Palladium-Catalyzed Intramolecular C−O Bond Formation

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Abstract: A number of oxygen heterocycles were synthesized using the palladium-catalyzed intramolecular etherification of aryl halides by employing di-*tert*-butylphosphinobiaryl ligands. The reaction proceeds under mild conditions using weak bases such as Cs_2CO_3 or K_3PO_4. A variety of functional groups are tolerated in the reaction, and enantioenriched alcohols can be coupled without erosion of optical purity. The mildness of the reaction conditions allows for the use of polyfunctionalized substrates. This method was used as the key step in the synthesis of MKC-242, an antidepressant currently in clinical trials. The synthesis of MKC-242 was achieved in 40% overall yield from commercially available sesamol and acrylonitrile.

Introduction

Aryl ethers and oxygen heterocycles are common structures in many pharmaceutically and agriculturally important compounds.[1,2] Traditional methods for the preparation of these compounds include the Williamson ether synthesis,[3] direct nucleophilic substitution reactions,[4] and Ullman-type couplings of alkoxides with aryl halides.[5,6,7] Each of these reactions, however, typically requires either highly reactive aryl halides, an excess of the alkoxide, or harsh conditions.

A promising transformation used to construct these heterocycles involves the intramolecular Cu-catalyzed C−O bond formation between aryl halides and alcohols. Zhu has reported the efficient copper-catalyzed conversion of 2′-chlorophenethyl alcohol to furnish dihydrobenzofuran.[7] Similarly, Fagan and Hauptman have described the copper-catalyzed cyclization of 2′-bromophenethyl alcohol and 3-(2′-bromophenyl)-propan-1-ol, using 2-aminopyridine as ligand to provide, respectively, dihydrobenzofuran or chromane.[6a] These reports, in combination, had a substrate scope that was limited to the three halo alcohols described.

The intramolecular[8] Pd-catalyzed C−O bond formation is a potentially attractive means to assemble oxygen heterocycles. In the first report in this area, we disclosed that *p*-tol-BINAP or DPPF could be used as supporting ligands for such C−O bond forming processes.[9] However, the method, in general, worked well only for tertiary alcohols. Cyclizations of secondary alcohols proceeded in low to moderate yields (32−66%) because of competitive formation of the reduced aldehyde **B**. This arises because of β-hydride elimination from palladacycle **A** being competitive with or faster than reductive elimination to form the desired product. Hartwig subsequently reported that using di-*tert*-butylphosphinopentaphenylcyclopentadienylferrocenyl as a ligand was effective for the cyclization of substrates bearing tertiary alcohols, but application of these conditions to primary and secondary alcohol substrates afforded the cyclized product in only moderate yields, presumably because of competitive β-hydride elimination.[8h]

Recent studies in our group have focused on extending the scope and utility of the intramolecular C−O bond forming reaction, and we have reported our initial findings as a Communication.[10] Herein, we report in full the results of this investigation as well as the application of this methodology in the synthesis of MKC-242, a benzodioxane antidepressant.

Results and Discussion

Initial studies focused on the development of a new ligand for palladium that would accelerate the desired reductive

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(2) For recent reports involving 1,4-benzoxazine derivatives, see: (a) Matsumoto, Y.; Uchida, W.; Nakahara, H.; Yanagisawa, I.; Shibanuma, T.; Nohira, H. *Chem. Pharm. Bull.* **2000**, *48*, 428. (b) Kuroita, T.; Marubayashi, N.; Sano, M.; Kanzaki, K.; Inaba, K.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 2051. (c) Largeron, M.; Lockhart, B.; Pfeiffer, B.; Fleury, M. *J. Med. Chem.* **1999**, *42*, 5043. (d) Buon, C.; Chacun-Lefevre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605. (e) Bourlot, A.; Sánchez, I.; Dureng, G.; Guillaumet, G.; Massingham, R.; Monteil, A.; Winslow, E.; Pujol, M. D.; Mérour, J. *J. Med. Chem.* **1998**, *41*, 3142.

