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A novel aza-Prins-Friedel–Crafts reaction for the synthesis of 4-arylpiperidines

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ABSTRACT

Aldehyde, homoallylic amine and arene undergo smooth cyclization in the presence of $BF_3{\cdot}OEt_2$ to afford 4-arylpiperidines in good yields and with high trans-selectivity. This is the first report on the preparation of 4-arylpiperidines via aza-Prins-Friedel–Crafts reaction.

The multi-component one-pot synthesis has received great importance because of its wide application in pharmaceutical chemistry for generating combinatorial libraries for drug discovery.[1] In particular, three-component coupling (3CC) reactions have proven remarkably successful in generating molecular complexities in a single-step operation.[2] The coupling of aldehyde, homoallylic alcohol and nucleophile is one of the best examples of such a process and has received much attention in recent years to produce tetrahydropyran scaffolds.[3] Similarly, aza-Prins cyclization is the method of choice for the synthesis of piperidines.[4] They are common subunits in many biologically relevant molecules[5] (Fig. 1) including alkaloids[6] and are attractive structural scaffolds for drug discovery. In particular, they are the most promising therapeutic agents for a wide range of diseases such as respiratory illnesses which include asthma, bronchitis and pneumonia[7] and for neurological disorders like Alzheimers and Parkinson disease.[8] Consequently, many efforts have been made in developing efficient protocols for the synthesis of piperidine scaffolds in a stereo- and enantioselective manner.[9] However, the development of simple, convenient and efficient methods for aza-Prins cyclization would provide a wide range of piperidine derivatives for drug-discovery processes.[10] Furthermore, to the best of our knowledge, there have been no report on the synthesis of 4-arylpiperidines via aza-Prins-Friedel–Crafts reaction sequence.

In continuation of our research programme on Prins-cyclization,[4c,d,11] we herein report a novel method for the synthesis of 4-arylpiperidines from aldehydes and *N*-tosyl homoallylic amine by means of aza-Prins-Friedel–Crafts reaction using boron trifluoride etherate under mild conditions. Initially, we have attempted the coupling of cyclohexanecarboxaldehyde with *N*-tosylhomoallylic amine in the presence of 1.2 equiv of boron trifluoride etherate in benzene at room temperature. The reaction was complete in 10 h and the corresponding 4-aryl-2-cyclohexylpiperidine **3a** was obtained in 90% yield with trans-selectivity (Scheme 1).

The structures of products were established by various NMR experiments. The structure of **3a** shown in Figure 2 was deduced

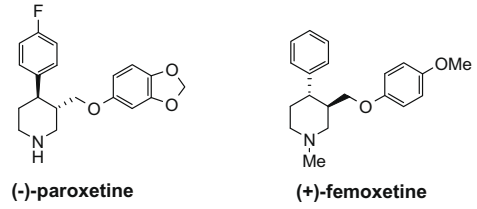
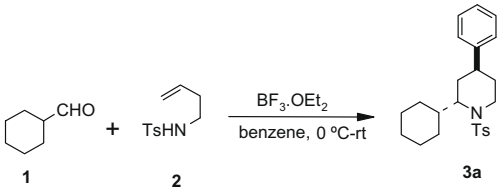


Figure 1. Some biologically active 4-arylpiperidine derivatives.



Scheme 1. Synthesis of 4-phenyl-2-cyclohexyl-piperidine **3a**.

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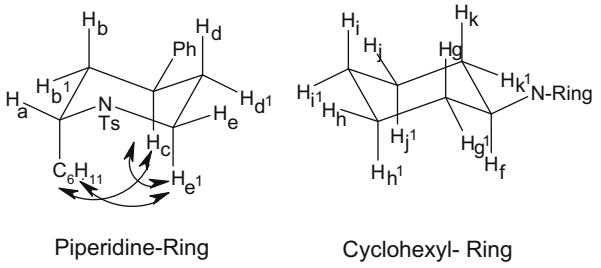
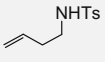
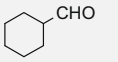
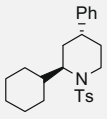
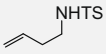
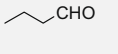
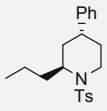
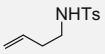
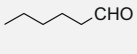
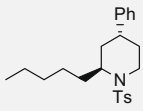
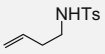
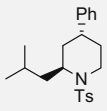
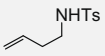
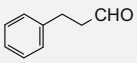
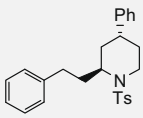
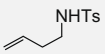
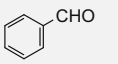
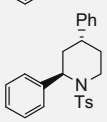
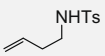
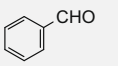
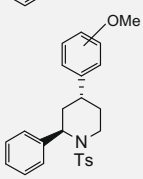
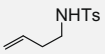
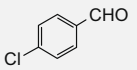
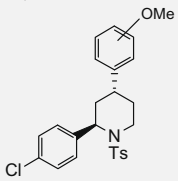
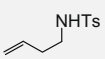
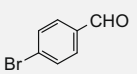
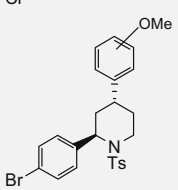


