Tetrahedron Letters 49 (2008) 6781–6783

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed cyclopropanation of electron-deficient olefins with aryldiazocarbonyl compounds

Shufeng Chen, Jian Ma, Jianbo Wang *

Beijing National Laboratory of Molecular Sciences (BNLMS), and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education,
College of Chemistry, Peking University, Beijing 100871, China
The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 1 July 2008
Revised 1 September 2008
Accepted 9 September 2008
Available online 11 September 2008

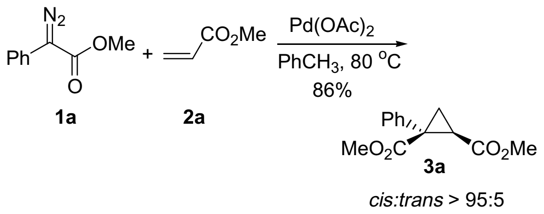
Keywords:
Diazo compounds
Cyclopropanation
Pd-catalyzed reaction
Electron-deficient olefin

ABSTRACT

A concise and efficient protocol for the preparation of cyclopropanes from various aryldiazocarbonyl compounds and electron-deficient olefins catalyzed by $Pd(OAc)_2$ is reported.

The cyclopropane units have received considerable attention because of their common structural motifs in biologically active natural and unnatural compounds and of their importance as valuable synthetic intermediates.[1,2] Among the various methods available for the preparation of cyclopropanes, transition metal-catalyzed cyclopropanation of olefins with diazo reagents has attracted great interest for its high efficiency and high regio-, diastereo-, and enantioselectivity.[2] It is well documented that the Cu(I) and Rh(II) are generally efficient catalysts for the synthesis of cyclopropane derivatives from olefins and α-diazocarbonyl compounds. However, because of the electrophilic nature of the metal carbene intermediates in the catalytic cycle, the alkenes used in this type of reactions are generally electron-rich olefins.[2] Cyclopropanations of electron-deficient olefins, such as α,β-unsaturated carbonyl compounds, remain to be a challenging problem. Among several previous efforts toward transition metal-catalyzed cyclopropanation of electron-deficient olefins with diazo reagents,[3–7] a notable example is the Co(II)-based asymmetric catalytic system recently reported by Zhang and co-workers.[7]

During our recent research in palladium-catalyzed reaction of diazo compounds,[8] we found that $Pd(OAc)_2$ could catalyze cyclopropanation of methyl acrylate with methyl phenyldiazoacetate **1a** in high yield and stereoselectivity (Scheme 1).



Scheme 1. $Pd(OAc)_2$-catalyzed cyclopropanation of methyl phenyldiazoacetate **1a** with methyl acrylate **2a**.

Although palladium salts are already found as catalysts in cyclopropanation of electron-deficient olefins with diazomethane, to our knowledge the corresponding reaction with aryldiazoacetates is unknown.[2a,9] On the other hand, the general synthetic routes to 1-arylcyclopropane-1,2-dicarboxylate derivatives involve the reaction of α-bromophenylacetates with acrylic esters under strong basic conditions,[10] or the reaction of ammonium ylides in basic two-phase systems.[11] Considering the fact that cyclopropanes containing two or more electron-withdrawing groups are valuable synthetic intermediates for various applications,[12] and there are only limited methods available for their preparation, we believe the Pd-catalyzed reaction shown in Scheme 1 will be highly attractive. In this Letter, we wish to report the results of a detailed study on the reaction of electron-deficient olefins with aryldiazocarbonyl compounds catalyzed by Pd(II) complex.

At the outset of this investigation, various transition metal complexes were examined as the catalysts in the reaction of methyl phenyldiazoacetate **1a** with methyl acrylate **2a**. For comparison, we first examined $Rh_2(OAc)_4$, $Cu(CH_3CN)_4PF_6$, and $AgSbF_6$ as the

---

* Corresponding author. Tel.: +86 10 6275 7248; fax: +86 10 6275 1708.
E-mail address: wangjb@pku.edu.cn (J. Wang).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.024

Table 1
Transition metal-catalyzed cyclopropanation of methyl phenyldiazoacetate **1a** with methyl acrylate **2a**

