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Communications

Palladium(II)-Catalyzed Synthesis of Optically Active Tetrahydro-1,4-oxazine Derivatives[1]

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Summary: Three different types of morpholine derivatives 1–3 could be obtained from allylic amine substrates 4 in high yield and excellent diastereoselectivity by slight variation of the Pd(II)–Cu(II) reagents system.

The use of transition-metal complexes as reagents for the construction of various cyclic compounds has attracted the interest of synthetic chemists. Among the transition metals, palladium has been extensively used. In addition to the formation of carbocyclic compounds,[2] Pd-based methodology has also provided valuable synthetic routes to many kinds of heterocycles.[3] Oxygen heterocycles, such as furan and pyran,[4,5] have been obtained via an intramolecular oxypalladation reaction. There are also many examples of synthesis of five- and six-membered nitrogen heterocycles via intramolecular aminopalladation reactions[6,7] using aromatic amines or protected aliphatic amines (amides, carbamates, ureas, etc.). However, the synthesis of tetrahydro-1,4-oxazines (morpholines) has not been reported by this Pd-based methodology. On the other hand, many morpholine derivatives are important physiologically active compounds and medicinal agents.[8] Based on our study of the regiochemistry of heteroatom-directed Wacker-type reactions[9] and of asymmetric intermolecular

Scheme I

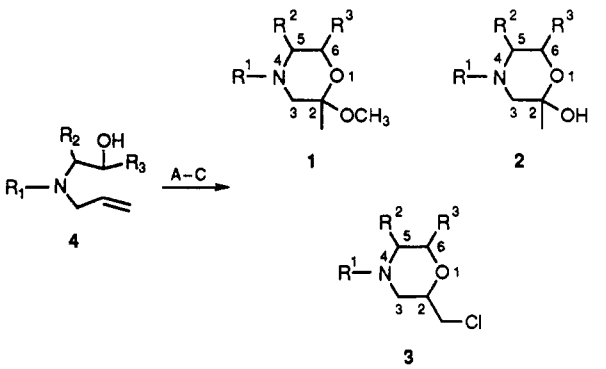

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Table I. Synthesis of Optically Active Morpholines

entry	substrates R¹	R²	R³	reactn[a] conditn	time (h)	products	yield, %[b]	%de[c]	config[d]
1	PhCHCH₃ (*S*)	H	H	A	36	**1a**	76.0	<1	
			4a						
2	PhCHCH₃ (*S*)	H	CH₃	A	36	**1b**	82.9	76	2*R*,6*S*,*S*
			4b						
3	PhCHCH₃ (*R*)	H	CH₃	A	36	**1c**	91.9	71.3	2*R*,6*S*,*R*
			4c						
4	Bn	H	CH₃	A	36	**1d**	95.7	91.3	2*R*,6*S*
			4d						
5	CH₃ (2*S*, 5*R*)	CH₃	Ph	A	48	**1e**	73.3	>99	2*S*,5*S*,6*R*
			4e						
6	PhCHCH₃ (*S*)	H	CH₃	B	24	**2b**	84.0	86.8	2*R*,6*S*,*S*
			4b						
7	Bn	H	CH₃	B	24	**2d**	78.0	91.3	2*R*,6*S*
			4d						
8	CH₃ (5*S*, 6*R*)	CH₃	Ph	B	48	**2e**	73.5	>99	2*S*,5*S*,6*R*
			4e						
9	PhCHCH₃ (*S*)	H	H	C	36	**3a**	73.0	<1	
			4a						
10	PhCHCH₃ (*S*)	H	CH₃	C	48	**3b**	70.3	83	2*S*,6*S*,*S*
			4b						
11	PhCHCH₃ (*R*)	H	CH₃	C	48	**3c**	74.2	73.1	2*S*,6*S*,*R*
			4c						
12	Bn	H	CH₃	C	48	**3d**	82.3	90.5	2*S*,6*S*
			4d						
13	CH₃ (5*S*, 6*R*)	CH₃	Ph	C	60	**3e**	73.3	>98	2*R*,5*S*,6*R*
			4e						
14	PhCHCH₃ (*R*)	H	CH₃	D	48	**3c**	80.4	82.3	2*S*,6*S*,*R*
			4c						
15	CH₃ (5*S*, 6*R*)	CH₃	Ph	D	72	**3e**	74.6	>98	2*R*,5*S*,6*R*
			4e						

[a] Reaction conditions A–C: see ref 11. Reaction condition D: 10 mol % Li_2PdCl_4/300 mol % $CuCl_2$/THF–CF_3COOH. [b] Isolated yield. [c] de value was determined by ^1H NMR spectroscopy. [d] Absolute configuration was determined by ^1H–^1H 2D NOESY spectroscopy.

oxypalladation reactions,[10] we have discovered that three types of morpholine products (**1–3**) can be obtained from an allylic amine substrate (**4**) by a slight variation of the Li_2PdCl_4(LTP)–$CuCl_2$ reagent system (A–C).

