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Dicationic ((−)-sparteine)palladium-catalyzed enantioselective aldol reaction of aldehydes with 1-phenyl-1-trimethylsilyloxyethene, proceeding via a palladium enolate

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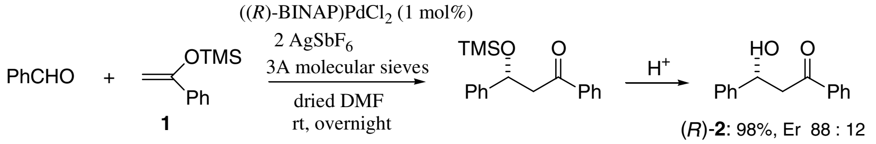
Abstract—A dicationic ((−)-sparteine)palladium complex underwent a superior catalytic enantioselective aldol reaction of aldehydes with 1-phenyl-1-trimethylsilyloxyethene performing satisfactorily, starting with ((−)-sparteine)$PdCl_2$ and $AgSbF_6$ as catalyst precursors (1 mol % loading) in the presence of 3 Å molecular sieves over the reaction.

Significant progress in modern aldol reactions[1] has been limited to utilizing late transition metal enolates for aldol reactions since the pioneering work on rhodium O-bound enolates obtained by metathesis of the corresponding silyl enol ethers was reported.[2] The first late transition metal-catalyzed enantioselective aldol reaction had to await the appearance of the cationic BINAP-palladium catalysts.[3] The successive studies[4] found an effective method generating the chiral palladium enolates from the corresponding silyl enol ethers by using effective starting palladium complexes: Pd aqua complexes and binuclear Pd hydroxo complexes. However, other remarkable developments related to the field have not been reported until now. We have recently found a practical reaction procedure[5] without utilizing such pre-formed complexes for the dicationic ((*R*)-BINAP)palladium-catalyzed enantioselective aldol reaction of benzaldehyde with 1-phenyl-1-trimethylsilyloxyethene **1** to give (*R*)-**2** in a perfect yield with a similar level to the reported enantioselectivity[3] (Eq. 1). By applying the practical one-pot procedure, we have started to search other chiral ligand systems in which this aldol reaction would be effective. We disclose herein that dicationic ((−)-sparteine)palladium complex is quite useful for the purpose proposed in this research; this is the first example of the dicationic palladium-catalyzed enantioselective aldol reaction with a chiral dinitrogen bidentate alkyl ligand. Perhaps the most phenomenal aspect of this is that sparteine serves as an alternative for BINAP in spite of the extreme differences in their structure.



1

(*R*)-**2**: 98%, Er 88 : 12

(1)

Numerous chiral ligands, useful for a variety of Pd-catalyzed enantioselective reactions, are known, of which chiral oxazoline derivatives were found to be especially effective.[6,7] In searching for effective ligands other than

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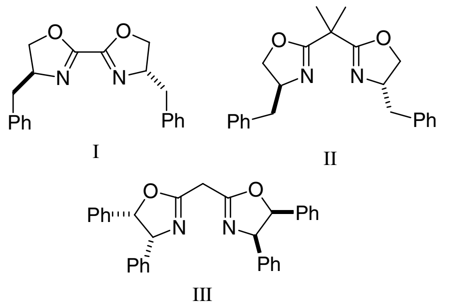


Scheme 1. Commercially available chiral oxazoline ligands tentatively used.

BINAP, we preliminarily adapted commercially available chiral oxazoline derivatives,[8] I, II, and III, to the reaction under consideration, as depicted in Scheme 1. The corresponding catalyst precursors were prepared from the above oxazoline derivatives and $PdCl_2(CH_3CN)_2$. However, the Pd-catalyzed aldol reactions of benzaldehyde with **1**, starting with the (chiral oxazoline ligand)palladium chloride complexes, led to unfavorable results in that the expected enantioselectivity was not observed at all. On the basis that the above ligands exhibited such unpredictable behavior, we could draw a conclusion that the transient dicationic palladium complexes with these ligands might be more labile[9] than the expected stable coordination states, in which the two nitrogen atoms are fixed to the same side (cis configuration) toward the palladium atom in complexation. Then, we directed much of our attention to *N*,*N*-bidentate ligands, having an inherently rigid cis structure. Consequently, (−)-sparteine was selected; the preparation of ((−)-sparteine)$PdCl_2$, with respect to the catalytic kinetic resolution of secondary alcohols as a neutral catalyst in aerobic oxidation, has been reported.[10] The palladium complex was obtained by mixing $PdCl_2(CH_3CN)_2$ and (−)-sparteine in acetone and could be converted in situ to the corresponding dicationic species (Scheme 2).

