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Enantioselective Palladium-Catalyzed [3 + 2] Cycloadditions of Trimethylenemethane with Nitroalkenes

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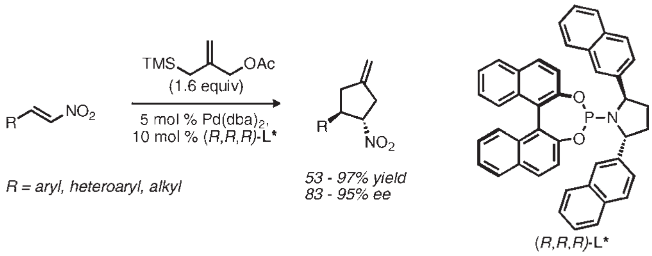
ABSTRACT



Nitroalkenes readily undergo palladium-catalyzed [3 + 2] cycloaddition with trimethylenemethane to generate nitrocyclopentanes in excellent yield and enantioselectivity. Furthermore, the products thus formed are highly versatile synthetic intermediates and provide convenient access to both cyclopentylamines and cyclopentenones.

The palladium-catalyzed cycloaddition of trimethylenemethane (TMM) represents a powerful method for the construction of carbo- and heterocycles and proceeds with high chemo-, regio-, and diastereoselectivity.[1] First described over 30 years ago as a racemic method,[2] a general, asymmetric protocol was only recently achieved with the discovery that phosphoramidites bearing bulky 2,5-diarylpyrrolidines were effective chiral ligands.[3a] Using these ligands, we have demonstrated asymmetric [3 + 2] cycloadditions with several olefins,[3] imines,[4] and aldehydes.[5]

Although electron-deficient olefins were among the first substrates demonstrated in the asymmetric TMM reaction, the examples to date are nearly completely restricted to alkenes activated by functional groups bearing a carbonyl. The lone exception is the reaction of cinnamyl nitrile,[3a] which proceeded in moderate enantioselectivity under the reaction conditions. During the course of these studies, however, we identified nitroalkenes (**2**, Scheme 1) as attractive substrates for the asymmetric TMM reaction. The substrates themselves are widely available and have been demonstrated in racemic TMM cycloadditions;[6] however, the known sensitivity of the asymmetric method to changes in the electron-withdrawing group[3,4] make their success far from certain. Furthermore, the nitrocyclopentanes (**3**) thus formed would possess considerable synthetic utility.[7] Simple reduction of the nitro group would provide access to cyclopentylamines (**4**), which have been the focus of synthetic efforts and represent potential therapeutic

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(1) Chan, D. M. T. Recent Advances in Palladium-Catalyzed Cycloadditions Involving Trimethylenemethane and its Analogs. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 57–83.

(2) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.

(3) Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schworer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328. (b) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.

(4) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398. (b) Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2010**, *132*, 8238.

(5) Trost, B. M.; Bringley, D. A.; Silverman, S. M. *J. Am. Chem. Soc.* **2011**, *133*, 7664.

(6) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276. (b) Holzapfel, C. W.; van der Merwe, T. L. *Tetrahedron Lett.* **1996**, *37*, 2307.

(7) Noboru, O. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(8) Zhou, J. (S.); Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220. (b) Bournaud, C.; Chung, F.; Luna, A. P.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin, L. *Synthesis* **2009**, *6*, 869. (c) Noonan, G. M.; Cobley, C. J.; Lebl, T.; Clarke, M. L. *Chem.—Eur. J.* **2010**, *16*, 12788.

(9) Kurteva, V. B.; Afonso, C. A. *Chem. Rev.* **2009**, *109*, 6809.

(10) Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchinson, T. L.; Babu, Y. S.; Bantia, S; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379. (b) De Clercq, E. *Nat. Rev. Drug Discovery* **2006**, *5*, 1015.

