

Highly Substituted Enantioenriched Cyclopentane Derivatives by Palladium-Catalyzed [3 + 2] Trimethylenemethane Cycloadditions with Disubstituted Nitroalkenes

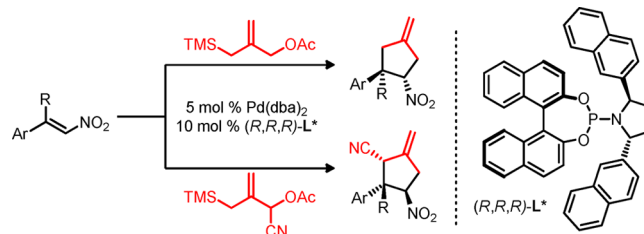
Barry M. Trost,* Dustin A. Bringley, and B. Michael O'Keefe

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

bmtrost@stanford.edu

Received August 29, 2013

ABSTRACT



β,β -Disubstituted nitroalkenes readily undergo palladium-catalyzed [3 + 2] cycloaddition with trimethylenemethane to generate nitrocyclopentanes in excellent yield and enantioselectivity. The reaction provides access to heavily substituted cyclopentanes containing up to three contiguous stereocenters, and the products may be converted to both cyclopentylamines and cyclopentenones. A rare dependence of the sense of chirality of the cycloadducts was observed to be exclusively dependent on the structure of the palladium-bound trimethylenemethane intermediate.

Nitroalkenes are versatile synthetic precursors that have been widely used in organic synthesis.¹ As part of a long-standing interest in the palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (TMM) with electron-deficient olefins,^{2,3} our group recently developed conditions for the enantioselective synthesis of five membered rings by Pd-TMM cycloaddition, using phosphoramidites⁴

and diaminophosphites⁵ as the chiral ligands. We anticipated that asymmetric cycloaddition with nitroalkenes would provide rapid access to nitrocyclopentanes^{6,7} and, in a previous report,⁸ demonstrated that simple nitrostyrene and monosubstituted nitroalkene derivatives underwent Pd-TMM cycloadditions with high enantioselectivity. The success of these nitroalkenes prompted us to examine disubstituted derivatives, focusing our efforts on β,β -disubstitution since the resultant cyclopentanes would bear a quaternary stereocenter. In addition, precedent for

(1) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(2) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432.

(3) 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.

(4) Selected examples: (a) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 19483. (b) Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2012**, *134*, 4941. (c) Trost, B. M.; Bringley, D. A.; Silverman, S. M. *J. Am. Chem. Soc.* **2011**, *133*, 7664.

(5) (a) Trost, B. M.; Lam, T. M. *J. Am. Chem. Soc.* **2012**, *134*, 11319. (b) Trost, B. M.; Lam, T. M.; Herbage, M. *J. Am. Chem. Soc.* **2013**, *135*, 2459.

(6) For racemic examples of Pd-TMM cycloadditions with nitroalkenes, see: (a) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436. (b) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276. (c) Holzapfel, C. W.; van der Merwe, T. L. *Tetrahedron Lett.* **1996**, *37*, 2307.

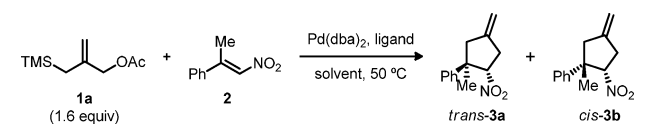
(7) For recent examples of asymmetric synthesis of nitrocyclopentanes involving formal cycloaddition, see: (a) Zhao, G.-L.; Ibrahim, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Cordova, A. *Chem.—Eur. J.* **2008**, *14*, 10007. (b) Hong, B.-C.; Chen, P.-Y.; Kotame, P.; Lu, P.-Y.; Lee, G.-H.; Liao, J.-H. *Chem. Commun.* **2012**, *48*, 7790.

