(μ-Hydroxo)-platinum complex-catalyzed enantioselective aldol reaction of aldehydes with 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene in DMF

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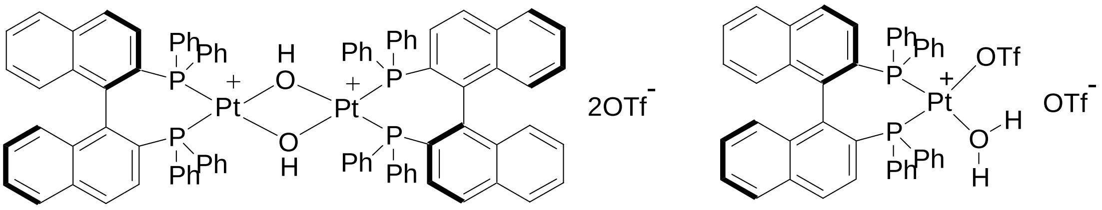
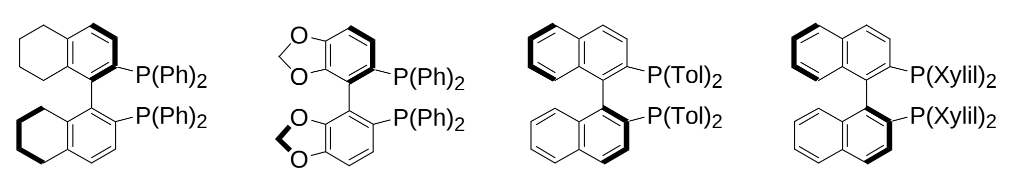
Abstract [((*R*)-BINAP)Pt(μ-OH)]$_2$·2OTf catalyzed the enantioselective aldol reaction of aldehydes with 1-methoxy-2-methyl-(1-trimethylsilyloxy)propene at room temperature in dry DMF in high yields with enantioselectivity up to 92%. This is a versatile example of the catalytic enantioselective aldol reaction using a silyl ketene acetal promoted by (μ-hydroxo)-platinum complexes under mild conditions.

Although late transition metal complex-catalyzed enantioselective aldol reactions are expected for industrial processes, the effective catalytic systems have not been developed yet.[1] The preceding results were quite limited to group 10 metal-catalyzed reactions (palladium[2] and platinum[3]). We have recently reported a practically simplified reaction procedure available for the dicationic (BINAP)- and (sparteine)-palladium-catalyzed aldol reactions with 1-phenyl-(1-trimetylsilyloxy)ethene, *in situ* providing an active catalyst from ((*R*)-BINAP)- or ((-)-sparteine)-PdCl$_2$ and AgSbF$_6$ in the presence of 3Å molecular sieves in dry DMF.[4] However, the palladium-catalyzed aldol reactions do not work well with silyl ketene acetals, which are advantageous for the sequential aldol strategy in constructing 1,3-diol frameworks in natural products because it allows preparation of the next aldehyde by the direct reduction of the ester moiety in the aldol products.[5] On the other hand, a silyl ketene acetal, 1-methoxy-2-methyl-(1-trimethylsilyloxy)propene **1**, underwent the platinum-catalyzed aldol reaction as reported merely by Fujimura,[3] where an active platinum cationic species was prepared *in situ* from a Pregosin complex,[6] 3,5-di-*tert*-butylsalicylaldehyde-chelating (BINAP)platinum(II) complexes, according to the Strukul method[7] by treatment with HOTf and lutidine in CH_2Cl_2. The *in situ* formed catalyst (5 mol% loading) led the aldol reaction of benzaldehyde with **1** in CH_2Cl_2 at -25˚C (21 h) to give the corresponding aldol in a quantitative yield with 59% ee, although high enantioselectivity was achieved in the reaction with linear aliphatic aldehydes. The valid structure of the active platinum catalyst has not been elucidated yet. In addition, alternative cationic catalysts can also be formed *in situ* from (BINAP)$PtCl_2$ and AgX, but the behavior is different from the above in some reactions.[8] It is obvious that the catalytic reaction with isolated complexes is advantageous more than that with *in situ* formed[6] catalysts or catalyst precursors with regard to the simplicity of handling catalysts and the reproducibility of the results.[9] Then, we investigated the platinum-catalyzed enantioselective aldol reaction by utilizing the known platinum complexes as the starting catalysts. We disclose herein the (μ-hydroxo)-platinum complex-catalyzed enantioselective aldol reaction with **1** in DMF. Some platinum complexes furnished with BINAP auxiliary are known: [((*R*)-BINAP)Pt(μ-OH)]$_2$·2BF_4 was used for enantioselective Baeyer-Villiger oxidations of cyclic ketones with hydrogen peroxide[7b] and [((*R*)-BINAP)Pt(H_2O)(OTf)]·OTf was provided for ligand exchange reactions.[10] Thus, we first chose μ-hydroxo-platinum complex **2**[11] and monoaqua-platinum complex **3**[12] as the catalysts having the same counter anion for the platinum-catalyzed enantioselective aldol reaction, as depicted in Figure 1.