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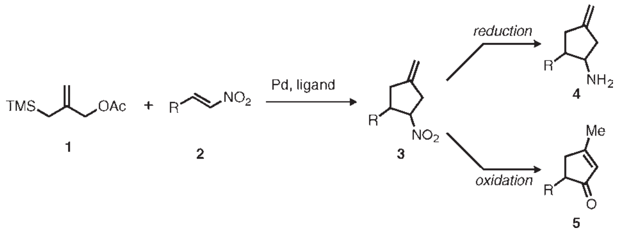
Scheme 1. Synthesis and Derivatization of Nitrocyclopentanes



agents.[8,9] For example, peramivir, an antiviral currently under development for the treatment of influenza, possesses a cyclopentylamine core.[10] Alternatively, oxidation of the nitro group to a ketone (the Nef reaction) generates an enantioenriched cyclopentenone (**5**), a widely studied and important intermediate in organic synthesis.[11,12]

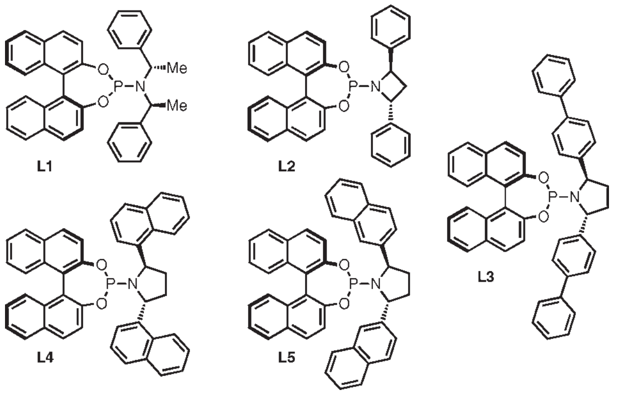
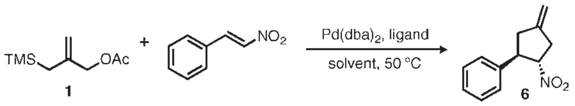


Figure 1. Chiral ligands used in this study.

To evaluate the viability of nitroalkenes as a substrate class, we began our studies using *trans*-β-nitrostyrene. Although ligands **L1** and **L2** (Figure 1) gave cycloaddition with nitrostyrene in good yield, the ee was poor (Table 1, entries 1 and 2). Consistent with our earlier reports, phosphoramidites bearing a pyrrolidine gave higher ee's. Bis-*p*-biphenyl **L3** and bis-1-naphthyl **L4** led to a significant improvement, but bis-2-naphthyl **L5** proved best, yielding the nitrocyclopentane in 93% yield and 87% ee. Briefly examining other solvents (entries 6–7) gave no advantage over toluene; while selectivity was highest in THF, the yield was only moderate.

Table 1. Initial Optimization with *trans*-β-Nitrostyrene[a]



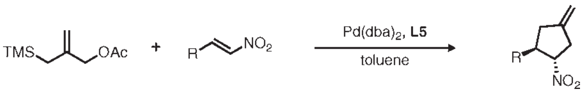
entry	ligand	solvent	% yield	% ee
1	L1	toluene	85	−3
2	L2	toluene	70	18
3	L3	toluene	79	53
4	L4	toluene	79	84
5	**L5**	**toluene**	**93**	**87**
6	L5	dioxane	79	85
7	L5	THF	57	91

[a] All reactions were conducted at 0.15 M in the indicated solvent, at 50 °C, with 1.6 equiv of **1a**, 5% Pd(dba)$_2$, and 10% ligand. Yields are isolated values; ee's were determined by chiral HPLC.

Various types of *trans*-β-substituted nitroalkenes were successfully utilized under these optimized conditions (Table 2). Both electron-rich and -poor nitrostyrene derivatives, possessing various substitution patterns, gave the nitrocyclopentanes in good yield and excellent enantioselectivity (entries 1–5). A reaction temperature of 50 °C was adequate for most substrates, although a lower temperature gave improved ee's in select cases with minimal impact on the yield.

Disubstituted nitrostyrenes could also be used, as seen in the reactions of both 1- and 2-naphthyl-substituted nitroalkenes (entries 6 and 7, respectively). 3,4-Methylenedioxy-β-nitrostyrene was previously used in a racemic