Figure 2. Characteristic NOE's of **3a**.

from the NMR data, where the two substituents, aryl and cyclohexyl, are trans to each other. The coupling constants observed for J_{Hc-Hb}, J_{Hc-Hd} and J_{Hd-He} were all greater than 10.0 Hz clearly indicating the *anti* configuration of these protons. Whereas small couplings were obtained for Ha with both Hb and Hb^1 showing that Ha is an equatorial proton, and clearly indicating the trans configuration for Ha and Hc. This was further confirmed by NOE's between (He^1–Hf), (Hc–Hf) and (Hc–He^1). Thus stereochemistry of the compound **3a** is assigned to be trans between the phenyl and cyclohexyl groups.

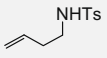
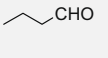
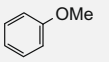
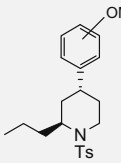
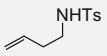
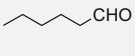
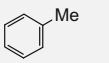
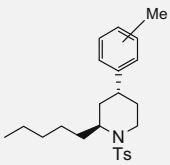
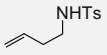
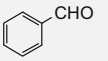
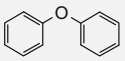
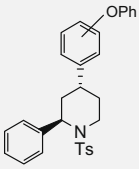
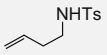
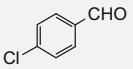
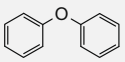
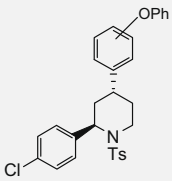
This result provided an incentive for the further study of reactions with various aldehydes such as *n*-butanal, *n*-hexanal, isovaleraldehyde, hydrocinnamaldehyde and benzaldehyde. In all cases, the corresponding trans-2,4-disubstituted piperidines were obtained in good yields (Table 1, entries b–f). To extend the utility of this method, various arenes were systematically investigated under these reaction conditions. Interestingly, anisole gave *para* isomer **3g** (Table 1, entry g, Scheme 2) as a major product.

Table 1
$BF_3{\cdot}OEt_2$-promoted three-component synthesis of 4-arylpiperidines

Entry	Homoallyl amine	Aldehyde	Arene	Arylpiperidine[a]	Time (h)	Yield[b] (%)
a					10.0	90
b					9.5	85
c					11.0	86
d					10.5	86
e					10.0	87
f					18.0	80
g					15.0	79(1:9)[c]
h					16.0	70(1:9)[c]
i					16.0	65(1:9)[c]

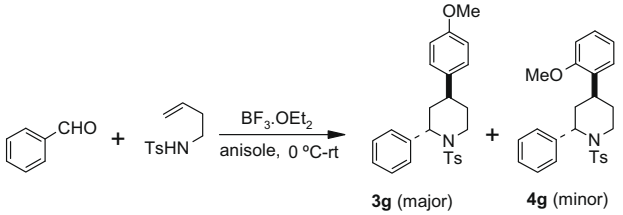
(*continued on next page*)

Table 1 (*continued*)

Entry	Homoallyl amine	Aldehyde	Arene	Arylpiperidine[a]	Time (h)	Yield[b] (%)
j					11.0	88(2:8)[c]
k					10.0	84(2:1)[c]
l					18.0	83(9:1)[c]
m					18.0	79(9:1)[c]

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to the pure products after chromatography.
[c] Inseperable mixtures of *ortho*/*para* isomers. Ratio was determined by ^{1}H NMR spectroscopy.

