ORGANIC LETTERS

2005
Vol. 7, No. 13
2639−2641

# Palladium-Catalyzed Cyanoesterification of Norbornenes with Cyanoformates via the NC–Pd–COOR (R = Me and Et) Intermediate

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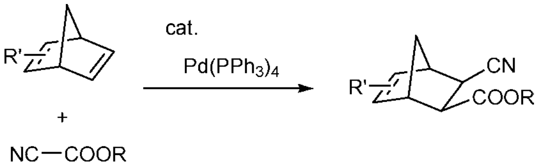
Received April 7, 2005

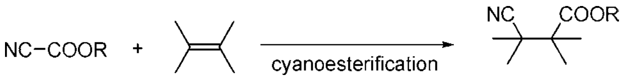
## ABSTRACT



**Palladium-catalyzed cyanoesterification of norbornenes proceeds stereoselectively via NC–Pd–COOR (R = Me and Et) complexes as intermediates.**

The direct activation of C−C $\sigma$-bonds and the subsequent insertions into carbon−carbon multiple bonds are of current interest in synthetic organic chemistry, because such reactions can provide a simultaneous construction of two C−C bonds from simple starting compounds.[1] Nevertheless, double functionalization of unsaturated organic molecules via C−C bond addition to unstrained molecules is quite rare.[2,3] On the other hand, several examples of individual cyanation[4] and esterification[5] of unsaturated organic molecules by addition reactions have been reported, but, to the best of our knowledge, there has been no precedent for cyanoesterification,[6] depicted in Scheme 1.

**Scheme 1**



We herein disclose the direct cleavage and insertion of alkenes into C−C $\sigma$-bonds, i.e., cyanoesterification of alkenes with cyanoformates, and the first example of oxidative addition of NC−COOR to Pd(0).

The results of a representative catalytic reaction, ethyl cyanoformate (**1a**; 0.2 mmol) and norbornene (**2a**; 0.2 mmol) in toluene containing various catalysts (10 mol %), are listed in Table 1. When $Pd(PPh_3)_4$ was used, GC and GC-MS (in

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[1] Recent review on C−C bond activation: Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618 and references therein.

[2] Palladium-catalyzed addition of acyl cyanides to terminal acetylenes: Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629−1637.

[3] Very recently, nickel-catalyzed addition of arylnitriles into internal alkynes was reported: Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904−13905 and references therein.

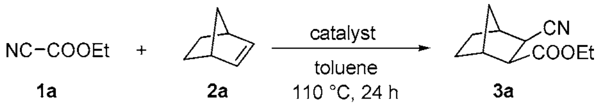
[4] (a) Jackson, W. R.; Lovel, C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1231−1232. (b) Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539−3548. (c) Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635−8638. (d) Obora, Y.; Baleta, A. S.; Tokunaga, M.; Tsuji, Y. *J. Organomet. Chem.* **2002**, *660*, 173−177. (e) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358−6359.

[5] (a) El Ali, B.; Alper, H. *J. Mol. Catal*. **1995**, *96*, 197−201. (b) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365−12366. (c) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228−3229.

[6] Cyanoethoxycarbonylation reactions of aldehydes have been reported. (a) Tian, J.; Yanagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636−3638. (b) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413−3422.

10.1021/ol050749k CCC: $30.25

**Table 1.** Palladium-Catalyzed Cyanoesterification of Norbornene (**2a**) with Ethyl Cyanoformate (**1a**)[a]



| run | catalyst | % yield of **3a**[b] |
|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 94 (80) |
| 2 | $Pd(dba)_2$/2 $PPh_3$ | 82 |
| 3 | $Pd(dba)_2$/2 $PMe_3$ | 0 |
| 4 | $Pd(dba)_2$/2 $PCy_3$ | 0 |
| 5 | $Pd(dba)_2$/2 P(*t*-Bu)$_3$ | 11 |
| 6 | $Pd(dba)_2$/2 $P(OPh)_3$ | 40 |
| 7 | $Pd(dba)_2$/DPPE | 0 |
| 8 | $Pd(dba)_2$/DPPF | 13 |
| 9[c] | $Pd(PPh_3)_4$ | 43 |

[a] Reactions were carried out at 110 °C for 24 h by using 0.2 mmol of **1a**, 0.2 mmol of **2a**, and 0.02 mmol of $Pd(PPh_3)_4$ in 2 mL of toluene. [b] Determined by GC using dodecane as an internal standard. Isolated yield is shown in parenthesis. [c] Reaction was performed in *n*-octane.

