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Dicationic (BINAP)palladium-catalyzed enantioselective aldol reaction of aldehydes with a silyl enol ether: a simplified practical procedure

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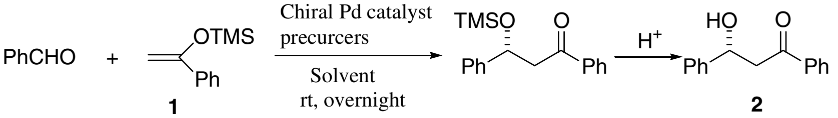
Abstract—The dicationic ((*R*)-BINAP)palladium-catalyzed enantioselective aldol reaction of benzaldehyde with 1-phenyl-1-trimethylsilylethene has been reinvestigated regarding the reaction conditions in the presence of ((*R*)-BINAP)palladium chloride and $AgSbF_6$ with 3 Å molecular sieves. The simplified practical procedure with 1 mol % catalyst loading realized the high performance of 98% yield and 76% ee with reliable reproducibility.

Modern aldol reactions provide one of the most exciting advancements in synthetic chemistry as a reliable method of diastereo- and enantioselectively constructing the demanded C–C skeletons of natural products.[1] Significant progress has, however, been limited to utilizing late transition metal enolates for aldol reactions, except in the extensive development of reductive aldol reactions via their enolates obtained from α,β-unsaturated esters,[2] since the pioneering work made by Bergman and Heathcock, where the preparation of rhodium O-bound enolates, was examined by metathesis of the corresponding silyl enol ethers.[3] The first late transition metal-catalyzed enantioselective aldol reaction had to await the appearance of the cationic BINAP–palladium catalyzed reaction, realized by Shibasaki and Sodeoka.[4] Sodeoka has discovered the methods for generating the chiral palladium enolates from the corresponding silyl enol ethers and has clarified the structure of the effective starting palladium complexes: Pd aqua complexes and binuclear Pd μ-hydroxo complexes. The most important finding was that *water is essential* for the reaction to generate the effective catalyst species and/or the palladium enolate formation reaction.[5,6] In developing the palladium-catalyzed enantioselective aldol reaction, it was necessary to adopt a conventional procedure without the use of special complexes. However, the one-pot procedure starting with the precursor complex has not been reported. We disclose herein a practical reaction procedure in the presence of 3 Å molecular sieves over the reaction.



(1)

By starting with the catalyst precursors, ((*R*)-BINAP)-$PdCl_2$ and $AgSbF_6$, we searched for appropriate reaction conditions which would provide sufficient yields along with high % ee in the reaction of benzaldehyde with 1-phenyl-1-trimethylsilylethene **1** (Eq. 1). Exploration processes toward the optimal conditions

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Keywords: Enantioselective aldol reaction; Palladium-catalyzed aldol reaction; Palladium enolate.

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Table 1. Reactions of benzaldehyde and **1** to explore the sufficient conditions in the presence of chiral Pd catalyst precursors (Eq. 1)[a]

Entry	Catalyst precursors		Solvents	Additives	Yields of **2** (%)	% ee
	Pd complexes	$AgSbF_6$ (mol %)				
1	((*R*)-BINAP)$PdCl_2$[b] 5 mol %	5	Dried DMF[c]	—	7	62
2	((*R*)-BINAP)$PdCl_2$[b] 5 mol %	10	Dried DMF[c]	—	28	75
3	((*R*)-BINAP)$PdCl_2$[b] 5 mol %	10	Dried CH_2Cl_2	—	19	56
4	((*R*)-BINAP)$PdCl_2$[b] 5 mol %	10	Dried DMF[c] + 5% H_2O	—	9	73
5	((*R*)-BINAP)$PdCl_2$[b] 5 mol %	10	Dried DMF[c]	3 Å Molecular sieves[d]	97	78
6	**((*R*)-BINAP)$PdCl_2$[b] 1 mol %**	**2**	**Dried DMF**[e]	**3 Å Molecular sieves**[d]	**98**	**76**
7	((*R*)-Tol-BINAP)$PdCl_2$[b] 5 mol %	10	Dried DMF[c]	3 Å Molecular sieves[d]	96	79
8	((*R*)-Xylyl-BINAP)$PdCl_2$[b] 5 mol %	10	Dried DMF[c]	3 Å Molecular sieves[d]	98	74

[a] The reaction was carried out at rt with stirring overnight: benzaldehyde (1.0 mmol), **1** (1.5 mmol), Pd complex (5 mmol), $AgSbF_6$ (5 or 10 mmol) and/or 3 Å molecular sieves (300 mg) in DMF (2 mL). The product was obtained as the corresponding desilylation one after acidic workup (10% HCl).