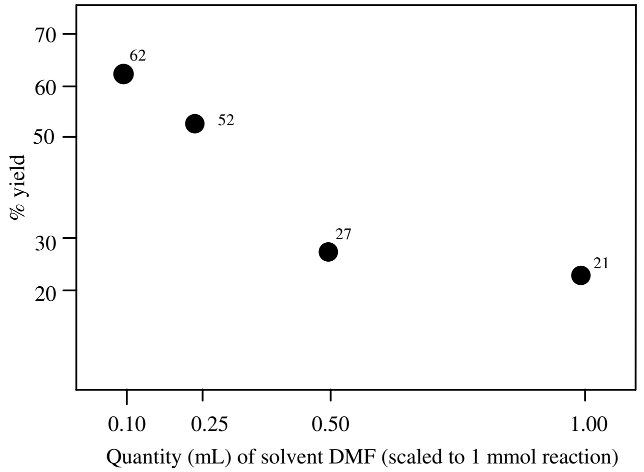
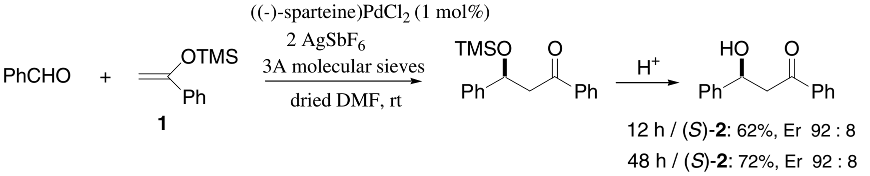
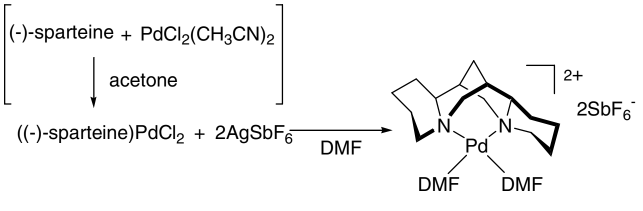


Figure 1. Remarkable effects of DMF quantity on the yields in the cationic ((−)-sparteine)palladium-catalyzed enantioselective aldol reaction (reaction time: 12 h) of benzaldehyde with **1** along with the same enantiomeric ratio (92:8).

The reaction of benzaldehyde with silyl nucleophile **1** in the presence of ((−)-sparteine)palladium complex was investigated using the one-pot procedure, mentioned above. After detailed investigation, we became aware of the apparently different dependence that yield had on the solvent dilution in both reactions using sparteine and BINAP: the reaction with sparteine gave relatively good yields when the quantity of solvent DMF was more limited than the reaction with BINAP. The total use of DMF (0.25 mL) in the reaction with sparteine (1 mol % catalyst loading) was appropriate for the 1 mmol scale of the substrate, in comparison with the effective use of DMF (1 mL) under similar reaction conditions with BINAP, as shown in Figure 1. According to the optimized solvent quantity, the reaction (1 mol % catalyst loading) of benzaldehyde with **1** resulted in a fairly good yield of (*S*)-aldol product with high % ee, as shown in Eq. 2. In addition, it was found that long reaction time improved the % yield. The dicationic palladium species having *N*,*N*-bidentate ligand (sparteine) was revealed to work well, not inferior to the case of *P*,*P*-bidentate ligand (BINAP). The dilution causes only the lowering of the yield without leading to any detectable loss in the % ee so that excess DMF would disturb the in situ regeneration of the active catalyst species. Conclusively, that is characteristic of this dinitrogen ligand but the electronic effect on the dicationic palladium has not been made clear to date.



(2)



Scheme 2. A procedure toward the dicationic ((−)-sparteine)palladium catalyst.

