Short Synthesis of Enantiopure trans-3-Arylpiperazine-2-carboxylic Acid Derivatives via Diaza-Cope Rearrangement

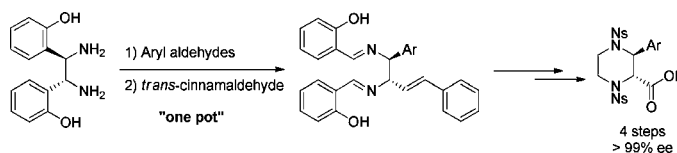Soon Ho Kwon,[†] Sang Min Lee,[†] Sang Moon Byun,[†] Jik Chin,*[‡] and B. Moon Kim*[†]

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, South Korea, and Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

kimbm@snu.ac.kr; jchin@chem.utoronto.ca

ABSTRACT

An efficient synthetic method was developed for the construction of enantiomerically pure *trans*-3-arylpiperazine-2-carboxylic acid derivatives using diaza-Cope rearrangement (DCR) as a key step starting from (*R,R*)/(*S,S*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN). A complete transfer of stereochemical integrity was observed for the transformation. Piperazine ring formation from the chiral 1,2-ethylenediamine derivatives using diphenylvinylsulfonium triflate followed by oxidation using ruthenium(III) chloride monohydrate in the presence of sodium periodate provided the desired enantiopure *trans*-3-arylpiperazine-2-carboxylic acid derivatives.

Piperazine is a useful building block often employed in the design of physiologically active molecules.[1] Among various substituted piperazine structures, piperazine-2-carboxylic acid derivatives can be regarded as novel amino acid analogues and therefore have been utilized in many peptidomimetic structures for therapeutically important compounds. Examples of chiral piperazine-2-carboxylic acid derivatives embedded in drug candidates include a human immunodeficiency virus (HIV) protease inhibitor,[2] cholecystokinin-1 receptor (CCK1R) agonists,[3] κ-receptor agonists,[4] substance P (SP) receptor antagonists,[5] *N*-methyl-D-aspartic acid (NMDA) antagonists,[6] and MMP-13 and TNF-α converting enzyme inhibitors (Figure 1).[7]

Although many reports exist for the synthesis of optically active piperazine-2-carboxylic acid derivatives, preparation of stereodefined 3-, 5-, or 6-substituted piperazine-2-carboxylic acid derivatives in an enantiomerically pure form is still a challenging synthetic problem. Previously, chiral piperazine-2-carboxylic acid derivatives have been synthesized through cyclizations,[8] multicomponent synthesis,[9] amino-acid-based synthesis,[10] enzymatic resolution,[11] asymmetric hydrogenation of pyrazine derivatives,[12] α-lithiation of piperazine using

[†] Seoul National University.

[‡] University of Toronto.

(1) (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (c) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923–9932. (d) Jida, M.; Soueidan, M.; Willand, N.; Agbossou-Niedercorn, F.; Pelinski, L.; Laconde, G.; Deprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2011**, *52*, 1705–1708 and references therein.

(2) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443–3451.

(3) Berger, R.; Zhu, C.; Hansen, A. R.; Harper, B.; Chen, Z.; Holt, T. G.; Hubert, J.; Lee, S. J.; Pan, J.; Qian, S.; Reitman, M. L.; Strack, A. M.; Weingarth, D. T.; Wolff, M.; MacNeil, D. J.; Weber, A. E.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4833–4837.

(4) Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1993**, *36*, 2075–2083.

(5) Mills, S. G.; Wu, M. T.; MacCoss, M.; Budhu, R. J.; Dorn, C. P., Jr.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2707–2712.

(6) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.

