NJC

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Synthesis of macrocyclic ketones exploiting palladium-catalyzed activation of carboxylic acids as an enabling step†

Cite this: *New J. Chem.*, 2013, **37**, 961

Received (in Montpellier, France) 17th October 2012, Accepted 10th January 2013

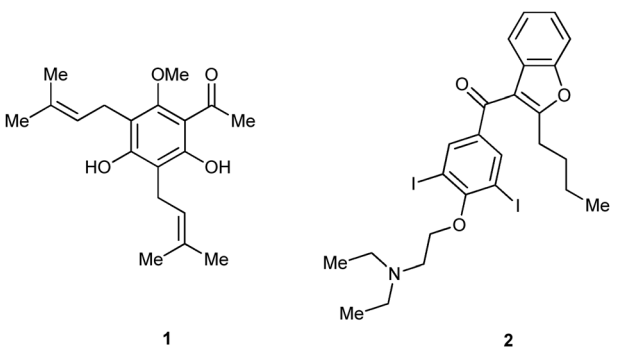
DOI: 10.1039/c3nj40943k

www.rsc.org/njc

Anant R. Kapdi*[ab] and Ian J. S. Fairlamb*[a]

The novel synthesis of macrocyclic arylketones *via* palladium-catalyzed cross-coupling of arylboronic acids and carboxylic acids, activated by the treatment with di(*N*-succinimidyl) carbonate, is disclosed. This allows the high yielding synthesis of various functionalized arylketones, which can be converted into macrocycles *via* a Mitsunobu protocol.

Aryl ketones play a central role in the synthesis of a wide variety of organic compounds. They are important building blocks in natural products as well as in functional materials (Scheme 1).[1] The classical routes to the synthesis of aryl ketones rely on the reaction of various carboxylic acid derivatives with carbon nucleophiles making them some of the most common and efficient C–C bond forming reactions in organic synthesis.[2] Acid chlorides are regarded as the most reactive carboxylic acid derived electrophilic coupling partner. Organo-tin, -zinc, -copper, and -boron reagents which act as mild nucleophiles are the most common organometallic reagents employed for effecting such transformations.[3–5] Similarly, other less reactive acid derivatives such as anhydrides, nitriles as well as amides (Weinreb amides) require stronger nucleophilic reagents such as Grignard or organolithium compounds. However, addition of the organometallic reagent to the ketone to form tertiary alcohols is the main drawback of all these methods.[6]



Scheme 1 Arylketone containing natural products.

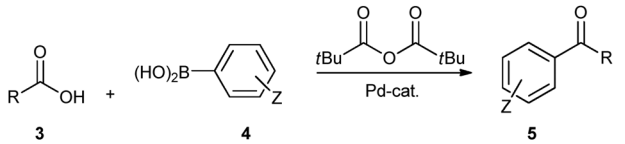
Metal-mediated processes have undergone tremendous development in the last few decades. The application of transition-metal complexes as homogeneous as well as heterogeneous catalysts has led to the development of simple and efficient methods for carbon–carbon and carbon–heteroatom bond formation.[7] Such complexes have shown a wide range of applications such as in catalysis,[8] material synthesis,[9,10] photochemistry and biological systems.[11] More recently, palladium-catalyzed cross-coupling of acid chlorides with boronic acids[12] and organotin reagents[13] has been reported. Although, mild organotin reagents are less preferred over organoboronic acids, mainly due to their inherent toxicity. Conversely, the availability, low toxicity and excellent shelf-life make organoboronic acids an attractive alternative for this type of transformation.[14]

The utilisation of coupling reagents for the activation of carboxylic acids has become an indispensable tool in organic synthesis due to their ease of handling and high functional tolerance. Mild coupling reagents such as DCC, HOBt and CDI are known to cleanly convert carboxylic acids into stable intermediates and have been employed efficiently in peptide synthesis.[15] Recently, Gooβen and Ghosh reported a novel palladium-catalyzed synthesis of arylketones from carboxylic acids and organoboron reagents using pivalic anhydride as the coupling reagent (Scheme 2).[16] However, the protocol suffers from a major drawback as the use of pivalic anhydride makes it very difficult to separate the product from the pivalic acid by-product formed during the reaction.

