3622 *Organometallics* **2008,** *27,* 3622–3625

Tuning the Reactivity of Palladium Carbenes Derived from Diphenylketene

Julie M. Goll and Eric Fillion*

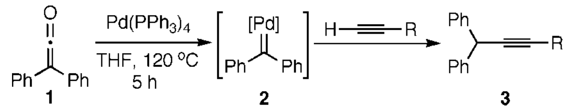
Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Received May 2, 2008

Summary: The ability to tune the reactivity of palladium carbenes derived from diphenylketene, which is dependent on the oxidation state of the metal center, is presented. Competition experiments illustrated that Pd(0) catalysts favor direct C−H functionalization of terminal alkynes and that Pd(II) catalysts lead to cyclopropanation of strained alkenes. In addition, a $PdCl_2$-catalyzed cyclopropane isomerization of diphenylcyclopropanes and an unprecedented Pd(II)-catalyzed domino cyclopropanation/isomerization reaction are described.

Ligation of a carbene to a metal center can have a dramatic effect on the reactivity of both the metal and the carbene carbon. On one hand, the use of N-heterocyclic carbene ligands in Pd-catalyzed reactions has been studied extensively.[1] In these transformations, the carbene ligands play a crucial role in stabilizing and controlling the reactivity of the palladium center but are not directly involved in the bond-breaking and -forming events, as the chemistry occurs exclusively on the adjacent palladium center.[2] Conversely, a wide array of transformations are accessible from metal carbenes in which the carbene is the reactive species and participates in the bond-forming events, while the metal stabilizes and controls the reactivity and selectivity of the electrophilic carbene.[3] In that regard, with the exception of Pd(II)-catalyzed cyclopropanation of alkenes using diazomethane,[4] Pd carbenes have received negligible attention.[5,6] To date, the nature and reactivity of Pd-stabilized carbenes remain elusive, specifically in relation to the oxidation state of the metal center. A number of studies suggest that Pd(II) salts decompose diazomethane, with concomitant formation of nitrogen, to generate Pd(II)-stabilized carbenes.[3,4,7] However, the reduction of palladium(II) salts to Pd(0) by diazomethane has been reported.[7] It was also noted that $Pd(dba)_2$, a Pd(0) catalyst lacking phosphine ligands, has the ability to catalyze the decomposition of diazomethane and the cyclopropanation of alkenes.[8]

Scheme 1. Pd(0)-Catalyzed Functionalization of Terminal Alkynes



The contrasting results described in the literature and the synthetic importance of Pd-catalyzed cyclopropanation of alkenes prompted us to establish a link between the oxidation state at the metal center and Pd−carbene reactivity. Our results in this area, as well as an investigation into an unprecedented Pd(II)-catalyzed cyclopropane isomerization are described herein.

The effect of the Pd center oxidation state on the reactivity of the carbene was probed by exploring the cyclopropanation of strained alkenes with diphenylketene (**1**). Watanabe and coworkers reported the reaction of terminal alkynes with diphenylketene in the presence of $Pd(PPh_3)_4$ (5 mol %) to furnish the internal alkynes **3**.[9] The authors postulated that the reaction proceeded via the decarbonylation of diphenylketene by Pd(0) to generate the Pd carbene **2** (Scheme 1). Metal-assisted cleavage of carbon−carbon double bonds, under stoichiometric or

---

* To whom correspondence should be addressed. E-mail: efillion@uwaterloo.ca.

(1) Díez-González, S.; Nolan, S. P. *Top. Organomet. Chem.* **2007**, *21*, 47–82.

(2) An exception is the relatively rare reductive elimination of Pd(II) N-heterocyclic carbene complexes to yield Pd(0) and an imidazolium salt; see: (a) Danopoulos, A. A.; Tsoureas, N.; Green, J. C.; Hursthouse, M. B. *Chem. Commun.* **2003**, 756–757. (b) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 1591–1593. (c) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Leonard, J.; de K. Lewis, A. K.; McKerrecher, D.; Titcomb, L. R. *Organometallics* **2002**, *21*, 4318–4319. (d) Nielsen, D. J.; Magill, A. M.; Yates, B. F.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Chem. Commun.* **2002**, 2500–2501. (e) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029–4040. (f) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 4918–4920. (g) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596–1605. (h) McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165–178.

(3) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999.

(4) Reiser, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1561−1577.

(5) (a) Trépanier, V. É.; Fillion, E. *Organometallics* **2007**, *26*, 30–32. (b) Fillion, E.; Taylor, N. J. *J. Am. Chem. Soc.* **2003**, *125*, 12700–12701.

