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Brønsted Acid Catalyzed Cyclization of Inert N-Substituted Pyrroles to Benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepines

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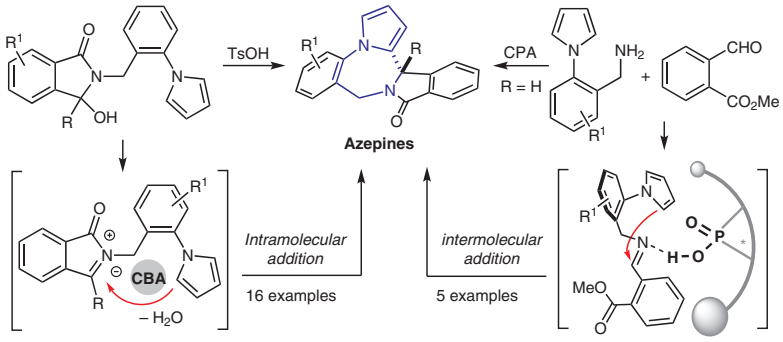

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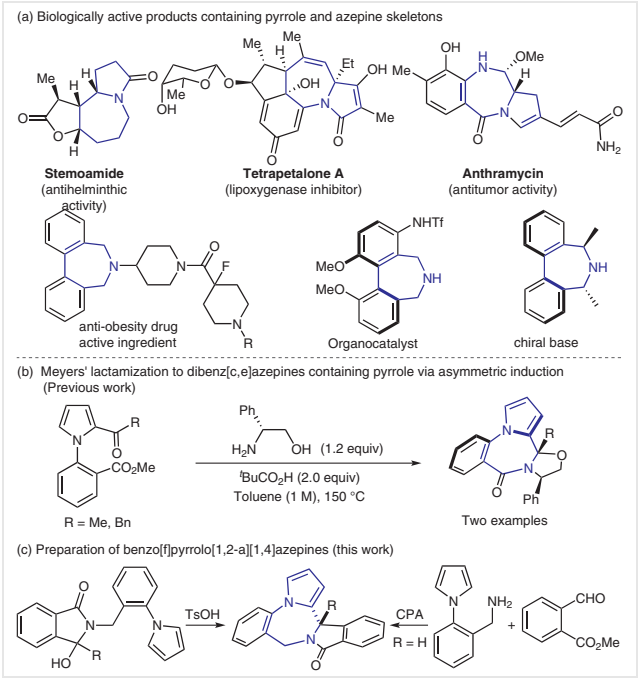
Abstract Two approaches involving intramolecular and intermolecular cyclization, respectively, have been developed for the direct and practical construction of a series of important benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines by using Brønsted acid catalysts. Upon catalysis by TsOH, the intramolecular dehydroxylation/ring closure of 3-hydroxy-2-[2-(1*H*-pyrrol-1-yl)benzyl]isoindolin-1-ones provided various racemic benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines in high yields. Furthermore, enantioenriched benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines were also obtained by chiral phosphoric acid catalyzed intermolecular addition of [2-(1*H*-pyrrol-1-yl)phenyl]methanamines to 2-formylbenzoates under mild conditions.

Key words Brønsted acid catalysis, cyclization, pyrroles, intermolecular addition, azepines, asymmetric catalysis



Scheme 1 Natural products containing ring-fused azepine moieties, and two current strategies for constructing azepines containing fused pyrroles

Five-membered pyrrole and seven-membered azepine heterocycles are ubiquitous structural motifs, found in many natural products and pharmaceuticals such as stemoamide, tetrapetalone A, and anthramycin (Scheme 1a).[1] Among these molecules, dibenzo[*c*,*e*]azepines possess a unique feature in that the conformation of the Ar–Ar stereogenic axis can be influenced by the adjacent stereogenic center (axis-center stereochemical relay) to generate an axially chiral biaryl microstructure. As a family of important chiral compounds that bear two kinds of chirality element in most cases, these compounds have been synthesized as anti-obesity drug analogues,[2] chiral organocatalysts,[3] and chiral bases.[4]