The typical procedure (1 mol % catalyst loading) is as follows: Onto a mixture of ((−)-sparteine)$PdCl_2$

(17 mg, 0.04 mmol) and 3 Å molecular sieves (dried over an open flame, cooled under reduced pressure, and stored under Ar) (powder: 120 mg), DMF[11] (0.2 mL) was added and the suspension was stirred for 15 min, the color then become yellow brown. A DMF solution (0.2 mL) of $AgSbF_6$ (28 mg, 0.08 mmol) was added to the resulting mixture, followed by precipitation of AgCl. The color of the solution changed to being slight yellow. A mixture of benzaldehyde (0.41 mL, 4.0 mmol) and silyl nucleophile **1** (1.24 mL, 6.0 mmol) was added in one portion to the solution. The resulting solution was stirred for 12 h. During the term the color of the solution gradually changed to black. The formation of the silylated aldol product was indicated from the corresponding spot (R_f; 0.65) on TLC (20% AcOEt/*n*-hexane). The reaction was quenched by 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 (10 mL, twice). The organic layers were dried over anhydrous $MgSO_4$. After the ether had evaporated, the residue was purified by flash column chromatography (SiO_2) (10% AcOEt/*n*-hexane) to give 561 mg of the (*S*)-isomer in a 62% yield. The optical purity was determined by HPLC analysis with DAICEL CHIRALPAC OD-H (5% 2-propanol/*n*-hexane) to be 83% ee (R_{fs}, (*S*): 20 min and (*R*): 23 min).

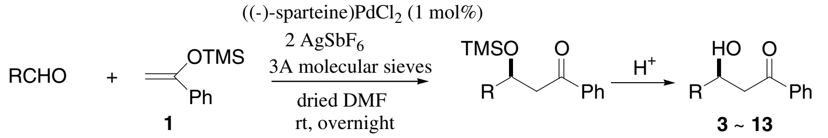
Table 1. Dicationic ((−)-sparteine)Pd-catalyzed enantioselective aldol reaction of a variety of aldehydes with **1** (Eq. 3)[a]

Entry	Aldehydes	Products	Yields (%)	Er[b]
1	*p*-Methylbenzaldehyde	**3**	64	91:9 (84:16)[c]
2	*p*-Methoxybenzaldehyde	**4**	54	70:30
3	*o*-Methoxybenzaldehyde	**5**	72	87:13
4	*p*-Phenylbenzaldehyde	**6**	75	94:6
5	Cinnamaldehyde	**7**	67	80:20
6	3-Phenylpropionaldehyde	**8**	53	92:8 (88:12)[c]
7	Phenylethanaldehyde	**9**	53	82:18
8	Isobutyraldehyde	**10**	28	76:24
9	Pivalaldehyde	**11**	15	69:31
10	1-Naphthylaldehyde	**12**	72	91:9
11	2-Naphthylaldehyde	**13**	75	96:4 (81:19)[c]

[a] The reaction was carried out according to the typical procedure (1 mol % catalyst loading) described in text: ((−)-sparteine)palladium chloride (0.04 mmol), $AgSbF_6$ (0.08 mmol), benzaldehyde (4 mmol), **1** (6 mmol), DMF (0.4 mL), and 3 Å molecular sieves (120 mg).

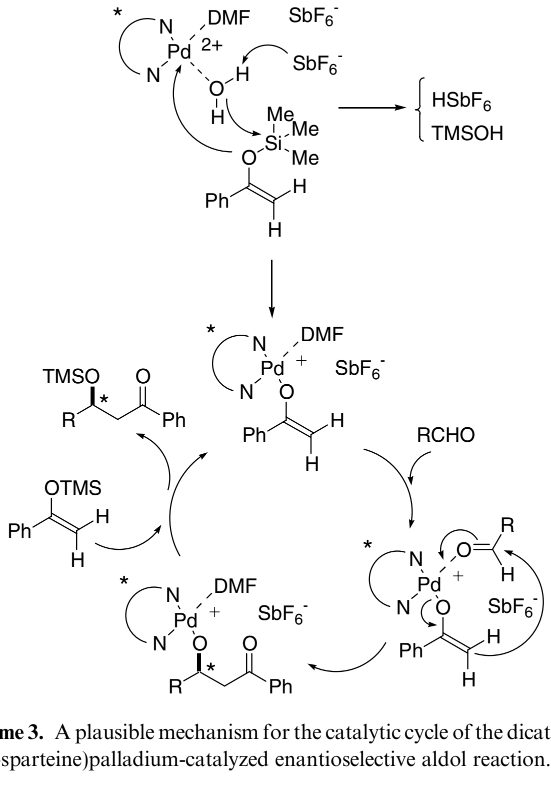
[b] Enantiomeric ratios determined by chiral HPLC (Chiralcel OD).

[c] The data (parentheses) given from the corresponding (BINAP)Pd-catalyzed reaction (Eq. 2).

