Asymmetric Catalysis

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

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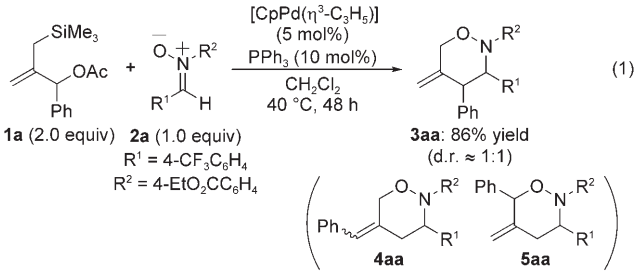
In memory of Yoshihiko Ito

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 six-membered cyclic compounds,[1] transition-metal-catalyzed asymmetric [3+3] cycloaddition reactions have been much less studied to date.[2] 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.[3]

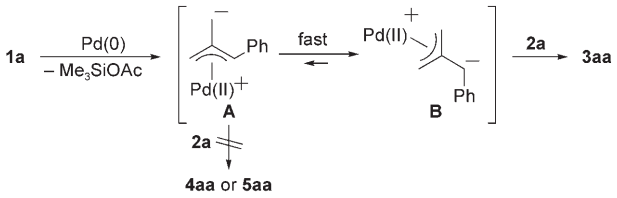
Since their first introduction by Trost and Chan in 1979,[4] Pd-TMM complexes have served as an efficient source of three-carbon units in various cyclic frameworks, particularly in the context of [3+2] cycloaddition reactions.[5] Unfortunately, however, the application of this useful chemistry to asymmetric catalysis is very limited. In fact, only two reports, by Ito, Hayashi, and co-workers with ferrocene-based chiral bisphosphine ligands in 1989[6] and by Trost et al. with chiral phosphoramidite ligands in 2006,[7] 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.[3,8]

In an initial investigation, we conducted a reaction of the TMM precursor **1a** with nitrone **2a** in the presence of 5 mol% [CpPd(η^3-C_3H_5)] (Cp = cyclopentadienyl) and 10 mol% PPh_3 at 40 °C, and found that product **3aa** was obtained in 86% yield as a mixture of two diastereomers (d.r. ≈ 1:1), with almost no formation of the structural isomers **4aa** and **5aa** [Eq. (1)].[9,10] The observed high selectivity to generate **3aa** over **4aa** or **5aa** indicates that the initially formed Pd-TMM



(1)

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).[11]



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

On the basis of the result obtained using PPh_3 as a ligand [Eq. (1)], we investigated the use of (*S*)-MeO-mop,[12] 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,[13] 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*)-**6a**[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*)-**6b**[14,15] and its diastereomer (*S*,*S*,*S*)-**6b**,[14] 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*

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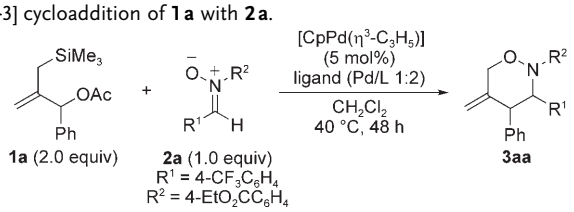
Table 1: Ligand effects in the palladium-catalyzed asymmetric [3+3] cycloaddition of **1a** with **2a**.



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

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

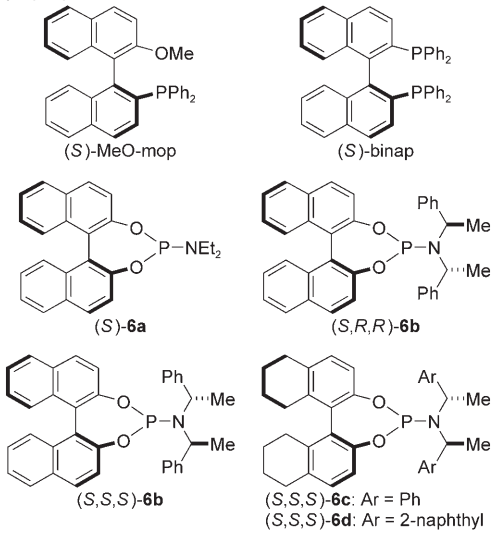
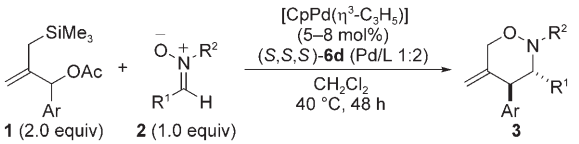


Table 2: Scope of the palladium-catalyzed asymmetric [3+3] cycloaddition.

