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Highly enantioselective palladium-catalyzed asymmetric Diels–Alder reactions with chiral phosphino–oxazoline ligands

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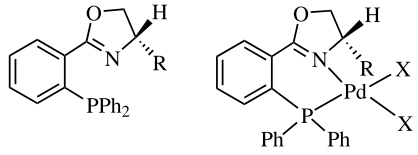
Abstract—A highly efficient catalytic asymmetric Diels–Alder reaction has been developed by using palladium catalysts with chiral 1,3-oxazoline ligands. Almost complete enantioselectivity was realized in reactions mediated by the palladium catalyst formed from ($PdCl_2(CH_3CN)_2$) and (*S*)-2-[2-(diphenylphosphino)phenyl]-4-*t*-butyl-1,3-oxazoline in nitroethane at −78°C.

Catalytic asymmetric Diels–Alder reactions have received much attention for the stereoselective construction of six-membered carbocycles.[1] To date, a number of methodologies for catalytic asymmetric Diels–Alder reactions have been developed with Lewis acidic catalysts such as aluminum,[2] silicon,[3] titanium,[4] boron,[5] zinc,[6] magnesium derivatives,[7] and so on. Currently, much attention is being focused on catalytic asymmetric Diels–Alder reactions with transition metals (chromium,[8] iron,[9] cobalt,[10] copper,[11] ruthenium,[12] and rhodium catalysts[13]) and lanthanide catalysts[14] (europium and ytterbium compounds). However, there have been few precedents of asymmetric Diels–Alder reactions mediated by palladium catalysts.[15] We wish to communicate herein a novel palladium-catalyzed asymmetric Diels–Alder reaction with a chiral 1,3-oxazoline ligand, in which almost complete enantioselectivity was realized.

The palladium complex **2a** was prepared by reacting $PdCl_2(CH_3CN)_2$ with the chiral 1,3-oxazoline ligand **1**[16] under reflux in methanol for 6 h (Fig. 1). However, almost no Diels–Alder reaction occurred with catalyst **2a**: for example, the reaction of **3a** with cyclopentadiene **4** using complex **2a** (derived from ligand **1c**) at −78°C for 120 h gave the Diels–Alder cycloadducts **5a** and **6a** in very poor yield (10%) with extremely low enantioselectivity (4%). Exchange of the counter-ion with other anions such as hexafluoroantimonate, perchlorate, or trifluoromethanesulfonate was required to increase the reactivity of the complex and the potential for asymmetric induction. Exchange of the counter ion was effected by treating the palladium complex **2a** in dichloromethane with either silver hexafluoroantimonate, silver perchlorate, or silver trifluoromethanesulfonate at room temperature for 1 h.

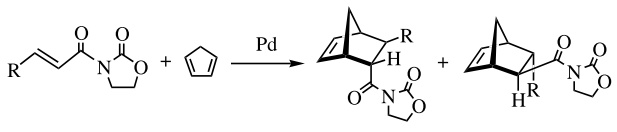


1a R = *i*-Pr
b = $MeOCMe_2$
c = *t*-Bu
d = Ph

2a X = Cl
b = SbF_6
c = ClO_4
d = OTf

Figure 1.

The Diels–Alder reactions of **3** with cyclopentadiene **4** were carried out at −78–20°C in the presence of the palladium complexes **2b–d** obtained above to afford



3a R = H
b = Me
c = Ph

4

(2*S*)-*endo*-**5a**
(2*S*,3*R*)-*endo*-**5b**
(2*R*,3*S*)-*endo*-**5c**

(2*R*)-*exo*-**6a**
(2*R*,3*S*)-*exo*-**6b**
(2*S*,3*R*)-*exo*-**6c**

Scheme 1.