In this reaction, anisole acts as solvent and nucleophile. The product was obtained as a mixture of *ortho* and *para* isomers in a 1:9 ratio. These regioisomers could not be separated by column chromatography. In case of toluene and diphenyl ether, surprisingly, *ortho*-isomer was obtained as a major product. The reaction in toluene gave *ortho* and *para* isomers in a 2:1 **ratio** as an inseparable regioisomers. On the other hand the reaction in diphenyl ether gave *ortho* and *para* isomers in a 9:1 **ratio** as an inseparable regioisomers. The reactions proceeded effectively with aliphatic as well as aromatic aldehydes. Both activated and unactivated arenes also participated well in this reaction. To optimize the reaction conditions, we have performed the reaction with various amounts of $BF_3{\cdot}OEt_2$ ranging from 10 mol % to stoichiometric. However, the best results were obtained with 1.2 equiv of $BF_3{\cdot}OEt_2$. In all cases, the reactions are highly stereoselective affording trans-2,4-disubstituted piperidines exclusively. It is important to mention that no *N*-tosyl deprotection was observed during the aza-Prins cyclization. In the absence of boron triflouride etherate, no reaction was observed even in refluxing arene. The formation of the products may be explained by initial aminal formation and a subsequent Prins-type cyclization. The resulting carbocation might be trapped by arene to afford 4-arylpiperdine (Scheme 3). The scope and generality of this process is illustrated in Table 1.[12]



Scheme 2. Synthesis of 4-anisyl-2-phenylpiperidine **3g** and **4g**.

In summary, we have demonstrated for the first time the utility of aza-Prins-Friedel–Crafts reaction for producing structurally diversified piperidines. The use of $BF_3{\cdot}OEt_2$ makes this method simple, convenient and practical. We believe that these piperidine derivatives may find applications in drug discovery programmes.

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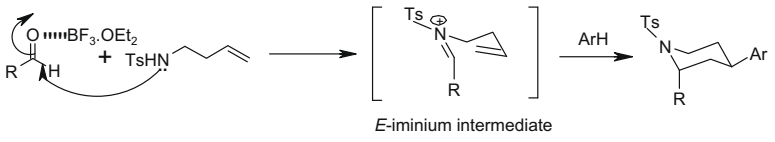

Scheme 3. A plausible reaction mechanism.

