Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3849–3853
Tetrahedron Letters

Suzuki–Miyaura coupling with high turnover number using an *N*-acyl-*N*-heterocyclic carbene palladacycle precursor ☆

Hector Palencia,[a,b,*] Federico Garcia-Jimenez[a] and James M. Takacs[b,*]

[a]*Instituto de Quimica/UNAM, Circ., Ext. S/N, Coyoacan, DF, 04510 Mexico*
[b]*Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE 68588-0304, USA*

Received 2 March 2004; revised 19 March 2004; accepted 24 March 2004

Abstract—A simple *N*-acylimidazolium salt precursor to a NHC-complexed palladacyclic ligand gives high turnover numbers ($>10^7$) for Suzuki–Miyaura coupling and is applied to the preparation of biaryls used in the synthesis of coumarins. The results suggest that *N*-acyl-NHC derivatives can contribute to further expanding the rich chemistry of NHCs.

We are interested in palladium-catalyzed carbon–carbon bond forming reactions,[1] and in that regard, seek to understand and exploit the unique features of novel ligand systems to generate catalyst systems exhibiting broad scope and high efficiency. Since their first report by Arduengo,[2] *N*-heterocyclic carbenes (NHCs) have emerged as attractive alternatives to phosphine ligands in a variety of catalytic reactions, including numerous palladium-catalyzed reactions.[3] Similarly, palladacyclic complexes have recently generated significant interest and such catalyst systems often exhibit excellent thermal stability and high turnover numbers (TONs).[4] Hybrid systems can combine the advantages of different ligand types to give new ligand systems with attractive features,[5] and in view of the successes of NHCs and palladacycles, we decided to synthesize ligands incorporating both features.

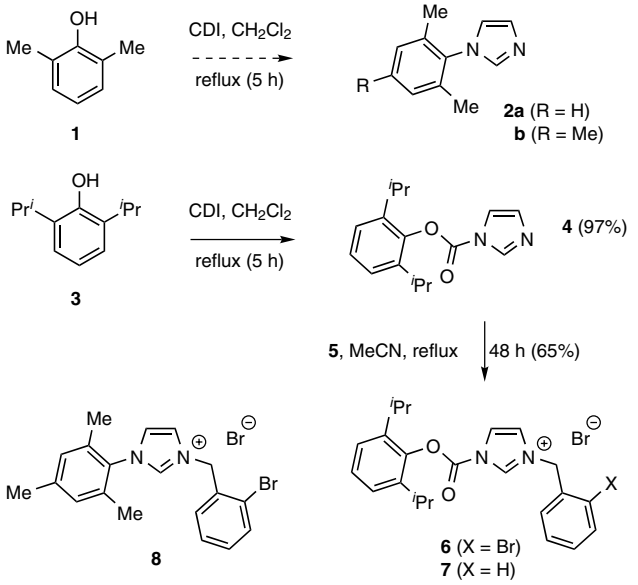
NHCs are typically prepared via deprotonation of an imidazolium salt, their generation often carried out in situ. Unsymmetrical NHC precursors are prepared via *N*-alkylation of *N*-substituted imidazoles. At the time we initiated our studies, an interesting approach to the preparation of *N*-substituted imidazoles had recently been described, wherein the desired imidazoles were said to be obtained via the reaction of an alcohol or phenol with *N*,*N*-carbonyldiimidazole (CDI). For example, it was reported that **1** was converted to *N*-aryl imidazole **2a** upon treatment with CDI.[6] While this procedure was subsequently used with success in at least one other published case,[7] we found that treating 1,5-diisopropylphenol (**3**) with CDI under the prescribed conditions, or at substantially elevated temperatures, gave only the carbamate **4**. A similar observation was reported by Fisher.[8]

