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Synthesis of Chiral Piperazines via Hydrogenation of Pyrazines Activated by Alkyl Halides

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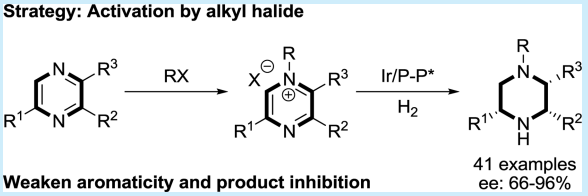
Supporting Information

ABSTRACT: A facile method has been developed for the synthesis of chiral piperazines through Ir-catalyzed hydrogenation of pyrazines activated by alkyl halides, giving a wide range of chiral piperazines including 3-substituted as well as 2,3- and 3,5-disubstituted ones with up to 96% ee. The high enantioselectivity, easy scalability, and concise drug synthesis demonstrate the practical utility.



Chiral piperazines have received much attention due to their wide distribution in natural products and drugs (Figure 1).[1]

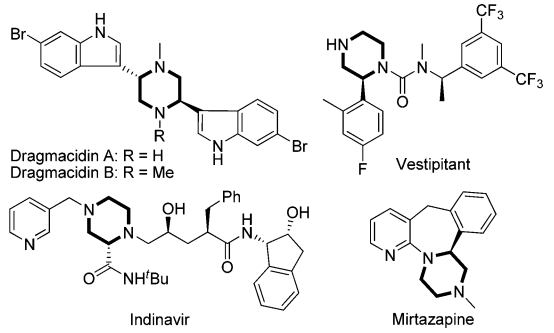
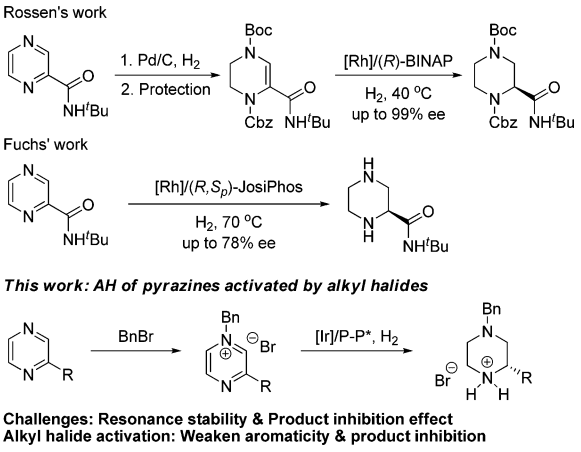


Figure 1. Natural products and drugs containing chiral piperazines.

Some piperazines are also useful catalysts and ligands in asymmetric catalysis.[2] The commonly used methods to chiral piperazines are reduction of ketopiperazines[3] and classical resolution.[1d] Recently, kinetic resolution and dynamic kinetic resolution were employed to access chiral piperazines by Bode[4a] and Guercio.[4b] Wolfe and Michael utilized Pd-catalyzed carboamination or hydroamination of alkenes to synthesize chiral piperazines.[5] More recently, the asymmetric lithiation−substitution of *N*-Boc piperazines provided a new approach.[6] Other synthetic methods included asymmetric addition of a Grignard reagent to pyrazine *N*-oxides,[7a] chiral pool synthesis,[7b] asymmetric hydrogenation (AH) of partially reduced pyrazines,[7c−e] and so on.[7f,g] However, given the great importance of chiral piperazines, there is still a great need to develop a more direct, efficient, and general route to such motifs.

AH of readily available pyrazines is among the most convenient methods for chiral piperazines. But in sharp contrast to other six-membered azaarenes[8] such as pyridine,[9] quinoline,[10] isoquinoline,[11] and others,[12−14] there are only two reports on AH of pyrazines with a fairly narrow substrate scope: working only for pyrazine-2-carboxylic acid derivatives (Scheme 1).[15]

