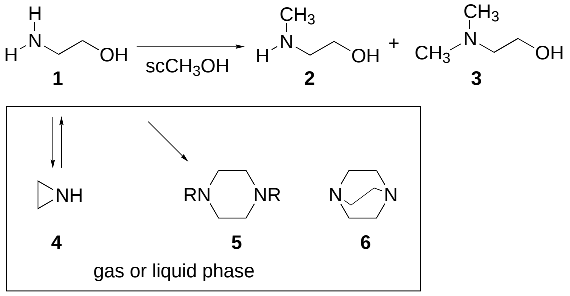
Enhanced Product Selectivity in Continuous N-Methylation of Amino Alcohols over Solid Acid–Base Catalysts with Supercritical Methanol

Tomoharu Oku and Takao Ikariya*

Supercritical fluids (SCFs) used as reaction media for homogeneous molecular catalysis or as compressed carriers for heterogeneous catalysis[1–4] have great potential for the manipulation of catalytic reactions. We have demonstrated that the pressure-tunable, unique properties of SCFs can remarkably enhance the reactivities and selectivities of molecular catalysts.[1] Besides these benefits for homogenous catalysis, when heterogeneously catalyzed reactions are performed over solid catalysts under supercritical conditions, the pressure-tunable, liquidlike solubility and gaslike diffusivity of the SCFs can significantly enhance the selectivity of the reactions if the unique properties of SCFs favor one of the reactions. Rapid deactivation of the catalyst resulting from coke formation on the surface can also be suppressed. Furthermore, applications of SCFs as a reactant and carrier medium can influence the outcome of the reaction owing to an increase in the concentration of the reactant on the catalyst surface. In fact, Baiker et al. reported that the selectivity of the amination of alkanediols or alkanolamines to give diamines conducted with scNH$_3$ over a Co–Fe catalyst increased remarkably when the pressure of the scNH$_3$ was changed.[3] Thus, heterogeneous catalysis in SCF media has received considerable attention as researchers have tried to manipulate the catalyst performance in terms of the selectivity.[3,4] However, fine-tuning the product selectivity of supercritical-phase reactions over solid catalysts has remained largely unexplored. Here we report the successful chemoselective alkylation of functionalized amines such as 2-aminoethanol (**1**) over solid acid or acid–base bifunctional catalysts with supercritical methanol (scCH$_3$OH, P_c = 8.1 MPa, T_c = 239.5 °C). A significant increase in the selectivity of N-alkylation was achieved by using scCH$_3$OH as a reactant and carrier medium for continuous-flow reactions.

For the reaction of **1** with CH$_3$OH to provide industrially useful chemicals,[5] the product distribution is highly influenced by the reaction phase as well as by the catalyst (Scheme 1). For example, the vapor-phase reaction of **1** over conventional solid acid catalysts such as H-β zeolites[6] provides predominantly the products of intermolecular dehydration, piperazine (**5**) and triethylenediamine (**6**), in addition to N-methylated products, *N*-methylaminoethanol (**2**) and *N*,*N*-dimethylaminoethanol (**3**). Alkaline earth metal–silicon or alkali metal—phosphorus–silicon oxides in the gas phase selectively afford the product of intramolecular dehydration, ethyleneimine (**4**), at higher temperatures instead of **5** and **6**.[7] Therefore, in general, the N-alkylation of **1** with methanol under such severe conditions proceeds in a nonselective manner and leads to various side reactions, cyclization, oligomerization, and decomposition through C–N bond cleavage.



Scheme 1. The reaction of **1** with methanol.

