under argon in a 50 mL double-necked flask equipped with a reflux condenser. The flask was heated at 140 °C and the solution of freshly prepared catalyst (1 equiv, 1 mL DMA) (see above), was added rapidly. The conversion of the aryl bromide was monitored by GC on 50 µL samples of the crude mixture dissolved in acetone (2 mL).

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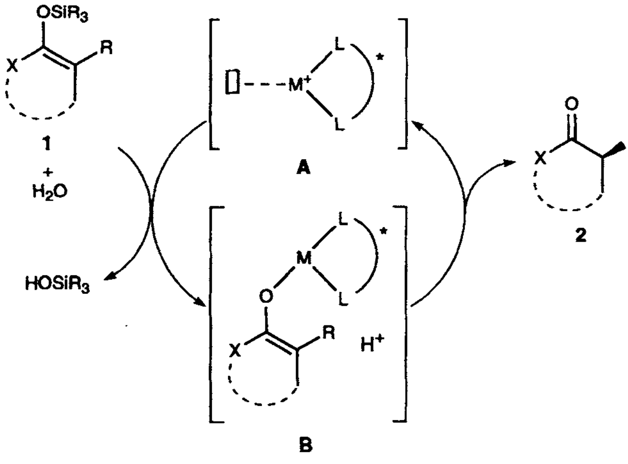
Asymmetric Catalytic Protonation of Silyl Enol Ethers with Chiral Palladium Complexes**

Masaharu Sugiura and Takeshi Nakai*

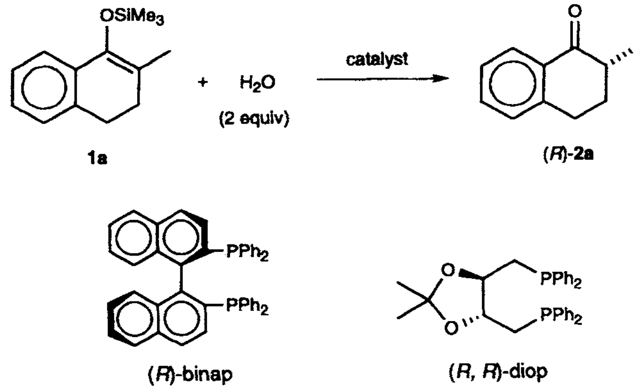
The enantioselective protonation of prochiral enolates with a chiral proton source has attracted much attention as a general methodology for the asymmetric synthesis of α-substituted carbonyl compounds.[1] While most of the methods reported so far require the use of more than a stoichiometric amount of a chiral Brønsted acid, the catalytic use of a chiral acid, combined with a stoichiometric amount of an achiral proton source, has also been successful.[2] Disclosed here is a conceptually new approach to the asymmetric catalytic protonation of enol silyl ethers, which employs water as the proton source and a chiral palladium complex as the catalyst.

Scheme 1 illustrates our working hypothesis.[3] Chiral transition metal complex **A**, if coordinatively unsaturated, should activate silyl enol ether **1** and promote attack by water onto the silyl group to afford chiral metal enolate **B** and a silanol. Enolate **B** would then be diastereoselectively protonated by water to afford the enantiomerically enriched ketone **2** with regeneration of **A**. To realize this new concept, the chiral transition metal catalyst should be capable of preferentially activating the enol ether over the coexisting water and product ketone. Based on these considerations, we selected chiral cationic Pd complexes as the catalyst. Shibasaki et al. recently reported that the chiral cationic Pd complex prepared from $[\mathrm{PdCl_2}\{(R)\text{-binap}\}]$ (binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl) and AgOTf (1:1) in the presence of 4-Å molecular sieves (MS) in wet DMF serves as an efficient asymmetric catalyst for aldol reactions due to the intermediacy of a chiral Pd enolate.[4]



Scheme 1. The working hypothesis.

