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Facile synthesis of indenones by cyclopalladated ferrocenylimine-catalyzed annulation of internal alkynes

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An efficient and facile protocol for the annulation of *o*-halobenzaldehyde derivatives with diverse internal alkynes has been developed using cyclopalladated ferrocenylimine as the catalyst, and the indenones as the products could be obtained in moderate to good yields. It was found for the first time that the addition of benzoic acid could remarkably speed up the reaction process.

Supporting information may be found in the online version of this article.

Keywords: annulation; palladium catalysis; internal alkynes; indenones

Introduction

Indenones are a family of important synthetic intermediates for the construction of various organic and bioorganic compounds.[1] Among the diverse routes for the synthesis of carbocycles such as indenones, the palladium-catalyzed annulation of internal alkynes could be the most facile and efficient.[2] The formation of 2,3-diphenylindenone can be realized by annulation of *o*-iodobenzaldehyde with diphenylacetylene, promoted by stoichiometric amounts of palladium species, as first discovered by Heck and coworkers in 1989.[3] Subsequently, Vicente and coworkers also described a stoichiometric palladium-assisted synthesis of indenols and indenones.[4] Remarkable work in this area was done be Larock *et al*., who introduced the first catalytic protocol for the efficient synthesis of indenones, which represents a new synthetic strategy for indenones, albeit this catalytic system has some limitations in scope of the substrates.[5]

On the other hand, palladacycles have become a family of versatile catalysts and exhibited high catalytic ability in the C–C and C–heteroatom forming reactions.[6] Nájera *et al*. realized the facile preparation of 2,3-diphenylindenone assisted by this kind of palladacycle.[7] However, there are still a few examples of the synthesis of carbocycles involving palladacycles as the catalysts. Recently, we found that cyclopalladated ferrocenylimine could act as the palladacyclic catalyst in a wide variety of useful and well-known coupling processes, ranging from classical reactions such as Heck, Suzuki, Sonogashira and Buchwald–Hartwig couplings to cyanation, addition reactions of arylboronic acids and coupling reactions involving terminal alkynes (Fig. 1).[8] Inspired by these promising reports and our own works, our research interests have focused on exploring the possibility of using cyclopalladated ferrocenylimine as catalysts in the annulation of internal alkynes.

Results and Discussion

On the basis of previous reports, we investigated the effect of bases and solvents on the reaction of 2-bromobenzaldehyde and diphenylacetylene (Table 1). Initially, a series of bases were screened, and K_2CO_3 was shown to be the better choice (Table 1, entries 1–9). Then, a variety of solvents, including DMAc, acetonitrile, DMF, HMPA, DMSO, H_2O and THF were checked, and the results revealed that DMF was the best solvent, giving the product with a high yield of 85% (Table 1, entries 10–15). The addition of PhCOOH played an important role for the successful reaction. In the absence of PhCOOH, a relatively lower yield of 60% was observed even after a prolonged reaction time of 24 h (Table 1, entry 16). Other palladium catalysts, such as 5 mol% of $PdCl_2$ and $Pd(OAc)_2$, were also checked and did not exhibit higher catalytic activity (Table 1, entries 17 and 18).

Under these optimized conditions, the scope of the substrates was also surveyed (Table 2). This catalytic system has been proven to be effective for electron-neutral 2-halobenzaldehydes (e.g. *o*-iodobenzaldehyde, *o*-bromobenzaldehyde and *o*-chlorobenzaldehyde), affording the corresponding products in moderate to good yields (Table 2, entries 1–3). For *o*-halobenzaldehydes containing electron-donating groups, the corresponding products were obtained in a good yield using LiCl as the additive (Table 2, entries 4 and 5), while the annulation of *o*-halobenzaldehydes bearing electron-withdrawing groups did not occur at all (Table 2, entry 6). This indicated that the electronic factor played a crucial role in the successful reaction of *o*-halobenzaldehydes (Table 2, entries 1–6). For asymmetrical internal alkynes, the reactions exhibited high regioselectivity with the more sterically hindered group in the 3-position of the

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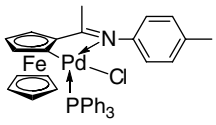
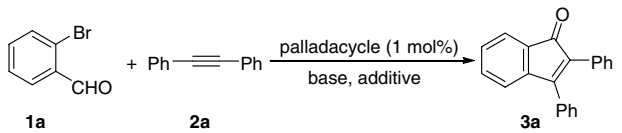


Figure 1. Palladacycle catalyst: cyclopalladated ferrocenylimine.