We screened various solid acid catalysts for the reaction of **1** with scCH$_3$OH by using a continuous-flow fixed-bed tubular reactor at 250–300 °C and a pressure range of 0.1 to 15 MPa (contact time of amine to catalyst, W/F = 55–111 g-cat h/mol-amine, amine/CH$_3$OH molar ratio = 1/10.8). The catalysts tested—H-mordenite,[8] H-β zeolite,[6] amorphous silica-alumina,[9] γ-alumina,[10] and the Cs-P-Si mixed oxide—effected N-methylation under supercritical conditions to give predominantly N-methylation products **2** and **3** in good to excellent yields. Compounds **4**, **5**, and **6** were also obtained as minor products as listed in Table 1. A visual inspection of the inside of a 10-mL high-pressure vessel equipped with sapphire windows confirmed that the reactants and expected products are all dissolved into scCH$_3$OH to make a single supercritical phase under the reaction conditions examined here. Obviously, application of supercritical conditions improves the conversion of amine as well as the selectivity for N-methylated products in comparison to gas-phase reactions which give only low conversion.[11]

Among the most efficient catalysts in scCH$_3$OH are combined ternary mixed-oxide catalysts, M-P-Si (M = alkali metal), which have both very weak acidic and basic sites. The product selectivity is delicately influenced by the alkali metal components in these catalysts and by the reaction conditions. A Cs-P-Si mixed-oxide catalyst effected the efficient N-methylation of **1** at 300 °C and under otherwise the same conditions as described in Table 1 to give the desired products **2** and **3** in 67 % yield (71 % conversion and 94 % cumulated selectivity). When the reaction was performed with a W/F value of 133 g h mol^{-1} and an amine/CH$_3$OH ratio of 1/20 under otherwise identical conditions, the yield of the desired products increased to 81 % (86 % conversion and 94 % selectivity). An increase in the temperature from 300 to 400 °C caused a serious drop in the selectivity to 25 %, although the conversion of **1** increased, as shown in Figure 1. At the higher reaction temperature of 400 °C, the supercritical-phase reaction gave a complicated mixture of **4**, methoxyethylamine, and some other degradation compounds. In contrast to the scCH$_3$OH phase, the gas-phase reaction

---

[*] Prof. T. Ikariya
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2637
E-mail: tikariya@o.cc.titech.ac.jp
T. Oku
Joint Research Center for Supercritical Fluids
Japan Chemical Innovation Institute (JCII)

Table 1. Reaction of **1** with methanol over various solid catalysts in both gas and supercritical phases.[a]

Entry	Catalyst	T[°C]/P [MPa]	W/F [g h mol^{-1}]	Conv. [%]	Yield [%]		Selectivity [%]		
					2	**3**	**2**+**3**	**4**	**5**+**6**
1	H-mordenite	300/0.1	111	0	0	0	0	0	0
2	H-mordenite	300/15	111	26	12	4	61	0	0
3	H-β zeolite	250/0.1	55	18	2	1	17	0	46
4	H-β zeolite	250/15	55	32	12	8	63	0	0
5	SiO_2–Al_2O_3	300/0.1	66	34	7	2	26	0	0
6	SiO_2–Al_2O_3	300/8.2	66	77	15	10	32	0	10
7	SiO_2–Al_2O_3	300/15	66	81	15	13	35	0	8
8	γ-Al_2O_3	300/0.1	79	21	12	3	71	tr	9
9	γ-Al_2O_3	300/8.2	79	48	24	9	69	0	3
10	γ-Al_2O_3	300/15	79	48	26	10	75	0	1
11	Na-P-Si oxide	270/8.2	55	100	1	36	37	0	16
12	K-P-Si oxide	300/8.2	55	74	35	12	64	0	0
13	Cs-P-Si oxide	300/0.1	55	12	6	1	58	37	4
14	Cs-P-Si oxide	300/8.2	55	71	51	16	94	0	1
15	Cs-P-Si oxide	300/8.2	133	79	48	24	91	0	0
16	Cs-P-Si oxide	300/8.2[b]	133	86	48	33	94	0	0

[a] Conditions: The reaction was conducted in a fixed-bed, tubular reactor with an amine/CH_3OH molar ratio of 1/10.8 and W/F = 55–133 g h mol^{-1}. The product ratio was determined by GC after the reaction conditions had been at steady state for 6 h. [b] Amine/CH_3OH = 1/20.

