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The First Practical Method of Selective Heteroatom-Directed Chlorohydroxylation[1]

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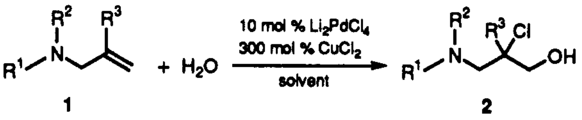
Summary: A new Pd(II)-catalyzed nucleophilic chlorohydroxylation reaction of allylic amines and sulfides was achieved, and the regioselective reaction gives high yields of the chlorohydrin products, which can be transformed into epoxy compounds or aziridine compounds by simple manipulations.

Transition metal-catalyzed asymmetric reactions of alkenes have been significant in modern synthetic organic chemistry. Asymmetric hydrogeneration,[2] asymmetric cyclopropanation,[3] asymmetric epoxidation,[4] and recently developed asymmetric dihydroxylation[5] are of great importance and have broad applicability. In this paper, we report a new Pd(II)-catalyzed chlorohydroxylation reaction of allylic amines and sulfides, which may be regarded as a new entry in the field of oxidative multifunctionalization of alkenes.

Chlorohydroxylation has usually been realized by electrophilic addition to alkenes. The electrophiles used have been either electrophilic chlorine species, such as hypochlorous acid,[6] alkyl hypochlorite,[7] chlorourea,[8] and chloramine T,[9] or electrophilic oxygen species, such as trimethylsilyl chloride–hydrogen peroxide[10] and *tert*-butyl hydroperoxide–titanium tetrachloride.[11] Oxidative halogenation by CrO_2Cl_2 has also been used.[12,13] However, the above reagents either give low selectivity or are hazardous. The chlorohydroxylation reaction of allylic amines and sulfides presented herein is different from any of the previously described methods for the preparation of chlorohydrin and avoids the drawbacks mentioned above. Our method involves a nucleophilic attack by water on a Pd(II)-activated alkene, as described in eqs 1 and 2.



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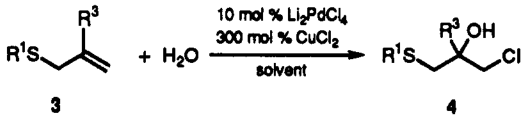

(2)

The Pd(II)-catalyzed chlorohydroxylation is operationally simple.[14] The reaction conditions are mild and convenient; no moisture-free and oxygen-free manipulations are involved. The reaction is different from our recently reported alkoxychlorination reaction,[15] in which an alcohol was used as the nucleophile and moisture-free reaction conditions were necessary. The exclusive regioselectivity of this reaction results in a single product in high yield. The reaction is applicable to primary, secondary, and tertiary allylic amines with yields ranging from 80 to 90%. Allylic sulfides are also good substrates with yields >70%.[16] The diastereoselectivity of the reaction of the (*R*)-(−)-phenethyl group-containing substrate is dependent on the temperature of the reaction; lower temperatures yield higher diastereomeric excess (de) values (compare entries 1–5 and 6–7 in Table I). Tertiary amines **1b** and **1c** show higher de values than do secondary amines **1a** and **1d**, with the highest de value being 76.5% for **1b** (entry 5, Table I). The diastereoselectivities with *gem*-disubstituted olefins are higher than those with monosubstituted olefins (compare entries 3–5 with entries

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(14) **Typical Procedure for Chlorohydroxylation.** Into a side-armed Pyrex tube containing a magnetic stirring bar were added 26.2 mg (0.1 mmol) of Li_2PdCl_4 and 403.5 mg (3 mmol) of $CuCl_2$. Substrate (1 mmol) in 10 mL of THF or 5 mL of DMF was added, and then 0.5 mL water was added. The mixture was stirred at the defined temperature and monitored by TLC. After the reaction was complete, excess Na_2S powder was added. The mixture was stirred for 30 min and extracted with 5 × 40-mL portions of ether. The combined extracts were washed twice with H_2O (5 mL), dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and purified by preparative TLC. If DMF is used as solvent, the combined extracts should be washed three times with H_2O (30 mL). If the products (such as **2a**, **2d**) are fairly water soluble, the combined H_2O washings should be back-extracted twice with ether (40 mL), and all ether extracts should be combined.