Table 1. Annulation of 2-bromobenzaldehyde with diphenylacetylene[a]



1a **2a** **3a**

Entry	Base	Additive	Solvent	*t* (h)	Yield (%)[b]
1	KOAc	*n*-Bu_4NBr/PhCOOH	DMF	5	35
2	$K_3PO_4 \cdot 3H_2O$	*n*-Bu_4NBr/PhCOOH	DMF	4	20
3	$KHCO_3$	*n*-Bu_4NBr/PhCOOH	DMF	4	68
4	NaOAc	*n*-Bu_4NBr/PhCOOH	DMF	7	31
5	Na_2CO_3	*n*-Bu_4NBr/PhCOOH	DMF	4	48
6	$NaHCO_3$	*n*-Bu_4NBr/PhCOOH	DMF	4	20
7	K_2HPO_4	*n*-Bu_4NBr/PhCOOH	DMF	4	10
8	*t*-BuOK	*n*-Bu_4NBr/PhCOOH	DMF	24	–
9	**K_2CO_3**	***n*-Bu_4NBr/PhCOOH**	**DMF**	**4**	**85**
10	K_2CO_3	*n*-Bu_4NBr/PhCOOH	DMAc	4	75
11	K_2CO_3	*n*-Bu_4NBr/PhCOOH	CH_3CN	4	Trace
12	K_2CO_3	*n*-Bu_4NBr/PhCOOH	HMPA	4	70
13	K_2CO_3	*n*-Bu_4NBr/PhCOOH	DMSO	4	21
14	K_2CO_3	*n*-Bu_4NBr/PhCOOH	THF	4	16
15	K_2CO_3	*n*-Bu_4NBr/PhCOOH	H_2O	4	25
16	K_2CO_3	*n*-Bu_4NBr	DMF	24	60
17[c]	K_2CO_3	*n*-Bu_4NBr/PhCOOH	DMF	4	55
18[d]	K_2CO_3	*n*-Bu_4NBr/PhCOOH	DMF	4	61

[a] Reaction conditions: 2-bromobenzaldehyde (0.25 mmol), diphenylacetylene (0.30 mmol), base (0.50 mmol), *n*-Bu_4NBr (0.25 mmol), PhCOOH (20 mol%), palladacycle (1 mol%) and solvent (1.50 ml) at 110 °C for 4 h. [b] Isolated yields. [c] With 5 mol% of $PdCl_2$. [d] With 5 mol% of $Pd(OAc)_2$.

indenones as the major isomer. For example, the annulation of 1-phenyl-1-propyne (**2b**) gave the corresponding 2-methyl-3-phenyl-1H-indenone (**3d**) with high regioselectivity (Table 2, entries 7 and 8). When the substituents provided no steric hindrance, an inseparable 1 : 1 mixture of isomers was obtained (Table 2, entries 9 and 10).

Based on the above-mentioned reports and our own results,[5,8d,9] the mechanistic study was carried out and is outlined in Scheme 1. Palladacycle was a reservoir of the catalytically active Pd(0) species. The oxidative addition of *o*-halobenzaldehyde **1** to the active Pd(0) species first took place, leading to palladium(II) intermediate **I**. Then insertion of the alkyne **2** into the newly formed C–Pd bond occurred, affording to the palladium(II) intermediate **II**. The intramolecular insertion of the Cdbond;O bond into the C–Pd bond in intermediate **II** could form the palladium(II) intermediate **III**. The β-H elimination of intermediate **III** would give the desired product **3** and HPdX species. In the presence of the base, HPdX species would be converted to the active Pd(0) species to close the catalytic cycle (Pathway 1).

