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

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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

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**.

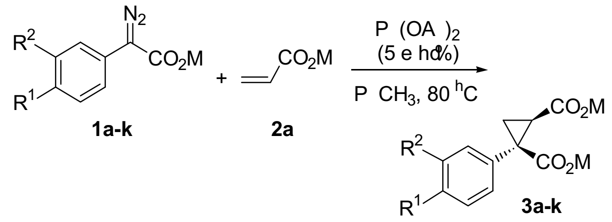
Next, we examined the scope of electron-deficient olefin substrates, as shown in Table 3. The ester moiety of the acrylate did not affect the reaction, and cyclopropanation proceeded smoothly to give the products with high yields and selectivities (Table 3, entries 1 and 2). However, when the substituted 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).

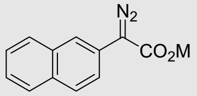
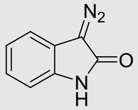
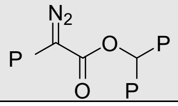
In the previous report on the Pd-catalyzed cyclopropanation with diazo substrates, Pd carbene generation followed by [2+2] cyclization and reductive elimination has been suggested to be the possible mechanism. However, in the present investigation, the following observation led us to consider an alternative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

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



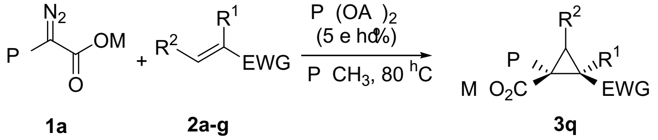
Entry	**1a**–**k**, R^1, R^2		t (h)	Yield[a] (%)	cis:trans[b]
1	**1a**, H, H		0.5	**3a**, 86	>95:5
2	**1b**, Me, H		0.5	**3b**, 70	>95:5
3	**1c**, OMe, H		1	**3c**, 48	>95:5
4	**1d**, Cl, H		1	**3d**, 81	91:9
5	**1e**, Br, H		1	**3e**, 72	88:12
6	**1f**, NO_2, H		2	**3f**, 73	83:17
7	**1g**, H, Cl		0.5	**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.

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

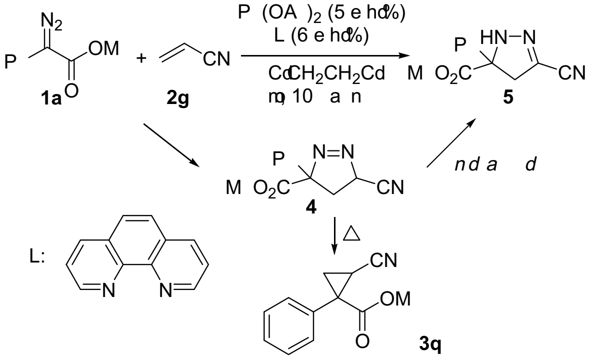
[a] Yield of isolated product after chromatography.

[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.

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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}; ^1H 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.