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# An Efficient Assembly of Heterobenzazepine Ring Systems Utilizing an Intramolecular Palladium-Catalyzed Cycloamination

Brandon J. Margolis, Jacob J. Swidorski,[1] and Bruce N. Rogers*

*Medicinal Chemistry, Pharmacia Corporation, 301 Henrietta St., Kalamazoo, Michigan 49007*

*bruce.rogers@pharmacia.com*

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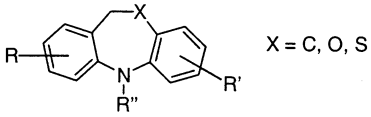
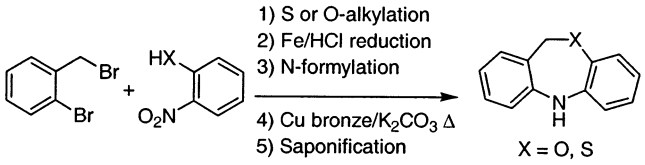
**Abstract:** Azaheterocyclic compounds are interesting and medicinally relevant targets. Herein we disclose an improved synthesis into the oxazepine and thiazepine ring systems. The key step in the synthesis exploits recent advancements in the palladium-catalyzed amination reaction, which was utilized to form the seven-membered rings. General conditions for this reaction were $Pd_2dba_3$, P(*t*-Bu)$_3$, NaO-*t*-Bu alone or with $K_2CO_3$, in toluene. The scope of the reaction was investigated, and has been shown to be effective on a variety of substrates as illustrated.

Tricyclic heterocycles are important scaffolds in medicinal chemistry.[2] Of particular interest are the azaheterocycles shown below. Numerous important therapeutic agents, including those with antiarrhythmic,[3] angiogenic,[4] antispasmotic,[5] and CNS[6] activity, contain these tricyclic core structures.

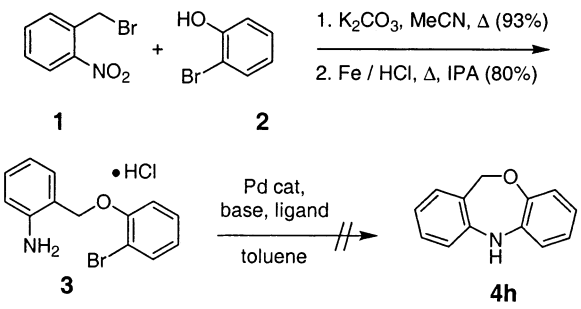



Yale and Sowinski disclosed the synthesis of compounds of this class in the mid-1960s using the 5-step route illustrated in Scheme 1.[6c] Key to this synthesis was a copper-catalyzed cyclization of a formyl-activated aniline. Interest in this template prompted us to evaluate an alternative synthesis of these azaheterocycles. Our approach was inspired by the recent advances in palladium-catalyzed amination reactions in the labs of Nishiyama, Buchwald, and Hartwig.[7] The application of our intramolecular cycloamination would circumvent the need to activate the aniline, thereby shortening the synthesis by two steps. Although Buchwald and co-workers have assembled a seven-membered ring via an intramolecular cycloamination,[8] to our knowledge this is the first application of this cyclization to form these important tricyclic oxazepine and thiazepine ring systems.

**SCHEME 1. Classical Assembly of Azaheterotricycles**




**SCHEME 2. Initial Strategy to Assemble the Oxazepine Core**




Due in part to the large number of commercially available bromo and chloro phenols, our initial approach to the preparation of these compounds was via the route outlined in Scheme 2. The sequence began with *O*-alkylation of 2-bromophenol (**2**) with 2-nitrobenzyl bromide (**1**). Iron reduction of the nitro group afforded the amine hydrochloride **3** in high yield. Initial attempts at the intramolecular amination on this substrate, using a variety of palladium catalysts and ligands,[7] were not fruitful.[9]

This failure was circumvented by exchanging the positions of the halogen and the amine by using compound **7h** (Scheme 3)**,** in which the aryl−halogen bond is on the opposite aromatic ring. Substrate **7h** was prepared by the same alkylation and reduction sequence used to prepare compound **3**. Our initial evaluation of the conditions for the only published intramolecular cycloamination to form seven-membered rings ((Pd(PPh$_3$)$_4$, NaO-*t*-Bu, toluene)[8] produced poor yields of the

(1) Participant in Pharmacia Corporation's Summer Intern Program.

