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Three-Component, Stereoselective Palladium-Catalyzed Synthesis of Functionalized Bicyclopentanoids

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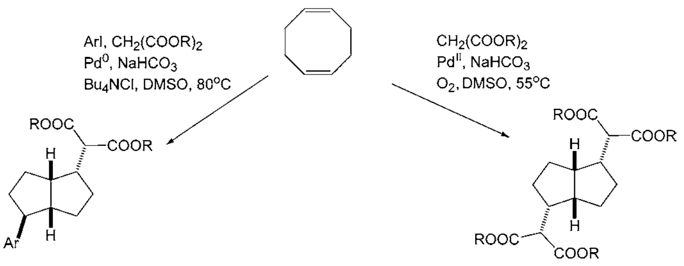
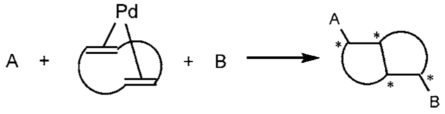
ABSTRACT



1,5-Cyclooctadiene can be stereoselectively transformed into a substituted bicyclo[3.3.0]octane ring system under palladium catalysis with concomitant formation of three carbon–carbon bonds. Reaction with an aryl iodide or triflate and malonate gives an *exo*-*endo* product, while the reaction with a malonate in the presence of oxygen affords a bis-*endo* adduct.

Three-component reactions have emerged as powerful tools for organic synthesis.[1] Of particular value for the construction of stereochemically complex scaffolds are reactions involving the stereoselective formation of two or more carbon−carbon bonds between the three components, transforming three achiral starting materials into a product with three or more defined stereocenters.[2] Palladium is well-suited for such processes because of its ability to catalyze stereoselective additions to olefins such as Heck insertions[3] or allylic alkylations[4] and to promote polyene cyclizations,[5] so that reactions whereby a cyclic diene reacts with two agents A and B with concomitant cyclization, forming three C−C bonds sequentially with stereocontrol, may be feasible (eq 1). We herein report two such reactions using 1,5-cyclooctadiene (COD) as the template.



(1)

Many examples of transannular reactions with 1,5-cyclooctadiene to form the bicyclo[3.3.0]octane ring system are known, particularly in free radical conditions; however, these reactions are rarely stereoselective and provide as major isomers the bicyclooctane products with bis-*exo* substituents, corresponding to substitution on the least hindered face of

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[1] Leading references: (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (b) Adrian, J. C. Jr, Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143. (c) Armstrong, W. R.; Combs, A. P.; Tempest, P. A.; Brown, D. B.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Kobayashi, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 338.

[2] Examples of such processes: (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348 and references therein. (b) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815.

[3] (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (d) Link, J. T. *Org. React.* **2002**, *60*, 157−534.

[4] (a) Tsuji, J. *Pure Appl. Chem.* **1989**, *61*, 1673. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

[5] (a) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813. (b) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (c) Overman, L. E.; Madin, A. *Tetrahedron Lett.* **1992**, *33*, 4859. (d) Ojima, I.; Tzamariaoudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (a) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882.

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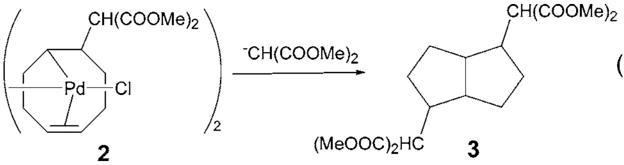
the bicyclic system.[6] The combination of COD and palladium appeared to be particularly attractive since COD's accessible tub-shaped conformation lends itself readily to the binding of transition metals, placing the two double bonds in close proximity to each other. Indeed, Tsuji et al. have shown that the palladium complex **2**, resulting from malonate addition to $[PdCl_2(COD)]_2$, reacts with a second malonate molecule to form the bicyclic product **3**. This reaction proceeds only stoichiometrically with respect to palladium, since the Pd(0) produced is not reoxidized to Pd(II) under the reaction conditions. The stereochemistry of **3** was not determined.[7]



(2)

Our first attempts involved the addition of aryl iodides and malonates to COD. Larock has shown that palladium(0) catalyzes the addition of aryl iodides and malonates to α,ω-dienes; in that reaction, the Heck-type insertion is followed by a migration of the palladium along the hydrocarbon chain to form an allyl complex with the distant double bond, which is trapped by malonate.[8] We endeavored to test whether in a cyclic diene such as COD the proximity of the double bonds might favor transannular reaction over palladium migration. Accordingly, following the Larock conditions, 1-chloro-4-iodobenzene, dimethyl malonate, COD, tetrabutylammonium chloride, and a catalytic amount of dipalladium (tris)dibenzylideneacetone, were heated to 80 °C overnight in DMSO, yielding the bicyclic product **4a** in 49% yield as a single isomer (eq 3). The stereochemistry of **4a** was established by X-ray crystallography (Figure 1).