Scheme 1. AH of Pyrazines and Pyrazinium Salts



This is due to the fact that pyrazine not only is a single-ring aromatic compound with relative high aromaticity but also has two strong coordinative nitrogen atoms which easily poison the catalyst. Furthermore, the piperazine product has two secondary amines that deactivate the catalyst, too. Recently, a unique strategy was developed by our group, which employed alkyl halides to activate azaarenes to realize their AH.[9b,11b] Specially, the asymmetric hydrogenation of pyrrolo[1,2-*a*]pyrazinium salts had been realized using such a strategy.[16] Considering the structural similarity, we envisioned that such a strategy might be applied to pyrazines. First, *N*-alkylation made the pyrazine ring more electron deficient, weakened its coordination ability, and

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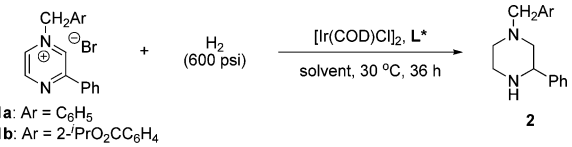
facilitated its reduction. Additionally, one nitogen of the product was blocked by alkylation, and the more basic secondary piperazine nitrogen formed a salt with *in situ* generated acid. Thus, catalyst poisoning of the product was greatly inhibited. Based on these considerations, herein we report the AH of pyrazines using alkyl halides as avtivators with a broad substrate scope.

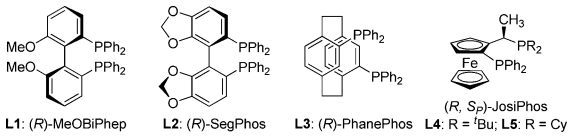
To begin the study, pyrazinium salt **1a** was employed as a model substrate (Table 1). The hydrogenation of **1a** was

Table 1. Condition Optimization[a]



entry	solvent	ligand	conv (%)[b]	ee (%)[c]
1	THF	**L1**	>95	24
2	toluene (T)	**L1**	>95	52
3	benzene	**L1**	>95	51
4	1,4-dioxane (D)	**L1**	>95	38
5	EtOAc	**L1**	>95	35
6	toluene	**L2**	>95	62
7	toluene	**L3**	>95	29
8	toluene	**L4**	>95	79
9	toluene	**L5**	>95	21
10[d]	toluene	**L4**	>95	85
11[e]	toluene	**L4**	50	88
12[f]	toluene	**L4**	88	86
13[f,g]	toluene	**L4**	>95	88
14[f,g]	T/D (1/1)	**L4**	>95	91

[a]Conditions: **1a** (0.20 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), **L*** (2.2 mol %), H_2 (600 psi), solvent (3.0 mL), 30 °C, 36 h. [b]Determined by ^1H NMR. [c]Determined by chiral HPLC. [d]0 °C. [e]−20 °C. [f]−20 °C, H_2 (1200 psi). [g]**1b** (0.20 mmol).

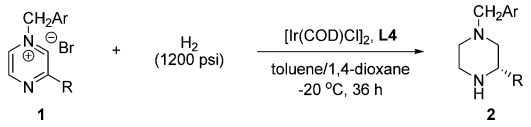


L1: (*R*)-MeOBiPhep **L2**: (*R*)-SegPhos **L3**: (*R*)-PhanePhos **L4**: R = ^{t}Bu; **L5**: R = Cy (*R*, S_P)-JosiPhos

sensitive to solvent, and toluene was the best choice with respect to enantioselectivity (entries 1−5). Subsequently, some commercially available chiral diphosphine ligands were evaluated to identify an efficient catalyst (entries 6−9). To our delight, much better ee was obtained with ferrocene-derived JosiPhos **L4** (79%). The substituent on the phosphine was crucial; a dramatic drop of the ee was observed using **L5** (21%). Decreasing the temperature gradually improved the ee, albeit with some loss of reactivity (entries 10−11). So, high pressure was employed (entry 12). Then, different activation reagents such as iodomethane, benzyl chloride, or substituted benzyl bromide were tested. It was found that both the alkyl group and counterion had a great impact on the reactivity and enantioselectivity (for details, see the Supporting Information (SI)). While the *N*-methyl group gave poor reactivity, the 2-isopropoxycarbonyl substituted benzyl group delivered full conversion with 88% ee (entry 13). Finally, 91% ee was achieved with a mixed solvent of toluene and 1,4-dioxane (entry 14).

