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Direct Synthesis of Chiral 1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines via a Catalytic Asymmetric Intramolecular Aza-Friedel–Crafts Reaction

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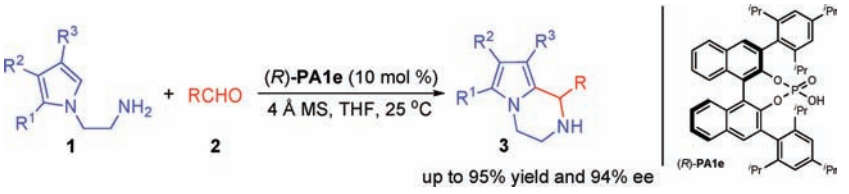
ABSTRACT



The direct asymmetric intramolecular aza-Friedel–Crafts reaction of *N*-aminoethylpyrroles with aldehydes catalyzed by a chiral phosphoric acid represents the first efficient method for the preparation of medicinally interesting chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines with high yields and high enantioselectivities. This strategy has been shown to be quite general toward various aldehydes and pyrrole derivatives.

The intramolecular aza-Friedel–Crafts reaction has been extensively investigated in the past century.[1] While tremendous progress has been made, the catalytic enantioselective intramolecular variant has only been recently reported. Seminal work by Jacobsen,[2] List,[3] and others[4,5] describes several types of catalytic asymmetric intramolecular aza-Friedel–Crafts reactions. One such example is the Pictet–Spengler reaction, an invaluable method for the synthesis of tetrahydro-β-carbolines, from tryptamines or phenyl ethylamines and carbonyl compounds. Despite those breakthroughs, the development of novel asymmetric intramolecular aza-Friedel–Crafts reactions, which tolerate various nucleophilic aryl moieties, would be of great importance. As part of our continuing efforts in the development of novel Brønsted acid catalyzed reaction methodologies,[6,7] we chose to explore pyrrole derivatives as competent substrates for asymmetric intramolecular

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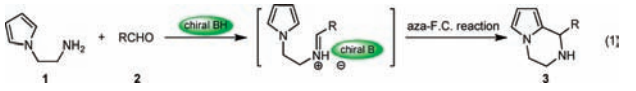
aza-Friedel–Crafts reactions. While demonstrative of biological and medicinal importance, pyrroles are considerably less explored for asymmetric intramolecular aza-Friedel–Crafts reactions.[8] A lone example highlighting pyrroles in an elegant intermolecular *N*-acyliminium cyclization was reported by Jacobsen.[2c] Their previous thiourea scaffold for transformations of indole derivatives[2b] was further optimized for use with 3-pyrrole ethyl hydroxylactams.

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines represent a class of particularly interesting heterocycles, due to their potential antiarrhythmic,[9] antiamnesic, antihypoxic,[10] psychotropic,[11] antihypersensitive,[12] and aldose reductase inhibition activities.[13] In addition, these compounds have been reported as potassium channel ligands,[14] serotonin and noradrenaline reuptake inhibitors,[15] and cannabinoid receptor agonists.[16] To our knowledge, no example of an efficient catalytic asymmetric methodology for the preparation of chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines has been reported.[7] Herein, we report a catalytic asymmetric synthesis of chiral 1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazines with high enantioselectivities. This strategy features a direct condensation of *N*-aminoethylpyrrole and an aldehyde, followed by an intramolecular aza-Friedel–Crafts reaction under very mild reaction conditions (Scheme 1).

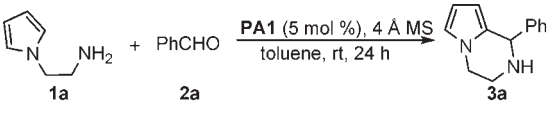
Scheme 1. Proposed Pathway for the Preparation of Chiral 1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines

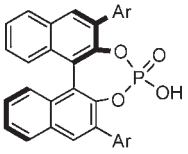


Asymmetric transformations catalyzed by chiral phosphoric acids[17] represent one of the most remarkable developments in organocatalysis. Their tremendous utility was first reported in 2004 through independent work from Akiyama[18] and Terada.[19] In light of this work we believed that the plan outlined in Scheme 1 could also be catalyzed by chiral phosphoric acids. We began our investigation with *N*-aminoethylpyrrole (1.0 equiv) and benzaldehyde (1.0 equiv), a 3,3′-phenyl substituted BINOL derived phosphoric acid (**PA1a**, 5 mol %, Table 1) as the catalyst, toluene as the solvent, and 4 Å MS as a desiccant. The reaction was performed under ambient temperature (25 °C). To our delight, the cyclization proceeded smoothly and generated the desired 1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine **3a** in high yield (86%). A very low enantiomeric excess (8% *ee*) was initially observed. Encouraged with the reactivity, we screened additional BINOL derived chiral phosphoric acids under similar reaction conditions (Table 1). Bulky catalyst **PA1c** provided a moderate yield but still an extremely poor *ee* (71% yield and 6% *ee*). Use of 9-anthryl substituted catalyst **PA1d** furnished the product in high yield but with only a moderate improvement in enantioselectivity (85% yield and 30% *ee*). Gratifyingly, the 2,4,6-triisopropylphenyl substituted phosphoric acid (*R*)-**PA1e**[20] was found to be a superior catalyst for this cyclization sequence. The reaction yielded product **3a** in 91% yield and 76% *ee* under mild reaction conditions in toluene.

A solvent screen revealed that nonpolar solvents, as well as polar solvents, allow the transformation to proceed with good enantioselectivity and yield (Table 2). Toluene provided a high isolated yield with only moderate ee. Benzene allowed for an increase in ee to 86%, with slightly diminished yields of the product (80% yield, entry 2). Similar

Table 1. Catalyst Screening[a]





(*R*)-**PA1a-1e**

PA1a: Ar = Ph
86% yield, 8% *ee*
PA1b: Ar = 2-naphthyl
74% yield, 8% *ee*
PA1c: Ar = $SiPh_3$
71% yield, 6% *ee*
PA1d: Ar = 9-anthryl
85% yield, 30% *ee*
PA1e: Ar = 2,4,6-(^{i}Pr)C_6H_2
91% yield, 76% *ee*

[a] All reactions were run on a 0.1 mmol scale in 1.0 mL of toluene; yield refers to isolated yield; % ee was determined by Chiral HPLC. See Supporting Information for details.

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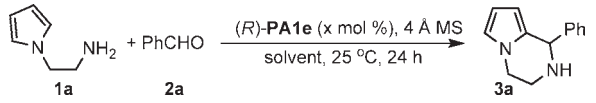
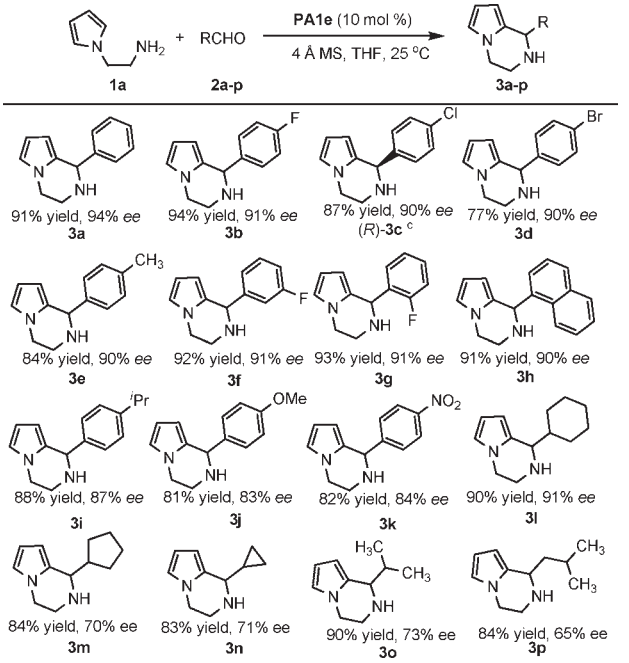
Table 2. Optimization of Reaction Conditions[a]



entry	solvent	PA1e [mol %]	temp [°C]	ratio 1a/2a	yield [%][b]	ee [%][c]
1	$PhCH_3$	5	25	1/1	91	76
2	C_6H_6	5	25	1/1	80	86
3	CH_2Cl_2	5	25	1/1	88	86
4	$CHCl_3$	5	25	1/1	97	85
5	Et_2O	5	25	1/1	80	85
6	CH_3CN	5	25	1/1	82	81
7	THF	5	25	1/1	82	94
8	*THF*	*10*	*25*	*1/1*	*91*	*94*
9	THF	10	25	1.5/1	86	86
10	THF	10	25	1/1.5	87	94
11	THF	10	0	1/1	76	64
12	THF	10	50	1/1	86	88

[a] Unless otherwise noted, all reactions were run on a 0.1 mmol scale in 1.0 mL of solvent. [b] Isolated yield. [c] Ee was determined by Chiral HPLC; see Supporting Information for details.