Alternatively, intramolecular oxidative addition may take place in palladium(II) intermediate **II** to yield a palladium(IV) intermediate **IV**. The reductive elimination of the intermediate **IV** would also generate the desired product **3** and HPdX species to fulfill the catalytic cycle (Pathway 2). Both pathways gave the same product, but they should be competitive with each other. Additives such as *n*-Bu_4NBr, LiCl and PhCOOH can be used to stabilize the catalytically active Pd(0) species, avoiding the formation of palladium black.[5,7,8b] In addition, *n*-Bu_4NBr also acts as a phase transfer catalyst for the inorganic base/polar solvent/organic substrates/product phases.[10]

Conclusion

In summary, we have described a convenient and one-step synthesis of indenones via cyclopalladated ferrocenylimine-catalyzed annulation of *o*-halobenzaldehydes with internal alkynes. The reactions proceeded smoothly to afford the indenones in moderate to good yields. Further application of this synthetic methodology in the synthesis of organic intermediates is currently in progress in our laboratory.

Experimental

General Methods and Materials

All commercial materials were used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker DPX-400 spectrometer. Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. GC analysis was performed on an Agilent 4890D gas chromatograph. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were obtained on a Waters Q-Tof MicroTM spectrometer. Ethyl acetate and hexane (analytical-grade) were used for column chromatography without purification. The other chemicals were bought from commercial sources and used as received unless otherwise noted.

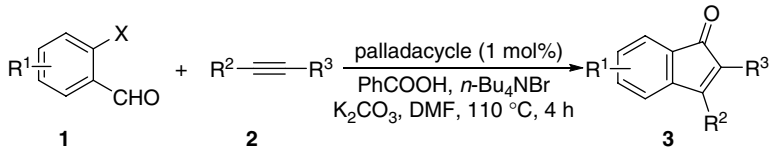
General Procedure for the Palladacyclic Catalyst[8a]

After a solution of Li_2PdCl_4 (1.0 mmol) in methanol (10 ml) was added to a solution of mole equivalents of NaOAc and ferrocenylimine in methanol (30 ml), the resulting red solution was stirred at room temperature for about 24 h and filtered. The obtained solid was treated with PPh_3 (2.0 mmol) in CH_2Cl_2 at room temperature for 0.5 h and then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the red solid. Finally, the red solid was crystallized from CH_2Cl_2–petroleum ether (60–90 °C) to afford the pure cyclopalladated ferrocenylimine.

General Procedure for Synthesis of Indenones

o-Halobenzaldehyde (0.25 mmol), alkyne (0.30 mmol), palladacycle (1 mol%), K_2CO_3 (0.50 mmol), *n*-Bu_4NBr (0.25 mmol) and PhCOOH (20 mol%) were dissolved in DMF (1.50 ml) in a 5 ml vial under a nitrogen atmosphere at 110 °C for 4 h. The reaction mixture was then cooled, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. After filtration, the organic solutions were

Table 2. Annulation of *o*-halobenzaldehydes with internal alkynes[a]



