ORGANIC LETTERS

2004
Vol. 6, No. 19
3337−3340

Synthesis of Novel Palladacycles and Their Application in Heck and Suzuki Reactions under Aerobic Conditions

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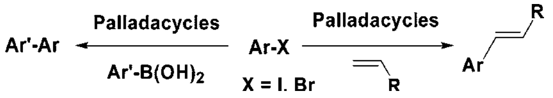
Received July 1, 2004

ABSTRACT



Design and synthesis of a novel family of furancarbothioamide-based palladacycles are reported herein. These palladacycles are thermally stable, not sensitive to air or moisture, and are applied effectively in the Heck reaction of aryl halides with terminal olefins and in the Suzuki reaction of aryl halides with arylboronic acids. These reactions were performed under aerobic conditions, leading to turnover numbers (TONs) up to 1 × 10^5.

Palladacycles are one of the most important and intensively investigated classes of organometallic compounds, and some are efficient catalysts or catalyst precursors in the Pd-catalyzed C−C bond formation reactions.[1]

However, certain published phosphapalladacycles (**1**−**4**, Figure 1) and phosphine-free N-heterocyclic carbenes (NHC) (**5**−**9**, Figure 1) are air- and moisture-sensitive, and the reactions have to be handled under an inert atmosphere.

Thiourea has been proven to be very useful in some Pd-catalyzed reactions.[2] One important aspect of the thiourea-based ligand is its thermal stability and lack of sensitivity to air and moisture. Our continuing interest in the development of thiourea-related ligands in the Pd-catalyzed C−C bond formation led us to explore the carbothioamide-derived palladacycle because of its structural similarity with thiourea.

With the aim of studying C−C bond formation catalyzed by the carbothioamide-derived palladacycle in a systematic manner, we wanted our selected scaffolds to be amenable to both electronic and steric variations. Thus, the arylcarbothioamide-derived palladacycle was our primary choice

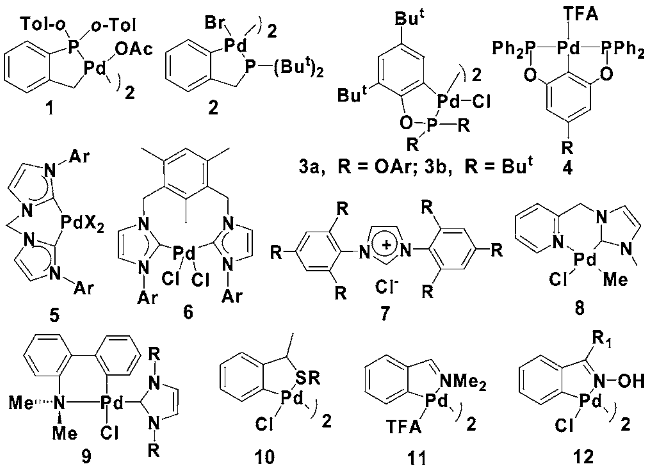


Figure 1. Selected existing palladacycles.

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10.1021/ol048749s CCC: $27.50

because both electronic and steric effects can be addressed effectively by changing different electron-donating and -withdrawing groups (R_1) on the aromatic ring (electronic effect) and by changing various substitutions (R_2) on the nitrogen (steric effect), respectively (Figure 2).

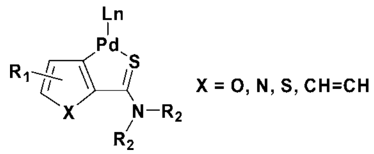


Figure 2. Carbothioamide-derived palladacycles.

As a matter of fact, such a furancarbothioamide-based palladacycle **13** (Figure 3) was synthesized 25 years ago, and its structure was fully characterized by X-ray diffraction.[3] However, its catalytic activity for C−C bond formation was not evaluated, which encouraged us to synthesize a number of furancarbothioamide-based palladacycles (**13**−**17**, Figure 3) and evaluate them in the Heck and Suzuki reactions. We herein report the preliminary results of our research.