(3) For a review, see: Feuer, H.; Hooz, J. In *Chemistry of the Ether Linkage*; Patai, S., Ed.; Wiley Interscience: New York, 1967; p 445.

(4) For a review, see: Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 423.

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(6) (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (b) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633. (c) Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374.

(7) (a) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011. (b) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5556. (c) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 312. (d) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.

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(9) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333.

(10) Torraca, K. E.; Kuwabe, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907.

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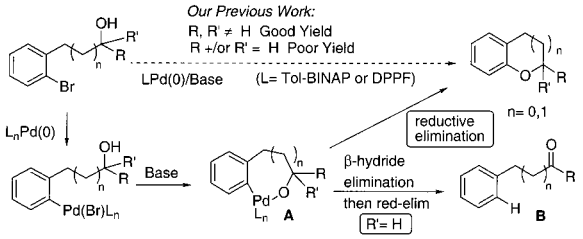
Scheme 1



elimination of intermediate **A** relative to β-hydride elimination (Scheme 1).[11] We have recently shown that bulky, electron-rich *o*-biaryl phosphines are effective in a variety of Pd-catalyzed cross-coupling reactions including amine arylation,[12] enolate arylation,[13] and Suzuki couplings.[14] After screening these and related ligands in the cyclization of 2-bromophenethyl alcohol, it was found that choice of ligand is key to the formation of the desired product in high yield.

The Pd complexes prepared from ligands **1** and **3** (Figure 1) display high catalytic activity to form 5-methyl chroman with minimal reduction (Table 1). Typically, these transformations required 24 h for complete cyclization. It is believed that such bulky ligands possessing the di-*tert*-butylphosphino moiety facilitate reductive elimination to release the steric strain of the palladium (II) aryl−alkoxide intermediate. Steric bulk has been shown to accelerate reductive elimination in other processes.[15]

As shown in Table 2, five-, six-, and seven-membered rings can be formed in good yield with no observed reduced byproduct being formed using this method. Primary as well as secondary alcohol substrates were efficiently cyclized. In general, primary alcohols were more reactive, and the desired transformation could be effected at slightly lower temperatures (24 h). Substrates bearing an electron-donating methoxy group *para* to the bromide are often difficult substrates for these palladium-catalyzed reactions; however, cyclization proceeded in good yield without formation of the reduced arene (entry 7). Both aryl chlorides and bromides could be cyclized using the **1**/Pd(OAc)$_2$ catalyst system, although the reactions of aryl bromides proceeded more rapidly and cleanly than those of the corresponding aryl chlorides. Binaphthyl ligand **1** proved to be most generally useful in these cyclizations, although, in some instances, commercially available phosphine **4** could be used to attain the desired products in comparable yields (entries 1, 3, 4, 7, 8). Ligand **4** proved to be ineffective in reactions involving aryl chlorides. It should be noted that dicyclohexyl-substituted ligand **7**, one of the most useful phosphines for the Pd-catalyzed amination, is ineffective for C−O bond formation.[12]

Application of this method for the formation of heterocycles containing multiple heteroatoms is important because those

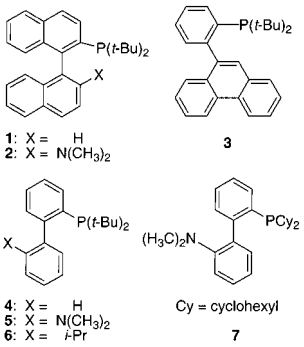
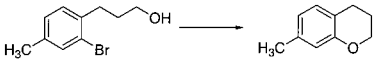


Figure 1. Bulky dialkylphosphinobiaryl ligands.