Having identified a highly enantioselective catalytic system, a range of 3-substituted pyrazinium salts were hydrogenated to test the generality (Table 2). Both electron-donating and electon-

Table 2. Substrate Scope: 3-Substituted Pyrazinium Salts[a]



entry	R	yield (%)[b]	ee (%)[c]
1	Ph	90 (**2b**)	91 (*S*)
2	3-MeC_6H_4	93 (**2c**)	91 (−)
3	4-MeC_6H_4	92 (**2d**)	92 (−)
4	3,5-$Me_2C_6H_3$	93 (**2e**)	90 (−)
5	3-$MeOC_6H_4$	86 (**2f**)	86 (−)
6[d]	4-FC_6H_4	91 (**2g**)	90 (−)
7	4-ClC_6H_4	80 (**2h**)	87 (−)
8[d]	4-BrC_6H_4	85 (**2i**)	87 (−)
9[d,e]	4-$CF_3C_6H_4$	91 (**2j**)	85 (−)
10[e,f]	4-PhC_6H_4	82 (**2k**)	88 (−)
11	2-naphthyl	87 (**2l**)	86 (−)
12[d,e]	2-Me-4-FC_6H_3	95 (**2m**)	66 (+)
13[e,f]	cyclopropyl	68 (**2n**)	81 (+)

[a]Conditions: **1** (0.2 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), **L4** (2.2 mol %), H_2 (1200 psi), toluene/1,4-dioxane (1/1), −20 °C, 36 h; if not noted, Ar = 2-^{i}PrO$_2$CC$_6$H$_4$. [b]Isolated yields. [c]Determined by chiral HPLC. [d]−10 °C. [e]Ar = Ph. [f]0 °C.

withdrawing groups were well tolerated, affording piperazines with high yields and ee's (entries 2−9). Meanwhile, products with electron-donating groups tended to have slightly higher enantioselectivities than those with electon-withdrawing groups. Biphenyl and 2-naphthyl substituted substrates underwent reduction smoothly, delivering 88% and 86% ee, respectively (entries 10−11). Product **2m** with a substitution pattern present in drug Vestipitant[1b] was isolated with a diminished ee value, which was possibly caused by the steric hindrance of the *ortho* methyl group (entry 12). For 3-alkyl substituted **2n**, moderate yield and ee were obtained (entry 13).

Next, we turned our attention to the AH of 3,5-disubstituted pyrazinium salts. After a condition reoptimization (see the SI), our strategy turned out to be successful, and a range of 3,5-disubstituted pyrazinium salts could be well reduced (Table 3). The electronic property and position of the substituent on the 5-aryl ring had little effect on the yield and ee (entries 1−13, 82−93% ee). All the products except **4i** were delivered with excellent d.r. (>20:1). Interestingly, product **4m** with the more sterically demanding 1-naphthyl group afforded a higher ee than 2-naphthyl **4l** (86% vs 78%). A longer alkyl or cyclopropyl group instead of a methyl group at the 3-position led to slight erosion of the ee, but a good yield and d.r. were maintained (entries 14−18). When the hydrogenation of **3a** was performed on a gram scale, 90% yield and 89% ee were obtained with 0.5 mol % catalyst loading (see the SI).

Encouraged by the successful AH of 3-substitued and 3,5-disubstitued pyrazinium salts, we sought to further examine the feasibility of the current strategy on 2,3-disubstituted pyrazines. Being different from the former substrates, a high reaction temperature and low hydrogen pressure were propitious to the enantiocontrol (see the SI). Under the optimal conditions, a range of 2,3-disubstituted piperazines were readily obtained with high yields and ee's (Table 4, entries 1−8). 2,3-Dimethyl pyrazinium salt was also a suitable substrate, giving the desired product **6i** in 91% ee (entry 9). The **6j** with a decahydroquinoxaline framework was obtained with 96% ee (entry 10). Notably, all