[b] Dried and the absence of water checked with the IR spectra.

[c] Distilled from CaH_2 prior to use.

[d] The dried powder of 300 mg was used.

[e] Reaction (1 mol % catalyst loading) was performed in DMF (1 mL); see text for the typical procedure.

are listed in Table 1. The reaction was carried out at rt being stirred overnight. $AgSbF_6$ was used exclusively for the reaction since any specific effects on the counter anions of silver salts were not observed, as reported.[4] Anhydrous DMF (water content: 0.005%), purchased from Kanto Chemical, was used after being distilled (60–65 °C/20 mmHg) from CaH_2 as a suitable solvent for the reaction. $AgSbF_6$ (1 equiv) relative to ((*R*)-BINAP)$PdCl_2$ resulted in a poor performance (entry 1). The use of two equivalents of $AgSbF_6$, which was meant to produce dicationic Pd species, considerably improved both the yield and the % ee (entry 2) but the level was not satisfied. The use of CH_2Cl_2, which is known to be effective for Lewis acid-catalyzed reactions, was not suitable for the reaction in this case (entry 3). The presence of 3 Å molecular sieves (dried over an open flame, cooled under a reduced pressure, and stored under Ar), which selectively absorb smaller molecules like H_2O, surprisingly provided extensive improvements in the yield (to 97%) and the enantiomeric excess (to 78%) in the reaction (entry 5). The catalytic reaction conditions with 1 mol % catalyst loading allowed for the satisfactory performance (entry 6). The aryl substituents in the Pd precursors scarcely affected both the yield and the % ee (entries 7 and 8). The resulting % yields under the improved reaction conditions are a little bit higher than the data reported in the reactions started with the prepared aqua- and hydroxo-Pd complexes.[5]

Typical procedure (1 mol % catalytic reaction): Onto a mixture of ((*R*)-BINAP)$PdCl_2$ (8 mg, 0.01 mmol) and 3 Å molecular sieves (300 mg) DMF (0.7 mL) was added and the suspension was stirred for 15 min, the color then become pale yellow. A DMF solution (0.3 mL) of