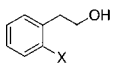
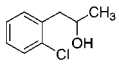
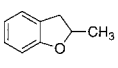
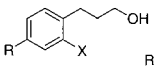
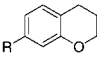
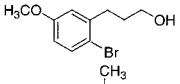
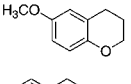
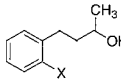
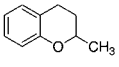
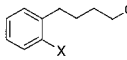
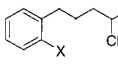
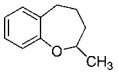
Table 1. Ligand Effects in the Pd-Catalyzed Etherification[a]



entry	L	yield (%)
1	**1**	81
2	**3**	81
3	**4**	51
4	**7**	<5

[a] Reaction conditions: 2 mol % Pd(OAc)$_2$, 2.5 mol % L, 1.5 equiv of Cs_2CO_3, toluene, 70 °C, 24 h.

Table 2. Palladium-Catalyzed Synthesis of Cyclic Aryl Ethers[a]

Entry	Substrate		mol% Pd[a]	T (°C), t (h)	Product	Yield (%)[b]
1		X = Br	2	50, 26		85 (82)
2		X = Cl	2	50,23		71
3			3	60, 26		71 (75)
4		R = H, X = Br	2	50, 21		85 (72)
5		R = H, X = Cl	2	65, 21		85
6		R = CH$_3$, X = Br	2	50, 24		83
7			2	50, 24		71
8		X = Br	3	65, 25		79 (83)
9		X = Cl	3	80, 24		78 (82)
10		X = Br	2	70, 23		73
11		X = Cl	2	70, 23		74
12		X = Br	3	80, 28		71
13		X = Cl	3	80, 28		65

[a] Reaction conditions: 2−3 mol % Pd(OAc)$_2$, 1.5 equiv of Cs_2CO_3, 2.5−3.5 mol % **1** in toluene. Yields in parentheses were obtained using **4** and were carried out at 80 °C. [b] Yields refer to average isolated yields of two separate experiments.

structures are widely found in nature and biologically active compounds.[1,2] While the construction of benzodioxanes and benzoxazines via palladium catalysis proved successful, the efficient coupling of these substrates proved to be highly ligand dependent (Table 3). The use of a mild base such as Cs_2CO_3 in these reactions allows for the use of an ester-containing aryl bromide (entry 3). Notably, the presence of an unprotected aniline NH does not inhibit the desired C−O bond formation, and no amination side products were observed (entry 4). A sulfur-containing substrate which would form 2,3-dihydrobenzo[1,4]oxathiine cyclized only in trace amounts; the analogous sulfoxide and sulfone were also poor substrates for this transformation. Typically, these transformations require 21−27 h to proceed to completion.

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(12) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158 and references therein. (d) Fox, J. M.; Buchwald, S. L. Unpublished results.

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(14) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem Soc.* **2000**, *122*, 12051 and references therein.

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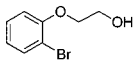
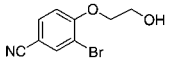
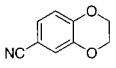
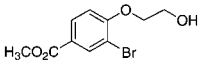
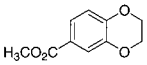
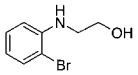
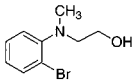
Table 3. Palladium-Catalyzed Synthesis of Benzodioxanes and Benzoxazines[a]

Entry	Substrate	L	T (°C), t (h)	Product	Yield (%)[b]
1		**5**	70, 40		81
2		**3**	50, 48		82
3		**3**	50, 40		67
4		**1**	70, 24		84
5		**3**	70, 48		74

[a] Reaction Conditions: 2 mol % $Pd(OAc)_2$, 1.5 equiv of Cs_2CO_3, 1.2 equiv of L, in toluene. [b] Yields refer to average isolated yields of two separate experiments.