These reactions are depicted in Scheme I. Both Pd(II) and Cu(II) are necessary for carrying out these reactions (no intramolecular cyclization occurs using only Pd(II)). When MeOH is used as the nucleophile (condition A), methyl acetal **1** is the only product. When H_2O is used (condition B), hemiacetal **2** is obtained as the main product. These two processes proceed via Wacker-type reaction and only require a catalytic amount of Pd(II). For condition C, the reaction gives only product **3**, and a stoichiometric amount of Pd(II) is necessary. The chemical yields of these three types of reactions are good to excellent for synthesis of morpholines.[11] The results are listed in Table I.

The regiochemistry of the reactions presented in Scheme I is different from that of the Wacker-type reaction of allylic amines reported in our previous paper (nucleophilic attack at the terminal carbon atom).[9] The regiochemistry here is probably controlled by the ring size of the product. Thus, the nucleophile prefers to attack the inner carbon atom of the double bond in order to form a six-membered morpholine ring rather than to attack the external carbon to form a seven-membered heterocycle.

The stereochemical outcome of these reactions is noteworthy. (*R*)-(−)- or (*S*)-(+)-phenethylamine and/or (*S*)-(+)-lactic acid or (1*R*,2*S*)-(−)-ephedrine[12] have been used as chiral auxiliaries. The diastereoselectivities of these reactions are very high, with the diastereomeric excess (de) values ranging from 71% up to >99% (except entries 1 and 9). From entries 1–4 and entries 9–12, we may conclude that the chirality on the extraannular phenethyl group has no, or very little, effect on the newly formed C_2 chiral center. Substrates **4e** derived from (1*R*,2*S*)-(−)-ephedrine (entries 5, 8, and 13) show almost complete chiral induction; de values are 98% or higher in each of these three types of reactions (entries 5, 8, and 13), and also higher than those from **4d** derived from (*S*)-(+)-lactic acid (entries 4, 7, and 12). The latter gives de values ranging between 90% and 95%.

The absolute configurations of products **1–3** were determined by the ^1H–^1H 2D NOESY NMR spectroscopic method.[13] It seems that the absolute configuration of the newly formed chiral center C_2 is controlled by the C_6 chirality where the OH group is situated. 6*S* in the

(10) Lai, J.-Y.; Shi, X.-X.; Dai, L.-X. Submitted for publication.

(11) **General Experimental Procedure. Condition A.** Into a side-armed Pyrex tube with a magnetic stirring bar were placed LTP (26.2 mg, 0.1 mmol) and cupric chloride (403.5 mg, 3 mmol). The tube was evacuated on a vacuum line at 100 °C for 30 min. A solution of substrate (1 mmol, 0.1 M) in 10 mL of MeOH was added under argon. The mixture was stirred at rt and monitored by TLC. After the reaction was complete, excess Na_2S powder was added, and the mixture was stirred for 20 min and extracted with 4 × 50 mL of ether. The extracts were combined, washed with 10 mL of 10% NaOH solution and 10 mL water, and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure and the crude product was purified by preparative TLC. **Condition B.** Same as condition A, except 1 mL of THF and 10 mL of H_2O were used as solvent instead of MeOH in condition A; Oxygen-free and moisture-free conditions are not required. **Condition C.** Same as condition A, except THF was used as solvent instead of MeOH in condition A and 262.2 mg (1 mmol) of LTP (stoichiometric amount) was used. **Condition D.** Same as condition C, except a catalytic amount of LTP (26.2 mg, 0.1 mmol) was used and 0.5 mL of CF_3COOH was added to the THF.

(12) Chiral substrate **4a** was obtained by allylation of (*S*)-(+)-phenethylamine and followed by reaction with ethylene oxide; **4b** was obtained by acylation of (*S*)-(+)-phenethylamine with (*S*)-(+)-lactic acid, followed by $LiAlH_4$ reduction and allylation; **4c** was obtained using (*R*)-(−)-phenethylamine as the starting material; **4d** originated from benzylamine and (*S*)-(+)-lactic acid in a similar reaction sequence as that for **4b**; and **4e** was obtained by allylation of the (1*R*,2*S*)-ephedrine.