1 **2** **3**

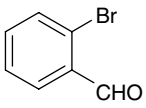
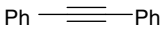
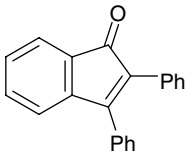
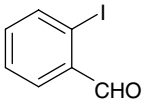
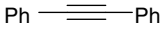
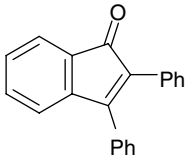
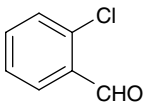
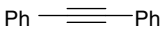
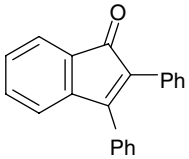
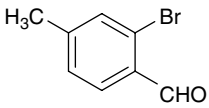
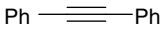
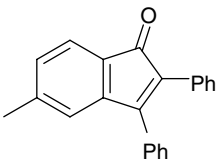
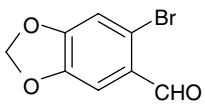
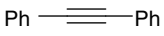
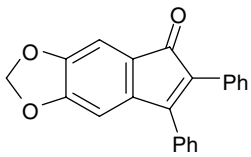
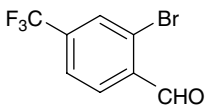
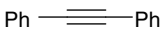
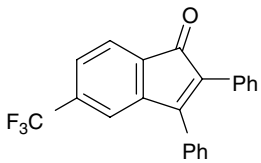
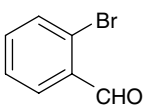
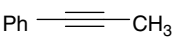
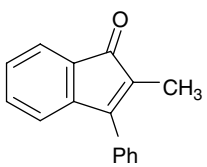
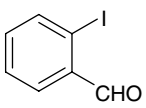
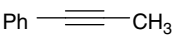
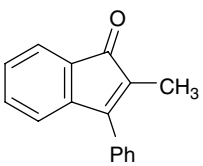
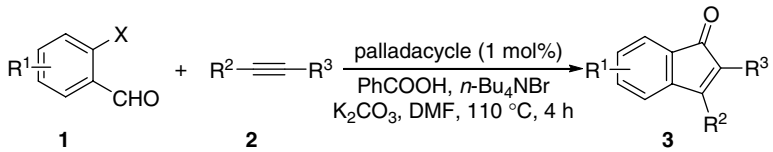
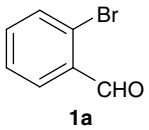
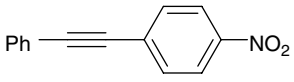
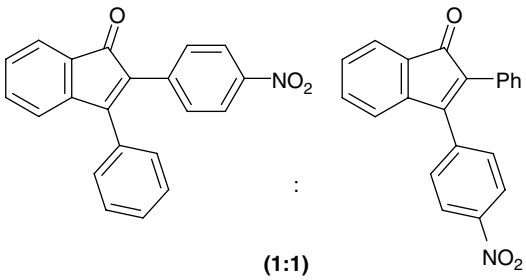
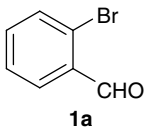
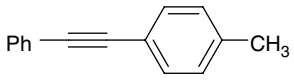
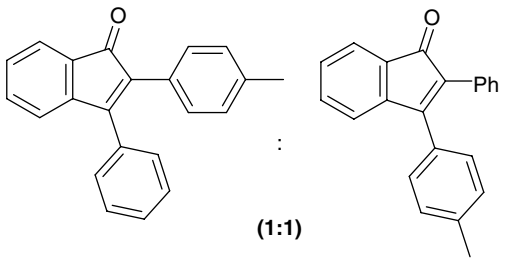
Entry	*o*-Halobenzaldehyde	Alkyne	Product	Yield (%)[b]
1	 **1a**	 **2a**		85 (**3a**)
2	 **1b**	 **2a**		92 (**3a**)
3	 **1c**	 **2a**		57 (**3a**)
4[c]	 **1d**	 **2a**		83 (**3b**)
5[c]	 **1e**	 **2a**		75 (**3c**)
6	 **1f**	 **2a**		Trace
7	 **1a**	 **2b**		63 (**3d**)
8	 **1b**	 **2b**		82 (**3d**)

Table 2. (*Continued*)



1 2 3

Entry	*o*-Halobenzaldehyde	Alkyne	Product	Yield (%)[b]
9[d]	 **1a**	 **2c**	 **(1:1)**	41 (**3e**/**3f**)
10[d]	 **1a**	 **2d**	 **(1:1)**	83 (**3g**/**3h**)

[a] Reaction conditions: *o*-halobenzaldehydes (0.25 mmol), internal alkyne (0.30 mmol), K_2CO_3 (0.50 mmol), *n*-Bu_4NBr (0.25 mmol), PhCOOH (20 mol%), palladacycle (1 mol%) and DMF (1.50 ml) at 110 °C. [b] Isolated yields. [c] With the addition of LiCl (0.25 mmol). [d] A colon indicates that the products were inseparable.

concentrated and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to give the pure product. The isolated products were further determined by ^1H and ^{13}C NMR (Bruker-400, 400 MHz for ^1H NMR, and 100 MHz for ^{13}C NMR).

