ORGANIC LETTERS

2006
Vol. 8, No. 25
5777−5780

Highly Regioselective Synthesis of 2,3-Disubstituted Indenes via a Novel Palladium-Catalyzed Cyclization Reaction of Propargylic Carbonates with Carbon Nucleophiles

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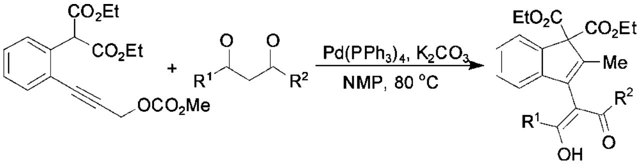
Received September 29, 2006

ABSTRACT



Palladium-catalyzed reaction of propargylic carbonates with carbon nucleophiles offers an efficient, direct route to highly substituted indenes. The reaction conditions and the scope of the process are examined, and a possible mechanism is proposed.

The reaction of π-allylpalladium complexes with carbon nucleophiles such as malonates and β-keto esters has proven to be a powerful method for the formation of carbon−carbon bonds.[1] Among these processes, those involving palladium-catalyzed reactions are particularly attracting the attention of synthetic organic chemists, and many useful synthetic reactions based on π-allylpalladium compounds have been discovered.[2] In contrast to the extensive studies conducted on palladium-catalyzed reactions of allylic compounds, studies on the analogous reactions of propargylic compounds were initiated much later and are less extensive.[3] Tsuji has reported a one-pot furan annulation reaction by a palladium-catalyzed reaction of propargylic carbonates with carbon nucleophiles,[4] and Lu reported another palladium-catalyzed annulation reaction with bifunctional nucleophiles.[5]

As part of our ongoing interest in developing methods for the preparation of indene derivatives via organometallic catalysis,[6] we herein wish to report a new palladium-catalyzed cyclization reaction of propargylic carbonates with a variety of carbon nucleophiles to offer an efficient, direct route to highly substituted indenes (Scheme 1).

We first investigated the reaction of propargylic carbonate **1a** with methyl acetoacetate (**2a**) in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in DMF at 80 °C for 10 h. To our delight, only diethyl 3-((*Z*)-1-(methoxycarbonyl)-2-hydroxyprop-1-enyl)-

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(1) (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. (b) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144.

(2) (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) Trost, B. M., Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E., Eds.; Pergamon: Oxford, 1982; Vol. 8, p 799. (c) Godleski, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 585. (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

(3) Tsuji, J.; Mandai. T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

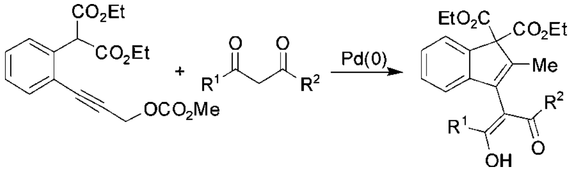
(4) (a) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225.

(5) (a) Geng, L.; Lu, X. *Tetrahedron Lett.* **1990**, *31*, 111. (b) Geng, L.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1992**, 17.

(6) (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325. (b) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 3053.

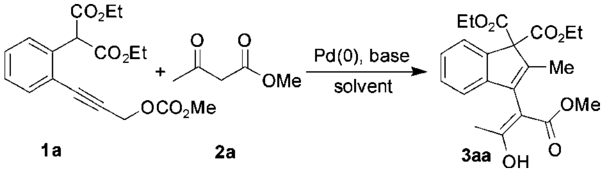
10.1021/ol062405f CCC: \$33.50

Scheme 1



2-methyl-1*H*-indene-1,1-dicarboxylate (**3aa**) was isolated in 70% yield and no 2-substituted indene was observed (Table 1, entry 1).[7] K_2CO_3 proved to be the best base, whereas KOAc and KO*t*-Bu were less effective (entries 2 and 3). Changing the solvent from DMF to DMSO did not enhance the yield of **3aa** (entry 4), and using THF as the solvent gave no reaction at all (entry 5). Fortunately, the yield increased to 83% when the solvent NMP was employed instead of DMF (entry 6). Therefore, NMP was found to be the best solvent for the cyclization reaction. Among the palladium catalysts tested, $Pd(PPh_3)_4$ was the most effective catalyst for this reaction. $Pd(OAc)_2/PPh_3$ was less effective (entry 7), and no reaction was observed when the catalyst was replaced with $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 8 and 9).