Table 3. Scope of Aldehyde Substrates[a,b]



[a] Isolated yield. [b] Ee was determined by Chiral HPLC; see Supporting Information for details. [c] The absolute configuration was determined by single X-ray crystal diffraction; see Supporting Information for details.

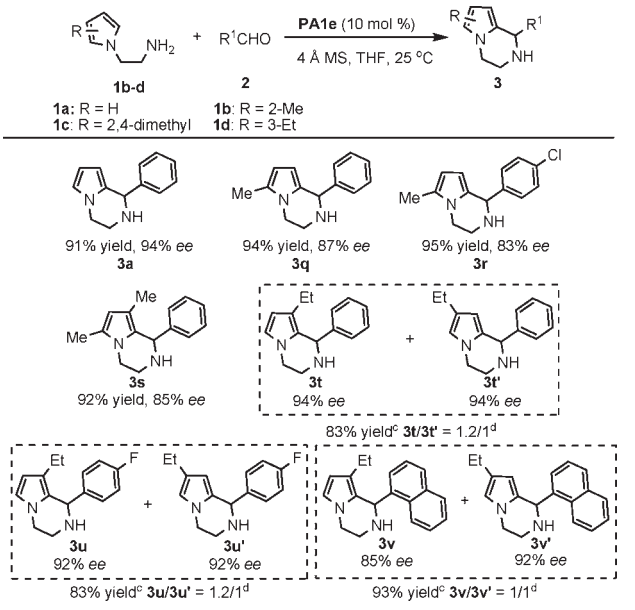
results were obtained using ether (entry 5). The cyclization in dichloromethane and chloroform produced chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine **3a** in excellent yields and high enantioselectivities (88% and 97% yield; 86% and 85% ee, respectively; entries 3 and 4). Additionally, a more polar solvent, acetonitrile, gave a lower yield and ee (entry 6; 82% yield and 81% ee). THF was found to be the optimal solvent for the cyclization with respect to enantioselectivity (ee up to 94%, entry 7). Increasing the catalyst loading to 10 mol % further improved the yield to 91% without detriment to the enantiomeric excess (entry 8). It is interesting to note that temperature plays a crucial role in rendering the cyclization highly enantioselective. When the reaction was conducted at 0 and 50 °C, a noticeable drop in enantioselectivity (65% and 88% ee; entries 9 and 10) was observed. Further optimization of the substrate ratio showed that when *N*-aminoethylpyrrole was used in excess, the ee dropped (86% ee, entry 11). In the presence of excess benzaldehyde the ee remained unaffected (94% ee, entry 12). In order to exclude the possibility of *N*-aminoethylpyrrole negatively affecting the enantioselectivity, a small excess of aldehyde was utilized in most cases for the following studies on the substrate scope.

Substituted benzaldehyde derivatives were screened as substrates in combination with *N*-aminoethyl pyrrole **1a**, affording chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine products **3a**–**p** in good to excellent yields and ee's (Table 3). Halogen substitutions are tolerated at all ring positions on the aromatic aldehydes (90–91% *ee*; **3b**, **3c**, **3d**, **3g**). The sterically hindered α-naphthaldehyde provided the cyclization product in excellent yield and enantioselectivity (91% yield and 90% *ee*, **3h**). Aromatic aldehydes containing a 4-methyl substituent, or a much bulkier 4-isopropyl substituent, proved viable and gave products with high *ee*'s (90% and 87% ee's, respectively; **3e** and **3i**). Aldehydes bearing a strong electron-donating group (4-methoxy, **3j**) or a strong electron-withdrawing group (4-nitro, **3k**) gave relatively lower *ee* values. The decrease in *ee* can possibly be attributed to hydrogen-bonding interactions between the aldehyde substituents and the catalyst, although at this time the exact reason is unclear. Aliphatic aldehydes underwent cyclization smoothly to produce the corresponding chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines. Cyclohexanecarbaldehyde gave product **3l** in 90% yield and 91% ee. However, other cyclic aliphatic aldehydes bearing smaller rings, for example, cyclopentanecarbaldehyde and cyclopropanecarbaldehyde, gave lower ee's (**3m** and **3n**). Some branched aliphatic aldehydes such as isobutyraldehyde and 3-methylbutanal also provided moderate enantioselectivities (**3o** and **3p**). Linear aliphatic aldehydes showed poor enantioselectivity under the optimized reaction conditions.[21]