(2) Baldessarini, R. J. In *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 10th ed., Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill: New York, 2001; pp 447−83.

(3) Katano, K.; Satoh, T.; Soneda, T.; Kamitoh, N.; Fujishima, K.; Hachisu, M. (Meiji Seika Kaisha, Ltd., Japan) European Patent Application 878475, 1998.

(4) Hansen, A. J.; Jorgensen, T. K.; Olsen, U. B. (Novo Nordisk A/S, Den.). PCT International Application 0032193, 2000.

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(7) For reviews of palladium-catalyzed aminations see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−18. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, 37, 2046−67. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C−N and C−O Bond Formation. In *Cross-Coupling Reaction: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry Ser. 219; Springer-Verlag: New York, NY, 2002; pp 131−209.

(8) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−46.

(9) Although there are examples in the literature where a sulfur or oxygen atom α to the site of insertion is a successful transformation, in our substrate these attempts provided only decomposition products and no tricyclic product. Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinki, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973−6.

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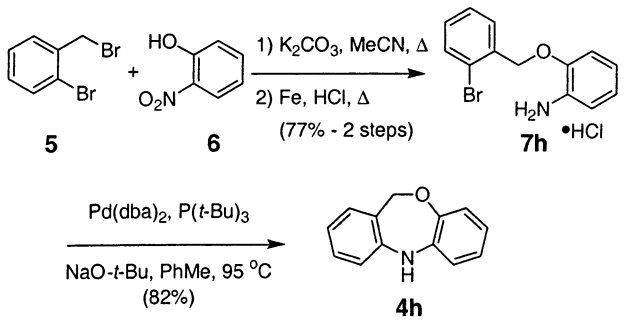
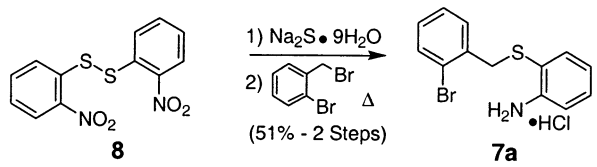
**SCHEME 3. Synthesis of the Oxazepine Utilizing Exchanged Coupling Partners**




**SCHEME 4. Synthesis of Thioether Cyclization Substrates**




desired product **4h**. However, application of more recently disclosed conditions, $Pd(dba)_2/P(t\text{-}Bu)_3/NaO\text{-}t\text{-}Bu$,[10] to substrate **7h** gave the desired cyclic product **4h**, in 82% yield. This catalyst system facilitates the intramolecular amination in yields competitive with the classic conditions to assemble this heterocycle, yet eliminates two synthetic steps.[11]

With the successful assembly of **4h**, we sought to prepare the thioether-linked compound **7a** depicted in Scheme 4 to evaluate initially the scope of the substrates for this reaction. Thioether **7a** was generated from an exhaustive reduction of disulfide **8**, followed directly by *S*-alkylation with 2-bromobenzyl bromide. The aminothiol intermediate that results from the reduction of **8** is very reactive, and forms the diamino disulfide upon exposure to atmospheric oxygen.[12] We found it convenient to generate the aminothiol intermediate in situ under an inert atmosphere, followed by addition of the benzyl bromide to the same pot. This procedure avoids oxidation of the resulting thiol intermediate to its disulfide, thus ensuring a consistent yield of **7a**.

Since we were only able to identify a single example of an intramolecular cycloamination in the literature to prepare seven-membered heterocyclic rings,[8] and the reported conditions did not efficiently provide access to the desired ring systems, we sought to explore further the scope of this reaction (Table 1). After completing a quick screen of several phosphine ligands,[13] we chose to pursue the optimization of the conditions reported by Hartwig et al. as they gave a cleaner reaction as judged by analytical HPLC.[10b] The choice to explore the thioether-linked substrate was largely due to the fact that we saw it as the more challenging system to assemble. In addition, to minimize steric and electronic effects, the unsubstituted aryl ring substrate **7a** was used for these studies.