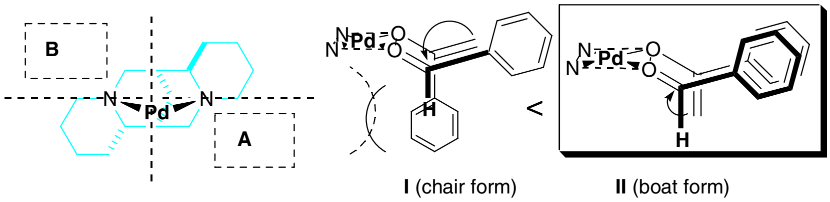


(3)

The results of the dicationic ((−)-sparteine)palladium-catalyzed enantioselective aldol reaction (1 mol % catalyst loading) of a variety of aldehydes with **1** are shown in Table 1 (Eq. 3). The yields were generally slightly lower than the case with BINAP.[5] As was previously mentioned, the decrease in yield might be owing to the labile character of the dicationic (sparteine)palladium complex against the solvent DMF. Conversely, the enantiomeric ratios were apparently higher than the case of BINAP. The steric demands of sparteine at the active catalytic center might play a more suitable role for enantioselective induction. The aldehyde, having a methoxy substituent, led to a considerable reduction not only in the % yield, but also in the enantiomeric ratio presumably via transition states involving different complexations because of the methoxy substituent's ability to preferentially coordinate with the cationic palladium center (entry 2). However, there was no prevailing tendency for *o*-methoxybenzaldehyde (entry 3). The aldehydes, composed of extended π electron systems, were prone to enhance the enantioselectivity (entries 4, 10, and 11). Although reactions with primary aldehydes having a phenyl moiety produced satisfactory yields (entries 6 and 7), the reaction with aliphatic aldehydes decreased the yields and, in addition, the branching at α of these aldehydes seriously suppressed the yields (entries 8 and 9). The effects on the steric bulkiness were also found to decrease the corresponding selectivity (entries 7, 8, and 9).



Scheme 3. A plausible mechanism for the catalytic cycle of the dicationic ((−)-sparteine)palladium-catalyzed enantioselective aldol reaction.



Scheme 4. The most vacant space **A** toward the background of (−)-sparteine and the preferential boat conformer for the transition state assembly at **A**.

As reported in the study using the ^{1}H NMR experiment of the reaction with BINAP,[4,5] the singlet resonances at 4.40 and 4.62 ppm, correlated to the vinyl methylene protons of the O-bound palladium enolate, were also observed in the ^{1}H NMR spectra of the species in situ formed from (sparteine)$PdCl_2$ (1 equiv) and $AgSbF_6$ (2 equiv) in the presence of 3 Å molecular sieves in DMF-d_7. This observation reveals that the reaction with (−)-sparteine proceeds via a similar active intermediate like that found in the reaction with BINAP. Both enantioselective reactions can be presumably explained by the same mechanism, as shown in Scheme 3. On the basis of the 16-electron square-planar geometry, characteristic of dicationic palladium complexes, we can estimate an adequate transition state assembly leading to the (3*S*)-configuration of the product aldol. The bottom part is more open than the upper part of the *N*–Pd–*N* plane, owing to the inherent steric bulkiness of (−)-sparteine, as depicted in Scheme 4. The A part, namely, the right side of the bottom part, seemingly provides the most suitable space available for the aldol condensation process. The high enantioselectivity to *S* may be achieved via a cyclic model, consisting of the palladium enolate, pre-formed at the vacant A space, and the benzaldehyde, coordinated after substituting a solvent DMF, in the square-plane containing the cationic Pd atom. The bulky part of the sparteine near the palladium center considerably affects the geometry of the palladium enolate and allows trans orientation between the Pd atom and the phenyl part with respect to its O–C bond. In addition, the bulkiness also synchronously prevents the approach of the phenyl part of the benzaldehyde and leads to trans orientation between the Pd atom and the phenyl part. Consequently, a boat-like conformer (II) might be more preferential than a chair-like one (I) as a cyclic model in the transition state assembly.

In conclusion, (−)-sparteine was found to be quite suitable as a chiral bidentate ligand for the chiral dicationic palladium-catalyzed enantioselective aldol reactions under the improved practicable reaction conditions. The reaction is effective even with a 1 mol % catalyst loading.

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11. DMF (water content: 0.005%) was purchased from Kanto Chemical and distilled (60–65 °C/20 mmHg) from CaH_2 prior to use.