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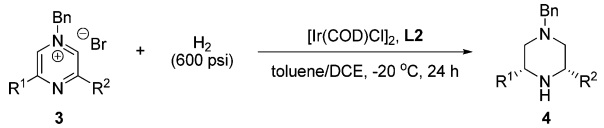
Table 3. Substrate Scope: 3,5-Disubstituted Pyrazinium Salts[a]



entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	Me	Ph	94 (**4a**)	91 (3*R*,5*S*)
2	Me	3-MeC_6H_4	93 (**4b**)	90 (−)
3	Me	4-MeC_6H_4	95 (**4c**)	88 (−)
4[d]	Me	3,5-$Me_2C_6H_3$	81 (**4d**)	90 (−)
5	Me	3-$MeOC_6H_4$	92 (**4e**)	92 (−)
6	Me	4-$MeOC_6H_4$	95 (**4f**)	84 (−)
7	Me	4-$BnOC_6H_4$	97 (**4g**)	82 (−)
8	Me	4-FC_6H_4	93 (**4h**)	92 (+)
9[d,e]	Me	3-ClC_6H_4	87 (**4i**)	93 (−)
10[d]	Me	4-$CF_3C_6H_4$	94 (**4j**)	93 (−)
11	Me	4-PhC_6H_4	96 (**4k**)	90 (−)
12	Me	2-naphthyl	94 (**4l**)	78 (−)
13[d]	Me	1-naphthyl	91 (**4m**)	86 (+)
14	Et	Ph	96 (**4n**)	80 (+)
15	^{n}Pr	Ph	90 (**4o**)	77 (+)
16	^{n}Bu	Ph	92 (**4p**)	86 (+)
17[d]	^{i}Bu	Ph	86 (**4q**)	76 (+)
18[f]	cyclopropyl	Ph	90 (**4r**)	83 (+)

[a]Conditions: **3** (0.2 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), **L2** (2.2 mol %), H_2 (600 psi), toluene/DCE (1/1), −20 °C, 24 h. If not noted, the d.r. > 20:1. [b]Isolated yield. [c]Determined by chiral HPLC. [d]H_2 (1000 psi). [e]d.r. = 12:1. [f]0 °C.

Table 4. Substrate Scope: 2,3-Disubstituted Pyrazinium Salts[a]

entry	R	yield (%)[b]	ee (%)[c]
1	Ph	96 (**6a**)	94 (2*R*,3*S*)
2	3-MeC_6H_4	98 (**6b**)	92 (+)
3[d]	4-MeC_6H_4	93 (**6c**)	93 (+)
4[d]	3-$MeOC_6H_4$	94 (**6d**)	95 (+)
5	4-FC_6H_4	95 (**6e**)	93 (+)
6	3-ClC_6H_4	94 (**6f**)	82 (+)
7	4-$CF_3C_6H_4$	92 (**6g**)	81 (+)
8[d]	2-naphthyl	96 (**6h**)	93 (+)
9[e]	Me	95 (**6i**)	91 (+)
10[e]	-$(CH_2)_4$-	93 (**6j**)	96 (+)

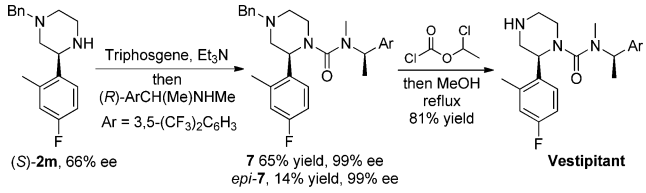
[a]Conditions: **5** (0.2 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), **L*** (2.2 mol %), H_2 (400 psi), THF/EtOAc (1/1), 50 °C, 24 h. In all cases, the d.r. > 20:1 [b]Isolated yields. [c]Determined by chiral HPLC. [d]H_2 (200 psi), 60 °C. [e]**L***: (*S*,*S*)-f-Binaphane, H_2 (600 psi), THF, 30 °C, 24 h; BnBr was used as an activator.

the 2,3-disubstituted pyrazinium salts were reduced with excellent d.r. (>20:1).

With readily available chiral piperazines in hand, we were keen to synthesize piperazine-containing drugs. Vestipitant is a potent and selective NK1 receptor antagonist, which is now under development as an antiemetic and anxiolytic drug. Currently, the syntheses of Vestipitant require 6−9 steps.[17] Starting from the piperazine **2m**, Vestipitant can be obtained in just two steps, significantly shortening the synthetic route (Scheme 2).