Therefore, we focused on the two chiral cationic Pd species generated from $[\mathrm{PdCl_2}\{(R)\text{-binap}\}]$ (**3a**) or $[\mathrm{PdCl_2}\{(R,R)\text{-diop}\}]$ (**3b**) and silver salts for the protonation of cyclic enol ether **1a** with water (Scheme 2). Whereas the Pd species generated by mixing **3a** and two equivalents of $\mathrm{AgPF_6}$ showed high catalytic activity but low enantioselectivity (Table 1, entry 1), that generated by the method of Shibasaki et al.[4] provided higher enantiomeric excesses; however, the reproducibility was very poor (entry 2). We therefore suspected that a contaminant plays a vital role in this reaction. Significantly enough, when a small amount of diisopropylamine—a possible contaminant of **1a**—was added to the catalyst solution, the enantioselectivity remarkably improved to 79% *ee*; the reproducibility was also very good (entry 3).[5] Analogous use of the diop complex **3b**



Scheme 2. Protonation of cyclic enol ether **1a** by water in the presence of chiral, cationic Pd complexes generated from $[\mathrm{PdCl_2}\{(R)\text{-binap}\}]$ (**3a**) or $[\mathrm{PdCl_2}\{(R)\text{-diop}\}]$ (**3b**) and silver salts.

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[*] Prof. T. Nakai, Dr. M. Sugiura
Department of Chemical Technology
Tokyo Institute of Technology
Meguro-ku, Tokyo 152 (Japan)
Fax: Int. code +(3)5734-2885
e-mail: takeshi@o.cc.titech.as.jp

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Table 1. Optimization of asymmetric catalysis for the protonation of **1a** with water [a].

Entry	Catalyst	Conditions	Yield [%][b]	*ee*[%][c] (Config.[d])
1	[PdCl$_2${(*R*)-binap}] (**3a**, 5 mol%) AgPF$_6$ (10 mol%) CH$_2$Cl$_2$/MeOH	RT 0.5 h	95	4–13 (*S*)
2	**3a** (5 mol%) AgOTf (5 mol%) 4-Å MS, DMF/H$_2$O	RT–30 °C 84–5 h	25–85	44–73 (*R*)
3	**3a** (5 mol%) AgOTf (5 mol%) 4-Å MS, DMF/H$_2$O then *i*Pr$_2$NH (0.5 mol%)	50 °C 18 h	83	79 (*R*)
4	[PdCl$_2${(*R*,*R*)-diop}] (**3b**, 5 mol%) AgOTf (5 mol%) 4-Å MS, DMF/H$_2$O then *i*Pr$_2$NH (0.5 mol%)	50 °C 5 h	78	3 (*S*)
5	[PtCl$_2${(*R*)-binap}] (5 mol%) AgOTf (5 mol%) 4-Å MS, DMF/H$_2$O then *i*Pr$_2$NH (0.5 mol%)	50 °C 118 h	62	4 (*R*)

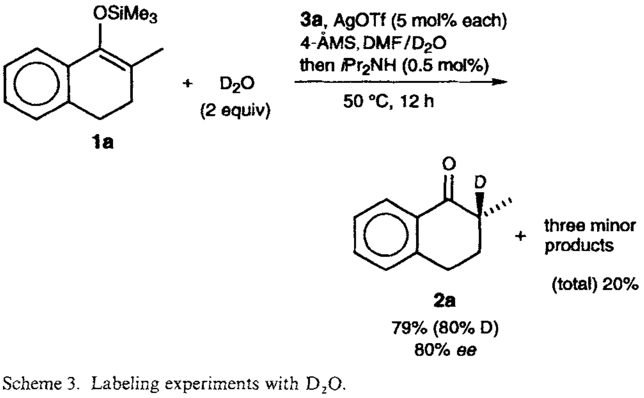
[a] All reactions were carried out with **1a** (0.5 mmol, see Experimental Section). [b] Yield of isolated product. [c] Determined by HPLC analysis on CHIRALCEL OD. [d] Assigned by comparing the optical rotation with literature values [6].

provided a lower enantiomeric excess (entry 4). A similar Pt–binap complex was also inferior to **3a** in both activity and enantioselectivity (entry 5). Furthermore, using AgPF$_6$ instead of AgOTf afforded **2a** in 81% yield and 76% *ee* (*R*), and using basic alumina instead of 4-Å molecular sieves resulted in 91% yield and 63% *ee*.