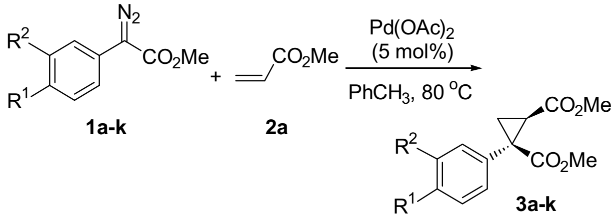
Entry	Cat. (mol %)	*t* (h)	Yield[a] (%)	*cis*:*trans*[b]
1	$Rh_2(OAc)_4$ (0.5)	24	0	—
2	$Cu(CH_3CN)_4PF_6$ (10)	24	0	—
3	$AgSbF_6$ (10)	24	0	—
4	$Pd(OAc)_2$ (5)	0.5	86	>95:5
5	$Pd(PPh_3)_4$ (5)	0.5	72	>95:5
6	$PdCl_2$ (5)	0.5	71	84:16
7	$Pd(OAc)_2$ (1)	3	67	>95:5

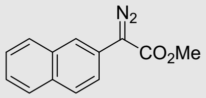
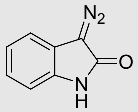
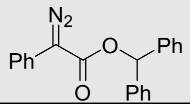
[a] Yield of isolated product after chromatography.
[b] Ratio was determined by ^1H NMR (300 MHz) of the crude product.

catalysts. These transition metal complexes have been proven to be the efficient catalysts for cyclopropanation of electron-rich olefins by diazo compounds. However, in the reaction with **2a**, no expected product **3a** could be observed under the similar conditions (Table 1, entries 1–3). The following experiment showed that $Pd(OAc)_2$ could give the highest yield in this reaction, generating the cyclopropane **3a** with very high diastereoselectivity (entry 4). Next we screened the commonly available palladium salts in this cyclopropanation, $Pd(PPh_3)_4$ gave the moderate yield of **3a** under the same condition (entry 5), while $PdCl_2$ could only afford **3a** with moderate yield and selectivity (entry 6). Finally, when we decreased the catalyst loading of $Pd(OAc)_2$ from 5 mol % to 1 mol %, the yield diminished and the reaction took longer (entry 7).

Having established the optimal reaction conditions, we next examined the scope of the reaction with an assortment of methyl acrylate **2a** and aryldiazocarbonyl compounds **1a**–**k**, and the corresponding results are listed in Table 2.[13] Various substitutions on the aromatic ring could be tolerated, and the reaction gave moderate to good yields and selectivities of the products **3a**–**k**. It was found that substrates with phenyl ring bearing electron-donating group generally gave slightly lower yields with high selectivity (Table 2, entries 2 and 3), while substrates with electron-withdrawing substituent on the phenyl ring, such as halogen and nitro, gave good yields with moderate selectivities (entries 4–9). To our delight, when the less reactive diazo compound **1j** was subjected to this reaction, the cyclopropanation product **3j** was obtained in moderate yield and with high selectivity (entry 10). Moreover, it was noted that the ester moiety of the diazo compounds did not affect the reaction (entry 11). The cis configuration of product was determined by NOE experiment with **3d**.

Table 2
$Pd(OAc)_2$-catalyzed reaction of aryldiazo compounds **1a**–**k** with methyl acrylate **2a**



Entry	**1a**–**k**, R^1, R^2	*t* (h)	Yield[a] (%)	*cis*:*trans*[b]
1	**1a**, H, H	0.5	**3a**, 86	>95:5
2	**1b**, Me, H	0.5	**3b**, 70	>95:5
3	**1c**, OMe, H	1	**3c**, 48	>95:5
4	**1d**, Cl, H	1	**3d**, 81	91:9
5	**1e**, Br, H	1	**3e**, 72	88:12
6	**1f**, NO_2, H	2	**3f**, 73	83:17
7	**1g**, H, Cl	0.5	**3g**, 72	89:11
8	**1h**, Cl, Cl	1	**2h**, 83	85:15
9	**1i**, 	3	**3i**, 73	84:16
10	**1j**, 	1	**3j**, 51	>95:5
11	**1k**, 	1.5	**3k**, 75	>92:8

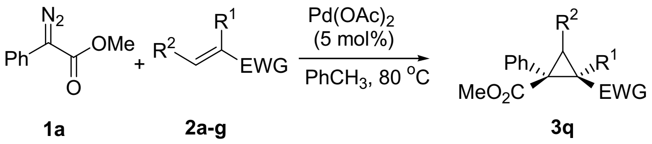
[a] Yield of isolated product after chromatography.
[b] Ratio was determined by ^1H NMR (300 MHz) of the crude product.