(7) Letavic, M. A.; Barberia, J. T.; Carty, T. J.; Hardink, J. R.; Liras, J.; Lopresti-Morrow, L. L.; Mitchell, P. G.; Noe, M. C.; Reeves, L. M.; Snow, S. L.; Stam, E. J.; Sweeney, F. J.; Vaughn, M. L.; Yu, C. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3243–3246.
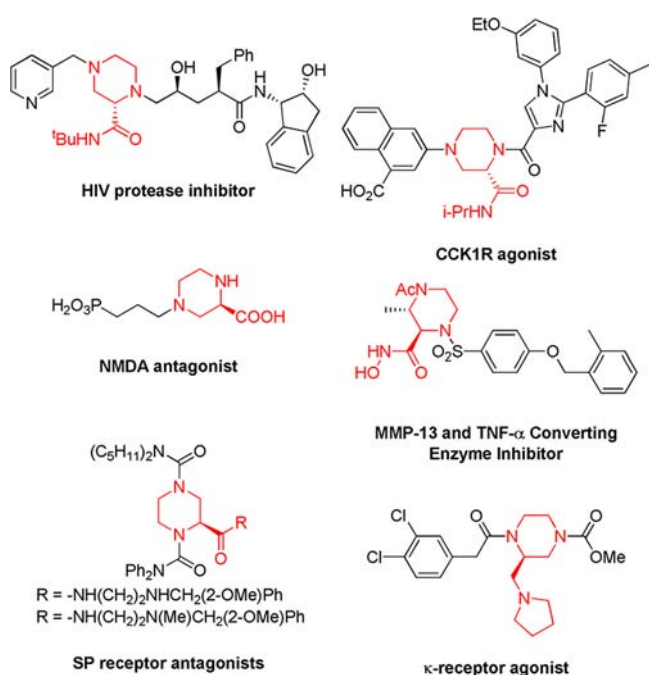
Figure 1. Compounds containing chiral piperazine-2-carboxylic acid derivatives.

s-BuLi/(−)-sparteine,[13] and Pd-catalyzed asymmetric allylic allylation.[14] However, some of these methods suffer from shortcomings such as the problem of catalyst traces remaining in final product(s), low enantiomeric purities of

final compounds, and low yields resulting from complicated multistep syntheses. In the course of our medicinal chemistry programs, we were in search of an efficient method for the preparation of *trans*-3-arylpiperazine-2-carboxylic acid derivatives and have found that there are scarce reports on them.[8g] To obtain 3-substituted piperazine-2-carboxylic acids, S_N2-type cyclization and the reduction of 2,3-disubstituted ketopiperazines derived from chiral 1,2-diamines have been previously used.[7,8g] For the latter method, synthesis of suitably substituted enantiopure chiral vicinal diamines is essential. We have recently developed a stereospecific synthesis of symmetric chiral vicinal diamines through the rearrangement of chiral diimines prepared from the reaction of $(R,R)/(S,S)$-1, 2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN) and 2 equiv of aldehydes.[15] The rearrangement reaction was nicely extended to a stereospecific "one pot" route to α-substituted syn-α,β-diamino esters.[16] We envisioned that the chiral nonsymmetrical 1,2-disubstituted vicinal diamines synthesized by diaza-Cope rearrangement (DCR) could serve as suitable intermediates for the preparation of chiral nonsymmetrical 2,3-substituted piperazines. Herein, we report on the development of an efficient route to enantiopure *trans*-3-arylpiperazine-2-carboxylic acids starting from optically pure HPEN via DCR using various aryl aldehydes and *trans*-cinnamaldehyde.

Toward the construction of structurally diverse *trans*-3-arylpiperazine-2-carboxylic acids, formation of the unsymmetrically substituted diimines was studied from the reaction of HPEN, benzaldehyde, and *trans*-cinnamaldehyde. To find optimal reaction conditions, factors such as solvent and stoichiometry of aldehydes were investigated. From solvent screening experiments using DMSO, THF, and toluene, DMSO was quickly identified as the solvent of choice. As for the reaction stoichiometry, 1 equiv of aryl aldehyde and 1 equiv of *trans*-cinnamaldehyde were found to be optimal for the reaction. The reactions proceeded smoothly at room temperature, and reactions at higher temperatures did not improve the yield. Since two different aldehydes are involved in the reaction to form heterodimeric diimine product, the hetero- versus homodimer selectivity is critical. It was found that the best heterodimer