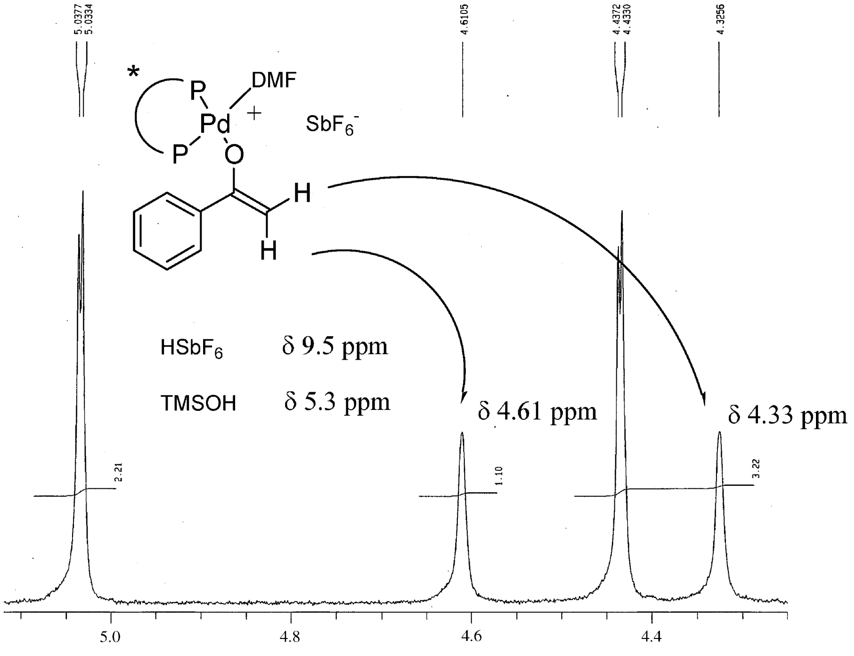
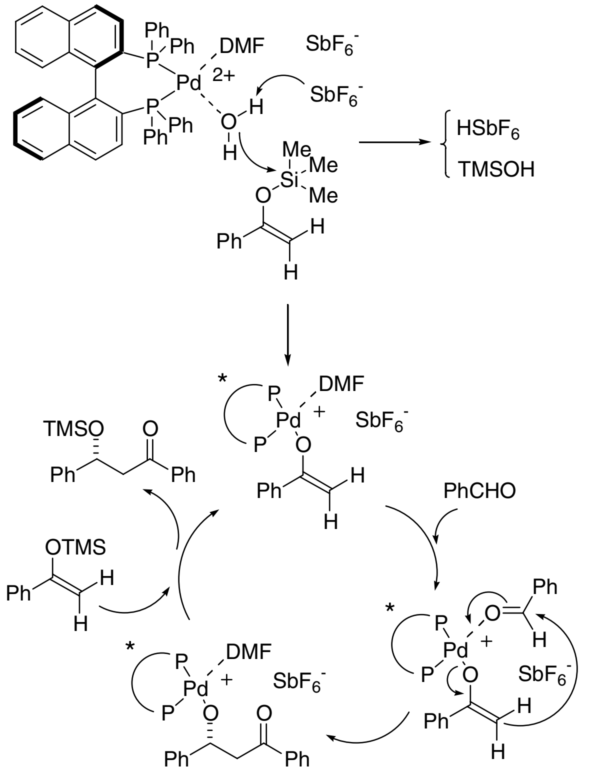


Figure 1. The ^1H NMR spectra of the reaction in DMF-d_7 under the nearly same conditions as the preparative experiment were measured at rt after 10 min of the addition of **1** in the presence of 3 Å molecular sieves.

$AgSbF_6$ (7 mg, 0.02 mmol) was added to the resulting mixture, followed by precipitation of AgCl. The yellow color of the solution was then slightly reduced. A mixture of benzaldehyde (102 μL, 1.0 mmol) and silyl nucleophile **1** (305 μL, 1.5 mmol) was added in one portion to the solution. The resulting solution was stirred for 10 h. The color of the solution then gradually changed to dark brown. The formation of the silylated aldol product was traced by the use of the corresponding spot (Rf, 0.65) 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 × 2). The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the ether, the residue was purified by flash column chromatography (SiO_2) (10% AcOEt/*n*-hexane) to give 222 mg at a 98% yield. The optical purity of the obtained (*R*)-isomer was determined by HPLC analysis with DAICEL CHIRALPAC OD-H (5% 2-propanol/*n*-hexane) to be 76% ee (Rfs, (*S*)-isomer: 20 min and (*R*)-isomer: 23 min). The optical rotation was measured to be $[\alpha]_D^{22}$ +24.07 (*c* 0.19, MeOH).[7]

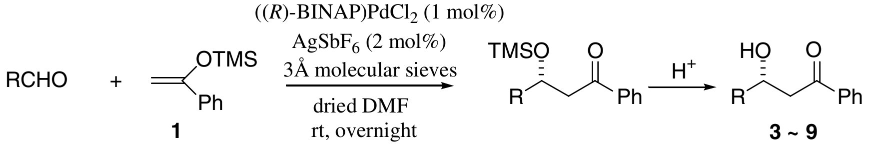
The ^1H NMR study of the reaction under nearly the same conditions as the preparative experiment, was undertaken to obtain information on the reaction conditions and to compare it with the reported data.[4] An aliquot of DMF-d_7 (500 μL) was transferred via a syringe from a purchased ampule (Merck: water content; 0.05%) into an NMR tube containing 3 Å molecular sieves (30 mg) under Ar. Any signals related to the existence of water between δ 2.0 and 5.0 were not detected in the ^1H NMR spectrum just after the addition of ((*R*)-BINAP)$PdCl_2$ (0.025 mmol) and $AgSbF_6$ (0.05 mmol). After 10 min of the addition of excess **1** (0.20 mmol), the ^1H NMR spectrum showed the formation of η^1 oxygen-bound Pd enolate indicating two signals (δ 4.33 and 4.61), which are in fair agreement with the reported data, as shown in Figure 1.[4,5] Two other signals (δ 5.4 and 9.5) were found in addition to the two signals (δ 5.03 and 4.35) related to the starting silyl enolate. It is an interesting observation that the two other signals have the same intensity as the singlet signal of each Pd enolate methylene. In addition, the two peaks folding the intensity are maintained so long as the enolate's signals are present during the reaction. The appearance of these peaks is surely responsible for the Pd enolate formation. The NMR spectra related to the silyl aldol product **2** was observed after the addition of benzaldehyde. The δ 5.4 signal is assigned to the hydroxyl of TMSOH, while the δ 9.5 signal should be related to the acidic hydrogen, $HSbF_6$, which is in equilibrium as the protonated state to solvent DMF.