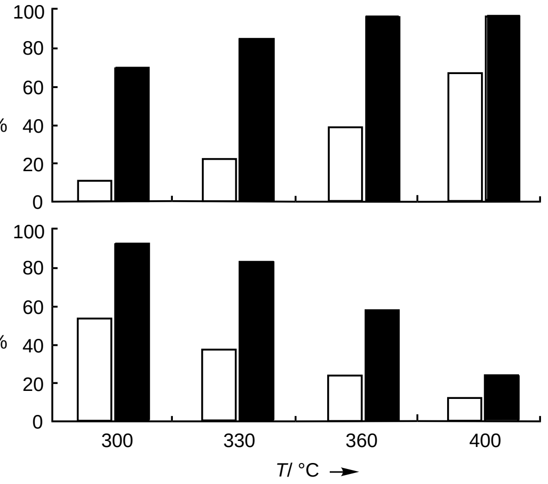


Figure 1. The effect of temperature on the conversion of **1** (x) and selectivity for N-methylated products (y) in the gas phase (white bars) and the supercritical phase, P = 8.2 MPa, (black bars) in the methylation of **1** over the Cs-P-Si catalyst. Conditions: W/F = 25 g h mol^{-1}, CH_3OH/amine = 10.8/1.

under otherwise identical conditions at 300 °C exhibited unsatisfactory productivity, 12 % conversion, and 58 % selectivity. The reaction at the higher reaction temperature of 400 °C afforded **4** with 72 % selectivity as the major product. Thus, the use of scCH_3OH as a carrier medium and reactant improved the productivity of N-methylation significantly over that of the gas-phase reaction. The change in the selectivities might be attributed to the milder reaction conditions possible with scCH_3OH, as well as the increased concentration of CH_3OH on the catalyst surface.

The scope and limitation of this N-methylation over the Cs-P-Si mixed-oxide catalyst in scCH_3OH was investigated at 300 °C and 8.2 MPa with an amine/CH_3OH molar ratio of 1/20. N-Methylation of various functionalized amines proceeded smoothly to provide the corresponding N-methylated products with a high selectivity (Table 2). Noticeably, the structures of the amino alcohols influenced the outcome of the reaction. The reactivity decreases in the order of 2-aminoethanol > 3-aminopropanol > 5-aminopentanol, although 4-aminobutanol gave predominantly the cyclization product, pyrrolidine, in 87 % selectivity, possibly because of thermodynamic reasons. Diglycolamine with a structural similarity to 5-aminopentanol provided N-methylated products along with morpholine as a byproduct. Unlike bifunctionalized amines, simple amines including n-butylamine, aniline, and 2-pyrrolidone were far less reactive regardless of their structures; the conversion of the amines ranged from 10 to 20 % with high selectivity for N-methylation. The hydroxy group on the other terminus in the functionalized amines is a crucial structural factor in achieving high reactivity, possibly because of the anchoring effect of the hydroxy group on the catalyst surface. In fact, ethoxyethylamine bearing no hydroxy group was far less reactive than **1**.

Table 2. N-Methylation of various amines over the Cs-P-Si catalyst in scCH_3OH.[a]

Entry	Amine	Conv. [%]	Sel. **2**+**3** [%]	Sel. **4**+**5**+**6** [%]
1	$HO(CH_2)_2NH_2$	90	94	1
2	$HO(CH_2)_3NH_2$	81	93	1
3	$HO(CH_2)_4NH_2$	87	12	87
4	$HO(CH_2)_5NH_2$	51	80	20
5	$HO(CH_2)_2O(CH_2)_2NH_2$	71	87	13
7	$HO(CH_2)_2NHCH_3$	76	88	0.1
8	$HO(CH_2)_2NHC_2H_5$	45	82	0.5
9	$HO(CH_2)_2NHCH(CH_3)_2$	24	78	1
10	n-$C_4H_9NH_2$	18	94	–
11	$C_6H_5NH_2$	15	94	–
12	2-pyrrolidone	16	88	–
13	$C_2H_5O(CH_2)_2NH_2$	11	98	–

[a] Conditions: The reaction was conducted over the Cs-P-Si catalyst at 300 °C in a fixed-bed tubular reactor with an amine/CH_3OH molar ratio of 1/20 and W/F = 140 g h mol^{-1}.