(8) Trost, B. M.; Bringley, D. A.; Seng, P. S. *Org. Lett.* **2012**, *14*, 234.

asymmetric Pd-TMM cycloadditions with such highly substituted substrates is relatively limited. While we have demonstrated highly efficient reactions with both 3-alkylidene oxindoles⁹ and ketimines,^{4b} these reactions required the use of a cyano donor to achieve high ee. Herein, we describe our efforts to expand the scope of this reaction to include β,β -disubstituted nitroalkenes, a type of substitution rarely examined due to the anticipated low reactivity of such acceptors. These studies also revealed, for the first time, an unusual reversal of asymmetric induction as a function of the substitution on the TMM donor.

Our study was initiated using *trans*- α -methyl- β -nitrostyrene (**2**) as a model substrate (Table 1). Surprisingly, the reaction provided a pair of diastereomeric products under all conditions examined, in contrast to all previous studies using standard donor **1a** in asymmetric cycloadditions. These cycloadducts were fully separable by chromatography and were later identified as epimeric at the quaternary stereocenter (vide infra). Interestingly, ligand **L1** (Figure 1) gave predominately the *cis* product **3b**, albeit in poor ee (entry 1). On the other hand, phosphoramidites **L2** and **L3**, bearing a cyclic amine bound to the phosphorus, favored formation of *trans*-**3a** (entries 2–3). While the diastereo- and enantioselectivity were highest with the latter, the yield under these conditions was modest, and there was evidence of an open-chain side product¹⁰ that appeared to poison the catalyst as unreacted donor **1a** was always observed in the crude reaction mixture. A slight improvement in yield was observed upon increasing the concentration in toluene to 0.5 M (entry 4), or by increasing the catalyst loading to 7.5 mol % (entry 5). Alternatively, we found that the use of dioxane suppressed formation of the open-chain impurity, allowing good yields of the product without requiring a higher catalyst loading (entry 7).

Table 1. Initial Reaction Optimization^a



entry	ligand	solvent	% yield	dr ^b	% ee ^c
1	L1	toluene	89	1:3	83, 29
2	L2	toluene	78	1.2:1	83, 48
3	L3	toluene	52	3:1	89, 45
4 ^d	L3	toluene	57	3:1	92, 53
5 ^e	L3	toluene	66	3:1	90, 56
6	L3	THF	38	3:1	93, 55
7	L3	dioxane	75	2:1	92, 43

^a All reactions were conducted at 0.15 M in the indicated solvent, at 50 °C, with 1.6 equiv of **1a**, 5 mol % Pd(dba)₂, and 10 mol % ligand. Yields are isolated, combined values; ee's were determined by chiral HPLC. ^b dr's are reported as the ratio of **3a:3b**. ^c ee's shown for **3a** and **3b**, respectively. ^d Reaction conducted at 0.5 M. ^e Reaction conducted using 7.5 mol % Pd(dba)₂ and 10 mol % ligand at 0.33 M.

(9) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.

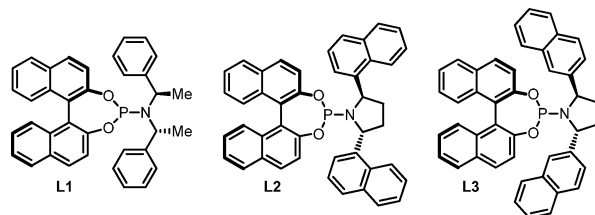
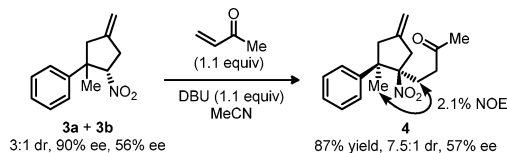


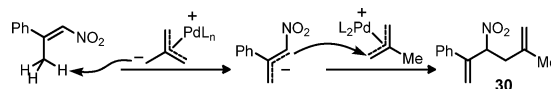
Figure 1. Chiral ligands explored during optimization.