An improved procedure was developed by Gooβen and Ghosh[17] which utilises *N*-alkoxysuccinimides as an alternative coupling partner due to their high stability and ease of handling. Although such a methodology has been developed it is yet to be applied for the synthesis of arylketones with further application

[a] *Department of Chemistry, University of York, York, YO10 5DD, UK. E-mail: ian.fairlamb@york.ac.uk*
[b] *Department of Chemistry, Institute of Chemical Technology, Matunga, Mumbai 400019, India. E-mail: ar.kapdi@ictmumbai.edu.in; Fax: +91 22-33611020; Tel: +91 22-33612682*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3nj40943k



Scheme 2 Arylketone synthesis using pivalic anhydride.

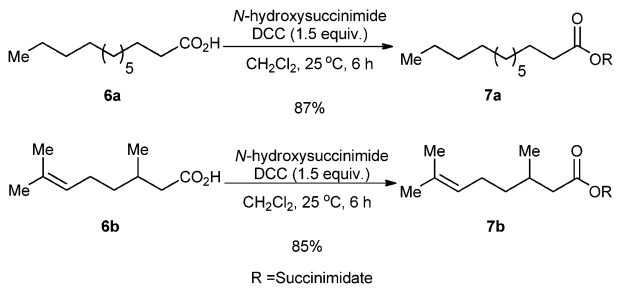
towards the formation of macrocyclic ring systems. Herein we report the novel synthesis of arylketones *via* palladium-catalyzed cross-coupling of arylboronic acids and *N*-alkoxysuccinimide esters of carboxylic acids. A protocol for the *in situ* activation of carboxylic acids using di(*N*-succinimidyl) carbonate (DSC)[17,18] has also been employed towards the synthesis of two novel macrocyclic ketones.

At the outset of our studies, *N*-alkoxysuccinimide esters **7a** and **7b** of carboxylic acids **6a** and **6b** were synthesized in the presence of a mild coupling reagent DCC (Scheme 3).[19] *N*-Alkoxysuccinimides are stable intermediates which are reactive enough to undergo smooth coupling reaction with different nucleophilic reagents such as aryl boronic acids.

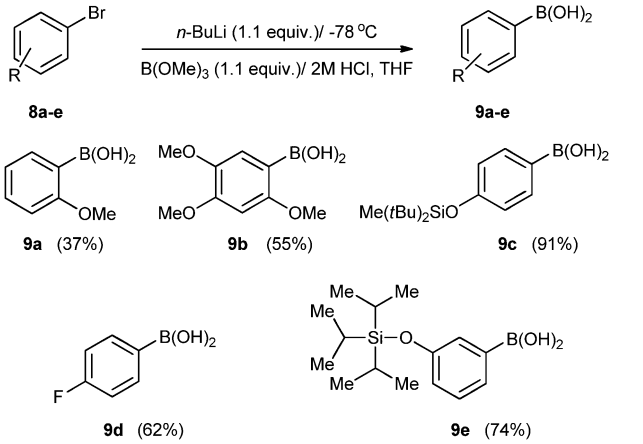
In the literature Gooβen and Ghosh have already shown that the reactivity of *N*-alkoxysuccinimide esters in palladium catalysis is poorer when triarylphosphines are used as ligands.[17] This may indicate that oxidative addition is the rate determining step which is facilitated by increasing the electron density on the palladium centre with sterically demanding and highly electron-rich phosphines such as tricyclohexylphosphine. Accordingly, to test the reactivity of the esters several substituted arylboronic acids **9a–f** were synthesized with the view of obtaining arylketones (Scheme 4).

Borylation of different substrates proceeded in good yields allowing access to sterically hindered aryl boronic acids. Incorporation of more labile silyl protecting groups (**9c** and **9e**) enhances the possibility of further functionalization of the cross-coupled product. Initial studies were focussed on understanding the effect of different ligands on the coupling of *N*-alkoxysuccinimides with 2-methoxyphenyl boronic acid (Table 1).