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Table 1. Studies on palladium-catalyzed asymmetric Diels–Alder reactions with chiral phosphino–oxazoline ligands[a]

Entry	Substrate	X in **2**	Ligand (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)	*endo*/*exo* **5**/**6**	e.e. (%) of **5**
1	**3a**	SbF_6	**1a** (20)	CH_2Cl_2	−78	3.5	88	92/8	82 (2*S*)
2	**3a**	SbF_6	**1b** (20)	CH_2Cl_2	−78	3.5	91	91/9	91 (2*S*)
3	**3a**	SbF_6	**1b** (20)	$EtNO_2$	−78	48	68	95/5	94 (2*S*)
4	**3a**	ClO_4	**1b** (20)	$EtNO_2$	−78	48	45	91/9	91 (2*S*)
5	**3a**	OTf	**1b** (20)	$EtNO_2$	−78	48	51	92/8	93 (2*S*)
6	**3a**	Cl	**1c** (20)	CH_2Cl_2	−78	120	10	87/13	4 (2*S*)
7	**3a**	SbF_6	**1c** (5)	CH_2Cl_2	−78	72	68	89/11	57 (2*S*)
8	**3a**	SbF_6	**1c** (10)	CH_2Cl_2	−78	44	70	92/8	81 (2*S*)
9	**3a**	SbF_6	**1c** (15)	CH_2Cl_2	−78	3.5	83	93/7	87 (2*S*)
10	**3a**	SbF_6	**1c** (20)	CH_2Cl_2	−78	3.5	93	93/7	92 (2*S*)
11	**3a**	SbF_6	**1c** (20)	Toluene	−78	48	8	75/25	32 (2*S*)
12	**3a**	SbF_6	**1c** (20)	CCl_4	−20	36	72	85/15	16 (2*S*)
13	**3a**	SbF_6	**1c** (20)	$EtNO_2$	−78	48	76	97/3	99 (2*S*)
14	**3a**	ClO_4	**1c** (20)	$EtNO_2$	−78	48	43	93/7	84 (2*S*)
15	**3a**	OTf	**1c** (20)	$EtNO_2$	−78	48	56	91/9	91 (2*S*)
16	**3a**	SbF_6	**1c** (20)	THF	−78	48	29	80/20	20 (2*S*)
17	**3a**	ClO_4	**1c** (20)	CH_2Cl_2	−78	3.5	87	94/6	89 (2*S*)
18	**3a**	OTf	**1c** (20)	CH_2Cl_2	−78	4	95	94/6	95 (2*S*)
19	**3b**	SbF_6	**1c** (20)	CH_2Cl_2	−78	12	81	91/9	71 (2*S*,3*R*)
20	**3b**	OTf	**1c** (20)	CH_2Cl_2	−78	12	75	89/11	68 (2*S*,3*R*)
21	**3c**	SbF_6	**1d** (20)	CH_2Cl_2	−78	48	73	89/11	69 (2*R*,3*S*)
22	**3c**	OTf	**1d** (20)	CH_2Cl_2	−78	48	61	87/13	64 (2*R*,3*S*)

[a] The palladium complex **2a** was prepared by reacting $PdCl_2(CH_3CN)_2$ (5, 10, or 20 mol%) with the corresponding amount of ligands **1a**–**d** under reflux in MeOH for 2 h. Conversion of **2a** into **2b**–**d** was carried out by treating the palladium complex **2a** with $AgSbF_6$, $AgClO_4$, or AgOTf, respectively, in CH_2Cl_2 at room temperature for 1 h. The reactions of **3a**–**c** with **4** (5.0 equiv.) were carried out in the presence of the palladium complexes **2a**–**d** obtained above.

optically active Diels–Alder adducts **5** and **6** (Scheme 1). The results obtained under various reaction conditions are summarized in Table 1.

In all cases, the *endo* adduct **5a** with the same absolute configuration was preferentially obtained with extremely high diastereoselectivity.

The effects of the counter ion in the palladium complex were examined in order to improve the reactivity and the level of asymmetric induction. Compared to the chloro palladium complex **2a** (entry 6), the hexafluoroantimonate **2b**, perchlorate **2c**, and trifluoromethanesulfonate palladium complexes **2d** provided high chemical yields and e.e.s of (*S*)-**5a** (entries 10, 17, and 18).