While it wasn't the derivative we originally intended, having **4** in hand we decided to prepare the unsymmetrical *N*-acylimidazolium salt **6** via *N*-alkylation with 2-bromobenzyl bromide (**5**) (MeCN, 75 °C, 48 h); **6** is obtained in 65% overall yield from phenol **3** (Scheme 1). While many NHC structural motifs have been prepared, *N*-acyl-NHC ligands have not been extensively examined.[9] We reasoned that the 2-bromobenzyl group should facilitate formation of the carbene-complexed palladacycle **9**, and furthermore, the carbonyl group might be suitably disposed to act as a hemilabile ligand,[10] essentially forming a pincer-type ligand. Pincer ligands themselves have attracted significant attention in recent years due to their enhanced thermal stability in Heck and related reactions.[11]

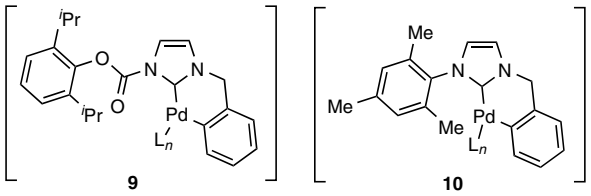
Two additional NHC precursors were prepared for comparison. Aryl C–H insertion provides an alternative route to chelated palladacycles, and therefore, the *N*-benzyl derivative **7** was prepared in anticipation that it too would serve as a precursor to **9**. We included a

Keywords: *N*-Acyl-*N*-heterocyclic carbene; *N*-Heterocyclic carbene ligand; NHC; Suzuki–Miyaura coupling; Coumarin synthesis; Biaryls; Palladium catalyst; Catalysis.
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.03.138
* Corresponding authors. Tel.: +1-402-472-6232; fax: +1-402-472-9402; e-mail: jtakacs1@unl.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.138



Scheme 1. Preparation of *N*-acyl-NHC precursor **6** and related derivatives.



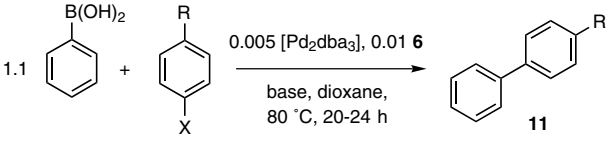
Scheme 2. Presumed carbene-complexed palladacycles from **6**, **7**, and **8**.

precursor to a carbene-complexed palladacycle lacking the carbonyl group for comparison as well. The known imidazolium salt **8**,[12] prepared via *N*-alkylation of **2a**,[13] had previously been used in the palladium-catalyzed preparation of oxyindoles from *o*-haloanilides and is expected to form complex **10**. (Scheme 2).

Biaryls are building blocks and subunits present in many natural products and have important applications, including use as pharmaceuticals, agrochemicals, and polymer constituents.[14] A number of C_{sp2}–C_{sp2} cross-coupling methods have proven useful for the synthesis of unsymmetrical biaryls;[15] the Suzuki–Miyaura palladium-catalyzed coupling of aryl halides or triflates with boronic acids or esters is among the most powerful.[16] Tertiary phosphines are the most commonly employed ligands for such reactions, however, phosphines are sensitive to air and moisture and suffer from competing P–C bond cleavage at elevated temperatures.[17] Thus, NHC catalyst systems can exhibit significant advantages in the reaction.[18]

A brief study directed toward optimizing Suzuki–Miyaura couplings using **6** is summarized in Table 1. Two simple aryl halides substrates, methyl 4-bromobenzoate and 4-iodotoluene, were coupled with phenylboronic acid using 1 mol% palladium (1:2 Pd_2dba_3/**6**) in dioxane. Base is needed for the in situ formation of *N*-acyl carbene-complexed palladacycle **9** from its imidazolium salt precursor **6** and the nature of that base is an important variable in such reaction.[19] Several frequently used bases were screened, and in the case of 4-iodotoluene, both NaOH (Table 1, entry 7) and Cs_2CO_3 (entry 8) give high yields of the biaryl product. With methyl 4-bromobenzoate, Cs_2CO_3 (entry