Triarylphosphines such as PPh_3 and P(*o*-Tol)$_3$ when employed for catalyzing the above transformation led to complete recovery of starting *N*-alkoxysuccinimides. Similar observations were made in the case of diphosphines such as DPPE and DPPB. Highly electron-rich ligands P(*t*Bu)$_3$ and X-Phos gave improved yields of the desired products suggesting a definitive activating effect on the coupling reaction. Interestingly, N-heterocyclic carbenes when employed as ligands failed to furnish the desired cross-coupled product.

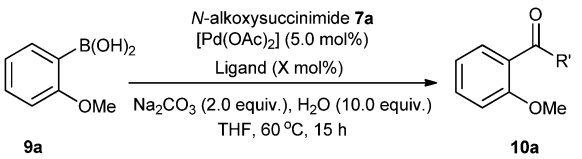


Scheme 3 Synthesis of *N*-alkoxysuccinimide esters of carboxylic acids.



Scheme 4 Synthesis of substituted arylboronic acids.

Table 1 Ligand screening studies for arylketone synthesis[a]

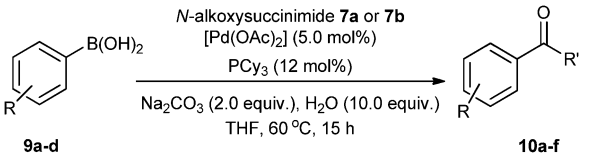


S. no.	Ligand employed	Amount of ligand (*X* mol%)	Yield[b] (%)
1	PPh_3	12	0
2	P(*o*-Tol)$_3$	12	0
3	DPPE	12	<2
4	DPPB	12	<2
5	X-Phos	12	16
6	P(*t*Bu)$_3$	12	19
7	SIPr·HCl	12	<2
8	Mes·HCl	12	<2
9	PCy_3	12	61
10	PCy_3	5	32
11	PCy_3	15	50

[a] Conditions: 0.37 mmol *N*-alkoxysuccinimide, 0.41 mmol phenylboronic acid, 5 mol% $Pd(OAc)_2$, *X* mol% ligand, 0.74 mmol Na_2CO_3, 3.7 mmol H_2O, 60 °C, 15 h. [b] Isolated yields following chromatography on silica gel.

Tricyclohexylphosphine gave the best yields as also suggested by Gooβen. The metal to ligand ratio in each of these transformations was maintained at 1 : 2.4. Any alteration in the ratio of metal to ligand (PCy_3) brought about a drastic reduction in the yield of the product.

With these optimum conditions in hand we then set about exploiting the cross-coupling of *N*-alkoxysuccinimides **7a** and **7b** with different aryl boronic acids (**9a–d**). Unfortunately, 2,4,5-trimethoxyphenylboronic acid **9b** when cross-coupled with *N*-alkoxysuccinimides under the standard conditions resulted in quantitative formation of the hydrodeborylation product (Scheme 5 and Table 2). This suggests that the rate of hydrolysis of the organoboron species is much faster than the rate of transmetallation. In contrast, a promising conversion of the starting materials was observed when employing other substituted arylboronic acids (**9b–d**). Interestingly, silyl-protected arylboronic acid **9c** gave a good yield from the cross-coupling utilising



Scheme 5 Cross-coupling of *N*-alkoxysuccinimides.

Table 2 Pd-catalyzed synthesis of arylketones[a]

Entry	R	From **7a** (yield[b] %)	From **7b** (yield[b] %)
1	2-Methoxy	61 (**10a**)	81 (**10b**)
2	2,4,5-Trimethoxy	0[c]	0[c]
3	4-Silyloxy	72 (**10c**)	42 (**10d**)[d]
4	4-Fluoro	71 (**10e**)	79 (**10f**)

[a] Conditions: 0.37 mmol *N*-alkoxysuccinimide, 0.41 mmol phenylboronic acid, 5 mol% $Pd(OAc)_2$, 12 mol% PCy_3, 0.74 mmol Na_2CO_3, 3.7 mmol H_2O, 60 °C, 15 h. [b] Isolated yields following chromatography on silica gel. [c] Hydrodeborylated product obtained. [d] Addition product **10d** obtained.