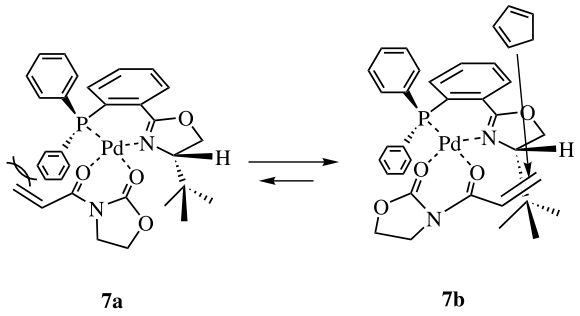
The effects of the catalyst loading on the asymmetric Diels–Alder reaction were next examined: as shown in entries 7–10 of Table 1, a loading of 10–20 mol% of the palladium catalyst was the most effective for completion of the reaction.

The effects of the solvent were studied by completing the reaction using dichloromethane, toluene, tetrahydrofuran, carbon tetrachloride and nitroethane (entries 10–13, and 16). Dramatic solvent effects were observed: The reactions of **3a** with **4** in the presence of the palladium complex **2b** (derived from ligand **1c**) in toluene, carbon tetrachloride or tetrahydrofuran gave (*S*)-*endo*-**5a** as the main product with rather low e.e. (32, 16, or 20%, respectively). However, the reactions in dichloromethane or nitroethane provided excellent enantioselectivity (92 or 99%, respectively). Use of dichloromethane as the solvent provided high efficiency both in chemical yield and enantioselectivity (entry 10). The highest enantioselectivity (99%) of (*S*)-*endo*-**5a** was obtained from the reaction in nitroethane at −78°C using 20 mol% of **2b** (derived from **1c**) with high diastereoselectivity (entry 13).

The steric effects of the substituents attached to the stereogenic center of ligands **1** were studied by changing the steric bulk (*i*-propyl, methoxy-*i*-propyl, *t*-butyl, and phenyl groups). Extremely high enantioselectivity (over 90%) was observed with ligands **1b** and **1c** (entries 2–5, 10, 13, 15, and 18).

Introduction of alkyl and aryl substituents in the dienophiles **3b**,**c** led to a slight decrease in the enantioselectivity. The palladium-catalyzed Diels–Alder reactions of substrates **3b**,**c** with **4** were carried out in dichloromethane at −78°C in the presence of 20 mol% of the palladium complexes **2b**,**d** (derived from ligands **1c** and **1d**, respectively) to give (2*S*,3*R*)-*endo*-**5b**, and (2*R*,3*S*)-*endo*-**5c**, respectively, with slightly lower enantioselectivity: the reaction of **3b** or **3c** with **4** using **2b** (derived from ligand **1c** or **1d**) gave (2*S*,3*R*)-*endo*-**5b** or (2*R*,3*S*)-*endo*-**5c** as the main products with 71 or 69% e.e. (entries 19 and 21), respectively.

As indicated in this report, the chiral palladium–phosphino–oxazoline complex we have reported was very



7a **7b**

Scheme 2.

useful as a catalyst for asymmetric Diels–Alder reactions, since it provides much higher enantioselectivities than those observed with other metal catalysts such as Fe, Cu, and Mg.

The mechanism of asymmetric induction was rationalized on the basis of the stereochemical outcome of the reactions. In the conformational equilibrium of the six-membered square planar palladium complex, **7b** is favored over **7a** because of the existence of steric interference between the acryloyl group and the diphenyl substituents on the phosphine moiety in **7a** (Scheme 2). Thus, cyclopentadiene attacks the acryloyl olefin from the *Re*-face in **7b** preferentially in an *endo* fashion, to give (2*S*)-*endo*-**5a**,**b** and (2*R*)-*endo*-**5c** as the main products with almost complete efficiency.

Thus, a highly enantioselective catalytic asymmetric method for Diels–Alder reactions has been developed by using a palladium catalyst derived from the chiral ligand, 2-[2-(diphenylphosphino)phenyl]-4-*t*-butyl-1,3-oxazoline. Almost complete efficiency in chemical yield and enantioselectivity has been realized using the palladium–hexafluoroantimonate complex as a chiral catalyst.

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