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# Diastereoselective Synthesis of Piperazines by Manganese-Mediated Reductive Cyclization

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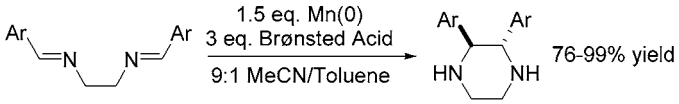
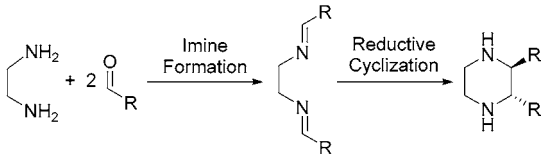
## ABSTRACT




**A simple and effective synthesis of *trans* aryl-substituted piperazines using a Brønsted acid and manganese(0) is described.**

A piperazine ring gives inherent rigidity to two hydrogen bond participants and lends itself well to binding within biological systems. Accordingly, piperazines are found in a large number of biologically active compounds.[1] Additionally, this structural rigidity has led to the use of piperazines as ligands in asymmetric catalysis.[2] Whereas piperazines with 2,5-substitution can be synthesized via reduction of the corresponding diketopiperazine,[3] 2,3-substituted piperazines are much more difficult to access. This substitution can have an influence on their biological activity.[1f] Therefore, the development of an effective, simple method for their synthesis is desirable. An attractive strategy for the synthesis of 2,3-substituted piperazines is the reductive cyclization of a bisimine (Scheme 1). The imine substrates are easy to access by condensation of the corresponding diamine and carbonyl compound, and the carbon−carbon bond forming procedure sets two stereocenters in one step. Intermolecular reductive dimerization of imines has been previously accomplished to form vicinal diamines using various methods including Mg and alkali metal,[4] photolysis,[5] other metal reductants,[6−14] and electrochemistry.[15] Stereoselectivity has been a significant issue, with only a few methods yielding

**Scheme 1.** Reductive Dimerization of Imines




(1) For examples, see: (a) Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S.; Neustadt, B. R.; Cox. K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Stizki, J. M. *J. Med. Chem.* **2001**, *44*, 3343−3346. (b) Zhang, Y.; Rothman, R. B.; Dersch, C. M.; de Costa, B. R.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2000**, *43*, 4840−4849. (c) Matecka, D.; Rothman, R. B.; Radesca, L.; de Costa, B. R.; Dersch, C. M.; Partilla, J. S.; Pert, A.; Glowa, J. R.; Wojnicki, F. H. E.; Rice, K. C. *J. Med. Chem.* **1996**, *39*, 4704−4716. (d) Glowa, J. R.; Fantegrossi, W. E.; Lewis, D. B.; Matecka, D.; Rice, K. C.; Rothman, R. B. *J. Med. Chem.* **1996**, *39*, 4689−4691. (e) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202−9203. (f) Giardiná, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G.; Melchiorre, C. *J. Med. Chem.* **1993**, *36*, 690−698. (g) Giardiná, D.; Brasili, L.; Gregori, M.; Massi, M.; Picchio, M. T.; Quaglia, W.; Melchiorre, C. *J. Med. Chem.* **1989**, *32*, 50−55. (h) Witiak, D. T.; Trivedi, B. K. *J. Med. Chem.* **1981**, *24*, 1329−1332. (i) Manoury, P. M.; Dumas, A. P.; Najer, H. *J. Med. Chem.* **1979**, *22*, 554−559.

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(3) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909−4913.

(4) (a) Bachmann, W. E. *J. Am. Chem. Soc.* **1931**, *53*, 2672−2676. (b) Smith, J. G.; Veach, C. D. *Can. J. Org. Chem.* **1966**, *44*, 2497−2502. (c) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Am. Chem. Soc.* **1966**, *88*, 453−456. (d) Smith, J. G.; Ho, I. *J. Org. Chem.* **1972**, *37*, 653−656.