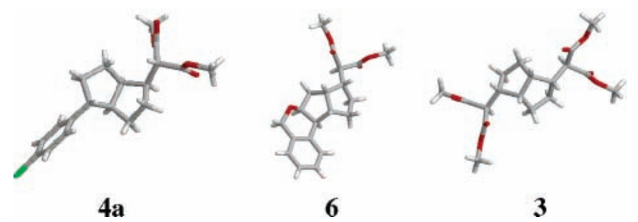
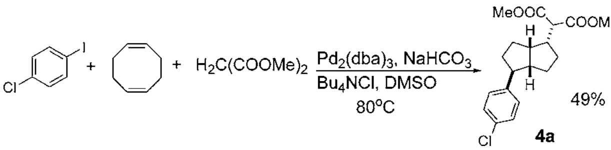


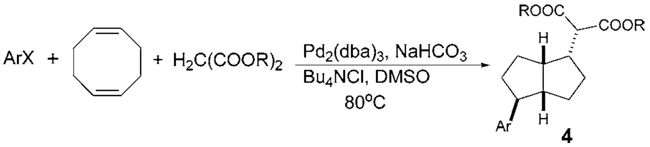
Figure 1. Crystal Structures of compounds **4a**, **6**, and **3**.

The yield could be improved by slow addition of the methyl malonate or by using dibenzyl malonate, which is less prone to Krapcho decarboxylation under the reaction conditions.[9] Aryl triflates also are suitable substrates in the reaction (Table 1). Although the yields are sometimes moderate, it is worth noting that in a single step the reaction transforms three simple starting materials into a functionalized complex product, forming three carbon−carbon bonds and fixing four stereogenic centers with complete selectivity. Unlike in the radical reactions, which usually provide the bis-*exo* isomer as the major product, the reaction introduces the malonate moiety on the more hindered *endo* side of the bicyclooctane ring system.



(3)

Table 1. Substrate Scope in the Three-Component Reaction with Malonate and 1,5-Cyclooctadiene



Ar	X	R	product[a]	yield (%)[b]
4-Cl−C_6H_4	I	Me	**4a**[c]	63
4-Cl−C_6H_4	I	Bn	**4b**	63
4-Me−C_6H_4	I	Bn	**4c**	67
Ph	I	Bn	**4d**	53
4-OMe−C_6H_4	I	Me	**4e**	28
Ph	OTf	Bn	**4d**	40
4-Me−C_6H_4	OTf	Bn	**4c**	63
4-Ac−C_6H_4	OTf	Bn	**4f**	35
1-naphthyl	OTf	Bn	**4g**[d]	41
3-pyridyl	I	Bn	**4h**[d]	39

[a] Standard conditions: 0.3 M ArX in DMSO, 2 equiv of COD, 5 equiv of malonate, 0.05 equiv of catalyst, 2 equiv of sodium bicarbonate, 1.1 equiv of tetrabutylammonium chloride. [b] Yield of purified product. [c] Malonate added via syringe pump over 24 h. [d] Performed with 1.5 equiv of malonate.

To expand the scope of this chemistry, the linked COD-aryl iodide **5**[10] was prepared and subjected to the reaction conditions. The transformation proceeded in 36% yield to provide the tetracyclic product **6**, again with complete stereoselectivity (eq 4). The stereochemistry was determined by X-ray crystallography (Figure 1) and is consistent with that of **4**.

The stereochemical course of the reaction can be explained by a syn addition of the aryl palladium iodide to COD followed by malonate addition from the opposite side of the palladium and reductive elimination of the resulting bridged

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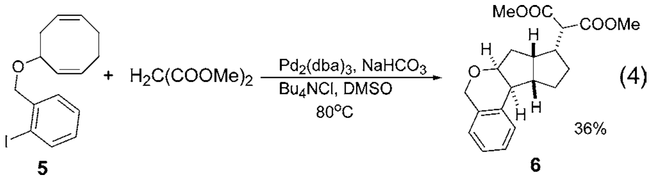
[6] (a) Dowbenko, R. *Tetrahedron* **1964**, *20*, 1843. (b) Udding, J. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 3721. (c) Toshimitsu, A.; Uemura, S.; Okano, M. *Chem. Commun* **1982**, 87. (d) Fang, J.-M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, *28*, 2853. See also: (e) Linker, U.; Kersten, B.; Linker, T. *Tetrahedron* **1995**, *51*, 9917. (f) Cambie, R. C.; Rutledge, P. S.; Stewart, G. M.; Woodgate, P. D.; Woodgate, S. D. *Aust. J. Chem.* **1984**, *37*, 1689. For the palladium-catalyzed conversion of COD into bis-*endo*-2,6-dihydroxy-*cis*-bicyclo[3.3.0]octane or its diacetate, see: (g) Mehta, G.; Sreenivas, K. *Chem. Commun.* **2001**, 1892. (h) Perard-Viret, J.; Rassat, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1.