(8) (a) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297–3312. (b) Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int.* **2002**, *34*, 367–404. (c) Nyerges, M.; Arany, A.; Fejes, I.; Groundwater, P. W.; Zhang, W.; Bendell, D.; Anderson, R. J.; Tóke, L. *Tetrahedron* **2002**, *58*, 989–995. (d) Fischer, P. M. *J. Pept. Sci.* **2003**, *9*, 9–35. (e) Powell, N. A.; Ciske, F. L.; Clay, E. C.; Cody, W. L.; Downing, D. M.; Blazecka, P. G.; Holsworth, D. D.; Edmunds, J. J. *Org. Lett.* **2004**, *6*, 4069–4072. (f) Chai, C. L. L.; Elix, J. A.; Huleatt, P. B. *Tetrahedron* **2005**, *61*, 8722–8739. (g) Kim, Y.; Ha, H.-J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, H. J.; Kim, M. S.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407–4409. (h) Viso, A.; Pradilla, R. F.; Flores, A.; García, A.; Tortosa, M.; López-Rodríguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448. (i) Viso, A.; Fernández de la Pradilla, R.; Flores, A.; García, A. *Tetrahedron* **2007**, *63*, 8017–8026. (j) Hirose, T.; Sunazuka, T.; Tsuchiya, S.; Tanaka, T.; Kojima, Y.; Mori, R.; Iwatsuki, M.; Ōmura, S. *Chem.—Eur. J.* **2008**, *14*, 8220–8238. (k) Limbach, M.; Lygin, A. V.; Korotkov, V. S.; Es-Sayed, M.; de Meijere, A. *Org. Biomol. Chem.* **2009**, *7*, 3338–3342. (l) Ottesen, L. K.; Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Chem.—Eur. J.* **2009**, *15*, 2966–2978. (m) Taylor, A. M.; Schreiber, S. L. *Tetrahedron Lett.* **2009**, *50*, 3230–3233. (n) De Risi, C.; Pelà, M.; Pollini, G. P.; Trapella, C.; Zanirato, V. *Tetrahedron: Asymmetry* **2010**, *21*, 255–274. (o) D'Hooghe, M.; Dekeukeleire, S.; Leemans, E.; De Kimpe, N. *Pure Appl. Chem.* **2010**, *82*, 1749–1759.

(9) (a) Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*, 1113–1116. (b) Nenajdenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. *Tetrahedron* **2007**, *63*, 3031–3041. (c) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23–41. (d) Dömling, A.; Huang, Y. *Synthesis* **2010**, 2859–2883. (e) Zhu, D.; Xia, L.; Pan, L.; Li, S.; Chen, R.; Mou, Y.; Chen, X. *J. Org. Chem.* **2012**, *77*, 1386–1395.

(10) (a) Rubsam, F.; Mazitschek, R.; Giannis, A. *Tetrahedron* **2000**, *56*, 8481–8487. (b) Bedürftig, S.; Weigl, M.; Wünsch, B. *Tetrahedron: Asymmetry* **2001**, *12*, 1293–1302. (c) Bedürftig, S.; Wünsch, B. *Bioorg. Med. Chem.* **2004**, *12*, 3299–3311. (d) Pollini, G. P.; Baricordi, N.; Benetti, S.; De Risi, C.; Zanirato, V. *Tetrahedron Lett.* **2005**, *46*, 3699–3701. (e) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196.

(11) (a) Eichhorn, E.; Roduit, J. P.; Shaw, N.; Heinzmann, K.; Kiener, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2533–2536. (b) Wu, G.; Zhao, H.; Luo, R. G.; Wei, D.; Malhotra, S. V. *Enantiomer* **2001**, *6*, 343–345. (c) Hietanen, A.; Lundell, K.; Kanerva, L. T.; Liljeblad, A. *ARKIVOC* **2012**, *2012*, 60–74.