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the more useful *trans* product in good yields.[15,16] In most of these cases, nontrivial imine substrates are required. In contrast, considerably less effort has been afforded to piperazine synthesis via reductive cyclization.[17] Electrochemical methods are most commonly used to generate piperazine products in moderate to good yields and diastereoselectivity. A general metal-mediated method would thus be an attractive alternative.

Our approach was based on a serendipitous observation from a related project directed at carbon−carbon bond forming reactions of imines. We found that intermolecular imine reductive dimerization was a significant byproduct. After determining the necessary reagents for this transformation, dimerization product **2** was found to result from the combination of Mn(0) metal, a silyl chloride, and a Lewis acid (Figure 1). Optimization of this process was initially

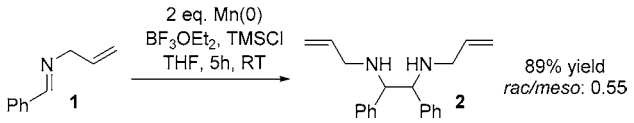


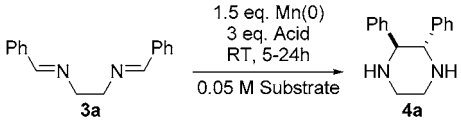

**Figure 1.** Original observation.

sought through evaluation of combinations of different Lewis acids and silyl chlorides, with limited success. Since the diastereoselectivity for this transformation was poor, we sought to explore and optimize a Mn-mediated intramolecular reductive dimerization for piperazine synthesis.

In applying this method to piperazine formation, an experimentally simple procedure was desired. Therefore, substitution of both the Lewis acid and silyl chloride with a single reagent seemed prudent. It was reasoned that these additives could be acting as Lewis acids by binding imine substrate to facilitate reduction, by activating the manganese surface in situ, and/or by turning over any intermediates. Thus, a simple Brønsted acid was considered a reagent that could potentially fulfill all of these roles.

On the basis of previous uses of Brønsted acids in pinacol couplings,[18] the investigation was initiated by treating bisimine **3a** with Mn(0) (325 mesh) and pyridinium hydrochloride in various solvents. It was found that reductive cyclization occurred in most solvents with the best yield of 93% obtained in 10% toluene/acetonitrile (Table 1, entry 2).

**Table 1.** Screen of Solvents and Brønsted Acids




| entry | Brønsted acid | solvent[a] | yield (%) |
|---|---|---|---|
| 1 | pyridine-HCl | acetonitrile | 83 |
| **2** | **pyridine-HCl** | **acetonitrile[b]** | **93** |
| 3 | pyridine-HCl | dichloroethane | 46 |
| 4 | pyridine-HCl | methanol | 57 |
| 5 | pyridine-HCl | dimethoxyethane | 67 |
| 6 | pyridine-HCl | toluene | 55 |
| 7 | triethylamine-HCl | acetonitrile[b] | 26 |
| 8 | triethylamine-HCl | dimethoxyethane | 33 |
| 9 | lutidine-HCl | acetonitrile[b] | 80 |
| 10 | lutidine-HCl | dimethoxyethane | 67 |
| **11** | **trifluoroacetic acid** | **acetonitrile[b]** | **95** |
| 12 | acetic acid | acetonitrile[b] | nr |

[a] The use of diethylether, DMF, DMSO, acetone, and ethyl acetate resulted in little product formation. [b] 10% toluene was added to enhance solubility of the substrate.

Additionally, low substrate concentration was necessary to avoid oligomerization. Furthermore, this process is chemoselective in that benzaldehyde does not undergo a pinacol coupling under these reaction conditions.

Encouraged by the excellent yields obtained with pyridine-HCl, other simple Brønsted acids were explored. Of these, trifluoroacetic acid (TFA) gave a comparable success with a yield of 95% (entry 11). It is important to note that the acidity seemed to directly correlate with yield of the process. Both pyridine-HCl and TFA, the most effective acids investigated, are considerably more acidic in DMSO than triethylamine-HCl and acetic acid.[19]

Using the optimized conditions (either 3 equiv of pyridine-HCl or TFA, 1.5 equiv of 325 mesh Mn(0), 0.05 M substrate in 10% toluene/acetonitrile), the scope of the reductive

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(9) Mn: Rieke, R. D.; Kim, S. *J. Org. Chem.* **1998**, *63*, 5235−5239.