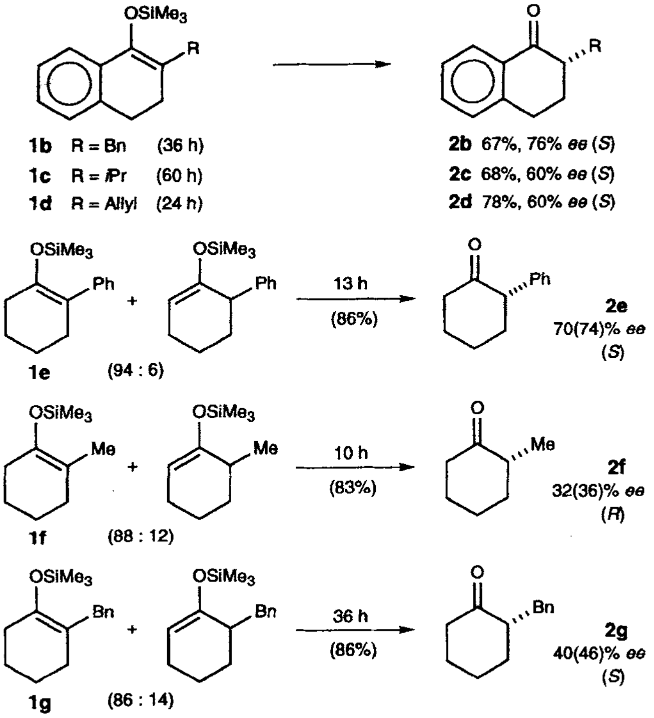
The question of what role the added diisopropylamine plays arises. Interestingly, addition of triethylamine gave essentially the same results (84% yield and 76% *ee*), indicating that the amine might act as a Lewis base, and not as a proton source. Moreover, ^{31}P NMR spectroscopic measurements of the catalyst solutions before and after addition of diisopropylamine[7] suggest that the amine might selectively deactivate one of the binap-bound Pd species initially formed. In other words, it appears that upon addition of the amine, the surviving Pd species act as the predominant catalyst(s), thus making the reaction slower but providing enhanced enantiomeric selectivity.

To gain further insight into the reaction mechanism, a labeling experiment with D$_2$O was carried out (Scheme 3).[8] Ketone **2a**, with 80% deuterium content at the α-position, was obtained together with traces of unexpected by-products,[9] implying that the reaction is more complicated than anticipated. More detailed studies must be awaited.

Finally, the present asymmetric catalysis was also applied to silyl enol ethers **1b–g**[5] under optimized conditions (Scheme 4).



Scheme 3. Labeling experiments with D$_2$O.



Scheme 4. Asymmetric catalytic protonation of various silyl enol ethers under optimal conditions. Values for **2e–g** that are corrected for the regioisomeric purity of the silyl enol ethers are given in parentheses.

While comparably high levels of enantiomeric selectivity were obtained with **2b–e**,[10] **1f** and **1g** gave moderate enantiomeric selectivity.

Experimental Section

In a typical reaction a mixture of **3a** (20 mg, 0.025 mmol), AgOTf (6.4 mg, 0.025 mmol), 4-Å MS powder (150 mg), DMF (1 mL), and water (36 μL) was stirred at room temperature for 2 h under an argon atmosphere. The resulting mixture was filtrated through a short Celite column to provide a red solution. An aliquot (10 μL) of a solution containing *i*Pr$_2$NH (33 μL) and DMF (1 mL) was added along with water (18 μL), and the mixture stirred at room temperature for 30 min. Then, **1a** (116 mg, 0.5 mmol) was added, and the resulting solution stirred at 50 °C for 18 h. After dilution with ether (40 mL), addition of water (10 mL), and filtration through a Celite pad, the organic layer was washed with brine, dried over magnesium sulfate, and freed of solvent under reduced pressure. Purification by preparative thin-layer chromatography afforded **2a** (66 mg, 83%).

