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A New Strategy for the Synthesis of Substituted Morpholines

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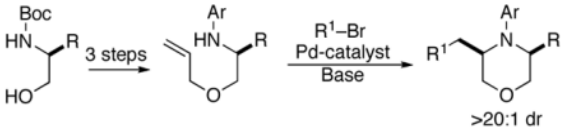
Abstract



A four-step synthesis of *cis*-3,5-disubstituted morpholines from enantiomerically pure amino alcohols is described. The key step in the synthesis is a Pd-catalyzed carboamination reaction between a substituted ethanolamine derivative and an aryl or alkenyl bromide. The morpholine products are generated as single stereoisomers in moderate to good yield. This strategy also provides access to fused bicyclic morpholines, as well as 2,3- and 2,5-disubstituted products.

In recent years drug discovery efforts have revealed several interesting biologically active compounds that contain C-substituted morpholine units.[1,2] However, despite the medicinal importance of these molecules, the development of new approaches to their synthesis remains relatively unexplored.[1,3] For example, few methods allow the preparation of 3,5-disubstituted morpholines,[4] and only two approaches to the stereoselective synthesis of *cis*-3,5-disubstituted derivatives have been described.[2a,5] Both of these strategies are limited in scope, as one affords symmetrically disubstituted (meso) products,[5] and the other was used only for the generation of one single compound (*cis*-3-carbomethoxy-5-allylmorpholine).[2a]

We recently reported a concise asymmetric synthesis of *cis*-2,6-disubstituted piperazines that involves Pd-catalyzed carboamination reactions of *N*-allyl ethylenediamine derivatives.[6,7] We felt that a similar strategy may be applied to the construction of 3,5-disubstituted morpholines. As shown in Scheme 1, enantiopure *N*-Boc amino alcohols (**1**) could be converted to *O*-allyl ethanolamines **2** using standard methods. These compounds would then be transformed to the desired heterocycles **3** through Pd-catalyzed coupling with an aryl or alkenyl halide.[8] This strategy should provide access to a broad array of enantiopure *cis*-3,5-disubstituted morpholines that are difficult to generate using existing methods.

The substrates for the Pd-catalyzed carboamination reactions were synthesized in three steps from commercially available starting materials **1a–e** as shown in Scheme 2. Treatment of the *N*-protected amino alcohols with NaH and allyl bromide afforded allyl ethers **4a–e**. Cleavage of the Boc-group followed by Pd-catalyzed *N*-arylation of the resulting amine trifluoroacetate salts provided **2a–f** in moderate to good yield.[9]

At the beginning of our studies we elected to examine the coupling of **2c** with 2-bromotoluene under reaction conditions that had proven optimal in related piperazine-forming

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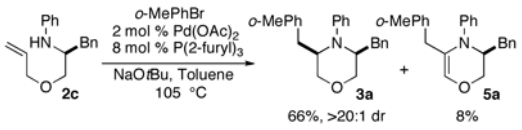
Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text (141 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

carboamination reactions.[6] As shown in eq 1, use of a catalyst composed of $Pd(OAc)_2$ and P(2-furyl)$_3$ provided **3a** in 66% yield. The main side product observed in this reaction was **5a**, although small amounts of several other unidentified side products were also detected. A survey of other ligands (e.g., PPh_3, Dpe-phos) did not provide improved results, and our initial choice of solvent (toluene) and base (NaO*t*Bu) also proved optimal. [10]

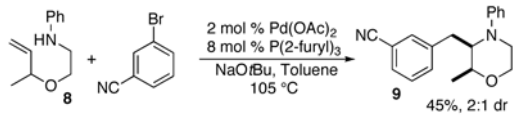


(1)

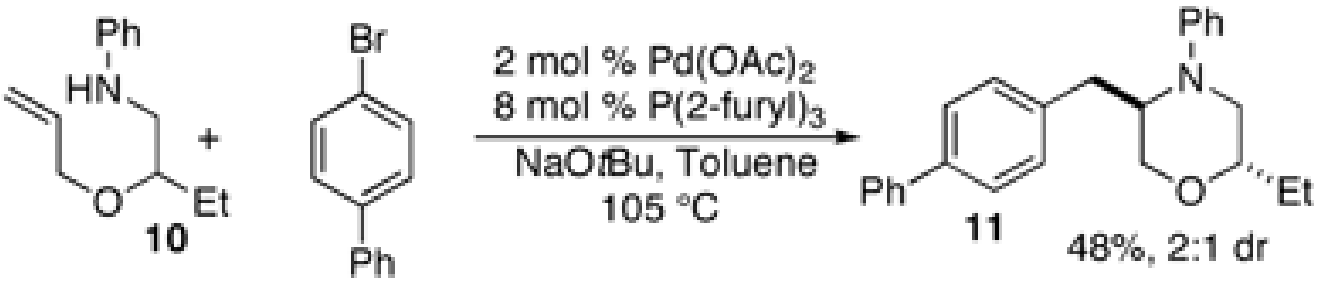
The results of our studies on the scope of 3,5-disubstituted morpholine-forming carboamination reactions are illustrated in Table 1. Several different 2-subsituted *O*-allylethanolamines were effectively converted to the desired heterocycles, including heteroatom-containing substrates derived from methionine (entry 7), serine (entry 8), and tryptophan (entry 9). Although the yields in these reactions were modest (46–66%),[11] the diastereoselectivities were uniformly high (> 20:1 dr). The presence of electron-neutral or slightly electron-deficient *N*-aryl groups on the substrates was tolerated. However, efforts to employ a morpholine precursor bearing an *N*-(*p*-methoxyphenyl) moiety led to a poor yield of **3d** due to competing *N*-arylation and Heck arylation of the substrate (entry 3).[12] Low yields were also obtained when starting materials with *N*-*p*-cyanophenyl groups were used, as competing Heck arylation of the substrate alkene group was again problematic. Similarly, efforts to couple *N*-Boc-protected substrate **4a** with 1-bromo-4-*tert*-butylbenzene afforded only a Heck arylation product.

