## Palladium-Catalyzed Asymmetric [3+3] Cycloaddition of Trimethylenemethane Derivatives with Nitrones\*\*

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In memory of Yoshihiko Ito

Transition-metal-catalyzed intermolecular cycloaddition reactions can provide rapid access to cyclic compounds in a convergent manner with high efficiency. The development of asymmetric variants is, therefore, of high value in synthetic organic chemistry. In this regard, although [4+2] cycloadditions, such as the Diels-Alder reaction, have been extensively investigated for the construction of enantioenriched sixmembered cyclic compounds,<sup>[1]</sup> transition-metal-catalyzed asymmetric [3+3] cycloaddition reactions have been much less studied to date.<sup>[2]</sup> Herein we describe the development of a palladium-catalyzed asymmetric [3+3] cycloaddition of trimethylenemethane derivatives (TMMs) with nitrones to produce six-membered heterocycles with high stereoselectivity.<sup>[3]</sup>

Since their first introduction by Trost and Chan in 1979,<sup>[4]</sup> Pd-TMM complexes have served as an efficient source of three-carbon units in various cyclic frameworks, particularly in the context of [3+2] cycloaddition reactions.<sup>[5]</sup> Unfortunately, however, the application of this useful chemistry to asymmetric catalysis is very limited. In fact, only two reports, by Ito, Hayashi, and co-workers with ferrocene-based chiral bisphosphine ligands in 1989<sup>[6]</sup> and by Trost et al. with chiral phosphoramidite ligands in 2006,<sup>[7]</sup> have met with reasonable success in the palladium-catalyzed asymmetric [3+2] cycloaddition of trimethylenemethane derivatives, and there have been no reports on the corresponding [3+3] cycloaddition reaction to date.<sup>[3,8]</sup>

In an initial investigation, we conducted a reaction of the TMM precursor **1a** with nitrone **2a** in the presence of 5 mol %  $[CpPd(\eta^3-C_3H_5)]$  (Cp = cyclopentadienyl) and 10 mol % PPh<sub>3</sub> at 40 °C, and found that product **3aa** was obtained in 86 % yield as a mixture of two diastereomers (d.r.  $\approx$  1:1), with almost no formation of the structural isomers **4aa** and **5aa** [Eq. (1)].<sup>[9,10]</sup> The observed high selectivity to generate **3aa** over **4aa** or **5aa** indicates that the initially formed Pd-TMM

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intermediate **A** rapidly isomerizes to Pd-TMM intermediate **B**, which contains a more stable benzylic anion, and this intermediate is engaged in the subsequent cycloaddition with **2a** (Scheme 1).<sup>[11]</sup>



**Scheme 1.** Proposed reaction pathway for the palladium-catalyzed [3+3] cycloaddition of **1 a** with **2 a**.

On the basis of the result obtained using PPh<sub>3</sub> as a ligand [Eq. (1)], we investigated the use of (S)-MeO-mop,<sup>[12]</sup> a chiral monodentate phosphine, as a ligand in the reaction of 1a with 2a, but the reaction was very sluggish and gave 3aa in only 17% yield with low diastereo- and enantioselectivity (Table 1, entry 1). No reaction was observed when (S)-binap,<sup>[13]</sup> a chiral bisphosphine ligand, was used (Table 1, entry 2). In contrast, the reaction proceeded smoothly in the presence of diethylamino-substituted phosphoramidite ligand (S)-**6** $a^{[14]}$  to give 3aa in 83% yield, but both the diastereoselectivity and enantioselectivity were only moderate (trans/cis 60:40 with 27% ee and 45% ee, respectively; Table 1, entry 3). Modification of the nitrogen substituents of the phosphoramidite ligands gave (S,R,R)-**6** $\mathbf{b}^{[14,15]}$  and its diastereomer (S,S,S)-**6b**,<sup>[14]</sup> both of which improved the diastereoselectivity for the formation of the trans isomer (Table 1, entries 4 and 5); the trans diastereomer was formed in 84% ee in the presence of (S,S,S)-6b. Changing the ligand framework from 1,1'binaphthyl ((S,S,S)-6b) to 5,5',6,6',7,7',8,8'-octahydro-1,1'binaphthyl  $((S,S,S)-6c)^{[16]}$  resulted in further improvement in the diastereoselectivity and enantioselectivity (trans/cis



## Communications

 Table 1:
 Ligand effects in the palladium-catalyzed asymmetric

 [3+3] cycloaddition of 1 a with 2 a.