*2,3-Diphenyl-1H-inden-1-one (**3a**)*[5]

This compound was characterized by comparing its m.p., ^1H, ^{13}C NMR with those previously reported.

*5-Methyl-2,3-diphenyl-1H-inden-1-one (**3b**)*

Orange solid, m.p. 178–180 °C;^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 6.95 (s, 1H,CH_3-C-CH-C), 7.07–7.09 (s, 1H, O=C–C–CH), 7.26 (m, 5H, O=C–C–C_6H_5), 7.37–7.42 (m, 5H, O=C–C–C–C_6H_5), 7.48–7.49 (d, 1H, CH_3–C–CH–CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.1(CH_3), 122.5 (C arom), 123.0 (C arom), 127.6 (C arom), 128.0 (C arom), 128.3 (C arom), 128.4 (C arom), 128.5 (C arom), 128.7 (C arom), 128.9 (C arom), 129.1 (C arom), 129.9 (C arom), 130.8 (C arom), 132.8 (C arom), 144.4 (C arom), 145.7 (CH–C–C=O arom), 154.9 (Ph–C–C=O arom), 196.2 (C=O). HRMS (positive ESI) calcd for $C_{22}H_{17}O$: 297.1279 $[M + H]^+$; found: 297.1295.

*6,7-Diphenyl-5H-indeno[5,6-d][1,3]dioxol-5-one (**3c**)*

Purple solid, m.p. 157–158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.02 (s, 2H, O–CH_2–O), 6.65 (s, 1H, O–C–CH–C–CO), 7.09 (s, 1H, O–C–CH–C–C–Ph), 7.22–7.26 (s, 5H, Ph–C–C=O), 7.32–7.35 (m, 2H, Ph),7.40 (m, 3H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.7 (CH_2), 102.1 (C arom), 104.0 (C arom), 105.3 (C arom), 124.7 (C arom), 127.5 (C arom), 128.0 (C arom), 128.4 (C arom), 128.9 (C arom), 129.3 (C arom), 129.8 (C arom), 130.8 (C arom), 132.7 (C arom), 141.8 (C arom), 147.7 (C arom), 151.6 (CH–C–C=O, arom), 153.7 (Ph–C–C=O arom), 195.2 (C=O); HRMS (positive ESI) calcd for $C_{22}H_{14}O_3Na$: 349.0841 $[M + Na]^+$; found: 349.0840.

*2-Methyl-3-phenyl-1H-inden-1-one (**3d**)*[11]

This compound was characterized by comparing its m.p., ^1H, ^{13}C NMR with those previously reported.

*2-(4-Nitrophenyl)-3-phenyl-1H-inden-1-one (**3e**) with 3-(4-nitrophenyl)-2- Phenyl-1H-inden-1-one(**3f**) (1 : 1)*[12]

This compound was characterized by comparing its m.p., ^1H, ^{13}C NMR with those previously reported.

*3-Phenyl-2-(p-tolyl)-1H-inden-1-one (**3g**) with 2-phenyl-3-(p-tolyl)-1H-Inden- 1-one (**3h**) (1 : 1)*[12]

This compound was characterized by comparing its m.p., ^1H, ^{13}C NMR with those previously reported.

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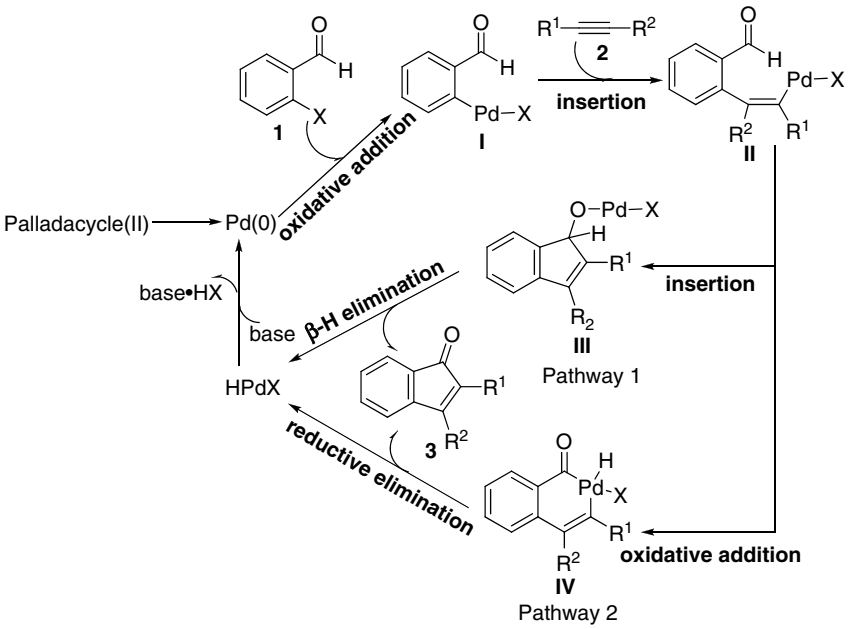