In order to further explore the utility of this method for the synthesis of other substituted morpholines, reactions of several *N*-aryl ethanolamine derivatives with different substitution patterns were examined. As shown in Table 2, substrates **6a**–**d**, which were prepared by *O*-allylation of 2-(*N*-phenylamino)cyclohexanol or –cyclopentanol,[13] were coupled with aryl bromides using our optimized reaction conditions. These transformations afforded the desired bicyclic morpholines **7a**–**e** in moderate to good yields with excellent diastereoselectivities (>20:1 dr). We also successfully converted **8** and **10** into 2,3-disubstituted morpholine **9** and 2,5-disubstituted morpholine **11** (eq 2–3). However, both **9** and **11** were produced with only modest (2:1) diastereoselectivity.

The nature of the aryl halide coupling partner had a significant effect on the yield of the morpholine-forming reactions. Use of electron-rich or electron-neutral derivatives provided acceptable yields of the desired heterocycles. In addition, the coupling of **2a** with an alkenyl halide (Table 1, entry 2) was also successful. However, most attempts to employ electron-poor aryl bromides led to complex mixtures of products, although the carboamination reactions of **6c–d** with 4-bromobenzophenone (Table 2, entries 4–5) and of **8** with 3-bromobenzonitrile (eq 2) gave useful quantities of desired products. The coupling of **2c** with the sterically hindered 2-bromotoluene provided a 66% yield of **3a** (Table 1, entry 5), but 1-bromo-2-methylnaphthalene failed to react with **2c** under similar conditions.



(2)

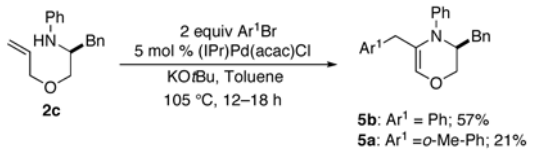


(3)

The mechanism of the morpholine-forming carboamination reactions is likely similar to that of related transformations that generate piperazines, pyrrolidines, and other nitrogen heterocycles.[6–8] As shown in Scheme 3, the key intermediate in the conversion of **2** to **3** is palladium(aryl)(amido) complex **12**, which is produced by oxidative addition of the aryl bromide to Pd(0) followed by Pd–N bond formation.[14] The relative stereochemistry of the substituted morpholine products is most consistent with a pathway involving *syn*-aminopalladation of **12** through a boat-like transition state (**13**) to afford **14**.[15] Reductive elimination from **14** would provide the *cis*-3,5-disubstituted morpholine products **3**. This mechanism also accounts for the conversion of **8** to *cis*-2,3-disubstituted morpholine **9**, and **10** to *trans*-2,5-disubstituted morpholine **11**. These products would arise from transition states **15** and **16**, respectively.[16]

As noted above in eq 1, we observed the formation of 3,4-dihydro-2*H*-1,4-oxazine **5a** as a side product in the Pd/P(2-furyl)$_3$ catalyzed coupling of **2c** with 2-bromotoluene. This compound is presumably generated via β-hydride elimination from intermediate **14** to provide **17**. This complex could then be transformed into unsaturated heterocycle **5a** by alkene dissociation and subsequent Heck arylation[17] of the resulting product **18** (Scheme 4).

We felt that it may be possible to optimize conditions so that unsaturated compounds such as **5a** would be generated as the major products in coupling reactions between **2** and aryl bromides. The mechanism outlined in Scheme 4 suggests that catalysts or ligands that either slow C–C bond-forming reductive elimination, facilitate β–hydride elimination, or both, may favor the conversion of **14** to **17**, which in turn leads to generation of **5**. Thus, we examined the use of catalysts supported by relatively electron rich monodentate ligands.[18] After some experimentation we discovered that use of (IPr)Pd(acac)Cl[19] for the coupling of bromobenzene with **2c** afforded **5b** in 57% yield (eq 4). However, the scope of this reaction is currently limited. For example, use of 2-bromotoluene as the electrophile afforded only 21% yield of **5a**. Purification of these products is also difficult due to their hydrolytic lability. Nonetheless, further optimization of conditions or use of this transformation in tandem/sequenced reactions may improve synthetic utility.



(4)

In conclusion, we have developed a concise asymmetric synthesis of *cis*-3,5-disubstituted morpholines from readily available enantiopure amino alcohol precursors. The modular nature of this approach permits variation of the morpholine substituents, and also provides access to fused-ring morpholine derivatives. In addition, we have demonstrated that modification of catalyst structure can lead to potentially useful 3,4-dihydro-2*H*-1,4-oxazine products. The strategies described above significantly expand the range of substituted morpholines that can be prepared in a concise, stereocontrolled manner.