Table 1. Optimizing Suzuki–Miyaura couplings using **6**: The effect of the base and co-ligand[a]



	Aryl halide	Co-ligand	Base	(%) Conversion	(%) Yield[b]
1	4-$MeO_2CC_6H_4Br$	—	$Ca(OH)_2$[c]	15	5
2	4-$MeO_2CC_6H_4Br$	—	K_3PO_4	81	31
3	4-$MeO_2CC_6H_4Br$	—	NaOH[c]	75	55
4	4-$MeO_2CC_6H_4Br$	—	Cs_2CO_3	92	89
5	4-MeC_6H_4I	—	$Ca(OH)_2$	26	15
6	4-MeC_6H_4I	—	K_2CO_3[d]	57	21
7	4-MeC_6H_4I	—	NaOH	100	95
8	4-MeC_6H_4I	—	Cs_2CO_3	100	92
9	4-MeC_6H_4I	Ph_2PH	Cs_2CO_3	100	>99
10	4-MeC_6H_4I	(t-Bu)$_2$PH	Cs_2CO_3	100	>99
11	4-MeC_6H_4I	Cy_3P	Cs_2CO_3	100	89[e]

[a] Unless indicated otherwise, all reactions are run in dioxane using 1 mol% palladium catalyst and co-ligand (if present) and 2 mol equiv of the indicated base relative to aryl halide.
[b] Isolated yield based upon starting aryl halide; not corrected for recovered starting material.
[c] 1.5 equiv of base used.
[d] 10 mol% *t*-BuOK added initially to generate the NHC.
[e] Yield improved to 94% using K_3PO_4 in place of Cs_2CO_3.

4) gives the best results, and it was used in all subsequent studies.

The addition of co-ligands can further stabilize and increase the reactivity of palladium catalysts. For example, Studer and co-workers found that secondary phosphines are excellent co-ligands in the coupling reactions of aryl chlorides,[20] and adding Ph_2PH (entry 10) or (*tert*-Bu)$_2$PH (entry 11) improved the yield of biphenyl **11** (R = Me), rendering the reaction essentially quantitative. The nature of the active species formed from the combination of palladacycles with secondary phosphines is not known, but it has been suggested that the reaction of the secondary phosphine with an aryl halide may form a tertiary phosphine in situ that is important in the active catalyst.[21] Tricyclohexylphosphine (PCy_3) has been used in conjunction with a palladacycle to give a very active catalyst for the Suzuki coupling with aryl chlorides.[22] However, adding PCy_3 in conjunction with **6** did not improve the yield (Table 1, entry 11).

The data in Table 1 were obtained using 1% catalyst loading. The search for coupling catalyst systems exhibiting high efficiency (i.e., high turnover frequency) and greater stability (i.e., high turnover number (TON)) is a very active area of research of late and good progress has been made.[23] Table 2 summarizes the effect of lower catalyst loading on the formation of biphenyl (**11** R = H) via the coupling of phenylboronic acid and iodobenzene. Using 0.1% catalyst (entry 3) or 0.01% catalyst (entry 4), biphenyl is formed quantitatively. The NHC precursor **6** is an essential component to the success of the coupling. Neither Pd_2dba_3 alone (i.e., omitting both **6** and (*tert*-Bu)$_2$PH, entry 1) nor Pd_2dba_3 plus (*tert*-Bu)$_2$PH (i.e., omitting **6**, entry 2) were as efficient.

Encouraged by the high yield obtained with **6** at 0.01%, we continued to reduce the catalyst loading. At 0.001% catalyst, the conversion is complete and the isolated yield, while no longer quantitative, remains high (97%) (Table 2, entry 5). At 1 ppm catalyst (0.0001%) both the degree of conversion (98%) and the isolated yield of biphenyl (88%) drop somewhat (entry 6). This downward trend continues at the 100 and 10 ppb levels; the isolated yields drop off markedly (47% and 33%, entries 7 and 8). Benzene is detected as a side-product in these latter reaction mixtures. Nonetheless, even with the drop off in yield, the latter reactions proceed with turnover numbers in the millions to tens of millions. We did not attempt to further optimize the reaction conditions at these low catalyst loadings, and thus it may be possible to further improve their efficiency.