Example 1 of Table 1 clearly indicates that the reaction worked under the reported conditions[8] but provided only a 22% isolated yield of **4a**. A brief solvent study utilizing $Pd(PPh_3)_4$ as a catalyst demonstrated that dioxane was a better solvent for this transformation affording a 32% yield,[14] but still, this catalyst generated a suboptimal yield compared to the classical conditions for assembly of this ring system established by Yale.[6a] We next applied other conditions reported to affect intermolecular aminations ($Pd(dba)_2$, $P(t\text{-}Bu)_3$, NaO-*t*-Bu in toluene), that in our initial evaluation effected the transformation in approximately 60% yield. Evaluation of solvents under these reaction conditions (Ex 2−7) shows that several solvents are effective, with the best outcomes obtained with toluene and dioxane. Catalyst loading appears quite important to achieve good yields in this transformation. Loadings of less than 10% were either ineffective or less effective.[14] The use of alternative bases in this reaction was also investigated, and a variety of bases, such as $Et_3N$, $K_2CO_3$, or $Cs_2CO_3$, did not activate the system.[14] The only base system that provided improved yields of **4a** was a combination of $K_2CO_3$ (2.0 equiv) and NaO-*t*-Bu (2.0 equiv), which gave a slight increase in yield and, in general, a cleaner reaction to purify (Ex 8). It is also notable that $Pd(dba)_2$ and $Pd_2(dba)_3$ are equally effective, and thus interchangeable, under these reaction conditions.[14]

Our final study evaluated ligands and palladium sources (Ex 9−14). In our hands, the first reported amination ligands such as $P(o\text{-tolyl})_3$ and $P(2\text{-furyl})_3$ (Ex 9 and 10) did not effect the transformation.[7d] More recently disclosed amination ligands such as BINAP[15] or dppf[16] (Ex 11 and 12) both provided cyclic product in a reasonable yield, but in the case of BINAP in particular, also produced a more complex reaction mixture thus complicating purification. Surprisingly, 2-(di-*tert*-butylphosphino)biphenyl (Ex 13) only produced a trace amount of cyclic product after >48 h at 95 °C.[17] Interestingly, palladium(II) acetate proved to be an inferior source of Pd(0) (Ex 14). Overall, the best conditions for this reaction were either $Pd(dba)_2$ or $Pd_2(dba)_3$ as a palladium source, $P(t\text{-}Bu)_3$ as the ligand, NaO-*t*-Bu alone or with $K_2CO_3$, in toluene or dioxane. It is noteworthy to mention that the free-base or salt of the starting aniline (**7a**) can be used with identical results in the cyclization.

In an attempt to demonstrate the generality of this reaction, additional substrates (Table 2) have been prepared according to the procedures outlined in Schemes 3 and 4, and have been elaborated into their respective cyclic analogues via the key palladium-catalyzed cycloamination reaction.

(10) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−20. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−80.

(11) The yield for the transformation of **7h** to **4h** by the 3-step method of Yale (see ref 6c) was 54%.

(12) Collings, A. J.; Morgan, K. J. *Tetrahedron* **1964**, *20*, 2167−75.

(13) The phosphine sources included di-*tert*-butylphosphinobiphenyl, BINAP, $P(t\text{-}Bu)_3$, and dicyclohexylphosphinobiphenyl.

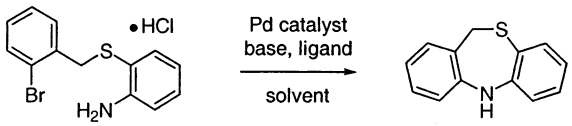
(14) For an expanded version of Table 1 with details of the optimization, see the Supporting Information.

(15) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−57. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−16.

(16) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−18.

(17) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−16. (b) Wolfe, J. P.; Hiroshi, T.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−74.