Although the mechanism of the reaction on the catalyst surface is not clear yet, valuable information was provided by the N-methylation of N-alkylaminoethanols with scCH_3OH under conditions similar to those described in Table 2. The reaction gave only *N*,*N*-alkylmethylaminoethanols without formation of any disproportionation products under these conditions. Substituents on the nitrogen atom of *N*-alkylaminoethanols affect the reactivity with $scCH_3OH$ mainly because of steric and electronic factors; the reactivity decreased in the substituent order of $H > CH_3 > C_2H_5 > CH(CH_3)_2$. Furthermore, the lack of formation of O-methylated products in the reaction of **1** with CH_3OH under supercritical conditions may exclude the possibility of the intramolecular dehydration producing ethyleneimine **4**, which is a main product in the gas-phase reaction over the Cs-P-Si mixed-oxide catalysts. These experimental results as well as those previously reported[7] suggest that the reaction proceeds by means of selective adsorption of **1** through the hydroxy group on the acid–base pair site of the catalyst to lead to the β-aminoethyl silylester or the β-aminoethyl phosphate species.[7] CH_3OH should form its methylester on the neighboring acidic sites in a similar manner. After N-methylation on the amino group with methyl moieties through deprotonation of the amino groups by the basic sites, these N-methylated adsorbates may be effectively desorbed with the aid of $scCH_3OH$. In contrast to the reactivity of the Cs-P-Si mixed-oxide catalyst, which has both acidic and basic sites on the surface, β-zeolite or amorphous silica-alumina catalysts with relatively strong acid sites exerted unsatisfactory selectivity, while the γ-alumina catalyst, which has both strong acid and base sites, exhibited comparatively good reactivity and selectivity.

In summary, we have described the first examples of the selective N-methylation of bifunctional amines over the solid acid–base bifunctional catalyst in $scCH_3OH$ as well as enhanced product selectivity on changing the pressure of CH_3OH. The use of $scCH_3OH$, which acts as a methylating agent and a reaction medium, as well as adjustment of the catalyst components results in the fine-tuning of the reaction conditions and particularly the reaction temperature for chemoselective methylation of the functionalized amines. Further investigations of the detailed mechanism of the methylation of the amines, the origin of the enhancement of the selectivity in $scCH_3OH$, and the effect of the cogenerated water on the reactivity[12] are now in progress.

Experimental Section

The Cs-P-Si mixed-oxide catalyst was prepared by the following procedure: Silica beads of 10 to 20 mesh size (CARiACT Q-30, Fuji Silysia Chemical Co. LTD.) were impregnated with an aqueous solution of cesium nitrate and ammonium dihydrogenphosphate. The crude mixture was then dried at 120 °C and calcined at 500 °C for 2 h in air. The Cs/P/Si atomic ratio in the catalyst was 1/0.8/5 and the specific surface area was $7\,m^2g^{-1}$. The acid and base strength measured by the Hammet indicator method was weaker than $H_0 = +6.3$ and $H_- = +8.3$, respectively. Chemisorption of NH_3 and CO_2 at room temperature from the vapor phase did not occur in temperature-programmed desorption (TPD) analysis.

The N-methylation reaction of **1** in the gas or supercritical phase was carried out isothermally in a continuous up-flow tubular reactor (SUS316 tubular reactor with a Swagelok VCR joint, 1/2 inch × 10 mm × 135 mm). The reactor was loaded with catalyst particles and placed in an oven. A mixture of amine and methanol was introduced into the reactor through the preheating coil with an HPLC pump (PU1580, JASCO Co.). The pressure in the reaction system was controlled by the automatic back-pressure regulator (880-81, JASCO Co.) at 0.1 to 15 MPa. Standard reaction conditions were used (5.0 mL catalyst, 300 °C, 8.2 MPa, methanol/amine molar ratio = 10.8/1 or 20/1 and the LHSV (mL-liquid/mL-cat h), which is the space velocity as normal liquid flow rate of the mixed solution of reactants, is $5\,h^{-1}$).