Imidazolium salt **7** could, via C–H insertion, also form complex **9**. At the 0.1% catalyst loading level, **7** performs well and affords biphenyl in near quantitative yield (entry 9). However, at 0.01% catalyst loading, both the conversion (71%) and the isolated yield (49%) are significantly lower (entry 10). NHC precursor **8** behaves similarly (entries 11 and 12). It is expected to generate a carbene-complexed palladacycle lacking the *N*-acyl group (i.e., **10**). These results suggest that the *N*-acyl group improves the activity of the catalyst system, perhaps due to the carbonyl functionality acting as a hemilabile donor ligand.[24]

We briefly explored the catalyst scope at the 0.1% loading level (Table 3). Aryl iodides generally give good to excellent yields and showing good tolerance toward steric hindrance on both the nucleophile as well as the electrophile. For example, the 2-alkoxy-substituted aryl iodide, 2-$MOMOC_6H_4I$, gives high yield of the coupled product based upon its conversion (entry 9). Methyl 2-iodobenzoate couples efficiently with phenyl boronic acid (93%, entry 1) as well as with a range of 2-methoxy-substituted aryl boronic acids (81–97%, entries 2–7). Some of these latter couplings have been reported using

Table 2. Comparing NHC precursors and catalyst loading for the coupling of phenylboronic acid with iodobenzene[a]

	NHC precursor	Catalyst (mol%)	Temperature (°C)	Conversion (%)	Yield[b] (%)	TON[c]
1[d]	—	0.1	95	80	77	7.7×10^2
2[e]	—	0.1	95	86	81	8.1×10^2
3	**6**	0.1	95	100	>99	10^3
4	**6**	0.01	160	100	>99	10^4
5	**6**	0.001	160	100	97	9.7×10^4
6[f,g]	**6**	0.0001	160	98	88	8.8×10^5
7[f,h]	**6**	0.00001	160	90	47	4.7×10^6
8[f,h]	**6**	0.000001	160	82	33	3.3×10^7
9	**7**	0.1	95	100	99	9.9×10^2
10	**7**	0.01	160	71	49	4.9×10^2
11	**8**	0.1	95	93	90	9.0×10^2
12	**8**	0.01	160	63	41	4.1×10^2

[a] Reaction conditions: iodobenzene (5 mmol, except as noted); phenylboronic acid (5.5–6.0 mmol); C_2CO_3 (10 mmol); the indicated percentage of catalyst mixture [composition: 1.0 **6**; 0.5 Pd_2dba_3; 1.1 *t*-Bu_2PH]; dioxane (6 mL); 48 h.

[b] Isolated yield based upon starting aryl halide; not corrected for recovered starting material.

[c] TON = mmol biphenyl/mmol Pd.

[d] Catalyst = Pd_2dba_3.

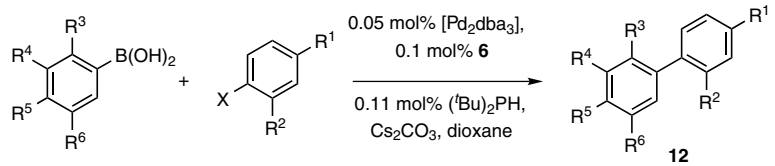
[e] Catalyst = Pd_2dba_3 plus *t*-Bu_2PH.

[f] 10 mmol of iodobenzene and 12 mmol of phenylboronic acid used.

[g] Average of two runs.

[h] Average of three runs.