Table 2. Reaction Scope with Nitroalkene Derivatives[a]



entry	R =	product	*T*, °C	% yield	% ee
1	3-bromophenyl	**7**	50	63	94
2	4-chlorophenyl	**8**	50	65	95
3	2-methylphenyl	**9**	23	91	93
4	4-methylphenyl	**10**	50	82	89
5	4-methoxyphenyl	**11**	23	72	94
6	1-naphthyl	**12**	23	67	92
7	2-naphthyl	**13**	50	82	93
8	3,4-methylene-dioxyphenyl	**14**	50	80	91
9	2-furyl	**15**	23	66	88
10	3-furyl	**16**	50	58	87
11	2-thiophenyl	**17**	23	75	91
12	*N*-Boc-3-indolyl	**18**	50	91	86
13	*n*-propyl	**19**	50	88	83
14	cyclohexyl	**20**	50	97	93
15	*tert*-butyl	**21**	50	97	88
16	(*E*)-styrenyl	**22**	50	53	93

[a] All reactions were conducted at 0.15 M in toluene with 1.6 equiv of **1a**, 5% Pd(dba)$_2$, and 10% **L5**. Yields are isolated values; ee's were determined by chiral HPLC.

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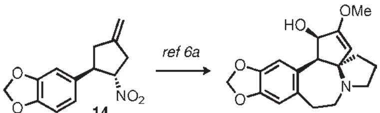
(11) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479.

(12) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, 789. (b) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328.

TMM reaction but gave the product as a mixture of diastereomers.[6a] Under the asymmetric conditions, however, the product was isolated as a single diastereomer in 80% yield and 91% ee (entry 8). Interestingly, this product was used in the synthesis of (±)-cephalotaxine, the major alkaloid from the *Cephalotaxus* species (Scheme 2). Our asymmetric synthesis therefore constitutes a formal synthesis of cephalotaxine, albeit as the unnatural enantiomer when using (*R*,*R*,*R*)-**L5**, a situation easily rectified by switching to the (*S*,*S*,*S*) enantiomer of **L5**.[13]

Scheme 2. Formal Synthesis of (+)-Cephalotaxine



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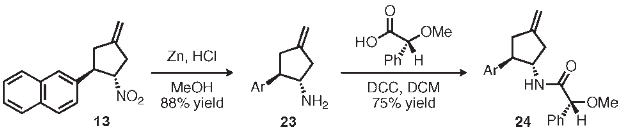
(+)-cephalotaxine

Nitroalkenes bearing heterocyclic rings or aliphatic groups could also be used. For reactions with the former, heterocycles such as furans, thiophenes, and indoles were all found to be compatible with the reaction conditions (Table 2, entries 9–10, 11, and 12, respectively). Notably, the substrates bearing the nitroalkene at the 2-position of the heterocycle gave lower selectivity than the corresponding 3-substituted heterocycles, and a lower reaction temperature was therefore required (compare, for example, entries 9 and 10). In the reactions with the latter, several alkyl substituents were tolerated, such as primary, secondary, and tertiary groups (entries 13, 14, and 15, respectively). Interestingly, the conjugated nitrodiene derived from cinnamaldehyde gave a reaction exclusively at the double bond proximal to the nitro group (entry 16). Although the yield was only moderate, the enantioselectivity remained high.

Having demonstrated that a range of nitrocyclopentanes could be easily synthesized, we were pleased to discover that the products could be readily functionalized. For example, reduction to cyclopentylamine **23** was accomplished with zinc in acidic methanol (Scheme 3). Converting this amine to either the (*R*)- or (*S*)-mandelamide allowed for the determination of absolute configuration by ^{1}H NMR analysis.[14] Alternatively, X-ray crystal analysis of the (*R*)-mandelamide (Figure 2) provided for an unambiguous assignment of absolute stereochemistry, and all other cycloadducts are proposed by analogy.

The nitro group also serves as a handle for further alkylation (Scheme 4). Both palladium-catalyzed prenylation and Michael addition, giving nitrocyclopentanes **25** and **26**, respectively, proceeded with excellent diastereoselectivity and good yield and provide access to cyclopentanes with a tetrasubstituted stereocenter.

Scheme 3. Generation of Cyclopentylamine **23** and Its Conversion to Mandelamide **24**



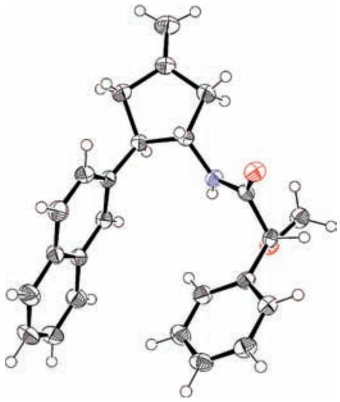


Figure 2. X-ray based ORTEP drawing of mandelamide **24**. Spheres are drawn at the 50% probability level.