Table 1. Optimization of the Palladium-Catalyzed Cyclization of Propargylic Carbonate **1a** with **2a**[a]

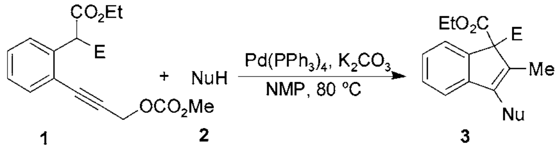


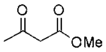
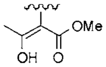
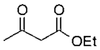
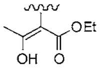
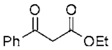
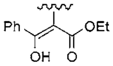
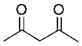
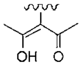
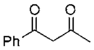
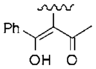
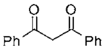
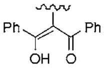
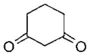
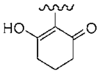
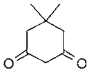
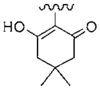
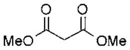
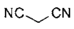
entry	catalyst	base	solvent	yield of **3aa** (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	DMF	70
2	$Pd(PPh_3)_4$	KOAc	DMF	52
3	$Pd(PPh_3)_4$	KO*t*-Bu	DMF	62
4	$Pd(PPh_3)_4$	K_2CO_3	DMSO	55
5	$Pd(PPh_3)_4$	K_2CO_3	THF	n.r.[c]
6	$Pd(PPh_3)_4$	K_2CO_3	NMP	83
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	NMP	65
8	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	NMP	n.r.[c]
9	$Pd_2(dba)_3{\cdot}CHCl_3$/dppe	K_2CO_3	NMP	n.r.[c]

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent at 80 °C using 1.0 equiv of **1a**, 1.2 equiv of **2a**, 2.0 equiv of base, and 0.05 equiv of [Pd] for 10 h. [b] Isolated yield. [c] n.r. = no reaction.

We next examined other β-keto esters to clarify the scope and limitations of this reaction. Similarly, the reaction of **1a** with β-keto esters **2b** and **2c** in the presence of $Pd(PPh_3)_4$ gave the corresponding multiply substituted indenes **3ab** and **3ac** in moderate to good yields (Table 2, entries 2 and 3).

Table 2. Palladium-Catalyzed Cyclization of Propargylic Carbonates with Nucleophiles[a]



entry	propargylic carbonate (**1**)	NuH	**3** Nu=	isolated yield (%)
1	E= CO_2Et **1a**	 **2a**	 **3aa**	83
2	**1a**	 **2b**	 **3ab**	72
3	**1a**	 **2c**	 **3ac**	56
4	**1a**	 **2d**	 **3ad**	75[b]
5	**1a**	 **2e**	 **3ae**	71[b]
6	**1a**	 **2f**	 **3af**	34[b]
7	**1a**	 **2g**	 **3ag**	80[b]
8	**1a**	 **2h**	 **3ah**	76[b]
9	**1a**			n.r.[c]
10	**1a**			n.r.[c]
11	E= SO_2Ph **1b**	**2a**		mixture

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of NMP at 80 °C using 1.0 equiv of **1**, 1.2 equiv of **2**, 2.0 equiv of base, and 0.05 equiv of [Pd]; all reactions were run for 5−10 h. [b] At 100 °C. [c] n.r. = no reaction.