Table 4. Palladium-Catalyzed Synthesis of an Optically Active Benzodioxane[a]

entry	ee (%)[a]	Pd precursor	L	base	*T* (°C), *t* (h)	yield (%)	ee (%)[b]
1[c]	96	$Pd(OAc)_2$	**1**	Cs_2CO_3	70, 48	66	94
2[c]	96	$Pd(OAc)_2$	**3**	Cs_2CO_3	70, 48	48	
3[c]	96	$Pd(OAc)_2$	**5**	Cs_2CO_3	70, 20	80	95
4[d]	90	$Pd_2(dba)_3$	**1**	*t*-BuONa	50, 24	89	90
5[d]	90	$Pd_2(dba)_3$	**5**	*t*-BuONa	50, 20	95	90
6[d]	90	$Pd_2(dba)_3$	**5**	*t*-BuOK	50, 20	33	
7[e]	90	$Pd_2(dba)_3$	**5**	Cs_2CO_3	70, 40	93	90

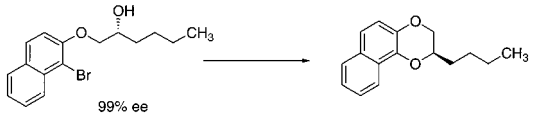
[a] Enantiomeric excess of starting material. [b] Enantiomeric excess of product. [c] Reaction run with 3 mol % $Pd(OAc)_2$, 3.5 mol % L, and 1.5 equiv of Cs_2CO_3 in toluene. [d] Reaction run with 1 mol % $Pd_2(dba)_3$, 2 mol % L, and 1.3 equiv of base. [e] Reaction run with 1 mol % $Pd_2(dba)_3$, 2 mol % L, and 1.5 equiv of Cs_2CO_3.

We next turned our attention toward the cyclization of optically active alcohols to the corresponding ethers to determine whether these substrates reacted with conservation of enantiomeric purity. As shown in Table 4, aryl bromides bearing a secondary alcohol were cyclized without erosion of optical purity using ligands **1** or **5**. Both $Pd(OAc)_2$ and $Pd_2(dba)_3$ were suitable palladium sources, although $Pd_2(dba)_3$ was preferable, particularly when NaO*t*-Bu was employed. Both Cs_2CO_3 and NaO*t*-Bu could function as the bases for this transformation. With NaO*t*-Bu, the reactions could be effected at a lower temperature (Table 4).

Surprisingly, the conditions that were successful with the 2-bromophenol-derived substrates were not applicable to the corresponding naphthalene compounds (Table 5). The combination of **5**/Pd_2dba_3 and either Cs_2CO_3 or NaO*t*-Bu as base resulted in low yields of the desired heterocycle (entries 1, 2). In this case, the combination of $Pd(OAc)_2$ and K_3PO_4 afforded better results. A catalyst derived from ligand **1** yielded the cyclized product with a slight loss of enantiomeric excess (entry 3); however, lowering the temperature (entry 4) or using ligand **2** (entry 5) led to a suppression of racemization.

The cyclization of the analogous aniline derivatives constitutes an efficient route to benzoxazines; our efforts to optimize such a transformation are summarized in Table 6. Using **1**/$Pd(OAc)_2$ as the precatalyst resulted in formation of the product with

Table 5. Cyclization of Optically Active Naphthalene-Derived Substrates[a]



entry	ee (%)[a]	Pd precursor	L	base	*T* (°C), *t* (h)	yield (%)	ee (%)[b]
1	96	$Pd_2(dba)_3$	**5**	*t*-BuONa	50, 48	24	
2[b]	96	$Pd_2(dba)_3$	**5**	Cs_2CO_3	70, 96	39	
3[c]	96	$Pd(OAc)_2$	**1**	K_3PO_4	70, 72	71	93
4[d]	90	$Pd(OAc)_2$	**1**	K_3PO_4	50, 72	82	99
5[c]	90	$Pd(OAc)_2$	**2**	K_3PO_4	70, 72	83	99

[a] Reaction conditions: 1 mol % $Pd_2(dba)_3$, 2.5 mol % L, 1.3 equiv of *t*-BuONa in toluene. [b] Reaction run with 1.5 equiv of Cs_2CO_3. [c] Reaction run with 3 mol % $Pd(OAc)_2$, 3.5 mol % L, 1.5 equiv of K_3PO_4.