μ-hydroxo complex **2**

monoaqua complex **3**



(*R*)-H$_8$-BINAP

(*R*)-SEGPHOS

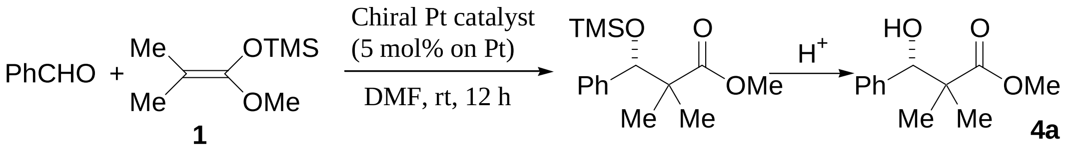
(*S*)-Tol-BINAP

(*S*)-Xylyl-BINAP

Figure 1. Structures of platinum complexes and chiral auxiliary used in this study

The results are shown in Table 1 on the platinum complex-catalyzed enantioselective aldol reaction of benzaldehyde with **1** in DMF; the experimental details are described in Ref. 13. The enantioselectivity in the reactions using **2** were remarkably affected by the counter anions (entries 1, 2, 3, 5): The two anions, BF_4^- and PF_6^-, are prone to give relatively lower % ee.[14] The optimized reaction (rt, 12 h, DMF) in the presence of ((*R*)-BINAP)-**2**-OTf (5 mol% on Pt) resulted in a high yield (86%) with a high enantioselectivity (84% ee). When ((*R*)-BINAP)-**2**-SbF_6 was used in CH_2Cl_2, the enantioselectivity was considerably reduced (entry 4). Apparently, DMF is suitable for the reaction as likely emphasized in the case of the corresponding Pd-catalyzed reaction.[2,4] However, the quantity of DMF also affected both the % yield and % ee: Increasing from 0.3 mL to 1.5 mL of DMF seriously reduced them on the 1 mmol scale reaction (entry 6). Moreover, lower loading of the catalyst (1 mol%) could not maintain the selectivity obtained in the 5 mol% reaction (entry 7). With respect to the above results on DMF, the transition assembly determining the selectivity is supposed to be susceptible to the role of the solvent DMF. Structural effects of chiral modified BINAP ligands were examined in place of BINAP under the same conditions. Only (*R*)-SEGPHOS was capable of providing the aldol product of nearly the same selectivity as (*R*)-BINAP, and the other three ligands were not favored (entries 8-11). The complex, ((*R*)-BINAP)-**3**-OTf, underwent the reaction under similar conditions to give the aldol in a moderate yield with a moderate % ee but how the structure of the starting catalysts influences the reaction rate and selectivity is unclear (entry 12).

Table 1. Platinum complex-catalyzed enantioselective aldol reaction of benzaldehyde with 1-methoxy-2-methyl-(1-trimethylsilyloxy)propene **1** in DMF[a]



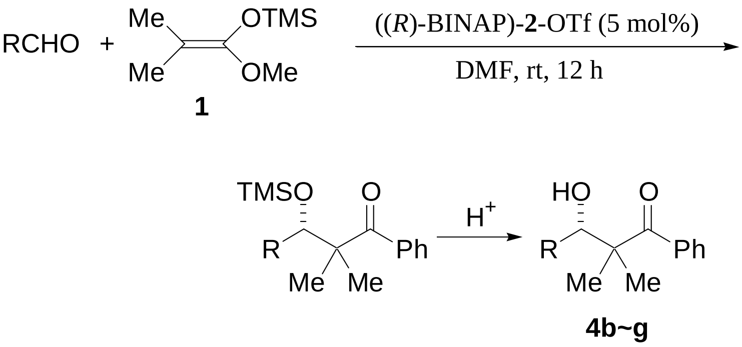
Entry	Catalysts	Yield (%)[b]	% ee[c]
1	((*R*)-BINAP)-**2**-BF_4	53	68
2	((*R*)-BINAP)-**2**-PF_6	77	69
3	((*R*)-BINAP)-**2**-SbF_6	74	80
4[d]	((*R*)-BINAP)-**2**-SbF_6	85	57
5	((*R*)-BINAP)-**2**-OTf	86	84
6[e]	((*R*)-BINAP)-**2**-OTf	54	74
7[f]	((*R*)-BINAP)-**2**-OTf	27	36
8	((*R*)-SEGPHOS)-**2**-OTf	85	83
9	((*R*)-H_8-BINAP)-**2**-OTf	84	75
10	((*R*)-Tol-BINAP)-**2**-OTf	81	79[g]
11	((*S*)-Xylyl-BINAP)-**2**-OTf	85	58[g]
12	((*R*)-BINAP)-**3**-OTf	72	68