The cyclization of **1a** with various β-diketones was also investigated. Not only simple β-diketones, such as pentane-2,4-dione (entry 4), but also cyclic β-diketones, such as 1,3-cyclohexanedione and 5,5-dimethylcyclohexane-1,3-dione, were effective nucleophiles (entries 7 and 8). When phenyl-substituted 1,3-dicarbonyl substrates were used, the desired

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[7] For some recent examples of palladium-catalyzed reactions of propargylic carbonates with nucleophiles for the syntheses of 2-substituted benzofurans and indoles, in which nucleophiles attack on the less hindered carbon of the π-allylpalladium complex, see: (a) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381. (c) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083.

products were isolated in 71% and 34% yields, respectively (entries 5 and 6). The use of 3-methylpentane-2,4-dione was also effective; however, it gave a complicated mixture that is still under investigation. No reactions were observed when dimethyl malonate and malononitrile were treated with **1a** (entries 9 and 10). Under similar conditions, ethyl acetate propargylic carbonate with different electron-withdrawing groups, such as ethyl 2-[2-{3-(methoxycarbonyloxy)prop-1-ynyl}phenyl]-2-(phenylsulfonyl)acetate (**1b**) produced a complex mixture of unidentified products (entry 11).

Although the NMR spectroscopic data support the formation of 2,3-disubstituted indenes **3**, the structure was unambiguously secured by an X-ray crystal structure analysis of compound **3ad** (Figure 1).[8]

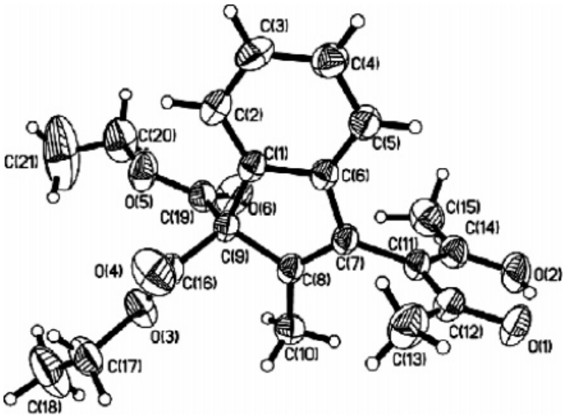
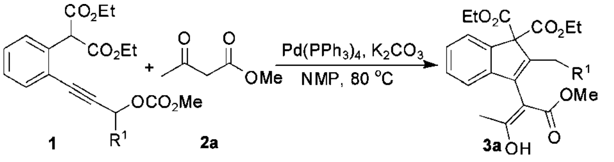


Figure 1. Structure of **3ad**.

We then turned our attention to the cyclization reaction using secondary carbonates. As expected, substituted secondary carbonate **1c** react with **2a** led to the desired product **3ca** in 65% yield (Table 3, entry 1). Substituted secondary carbonates **1d** and **1e**, having phenyl substituents, produced 56% and 32% yields of the multiply substituted indenes, respectively (entries 2 and 3).

Table 3. Palladium-Catalyzed Cyclization of Propargylic Carbonates with **2a**[a]

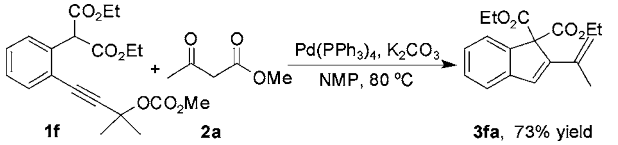


entry	R^1	time (h)	3a	isolated yield (%)
1	R^1 = Me (**1c**)	10	**3ca**	65
2	R^1 = Ph (**1d**)	10	**3da**	56
3	R^1 = *p*-ClC_6H_4 (**1e**)	12	**3ea**	32

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of NMP at 80 °C using 1.0 equiv of **1**, 1.2 equiv of **2a**, 2.0 equiv of base, and 0.05 equiv of [Pd].