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[8] For this experiment 4-Å MS powder was dried at 300 °C for 8 h under vacuum (< 0.05 Torr) to prevent contamination by water; otherwise, a lower deuterium content (55 %) resulted. We thank Dr. Masahiro Terada for suggesting this procedure.

[9] The by-products were α-deuterated (to 70 %) α-(trimethylsilylmethyl)tetralone (4 %, 81 % *ee*), α-hydroxy-α-methyltetralone (6 %, 0 % *ee*), and β-methyltetrahydro-α-naphthol (10 %, 0 % *ee*).

[10] Enantiomeric excesses were determined by HPLC on CHIRALCEL OD-H for **2b–e** and by capillary GLC on CP-chirasil-DEX CB for **2f** and **2g**. The configurations were assigned by comparing optical rotations with literature values: **2b**: M. Murata, M. Nakajima, K. Koga, *J. Chem. Soc. Chem. Commun.* **1990**, 1657–1658; **2c**: T. Yasukata, K. Koga, *Tetrahedron: Asymmetry* **1993**, *4*, 35–38; **2e**: G. Berti, B.Macchia, F. Macchia, L. Menti, *J. Chem. Soc. C* **1971**, 3371–3375; **2g**: A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, M. Druelinger, *J. Am. Chem. Soc.* **1981**, *103*, 3081–3087. The configurations of **2d** and **2f**, though not yet determined, were assigned based on the similarity of the values.

Selective Enhancement of NMR Signals for α-Cyclodextrin with Laser-Polarized Xenon[**]

Yi-Qiao Song, Boyd M. Goodson, Rebecca E. Taylor, David D. Laws, Gil Navon, and Alexander Pines*

Xenon, hydrophobic and chemically inert, has been widely used as an NMR probe of chemical environments, both in solution and in the solid state.[1] With the application of optical pumping,[2] a large (> 10 %) ^{129}Xe nuclear-spin polarization can be generated. This polarization has been used to increase the sensitivity of ^{129}Xe NMR spectroscopy[3, 4] and magnetic resonance imaging (MRI),[5] and to supply polarization to neighboring spins on surfaces.[6] It was recently shown that enhanced xenon polarization can also be transferred to molecules in solution[7] by cross-relaxation, a process dubbed the *s*pin *p*olarization *i*nduced *n*uclear *O*verhauser *e*ffect (SPINOE). Because the SPINOE depends on the proximity of ^{129}Xe atoms to neighboring spins, as well as their relative motion, more rapid transfer of polarization is expected when xenon is temporarily bound, thereby permitting selective enhancement of NMR signals of nuclear spins near xenon binding sites.

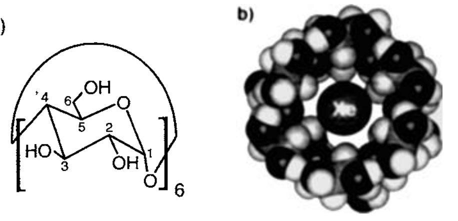

Figure 1. a) Structural formula of α-cyclodextrin. b) CPK model of α-cyclodextrin [16] in which a xenon atom is placed within the hydrophobic pocket containing the hydrogen atoms H3 and H5.

Here we report polarization transfer from laser-polarized ^{129}Xe to ^{1}H spins in two molecular systems in solution: *p*-nitrotoluene (*p*-NT), which couples mainly diffusively to xenon, and α-cyclodextrin (α-CD, Figure 1), a cyclic oligosaccharide with a hydrophobic pocket known to bind xenon[8, 9] and other guest species.[10] Binding of xenon to α-CD gives rise to cross-relaxation rates up to 150 times greater than those between xenon and *p*-NT; this results in more rapid transfer of polarization. Furthermore, enhancements of ^{1}H spins adjacent to the xenon binding site in α-CD are greater than those of ^{1}H spins further away.

