyl (TMS) protected alkynes. Although both substrates reacted smoothly in the Michael addition, no desired product could be isolated after the gold-catalyzed cycloisomerization.^[16]

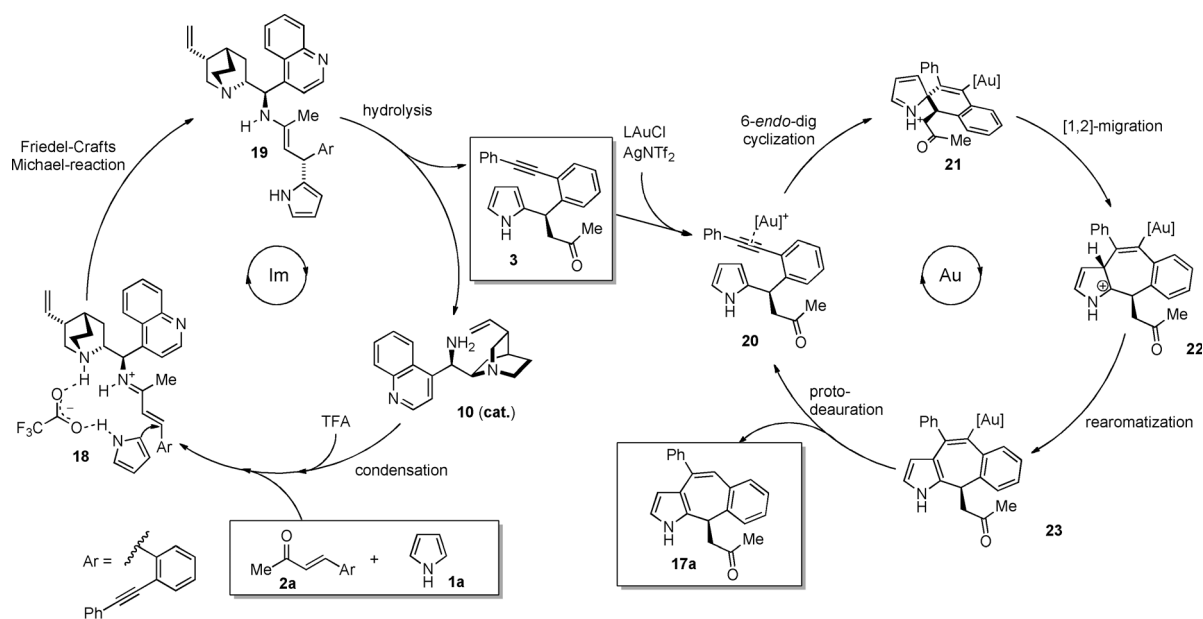
The absolute configuration was assigned by X-ray crystal structure analysis of (*R*)-**17b** (Figure 2).^[17] The absolute configuration of the other products was assigned assuming a uniform reaction pathway. To demonstrate the practicability of this protocol, we conducted the asymmetric synthesis of **17b** on a larger scale with slightly lower yields, but improved enantioselectivity (Scheme 4). The product was converted to the corresponding alcohol by reduction with sodium borohydride at



Scheme 3. Scope of the sequential Michael addition/cyclization reaction.



Scheme 4. Large-scale synthesis of compound **17b** followed by reduction to the alcohol **18**.



Scheme 5. Plausible reaction mechanism.

-78°C to give a mixture of two diastereomers **18** in good yield (Scheme 4).

Although we still lack further information on the mechanism, a plausible reaction pathway is depicted in Scheme 5. The organocatalytic reaction is driven by the formation of the iminium ion by condensation of the TFA salt of the primary amine **10** and the enone **2a**. This LUMO activation of the substrate facilitates the nucleophilic attack of pyrrole. The observed stereoselectivity can be attributed to the covalent bonding between the enone and the primary amine, as well as hydrogen bonding between pyrrole and the quinuclidine backbone of the catalyst with trifluoroacetate as mediator.^[12]

After hydrolysis, the intermediate **3** can enter the gold-catalyzed cycle. In consent with the reported literature, we believe that the mechanism for the gold-catalyzed step can be rationalized by an initiating 6-endo-dig cyclization of the more nucleophilic C2 position of pyrrole to the internal alkyne.^[9,18] The alkyne is activated by coordination via the π -acidic Au^{I} complex **20** to form a non-aromatic spirocyclic intermediate **21**, which undergoes fast rearrangement to the seven-membered ring **22** followed by rearomatization and protodeauration. Thus, the final products **17** seem to be derived from a 7-endo-dig cyclization.

In summary, we have developed a convenient one-pot asymmetric synthesis of annulated pyrroles based on a rare 7-endo-dig cyclization, thus functionalizing two adjacent carbon atoms on pyrrole by direct C–H functionalization. The combination of a cinchona-alkaloid-derived primary amine and a Au^{I} -phosphine catalyst gave excellent yields and enantioselectivity values, which are rarely achieved in pyrrole chemistry.

Experimental Section

Typical procedure

Freshly distilled pyrrole (69 μL , 1.00 mmol) was added to a solution of 9-amino(9-deoxy)*epi* cinchonine (**10**; 29 mg, 0.20 mmol), TFA (16 μL , 0.15 mmol), and enone (0.5 mmol) in toluene (3 mL) at 0°C . The reaction mixture was stirred at 0°C , and the progress of the reaction was monitored by TLC analysis. After completion, a suspension of AgNTf_2 (10 mg, 0.10 mmol) and catalyst **13** (13 mg, 0.10 mmol) in toluene (1 mL) was added to the reaction mixture at room temperature. After complete conversion, the crude product was directly subjected to flash chromatography (silica, *n*-pentane/diethyl ether).

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Keywords: annulation • gold catalysis • organocatalysis • primary-amine catalysis • pyrroles

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