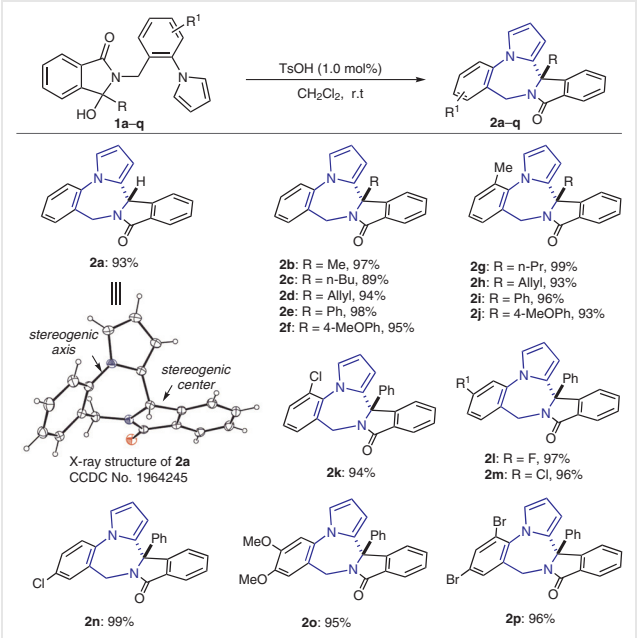
In general, hydrogenation[5] of various seven-membered cyclic imines through transition-metal catalysis has been widely used by the groups of Buchwald, Fan, Zhou, Turner, and others as a valuable and useful strategy for obtaining these synthetic targets.[6] In sharp contrast, the construction of azepine scaffolds containing an axially chiral heterobiaryl is far less developed. In principle, the intramolecular nucleophilic addition of pyrroles at the 2-position should be an efficient and convenient method for preparing benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines with a center-axis stereochemical relay. In 2013, the Levacher group realized an atroposelective synthesis of biaryl azepines through an asymmetric induction based on the Meyers lactamization with chiral 2-amino-2-phenylethanol under microwave irradiation (Scheme 1b).[7] However, the direct asymmetric alkyla-

tion of pyrroles remains underdeveloped because: (a) the more-electron-rich N-containing heterocycle renders the compound more vulnerable to attack by acid, base, or air;[8] (b) catalytic mono C-alkylation of pyrrole is rather impractical due to several competing transformations such as polyalkylation, ring opening, and polymerization;[9] and (c) compared with unprotected pyrroles that can be activated by interaction with the N–H portion and which show less steric hindrance,[10] the inert N-substituted pyrroles are less prone to undergo nucleophilic addition reactions because of a lack of a free N–H moiety to interact with the catalyst by hydrogen bonding or chelation.[11] As part of our continuing efforts to develop asymmetric cyclization of inert N-substituted pyrroles,[11m–p] we report a straightforward and practical preparation of biaryl azepines containing both pyrrole and azepine skeletons by two different strategies involving Brønsted acid catalyzed intramolecular or intermolecular cyclizations, respectively, from simple starting materials (Scheme 1c).