Entry	Ligand	Yield [%] <sup>[a]</sup>	trans/cis <sup>[b]</sup>	trans ee $[\%]^{[c]}$	<i>cis ee</i> [%] <sup>[c]</sup>
1	(S)-MeO-mop	17	57:43	21	32
2	(S)-binap	0	-	-	-
3	(S)- <b>6</b> a	83	60:40	27	45
4	(S,R,R)- <b>6b</b>	79	79:21	21	2
5	(S,S,S)- <b>6b</b>	90	85:15	84	39
6	(S,S,S)- <b>6c</b>	85	87:13	91	62
7	(S,S,S)-6d	95	89:11	92	77

[a] Yield of isolated product. [b] Determined by  $^1H$  NMR spectroscopy. [c] Determined by HPLC on chiral stationary phases (AD-H + OG) with hexane/2-propanol 95:5.



87:13, *trans* isomer: 91% *ee*; Table 1, entry 6). A slightly better result was achieved (*trans/cis* 89:11, *trans* isomer: 92% *ee*) by employing (*S*,*S*,*S*)-**6d** as the ligand, which has a bis((S)-1-(2-naphthyl)ethyl)amino group<sup>[17]</sup> rather than a bis((S)-1-phenylethyl)amino group (Table 1, entry 7).

The scope of this asymmetric [3+3] cycloaddition reaction was investigated under these conditions using (*S*,*S*,*S*)-**6d** as the ligand (Table 2). It was found that various aryl groups can be tolerated on the electrophilic carbon atom of the nitrone (Table 2, entries 1–5), with [3+3] cycloadducts obtained in excellent yield (92–99% yield) and relatively high diastereoselectivity (*trans/cis* 76:24–89:11) and high enantioselectivity (91–92% *ee*).<sup>[18]</sup> Several TMM precursors with different aryl groups can also be used in the [3+3] cycloaddition reaction with similarly high efficiency (Table 2, entries 6–10). Unfortunately, the use of unsubstituted TMM precursor **1e** gives the cycloadduct with almost no enantioselectivity (Table 2, entry 11).

The ethyl ester of *trans*-3dc (Table 2, entry 10) was hydrolyzed to give *trans*-7 [Eq. (2)], the absolute configura-

**Table 2:** Scope of the palladium-catalyzed asymmetric [3+3] cycloaddition.



[a] Yield of isolated product. [b] Determined by <sup>1</sup>H NMR spectroscopy. [c] Determined by HPLC. [d] 5 mol% Pd catalyst was used. [e] 8 mol% Pd catalyst was used. [f] Ligand (*S*,*S*,*S*)-**6** was used.



tion of which was determined to be S,S by X-ray crystallographic analysis of its benzylamine salt (Figure 1).<sup>[19]</sup>

In summary, we have developed a palladium-catalyzed asymmetric [3+3] cycloaddition of trimethylenemethane derivatives with nitrones to produce the corresponding 1,2-oxazines in high yield. The use of a modified phosphoramidite ligand has led to the formation of these compounds with high stereoselectivity.



*Figure 1.* X-ray structure of (S,S)-7·H<sub>2</sub>NCH<sub>2</sub>Ph with thermal ellipsoids drawn at the 50% probability level.

## **Experimental Section**

General procedure for the reaction in Table 2: A solution of  $[CpPd(\eta^3-C_3H_5)]$  (2.1 mg, 9.9 µmol or 3.4 mg, 16 µmol) and ligand (*S,S,S*)-6d (12.9 mg, 19.9 µmol or 20.7 mg, 32.0 µmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.30 mL) was stirred for 10 min at room temperature. Nitrone 2 (0.200 mmol), 1 (0.400 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (0.20 mL) were then added, and the resulting mixture was stirred for 48 h at 40 °C. The reaction mixture was directly passed through a pad of silica gel with EtOAc and the solvent removed under vacuum. The residue was purified by preparative TLC on silica gel to afford 3.

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