N-alkoxysuccinimide **7a**, while desilylation followed by etherification of the deprotected phenol with *N*-alkoxysuccinimide **7b** occurred resulting in poor yields of the coupled product **10d**. The catalytic system thus allowed the efficient synthesis of arylketones bearing useful functionalities.

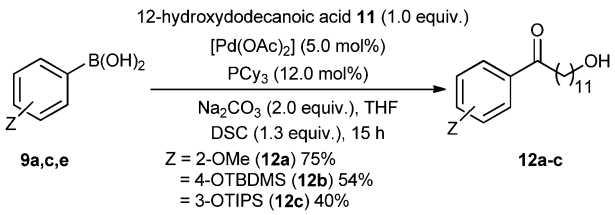
An efficient protocol for the *in situ* activation of carboxylic acids using coupling reagent di(*N*-succinimidyl)carbonate (DSC) followed by cross-coupling with arylboronic acid for the synthesis of arylketones in a one-pot procedure was developed by Gooβen and Ghosh.[17] The formation of the intermediate *N*-alkoxysuccinimide was found to proceed quantitatively. Functionalized arylketones possessing labile functional groups are synthetically important intermediates with the possibility of further manipulation of the coupled product. The one-pot procedure developed by Gooβen provided us with an opportunity to introduce labile functional groups such as an hydroxyl group in the alkyl chain, thus enabling the development of an efficient protocol for the synthesis of macrocyclic ketone motifs.

Following the literature procedure for the coupling of *in situ* generated *N*-alkoxysuccinimides of 12-hydroxy dodecanoic acid **11** with arylboronic acids **9a**, **9c** and **9e** using DSC as the coupling reagent a variety of differently substituted arylketones were synthesized in good yields (Scheme 6).

Strategically, the introduction of an hydroxyl group can act as a useful handle for formation of macrocyclic motifs. The successfully synthesized arylketones **12a–c** containing labile silyl protecting groups, which can be deprotected under relatively mild conditions,[20–23] can later serve as coupling sites for the macrocyclization to occur.‡ Synthesis of macrocyclic ring structures is important due to their occurrence in biologically important natural products,[24] polymers[25] and polydentate molecules.[26] Macrocyclic ring size can vary considerably from 8–19 membered macrocyclic rings, in addition to supramolecular ring structures. The ring-strain associated with these macrocyclic structures has been shown to reduce dramatically moving from smaller rings (*e.g.* 7 to 8) to the larger 16- or 17-membered rings which exhibit the least ring strain. However, in spite of these factors, suggesting that the formation of larger rings would be favoured, the efficient synthesis of such macrocyclic structures is still a synthetic challenge as these rings need to overcome their high conformational entropy – a particular challenge for alkyl-containing macrocyclic structures.[27]

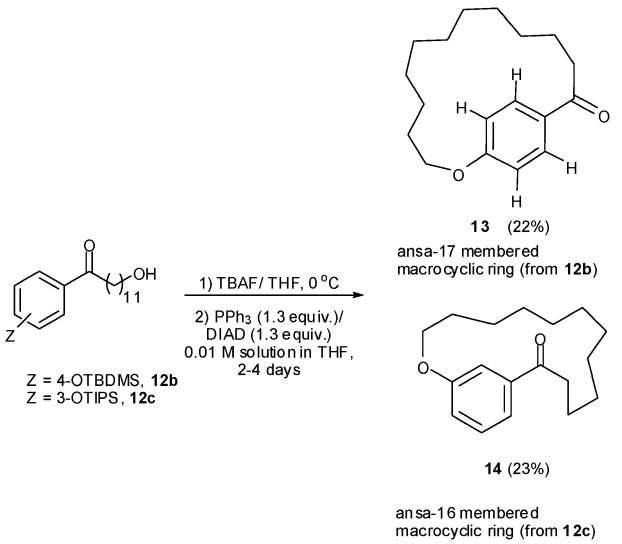
To achieve the synthesis of macrocyclic ketones the deprotection of the labile silyl protection was accomplished with tetra-*n*-butylammonium fluoride (TBAF) in THF in near quantitative yield. The subsequent step is crucial, and macrocyclisation of the diols could be achieved using the Mitsunobu reaction. In the literature formation of cyclic ethers *via* intramolecular Mitsunobu condensation has been shown to proceed in good yield.[28] Accordingly, we submitted the diols obtained from deprotection of the coupled products to Mitsunobu conditions at high dilution. The reaction was carried out in the presence of diisopropylazodicarboxylate (DIAD) to give good yield of two novel 16- and 17-membered macrocyclic ketones (Scheme 7). Development of such a methodology could facilitate the synthesis of more challenging naturally-occurring compounds having similar structural motifs, such as smenochromene D (likonides A and B), in the future.[29]