Table 6. Pd-Catalyzed Synthesis of an Optically Active Benzoxazapine[a]

entry	Pd precursor	L	base	*T* (°C), *t* (h)	yield (%)	ee (%)
1	$Pd(OAc)_2$	**1**	*t*-BuONa	50, 20	82	58
2[b]	$Pd(OAc)_2$	**1**	*t*-BuONa	50, 20	94	98
3[b]	$Pd(OAc)_2$	**1**	*t*-BuONa	70, 16	86	80
4[b]	$Pd_2(dba)_3$	**2**	*t*-BuONa	50, 16	95	98
5[b]	$Pd_2(dba)_3$	**5**	*t*-BuONa	50, 20	95	99
6[c]	$Pd_2(dba)_3$	**5**	*t*-BuONa	50, 16	83	85
7[d]	$Pd_2(dba)_3$	**1**	Cs_2CO_3	70, 64	78[e]	94
8[d]	$Pd_2(dba)_3$	**6**	Cs_2CO_3	70, 64	82[e]	92

[a] Reaction conditions: 3 mol % $Pd(OAc)_2$, 3.5 mol % L, 1.3 equiv of *t*-BuONa in toluene. [b] Reaction run with 1.5 mol % $Pd_2(dba)_3$. [c] Reaction run with 1.0 mol % $Pd_2(dba)_3$ and 2.5 mol % L. [d] Reaction run with 1.5 equiv of Cs_2CO_3. [e] 8−14% reduced arene was observed.

diminished enantiomeric purity (entry 1). This problem was alleviated by changing the Pd source to $Pd_2(dba)_3$ (entry 2). Cyclizations that employed Cs_2CO_3 as base were plagued with arene reduction as a side reaction (entries 7 and 8). A catalyst derived from $Pd_2(dba)_3$ and ligand **5** with NaO*t*-Bu as base provided the best results; the use of temperatures higher than 50 °C or catalyst loadings less than 3 mol % Pd led to the formation of the desired product with decreased enantiomeric excess (entries 3, 6). The racemization presumably occurs via reversible β-hydride elimination analogous to the situation that was observed in related Pd-catalyzed C−N bond forming processes (Scheme 2).[16]

The analogous aryl chlorides were also prepared, and their cyclization reactions were studied (Table 7). The yields were comparable to those realized using the corresponding aryl bromides. Partial racemization (1−10% ee), unfortunately, could not be suppressed in the cases examined. In these reactions, K_3PO_4 proved to be the base of choice; reaction times were on the order of 40−60 h. In the case of the amine-substituted aryl chloride (entry 5), the addition of 2,6-dimethylphenol resulted in improved yields while preserving enantiomeric purity in the product. At this point, the role of the phenol is unclear; the phenol may act as a catalytic base or may also serve as a transient ligand for palladium. Analogous additive effects have been observed in Pd-catalyzed C−N bond-forming reactions.[8a,17]

(16) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
(17) Harris, M. C.; Buchwald, S. L. Unpublished results.