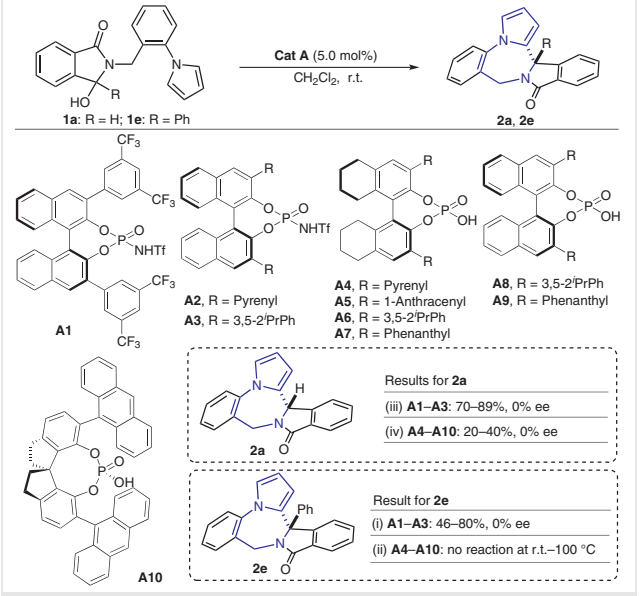
Initially, the intramolecular dehydroxylation/cyclization of 3-hydroxy-2-[2-(1*H*-pyrrol-1-yl)benzyl]isoindolin-1-ones **1** catalyzed by TsOH was employed as an efficient method for constructing azepines in CH_2Cl_2 at room temperature (Scheme 2). Isoindolinones containing alkyl (Me, Bu, or All) or aryl (Ph, 4-$MeOC_6H_4$) substituents were amenable to this transformation and gave the corresponding products **2a–f** in high yields. The relative configuration of product **2a** was determined by X-ray single-crystal analysis, which indicated the existence of a twisted C–N bond (stereogenic axis) that was influenced by the adjacent stereogenic center in the azepine. A methyl group at the 6-position of the substrate had no obvious influence on the results, and compounds **2g–k** were obtained in yields of 93–99%. Isoindolinones with a fluoro or chloro group at the 5-position reacted smoothly to deliver the desired products **2l** and **2m** in yields of 97 and 96%, respectively. Moreover, polysubstituted products **2a** and **2p** were obtained from **1a** and **1p** in yields of 95 and 96%, respectively.

We then switched our attention to an investigation of the asymmetric synthesis of these pyrroloazepines by using a chiral Brønsted acid catalyst. However, treatment of the typical substrates **1a** and **1e** with the chiral phosphoric amide catalysts **A1–A3** or the acid catalysts **A4–A10** gave the racemic products exclusively in all cases (Scheme 3).

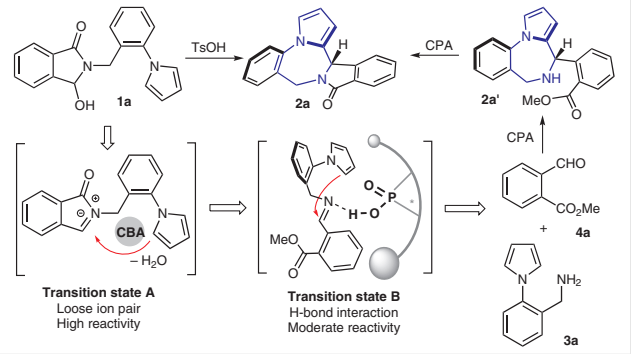
The poor enantioselectivity toward the desired product might have resulted from the high reactivity of the immonium ion generated in situ or from the weak interaction in the loose ion pair between the immonium ion and the catalyst (Scheme 4; transition state **A**). With this understanding of the reaction mechanism of the TsOH-catalyzed intramolecular cyclization of isoindolinone **1a**, we reasoned that the imine formed in situ from amine **3a** and aldehyde **4a** might be a potential reaction intermediate for the asymmetric synthesis of pyrroloazepines by virtue of their moderate reactivity and the stronger hydrogen bonding between the imine and the catalyst (Scheme 4; transition state **B**). In addition, similar polycyclic azepines were also obtained after a final annulation of intermediate **2a′**.



Scheme 2 Substrate scope for racemic synthesis of benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepines. *Reagents and conditions*: **1** (0.2 mmol), TsOH (1.0 mol%), CH_2Cl_2 (2.0 mL), stirring, r.t., 1 h. The yields of the isolated products are reported.



Scheme 3 Attempts at asymmetric reactions. Reactions were carried out at a 0.2 mmol scale. Yields of the isolated products are reported.