(10) Yb: Takaki, K.; Tsubaki, Y.; Tanaka, S.; Beppu, F.; Fujiwara, Y. *Chem. Lett.* **1990**, 203−204.

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(12) Ti: Talukdar, S.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 3468−3470.

(13) V: Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421−9424.

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(16) For *d*/*l* selective protocols, see: (a) Al/Sm: Yanada, R.; Okaniwa, M.; Kaieda, A.; Ibuka, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 1283−1286. (b) Mo: Cameron, T. M.; Ortiz, C. G.; Abboud, K. A.; Boncella, J. M.; Baker, R. T.; Scott, B. L. *Chem. Commun.* **2000**, 573−574. (c) Zn/Cu: Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609−610. (d) Ti: Mangeney, P.; Tjero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255−257. (e) Nb: Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152−3154.

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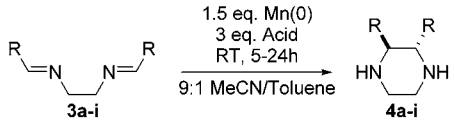
(18) Brønsted acids have been used in a similar manner for pinacol couplings; see: (a) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673−2676. (b) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070−2071.

(19) (a) Kolthoff, Z. M.; Chantooni, M. K., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 23. (b) Courtot-Coupez, J.; LeDemezet, M. *Bull. Soc. Chim. Fr.* **1969**, 1033. (c) Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2508.

**Table 2.** Intramolecular Reductive Dimerization Scope




| entry | Brønsted acid | R | product | yield (%)[a] |
|---|---|---|---|---|
| 1 | pyridine-HCl | Ph | **4a** | 93 |
| 2 | TFA | Ph | **4a** | 95 |
| 3 | pyridine-HCl | 2,5-$(CH_3)_2C_6H_3$ | **4b** | 96 |
| 4 | TFA | 2,5-$(CH_3)_2C_6H_3$ | **4b** | 96 |
| 5 | pyridine-HCl | 2,4-$(CH_3)_2C_6H_3$ | **4c** | 96 |
| 6 | TFA | 2,4-$(CH_3)_2C_6H_3$ | **4c** | 99 |
| 7 | pyridine-HCl[b] | *p*-$CH_3OC_6H_4$ | **4d** | 89 |
| 8 | TFA[b] | *p*-$CH_3OC_6H_4$ | **4d** | 90 |
| 9 | pyridine-HCl | *p*-$ClC_6H_4$ | **4e** | 76 |
| 10 | TFA | *p*-$ClC_6H_4$ | **4e** | 99 |
| 11 | pyridine-HCl[c] | 2-furyl | **4f** | 93 |
| 12 | TFA[c] | 2-furyl | **4f** | 85 |
| 13 | pyridine-HCl | 2-naphthyl | **4g** | 80 |
| 14 | TFA | 2-naphthyl | **4g** | 97 |
| 15 | pyridine-HCl | cyclohexyl | **4h** | nr |
| 16 | TFA | *tert*-butyl | **4i** | nr |

[a] Average of at least two experiments. [b] 4 equiv of acid is used for optimal yields. [c] 0.01 M in substrate.

dimerization of imines was evaluated.[20] Overall, aryl-substituted imines were excellent substrates, producing the desired piperazines in yields ranging from 76% to 99%. Both electron-rich (entries 3−8) and electron-poor imines (entries 9 and 10) undergo reductive cyclization as well as aryl rings with multiple substituents (entries 3−6). Furyl- and naphthyl-substituted imines also cleanly react to yield substituted piperazines. Notably, only one diastereomer is observed for all cases by NMR analysis. This single diastereomer was confirmed to be *trans* both by NMR assignment and by separation of the enantiomers by HPLC equipped with a chiral stationary phase. Scale-up of this procedure to 10 g of **3b** resulted in a 96% yield of the piperazine product **4b**. This showcases the ability to produce laboratory scale quantities. Although the use of either Brønsted acid leads to similar yields, the TFA-mediated process is simpler in terms of overall workup.[20] Aliphatic substrates proved unreactive under the optimal conditions, which is likely due to the higher reduction potential of these substrates.[21]