conjunction with an NMR study) of the resulting mixture revealed that the starting materials were completely consumed and that (2*R**,3*S**)-ethyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (**3a**) was obtained as the sole product in 94% yield. When $Pd(dba)_2$ (dba = dibenzylideneacetone) combined with $PPh_3$ (P/Pd = 2.0; 10 mol %) was employed instead of $Pd(PPh_3)_4$, the cyanoesterification adduct **3a** was obtained in 82% yield (run 2). Other phosphine ligands gave unsatisfactory results. In addition, $Ni(cod)_2$/2 $PMe_3$, which is known to be an active catalyst for arylcyanation of alkynes,[3] was completely ineffective. Likewise, other complexes such as $PdCl_2(PPh_3)_2$, $PdCl_2(NCPh)_2$, $Pt(PPh_3)_4$, $RuCl_2(PPh_3)_2$, and $RhCl(PPh_3)_3$ were totally inactive. Under the standard reaction conditions, 1-octene, styrene, methyl acrylate, cyclopentene, and cyclopenten-3-one did not react with **1a**. Furthermore, ethylene (5 atm) was also subjected to the reaction with **1a**, but no cyanoesterification occurred.[7]

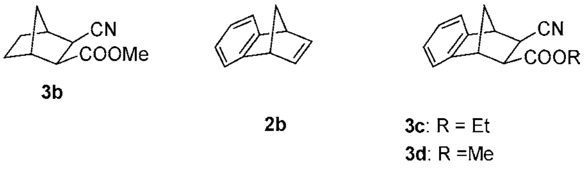
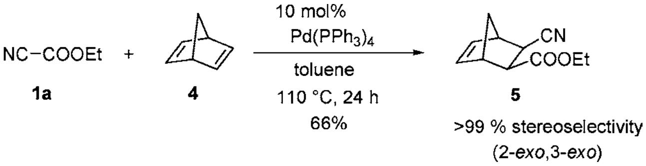


**Figure 1.**

As depicted in Figure 1, methyl cyanoformate (**1b**) also reacted with **2a** to afford the corresponding cyanoesterification adducts **3b**, albeit in low yield (28%). Also, from the reactions of 1,4-dihydro-1,4-methanonaphthalene (benzonorbornadiene) (**2b**) with **1a** and **1b**, the corresponding products **3c** and **3d** were produced in 83 and 65% yields, respectively. The stereochemistry determined by $^1H$ NMR spectra of the adduct **3** was revealed to be exclusively the 2-*exo*,3-*exo* configuration,[8] suggesting that cyanoformate **1** undergoes cis addition to **2** via coordination of the palladium center on the less hindered olefin face.

It is worth noting that the reaction of a 5-fold excess of **1a** with norbornadiene (**4**) gives the single cyanoesterification adduct **5** in 66% yield with high 2-*exo*,3-*exo* stereochemistry selectively (Scheme 2). Once formed, **5** seems to be less reactive than **4** and retards the second cyanoesterification significantly. The stereochemistry of **5** was compared by $^1H$ NMR and found to be opposite to that obtained from the Diels−Alder reaction of cyclopentadiene with ethyl (*Z*)-3-cyano-2-propenoate (**5** (2-*exo*,3-*exo*)/**5′** (2-*endo*,3-*endo*) = 20/80).

**Scheme 2**



Although the detailed mechanism of the cyanoesterification reaction still remains to be clarified, the reaction is envisioned to take place via oxidative addition of **1** to Pd(0). We succeeded in isolating *trans*-Pd(CN)(COOR)$(PPh_3)_2$ (**6a**, R = Et, 70%; **6b**, R = Me, 84%)[9] upon addition of a slight excess of **1a** and **1b** to $Pd(PPh_3)_4$ at room temperature for 24−48 h. Whereas palladium complexes containing Pd−CN[10] and Pd−COOR[11] bonds are known, no precedent for the structure for LnPd(CN)(COOR) has been reported. The first molecular structure determined by X-ray crystallography of cyano(ethoxycarbony)palladium complex[12] *trans*-Pd(CN)(COOMe)$(PPh_3)_2$ (**6b**) is shown in Figure 2.

Complex **6a** is relatively stable in the solid state but gradually decomposes to afford *trans*-$Pd(CN)_2(PPh_3)_2$[13] in

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[7] From this reaction, neither ethyl acrylate nor acrylonitrile, derived from $\beta$-hydrogen elimination, was detected.

[8] The signal assigned to the cyano-substituted methine proton at ca. $\delta$ 2.8 was observed as a doublet of doublets due to the coupling with the ester-substituted methine proton (9−10 Hz), and the anti proton at the bridging methylene (2 Hz) and its coupling with the bridgehead proton were not detected. These results support the 2-*exo*,3-*exo* geometry.

[9] Although isolated complexes **6a** and **6b** are stable in the solid state, they gradually converted into *trans*-$Pd(CN)_2(PPh_3)_2$ in solution after several weeks. See Supporting Information for details.