Experimental Section

Representative Procedure for Synthesis of Morpholines via Pd-Catalyzed Carboamination

A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), P(2-furyl)$_3$ (9.3 mg, 0.04 mmol), and NaO*t*Bu (96.1 mg, 1.0 mmol). The tube was evacuated and backfilled with nitrogen, then the aryl bromide (1.0 mmol) and a solution of the amine substrate (0.50 mmol) in toluene (1.25 mL) were added to the Schlenk tube (aryl bromides that were solids at room temperature were added as solids following the addition of NaO*t*Bu). The mixture was heated to 105 °C with stirring until the substrate was consumed as judged by GC analysis (12–18 h). The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were concentrated in vacuo and the crude product was purified by flash chromatography on silica gel.

(−)-(3*S*,5*R*)-3-Benzyl-5-(2-methylbenzyl)-4-phenylmorpholine (3a)

The representative procedure was employed for the coupling of 2-bromotoluene with **2c**. This procedure gave the title compound (121 mg, 68%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D - 3.1$ (c = 1.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2 H), 7.31–7.14 (m, 7 H), 7.14–7.07 (m, 4 H), 7.07–7.00 (m, 1 H), 3.71 (dd, J = 5.4, 11.5 Hz, 1 H), 3.66–3.46 (m, 5 H), 2.81–2.66 (m, 4 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 138.9, 137.0, 136.5, 130.4, 129.6, 129.5, 129.1, 128.5, 126.3, 126.3, 125.9, 121.7, 119.6, 69.6, 69.6, 57.9, 56.9, 37.0, 33.6, 19.6; IR (film) 1598 cm^{-1}; MS (ESI) 358.2174 (358.2171 calcd for $C_{25}H_{27}NO$, M + H^+).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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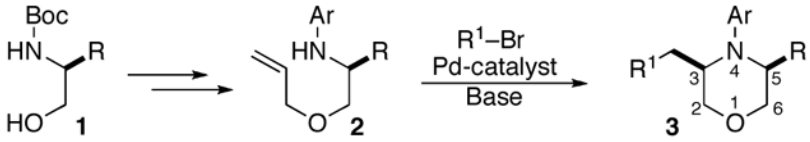
8. For reviews on Pd-catalyzed carboamination reactions, see: (a)Wolfe JP. Eur J Org Chem 2007:571. (b)Wolfe JP. Synlett 2008:2913.
9. For a representative reaction sequence, chiral HPLC analysis indicated complete retention of enantiomeric purity (99% ee) during the preparation of substrate **2a** from **1a**. The Pd-catalyzed carboamination reaction of **2a** to **3b** also proceeded with no erosion of ee.
10. Use of other ligands provided greater amounts of **5a**, led to formation of side products resulting from Heck arylation of the starting material, or both. See the Supporting Information for a table of results obtained with other phosphines.
11. Side products of general structure **5** were also observed in crude reaction mixtures. NMR analysis indicated these side products were formed as ca. 10–35% of the mixture. See the Supporting Information for further details.
12. In some instances side products resulting from sequential *N*-arylation and Heck arylation of the substrate were also isolated.
13. The known *trans*-2-(*N*-phenylamino)cycloalkanols were prepared in one step from aniline and cyclohexene oxide or cyclopentene oxide. See: (a)Wang Z, Cui Y-T, Xu Z-B, Qu J. J Org Chem 2008;73:2270. [PubMed: 18288864](b)Arai K, Lucarini S, Salter M, Ohta K, Yamashita Y, Kobayashi S. J Am Chem Soc 2007;129:8103. [PubMed: 17567008]The *cis*-2-(*N*-phenylamino) cycloalkanols were prepared in three steps from the epoxides. See the Supporting Information for further details.
14. (a) Barder TE, Buchwald SL. J Am Chem Soc 2007;129:12003. [PubMed: 17850080] (b) Yamashita M, Hartwig JF. J Am Chem Soc 2004;126:5344. [PubMed: 15113190]
15. Chair-like transition states for intramolecular *syn*-aminopalladation reactions that generate six-membered rings appear to be less favorable than boat-like transition states due to poor overlap between the alkene Π-system and the Pd–N bond. For additional discussion of boat-like vs. chair-like transition states in Pd-catalyzed carboamination reactions that afford piperazine products, see reference 6b.
16. The modest diastereoselectivities observed in the reactions of **8** and **10** are presumably due to relatively small differences in the energies of transition states in which the substrate R-group is oriented in a psueduoaxial vs. pseudoequatorial position. For further discussion, see reference 6b.

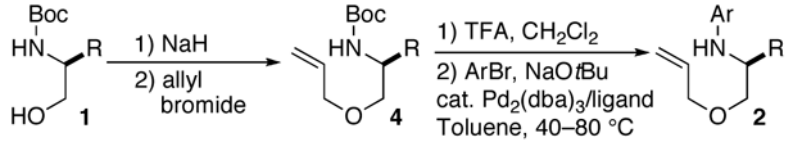
17. (a) Heck RF. Synlett 2006:2855.Beller, M.; Zapf, A.; Reirmeier, TH. Transition Metals for Organic Synthesis. Vol. 2. Beller, M.; Bolm, C., editors. Wiley-VCH: Weinheim, Germany; 2004. p. 271-305.