Scheme 2

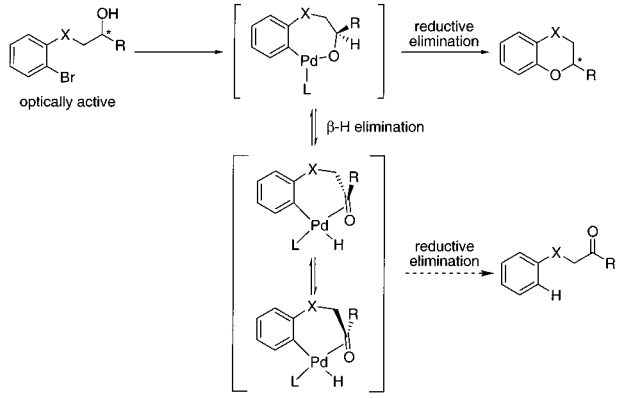
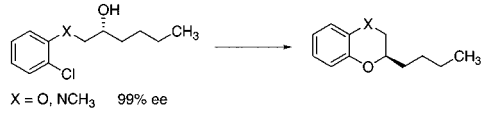


Table 7. Cyclization of Optically Active Aryl Chlorides[a]



entry	X	L	*T* (°C), *t* (h)	yield (%)	ee (%)
1	O	**1**	70, 96	92	90
2	O	**6**	50, 96	94	92
3	O	**6**	23, 96	88	93
4[b]	NCH_3	**5**	70, 64	71	98
5[c]	NCH_3	**5**	70, 44	95	99

[a] Reaction conditions: 3 mol % Pd $(OAc)_2$, 2.5 mol % L, 1.5 equiv of K_3PO_4 in toluene. [b] Reaction run with 5 mol % $Pd(OAc)_2$ and 6 mol % L. [c] Reaction run with 5 mol % $Pd(OAc)_2$, 6 mol % L, and 2 mol % 2,6-dimethylphenol.

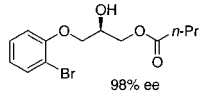
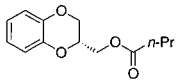
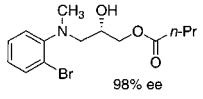
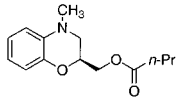
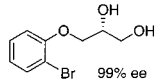
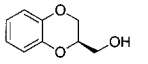
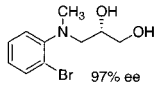
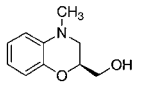
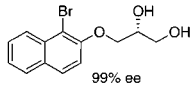
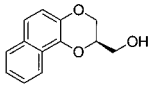
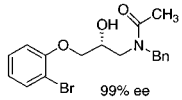
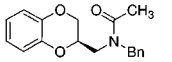
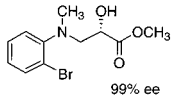
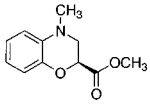
We next focused on the cyclization of aryl bromides in which the hydroxyl-bearing chain possessed additional functional groups (Table 8). Generally, 44−72 h was required to achieve complete cyclization under these conditions. The presence of ester groups was well tolerated under these reaction conditions (entries 1, 2, 7). Additionally, 1,2-diols were cleanly converted to the corresponding hydroxymethyl benzodioxanes without the need to protect the primary hydroxyl group. In no case was any of the seven-membered ring isomer observed (entries 3, 4, 5). Although 1,2-amino alcohols are poor substrates, the corresponding amide was cyclized in good yield without loss of optical purity (entry 6). Again, **1** is the most general ligand for these reactions, while **4** is effective in certain cases (entries 2, 4). Remarkably, an α-hydroxy ester was efficiently cyclized in good yield and without stereochemical erosion despite the relative sensitivity of the product toward base-mediated epimerization (entry 7). Whether the resistance of the product toward base-mediated epimerization is due to development of allylic strain or unwanted dipole−dipole interactions upon deprotonation is unknown.

Synthesis of MKC-242

To highlight the methodology described above, we undertook the synthesis of MKC-242, an antidepressant developed by Mitsubishi Chemical Co. that is currently in Phase II clinical trials.[18] The key feature of our synthesis involves the construction of the benzodioxane ring system from compound **11** via a Pd-catalyzed cyclization (Scheme 3).