[7] Takahashi, H.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 2387.

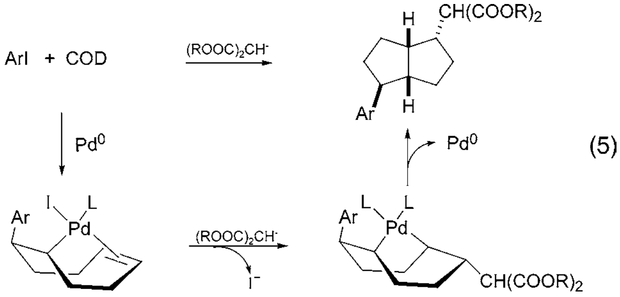
[8] (a) Larock, R. C.; Lu, Y.-de; Bain, A. C.; Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589. See also (b) Nylund, C. S.; Smith, D. T.; Klopp, J. M.; Weinreb, S. M. *Tetrahedron* **1995**, *51*, 9301.

[9] Krapcho, A. P. *Synthesis* **1982**, 805.

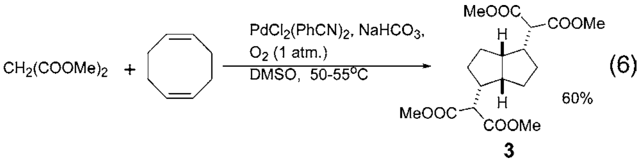
[10] (a) Prepared by alkylation of cycloocta-2,6-dienol[10b] with 2-iodobenzyl bromide. (b) Echter, T.; Meier, H. *Chem. Ber.* **1985**, *118*, 182.



palladacycle (eq 5). An alternate mechanism involving addition of malonate to the initial COD−arylpalladium iodide complex to form an intermediate analogous to **2**, followed by aryl transfer and reductive elimination, is also possible. The reaction with aryl triflates (and Bu_4NCl) may proceed similarly via the aryl palladium chloride complex.



We then proceeded to reexamine the Tsuji reaction as a way to prepare bicyclopentanoids with a different functionalization pattern and, possibly, different stereochemistry. It was envisioned that by including a stoichiometric oxidant in the reaction mixture, such as molecular oxygen, the Tsuji reaction could be carried out in a catalytic fashion with respect to palladium.[11] This was accomplished by combining COD with methyl malonate under 1 atm O_2 in the presence of 5% Pd(II), thus providing the Tsuji adduct **3** in 60% yield (eq 6).[12]



A likely mechanism involves the sequential addition of two malonates to the Pd(II)−COD complex, leading to intermediate **7** (Figure 2), which then undergoes reductive elimination to product **3**. The Pd(0) formed is then reoxidized by oxygen to Pd(II).

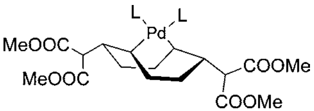


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Figure 2. Proposed intermediate **7**.

The stereochemistry of **3** was determined by X-ray crystallography (Figure 1) and is consistent with a mechanism involving sequential malonate addition to both double bonds from the opposite side to the palladium. It is noteworthy that in the C_2-symmetric adduct **3**, both malonate substituents are on the concave side of the bicyclic system, unlike in the aryl-malonate products **4**, thus providing additional flexibility in the preparation of stereochemically defined intermediates. Studies aimed at using these compounds for the synthesis of more complex systems, as well as efforts to broaden the scope to include other substrates, are underway and will be reported in due course.

Acknowledgment. We are grateful to Professors S. L. Buchwald and A. G. Myers for helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and X-ray data for **3**, **4a**, and **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For examples of palladium-catalyzed addition of carbon nucleophiles to nonconjugated olefins, see: Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Pergamon: London, 1982; Vol. 8.

(12) The palladium (catalyst)/oxygen system in DMSO has been used for transformations requiring the recycling of Pd(0) to Pd(II): (a) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766 and references therein. (c) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (d) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.