References and notes

1. (a) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486; (b) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300–1308.
2. (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131; (c) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187–191. and references therein.
3. For the Prins cyclisation, see for example (a) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432; (b) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739–747; (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed* **2005**, *44*, 3485–3488; (d) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett.* **2005**, *7*, 2683–3686; (e) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217; (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407–3410; (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919–3922; (h) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755–758; (i) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686; (j) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421; (k) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217–1219; (l) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022–3023; (m) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430; (n) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, *6*, 885–888; (o) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779–1783; (p) Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 8874–8877; (q) Yadav, J. S.; Reddy, B. V. S.; Aravind, S.; Narayana Kumar, G. G. K. S.; Madhavi, C.; Kunwar, A. C. *Tetrahedron* **2008**, *64*, 3025–3031; (r) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Aravind, S. *Synthesis* **2008**, *48*, 395–398.
4. (a) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padrón, J. L. *Org. Lett.* **2006**, *8*, 3837–3840; (b) Murty, M. S . R.; Ram, K. R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 1141–1145; (c) Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Narayana Kumar, G. G. K. S.; Aravind, S.; Kunwar, A. C.; Madavi, C. *Tetrahedron Lett.* **2008**, *49*, 3330–3334; (d) Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Narayana Kumar, G. G. K. S.; Naresh, P.; Jagadeesh, B. *Tetrahedron Lett.* **2009**, *50*, 1799–1802; (e) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876–3878.
5. Yamada, S.; Jahan, I. *Tetrahedron Lett.* **2005**, *46*, 8673–8676.
6. Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207.
7. Gershwin, M. E.; Terr, A. *Clin. Rev. Allergy Immunol.* **1996**, *14*, 241.
8. (a) Wenzel, B.; Sorger, D.; Heinitz, K.; Scheunemann, M.; Schliebs, R.; Steinbach, J.; Sabri, O. *Eur. J. Med. Chem.* **2005**, *40*, 1197–1205; (b) Guzikowski, A. P.; Tamiz, A. P.; Acosta-Burruel, M.; Hong-Bae, S.; Cai, S. X.; Hawkinson, J. E.; Keana, J. F.; Kesten, S. R.; Shipp, C. T.; Tran, M.; Whittermore, E. R.; Woodward, R. M.; Wright, J. L.; Zhou, Z.-L. *J. Med. Chem.* **2000**, *43*, 984–994. and references therein.
9. (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989; (c) Buat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729; (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640; (f) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712; (g) Couty, F. *Amino Acids* **1999**, *16*, 297–320; (h) Alex Cortez, G.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4534–4538.
10. (a) Sabine, L.; Tim, D. *Synthesis* **2000**, 1781–1813; (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729; (c) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80.
11. (a) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205–2208; (b) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Reddy, M. G. *Tetrahedron Lett.* **2007**, *48*, 4903–4906; (c) Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A. R. *Tetrahedron* **2007**, *63*, 2689–2694; (d) Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 7155–7159.
12. *General procedure*: To a mixture of *N*-tosylhomoallylic amine (1.0 equiv), aldehyde (1.0 equiv) in arene (3 mL) was added boron trifluoride etherate (1.2 equiv) at 0 °C. Then temperature was slowly brought to rt. The reaction mixture was stirred at room temperature for a specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 0.5:9.5) gave the pure 4-aryl tetrahydropyridine. The products thus obtained were characterized by IR, NMR and mass spectroscopy. Spectral data for the selected products **3a**: 2-cyclohexyl-1-[(4-methylphenyl)sulfonyl]-4-phenylpiperidine: Liquid, IR (KBr): ν 3028, 2925, 2864, 1597, 1509, 1451, 1339, 1157, 1092, 1016, 933, 815, 735, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, 2H's, J = 8.2 Hz, Tosyl, protons), 7.32 (d, 2H's, J = 8.2 Hz, Tosyl, protons), 7.22 (m, 2H's, phenyl protons), 7.16 (m, 1H, phenyl proton), 6.91 (m, 2H's, phenyl protons), 3.93 (d, 1H, J = 14.8 Hz, H_e), 3.80 (dd, 1H, J = 4.8 Hz, 10.6 Hz, H_a), 3.13 (ddd, 1H, J = 2.8 Hz, 13.8 Hz, 14.8 Hz, H_e^1), 2.74 (tt, 1H, J = 3.4 Hz, 12.8 Hz, Hc), 2.44 (s, 3H's, tosyl CH_3), 1.92 (bd, 1H, J = 13.8 Hz, H_g^1), 1.84 (m, 1H, H_b^1), 1.80 (m, 3H's, H_f, H_j^1, H_i), 1.72 (m, 1H, H_k^1), 1.66 (m, 2H's, H_h), 1.54 (m, 1H, H_d^1), 1.36 (ddd, 1H, J = 5.1 Hz, 13.4 Hz, 13.4 Hz, H_b), 1.26 (m, 2H's, H_d, H_j), 1.17 (m, 2H's, H_h^1, H_i^1), 0.98 (m, 1H, H_g), 0.92 (ddd, 1H, J = 3.3 Hz, 12.2 Hz, 12.2 Hz, H_k). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 142.8, 139.2, 129.6, 128.4, 127.1, 126.6, 126.4, 58.6, 41.2, 36.3, 35.5, 31.6, 30.3, 30.1, 26.1, 21.5. LCMS: m/z (%): (M^++Na) 420. HRMS calcd for $C_{24}H_{31}NO_2SNa$: 420.1973. Found: 420.1979. Compound **3g**: 4-(4-methoxyphenyl)-2-phenyl-1-tosylpiperidine: Liquid, IR (KBr): ν 3028, 2926, 2856, 1733, 1605, 1512, 1451, 1336, 1302, 1250, 1157, 1092, 1037, 936, 817, 758, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 2H, J = 8.7 Hz), 7.32 (d, 2H, J = 8.7 Hz), 7.36–7.10 (m, 5H), 6.84 (d, 2H, J = 8.7 Hz), 6.72 (d, 2H, J = 8.7 Hz), 5.40 (d, 1H, J = 4.0 Hz), 3.97 (dd, 1H, J = 2.9, 14.6 Hz), 3.74 (s, 3H), 3.08 (ddd, 1H, J = 2.9, 14.6, 15.4 Hz), 2.61 (tt, 1H, J = 3.6, 12.4 Hz), 2.47 (s, 3H), 2.35 (br d, 1H, J = 13.9 Hz), 1.77 (dt, 1H, J = 5.1, 13.1 Hz), 1.57–1.48 (m 1H), 1.47–1.39 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 143.1, 138.5, 137.2, 129.7, 128.7, 128.5, 127.8, 127.4, 127.0, 126.7, 113.8, 55.4, 49.7, 41.8, 35.5, 34.4, 31.9, 21.5. LCMS: m/z (%): (M^++NH_4^+) 439. HRMS calcd for $C_{25}H_{31}N_2O_3S$: 439.2055. Found: 439.2046.