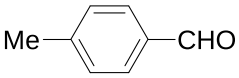
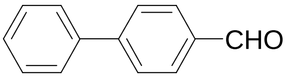
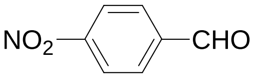
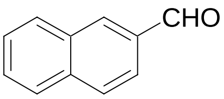
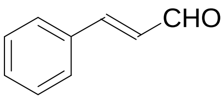
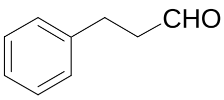
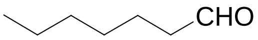
[a] All reactions were carried out at rt with stirring under Ar: benzaldehyde (1.0 mmol), **1** (2.0 mmol), Pt complex (5 mol%)) in DMF (0.3 mL), as described in Ref. 13. [b] Isolated yields. [c] The % ee values were determined with HPLC (Daicel Chiralcel OD-H). [d] CH_2Cl_2 was used. [e] DMF (1.5 mL) was used. [f] Pt (1 mol%) was used. [g] The opposite configuration.

Table 2 illustrates the structural effects of the substrate-aldehydes on reactivity and selectivity in the dicationic ((*R*)-BINAP)-**2**-OTf-catalyzed enantioselective aldol reaction with **1** which was carried out with the typical procedure in DMF. Both aromatic aldehydes having electron-attracting and

-releasing substituents gave comparable results on the yield and % ee with benzaldehyde. A typical primary aliphatic aldehyde, hydrocinnamaldehyde, led to superior enantioselectivity. As long as **1** is used as a silyl nucleophile, ((*R*)-BINAP)-**2**-OTf plays a reliable role in the platinum-catalyzed enantioselective aldol reaction over a wide range of aldehydes, having a phenyl functional group. A linear aliphatic aldehyde, heptanal, underwent the reaction in a low yield but a high % ee (entry 7) while secondary aldehydes did not work under the reaction conditions in analogy with Fujimura's case.

Table 2. [((*R*)-BINAP)Pt(μ-OH)]$_2$-2OTf-catalyzed enantioselective aldol reaction of a variety of aldehydes with **1**[a]



Entry	Aldehydes	Products	Yields (%)	% ee
1		**4b**	82	81
2		**4c**	89	82
3		**4d**	89	79
4		**4e**	92	82
5		**4f**	77	72
6		**4g**	82	92
7		**4h**	23[b]	90

[a] The reaction was carried out according to the typical procedure described in Ref. 13.
[b] The reaction time was 24 h.

In conclusion, our practically simplified mild procedure, starting with a known complex ((*R*)-BINAP)-**2**-OTf, turned out to be available for the platinum-catalyzed enantioselective aldol reaction of a variety of aldehydes with a silyl ketene acetal **1**. Studies with other silyl ketene acetals for acyclic stereoselection accompanying high enantioselectivity are in progress. Mechanistic studies of whether the reaction in question proceeds in a Lewis acid catalyzed manner or through a pathway involving platinum enolates are also under investigation.

Acknowledgements

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9. Unpublished results, Kiyooka, S. -i.; Matsumoto, S.: The dicationic species *in situ* formed from ((*S*)-BINAP)$PtCl_2$ and $AgPF_6$ in the presence of 3Å molecular sieves, according to the procedure used in the Pd enolate studies (Ref. 4), underwent the enantioselective aldol reaction in a good performance on yield and enantioselectivity.