(6) Pd carbenes have been proposed as intermediates in a number of transformations; see: (a) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567. (b) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44–53. (c) Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753–4757. (d) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763–4766. (e) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328–4331. (f) Schweizer, S.; Song, Z.-Z.; Meyer, F. E.; Parsons, P. J.; de Meijere, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1452–1454. (g) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997–7000. (h) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Roger, C. A. *J. Org. Chem.* **1994**, *59*, 7553–7556. (i) Monterio, N.; Goré, J.; van Hemelryck, B.; Balme, G. *Synlett* **1994**, 447–449. (j) Ogoshi, S.; Morimoto, T.; Nishio, K.; Ohe, K.; Murai, S. *J. Org. Chem.* **1993**, *58*, 9–10. (k) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085–1087. (l) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518–4520. (m) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638. (n) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479–1482. (o) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5143–5144. (p) Chakraborti, A. K.; Ray, J. K.; Kundu, K. K.; Chakrabarty, S.; Mukherjee, D.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 261–273. (q) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695–702.

(7) Tomilov, Y. V.; Dokichev, V. A.; Dzhemilev, U. M.; Nefedov, O. M. *Russ. Chem. Rev.* **1993**, *62*, 799–838.

(8) Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389.

(9) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 3697–3698.

10.1021/om800390w CCC: $40.75

Scheme 2. Attempted Cyclopropanation using Watanabe's Conditions

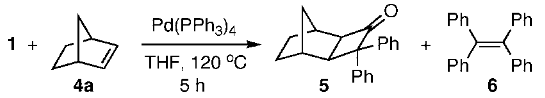
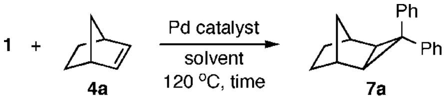


Table 1. Optimization of Palladium Catalyst[a]



entry	cat.	solvent	reacn time (h)	yield of **7a** (%)
1	$Pd(PPh_3)_4$	THF	5	0
2	$Pd(PPh_3)_4$	$(CH_2Cl)_2$	24	0
3	$Pd_2(dba)_3 \cdot CHCl_3$	THF	5	0
4	$Pd_2(dba)_3 \cdot CHCl_3$	$(CH_2Cl)_2$	24	0
5	$PdCl_2$	$(CH_2Cl)_2$	24	trace
6	PdI_2	$(CH_2Cl)_2$	24	7
7	$PdBr_2$	$(CH_2Cl)_2$	24	17
8	$Pd(OAc)_2$	$(CH_2Cl)_2$	24	17
9	$Pd(OCOCF_3)_2$	$(CH_2Cl)_2$	24	26
10	$PdCl_2(PPh_3)_2$	THF	5	9
11	$PdCl_2(PPh_3)_2$	$(CH_2Cl)_2$	24	6
12	$PdCl_2$(dppe)	$(CH_2Cl)_2$	24	trace
13	$PdCl_2$(dppf)	$(CH_2Cl)_2$	24	0
14	$PdCl_2(PhCN)_2$	THF	5	21
15	$PdCl_2(PhCN)_2$	THF	24	22
16	$PdCl_2(PhCN)_2$	$(CH_2Cl)_2$	5	25
17	$PdCl_2(PhCN)_2$	$(CH_2Cl)_2$	24	50
18	$PdCl_2(CH_3CN)_2$	$(CH_2Cl)_2$	24	54

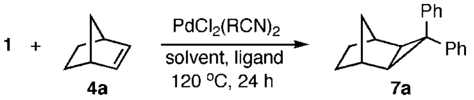
[a] In all reactions, 10 mol % of catalyst was used and the concentration of the solution was 0.2 M.

catalytic conditions, as an entry into metal carbenes is rare.[10] We elected to exploit this mode of metal carbene preparation due to the availability, ease of handling, and stability of diphenylketene (**1**). It was also postulated that potential problems associated with the reduction of Pd(II) catalysts by diazo compounds would be avoided, facilitating determination of the oxidation state of the reactive species.

Initial attempts to cyclopropanate norbornene (**4a**), in 10-fold excess, under Watanabe's conditions were unsuccessful. Instead, the [2 + 2] cycloadduct **5** and tetraphenylethylene (**6**) were the only products identified by GC-MS and ^{1}H NMR in undetermined amounts (Scheme 2). Formation of **6**, presumably via carbene dimerization, indicated that while a Pd carbene was generated under these conditions, its reactivity was not suited for cyclopropanation. We then turned our attention to varying the Pd source to modify the reactivity of the carbene and promote cyclopropanation. The results are summarized in Table 1. It quickly became apparent that the oxidation state of the Pd catalyst was the most important determinant of metal carbene reactivity.