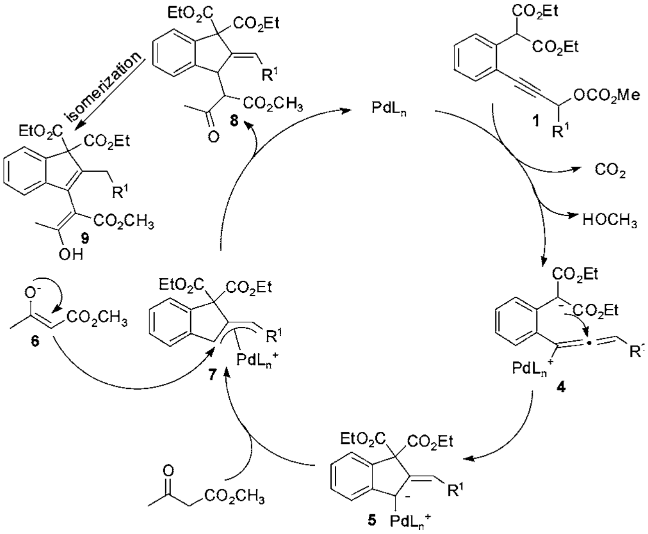
Propargylic tertiary carbonate **1f** with **2a** afforded none of the desired 2,3-disubstituted indenes and an identified 2-substituted indene **3fa** was isolated (Scheme 2). The formation of **3fa** could be attributed to steric hindrance, the more substituted and electrophilic end being now too crowded. This is in agreement with results observed by us in the palladium-catalyzed three-component annulation reaction.[9]

Scheme 2



A plausible mechanism is proposed in Scheme 3. It consists of the following key steps: (a) palladium(0) attack at propargylic carbonate through S_N2' substitution to form an allenylpalladium complex **4**;[7] (b) intramolecular nucleophilic attack of the carbanion at the central carbon of the allenylpalladium complex to form the palladium complex **5**, which picks up an active hydrogen from the nucleophile

Scheme 3



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[8] Crystal data for **3ad** have been deposited in CCDC as deposition number 620440: $C_{21}H_{24}O_6$, MW = 372.40, $T = 294(2)$ K, $\lambda = 0.71073$ Å, monoclinic space group, $P1$, $a = 11.0511(10)$ Å, $b = 20.5371(16)$ Å, $c = 9.0441(8)$ Å, $\alpha = 90.00°$, $\beta = 96.047(4)°$, $\gamma = 90.00°$, $V = 2041.2(3)$ Å^3, $Z = 4$, $D_c = 1.212$ mg/m^3, $\mu = 0.088$ mm^{-1}, $F(000) = 816$, crystal size $0.55 \times 0.50 \times 0.40$ mm^3, independent reflections 4008 [R (int) = 0.0363], reflections collected 11295, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.183, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0977$, $wR_2 = 0.2172$, R indices (all date) $R_1 = 0.0603$, $wR_2 = 0.1856$, extinction coefficient 0.030(5), largest diff peak and hole 0.401 and −0.233 e Å^{-3}

[9] Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2005**, *70*, 6980.

moiety to give the π-allylpalladium intermediate, **7**;[3,7,10] and (c) regioselective intermolecular nucleophilic attack of the carbon nucleophile at the more hindered allylic terminus of **7**[5b,11] to furnish the indene after isomerization and regenerate the Pd(0) catalyst. From our results, a dominant electronic effect in the transition state of this reaction leads to reactions at the more hindered side of the π-allylpalladium complex.

In conclusion, we have developed a straightforward, highly regioselective approach to multiply substituted indenes. This novel palladium-catalyzed cyclization reaction worked well with a broad range of nucleophiles to afford 2,3-disubstituted indenes in moderate to good yields. Current studies are focused on further exploration of the substrate scope and synthetic utility of this methodology, as well as on probing the mechanism of this transformation.

Acknowledgment. We thank the NSF (NSF-20021001, NSF-20672049) and the “Hundred Scientist Program” from the Chinese Academy of Sciences for financial support.

Supporting Information Available: Typical experimental procedure and characterization for all products, and X-ray data of **3ad** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, 553. (b) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583. (c) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (d) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616. (e) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634. (f) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (g) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874.

(11) For examples of π-allylpalladium complex and subsequent C-alkylation, see: Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett*. **1980**, *21*, 1475. For some examples of nucleophiles attack the more hindered side of the π-allylmetal complexes, see: (a) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757. (b) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837. (c) Trost, B. M.; Lautens, M. *Tetrahedron* **1987**, *43*, 4817.