The change in the ^{1}H magnetization due to the presence of highly polarized xenon is well approximated by Equation (1).[7]

$$\frac{\Delta M^{\mathrm{H}}}{M^{\mathrm{H}}_{\mathrm{eq}}} = -\,\sigma_n\, n^{\mathrm{Xe}}\, T_1^{\mathrm{H}} \frac{\gamma^{\mathrm{Xe}}}{\gamma^{\mathrm{H}}} \frac{\Delta M^{\mathrm{Xe}}}{M^{\mathrm{Xe}}_{\mathrm{eq}}} \left(1-\mathrm{e}^{-t/T_1^{\mathrm{H}}}\right) \tag{1}$$

$$\sigma_n\, n^{\mathrm{Xe}},\ \frac{1}{T_1^{\mathrm{Xe}}} \ll \frac{1}{T_1^{\mathrm{H}}} \tag{2}$$

Here, σ_n is the partial millimolar cross-relaxation rate, n^{Xe} is the concentration of ^{129}Xe in the solution, γ^{Xe}, γ^{H} are the magnetogyric ratios, M^{Xe}, M^{H} and $M^{\mathrm{Xe}}_{\mathrm{eq}}$, $M^{\mathrm{H}}_{\mathrm{eq}}$ are the enhanced and equilibrium magnetization of ^{129}Xe and ^{1}H, respectively, T_1^{Xe}, T_1^{H} (under condition (2)) are the ^{129}Xe and ^{1}H spin-lattice relaxation times, and $\Delta M = M - M_{eq}$. In the absence of laser polarization, the ^{129}Xe–^{1}H NOE enhancement is minuscule ($\approx 10^{-5}$) due to low xenon concentration and weak ^{129}Xe–^{1}H coupling. In previous work[9, 11] ^{129}Xe–^{1}H interactions were indirectly observed by detecting changes in the xenon signal during proton saturation. With the use of laser-polarized xenon, however, the ^{129}Xe–^{1}H NOE enhancement ($\approx 10^{-2}$)[12] is detected directly in the resolved ^{1}H NMR spectrum.

The technique used for optically pumping xenon has been described elsewhere;[4] ^{129}Xe polarizations are typically 5–10 %. To detect the SPINOE signals, we used a heteronuclear difference NOE pulse sequence (Figure 2), which suppresses the equilibrium ^{1}H magnetization and is therefore directly sensitive to the SPINOE. The ^{1}H SPINOE NMR spectra for 0.1 M *p*-NT in [D$_6$]benzene with laser-polarized xenon are shown in Figure 3. Equation (1) was used to determine values of σ_n for *p*-NT by assuming a linear dependence of the cross-relaxation rate on the concentration of polarized xenon (Table 1). The values are similar to that for the hydrogen atom of [D$_5$]benzene, which is in agreement with a rough theoretical

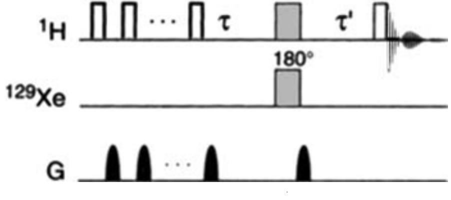

Figure 2. Heteronuclear difference NOE pulse sequence for ^{129}Xe–^{1}H SPINOE NMR spectroscopy based on sequences developed by Shaka [13]. The equilibrium ^{1}H NMR signal is saturated by 90° and gradient pulses (G); the saturation is maintained by a 180° pulse followed immediately by a gradient pulse. A xenon 180° pulse allows SPINOE signals to accumulate during the mixing periods τ and τ'. Each spectrum represents the difference of two scans.

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[*] Prof. A. Pines, Y.-Q. Song, B. M. Goodson, R. E. Taylor, D. D. Laws
Materials Sciences Division, Lawrence Berkeley National Laboratory
and
Department of Chemistry
University of California
Berkeley, CA 94720 (USA)
Fax: Int. code +(510)486-5744
e-mail: pines@cchem.berkeley.edu

Prof. G. Navon
School of Chemistry, Tel Aviv University (Israel)

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