We were able to determine which of the stereocenters in **3a** and **3b** was epimeric by performing a Michael addition with methyl vinyl ketone on the diastereomeric mixture (Scheme 1). In the event, **4** was obtained in 87% yield as a 7.5:1 mixture of diastereomers, as determined by the ¹H NMR signals for the diastereomeric methyl groups at δ 1.58 (major) and δ 1.41 (minor). Upon irradiation of the ring-bound methyl group in the major diastereomer, a 2.1% enhancement was observed at the proton β to the ketone, suggesting the *trans* configuration as depicted. Surprisingly, the major diastereomer was formed in only 57% ee; given the high yield, it seemed unlikely that kinetic discrimination was responsible for the poor ee. In the Michael addition, only the configuration at the quaternary carbon is expected to control the facial selectivity of alkylation; therefore, the ee of the product will be preserved if both diastereomers **3a** and **3b** have the same stereochemistry at the quaternary center. The observed 57% ee for **4**, however, indicates that the quaternary stereocenters in **3a** and **3b** have opposite absolute configurations. In addition, the absolute configuration for **3a** was established by preparing diastereomeric mandelamide derivatives and correlating their relative ¹H NMR shifts.¹¹ We note that the sense of stereoreduction is consistent with our previous efforts.⁸

Scheme 1. Functionalization and Subsequent Assignment of Diastereoselectivity



(10) A species tentatively assigned as **30** was observed in the crude reaction mixture by ¹H NMR. It likely arises via deprotonation of the nitroalkene by Pd-TMM, where the allylic anion thus formed is alkylated by the palladium- π -allyl. Such a pathway has been previously observed: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.



(11) See Supporting Information for details.

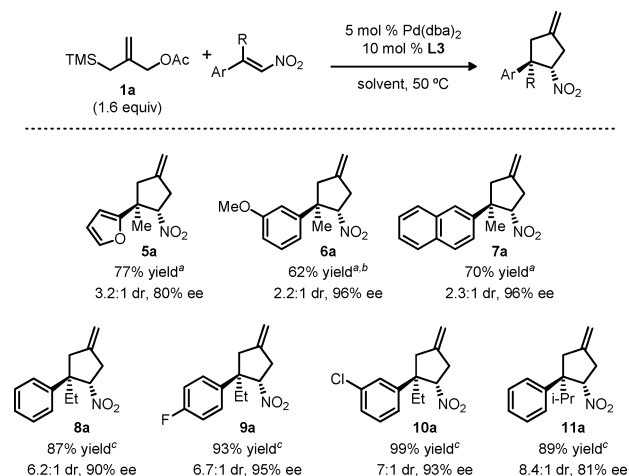
Although the dr remained modest, we decided to explore the scope of the reaction to see if other substrates might proceed with higher diastereoselectivity. Other β -methyl nitroalkenes provided comparable results (Scheme 2), generally giving the cycloadducts in good yield with excellent ee for the major diastereomer, and with similar levels of diastereoselectivity as seen in our initial optimization (**5a–7a**). The use of dioxane as solvent allowed for both electron-rich and moderately electron-poor substrates to be employed, although, for the latter, the increased acidity of the allylic proton led to more open-chain side products and a higher catalyst loading was required to obtain a good yield (**6a**). While we anticipated that nitroalkenes bearing higher-order β -substituents would be less likely to undergo allylic deprotonation, we also recognized that the desired cycloaddition would be more sterically hindered. Nevertheless, when *trans*- α -ethyl- β -nitrostyrene was subjected to our standard conditions in dioxane or toluene, an excellent yield of cycloadduct **8a** was obtained. Toluene provided a slightly better dr and was therefore used with these substrates. Substitution on the aryl ring was tolerated, with both 4-fluoro- and 3-chloro derivatives giving cycloadducts in excellent yield and ee (**9a** and **10a**, respectively). Finally, branched substituents could also be employed, as evidenced by the formation of **11a** in good yield, dr, and ee.