18. The rate of reductive elimination from Pd(II) decreases as ligand basicity increases and ligand size decreases. However, steric effects can outweigh electronic effects, as electron-rich ligands that are sterically bulky are known to promote reductive elimination. For reviews, see: (a)Christmann U, Vilar R. Angew Chem, Int Ed 2005;44:366.(b)Brown JM, Cooley NA. Chem Rev 1988;88:1031.

19. IPr = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene. Although this electron-rich ligand is also sterically bulky, it appears that ligand electronic properties play a larger role than steric properties in this particular reaction. For further discussion on the steric and electronic properties of NHC ligands, see: Diez-Gonzalez S, Nolan SP. Coord Chem Rev 2007;251:874.



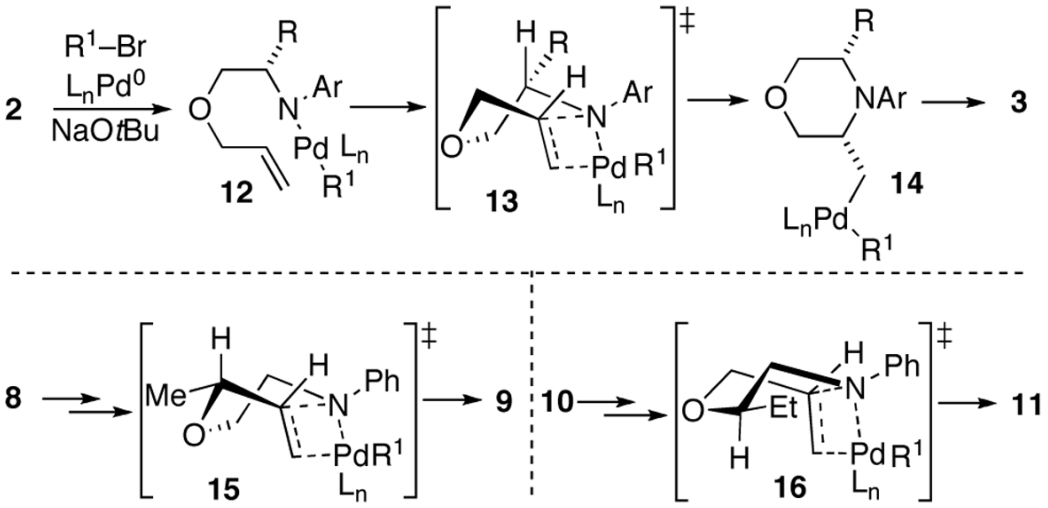
SCHEME 1. Synthetic Strategy



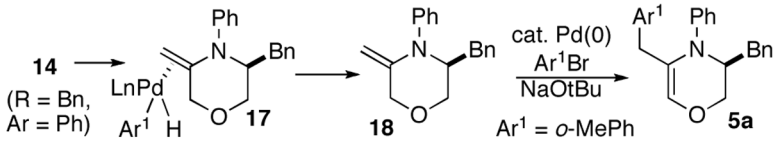
1a: R = Me	**4a**: 73%	**2a**: Ar = Ph (73%)[a]
1b: R = Bn	**4b**: 86%	**2b**: Ar = *p*-MeOPh (57%)[b]
		2c: Ar = Ph (59%)[c]
1c: R = $(CH_2)_2SMe$	**4c**: 59%	**2d**: Ar = Ph (71%)[a]
1d: R = CH_2OBn	**4d**: 73%	**2e**: Ar = *p*-Cl-Ph (59%)[c]
1e: R = CH_2[(*N*-Bn)-3-indolyl]	**4e**: 71%	**2f**: Ar = *m*-CN-Ph (60%)[c]

SCHEME 2. Synthesis of Substrates

[a] Ligand = (*o*-biphenyl)P*t*Bu_2. [b] Ligand = P(*t*Bu)$_3$•HBF_4. [c] Ligand = (±)-BINAP.



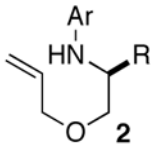
SCHEME 3. Mechanism and Stereochemistry

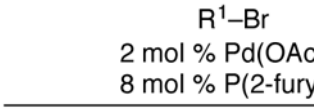


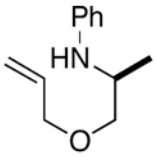
SCHEME 4. Formation of 3,4-dihydro-2*H*-1,4-oxazine 5a

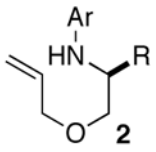
TABLE 1

Synthesis of *cis*-3,5-Disubstituted Morpholines[a]

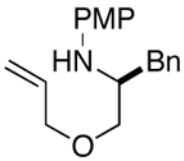
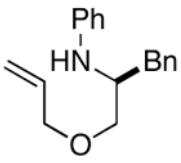