In either THF or $(CH_2Cl)_2$, Pd(0) sources gave no trace of cyclopropane; in all cases **5** and **6** were the only products observed by GC-MS in undetermined amounts (entries 1−4). On the other hand, Pd(II) sources such as Pd halides and Pd carboxylates were moderately competent catalysts (entries 5−9). A variety of $PdCl_2$-based catalysts containing phosphine ligands were then examined, but with poor results (entries 10−13). The best results were obtained using nitrile ligands (entries 14−18),

Table 2. Optimization of Catalyst Loading and Solvent[a]



entry	cat. $PdCl_2(RCN)_2$	loading (mol %)	ligand	solvent	yield of **7a** (%)
1	$PdCl_2(PhCN)_2$	20		$(CH_2Cl)_2$	49
2	$PdCl_2(PhCN)_2$	5		$(CH_2Cl)_2$	34
3	$PdCl_2(PhCN)_2$	10		PhCl	31
4	$PdCl_2(PhCN)_2$	10		$PhCH_3$	30
5	$PdCl_2(CH_3CN)_2$	10		CH_3CN	14
6	$PdCl_2(PhCN)_2$	10	PhCN	DMF	14
7	$PdCl_2(CH_3CN)_2$	10	CH_3CN	DMF	12
8	$PdCl_2(PhCN)_2$	10	PhCN	$(CH_2Cl)_2$	62
9	$PdCl_2(CH_3CN)_2$	10	CH_3CN	$(CH_2Cl)_2$	43

[a] In all reactions, 50 mol % of the ligand was used and the concentration of the solution was 0.2 M.

and conditions using these catalysts were further optimized in terms of solvent and catalyst loading (Table 2).

Increasing the catalyst loading had no effect on the reaction, while lowering it to 5 mol % was detrimental to the yield (entries 1 and 2); aromatic solvents and CH_3CN also caused a yield decrease (entries 3−5). When CH_3CN and PhCN were used as additives in DMF, low yields of **7a** were obtained (entries 6 and 7). However, on returning to the optimal solvent $(CH_2Cl)_2$, the beneficial effect of added benzonitrile over acetonitrile led to optimized conditions (entries 8 and 9).

The compatibility of Pd(II) carbenes with a wide variety of functional groups was then assessed. As shown in Table 3, the reaction proceeded in the presence of alkenes, ethers, esters, and anhydrides (entries 1−6). Benzannelated norbornyl derivatives were also competent cyclopropanation substrates (entries 7−9). In addition, the reaction of a less strained bicyclo[2,2,2]octene system, although in moderate yield, illustrated the high reactivity of these metal carbenes (entry 10).

From these studies it was determined that the oxidation state of the metal carbene was the key to its reactivity. The difference between Pd(0) and Pd(II) carbenes was further emphasized in the competition studies outlined in Table 4, in which an equimolar amount of (trimethylsilyl)acetylene and a 10-fold excess of norbornene (**4a**) was reacted with 1 equiv of diphenylketene (**1**) under either Watanabe's or our cyclopro-

---

(10) (a) Urtel, H.; Bikzhanova, G. A.; Grotjahn, D. B.; Hofmann, P. *Organometallics* **2001**, *20*, 3938–3949. (b) Grotjahn, D. B.; Collins, L. S. B.; Wolpert, M.; Bikzhanova, G. A.; Lo, H. C.; Combs, D.; Hubbard, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8260–8270. (c) Grotjahn, D. B.; Bikzhanova, G. A.; Collins, L. S. B.; Concolino, T.; Lam, K.-C.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 5222–5223.

(11) It should be pointed out that, under Watanabe's conditions, the yield of acetylenic material was near that achieved in the original publication, with the slight drop attributed to competitive formation of **5**.

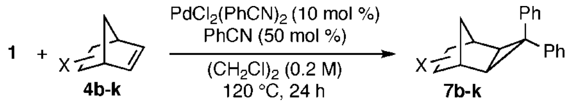
(12) For a study comparing the reactivity of Pd(II) carbenes versus Rh(II) carbenes in cyclopropanation reactions, see: Doyle, M. P.; Wang, L. C.; Loh, K.-L. *Tetrahedron Lett.* **1984**, *25*, 4087–4090. The degree of charge development in the transition state was postulated to rationalize the catalyst-dependent differences in regioselectivity for cyclopropanation.