The preparation of enantiomerically pure 2-substituted benzodioxanes typically involves the reaction of catechol and an optically active tosyl ester of glycerol acetonide prepared from mannitol.[19] These synthetic methods typically require a relatively large number of synthetic steps, however. Alternatively, resolutions of racemic 2-substituted benzodioxanes by recrystallizaton of diastereomeric derivatives or enzymatic resolution have been reported.[20,21] These methods are unattractive because 50% of the compound must be discarded, and additional transformations are necessary to recycle the undesired enantiomer.

Table 8. Pd-Catalyzed Cyclization of Functionalized Substrates[a]

Entry	Substrate	L	T (°C), t (h)	Product	Yield (%)	ee (%)
1		**1**	70, 44		84	98
2		**4**	50, 44		86	98
3		**1**	70, 72		72	99
4		**4**	70, 44		80	97
5		**1**	70, 44		86	99
6		**1**	70, 24		83	99
7		**1**	70, 48		80	99

[a] Reaction conditions: 3 mol % Pd $(OAc)_2$, 2.5 mol % L, 1.5 equiv of K_3PO_4 in toluene.

Our approach to the synthesis of benzodioxanes is relatively straightforward. In the case of MKC-242, epoxide **10** would be utilized as a chiral building block. This material can be easily prepared from racemic epichlorohydrin and 2-bromophenol using the chiral oligomeric (salen)-Co catalyst developed by Jacobsen.[22] The benzodioxane ring can then be constructed from aryl halide **11** via a Pd-catalyzed cyclization.

Our synthesis began with the addition of sesamol to acrylonitrile. Previously, a 30% yield was reported for this reaction using Triton B as base.[23] Using a catalytic amount (1 mol %) of Cs_2CO_3 improved the yield dramatically, presumably because of decreased decomposition of product **8** under these conditions.

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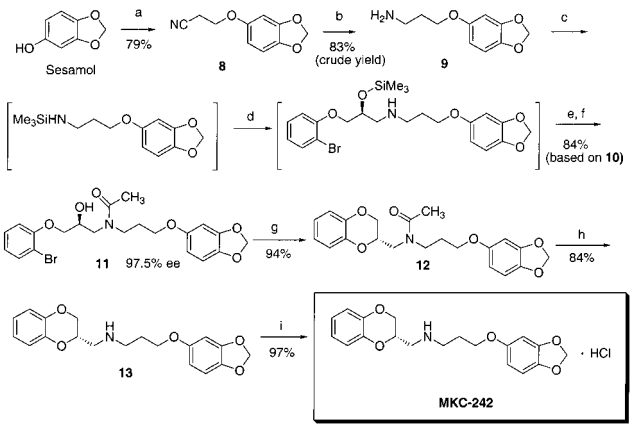
(22) Chiral epoxide **10** was kindly provided by Mr. Joseph M. Ready and Professor Eric N. Jacobsen (Harvard University). See: Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.

(23) Devakumar, C.; Saxena, V. S.; Mukerjee, S. K. *Agric. Biol. Chem.* **1985**, *49*, 725.

Scheme 3



[a] Acrylonitrile, Cs_2CO_3, THF. [b] BH_3−THF, THF. [c] *N*,*O*-Bis(trimethylsilyl)acetamide, THF. [d] (*S*)-2-(2-Bromo-phenoxy) methyloxirane (**10**), THF. [e] Ac_2O, Et_3N, THF. [f] 3 M aq NaOH, MeOH. [g] $Pd(OAc)_2$, **5**, K_3PO_4, toluene. [h] *n*-BuOH, 3 M HCl. [i] 1.1 M HCl−EtOH, EtOAc.