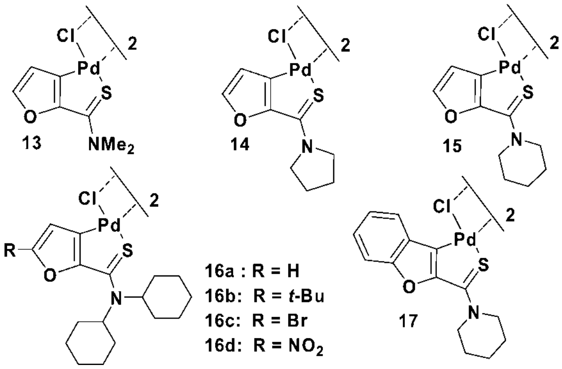
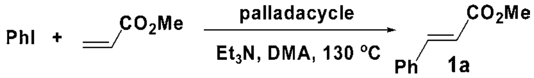


Figure 3. Structures of the synthesized furancarbothioamide-derived palladacycles.

Table 1. Palladacycle-Catalyzed Heck Reaction of Iodobenzene with Methyl Acrylate[a]



entry	palladacycle	mol % Pd	*t* (h)	yield (%)[b]
1	**13**	0.01	2	97%
2	**14**	0.01	2	97%
3	**15**	0.01	2	97%
4	**16a**	0.01	2	97%
5	**16b**	0.01	2	97%
6	**16c**	0.01	2	97%
7	**16d**	0.01	2	97%
8	**17**	0.01	2	97%
9	**13**	0.001	8	97%
10	**14**	0.001	8	97%
11	**15**	0.001	8	97%
12	**16a**	0.001	6	97%
13	**16b**	0.001	6	97%
14	**16c**	0.001	6	97%
15	**16d**	0.001	6	97%

[a] Reaction conditions: 3 mmol of PhI, 4.5 mmol of methyl acrylate, 3.6 mmol of Et_3N, 2 mL of DMA. [b] Isolated yields.

The preparation of the palladated complexes **13**−**17** was accomplished using a similar procedure described in the literature. Accordingly, these palladacycles were prepared by addition of furancarbothioamides to a methanol solution of Li_2PdCl_4 at room temperature.[4] The furancarbothioamides were made by thiolation with Lawesson's reagent from their corresponding furancarbamides,[5] which were easily synthesized from the commercially available furans.[6] Thus, eight different palladacycles **13**−**17** (Figure 3) with a variety of steric and electronic properties were made.

Palladacycles **13**−**17** are slightly soluble in hexanes, chloroform, and dichloromethane and moderately soluble in polar solvents such as DMF, DMA (dimethyl acetamide), and DMSO.

The catalytic efficacy of the synthesized palladacycles **13**−**17** was tested in the Heck cross-coupling reaction between phenyl iodide and methyl acrylate at 130 °C. The reactions

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(1) See for example: (a) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew, Chem., Int. Ed. Engl.* **1995**, *34*, 1848. (b) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371. (c) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun*. **1998**, 2095. (d) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun*. **1999**, 357. (e) Blackmond, D. G.; Rosner, T.; Pfaltz, A. *Org. Proc. Res. Dev*. **1999**, *3*, 275. (f) Herrmann, W. A.; Böhn, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem*. **1999**, *576*, 23. (g) Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem*. **1999**, *572*, 141. (h) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem*. **1999**, *64*, 3804. (i) Weissman, H.; Milstein, D. *Chem. Commun*. **1999**, 1901. (j) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett*. **2000**, *2*, 1823. (k) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741. (l) Bedford, R. B.; Draper, S. M.; Scully, P. N.; Welch, S. L. *New J. Chem*. **2000**, 745. (m) Zhang, C.; Trudell, M. L. *Tetrahedron Lett*. **2000**, *41*, 595. (n) Dupont, J.; Gruber, A. S.; Fonseca, G. S.; Monteiro, A. L.; Ebeling, G. *Organometallics* **2001**, *20*, 171. (o) Gibson, S.; Foster, D. F.; Eastham, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun*. **2001**, 779. (p) Bedford, R. B.; Welch, S. L. *Chem. Commun*. **2001**, 129. (q) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett*. **2003**, *5*, 1479. (r) Weissman, H.; Milstein, D. *Chem. Commun*. **1999**, 1901. (s) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett*. **2000**, *2*, 1823. (t) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett*. **2000**, *2*, 1287.