Next, we examined the scope of electron-deficient olefin substrates, as shown in Table 3. The ester moiety of the acrylate did not affect the reaction, and cyclopropanation proceeded smoothly to give the products with high yields and selectivities (Table 3, entries 1 and 2). However, when the substituted methyl acrylate was applied as substrate, we found that α-substituted methyl acrylate was suitable for this reaction, while β-substituted methyl acrylate could only give the lowest yield of cyclopropanation product (entries 3 and 4). With acrylaldehyde, only 15% yield product could be obtained even ligand was added to improve the reaction (entry 5). It was noted that acrylamide **2f** and acrylonitrile **2g** could react with methyl phenyldiazoacetate **1a** when 1,10-phenanthrolin ligand was added, albeit with essentially no selectivities (entries 6 and 7).

In the previous report on the Pd-catalyzed cyclopropanation with diazo substrates, Pd carbene generation followed by [2+2] cyclization and reductive elimination has been suggested to be the possible mechanism. However, in the present investigation, the following observation led us to consider an alternative reaction pathway for the cyclopropanations.

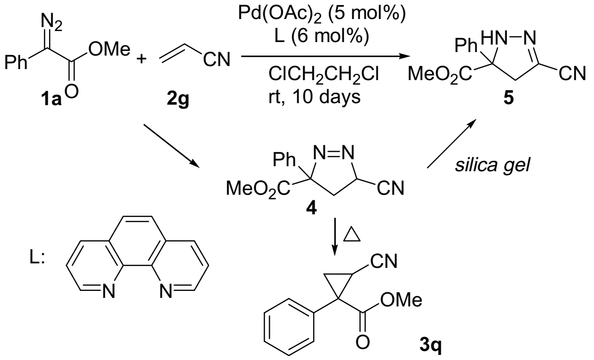
When the reaction of methyl phenyldiazoacetate **1a** with acrylonitrile **2g** was carried out at room temperature with $Pd(OAc)_2$/1,10-phenanthrolin as the catalyst, it proceeded very slowly. After 10 days, the pyrazole derivative **5** was isolated in 57% yield. Careful inspection of the reaction process indicated that cyclic azo product **4** was initially formed. Compound **4** was converted to **5** during the column chromatographic separation with silica gel. Compound **4** could be converted to cyclopropane product **3q** when it was heated (Scheme 2).[2a]

Table 3
$Pd(OAc)_2$-catalyzed cyclopropanation of methyl phenyldiazoacetate **1a** with electron-deficient olefin **2a**–**g**



Entry	**2a**–**g**, R^1, R^2, EWG	*t* (h)	Yield[a] (%)	*cis*:*trans*[b]
1	**2a**, H, H, CO_2Me	0.5	**3**,[a] 86	>95:5
2	**2b**, H, H, CO_2Bu	1	**3l**, 79	>95:5
3	**2c**, Me, H, CO_2Me	4	**3m**, 63	>95:5
4[c]	**2d**, H, Ph, CO_2Me	12	**3n**, 30	89:11
5[c]	**2e**, H, H, CHO	12	**3**,° 15	>95:5
6[d]	**2f**, H, H, $C(O)NEt_2$	12	**3p**, 58	50:50
7[e]	**2g**, H, H, CN	8	**3q**, **73**	50:50

[a] Yield of isolated product after chromatography.
[b] Ratio was determined by ^1H NMR (300 MHz) of the crude product.
[c] 10 mol % dppf ligand was added.
[d] 10 mol % 1,10-phenanthrolin ligand was added.
[e] 6 mol % 1,10-phenanthrolin ligand was added, chlorobenzene was used as solvent.



Scheme 2. Pd(OAc)$_2$-catalyzed reaction of methyl phenyldiazoacetate **1a** with acrylonitrile **2g**.