Converting the nitro group into a carbonyl (the Nef reaction) proved to be more challenging, in part because the product ketone would contain an α-stereocenter that could easily epimerize.[15] Despite a wide variety of known conditions for accomplishing the Nef reaction,[7] most synthetic protocols gave either no reaction or complete decomposition of the nitrocyclopentane. An encouraging lead was identified using the conditions of Palomo,[16] involving formation of the trimethylsilyl nitronate followed by oxidation with *m*-chloroperoxybenzoic acid. In contrast to Palomo's report, however, we recovered not the ketone but *gem*-chloro-nitrocyclopentane **27** in reasonable yield as a single diastereomer. This unusual result has been observed previously,[17] and the structure of **27** has been unambiguously assigned by X-ray crystal analysis (Figure 3). The propensity for the peroxy acid to react not with the silyl nitronate, but with the chloride counterion demonstrated a need for a more reactive nitronate species. The high reactivity of potassium nitronates[18] prompted us to test the conditions of Zhao, using potassium *tert*-butoxide to generate the nitronate anion followed by oxidation with dimethyldioxirane.[19] Gratifyingly, use of these conditions gave cyclopentenone **28** in 86% yield with only minimal racemization. This impressive result is further highlighted

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(13) Teichert, J. F.; Feringa, B. L. *Synthesis* **2010**, *7*, 1200.

(14) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202.

(15) Bures, J.; Isart, C.; Vilarrasa, J. *Org. Lett.* **2009**, *11*, 4414.

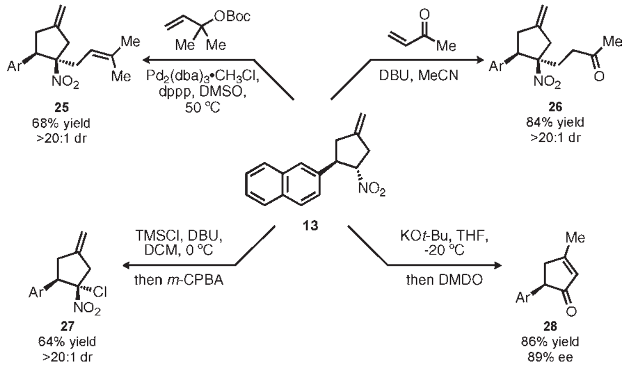
(16) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361.

(17) Zschiesche, R.; Hafner, T.; Reissig, H.-U. *Liebigs Ann. Chem.* **1988**, 1169.

(18) Hwu, J. R.; Josephraja, T.; Tsay, S.-C. *Synthesis* **2006**, *19*, 3305.

(19) Adam, W.; Makosza, M.; Saha-Moller, C. R.; Zhao, G.-G. *Synlett* **1998**, 1335.

Scheme 4. Synthetic Utility of Nitrocyclopentanes



by the rate at which the exocyclic methylene isomerizes; no trace of the product bearing the nonisomerized product is detected, yet the cyclopentenone is isolated with high ee.

To conclude, we have demonstrated a highly enantioselective palladium-catalyzed cycloaddition of TMM with nitroalkenes. The reaction tolerates a wide variety of nitroalkenes and gives products as single diastereomers in high yield and ee. The functionalization of these cycloadducts proceeds with excellent diastereoselectivity and minimal racemization where applicable, allowing for rapid access to several important synthetic intermediates such as cyclopentylamines, cyclopentenones, and cyclopentanes bearing tetrasubstituted stereocenters.

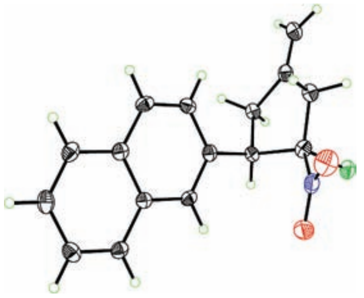


Figure 3. X-ray based ORTEP drawing of *gem*-chloronitrocyclopentane **27**. Spheres are drawn at the 50% probability level.

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Supporting Information Available. Experimental details and spectral data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.