(2) (a) Chiusoli, G. P.; Venturello, C.; Merzoni, S. *Chem. Ind. (London)* **1968**, 977. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem*. **1995**, *503*, 21. (c) Zhang, T.; Allen, M. J. *Tetrahedron Lett*. **1999**, *40*, 5813. (e) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 297. (e) Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 1765. (f) Hu, Y.; Yang, Z. *Org. Lett*. **2001**, *3*, 1387. (g) Dai, M. J.; Wang, C. H.; Dong, G. B.; Xiang, J.; Luo, T. P.; Liang, B.; Chen, J. H.; Yang, Z. *Eur. J. Org. Chem*. **2003**, 4346. (h) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett*. **2004**, 6, 221. (i) Yang, D.; Chen, Y.-C.; Zhu, N.-Y. *Org. Lett*. **2004**, *6*, 1577.

(3) (a) Mizuno, H.; Nonoyama, M. *Polyhedron* **1990**, *9*, 1287. (b) Nonoyama, M. *Transition Met. Chem*. **1990**, *15*, 366. (c) Grinter, T. J.; Leaver, D.; O'Neil, R. M. *Inorg. Nucl. Chem. Lett*. **1980**, *16*, 145.

(4) (a) Nojima, Y.; Noyo, Y. M. *Polyhedron* **1996**, *15*, 3795. (b) Onoue, H.; Minami, K.; Nakagawa, K. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 3480.

(5) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg*. **1978**, *87*, 229.

(6) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun*. **1990**, *20*, 1105.

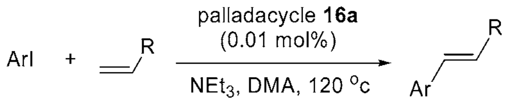
were conducted in air[7,2h] with all the reagents being used directly as received.

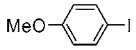
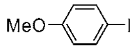
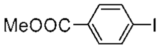
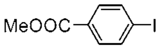
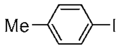
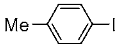
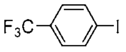
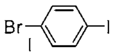
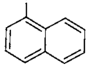
Table 1 illustrates the coupling results. Good to excellent yields were obtained within 1−3 h when 0.01 mol % palladacycles were applied. Reducing the catalyst loading to 0.001 mol % led to longer reaction times but did not influence the reaction conversion markedly (see entries 9−12, Table 1). Interestingly, the palladacycles formed with bulky substituents (such as **16a−d**) exhibit enhanced catalytic activities (cf. entries 12−15 vs entries 9−11). Moreover, no discernible influence was observed when the furan substituent was changed from H to nitro (cf. 12−15) or replacement of furan (entry 4) with benzofuran (entry 8).

It is noteworthy that all the palladacycles demonstrated good thermal stability, showing no decomposition (monitored by ^{1}H NMR) when heated in DMSO-d_6 for 4 h at 100 °C.

Due to its catalytic efficacy in the Heck reaction, palladacycle **16a** was studied further in the coupling of a number of aryl iodides and olefins. Table 2 indicates that high yields were obtained within 1−3 h using 0.01 mol % catalyst. We stress that the DMA stock solution of palladacycle **16a** was utilized for these coupling reactions and retained its activity even after standing in air at room temperature for weeks.

Table 2. Palladacycle **16a**-Catalyzed Heck Coupling Reaction of Aryl Iodides with Terminal Olefins[a]

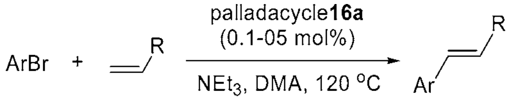


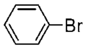
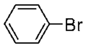
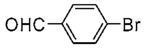
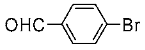
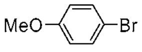
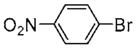
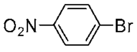
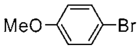
entry	ArI	R	t (h)	product	yield (%)[b]
1	PhI	$CO_2{}^nBu$	1	**2a**	98
2	PhI	CO_2Me	1	**1a**	95
3	PhI	phenyl	3	**2b**	84
4		$CO_2{}^nBu$	1	**2c**	91
5		CO_2Me	1	**2d**	90
6		$CO_2{}^nBu$	1	**2e**	88
7		CO_2Me	1	**2f**	97
8		CO_2Me	2	**2g**	91
9		$CO_2{}^nBu$	2	**2h**	96
10		CO_2OMe	2	**2i**	86
11		$CO_2{}^nBu$	2	**2j**	87
12		CO_2Me	3	**2k**	85

[a] Reaction conditions: 3 mmol of PhI, 4.5 mmol of methyl acrylate, 3.6 mmol of Et_3N, 2.0 mL of DMA. [b] Isolated yields.