**TABLE 1. Optimization of the Intramolecular Palladium-Catalyzed Amination**

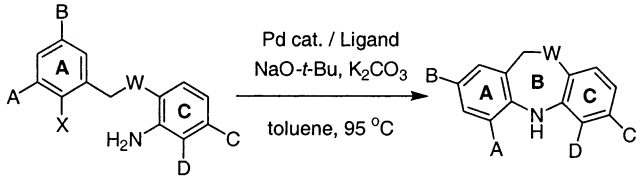



**7a** **4a**

| Ex | solvent | base | catalyst[b] | ligand | temp, °C | time,[c] h | yield,[d] % |
|---|---|---|---|---|---|---|---|
| 1[a] | toluene | NaO-*t*-Bu | $Pd(PPh_3)_4$ | none | 95 | 48 | 22 |
| 2 | toluene | NaO-*t*-Bu | $Pd(dba)_2$ | P(*t*-Bu)$_3$ | 95 | 2.5 | 60 |
| 3 | THF | NaO-*t*-Bu | $Pd(dba)_2$ | P(*t*-Bu)$_3$ | 75 | 4.5 | 53 |
| 4 | *o*-xylene | NaO-*t*-Bu | $Pd(dba)_2$ | P(*t*-Bu)$_3$ | 110 | 1 | 53 |
| 5 | dioxane | NaO-*t*-Bu | $Pd(dba)_2$ | P(*t*-Bu)$_3$ | 105 | 2 | 59 |
| 6 | DMF | NaO-*t*-Bu | $Pd(dba)_2$ | P(*t*-Bu)$_3$ | 160 | 0.5 | 10 |
| 7 | MeOH | NaO-*t*-Bu | $Pd_2(dba)_3$ | P(*t*-Bu)$_3$ | 95 | 24 | 13 |
| 8 | toluene | NaO-*t*-Bu/$K_2CO_3$ | $Pd_2(dba)_3$ | P(*t*-Bu)$_3$ | 95 | 2.5 | 65 |
| 9 | toluene | NaO-*t*-Bu | $Pd(dba)_2$ | P(*o*-tolyl)$_3$ | 95 | >48 | 0 |
| 10 | toluene | NaO-*t*-Bu | $Pd(dba)_2$ | P(2-furyl)$_3$ | 95 | >48 | 0 |
| 11 | toluene | NaO-*t*-Bu | $Pd(dba)_2$ | (±)-BINAP | 95 | 4 | 59 |
| 12 | toluene | NaO-*t*-Bu | $Pd(dba)_2$ | dppf | 95 | 4 | 49 |
| 13 | toluene | NaO-*t*-Bu | $Pd_2(dba)_3$ | DTBPBP | 95 | >48 | trace |
| 14 | toluene | NaO-*t*-Bu | $Pd(OAc)_2$ | P(*t*-Bu)$_3$ | 95 | >48 | 16 |

[a] Conditions as described by Buchwald.[8] [b] Unless otherwise noted, 10 mol % catalyst and ligand were used in each case. When $Pd_2dba_3$ was used, 5 mol % phosphine was used. [c] Reactions were run to completion as indicated by consumption of starting material by HPLC. [d] All yields are for chromatographed reactions. DTBPBP = 2-(di-*tert*-butylphosphino)biphenyl.