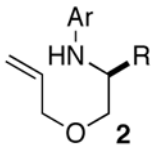


entry	substrate
1	 **2a**



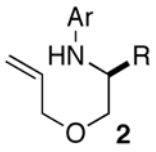
R^1–Br
2 mol % Pd(OAc
8 mol % P(2-fury
NaO*t*Bu, Toluene, 1
12–18 h

entry	substrate
2	**2a**
3	 **2b**
4	 **2c**

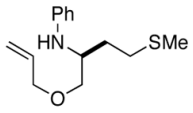
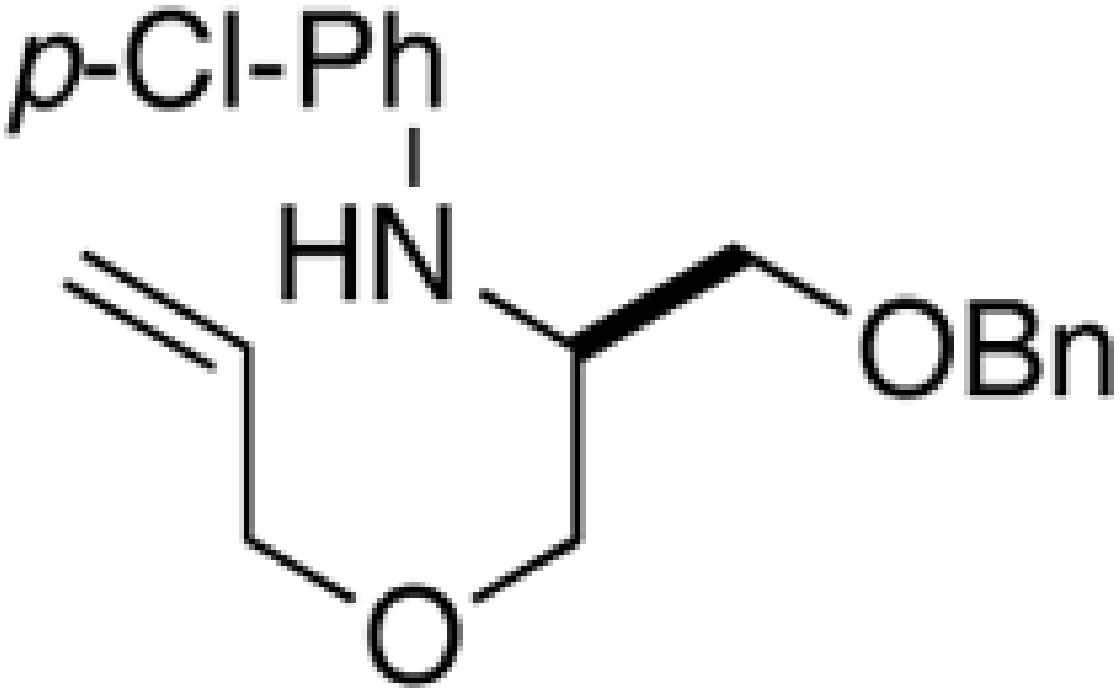


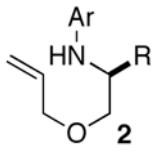
R^1–Br
2 mol % Pd(OAc
8 mol % P(2-fury
NaO*t*Bu, Toluene, 1
12–18 h

