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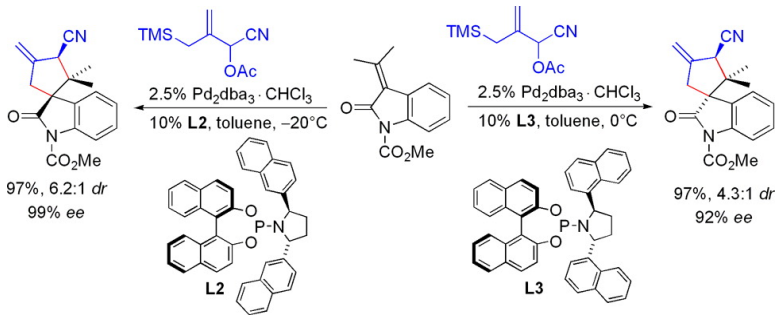

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Enantioselective Construction of Spirocyclic Oxindolic Cyclopentanes by Palladium-Catalyzed Trimethylenemethane-[3+2]-Cycloaddition

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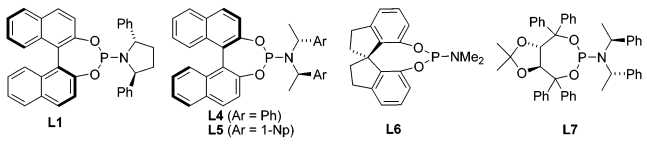
The transition metal-catalyzed [3+2] trimethylenemethane (TMM) cycloaddition is a powerful and versatile method for the construction of cyclopentanes.[1] Pd−TMM complexes generated from 3-acetoxy-2-trimethylsilylmethyl-1-propene and catalytic amounts of palladium react with electron deficient olefins to produce *exo*-methylenecyclopentanes in a highly chemo-, regio-, and diastereoselective manner.[2] The ubiquity of cyclopentane containing natural products makes the development of an efficient asymmetric process highly desirable. However, applications of this methodology in asymmetric catalysis are very rare.[3] Our ongoing efforts toward the synthesis of complex oxindole alkaloids prompted us to investigate the reactivity of 3-alkylidene-oxindoline-2-ones **1** toward Pd−TMM complexes.[4] We chose the cyano-substituted TMM-precursor **2**,[5] reasoning it could enhance the asymmetric induction. Furthermore, this provides an increase in molecular complexity by the creation of an additional stereogenic center as well as installation of a synthetically valuable and versatile functionality.

The initially formed Pd−TMM complex **3a** equilibrates rapidly to the most stabilized species **3b**,[6] which then adds across the activated double bond of **1** to form the *exo*-methylenecyclopentane (Scheme 1). Our initial experiments with hexamethylphosphorous triamide (HMPT) as ligand for palladium showed that the desired cycloadduct formed in excellent yield as a cis/trans mixture (Table 1, entry 1). A screen to elucidate the influence of the oxindole nitrogen substituent with our previously utilized ligand **L1**,[3a] revealed that electron withdrawing groups significantly improved the reactivity (entries 5−9). Among them, the methoxycarbonyl group provided the optimal balance between reactivity, selectivity, and ease of removal. In all these cases **L1** gave predominantly the *cis*-cyclopentane **5** (1:3 ratio for entry 9). This contrasts the reaction with HMPT as ligand (entry 1), where a 2:1 ratio favoring the corresponding trans product **4** was observed. Our attempts to optimize the conditions for the formation of *both* diastereomers resulted in good diastereo- and excellent enantioselectivities for either *trans*-**4** (95% ee and 4.3:1 dr with **L3**, entry 15) and *cis*-**5** (99% ee and 1:6.2 dr with **L2**, entry 16).[7] This remarkable divergence of **L2** and **L3**,[8] differing only by the position of their naphthyl-substituents on the pyrrolidine part of the ligand, might be rationalized as depicted in Scheme 1: The bulky 1-naphthyl-substituents of **L3** preferentially orient the aromatic oxindole part of the substrate **1** under the BINOL portion of the ligand. The 2-naphthyl-substituents of **L2** are shielding an area closer to the phosphorus center of the ligand, favoring an orientation of the oxindole benzene ring away from the BINOL-portion of the ligand.