substrates derived from (*S*)-(+)-lactic acid induces new 2*R* chirality in the products **1** and **2**, and 2*S* chirality in products **3**, while 6*R* in the substrate derived from ephedrine induces 2*S* in products **1** and **2**, and 2*R* in product **3**. In other words, the methyl or phenyl group at C_6 of morpholine is always cis relative to the C_2 alkyl group. The above stereochemistry can be rationalized by conformational analysis, Figure 1. In the LTP–$CuCl_2$ medium, a bimetallic complex with a chloride bridge is usually found.[14] On the basis of the HSAB theory,[15] the substrate coordinated with the above bimetallic complex either as **5a** or **5b**. Intermediate **6** is unfavorable, since it has a 1,3-diaxial interaction between substituents at N and C_6. This kind of nonbounded diaxial interaction does not exist in intermediate **7**, and thus it is favored. From intermediate **7**, either the C–Pd bond will be cleaved by $CuCl_2$ to give product **3**[16] (path a) or in the presence of another nucleophile (conditions A and B), intermediate **7** will follow β-hydride elimination to give (π-olefin)Pd hydride intermediate **8**, which is attacked by a nucleophile following reductive elimination of palladium hydride to give product **1** or **2** (path b). In every case, we obtain a *cis*-2,6-diequatorial substituent product which is in accordance with all the informations from ^1H–^1H 2D NOESY NMR.[13]

We were pleased to find that the stoichiometric nature of condition C can be successfully changed to Pd(II)-catalyzed cyclization by adding a small amount of the nonnucleophilic, protic solvent CF_3COOH to the reaction system (condition D) (entries 14 and 15). Again in these cases, the yields are good and the diastereoselectivities are high. Noteworthy, almost all palladium(II)-catalyzed cyclizations of aminoalkenes in previous work were successful in using protected aliphatic amines as substrates. In this paper, the presence of CF_3COOH permitted the Pd(II)-catalyzed cyclization of alkeneylamine. The role of CF_3COOH and the extension of this type of catalytic palladation will be reported in a subsequent paper.

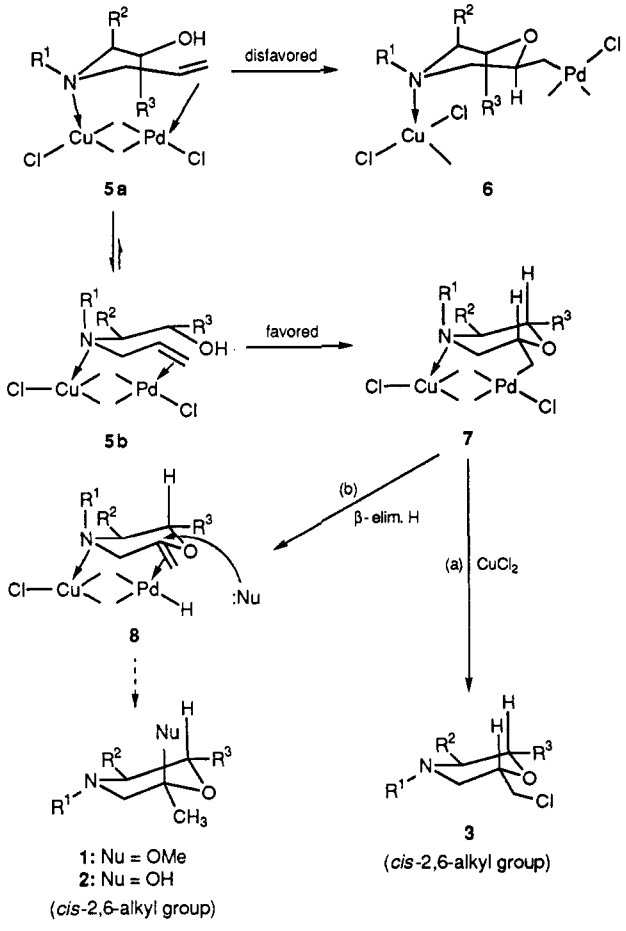
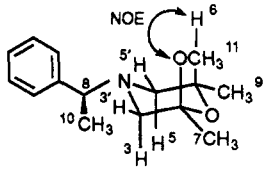
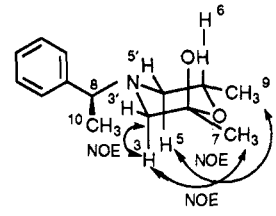
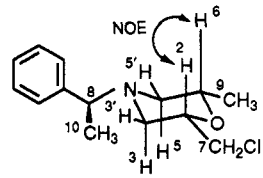


Figure 1.

(13) Complete NMR spectra and other data are in the supplementary material.







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Supplementary Material Available: Characterization data for products **1a–e**, **2b**, **2d**, **2e**, and **3a–e** and ^1H–^1H 2D NOESY data for **1b**, **2b**, and **3b** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.