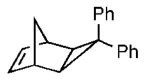
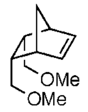
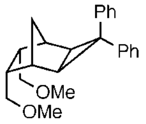
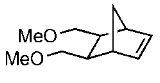
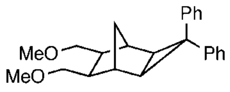
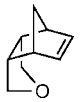
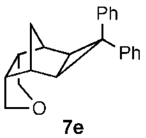
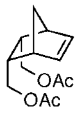
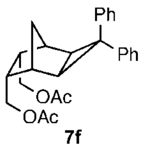
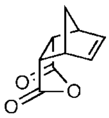
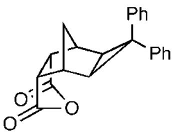
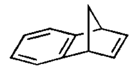
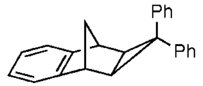
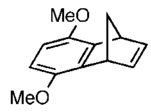
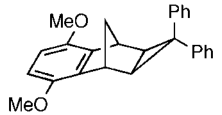
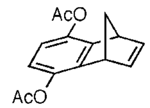
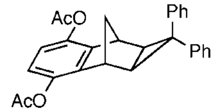
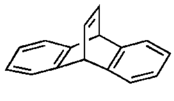
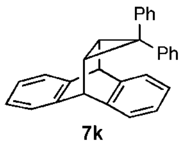
(13) He, Z.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 5829–5832.

(14) (a) Blomberg, M. R. A.; Siegbahn, P. E. M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 4450–4456. (b) Parra-Hake, M.; Rettig, M. F.; Williams, J. L.; Wing, R. M. *Organometallics* **1986**, *5*, 1032–1040. (c) Wilhelm, D.; Bäckvall, J.-E.; Nordberg, R. E.; Norin, T. *Organometallics* **1985**, *4*, 1296–1302. (d) Parra-Hake, M.; Rittig, M. F.; Wing, R. M.; Woolcock, J. C. *Organometallics* **1982**, *1*, 1478–1480. (e) Bäckvall, J.-E.; Björkman, E. E. *J. Chem. Soc., Chem. Commun.* **1982**, 693–694. (f) Ahmad, M. U.; Bäckvall, J.-E.; Nordberg, R. E.; Norin, T.; Strömberg, S. *J. Chem. Soc., Chem. Commun.* **1982**, 321–323. (g) Rittig, M. F.; Wilcox, D. E.; Fleischer, R. S. *J. Organomet. Chem.* **1981**, *214*, 261–272. (h) Albelo, G.; Wiger, G.; Rittig, M. F. *J. Am. Chem. Soc.* **1975**, *97*, 4510–4519. (i) Albelo, G.; Rittig, M. F. *J. Organomet. Chem.* **1972**, *42*, 183–198. (j) Bodor, N.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1971**, *93*, 6685–6686.

(15) For a tandem carbopalladation/cyclopropane isomerization of homoallylic cyclopropanes, see: Storsberg, J.; Yao, M.-L.; Öcal, N.; de Meijere, A.; Adam, A. E. W.; Kaufmann, D. E. *Chem. Commun.* **2005**, 5665–5666.

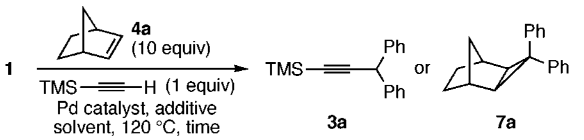
Table 3. Scope of Cyclopropanation



Entry	Substrate	Product	Yield(%)[a]
1	 **4b**	 **7b**	69
2	 **4c**	 **7c**	52
3	 **4d**	 **7d**	49
4	 **4e**	 **7e**	50
5	 **4f**	 **7f**	53
6	 **4g**	 **7g**	53
7	 **4h**	 **7h**	51
8	 **4i**	 **7i**	38
9	 **4j**	 **7j**	44
10	 **4k**	 **7k**	42

[a] The yields are the average of at least two runs.

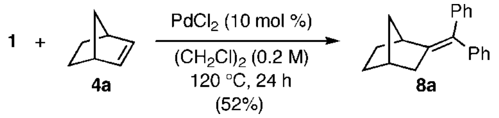
Table 4. Competition Studies[a]



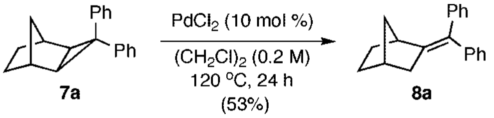
entry	Pd cat. (amt (mol %))	additive	solvent	time (h)	yield (%)
1	Pd(PPh$_3$)$_4$ (5)		THF	5	63 (**3a**)
2	PdCl$_2$(PhCN)$_2$ (10)	PhCN	THF	5	25 (**7a**)
3	Pd(PPh$_3$)$_4$ (5)		(CH$_2$Cl)$_2$	24	9 (**3a**)
4	PdCl$_2$(PhCN)$_2$ (10)	PhCN	(CH$_2$Cl)$_2$	24	61 (**7a**)

[a] In all reactions the amount of additive was 50 mol % and the concentration of the solution was 0.2 M.