With these conditions elaborated, we then turned our attention toward the scope of the reaction as summarized in Table 2. Variation

Scheme 1

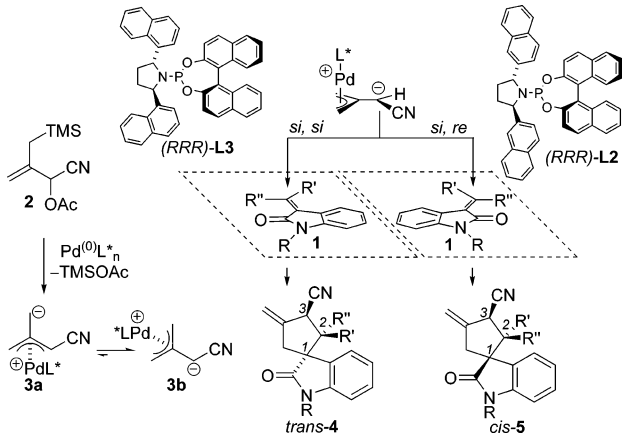


Table 1. Selected Optimization Studies[a]

entry	ligand	*T*, °C	R	% yield	**4** / **5**	**4** % ee	**5** % ee
1	HMPT	23	CO_2Me	99	2:1		
2	**L1**	23	H	*b*			
3	**L1**	23	Me	91	1:1	91	53
4	**L1**	23	PMB	60[c]	1:1		
5	**L1**	23	Ts	50	1:2		
6	**L1**	23	Boc	95	1:1.1	74	93
7	**L1**	23	Acetyl	98	1:2.2	85	89
8	**L1**	23	CO_2Me	94	1:2.3	72	73
9	**L1**	0	CO_2Me	93	1:3	80	97
10	**L4**	23	CO_2Me	86	4.3:1	83	73
11	**L4**	0	CO_2Me	84	4.5:1	87	60
12	**L5**	23	CO_2Me	0	-	-	-
13	**L6**	23	CO_2Me	99	1.1:1	27	27
14	**L7**	23	CO_2Me	0	-	-	-
15	**L3**	0	CO_2Me	97	4.3:1	92	95
16	**L2**	−20	CO_2Me	97	1:6.2	96	99

[a] R′ = R″ = Me; all reactions were performed at 0.2 M in toluene with 2.5% Pd_2dba_3·$CHCl_3$, 10% ligand, 1.5 equiv **2** and stirred for 12 h. Yields were combined isolated yields; ee's were determined by HPLC with a chiral stationary phase column. [b] Complex mixture. [c] Conversion.

of the substituents of the oxindole portion had little influence on the ee (85−96% with **L3** for *trans*-**4** and 92−99% with **L2** for *cis*-**5**).

However, the diastereoselectivity is sensitive to the benzenoid substitution pattern, wherein **L2** gave optimal dr with no substitution (entry 1) and **L3** gave optimal dr with the more highly substituted systems (entries 2, 4, and 5). An X-ray crystal structure analysis of 6-chloro-substituted cycloadduct **5b** (entry 2) unambiguously allowed the determination of the absolute configuration to be *R* at C3. Exchanging the oxindole residue by the related benzofuranone **1f** (entry 6) gave comparable results as illustrated by the parent substrate **1a** (entry 1).

We also explored the influence of an unsymmetrical substitution pattern on both sides of the double bond, thus creating a third stereocenter in the cycloadduct (Table 3). A smooth addition was observed even with the sterically demanding trisubstituted olefins

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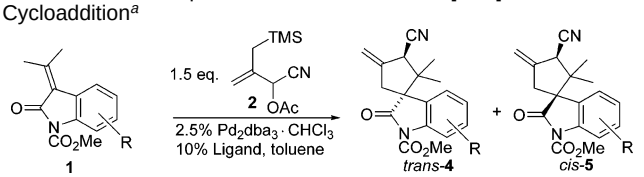
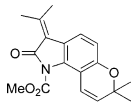
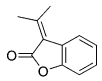
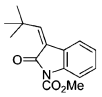
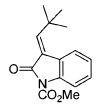
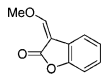
Table 2. Initial Scope of the Substituted TMM [3+2] Cycloaddition[a]



entry	substrate **1**	ligand	% yield	**4** / **5**	**4**	% ee	**5**	% ee
1	(R = H)	**L2**[b]	97	1:6.2	**4a**	96	**5a**	>99
	1a	**L3**[c]	97	4.3:1		92		95
2	(R = 6-Cl)	**L2**[b]	90	1:2.7	**4b**	99	**5b**	92
	1b	**L3**[c]	99	19:1		93		77
3	(R = 6-MeO)	**L2**[c]	94	1:2.7	**4c**	95	**5c**	99
	1c	**L3**[d]	94	4:1		85		84
4	(R = 6,7-MeO)	**L2**[b]	96	1.3:1	**4d**	>99	**5d**	99
	1d	**L3**[c]	97	14:1		96		80
5	 **1e**	**L2**[b]	99	1:2.3	**4e**	99	**5e**	>99
		L3[c]	99	15:1		86		76
6	 **1f**	**L2**[b]	99	1:5.7	**4f**	>99	**5f**	>99
		L3[c]	91	4.6:1		94		92