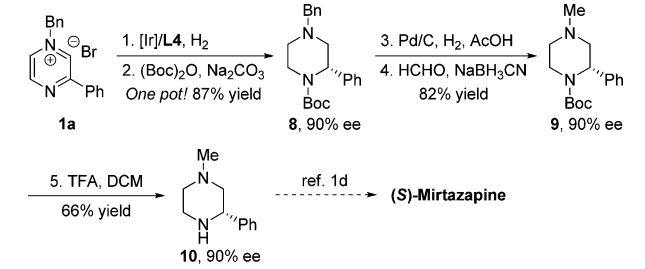
Mirtazapine is a tetracyclic antidepressant drug widely used as a racemate. But recent biological investigations reveal that only (*S*)-Mirtazapine shows potential in the treatment of insomnia and climacteric symptoms. To obtain the (*S*)-Mirtazapine, 1-methyl-3-phenylpiperazine **10** is an important intermediate. The

Scheme 2. Synthesis of Vestipitant



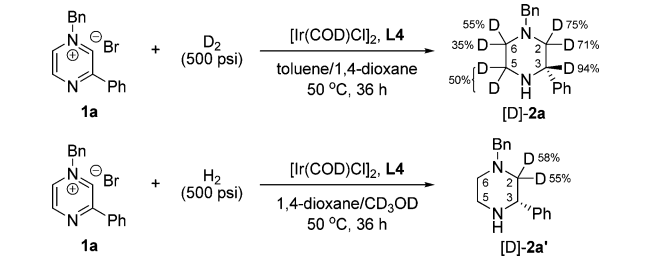
reported syntheses of **10** generally require 3−6 steps coupled with chemical resolution.[1d] Starting from salt **1a**, **10** was obtained in five steps with just three column separations in an overall 47% yield (Scheme 3).

Scheme 3. Formal Synthesis of (*S*)-Mirtazapine



To investigate the reaction pathway, an isotopic labeling experiment was carried out by reducing **1a** with D_2 (Scheme 4).

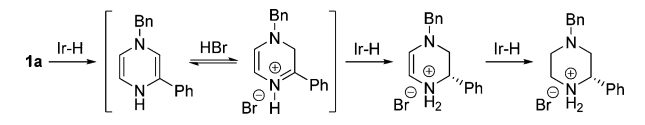
Scheme 4. Mechanistic Investigation



It was determined that each atom of C3, C5, and C6 incorporated one deuterium atom. Meanwhile, hydrogen/deuterium scrambling took place on the C2, which was possibly caused by enamine−iminium tautomerization. The deuteration extent at the two diastereotopic positions of C6 was slightly different (55% vs 35%), indicating that deuterium incorporation at C6 happened after stereocenter formation. When the reduction of **1a** was performed in deuterium solvent CD_3OD, a deuterium atom was only incorporated on C2, further confirming the possible enamine−iminium tautomerization.

On the basis of above-mentioned experimental data, a plausible reaction pathway was proposed in Scheme 5. The salt **1a** first undergoes 1,4-hydride addition to give a 1,4-dihydropyrazine intermediate. In the presence of HBr, the right side enamine is prone to tautomerize due to the adjacent

Scheme 5. Proposed Reaction Pathway



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phenyl group, which leads to the stabilization of the iminium salt via conjugation. Hydrogenation of the iminium salt delivers chiral tetrahydropyrazine. The residual double bond is directly hydrogenated for the lack of steric hindrance and stabilization.

In conclusion, an expedient method has been developed for the synthesis of chiral piperazines from readily available pyrazinium salts. The current system exhibits an impressively broad substrate scope, and 3-substituted as well as 2,3- and 3,5-disubstituted pyrazinium salts can be easily hydrogenated with high yields and ee's. The chiral products are mono-*N*-protected, which is advantageous for synthetic modification on either nitrogen. The practicability of the reaction has been demonstrated by the easy scalability and drug synthesis. In addition, preliminary mechanistic studies shed some light on the reaction pathway, which involves an initial 1,4-hydride addition, enamine−iminium tautomerization, and AH of an iminium salt. Further efforts to apply the related method to other challenging heteroaromatics are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01190.

Experimental procedures, characterization data, X-ray structures, data for the determination of ee, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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