entry	substrate
5	**2c**
6	**2c**

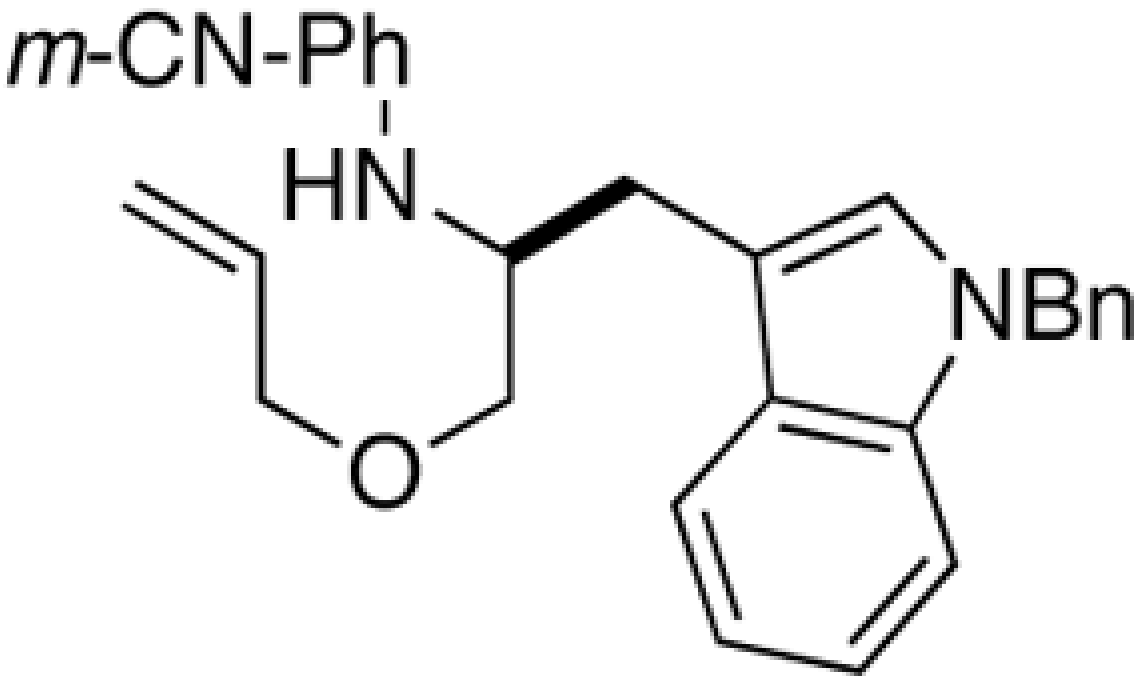


R^1–Br
2 mol % Pd(OAc
8 mol % P(2-fury
NaO*t*Bu, Toluene, 1
12–18 h

entry	substrate
7	 **2d**
8	 **2e**



R^1–Br
2 mol % Pd(OAc
8 mol % P(2-fury
NaO*t*Bu, Toluene, 1
12–18 h

entry	substrate
9	

2f

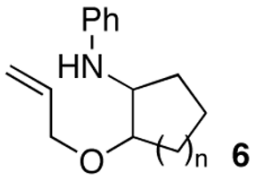
[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C.

[b] Isolated yield (average of two experiments). All products were formed with >20:1 dr as judged by ^1H NMR analysis of crude products prior to purification.

[c] The reaction was conducted using 4.0 equiv of β-bromostyrene, 4.0 equiv of NaO*t*Bu, 4 mol % $Pd(OAc)_2$ and 16 mol % P(2-furyl)$_3$.

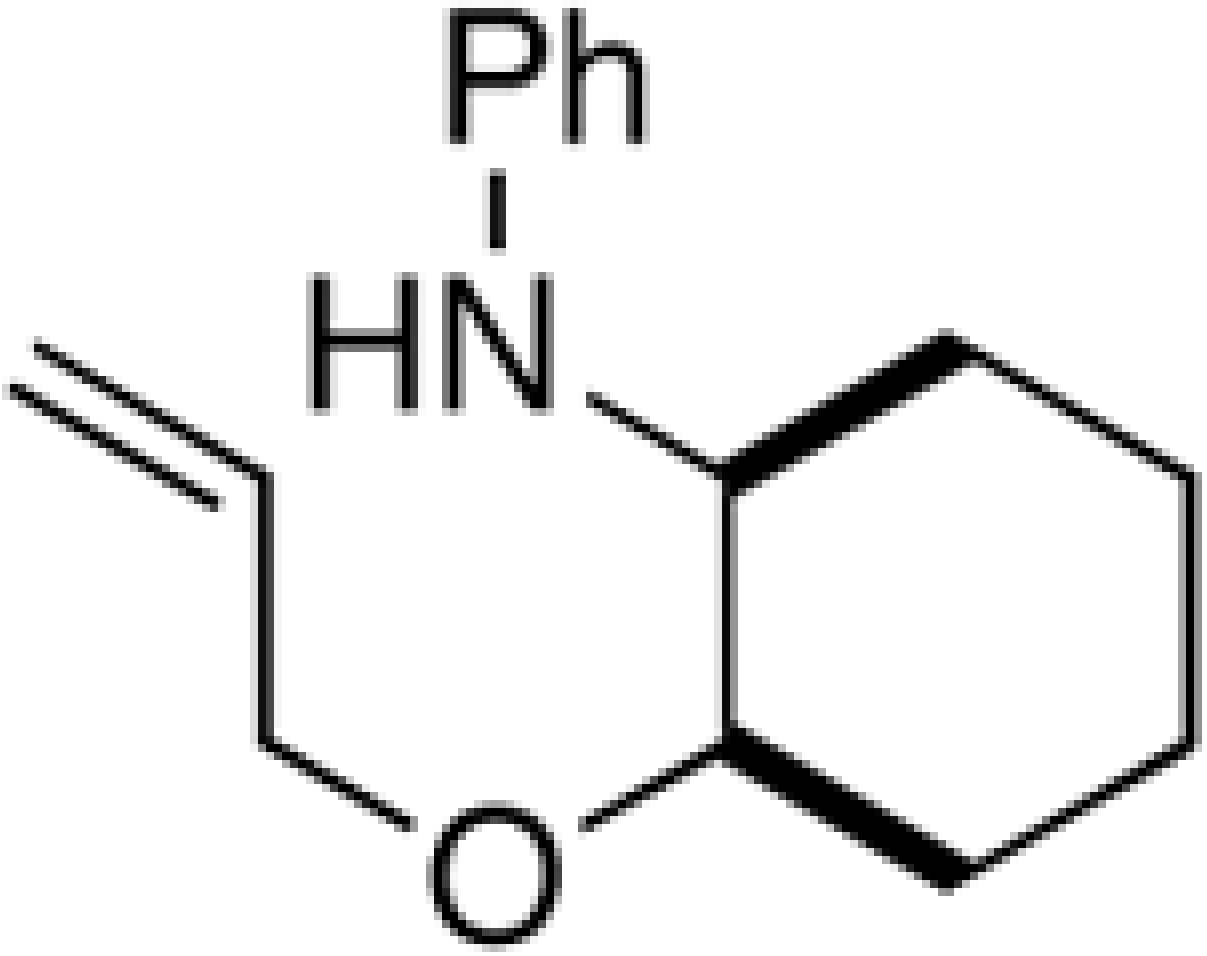
TABLE 2

Synthesis of Bicyclic Morpholines[a]