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(16) Approximately 10% benzylmercaptan is produced during the reaction.

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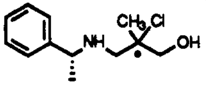
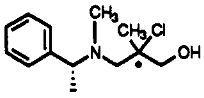
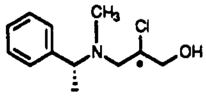
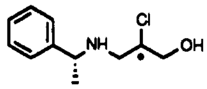
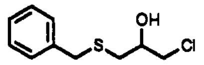
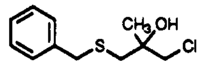
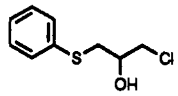
Table I. Chlorohydroxylation of Allylic Amines and Sulfides[a]

entry	substrates R^1	R^2	R^3	temp (°C)	solvent[b]	time (h)	yield[c]	% de[d]	product
1	PhCHCH$_3$	H (*R*)-1a	CH$_3$	50	THF	8	69.3[e]	30	 **2a**
2	PhCHCH$_3$	H (*R*)-1a	CH$_3$	50	THF	8	90.5	25	**2a**
3	PhCHCH$_3$	H (*R*)-1a	CH$_3$	15	THF	56	84.3	50	**2a**
4	PhCHCH$_3$	H (*R*)-1a	CH$_3$	−10	DMF	144	84.7	63	**2a**
5	PhCHCH$_3$	CH$_3$ (*R*)-1b	CH$_3$	−10	THF	120	86.6[f]	76.5	 **2b**
6	PhCHCH$_3$	CH$_3$ (*R*)-1c	H	20	THF	24	91.1	11	 **2c**
7	PhCHCH$_3$	CH$_3$ (*R*)-1c	H	−10	DMF	24	80.4	36.2	**2c**
8	PhCHCH$_3$	H (*R*)-1d	H	20	DMF	48	83.8	<1	 **2d**
9	H	H	H	20	THF	48	84[g]		 **2e**
10	Bn	3a	H	50	THF	24	73.2		 **4a**
11	Bn	3a	H	50	DMF	24	78.7		**4a**
12	Bn	3b	CH$_3$	50	DMF	48	72.6		 **4b**
13	Ph	3c	H	50	DMF	24	75.3		 **4c**

[a] Catalyst: 10 mol % Li$_2$PdCl$_4$/300 mol % CuCl$_2$. [b] Solvent: THF:H$_2$O = 10 mL:0.5 mL; DMF:H$_2$O = 5 mL:0.5 mL. [c] Isolated yield by preparative TLC. [d] De values were determined by 200- or 600-MHz ^{1}H NMR. [e] Catalyst: 10 mol % Li$_2$PdCl$_4$/300 mol % FeCl$_3$. [f] Some epoxy product was also obtained. [g] Product 2e was isolated as a N-tosylated epoxy compound after tosylation of the chlorohydrin product.

6–8 in Table I). Both Pd(II) and Cu(II) are indispensable in this reaction. Although FeCl$_3$ can be used instead of the cupric chloride, the yield is lower (compare entries 1 and 2 in Table I).

The regiochemistry with allyl sulfides is different from that with allylamines (eqs 1 and 2). The regioselectivity was established by reductive dechlorination of the chlorohydroxylated product.[17] The regioselectivity seems to be governed by the coordination of the heteroatom with the metal complex. According to the HSAB principle, N-atoms and S-atoms behave differently, in coordination to the Pd–Cu bimetallic complex linked with μ-chloride.[15,18] The regiochemistry of the reaction of allylamines is also noteworthy in that the hydroxyl group is added to the double bond in an anti-Markovnikoff fashion by means of the attack of water on the Pd(II)-activated double bond of allylamine. The reaction appears to be the first instance of hydration of olefins occurring in an anti-Markovnikoff way.[19]

In spite of the fact that chlorohydrins have been reported as components in complex product mixtures in some specific Wacker-type reactions,[20] these reactions have not been used as a general synthetic method for the preparation

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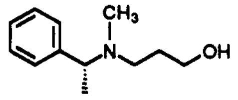
(17) Dechlorinated products 8 and 9 were obtained from the LiAlH$_4$ reductive dechlorination of 2c and 4a, respectively. ^{1}H NMR data are recorded in the supplementary material.