In summary we have reported a versatile protocol for the synthesis of arylketones. In comparison to the available protocols for arylketone synthesis the work presented in this manuscript represents a valuable methodology for the efficient formation of 16- and 17-membered novel macrocyclic arylketones which could be employed as a key step towards the synthesis of a variety of natural products.



Scheme 6 Synthesis of functionalized arylketones for macrocyclization.

‡ Synthesis of 1-(4-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyphenyl)-12-hydroxy-1-dodecanone (**12b**): a 10 mL flask was charged with $[Pd(OAc)_2]$ (15.00 mg, 0.05 mmol, 5.0 mol%), tricyclohexylphosphine (33.00 mg, 0.12 mmol, 12 mol%), 12-hydroxydodecanoic acid **11** (0.21 g, 1.0 mmol), Na_2CO_3 (0.21 g, 2.0 mmol), and di(*N*-succinimidyl) carbonate (0.33 g, 1.3 mmol). The reaction vessel was purged with argon and degassed THF (5 mL) was added. The yellow mixture was stirred at 60 °C for a few minutes until the gas evolution had ceased. Then, the solution was cooled down to 25 °C, a solution of 4-silyloxyphenylboronic acid **9c** (0.30 g, 1.2 mmol) in THF (3 mL) was added and the purple reaction mixture was stirred at 60 °C for 15 h. The reaction slurry was then poured into water (10 mL) and extracted 3 times with 10 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography with hexane : EtOAc (60 : 40) to give the title compound in good yield (0.27 g, 79%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 0.16 (s, 6H), 0.91 (s, 9H), 1.25–1.40 (m, 14H), 1.49–1.51 (m, 2H), 1.63–1.65 (m, 2H), 2.84 (t, 2H, J = 1.5 Hz), 3.56–3.58 (m, 2H), 6.80 (d, 2H, J = 7.8 Hz), 7.82 (d, 2H, J = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) −4.4, 18.4, 24.5, 25.5, 25.6, 29.3, 29.4, 29.5, 32.7, 38.0, 63.0, 119.8, 130.1, 130.6, 160.0, 199.4; LRMS (CI) m/z (rel.%): 407 ($M^+ + H^+$, 100%), 331 (10); HRMS (CI) m/z exact mass calculated for $C_{24}H_{43}O_3Si + H^+$ 407.3016, found 407.2976.



Scheme 7 Macrocyclization strategy using a Mitsunobu protocol.

We acknowledge the University of York for PhD Studentship funding awarded to A.R.K., and the Royal Society for a University Research Fellowship. Johnson-Matthey is thanked for a generous loan of palladium salts.