[a] All reactions were performed at 0.2 M in toluene and stirred for 12 h; yields were combined isolated yields; ee's were determined by HPLC with a chiral stationary phase column. [b] At −20 °C. [c] At 0 °C. [d] At 23 °C.

Table 3. Scope of the Substituted TMM [3+2] Cycloaddition[a]

entry	substrate **1**	ligand	% yield	**4** / **5**	**4** % *ee*	**5** % *ee*
1	 **1g**	**L2**[b]	89	1:2.6	**4g** 98	**5g** 99
		L3[c]	80	>20:1	20	-
2	 **1h**	**L2**[d]	86	3.4:1	**4h** 92	**5h** 92
		L3[d]	72	3.9:1	74	12
3	 **1i**	**L2**[b]	90	1:5.7	**4i** 80	**5i** 98
		L3[c]	78	3.2:1	80	41
4	 **1j**	**L2**[d]	72	3.1:1[e]	**4j** 87	**6**[e] -
		L3[d]	60	3.4:1[e]	55	-
5	 **1k**	**L2**[d]	76	4.2:1[e]	**4k** 90	**7**[e] -
		L3[d]	34	4.0:1[e]	50	-

[a] All reactions were performed at 0.2 M in toluene with 2.5% Pd_2dba_3·$CHCl_3$, 10% ligand, 1.5 equiv **2** and stirred for 12 h; yields were combined isolated yields; ee's were determined by HPLC with a chiral stationary phase column. [b] At −20 °C. [c] At 0 °C. [d] At 23 °C. [e] **4**:**6** and **4**:**7** with **6** and **7** being tentatively assigned structures.

bearing a *t*-butyl group (**1g**, **1h** entry 1 and 2). The observed stereochemistry at C1 and C2 of the resulting cycloadducts **4g**/**4h** and **5g**/**5h** reflects the double bond geometry of the substrate,[9] supporting our proposed approach depicted in Scheme 1.[10] However, the observed ee values with **L3** were only modest, compared to the reaction with **L2** which still proceeded in high selectivity (entry 1 and 2). Electron rich enol ethers (**1i**, entry 3**)** are tolerated as well as substrates bearing an additional electron withdrawing ethyl ester group on the double bond (**1j**, entry 4).[11] A substrate with a fully unsymmetrical tetrasubstituted double bond formed the expected cyclopentane with two adjacent all carbon quaternary stereogenic centers (**1k**, entry 5).[12] With this highly hindered substrate the use of the more reactive ligand **L2** was mandatory to maintain complete conversion. Interestingly, regardless of the used ligand, the trans adduct is formed preferentially.

In summary, we have demonstrated a catalytic asymmetric palladium-catalyzed [3+2] cycloaddition with cyano-substituted Pd−TMM-complexes leading to spirocyclic oxindolic cyclopentanes. Remarkably, **L2** and **L3** complement each other by providing the opposite diastereomers of the cycloadduct. The reaction proceeds with sterically demanding olefins under mild conditions generating arrays of up to three stereogenic centers with excellent yields and enantiomeric excesses. Further extension of the reaction scope and its application in the synthesis of complex target molecules using cycloadducts such as **4d** and **4e** of Table 2 are ongoing projects in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 5974.
(7) The parent unsubstituted TMM-donor gave under identical reaction conditions a quantitative yield and 71% ee with **L2**.
(8) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc*., in press.
(9) Partial equilibration of the double bond prior to the cycloaddition occurs when using the more nucleophilic HMPT as ligand.
(10) With this substrate class, a scrambling of the double-bond geometry through bond rotation of an intermediate species is not observed, which is in accordance with both a stepwise mechanism and fast ring closure (Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1980**, *102*, 6359. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.) or a concerted mechanism described by Singleton (Singleton, D. A.; Schulmeier, B. E. *J. Am. Chem. Soc.* **1999**, *121*, 9313).
(11) Double bond migration of preferentially one product isomer occurred.
(12) Peterson, E. A.; Overman, L. E. *Proc Natl Acad Sci U.S.A.* **2004**, *101*, 11943.

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