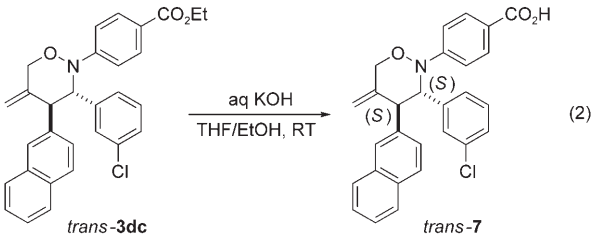


1a: Ar = Ph
1b: Ar = 4-MeC$_6$H$_4$
1c: Ar = 4-ClC$_6$H$_4$
1d: Ar = 2-naphthyl
1e: Ar = H

2a: R^1 = 4-CF$_3$C$_6$H$_4$, R^2 = 4-EtO$_2$CC$_6$H$_4$
2b: R^1 = 4-CF$_3$C$_6$H$_4$, R^2 = 4-PhMeNC(O)C$_6$H$_4$
2c: R^1 = 3-ClC$_6$H$_4$, R^2 = 4-EtO$_2$CC$_6$H$_4$
2d: R^1 = 2-FC$_6$H$_4$, R^2 = 4-EtO$_2$CC$_6$H$_4$
2e: R^1 = Ph, R^2 = 4-EtO$_2$CC$_6$H$_4$

Entry	TMM	Nitrone	Product	Yield [%][a]	*trans*/*cis*[b]	*trans ee* [%][c]
1[d]	**1a**	**2a**	**3aa**	95	89:11	92
2[e]	**1a**	**2b**	**3ab**	99	84:16	91
3[e]	**1a**	**2c**	**3ac**	98	85:15	91
4[e]	**1a**	**2d**	**3ad**	99	76:24	91
5[e]	**1a**	**2e**	**3ae**	92	85:15	92
6[d]	**1b**	**2a**	**3ba**	78	83:17	88
7[d]	**1c**	**2a**	**3ca**	91	86:14	90
8[e]	**1c**	**2c**	**3cc**	98	85:15	93
9[d,f]	**1d**	**2a**	**3da**	85	88:12	89
10[e,f]	**1d**	**2c**	**3dc**	99	85:15	93
11[d,f]	**1e**	**2a**	**3ea**	90	–	1

[a] Yield of isolated product. [b] Determined by ^{1}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*)-**6c** was used.



(2)

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[17] 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*).[18] 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 configuration of which was determined to be *S,S* by X-ray crystallographic analysis of its benzylamine salt (Figure 1).[19]

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.

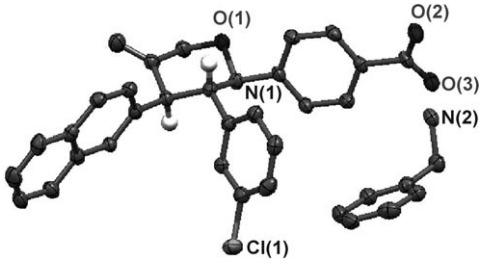


Figure 1. X-ray structure of (*S,S*)-**7**·H_2NCH_2Ph with thermal ellipsoids drawn at the 50% probability level.

Experimental Section

General procedure for the reaction in Table 2: A solution of $[CpPd(\eta^3\text{-}C_3H_5)]$ (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_2Cl_2 (0.30 mL) was stirred for 10 min at room temperature. Nitrone **2** (0.200 mmol), **1** (0.400 mmol), and CH_2Cl_2 (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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