(12) (a) Kukula, P.; Prins, R. *J. Catal.* **2002**, *208*, 404–411. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

(13) (a) Robinson, S. P.; Sheikh, N. S.; Baxter, C. A.; Coldham, I. *Tetrahedron Lett.* **2010**, *51*, 3642–3644. (b) McDermott, B. P.; Campbell, A. D.; Ertan, A. *Synlett* **2008**, *2008*, 875–879. (c) Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540–2544.

(14) Nakano, H.; Yokoyama, J.-i.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, *43*, 7761–7764.

(15) (a) Kim, H.; So, S. M.; Chin, J.; Kim, B. M. *Aldrichimica Acta* **2008**, *41*, 77. (b) Kim, H.; Nguyen, Y.; Yen, C. P.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184–12191. (c) Kim, H. J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16370–16371. (d) Kim, H.; Staikova, M.; Lough, A. J.; Chin, J. *Org. Lett.* **2009**, *11*, 157–160.

(16) Kim, H.; Chin, J. *Org. Lett.* **2009**, *11*, 5258–5260.

selectivity was obtained when an aminal **2** was first formed and then was subjected to the reaction with *trans*-cinnamaldehyde, as outlined in Scheme 1. The formation of the aminal **2** was accomplished through slow addition of an aryl aldehyde to the solution of HPEN. This aminal **2** was then subjected to the reaction with cinnamaldehyde without isolation. Addition of cinnamaldehyde to aminal **2** then allowed for the formation of diimine **3**, which was converted to the desired diimine **4** facilitated by the resonance-assisted hydrogen bonding (RAHB).[15b] The formation of diimine **4** was observed as a major product along with small amounts of homodimeric diimine products of each aldehyde.

Scheme 1. Stereospecific Synthesis of Diimine via Diaza-Cope Rearrangement
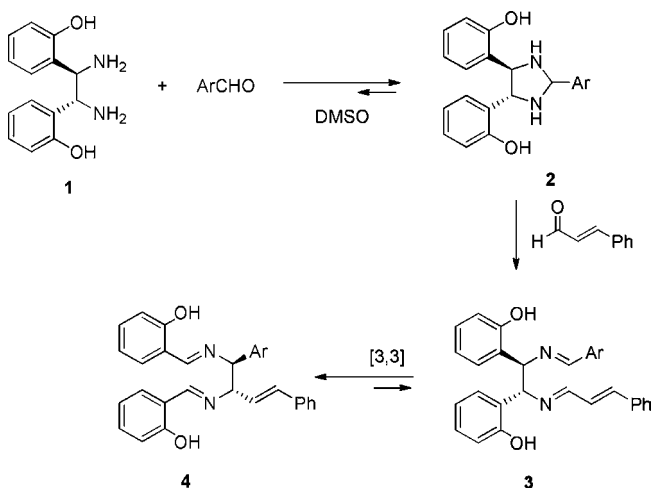
With the optimized reaction conditions in hand, various aryl aldehydes were investigated in the formation of compound **2** to ensure structural diversity of the chiral piperazine derivatives. Excellent yields (mostly >90%) of aminal intermediates **2** were observed as determined by NMR analysis (see Table 1).[17] In this step, slow addition of the aryl aldehyde was found to be critical to minimize the formation of homodimeric diimine product **5** or **6**. Subsequently, the formation of heterodimeric diimine **4** as a major product was confirmed 12 h after addition of 1 equiv of *trans*-cinnamaldehyde.

As can be seen in Table 1, the yields of heterodimeric diimine **4** were dependent upon the substituents on aryl aldehydes. Diimines formed from an aryl aldehyde containing electron-withdrawing or halide substituents were obtained in good to excellent yields (entries 2−6) with good hetero/homo product ratios, which were determined through ¹H NMR analysis.[17] Diimines formed from 1-naphthyl and heteroaromatic aldehydes were also obtained in satisfactory yields (entries 7 and 8). On the other hand, reactions of *p*-methoxybenzaldehyde and 4-acetamidobenzaldehyde gave moderate yields of product

(17) Mesitylene was used as an internal standard in NMR analysis.