The reaction products were identified by GC-MS analysis (Agilent 5973N-6890N, Agilent Technologies). The selectivity and chemical yield of the products were determined by GC analysis (GC-17A, Shimadzu Co.; FID detector and DB-1 capillary column, J&W)). Conversion of amines X_a, yield $Y_{\mathbf{n}}$, and selectivity $S_{\mathbf{n}}$ of each of the methylated products **2**, **3**, and **n** were defined as:

$$X_a = (F_{a(ini)} - F_a)/F_{a(ini)} \times 100\,(\%) \quad (1)$$

$$Y_{\mathbf{n}} = F_{\mathbf{n}}/F_{a(ini)} \times 100\,(\%) \quad (2)$$

$$S_{\mathbf{n}} = Y_{\mathbf{n}}/X_a \times 100\,(\%) \quad (3)$$

$F_{a(ini)}$ and F_a represent molar flow rates of reactant amine at the reactor inlet and outlet, respectively, and $F_{\mathbf{n}}$ represents that of methylated product **n** at the reactor outlet.

During the reaction, no degradation products of methanol such as dimethylether, carbon monoxide, and methane were detected. Methanol was only consumed as a reactant in the N-methylation reaction.

Received: May 16, 2002 [Z19317]

---

[1] a) P. G. Jessop, T. Ikariya, R. Noyori, *Nature* **1994**, *368*, 231–233; b) P. G. Jessop, T. Ikariya, R. Noyori, *Science* **1995**, *269*, 1065–1069; c) T. Ikariya, R. Noyori in *Transition Metal Catalyzed Reactions* (Eds.: S.-I. Murahashi, S. G. Davies), IUPAC, Blackwell Science, New York, **1999**, pp. 1–28; d) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, *99*, 475–493; e) *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**; f) R. Noyori, T. Ikariya in *Stimulating Concepts in Chemistry*, Wiley-VCH, **2000**, pp. 13–24.

[2] As reviews: a) P. E. Savage, S. Gopalan, T. I. Mizan, C. J. Martino, E. E. Brock, *AIChE J.* **1995**, *41*, 1723–1778; b) P. E. Savage in *Handbook of Heterogeneous Catalysis, Vol. 4* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), Wiley-VCH, Weinheim, **1997**, pp. 1339–1347; c) A. Baiker, *Chem. Rev.* **1999**, *99*, 453–473; d) L. Fan, K. Fujimoto in *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**, pp. 388–413; e) R. Wandeler, A. Baiker, *CATTECH* **2000**, *4*, 34–50; f) J. R. Hyde, P. Licence, D. Carter, M. Poliakoff, *Appl. Catal. A* **2001**, *222*, 119–131; g) B. Subramaniam, C. J. Lyon, V. Arunajatesan, *Appl. Catal. B* **2002**, *37*, 279–292; h) B. Subramaniam, *Appl. Catal. A* **2001**, *212*, 199–213; i) B. Subramaniam, M. A. McHugh, *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1–12.

[3] a) G. Jenzer, T. Mallat, A. Baiker, *Catal. Lett.* **1999**, *61*, 111–114; b) A. Fischer, M. Maciejewski, T. Bürgi, T. Mallat, A. Baiker, *J. Catal.* **1999**, *183*, 373–383; c) A. Fisher, T. Mallat, A. Baiker, *J. Catal.* **1999**, *182*, 289–291; d) A. Fischer, T. Mallat, A. Baiker, *J. Mol. Catal. A* **1999**, *149*, 197–204; e) A. Fischer, T. Mallat, A. Baiker, *Angew. Chem.* **1999**, *111*, 362–365; *Angew. Chem. Int. Ed.* **1999**, *38*, 351–354.

[4] a) W. K. Gray, F. R. Smail, M. G. Hitzler, S. K. Ross, M. Poliakoff, *J. Am. Chem. Soc.* **1999**, *121*, 10711–10718; b) M. G. Hitzler, F. R. Smail, S. K. Ross, M. Poliakoff, *Chem. Commun.* **1998**, 359–360; c) M. G. Hitzler, F. R. Smail, S. K. Ross, M. Poliakoff, *Org. Process Res. Dev.* **1998**, *2*, 137–146; d) M. G. Hitzler, M. Poliakoff, *Chem. Commun.* **1997**, 1667–1668; e) U. R. Pillai, E. Sahle-Demessie, *Chem. Commun.* **2002**, 422–423; f) R. J. Bonilla, P. G. Jessop, B. R. James, *Chem. Commun.* **2000**, 941–942; g) R. Wandeler, N. Kunzle, M. S. Schneider, T. Mallat, A. Baiker, *Chem. Commun.* **2001**, 673–674.