We also anticipated that moving to a less basic Pd-TMM intermediate would significantly improve the efficiency of the cycloaddition by reducing the propensity for allylic deprotonation. Accordingly, we investigated the use of cyano donor **1b**, as the resultant cyclopentanes would be highly substituted and possess multiple functional handles for synthetic elaboration. Gratifyingly, the reaction of **2** proceeded in nearly quantitative yield under slightly modified conditions to give nitrocyclopentane **12** as a single diastereomer with excellent ee (Scheme 3). Indeed, this reaction turned out to be extremely general, allowing for the formation of a variety of cyclopentanes bearing three contiguous stereocenters with nearly perfect diastereo- and enantioselectivity. The absolute configuration for spiro-cycle **21** was established by single crystal X-ray analysis, and all other examples are proposed by analogy.¹¹ Interestingly, this analysis showed that the sense of enantioinduction was opposite of that seen when standard donor **1a** was used in the cycloaddition!

Our observation that cycloadducts **12–21**, which were derived from cyano donor **1b**, were formed with the opposite sense of chirality as those products that were formed from standard TMM donor **1a** was quite unexpected. Indeed, this work establishes for the first time that cyclopentanes may be prepared with a complete reversal of chirality by switching between donors **1a** and **1b**, while using the same enantiomer of the ligand.¹²

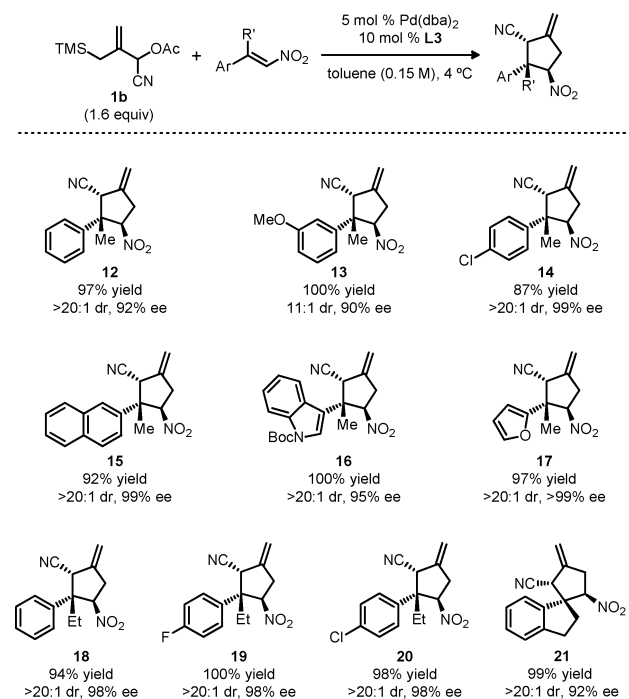
The initial nucleophilic addition of the Pd-TMM complex into the nitroalkene is the diastereodetermining event, as was determined in Scheme 1. When the more reactive

Scheme 2. Reaction Scope Using Parent TMM Donor



^a Reactions conducted in dioxane (0.5 M). ^b Reaction conducted using 7.5 mol % Pd(dba)₂ and 15 mol % L3. ^c Reactions conducted in toluene (0.15 M).

Scheme 3. Reaction Scope Using Cyano TMM Donor



TMM donor **1a** is used in the reaction, the positively charged Pd-TMM complex orients itself antiperiplanar to the carbon bearing the partially positively charged nitrogen atom (Figure 2). When the higher reactivity of donor **1a** is considered, when compared to **1b**, initial addition of the TMM to the nitroalkene may be less selective, leading to the modest diastereoselectivity. This initial addition is then rapidly followed by a ring closure event that is more closely associated with the ligand assembly,

(12) Similar behavior has been observed in the reaction of imines. See ref 4b.

resulting in high levels of enantioselectivity. These observations are in accord with previously observed reactions of donor **1a** with nitroalkenes.⁸

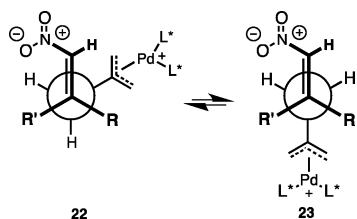


Figure 2. Transition states with standard donor **1a**.