Table 2. Synthesis of *N*-Ns-Protected Vicinal Diamines[a]
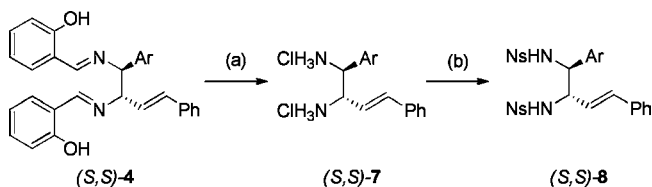
entry	product	Ar	yield (%)[b]	ee (%)[e]
1	**8a**	Ph	79	>99
2	**8b**	4-FC$_6$H$_4$	86	>99
3	**8c**	4-ClC$_6$H$_4$	84	>99
4	**8d**	2-BrC$_6$H$_4$	84	>99
5	**8e**	3-BrC$_6$H$_4$	83	>99
6	**8f**	4-BrC$_6$H$_4$	91	>99
7	**8g**	1-naphthyl	76	>99
8	**8h**	2-pyridyl	74[c,d]	>99
9	**8i**	4-OMeC$_6$H$_4$	76	>99
10	**8j**	4-acetamidophenyl	59	>99[f]

[a] Reagents and conditions: (a) 2.5 equiv of concd HCl in THF (0.1 M); (b) 4 equiv of 4-NsCl, 6 equiv of TEA in THF (0.1 M). [b] Yields of isolated products after column chromatography. [c] Excess (3.5 equiv) concd HCl was used. [d] In this reaction, 8 equiv of TEA was used in dichloromethane. [e] Values of ee were determined through chiral HPLC analysis using Chiralpak IA column. [f] Value of ee was determined at the chiral diimine **4j** stage.

diimines and slightly higher ratios of unwanted homodimeric diimines (entries 9 and 10, respectively).

Formation of the homodimeric product **6** of *trans*-cinnamaldehyde is believed to come from the very nature of the reaction, which involves an equilibrium from HPEN and two aldehydes to the very end product, thus allowing for disproportionation after addition of *trans*-cinnamaldehyde. Attempts to purify the heterodimeric diimine products from the homodimeric diimines on a silica gel column were accompanied by some decomposition of the diimine species. Therefore, we decided to purify the heterodimeric product at a later stage.

Hydrolysis of diimine **4** and subsequent protection of the resulting diamine **7** was carried out, and the data are shown in Table 2. Upon hydrolysis of diimines **4a−j** using concentrated HCl, diamine HCl salts **7a−j** were obtained as precipitates. HCl salts **7a−j** underwent smooth reaction with 4-nitrobenzenesulfonyl chloride (NsCl) and triethylamine in THF to give *N,N′*-bisNs-protected vicinal diamines **8a−j** in good overall yields (59−91% for the two steps). Enantiomeric purities of the product diamines were determined at this stage through chiral HPLC analyses, and all of them were uniformly high (>99% ee).

In 2008, Aggarwal et al. reported an annulation reaction for the synthesis of piperazines from ethylenediamine derivatives using diphenylvinylsulfonium triflate.[18] We took compound **7a** to study optimal reaction conditions for the construction of piperazine structures using Aggarwal's protocol. First, reactions using Aggarwal's

(18) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784−3786.

Table 1. Stereospecific Synthesis of Chiral Nonsymmetrical Disubstituted Diimines[a]
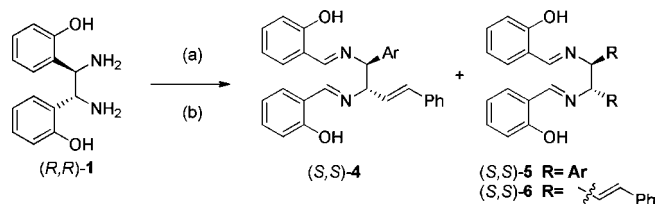
entry	product	Ar	yield (%)[b]	4/5/6 ratio[b,c]
1	**4a**	Ph	89	88/7/5
2	**4b**	4-FC$_6$H$_4$	91	88/7/5
3	**4c**	4-ClC$_6$H$_4$	91	91/4/5
4	**4d**	2-BrC$_6$H$_4$	86	97/2/1
5	**4e**	3-BrC$_6$H$_4$	91	91/6/3
6	**4f**	4-BrC$_6$H$_4$	83	91/4/5
7	**4g**	1-naphthyl	90	89/7/4
8	**4h**	2-pyridyl	82	94/4/2
9	**4i**	4-OMeC$_6$H$_4$	71	79/13/8
10	**4j**	4-acetamidophenyl	74	80/11/9