We then evaluated the catalytic efficacy of palladacycle **16a** in the Heck reaction with aryl bromides and chlorides as the substrates. In general, higher catalyst loading and longer reaction times were required to push to completion the reaction of aryl bromides, compared to the corresponding iodides. For phenyl bromide or activated bromides (entries 1−4, Table 3), complete conversions of the substrates were observed within 4−15 h in the presence of 0.1−0.5 mol % Pd using DMA as the solvent and Et_3N as the base. *n*-Butyl acrylate displayed a higher reactivity than styrene (cf. entries 1, 3, 6 vs 2, 4, 7). Under the "Jeffery conditions",[8] improved results were obtained for entries 6 and 7, using 0.2 equiv of Bu_4NBr in DMA and NaOAc as the base. On the other hand, we observed a low yield when a deactivated bromide (entry 8) was employed, and no reaction occurred using an aryl chloride as a substrate.

Table 3. Palladacycle **16a**-Catalyzed Heck Coupling Reaction of Aryl Bromides with Terminal Olefins[a]



entry	ArBr	R	t (h)	Pd (mol%)	product	yield (%)[b]
1		$CO_2{}^nBu$	8	0.1	**2a**	91
2		phenyl	15	0.5	**2b**	86
3		$CO_2{}^nBu$	8	0.1	**3a**	87
4		phenyl	15	0.5	**3b**	70
5		phenyl	15	0.5	**3c**	75
6		$CO_2{}^nBu$	4	0.1	**3d**	95[c]
7		phenyl	12	0.5	**3e**	86[c]
8		$CO_2{}^nBu$	15	0.5	**2c**	58[c]

[a] Reaction conditions: 1 mmol of PhI, 1.5 mmol of methyl acrylate, 1.2 mmol of Et_3N, 2.0 mL of DMA. [b] Isolated yields. [c] Reaction conditions: 1.0 mmol of ArBr, 1.3 mmol of methyl acrylate, 1.2 mmol of NaOAc, 0.2 mmol of *n*-Bu_4NBr, 2.0 mL of DMA.

The Pd-catalyzed Suzuki cross-coupling reaction is a useful method for C−C bond formation. Recent notable advances have been achieved in the Suzuki reaction under aerobic conditions with some novel palladium complexes (such as the complexes derived from diazabutadiene,[9] oxime,[10] *N*-acylamidine,[11] and di-2-pyridylmethylamine[12]) or even with

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(7) (a) For recent reports on Heck reactions using catalysts that are air- and moisture-stable, see: (a) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc*. **1999**, *121*, 11101. (b) Silberg, J.; Schareinia, T.; Kempe, R.; Wurst, K.; Buchmeiser, M. R. *J. Organomet. Chem*. **2001**, *622*, 6. (c) Masllorens, J.; Moreno-Manas, M.; Pla-Quintana, A.; Roglans, A. *Org. Lett*. **2003**, *5*, 1559.

(8) Jeffery, T. *Tetrahedron Lett*. **1985**, *26*, 2667.

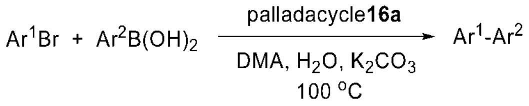
(9) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett*. **2001**, *3*, 1077.

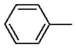
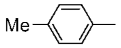
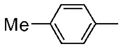
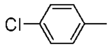
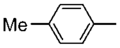
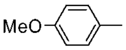
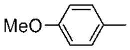
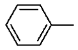
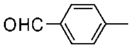
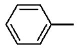
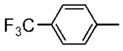
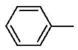
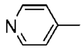
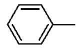
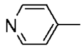
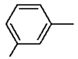
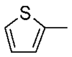
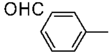
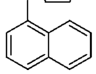
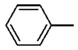
(10) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem*. **2002**, *67*, 5588 and related references therein.

polymer-incarcerated palladium,[13] which inspired us to test the palladacycle **16a** in the Suzuki reaction under aerobic conditions in consideration of its beneficial air- and moisture-stable properties.