[5] a) M. R. Edens, J. F. Lochary in *Kirk-Othmar Encyclopedia of Chemical Technology, Vol. 2*, 4th ed. (Eds.: J. I. Kroschwitz, M. Howe-Grant), Wiley, New York, **1991**, pp. 1–26; b) Electronic Release, “Ethanolamines and Propanolamines”: H. Hammer, W. Körnig, T. Weber, H. Kieczka in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., Wiley-VCH, Weinheim, **2001**; c) Electronic Release, “Amines, Aliphatic”: K. Eller, E. Henkes, R. Rossbacher, H. Höke in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed., Wiley-VCH, Weinheim, **2001**.

[6] H-β zeolite (CP811E-22, protonated form, ZEOLYST Int.; Si/Al atomic ratio of 12/1) was used after it had been pelletized to 0.3–0.8 mm.

[7] a) H. Tsuneki, *Appl. Catal. A* **2001**, *221*, 209–217; b) M. Ueshima, H. Tsuneki in *Catalytic Science and Technology, Vol. 1* (Eds.: S. Yoshida, N. Takezawa, T. Ono), Kodansha-VCH, Tokyo, **1991**, pp. 357–360; c) M. Ueshima, Y. Shimasaki, Y. Hino, H. Tsuneki in *Acid-Base Catalysis* (Eds.: K. Tanabe, H. Hattori, T. Yamaguchi, T. Tanaka), Kodansha, Tokyo, **1989**, pp. 41–52; d) M. Ueshima, H. Yano, H. Hattori, *Sekiyu Gakkaishi* **1992**, *35*, 362–365; e) H. Tsuneki, Y. Shimasaki, K. Ariyoshi, Y. Morimoto, M. Ueshima, *Nippon Kagaku Kaishi* **1993**, *11*, 1209–1216.

[8] H-Mordenite (HSZ640HOA, protonated form, Tosoh Co.; Si/Al atomic ratio of 9/1) was used after it had been pelletized to 0.3–0.8 mm.

[9] Amorphous silica-alumina (N632L, Nikki Chemical Co.; SiO_2/Al_2O_3 molar ratio of 11/1, specific surface area 400 $m^2 g^{-1}$) was used after it had been pelletized to 0.3–0.8 mm.

[10] γ-Alumina (N612N, Nikki Chemical Co.; specific surface area 200 $m^2 g^{-1}$) was used after it had been pelletized to 0.3–0.8 mm.

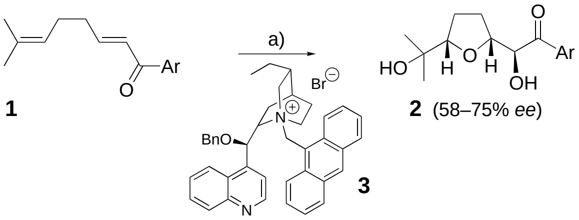
[11] After 6 h reaction time under supercritical conditions the H-mordenite catalyst was still white and very active. In contrast, reaction in the gas phase resulted in immediate blackening and deactivion of the catalyst due to coking.

[12] Effect of water: Water generated from methylation of **1** may possibly inhibit the reaction by competitive adsorption with the reactants on the catalyst surface. In fact, we found that the adsorption equilibrium constants (K) of CH_3OH and water are much larger than that of **1** by a simulation in the reaction kinetics by Langmuir–Hinshelwood mechanism, $K_{CH_3OH}/K_{\mathbf{1}} = 100$, $K_{water}/K_{\mathbf{1}} = 3000$. An increase in the portion of $scCH_3OH$ by changing the molar ratio of CH_3OH to **1** at the same amine contact time (*W/F*) improved the reaction conversion and the space–time yields, which suggests that desorption of the generated water from the catalyst surface could be promoted by $scCH_3OH$.