As previously seen in our studies with the reaction of cyano donor **1b** with oxindoles, a more stabilized Pd-TMM anion is generated which may result in a more concerted, although asynchronous, reaction mechanism.⁹ Electronically, the cyano group will now prefer to orient itself antiperiplanar to the nitro group to minimize dipolar interactions and the large Pd-ligand complex will arrange itself away from the nitro group, leading to preferred transition state **25** (which is also shown as a minimized SPARTAN model, Figure 3). As a direct consequence of the more concerted reaction mechanism, the chiral ligands on palladium have a much greater influence on the initial addition when donor **1b** is used, leading to increased levels of diastereoselectivity. The precise nature of the sense of enantioinduction depending on the donor is not known since the exact structure of the catalyst is also unknown. However, given the very different orientations of the reaction partners in the transition states as shown in Figures 2 and 3, the orientation of the substrates as a result of the interactions with the ligands may indeed be the cause of such a reversal. Such questions will be the subject of ongoing studies.

We also demonstrated that these products can serve as precursors to cyclopentenone derivatives, using the conditions we previously developed for the oxidative Nef reaction (Scheme 4).⁸ The presence of the vicinal quaternary stereocenter appeared to hinder the reactivity somewhat, resulting in a 65% yield of enone **27**. On the other hand, epoxidation using *m*-CPBA provided **28** in 97% yield as a 2.5:1 mixture of diastereomers. Treating this mixture with anhydrous potassium *tert*-butoxide followed by dimethyldioxirane (DMDO) gave **29** in 71% yield over two steps. As expected, the ee was completely conserved throughout this sequence.

To conclude, we have established a highly enantioselective palladium-catalyzed cycloaddition of TMM with β,β -disubstituted nitroalkenes. The reaction tolerates the use of either unsubstituted or substituted TMM donors, where the cyano-substituted TMM donor in particular allows for the formation of highly substituted cyclopentane products

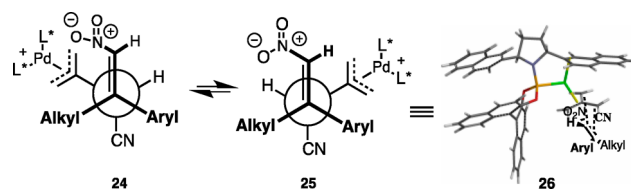
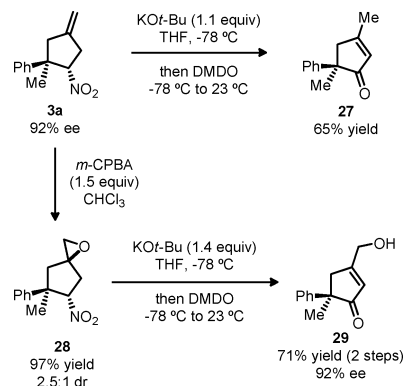


Figure 3. Transition states with donor **1b**.

Scheme 4. Epoxidation and Nef Reaction



in nearly perfect yield and selectivity. The functionalization of these cycloadducts proceeds with excellent diastereoselectivity when applicable and allows for rapid access to several important synthetic intermediates such as cyclopentylamines, cyclopentenones, and cyclopentanes bearing quaternary stereocenters. We have also demonstrated an unusual reversal of asymmetric induction that is dependent on the structure of the TMM intermediate. Further efforts to expand the scope of this cycloaddition to other nitro-activated acceptors are currently underway and will be reported in due course.

Acknowledgment. We thank the NSF and the NIH (GM 033049) for their generous support of our programs. Additional financial support was provided by the W.S. Johnson Graduate Fellowship (D.A.B.) and by the American Cancer Society for a postdoctoral fellowship (B.M.O.). We thank Dr. Allen Oliver (Notre Dame) for XRD analysis. Palladium salts were a generous gift from Johnson Matthey.

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>.

The authors declare no competing financial interest.