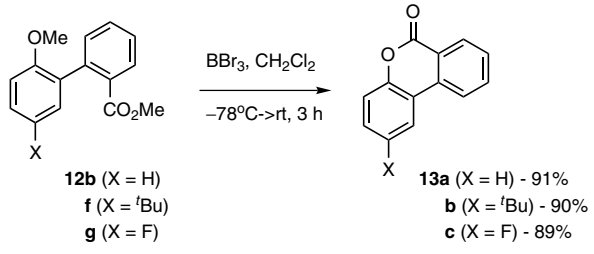
Table 3. Suzuki–Miyaura couplings using **6**: Substrate scope when using 0.1% catalyst loading



Entry	Aryl halide	Boronic acid	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)	12	R^1	R^2	R^3	R^4	R^5	R^6
1	2-$MeO_2CC_6H_4I$	$PhB(OH)_2$	95	72	100	93	**a**	H	CO_2Me	H	H	H	H
2	2-$MeO_2CC_6H_4I$	2-$MeOC_6H_4B(OH)_2$	150	48	100	86	**b**	H	CO_2Me	OMe	H	H	H
3	2-$MeO_2CC_6H_4I$	2,4-$(MeO)_2C_6H_3B(OH)_2$	150	48	100	76	**c**	H	CO_2Me	OMe	H	OMe	H
4	2-$MeO_2CC_6H_4I$	2,5-$(MeO)_2C_6H_3B(OH)_2$	150	48	100	95	**d**	H	CO_2Me	OMe	H	H	OMe
5	2-$MeO_2CC_6H_4I$	2,3,4-$(MeO)_3C_6H_2B(OH)_2$	150	48	100	92	**e**	H	CO_2Me	OMe	OMe	OMe	H
6	2-$MeO_2CC_6H_4I$	(5-^{t}Bu-2-MeO)$C_6H_3B(OH)_2$	150	48	100	97	**f**	H	CO_2Me	OMe	H	H	^{t}Bu
7	2-$MeO_2CC_6H_4I$	(5-F-2-MeO)$C_6H_3B(OH)_2$	150	48	100	81	**g**	H	CO_2 Me	OMe	H	H	F
8	2-$MeO_2CC_6H_4I$	(5-Cl-2-MeO)$C_6H_3B(OH)_2$	150	48	100	51	**h**	H	CO_2 Me	OMe	H	H	Cl
9	2-$MOMOC_6H_4I$	$PhB(OH)_2$	95	72	82	77	**i**	H	OMOM	H	H	H	H
10	4-$MeO_2CC_6H_4I$	$PhB(OH)_2$	95	72	100	90	**j**	CO_2Me	H	H	H	H	H
11	4-$MeO_2CC_6H_4Br$	$PhB(OH)_2$	150	48	79	78	**j**	CO_2 Me	H	H	H	H	H
12	4-$MeC(O)C_6H_4Cl$	$PhB(OH)_2$	150	48	30	–	**k**	C(O)Me	H	H	H	H	H

traditional catalysts, for example $Pd(PPh_3)_4$.[25] Using **6** at 50-fold lower catalyst loading, we obtain yields comparable to those previously reported. The reaction of methyl 4-bromobenzoate with phenylboronic acid is sluggish but gives high yield of coupled product based upon its conversion (entry 11). 4-Chloroacetophenone fails to couple under the conditions employed (entry 12).

Coumarins are an important class of natural products,[26] and the biaryls formed via the coupling of methyl 2-iodobenzoate with 2-methoxy-substituted aryl boronic acids are suitable precursors. To illustrate, several representative biaryl products were treated with BBr_3 to give coumarin derivatives **13a**–**c** in high yield (89–91%) (Scheme 3).



Scheme 3. Conversion of selected biaryls to coumarin derivatives **13a**–**c**.

In summary, we synthesized and evaluated compound **6**, a simple, new *N*-acylimidazolium salt precursor to an *N*-acyl-NHC-complexed palladacycle catalyst. In spite of the fact that acylimidazolium salts are reactive acylating agents,[27] catalysts derived from **6** give up to 3.3×10^7 turnovers in the Suzuki–Miyaura coupling. The results suggest that *N*-acyl-NHCs constitute another variant of the popular NHC framework with significant potential utility in catalysis. Further studies are in progress.