In conclusion, we have developed a concise and efficient protocol for the preparation of cyclopropanes from various aryldiazocarbonyl compounds with electron-deficient olefins catalyzed by Pd(OAc)$_2$. This catalytic methodology is highly attractive and provides a valuable choice for the organic synthesis.

Acknowledgments

The project is generously supported by Natural Science Foundation of China (Nos. 20572002, 20521202, 20772003) and the Ministry of Education of China (Cheung Kong Scholars Program).

References and notes

1. For review, see: Salaun, J. *Chem. Rev.* **1989**, *89*, 1247.
2. For comprehensive reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911; (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
3. Nakamura, A.; Konishi, A.; Tatsuno, Y.; Ostuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443.
4. (a) Doyle, M. P.; Davidson, J. G. *J. Org. Chem.* **1980**, *45*, 1538; (b) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059.
5. (a) Miller, J. A.; Jin, W.; Nguyen, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 2953; (b) Miller, J. A.; Gross, B. A.; Zhuravel, M. A.; Jin, W.; Nguyen, S. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3885.
6. Lin, W.; Charette, A. B. *Adv. Synth. Catal.* **2005**, *347*, 1547.
7. Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074.
8. (a) Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708; (b) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566; (c) Chen, S.; Wang, J. *Chem. Commun.*, **2008**, 4198.
9. (a) Paulissen, R.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1972**, *15*, 1465; (b) Kottwitz, J.; Vorbruggen, H. *Synthesis* **1975**, 636; (c) Suda, M. *Synthesis* **1981**, 714; (d) Mende, U.; Raduchel, B.; Skuballa, W.; Vorbruggen, H. *Tetrahedron Lett.* **1975**, *9*, 629; (e) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375; (f) Straub, B. F. *J. Am. Chem. Soc.* **2002**, *124*, 14195; (g) Illa, O.; Rodriguez-Garcia, C.; Acosta-Silva, C.; Favier, I.; Picurelli, D.; Oliva, A.; Gomez, M.; Branchadell, V.; Ortuno, R. M. *Organometallics* **2007**, *26*, 3306.
10. (a). *J. Org. Chem.* **1960**, *25*, 2078; (b) Bonavent, G.; Causse, M.; Guitard, M.; Fraisse-Jullien, R. *Bull. Soc. Chim. Fr.* **1964**, 2462; (c) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; Hofmann, C. M.; McKenzie, T. C.; Safir, S. R.; Osterberg, A. C.; Cosulich, D. B.; Lovell, F. M. *J. Med. Chem.* **1981**, *24*, 481; (d) Mangelinckx, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 1771.
11. Kowalkowska, A.; Sucholbiak, D.; Jonczyk, A. *Eur. J. Org. Chem.* **2005**, 925.
12. (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.
13. *General procedure for the cyclopropanation of aryldiazo compounds* ***1a–k*** *with olefins* ***2a–g*** *catalyzed by Pd(OAc)$_2$*: To a solution of Pd(OAc)$_2$ (0.025 mmol) with olefins **2a–g** (2.5 mmol) in anhydrous toluene (1 mL) at 80 °C under N_2 was added dropwise a solution of individual diazo compounds **1a–g** (0.5 mmol) in anhydrous toluene (2 mL). The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed by evaporation, and the residue was purified by column chromatography over silica gel to give the cyclopropane products **3a–q**. *Representative spectroscopic data*: **3d**: A colorless oil; IR (neat) 1725, 1258, 1162, 1093 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.90 (dd, $J = 4.5$, 8.4 Hz, 1H), 1.98 (dd, $J = 4.5$, 6.6 Hz, 1H), 2.76 (dd, $J = 6.6$, 8.4 Hz, 1H), 3.48 (s, 3H), 3.65 (s, 3H), 7.20 (d, $J = 6.6$ Hz, 2H), 7.28 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.5, 29.4, 35.9, 52.0, 52.9, 128.3, 131.8, 133.1, 133.6, 169.2, 172.2. EI-MS (*m/z*, relative intensity): 268 (M$^+$, 59), 209 (23), 149 (100); Anal. Calcd for $C_{13}H_{13}ClO_4$: C, 58.11; H, 4.88. Found: C, 58.13; H, 4.89.