Scheme 1. Proposed mechanism for the palladium-catalyzed annulation of internal alkynes.

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Supporting information

Supporting information may be found in the online version of this article.

References

[1] a) E. F. Ullmm, W. A. Henderson Jr, *J. Am. Chem. Soc.* **1966**, *88*, 4942; b) G. M. Anstead, J. L. Ensign, C. S. Peterson, J. A. Katzenellenbogen, *J. Org. Chem.* **1989**, *54*, 1485.
[2] G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644 and references therein.
[3] W. Tao, L. J. Siverberg, A. L. Rheingold, R. F. Heck, *Oganometallics* **1989**, *8*, 2550.
[4] J. Vicente, J.-A. Abad, J. Gil-Rubio, *J. Organomet. Chem.* **1992**, *436*, C9.
[5] R. C. Larock, M. J. Doty, S. Cacchi, *J. Org. Chem.* **1993**, *58*, 4579.
[6] a) W. A. Herrmann, V. P. M. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23; b) J. Dupont, M. Pfeffer, J. Spencer, *Eur. J. Inorg. Chem.* **2001**, 1917; c) R. B. Bedford, C. S. J. Cazin, D. Holder, *Coord. Chem. Rev.* **2004**, *248*, 2283; d) I. P. Beletskaya, A. V. Cheprakov, *J. Organomet. Chem.* **2004**, *689*, 4055; e) E. Alacid, D. A. Alonso, L. Botella, C. Nájera, M. C. Pacheco, *Chem. Rec.* **2006**, *6*, 117.
[7] a) D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2002**, *344*, 172; b) E. Alacid, C. Nájera, *ARKIVOC* **2008**, *viii*, 50.
[8] a) S.-Q, Huo, Y.-J. Wu, C.-X. Du, Y. Zhu, H.-Z. Yuan, X.-A. Mao, *J. Organomet. Chem.* **1994**, *483*, 139; b) F. Yang, J.-L. Zhang, Y.-J. Wu, *Tetrahedron* **2011**, *67*, 2969; c) Y.-J. Wu, F. Yang, J.-L. Zhang, X.-L. Cui, J.-F. Gong, M.-P. Song, T.-S. Li, *Chin. Sci. Bull.* **2010**, *55*, 2784; d) Y.-T. Leng, F. Yang, K. Wei, Y.-J. Wu, *Tetrahedron* **2010**, *66*, 1244; e) G.-R. Ren, X.-L. Cui, E.-B. Yang, F. Yang, Y.-J. Wu, *Tetrahedron* **2010**, *66*, 4022; f) F. Yang, Y.-J. Wu, *Eur. J. Org. Chem.* **2007**, 3476; g) F. Yang, X.-L. Cui, Y.-N. Li, J.-L. Zhang, G.-R. Ren, Y.-J. Wu, *Tetrahedron* **2007**, *63*, 1963.
[9] V. Gevorgyan, L.-G. Quan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4089.
[10] G. A. Grasa, R. Singh, E. D. Stevens, S. P. Nolan, *J. Organomet. Chem.* **2003**, *687*, 269.
[11] L. S. Liebeskind, M. S. South, *J. Org. Chem.* **1980**, *45*, 5426.
[12] M. Antonio, I. Mauro, *Tetrahedron Lett.* **1965**, *34*, 3023.