Acknowledgements

Support from the University of Nebraska Research Initiative and the NSF (CHE-0316825) is gratefully acknowledged. The NMR spectrometers used were purchased with shared instrument funds (NIH SIG-1-510-RR-06307) and (NSF CHE-0091975, MRI-0079750). We thank Prof. Kevin Shaughnessy for a helpful discussion.

References and notes

1. (a) Takacs, J. M.; Schroeder, S. D.; Han, J.; Gifford, M.; Jiang, X.-t.; Saleh, T.; Vayalakkada, S.; Yap, A. H. *Org. Lett.* **2003**, *5*, 3595–3598; (b) Takacs, J. M.; Leonov, A. P. *Org. Lett.* **2003**, *5*, 4317–4320; (c) Takacs, J. M.; Jiang, X.-t.; Leonov, A. P. *Tetrahedron Lett.* **2003**, *44*, 7075–7079.
2. (a) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534; (b) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917–1927.
3. Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.
4. Bedford, R. B. *Chem. Commun. (Cambridge UK)* **2003**, 1787–1796.
5. Danopoulos, A. A.; Tulloch, A. A. D.; Winston, S.; Eastham, G.; Hursthouse, M. B. *Dalton Trans.* **2003**, 1009–1015.
6. Njar, V. C. O. *Synthesis* **2000**, 2019–2028.
7. Bolm, C.; Kesselgruber, M.; Raabe, G. *Organometallics* **2002**, *21*, 707–710.

8. Fischer, W. *Synthesis* **2002**, 29–30.
9. (a) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411–1414; (b) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2002**, *21*, 5204–5208.
10. McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741–748.
11. (a) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759–1792; (b) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837–1857.
12. Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193–195.
13. Compound **2a** was prepared via the method of Arduengo: Arduengo, A. J., III; Gentry, F. P., Jr.; Taverkere, P. K.; Simmons, H. E., III. U.S. Patent 6177575, **2001**.
14. Bringmann, G.; Gunther, C.; Ochse, M.; Schupp, O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: New York, 2001; Vol. 82, pp 1–293.
15. (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
16. (a) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83–90; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
17. Garou, P. E. *Chem. Rev.* **1985**, *85*, 171–185.
18. (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82; (b) Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186–190.
19. Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511–1514.
20. Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668–3671.
21. Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Cat.* **2002**, *344*, 495–498.
22. Bedford, R. B.; Cazin, C. S. J. *Chem. Commun. (Cambridge UK)* **2001**, 1540–1541.
23. (a) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164–4174; (b) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *J. Org. Chem.* **2003**, *68*, 7733–7741; (c) Alonso, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588–5594;; (d) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667–6670; (e) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757–2759; (f) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830–1833; (g) Sava, X.; Ricard, L.; Mathey, F.; Le Floch, P. *Organometallics* **2000**, *19*, 4899–4903; (h) Weissman, H.; Milstein, D. *Chem. Commun. (Cambridge UK)* **1999**, 1901–1902; (i) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
24. Beletskaya, I. P.; Kashin, A. N.; Karlstedt, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89–96.
25. (a) Hesse, S.; Kirsch, G. *Tetrahedron Lett.* **2003**, *44*, 97–99; (b) Coghlan, M. J.; Kym, P. R.; Elmore, S. W.; Wang, A. X.; Luly, J. R.; Wilcox, D.; Stashko, M.; Lin, C. W.; Miner, J.; Tyree, C.; Nakane, M.; Jacobson, P.; Lane, B. C. *J. Med. Chem.* **2001**, *44*, 2879–2885; (c) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763–3768.
26. Estevez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Rep.* **1997**, *14*, 465–475.
27. Beier, M.; Stephan, A.; Hoheisel, J. D. *Helv. Chim. Acta* **2001**, *84*, 2089–2095.