In order to further evaluate the generality of this methodology, several derivatives of *N*-aminoethylpyrrole were screened. Table 4 reveals that 2-methyl substituted pyrrole **1b** reacts faster with benzaldehyde than pyrrole **1a**, yielding product **3q** in 94% yield, with a slightly lower ee of 87%. The analogous reaction with 4-chlorobenzaldehyde showed a similar reduction in ee (83%, **3r**, Table 4). Introduction of

(21) For example, butanal and 3-phenylpropanal were utilized as substrates. However, less than 60% *ee* was observed by estimation because baseline separation by chiral HPLC was unattainable. High isolated yields for both aliphatic aldehydes were obtained (>90%).

Table 4. Scope of Pyrrole Substrates[a,b]

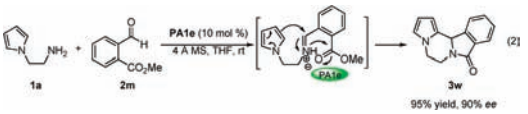


[a] Isolated yield. [b] Ee was determined by Chiral HPLC; see Supporting Information for details. [c] Total isolated yield. [d] Determined by ^{1}H NMR.

a methyl group at C-3 of the pyrrole ring (**1c**) gave a similar reactivity and enantioselectivity to those of the monosubstituted pyrrole **1b** (**3s**, Table 4). This result suggests that substitution at C-3 or C-4 of the pyrrole ring might not affect the enantioselectivity. This hypothesis was confirmed after 1-aminoethyl-3-ethylpyrrole (**1d**) was prepared and screened under the optimized reaction conditions. In the presence of an achiral Brønsted acid (phenylphosphinic acid), racemic **3t** was formed with high regioselectivity (**3t**/**3t**′ = 10:1 determined by ^{1}H NMR). Chiral catalyst **PA1e** gave nearly equal amounts of **3t** and **3t**′ (**3t**/**3t**′ = 1.2:1). We presume the poor regioselectivity can be attributed to the likely increased steric hindrance that chiral phosphoric acid **PA1e** introduces in proximity to the 3-ethyl group of the pyrrole ring. While poor regioselectivity was observed, excellent enantioselectivities were obtained for each regioisomer (85−94% ee, Table 4). The cyclization of α-naphthaldehyde with pyrrole **1d** produced one regioisomer with excellent ee (92% ee, **3v**′, Table 4) but gave way to the other regioisomer with a slightly lower enantioselectivity (85% ee, **3v**, Table 4).

The present intramolecular aza-Friedel−Crafts reaction provides potential access to polycyclic pyrrole derivatives, which represent a novel analogue or precursor of pyrrole-derived alkaloids. As shown in Scheme 2, a tandem intramolecular amidation sequence occurred in the reaction between *N*-aminoethylpyrrole (**2a**) and methyl 2-formylbenzoate (**2m**). The resulting product **3w**, a four-fused-ring

Scheme 2. Intramolecular Aza-Friedel−Crafts Reaction and Amidation Domino To Access a Fused Ring Pyrrole Derivative



system, was formed with excellent yield and *ee* in the one-pot reaction (90% *ee* and 95% yield).

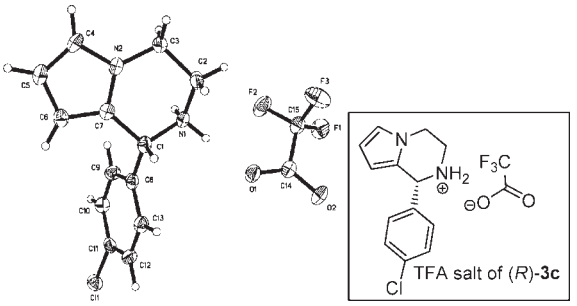


Figure 1. Single crystal X-ray structure of the TFA salt of product **3c**.

The absolute configuration of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine **3c** was unambiguously determined to be *R* according to the single crystal X-ray diffraction of its trifluoroacetic acid (TFA) salt (Figure 1; see Supporting Information for details).

In conclusion, we have developed the first direct catalytic asymmetric intramolecular aza-Friedel−Crafts reaction of *N*-aminoethylpyrroles catalyzed by chiral phosphoric acids. This one-pot sequence provides an efficient approach to preparing various medicinally important chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines in high yields and high to excellent enantioselectivities under mild reaction conditions. Further work with respect to extension and applications of this methodology is ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.