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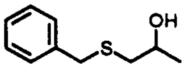

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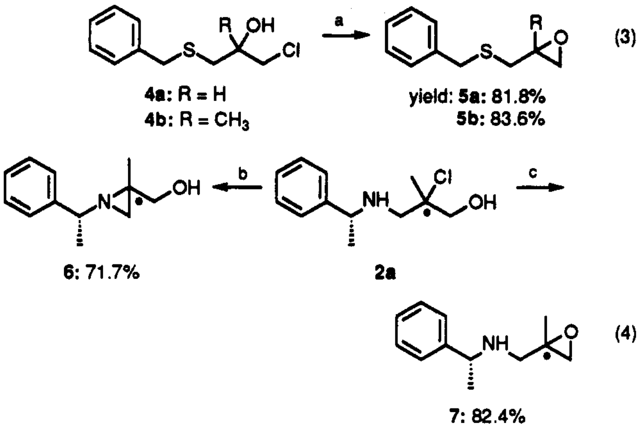
of chlorohydrins. The Pd(II)-catalyzed chlorohydroxylation is unique in its product selectivity. No other regioisomer or carbonyl compound has been isolated. The chlorohydrins obtained in this reaction can easily be transformed into many other synthetic intermediates, such as the valuable and versatile epoxy compounds and aziridines. In entry 9, *N*-tosyl-2,3-epoxypropylamine (**2e**) was obtained in 84% yield from the tosylation of reaction product 3-hydroxy-2-chloropropylamine, which is not easily isolable. Chlorohydrins **4a** and **4b** were transformed in high yield to the corresponding epoxy sulfides **5a** and **5b** by treatment with base (Scheme I, eq 3). Significantly, chlorohydrin **2a** can be transformed either to epoxy compound **7** or to aziridine **6** by treatment with base in the presence or absence, respectively, of added Cu(II) salt (Scheme I, eq 4).[21] The complexation of Cu(II) to the N-atom is crucial in governing the chemoselectivity of these transformations. Thus, these reactions provide easy access to epoxy amines, epoxy sulfides, and hydroxy aziridines, which are extremely useful synthons in organic synthesis because they can undergo selective ring-opening reactions in further transformations. The Sharpless asymmetric epoxidation has been applied to allylic alcohols with overwhelming success but is still not ideal for allylic amines and sulfides. Our Pd(II)-catalyzed method achieves epoxidation indirectly by means of the formation of chlorohydrins without concomitant oxidation of either nitrogen or sulfur.

Scheme I[a]



[a] Key: (a) 5 equiv of NaOH, THF, rt, 24 h; (b) 5 equiv of MeONa, MeOH, rt, 24 h; (c) 5 equiv of NaOH, 3 equiv of $CuCl_2$, THF, rt, 24 h.

In order to broaden the applicability of the reaction and to get more insight into the mechanism, studies of the chlorohydroxylation of cyclic allylic substrates and nonterminal acyclic allylic amines or sulfides are now in progress. In addition, we are searching for an external chiral ligand that would make this reaction more valuable in the area of asymmetric synthesis.

Acknowledgment. This work was supported by Chinese Academy of Sciences and the National Natural Science Foundation of China.

Supplementary Material Available: Compound characterization data for **2a–2e**, **4a–4c**, **5a–5b**, and **6–9** (3 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.

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(21) Detailed information on the stereooutcome of these transformations will be reported in a forthcoming paper.