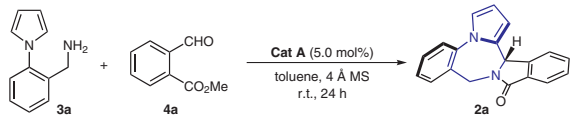
Scheme 4 Developing a working hypothesis for improving the chiral induction

With this idea in mind, we first investigated the catalytic activity of various catalysts **A1**–**A10** for the model reaction of amine **3a** with ester **4a** in toluene containing 4 Å molecular sieve (4 Å MS) at room temperature for 24 hours. As shown in Table 1, the designed cascade reaction took place smoothly, and the desired product **5a** was isolated in yields of 44–73% yields and enantioselectivities of 2–76% (Table 1, entries 1–10). Among the catalysts, **A5** provided the best outcome with a 76% ee of the desired product **2a** (entry 5). Examination of the solvent effect revealed that toluene is the optimal choice (entries 5 and 11–18). The reaction in THF gave rise to the imine product only, along with a large amount of the starting materials **3a** and **4a**, possibly due to the influence of the oxygen of the THF on the hydrogen bond (entry 12). Changing the ratio of **3a** to **4a** had an obvious effect on the reaction, and an excess of **3a** (**3a**/**4a** =1.5:1) was detrimental to enantioselectivity (entries 19–20). The choice of the molecular sieve desiccant did not have a significant effect on the results (entries 21 and 22), but the yield and enantioselectivity toward **5a** dramatically decreased in its absence (entry 23).

Having established the optimal reaction conditions, we next investigated the substrate scope of this cascade reaction (Scheme 5). On using a *tert*-butyl (**4b**) or benzyl ester (**4c**) instead of the methyl ester (**4a**), the enantioselectivity toward adduct **2a** improved slightly to 78% from the *tert*-butyl ester, but only a trace of product was detected from the benzyl ester. The 3-chloro-substituted product **2b** was also readily obtained in 65% yield and 76% ee. With a chloro or fluoro group at the 4-position of amine substrate, the reaction gave the corresponding product **2r** or **2s** exclusively in a lower 36 and 46% ee, respectively. Only a 14% ee was obtained for the methyl-substituted compound **2t**.

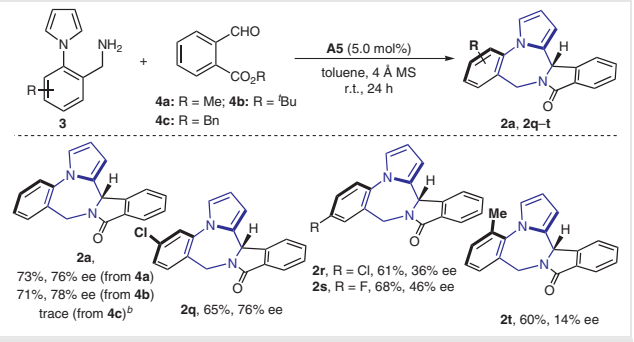
In conclusion, we have developed two strategies involving an intramolecular annulation and an intermolecular reaction, respectively, for the efficient and practical construction of pyrroloazepines. By catalysis with TsOH, a series of racemic benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines were readily synthesized from (pyrrolobenzyl)isoindolinones under mild conditions.[12] Additionally, enantioenriched pyrrole-containing azepines with a flexible biaryl stereogenic axis were obtained by a chiral phosphoric acid catalyzed intermolecular reaction of a pyrrolylbenzylamine and methyl 2-formylbenzoate. This latter reaction has great potential for the synthesis of pharmaceutically important molecules. Further explorations of the efficient asymmetric synthesis, as well as an examination of the biological activities of the useful products, are ongoing in our laboratory.