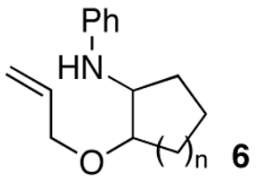


6

R[1]-
2 mol % P
8 mol % P
NaO*t*Bu, Tol
22

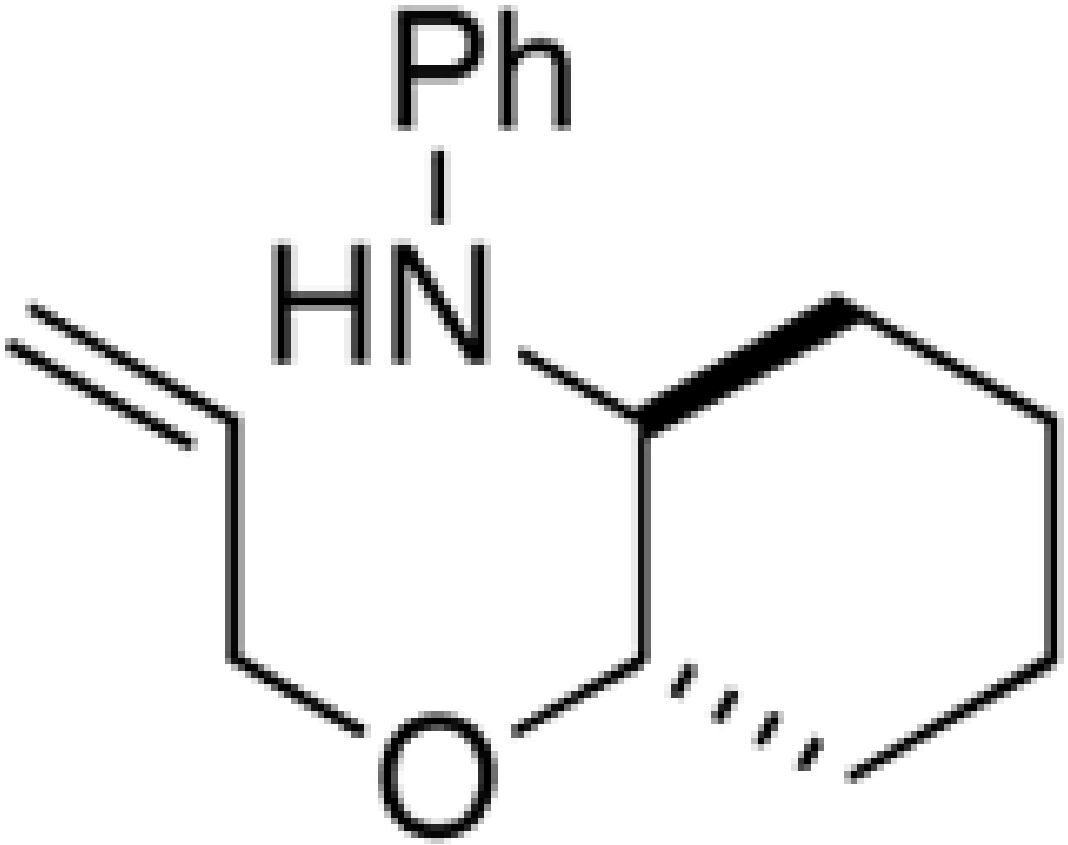
entry	substrate
1	

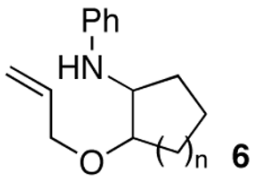
6a



6

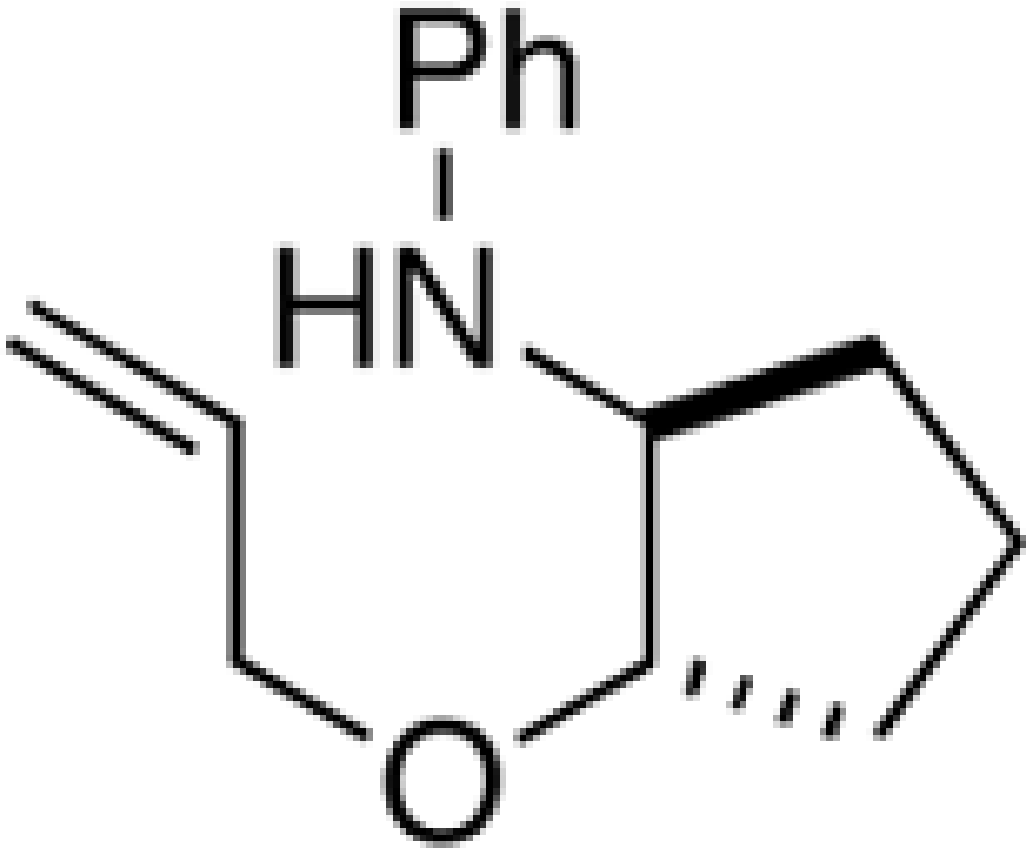
R1-
2 mol % P
8 mol % P
NaOtBu, Tol
22

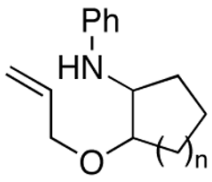
entry	substrate
2	 **6b**



6

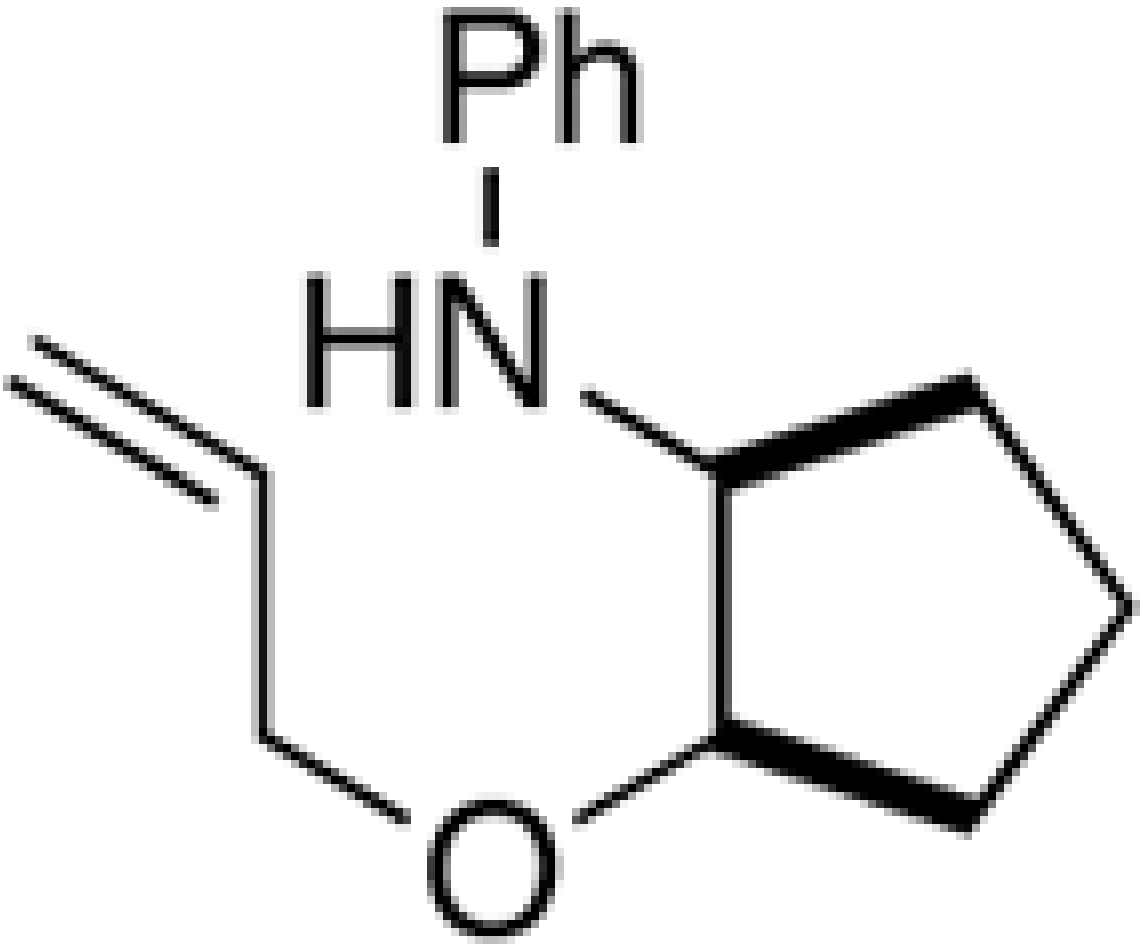
R1-
2 mol % P
8 mol % P
NaOtBu, Tol
22

entry	substrate
3	 **6c**
4	**6c**



6

R1-
2 mol % P
8 mol % P
NaOtBu, Tol
22

entry	substrate
5	

6d

[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0–2.7 equiv NaO*t*Bu, 2 mol %

[b] Isolated yield (average of $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.3 M), 105 °C. two or more experiments). All products were formed with >20:1 dr as judged by ^1H NMR analysis of crude products prior to purification.