Scheme 3. Product Formed with PdCl$_2$ as Catalyst



Scheme 4. PdCl$_2$-Catalyzed Isomerization



panation conditions. Under both sets of conditions, Pd(0) catalyst gave exclusively **3a**, the product of terminal alkyne C−H insertion, while Pd(II) furnished that of cyclopropanation, **7a**.[11] The yield difference with both catalysts as the conditions changed (entries 1 and 3 vs entries 2 and 4) highlights the interplay among catalyst, additive, solvent, and reaction time to achieving maximum yield from the same reactant. These results emphasize the high chemoselectivity of both processes and the different reactivities achievable by varying the oxidation state of Pd carbenes.[12]

During optimization studies of palladium catalysts it was observed that PdCl$_2$ afforded a different product in 52% yield, in addition to trace amounts of cyclopropane **7a** (Table 1, entry 5), which was identified as the tetrasubstituted alkene **8a**, shown in Scheme 3.

In order to determine whether **8a** was the result of a direct reaction between the palladium carbene and norbornene or a subsequent reaction occurring after formation of the cyclopropane, **7a** was treated with PdCl$_2$ under our reaction conditions (Scheme 4). To our delight, olefin **8a** was isolated in 53% yield. Catalytic activation of cyclopropanes by Pd(II) catalysts is rare[13] and typically requires an unsaturation in close vicinity (vinylic, allylic, or homoallylic) to coordinate to palladium and facilitate the insertion of the metal into the cyclopropane.[14,15] A plausible catalytic cycle is depicted in Figure 1. Cis chloropalladation would initiate the catalytic cycle and provide intermediate **9**;[14] regeneration of the catalyst would entail a 1,2-hydride shift, forming the tetrasubstituted olefin product **8**.

As shown in Table 5, the one-pot cyclopropanation/isomerization reaction was applied to olefins **4b** and **4h** to provide **8b** and **8c**, respectively, in good yields.

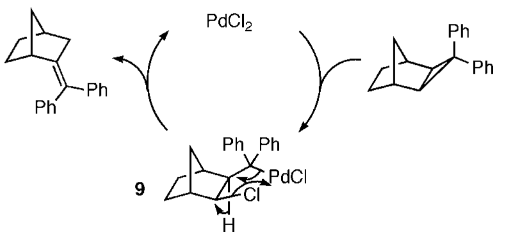
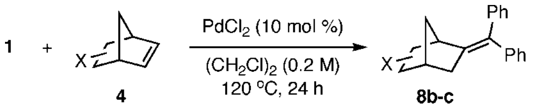
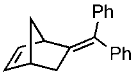
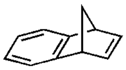
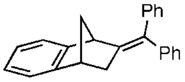


Figure 1. Proposed catalytic cycle for isomerization of diphenylcyclopropane by PdCl$_2$.

Table 5. Pd-Catalyzed Domino Cyclopropanation/Cyclopropane Isomerization Reaction



Entry	Substrate	Product	Yield(%)[a]
1	 **4b**	 **8b**	61
2	 **4h**	 **8c**	42

[a] The yields are the average of at least two experiments.

In summary, we have illustrated the ability to tune the reactivity of palladium carbenes derived from diphenylketene. These studies provide further insight into the reactivity of Pd carbenes and their ability to change that reactivity depending on the oxidation state of the metal center. The ready availability of various Pd(0) and Pd(II) complexes combined with the distinct reactivity of each oxidation state provides a level of customizability unavailable to other metals typically used to form carbene complexes: i.e., Rh(I), Cu(II), and Ru(II). In addition, we have illustrated a unique catalytic cyclopropane isomerization of diphenylcyclopropanes and a Pd-catalyzed domino cyclopropanation/isomerization reaction. Further results of our studies on Pd carbene formation and reactivity and on Pd-catalyzed cyclopropane isomerization will be reported in due course.

Acknowledgment. This work was supported by AstraZeneca Canada Inc., the Merck Frosst Centre for Therapeutic Research, Boehringer Ingelheim (Canada) Ltd., the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Foundation for Innovation, the Ontario Innovation Trust, and the University of Waterloo. J.M.G. thanks the Government of Ontario and the University of Waterloo for scholarships.

Supporting Information Available: Text and figures giving experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800390W