**TABLE 2. Substrate Generality of the Cyclization[a]**



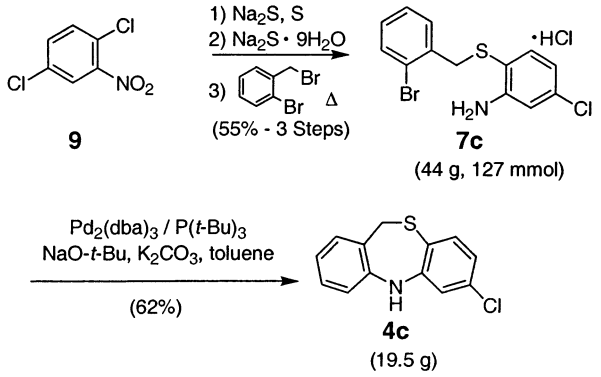

**7** **4**

| precursor | product | W | X | A | B | C | D | yield, % |
|---|---|---|---|---|---|---|---|---|
| **7a** | **4a** | S | Br | H | H | H | H | 67[b] |
| **7b** | **4b** | S | Br | Me | H | H | H | NR[b] |
| **7c** | **4c** | S | Br | H | H | Cl | H | 58/43[c] |
| **7d** | **4d** | S | Br | H | H | $CF_3$ | H | 70 |
| **7e** | **4e** | S | Br | H | F | H | H | 16[b]/46[c] |
| **7f** | **4f** | S | Br | H | OMe | H | H | 8[b] |
| **7g** | **4g** | O | Cl | H | H | H | H | 80 |
| **7h** | **4h** | O | Br | H | H | H | H | 87 |
| **7i** | **4i** | O | Br | H | H | H | Me | 65[b] |
| **7j** | **4j** | O | Br | H | H | Me | H | 87 |
| **7k** | **4k** | O | Br | H | CN | H | H | 79 |
| **7l** | **4l** | O | Br | H | F | H | H | 93[b] |
| **7m** | **4m** | O | Br | H | OMe | H | H | 69[b] |

[a] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 5 mol % P(*t*-Bu)$_3$, 2.0 equiv of NaO-*t*-Bu, 2.0 equiv of $K_2CO_3$, toluene (10 mL/mmol substrate), 95 °C for 2−6 h. [b] $Pd(dba)_2$ was used in place of $Pd_2(dba)_3$ and 10 mol % P(*t*-Bu)$_3$ was used. [c] 15 mol % (±)-BINAP was used in place of P(*t*-Bu)$_3$. NR = no reaction after 24 h.

In general, this chemistry worked very well to form the desired substituted oxazepine and thiazepine tricyclic cores (**4a**−**m**). Overall, the sulfur-containing thiazepine ring systems are more challenging and are lower yielding than the oxazepine system. Cyclizations to form the oxazepines followed the expected electronic trends (**7h**,**k**−**m**). Electron deficient and neutral substitution on the A ring para to the site of insertion were efficient transformations (**7h**,**k**,**l**), while yields in an electron-rich substrate were slightly lower (**7m**). Yields of the thiazepine

**SCHEME 5. Efficient Preparation of Thiazepine 4c on a 125-mmol Scale**




cyclizations also follow expected electronic trends (**7a**,**e**−**f**), albeit in lower yields. Both electron-rich and -deficient substitutions in the A ring were not well tolerated in terms of overall yields, but the general trend was similar to the oxazepine systems. In general, P(*t*-Bu)$_3$ was an effective source of phosphine for this transformation. For particularly problematic substrates such as **7e** in which the A ring contains an electron-withdrawing group, other sources of phosphine can be successfully employed. In general, substitution on the C ring was well tolerated under the reaction conditions to afford the desired products in good yield (**7c**,**d**,**i**,**j**). In evaluating steric effects, diortho-substitution on the A ring was not tolerated (**7b**) while diortho-substitution on the C ring was well tolerated (**7i**). Aryl chlorides were also demonstrated to be viable substrates for this reaction (**7g**).

In addition to possessing a robust reactivity with a variety of substrates, this chemistry is also scaleable as demonstrated by the efficient assembly of **4c** on a 125-mmol scale (Scheme 5). Disodium disulfide, generated in situ, reacts with **9** displacing the chloro group in the

2-position to form the intermediate disulfide.[18] Thioether **7c** was generated by exhaustive reduction, followed by direct *S*-alkylation with 2-bromobenzyl bromide to give **7c** in a good overall yield. The palladium-catalyzed cycloamination was performed on substrate **7c** on a 44-g scale, providing efficient access to the desired ring system **4c**. The overall yield from **9** to cyclic **4c** on this scale was competitive with the yield reported by Yale et al. through the copper bronze route, thereby shortening the synthesis of **4c** by two steps.[19]

In summary, an alternative synthesis of heterobenzazepine ring systems is disclosed. The key step in this synthesis exploits recent advancements in palladium catalysis to form oxazepine or thiazepine ring systems. Overall, the best conditions for this reaction were $Pd_2(dba)_3$ as a palladium source, P(*t*-Bu)$_3$ as the ligand, NaO-*t*-Bu alone or with $K_2CO_3$, in toluene. This reaction worked on a variety of substrates as shown in Table 2, and is scalable as demonstrated by the cyclization of **7c** on a 44-g scale.