Aryl bromides are cheaper and more readily available substrates than the corresponding iodides but are more reluctant to undergo the catalytic Suzuki reaction. Therefore, we tested the catalytic efficacy of palladacycle **16a** in the Suzuki reaction using aryl bromides as the substrates. To this end, eight aryl bromides with four aryl boronic acids were selected for the coupling reaction with palladacycle **16a** as a catalyst under aerobic conditions, and the coupling results are listed in Table 4. Under the optimized conditions, the selected aryl bromides were coupled with the typical boronic acids, and good to excellent yields were obtained.

Table 4. Palladacycle **16a**-Catalyzed Suzuki Coupling of Aryl Bromides and Arylboronic Acid[a]

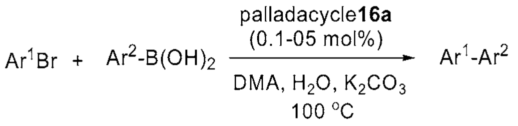


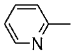
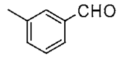
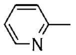
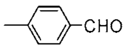
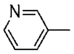
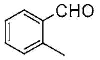
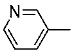
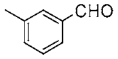
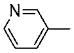
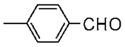
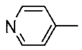
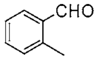
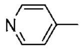
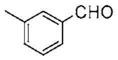
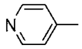
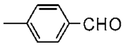
entry	Ar^1	Ar^2	t (h)	**16a**[b]	product	yield[c]
1			2	0.1	**4a**	82%
2			2	0.1	**4b**	80%
3			2	0.1	**4c**	72%
4			10	0.5	**4d**	79%
5			2	0.1	**4e**	91%
6			4	0.1	**4f**	88%
7			2	0.5	**4g**	83%
8			2	0.5	**4h**	78%
9			2	0.5	**4i**	86%
10			2	0.5	**4j**	89%

[a] Reaction conditions: 1 mmol of Ar_2Br, 1.2 mmol of $Ar_2B(OH)_2$, 2.0 mmol of K_2CO_3, 2 mL of 25% H_2O in DMA, 100 °C. [b] **16a** (mol%). [c] Isolated yield.

To verify its unique role in the Pd-catalyzed Suzuki reaction, **16a** was employed in the Suzuki reaction to build up the biaryl fragments in our SAG[14] library in a parallel format. To this end, eight coupling reactions were selected, and the results are shown in Table 5. All the reactions were perfomred by simply mixing the reagents in flasks under aerobic conditions, and the reactions were finished in 2 h at 100 °C. It is noteworthy that the same coupling reactions were tried using the other palladium complexes (such as Pd(Ph_3P)$_4$ and $PdCl_2(Ph_3P)_2$) in the same way as above, but no satisfying results were obtained, presumably due to their air sensitivity.

Table 5. Parallel Synthesis of Biaryl Molecules by Palladacycle **16a**-Catalyzed Suzuki Coupling Reaction[a]



entry	Ar^1	Ar^2	t (h)	Pd (mol%)	product	yield (%)[b]
1			2	0.1	**5a**	91
2			2	0.1	**5b**	89
3			2	0.1	**5c**	87
4			2	0.1	**5d**	86
5			2	0.1	**5e**	83
6			2	0.1	**5f**	90
7			2	0.5	**4h**	86
8			2	0.5	**5g**	79

[a] Reaction conditions: 1 mmol of Ar_1Br, 1.2 mmol of $Ar_2B(OH)_2$, 2.0 mmol of K_2CO_3, 2 mL of 25% H_2O in DMA, 100 °C. [b] Isolated yield.

In summary, we have synthesized a novel family of furancarbothioamide-derived palladacycles, and their catalytic activities were tested in the Heck and Suzuki coupling reactions with aryl halides and terminal olefins or aryl boronic acids. These novel palladacycles are air- and moisture-stable, and the reaction can be readily conducted under aerobic conditions. Further studies of their applicability in other synthetic transformations are currently under investigation.

Acknowledgment. We gratefully acknowledge financial support of this work by the National Science Foundation of China (Grants 20142004 and 20242002), and VivoQuest, Inc., through the sponsored research program.

Supporting Information Available: Experimental procedures and NMR and LC-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048749S

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