An Asymmetric Phase-Transfer Dihydroxylation Reaction[**]

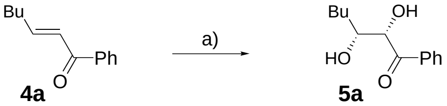
Riaz A. Bhunnoo, Yulai Hu, Dramane I. Lainé, and Richard C. D. Brown*

The asymmetric dihydroxylation of olefins using osmium tetraoxide is a powerful process that has found widespread application in organic synthesis.[1] Systems developed to date realize enantioinduction through the use of chiral ligands on the osmium center,[2] or chiral auxilliaries present in the substrate.[3,4] Here we report a conceptually different approach to asymmetric dihydroxylation using permanganate in the presence of a chiral phase-transfer reagent.[5,6]Recently, we reported the asymmetric oxidative cyclization of 1,5-dienes **1** by permanganate using a chiral phase-transfer catalyst (Scheme 1).[5] Whereas the permanganate promoted oxidative cyclization reaction of 1,5-dienes and the formation of α-ketols from olefins occur under slightly acidic conditions, permanganate oxidations conducted under basic conditions favor dihydroxylation.[7] Therefore, permanganate oxidations using chiral phase-transfer agents in alkaline media should provide a new approach to asymmetric dihydroxylation.



Scheme 1. Asymmetric oxidative cyclization of 1,5-dienes **1**. a) $KMnO_4$ (powder) (1.6 equiv), AcOH (6.5 equiv), **3** (0.1 equiv)/CH_2Cl_2, −30 °C.

Enones had been shown to undergo permanganate oxidative cyclization reactions to afford tetrahydrofuran diols **2** with good levels of enantioselectivity (Scheme 1),[5,8] and were therefore chosen as substrates for initial dihydroxylation studies (Scheme 2). Oxidation of **4a** under liquid–liquid achiral phase-transfer conditions gave racemic diol **5a** as the major isolated product in reasonable yield (entry 1, Table 1). The majority of the remaining mass balance was accounted



Scheme 2. Phase-transfer promoted dihydroxylation of enone **4a**. For conditions and yields see Table 1.

Table 1. Phase-transfer (PT) promoted dihydroxylation of enone **4a** (see Scheme 2).[a]

Entry	Method[b]	PT [equiv]	Time [min]	Yield of **5a** [%][c] [BRSM [%]]	*ee*[d] [%]
1	A	Adogen 464 (1.0)	45	55	N/A
2	A	**3** (1.0)	45	41 [45]	47
3	B	**3** (1.0)	30	41 [96]	63
4	B	**3** (1.0)	60	51 [87]	62
5	B	**3** (1.0)	180	27 [40]	62
6	B	**3** (0.2)	420	33 [64]	63
7[e]	B	**3** (3.0)	60	30 [42]	61

[a] Reactions were conducted on a 0.37 mmol scale. [b] Method A: $KMnO_4$ (s) (0.37 mmol), CH_2Cl_2 (16 mL), pH 9 buffer (8 mL), 0 °C. Method B: $KMnO_4$ (s) (1.5 equiv), CH_2Cl_2, −60 °C. [c] Yields represent analytically pure isolated material. BRSM indicates the isolated yield based on recoved enone. [d] Enantiomeric excess was determined by HPLC using a CHIRALCEL OD-H column, hexane/*i*PrOH (80:20) eluent. R_t = 5.28 min (major), R_t = 6.24 min (minor). [e] Reaction carried out with three equivalents of $KMnO_4$.

---

[*] Dr. R. C. D. Brown, R. A. Bhunnoo, Dr. Y. Hu
Department of Chemistry
University of Southampton
Highfield, Southampton SO17 1BJ (UK)
Fax: (+44) 23-80596805
E-mail: rcb1@soton.ac.uk
Dr. D. I. Lainé
GlaxoSmithKline
Medicines Research Centre
Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY (UK)

[**] We acknowledge GlaxoSmithKline/EPSRC for a CASE award (R.A.B.), the Leverhulme Trust (Y.H.), and the Royal Society (R.C.D.B.) for fellowships, Syngenta, AstraZeneca, and Merck Sharp and Dohme for unrestricted grants. We also thank Dr Barry Lygo (University of Nottingham) for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.