## Experimental Section[20]

**General Procedure for the Synthesis of Thioether-Linked Acyclic Precursors: 2-[(2-Bromobenzyl)thio]aniline Hydrochloride (7a).**[6a] To 2-nitrophenyl disulfide (6.0 g, 19.5 mmol) was added a solution of sodium sulfide nonahydrate (15.0 g, 62 mmol) in $H_2O$ (200 mL). The resulting yellow suspension was heated at reflux for 1 h, and then cooled in an ice bath. A solution of 2-bromobenzyl bromide (10.2 g, 41 mmol) in THF (150 mL) was slowly added, and the resulting biphasic mixture was heated at reflux for 1 h. The mixture was cooled and diluted with EtOAc, and the phases were separated. The basic aqueous phase was extracted with EtOAc, and the combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated to give an oil that was taken-up in MeOH and $Et_2O$. The hydrochloride salt was prepared by treatment with 2.0 N HCl in $Et_2O$ followed by crystallization from MeOH and $Et_2O$ to give a white solid (6.6 g, 51%): mp 189−193 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.61 (dd, $J$ = 1, 8 Hz, 1 H), 7.26−7.09 (m, 5 H), 6.99 (d, $J$ = 8 Hz, 1 H), 6.64 (m, 1 H), 4.07 (s, 2 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 137.6, 137.2, 134.3, 134.2, 132.6, 131.2, 130.7, 130.5, 130.3, 128.9, 125.7, 124.7, 41.4. Anal. Calcd for $C_{13}H_{12}BrNS\cdot HCl$: C, 47.22; H, 3.96; N, 4.24. Found: C, 47.03; H, 4.00; N, 4.17.

**General Procedure for the Cycloamination of Thioethers: 5,11-Dihydrodibenzo[*b,e*][1,4]thiazepine (4a).**[6a] An oven-dried 40-mL vial containing two 6-mm glass beads was charged with a mixture of **7a** (250 mg, 0.76 mmol), NaO-*t*-Bu (163 mg, 1.7 mmol), $K_2CO_3$ (235 mg, 1.7 mmol), and Pd(dba)$_2$ (49 mg, 8.5 $\mu$mol). After the air atomosphere was replaced with argon, toluene (9 mL) was added, followed by P(*t*-Bu)$_3$ (20 mg, 9.8 $\mu$mol). The resulting purple mixture was capped and placed on a shaker block heated to 95 °C. After 1 h, the reaction mixture was concentrated to dryness and absorbed to silica gel. Purification was carried out using silica gel chromatography and afforded the product as a pale brown solid (108 mg, 67%): $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.68 (s, 1 H), 7.15−7.01 (m, 6 H), 6.69−6.65 (m, 2 H), 3.98 (s, 2 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 144.2, 142.8, 131.9, 128.8, 128.3, 127.6, 127.4, 122.5, 119.7, 119.0, 118.3, 118.2, 38.4. Anal. Calcd for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 72.83; H, 5.35; N, 6.28.