[10] For examples, see: (a) Che, C.-M.; He, L.-Y.; Poon, C.-K.; Mak, T. C. W. *Inorg. Chem.* **1989**, *28*, 3081−3083. (b) Yip, H.-K.; Lai, T.-F.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1991**, 1639−1641. (c) Eisenberg, A. H.; Dixon, F. M.; Mirkin, C. A.; Stern, C. L.; Incarvito, C. D.; Rheingold, A. L. *Organometallics* **2001**, *20*, 2052−2058. (d) Hua, R.; Goto, M.; Tanaka, M. *Anal. Sci.* **2001**, *17*, 469−470.

[11] For examples, see: (a) Garrone, R.; Romano, A. M.; Santi, R.; Millini, R. *Organometallics* **1998**, *17*, 4519−4522. (b) Smith, G. D.; Hanson, B. E.; Merola, J. S.; Waller, F. J. *Organometallics* **1993**, *12*, 2, 568−570. (c) Gallo, E.; Ragaini, F.; Cenini, S.; Demartin, F. *J. Organomet. Chem.* **1999**, *586*, 190−195. (d) Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899−2900.

[12] Oxidative addition of ethyl cyanoformate with Ni(0) is known to afford Ni(CN)(COOEt)(triphos) (triphos = $MeC(CH_2PPh_2)_3$). See: Bianchini, C.; Masi, D.; Meli, A.; Sabat, M. *Organometallics* **1986**, *5*, 1670−1675.

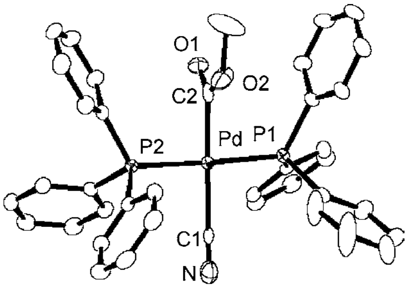


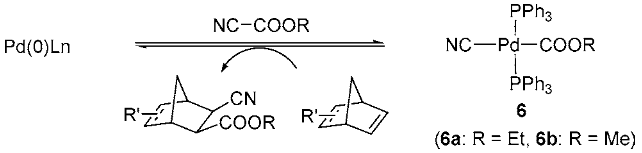
**Figure 2.** Structure of **6b** determined by X-ray crystallography with 50% thermal ellipsoidal plotting. Hydrogen atoms were omitted for simplicity. Selected bond distances (Å) and angles (deg): Pd−P(1) 2.3268(5), Pd−P(2) 2.3225(5), Pd−C(1) 2.106(2), Pd−C(2) 2.015(2), C(1)−N 1.056(3), C(2)−O(1) 1.217(3), C(2)−O(2) 1.311(3); P(1)−Pd−C(1) 92.62(5), P(1)−Pd−C(2) 86.72(7), P(2)−Pd−C(1) 89.90(5), P(2)−Pd−C(2) 90.80(7).

solution, whereas the methyl congener **6b** is much more stable. This difference of stability is presumably related to the lower yield of the products derived from methyl cyanoformate (**1b**).

As expected, isolated **6a** (0.05 mmol) in toluene-$d_8$ (0.6 mL) reacted with an excess (5 equiv) of norbornene (**2a**) at 110 °C for 24 h to afford **3a** in 70% yield. The cyanoesterification of **2a** with **1a**, on the other hand, proceeded in the presence of complex **6a** (10 mol %) as the catalyst to give **3a** in 52% yield under the standard conditions. We can thus conclude that the cyano(alkoxycarbonyl)palladium species **6** is involved in the catalytic cycle of the cyanoesterification process (Scheme 3).

Although insertion of alkenes into the Pd−COOR bond (alkoxycarbonylpalladation)[14] appears to be more likely from the viewpoint of the well-known palladium-catalyzed alkoxycarbonylation of alkenes, cyanopalladation cannot be ruled out as an alternative possibility for the insertion process.

**Scheme 3.** Plausible Mechanism



(**6a**: R = Et, **6b**: R = Me)

In summary, we have developed an unprecedented palladium-catalyzed cyanoesterification of alkenes that is initiated by the oxidative addition of the NC−COOR bond. This work offers another useful demonstration of the power of transition metal catalysis to activate unstrained C−C $\sigma$-bonds with compatible functional groups. Investigations into the mechanism of insertion of norbornenes into cyano(alkoxycarbonyl)palladium species **6** and further synthetic application in the construction of functionalized cyclopentanes bearing four stereodefined carbon centers will be the subject of forthcoming papers.

**Acknowledgment.** This work is dedicated to Prof. Kohtaro Osakada (Tokyo Institute of Technology) on the occasion of his 50th birthday. We are grateful to Prof. Kenji Uneyama at Okayama University for generous use of GC-MS facilities.

**Supporting Information Available:** Details of all experimental procedures and crystallographic data of **6b**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information (deposition no. CCDC 270657) may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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(13) Uson, R.; Fornies, J.; Uson, M. A.; Lalinde, E. *J. Organomet. Chem.* **1980**, *185*, 359−366.

(14) Hegedus, L. S.; Darlington, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 4980−4983.