Borane reduction of nitrile **8** was carried out to afford amine **9**, which was utilized in the next step without further purification.[24]

Although there are many examples of epoxide opening reactions with amines, an excess of amine is typically employed to suppress amine dialkylation. Several epoxide opening reactions have been reported in which a slight excess of amine was used in the presence of Lewis acids such as $MgBr_2 \cdot OEt_2$ or $Y(OTf)_3$.[25,26] In these cases, sterically hindered amines, such as *tert*-butylamine, or secondary amines were good substrates for this selective transformation. However, these conditions were unsuccessful, presumably because amine **9** is relatively unhindered. Eventually, we found that by using a silyl-protected amine, as reported by Atkins, epoxide opening could be successfully carried out with *N*,*O*-bis(trimethylsilyl)acetamide as the silylating reagent at room temperature in THF.[27] After treatment of the reaction mixture with acetic anhydride and subsequent desilylation with methanolic NaOH, the desired amide **11** was obtained in a one-pot procedure from primary amine **9** in 84% yield (based on **10**).

Palladium-catalyzed C−O bond formation of **11** was performed according to our optimized conditions. Using $Pd(OAc)_2$ and **2**, desired product was isolated in 94% yield. Cyclizations using ligands **1** and **4** were also successful, giving 90 and 83% yields of the desired heterocycle, respectively. With all three ligands, no diminution of optical purity relative to the substrate was observed. Acetamide **12** was hydrolyzed with HCl in *n*-BuOH (84% yield), and treatment with HCl in ethanol afforded MKC-242. MKC-242 was synthesized from commercially available starting materials such as sesamol and acrylonitrile in ∼40% overall yield. The synthesis required nine steps which were carried out in six reaction vessels. The preparation of MKC-242, thus, demonstrates the potential utility and practicality of the intramolecular Pd-catalyzed C−O bond forming process in the preparation of medicinally interesting substances.

Conclusion

We have developed a palladium-catalyzed method for the efficient cyclization of halo alcohols. This improved catalyst system is effective in coupling primary and secondary alcohol substrates, and reactions involving aryl bromides bearing stereogenic centers at the carbinol carbon can be effected without racemization via reversible β-hydride elimination. The analogous aryl chloride substrates can also be efficiently cyclized with this catalyst; however, small amounts of epimerization (1−10%) may be observed. The mild reaction conditions required for this C−O bond-forming process allow for the presence of a variety of functional groups including alcohols, esters, and amides. The utility of this Pd-catalyzed etherification was highlighted as the key step in the synthesis of antidepressant MKC-242.

General Procedures for the Intramolecular C−O Bond Formation

General Procedure A. An oven-dried 15 mL resealable Schlenk tube was charged with $Pd(OAc)_2$ (3.4 mg, 15 μmol, 2 mol %), **1** (7.5 mg, 18.8 μmol, 2.5 mol %), and Cs_2CO_3 (365 mg, 1.12 mmol, 1.5 equiv). The Schlenk tube was evacuated and back-filled with argon and fitted with a rubber septum. Aryl halide (0.75 mmol) and toluene (1.5 mL) were added via syringe. The resealable Schlenk tube was then sealed under argon and placed in a preheated oil bath until the aryl halide had been consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with pentane (2 mL), and filtered through a pad of Celite. The resulting solution was purified by flash chromatography on silica gel with an eluent of 99:1 hexanes/ethyl acetate.

General Procedure B. An oven-dried 15 mL resealable Schlenk tube was charged with $Pd(OAc)_2$ (3.4 mg, 15 μmol, 3 mol %), **1** (17.5 μmol, 3.5 mol %), and K_3PO_4 (159 mg, 0.75 mmol, 1.5 equiv). The Schlenk tube was evacuated and back-filled with argon and fitted with a rubber septum. Aryl halide (0.5 mmol) and toluene (1.0 mL) were added via syringe. The Schlenk tube was then sealed with a Teflon screwcap under argon and placed on a preheated oil bath until the aryl halide had been consumed as judged by GC analysis. The reaction mixture was cooled to room temperature and diluted with Et_2O (5 mL). Water (5 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (37 pages, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA012046D

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