**General Procedure for Preparation of Nitro Ethers: 2-Bromobenzyl 2-Nitrophenyl Ether.**[6c] To a flask containing 2-bromobenzyl bromide (10.0 g, 40 mmol), 2-nitrophenol (5.3 g, 38 mmol), and $K_2CO_3$ (13.1 g, 95 mmol) was added $CH_3CN$ (75 mL). The solution was heated to 70 °C with an oil bath for 2 h, at which time the reaction was complete as shown by HPLC. The reaction was quenched with $H_2O$ and extracted with EtOAc. The combined organics were washed with brine and dried with $Na_2SO_4$, and the solvent was removed under vacuum. The resulting solid was crystallized from hexanes and EtOAc to afford an off-white solid (11.2 g, 96%): mp 92−93 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90 (dd, $J$ = 2, 8 Hz, 1 H), 7.69 (d, $J$ = 7 Hz, 1 H), 7.57 (dd, $J$ = 1, 8 Hz, 1 H), 7.55 (m, 1 H), 7.37 (t, $J$ = 8 Hz, 1 H), 7.20 (ddd, $J$ = 1, 8, 9 Hz, 1 H), 7.17 (t, $J$ = 9 Hz, 1 H), 7.07 (m, 1 H), 5.27 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.6, 139.9, 134.9, 134.3, 132.8, 129.5, 128.5, 127.9, 125.9, 121.4, 120.9, 114.9, 70.3. Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55. Found: C, 50.64; H, 3.11; N, 4.54.

**General Procedure for the Synthesis of Ether-Linked Acyclic Precursors: 2-[(2-Bromobenzyl)oxy]aniline Hydrochloride (7h).**[6c] 2-Bromobenzyl 2-nitrophenyl ether (5.0 g, 16.2 mmol) was dissolved in IPA (100 mL) and heated to 60 °C with an oil bath. To this solution was added HCl (2.5 mL, 12 N) followed by Fe (13.5 g, 242 mmol). The reaction was allowed to stir for 17 h at 60 °C, at which time it was filtered hot through a pad of Celite. The solution was reduced to about 20 mL under vacuum at which time HCl/$Et_2O$ was added until a ppt formed. The resulting off-white solid was recrystallized from MeOH and EtOAc to afford a white solid (4.4 g, 80%): mp 194−196 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.68 (t, $J$ = 10 Hz, 2 H), 7.46 (m, 3 H), 7.30 (m, 2 H), 7.13 (dt, $J$ = 2, 10 Hz, 1 H), 5.37 (s, 2 H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 152.9, 136.5, 134.0, 131.7, 131.2, 130.8, 129.0, 125.2, 123.9, 122.8, 120.8, 114.6, 71.5; % water (KF) 4.93. Anal. Calcd for $C_{13}H_{12}BrNO\cdot HCl\cdot H_2O$: C, 46.94; H, 4.55; N, 4.21. Found: C, 46.89; H, 4.57; N, 4.16.

**General Procedure for the Cycloamination of Cthers: 5,11-Dihydrodibenzo[*b,e*][1,4]oxazepine (4h).**[6c] An argon-purged vial was charged with **7h** (345 mg, 1.1 mmol), NaO-*t*-Bu (192 mg, 2.0 mmol), $K_2CO_3$ (276 mg, 2.0 mmol), and $Pd_2(dba)_3$ (92 mg, 0.1 mmol). Toluene (10 mL) was added followed by P(*t*-Bu)$_3$ (10 mg, 0.05 mmol). The reaction vessel was again purged with argon, and heated to 95 °C. After 2.5 h, the reaction was cooled, concentrated, absorbed onto silica gel, and purified using silica gel chromatography to give an off-white solid (186 mg, 86%): mp 122−123 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.18 (t, $J$ = 7 Hz, 1 H), 7.08 (d, $J$ = 7 Hz, 1 H), 6.96 (dd, $J$ = 1, 8 Hz, 1 H), 6.90 (t, $J$ = 7 Hz, 1 H), 6.75 (m, 4 H), 5.95 (br s, 1 H), 5.03 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 149.3, 143.7, 134.9, 129.5, 129.2, 126.0, 123.8, 121.9, 119.9, 119.6, 118.8, 117.1, 74.7. Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.94; H, 5.63; N, 7.10.

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**Supporting Information Available:** Expanded version of Table 1 for the optimization of the reaction including all examples mentioned in the related text; experimental procedures and characterization for the preparation of all examples listed in Table 2 (**7a**−**m** and **4a**−**m**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The yield for the transformation of **7c** to **4c** by the 3-step method of Yale (see the tables for yields in ref 6a) was 40%.

(20) For general experimental considerations see the Supporting Information.