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11. $[((R)\text{-BINAP})\text{Pt}(\mu\text{-OH})]_2\cdot 2\text{OTf}$ was prepared according to the synthetic procedure for the corresponding BF_4 congener reported by Strukul (Ref. 7b): ^{31}P NMR (160 MHz, $CDCl_3$) δ 3.64 ($J_{\text{Pt-P}}$ = 3625 Hz).
12. $[((R)\text{-BINAP})\text{Pt}(H_2O)(\text{OTf})]\cdot\text{OTf}$ was prepared according to the procedure of Stang (Ref. 10): ^{31}P NMR (160 MHz, $CDCl_3$) δ 2.71 ($J_{\text{Pt-P}}$ = 4020 Hz).
13. A typical procedure (5 mol% catalytic reaction) is as follows: To a mixture of $[((R)\text{-BINAP})\text{Pt}(\mu\text{-OH})]_2\cdot 2\text{OTf}$ (49 mg, 0.025 mmol: 0.05 mmol on Pt) in dry DMF (0.3 mL) was added silyl nucleophile **1** (405 μL, 2.0 mmol) at rt under Ar. After the solution was stirred at room temperature for 10 min, benzaldehyde (102 μL, 1.0 mmol) was added. The solution was stirred for 12 h. The formation of the silylated aldol product was checked by the use of the corresponding spot (*Rf*, 0.70) on TLC (20% AcOEt/*n*-hexane). The reaction was quenched upon the addition of 10% aq HCl (5 mL) and diethyl ether (10 mL). After stirring for 10 min, the deprotected aldol was extracted with diethyl ether (20 mL x2). The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give a crude residue. The crude residue was purified by flash column chromatography (SiO_2) (10% AcOEt/*n*-hexane) to give 178 mg in a 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 3H, 1.15 (s, 3H), 2.17 (s, 3H), 3.08 (d, J = 4.16 Hz, 1H), 3.73 (s, 3H), 4.90 (d, J = 4.16 Hz, 1H), 7.35-7.28 (m, 5H). The optical purity of the product was determined by HPLC analysis with a DAICEL CHIRALCEL OD-H column to be 84% ee. The optical rotation was measured to be $[\alpha]_D^{22}$ = +21.50° (c 2.0, CH_2Cl_2). Although the absolute configuration of the product **4a** was not reported in Ref. 3, we decided it with the other products as follows: The absolute configurations were assigned in comparison with the authentic samples, which were prepared by our chiral oxazaborolidinone-catalyzed enantioselective aldol reactions: Kiyooka, S. -i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276. The reported data of **4a**: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861: Zirconium catalyzed enantioselective aldol reaction, (*S*)-isomer of 97% ee: $[\alpha]_D^{25}$ = +5.70° (c 2.49, MeOH). Fu, F.; Teo, Y. -C.; Loh, T. -P. *Tetrahedron Lett.* **2006**, *47*, 4267: Indium catalyzed enantioselective aldol reaction, (*S*)-isomer of 64% ee: $[\alpha]_D$ = +13.43° (c 8.43, CH_2Cl_2). The enantiomeric excesses in Table 1 and 2 were determined by HPLC analysis employing a DAICEL CHIRALCEL OD-H and DJ-H columns: *Rf* values (flow rate, 1 mL/ min) of the products; **4a** (OD-H, 0.7% 2-propanol/*n*-hexane) t_1 = 60 min (major) and t_2 = 66 min (minor): (OJ-H, 2% 2-propanol/*n*-hexane) t_1 = 20 min (major) and t_2 = 27 min (minor); **4b** (OD-H, 1% 2-propanol/*n*-hexane) t_1 = 29 min (major) and t_2 = 47 min (minor); **4c** (OD-H, 5% 2-propanol/*n*-hexane) t_1 = 30 min (major) and t_2 = 38 min (minor); **4d** (OD-H, 5% 2-propanol/*n*-hexane) t_1 = 34 min (major) and t_2 = 47 min (minor); **4e** (OD-H, 1%

2-propanol/*n*-hexane) t_1 = 101 min (major) and t_2 = 134 min (minor); **4f** (OD-H, 1% 2-propanol/*n*-hexane) t_1 = 63 min (major) and t_2 = 92 min (minor); **4g** (OD-H, 2% 2-propanol/*n*-hexane) t_1 = 19 min (major) and t_2 = 35min (minor); **4h** (OD-H, 0.5% 2-propanol/*n*-hexane) t_1 = 9 min (major) and t_2 = 12 min (minor).

14. $[((R)\text{-BINAP})\text{Pt}(\mu\text{-OH})]_2\cdot 2\text{BF}_4$ has been used only once under similar reaction conditions (-25℃, CH_2Cl_2) but the reaction failed miserably (27% yield, 16% ee) (Ref. 3).

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