[a] Reagents and conditions: (a) ArCHO, DMSO, rt, 1 h; (b) *trans*-cinnamaldehyde, rt, 12 h. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] The relative R_f values of the homodimeric side products compared to the desired heterodimeric product vary depending upon their structures.
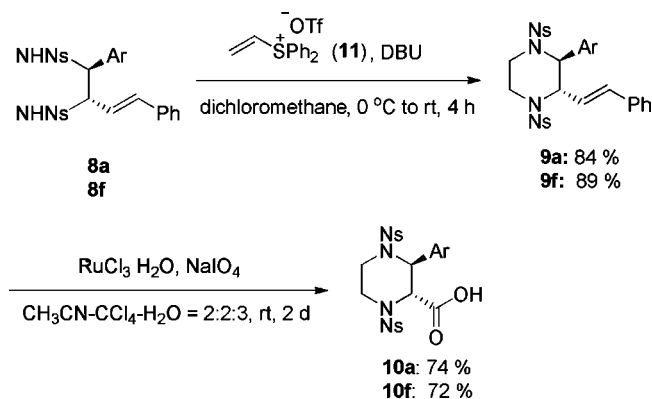
vinylsulfonium salt were attempted on the free diamine **7a**; however, the reaction was very sluggish, yielding only 11% of the desired piperazine product. Diamines having various N,N'-protecting groups such as Boc, CBz, CF$_3$CO, Ts, and Ns groups, which are associated with different pK_a values,[19] were screened for the construction of piperazine ring (the results are reported in the Supporting Information, Table S1). The reaction from N,N'-diBz-protected diamines gave almost no desired product at all. However, 47% yield of the desired piperazine ring was obtained in the reaction of the N,N'-di-Boc-protected diamine. When more acidic N,N'-diNs or diTs groups, which allow lower pK_a values on the nitrogen atoms compared to other protecting groups, were employed as protecting groups, the reactions proceeded in good yields (82 and 84%, respectively). Even though both N,N'-diTs- and N,N'-diNs-protected diamines provided good yields of the desired product, N,N'-diNs protection, which can be deprotected via treatment with PhSH and K$_2$CO$_3$ in dimethylformamide,[20] was preferred since harsh reaction conditions would be required for the

Scheme 2. Synthesis of Enantiopure 3-Arylpiperazine-2-carboxylic Acids

removal of the N,N'-diTs group. The N,N'-diNs protection provided another advantage where, at this stage, the heterodimeric amines were easily separable from the homodimeric diamine derivatives through silica gel column chromatography.

With the optimal protecting group selected, another substrate having a 4-bromophenyl substituent (compound **8f**) was tested for the ring forming reaction with diphenylvinylsulfonium triflate **11**, and the reaction proceeded in 89% yield, showing the generality of this cyclization. Eventually, the double bond moieties of **9a** and **9f** were efficiently oxidized into carboxylic acids via oxidation using ruthenium(III) chloride monohydrate with sodium periodate[21] in 74 and 72% yields, respectively (Scheme 2).

In conclusion, we have developed a simple, yet highly efficient synthetic route for enantiopure *trans*-3-arylpiperazine-2-carboxylic acids as exemplified in **10a** and **10f** starting from HPEN as a chiral starting material with various aryl aldehydes and *trans*-cinnamaldehyde. Use of the chiral 3-arylpiperazine-2-carboxylic acids as an artificial amino acid analogue in the construction of physiologically active compounds is in progress and will be reported in due course.

Supporting Information Available. Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
(20) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
(21) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.