Table 1 Optimization of the Enantioselective Reaction[a]



Entry	Solvent	Catalyst	Yield (%)	ee (%)
1	toluene	**A1**	50	2
2	toluene	**A2**	61	10
3	toluene	**A3**	53	27
4	toluene	**A4**	44	54
5	toluene	**A5**	73	76
6	toluene	**A6**	46	48
7	toluene	**A7**	69	74
8	toluene	**A8**	49	54
9	toluene	**A9**	65	67
10	toluene	**A10**	64	67
11	CH_2Cl_2	**A5**	70	71
12	THF	**A5**	n.r.[d]	–
13	Et_2O	**A5**	61	71
14	$CHCl_3$	**A5**	65	73
15	CCl_4	**A5**	61	71
16	xylene	**A5**	70	68
17	benzene	**A5**	72	73
18	MTBE	**A5**	64	72
19[e]	toluene	**A5**	70	56
20[f]	toluene	**A5**	69	0
21[g]	toluene	**A5**	69	72
22[h]	toluene	**A5**	62	70
23[i]	toluene	**A5**	35	40

[a] Reaction conditions: **3a** (0.1 mmol), **4a** (0.15 mmol, 1.5 equiv), CBA (5.0 mol%), 4 Å MS (100 mg), solvent (1.0 mL), stirring, 25 °C, 24 h.
[b] Yield of the isolated product.
[c] Determined by chiral HPLC.
[d] n.r. = no reaction.
[e] 0.1 mmol of **4a** (**3a**:**4a** = 1:1) was used.
[f] **3a** (0.15 mmol) and **4a** (0.1 mmol) were used (**3a**:**4a** = 1.5:1).
[g] 3 Å MS.
[h] 5 Å MS.
[i] No desiccant.



Scheme 5 Substrate scope for the asymmetric cascade reaction. *Reagents and conditions*: **3** (0.1 mmol), **4** (0.15 mmol, 1.5 equiv), **A5** (5.0 mol%), 4 Å MS (100 mg), toluene (1.0 mL), stirring, 25 °C, 24 h. Yields of the isolated products are reported. The ee values were determined by chiral HPLC analysis. [a] Detected by ^{1}H NMR.

Conflict of Interest

The authors declare no conflict of interest

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1468-5725.

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(12) **9*H*-Isoindolo[1,2-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepin-11(15b*H*)-ones 2a–q; General Procedure (Intramolecular Reaction)**

The appropriate isoindolone **1** (0.2 mmol, 1.0 equiv) and TsOH (1 mol%) were stirred in CH_2Cl_2 (1 mL) at r.t. When the reaction was complete, the solvent was removed and the crude mixture was purified by flash column chromatography (silica gel, hexane–EtOAc).

9*H*-Isoindolo[1,2-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepin-11(15b*H*)-ones 2a, 2q–t; General Procedure (Intermolecular Reaction)

The appropriate amine **3** (0.1 mmol, 1.0 equiv), methyl 2-formylbenzoate (**4a**, 0.15 mmol, 1.5 equiv), chiral phosphoric acid **A5** (5.0 mol%), and 4 Å MS (100 mg) were stirred in toluene (1.0 mL) at r.t. under N_2. Upon completion of the reaction, the solvent was removed and the crude mixture was purified by flash column chromatography.

9*H*-Isoindolo[1,2-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepin-11(15b*H*)-one (2a)

White solid; yield: 53.2 mg (93%); mp 192-195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.5 Hz, 1 H), 7.64–7.44 (m, 6 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.10 (d, *J* = 2.9 Hz, 1 H), 6.26 (t, *J* = 3.3 Hz, 1 H), 5.94 (d, *J* = 3.5 Hz, 1 H), 5.40 (s, 1 H), 5.06 (d, *J* = 13.9 Hz, 1 H), 4.17 (d, *J* = 13.9 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.0, 141.7, 140.2, 133.6, 131.5, 131.2, 130.0, 128.9, 128.5, 127.3, 124.0, 123.6, 121.8, 109.5, 107.2, 56.4, 44.6.

CCDC 1964245 contains the supplementary crystallographic data for compound **2a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.