Other substrates that yield cyclic diamines were evaluated using the optimal conditions (Table 3). Using a diamine derived from (*R*,*R*)-cyclohexyldiamine **3j**, a high yielding, diastereoselective reductive cyclization results.[22] Only one diastereomer is observed by NMR analysis. Diamines similar to **4j** have been used in the enantioselective addition of diethylzinc to aldehydes.[2] A ketimine **3k** undergoes a diastereoselective reductive cyclization to form piperazine

(20) See Supporting Information for details.

(21) Cyclic voltammetry of an aryl imine in $CH_3CN$ gave a reduction potential of −1.51 eV, whereas an aliphatic imine did not cleanly reduce before solvent reduction was observed (ca. −1.9 eV). See Supporting Information for details.

(22) Stereochemistry was assigned on the basis of a previous synthesis; see ref 2.

**Table 3.** Intramolecular Reductive Dimerization of Other Substrates

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1[a] | **3j** | **4j** | 99 |
| 2[b] | **3k** | **4k** | 30 |
| 3[a,c] | **3l** | **4l** | 73 |

[a] Conditions: 1.5 equiv of Mn(0), 3 equiv of TFA, 4 h, rt, 9:1 MeCN/toluene. [b] Conditions: 1.5 equiv Mn(0), 3 equiv pyridine-HCl, 4 h, rt, 9:1 MeCN/toluene. [c] 0.01 M substrate.

**4k** in a lower yield. Of particular note is the diastereoselective synthesis of the seven-membered heterocyclic ring **4l** in good yield.[23]

The high diastereoselectivity of this process deserves comment. Although the precise role of the Brønsted acid is currently unknown, the process presumably involves activation of the imine by the Brønsted acid followed by reduction of the iminium on the manganese surface to form a carbon-centered radical. Three possible scenarios can be considered for carbon−carbon bond formation: (1) radical addition cyclization; (2) a second one-electron reduction to form the carbanion, which undergoes rapid intramolecular nucleophilic addition to the activated imine; and (3) formation of the diradical with subsequent termination. Shono and co-workers' results from related electrochemical studies indicate that the carbanion is more difficult to form than the diradical.[2] If a radical cyclization is occurring, the piperazine product would arise from a potentially unfavorable 6-endo cyclization. Additionally, in the case of the seven-membered ring formation, no 6-exo product is observed. Therefore, the likely mode of cyclization is through intramolecular termination of a diradical (Figure 2).[24] A six-membered transition state

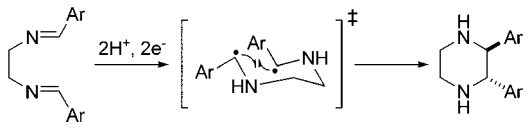



**Figure 2.** Model for diastereoselectivity.

model for diradical termination is consistent with the observed diastereocontrol. In this model, the imine substituents are oriented *trans* to each other in equatorial sites.

(23) The analogous eight-membered product is produced in significantly lower yields (10−20%).

(24) This is a similar model to that proposed by Shono and co-workers for electrochemically mediated reductive cyclization of imines in ref 2.

In summary, a simple method has been developed for the diastereoselective synthesis of 2,3-aryl-substituted piperazines. The use of both Mn(0) and a simple Bronsted acid provides for a convenient protocol for the synthesis of this important class of heterocycles. The method has been shown to work for a variety of aryl substrates and can be easily accomplished on a 10 g scale. Additionally, highly substituted piperazines and seven-membered heterocyclic rings can be formed in good yields. The applications of substituted piperazines to asymmetric catalysis and investigation into other Mn(0)-mediated processes are subjects of current and future research efforts.

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**Supporting Information Available:** Experimental details, characterization of new compounds, and $^1$H NMR spectra for all piperazines formed. This material is available free of charge via the Internet at http://pubs.acs.org.

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