Scheme 1. A plausible mechanism of the chiral dicationic Pd-catalyzed enantioselective aldol reaction.

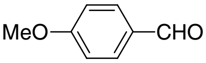
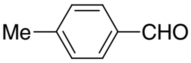
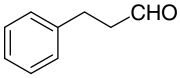
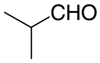
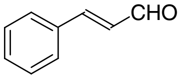
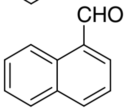
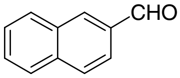
A plausible mechanism of our chiral dicationic Pd-catalyzed aldol reaction could be proposed on the basis of the ^1H NMR observation, which is similar to Sodeoka's mechanism,[5] as shown in Scheme 1. In spite of the severely applied anhydrous conditions, the appearance of TMSOH and $HSbF_6$ consequently suggests the presence of a trace quantity of water at the initial enolate formation reaction. The counter anion, SbF_6^-, abstracts a proton from water coordinated to the cationic Pd center, and then the resulting hydroxyl group successively attacks the silicone atom of the silyl nucleophile to form the corresponding Pd enolate. The following catalytic cycle is initiated by substitution of the coordinated solvent DMF with benzaldehyde, followed by the successive aldol condensation. From the Pd aldolate intermediate the silylated aldol product liberates through the transmetalation affected by the silyl nucleophile **1**.

The dicationic Pd-catalyzed enantioselective aldol reaction with **1** was applied to a variety of aldehydes with the improved typical procedure. The results are summarized in Table 2 (Eq. 2). The *p*-methyl and *p*-methoxy



(2)

Table 2. Dicationic Pd-catalyzed enantioselective aldol reaction of aldehydes with **1** (Eq. 2)[a]

Entry	Aldehydes	Products	Yields (%)	% ee
1		**3**	93	53
2		**4**	97	69
3		**5**	92	77
4		**7**	56	66
5		**6**	92	61
6		**8**	96	87
7		**9**	95	62

[a] The reaction was carried out according to the typical procedure described in the text.

congeners showed similar results to that of benzaldehyde (entries 1 and 2). Reaction with a primary alkyl aldehyde also provided comparable data to that of benzaldehyde (entry 3) while reaction with a secondary alkyl aldehyde somewhat reduced both the yield and the % ee, presumably due to its steric bulkiness (entry 4). An α,β-unsaturated bond is prone to reduce only the % ee, as shown in the case of *trans*-cinnamaldehyde (entry 5). Large aromatic moieties in aryl aldehydes consequently resulted in an efficient increasing of the % ee (entries 6 and 7). In any event, the validity of the effectiveness of the improved reaction conditions was verified in the reaction.

In conclusion, we have found out the practically simplified reaction conditions available for the chiral dicationic Pd-catalyzed enantioselective aldol reaction without utilizing the prepared cationic aqua and/or hydoxo Pd complexes. The reaction conditions, starting with ((*R*)-BINAP)PdCl$_2$ and AgSbF$_6$ in the presence of 3 Å molecular sieves, can be easily handled with reproducible high yield and high % ee. As additional evidence, silyl ketene acetals did not show any enantioselectivity in the reaction, regardless of the high yields. Further studies using other silyl enol ethers are currently under investigation in order to expand the application of the dicationic Pd-catalyzed enantioselective aldol reaction and will be reported in due course.

Acknowledgements

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