Notes and references

1 (*a*) W. Pathmasiri, H. R. El-Seedi, X. Han, J.-C. Janson, U. Huss and L. Bohlin, *Chem. Biodiversity*, 2009, **2**, 463–469; (*b*) J. A. Urbina, *Mem. Inst. Oswaldo Cruz*, 2009, **104**, 311–318.
2 (*a*) J. March, *Advanced Organic Chemistry*, Wiley, New York, 3rd edn, 1985; (*b*) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, 1989; (*c*) D. A. Shirley, *Organic Reactions*, Wiley, New York, 1954, vol. 8, pp. 28–58; (*d*) B. T. O'Neill, in *Comprehensive Organic Synthesis*, ed. B. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 1, pp. 397–458.
3 (*a*) M. J. Jorgenson, *Organic Reactions*, Wiley, New York, 1970, vol. 18, pp. 1–97; (*b*) C. R. Iwanow, *C. R. Hebd. Seances Acad. Sci.*, 1928, **186**, 442–444; (*c*) A. Meisters and T. Mole, *Aust. J. Chem.*, 1974, **27**, 1665–1672.
4 (*a*) G. M. Rubottom and C. Kim, *J. Org. Chem.*, 1983, **48**, 1050–1052; (*b*) Y. Ahn and T. Cohen, *Tetrahedron Lett.*, 1994, **35**, 203–206; (*c*) T. Fujisawa, S. Iida, H. Uehara and T. Sato, *Chem. Lett.*, 1983, 1267–1270.
5 (*a*) R. K. Dieter, *Tetrahedron*, 1999, **55**, 4177–4236; (*b*) M. P. Sibi, *Org. Prep. Proced. Int.*, 1993, **25**, 15–40; (*c*) V. Farina, V. Krishnamurthy and W. Scott, in *Organic Reactions*, ed. L. A. Paquette, Wiley, New York, 1997, vol. 50, pp. 16–52.
6 F. Sato, M. Inoue, K. Oguro and M. Sato, *Tetrahedron Lett.*, 1979, **20**, 4303–4306.
7 I. J. S. Fairlamb, R. J. K. Taylor, J. L. Serrano and G. Sanchez, *New J. Chem.*, 2006, **30**, 1695–1704.
8 R. B. King, *J. Organomet. Chem.*, 1999, **586**, 2–17.
9 I. J. S. Fairlamb, *Annu. Rep. Prog. Chem., Sect. B*, 2004, **100**, 113–148.
10 I. J. S. Fairlamb, *Chem. Rev.*, 2004, 31–32.
11 D. Y. Yegorov, O. V. Rogankova, O. A. Azizova and A. V. Kozlov, *Toxicol. Lett.*, 1995, **78**, 86.
12 (*a*) M. Haddach and J. R. McCarthy, *Tetrahedron Lett.*, 1999, **40**, 3109–3112; (*b*) N. A. Bumagin and D. N. Korolev, *Tetrahedron Lett.*, 1999, **40**, 3057–3060.
13 (*a*) J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, 1983, **105**, 6129–6137; (*b*) J. W. Labadie, D. Tueting and J. K. Stille, *J. Org. Chem.*, 1983, **48**, 4634–4642.
14 (*a*) T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508–7510; (*b*) M. Murata, T. Oyama, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 2000, **65**, 164–168; (*c*) M. Murata, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 1997, **62**, 6458–6459; (*d*) M. K. Tse, J.-Y. Cho and M. R. Smith III, *Org. Lett.*, 2001, **3**, 2831–2833; (*e*) J. Kristensen, M. Lysen, P. Vedso and M. Begtrup, *Org. Lett.*, 2001, **3**, 1435–1437.
15 M. Bodanszky and A. Bodanszky, in *The Practice of Peptide Synthesis*, ed. K. Hafner, J.-M. Lehn, C. W. Rees, P. V. R. Schleyer, B. M. Trost and R. Zahradnik, Springer, Berlin, 1984.
16 (*a*) L. J. Gooβen and K. Ghosh, *Eur. J. Org. Chem.*, 2002, 3254–3267; (*b*) L. J. Gooβen and K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 3566–3568.
17 L. J. Gooβen and K. Ghosh, *Chem. Commun.*, 2001, 2084–2085.
18 L. J. Gooβen, N. Rodriguez and K. Gooβen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100–3120.
19 S. Kim, E. Kim, D. Shin, H. Kang and K. Oh, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 895–898.
20 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190–6192.
21 D. R. Kelly, S. M. Roberts and R. F. Newton, *Synth. Commun.*, 1979, **9**, 295–299.
22 E. J. Corey, J. W. Ponder and P. Ulrich, *Tetrahedron Lett.*, 1980, **21**, 137–140.
23 (*a*) L. A. Carpino and A. C. Sau, *J. Chem. Soc., Chem. Commun.*, 1979, 514–515; (*b*) R. F. Newton, D. P. Reynolds, F. A. W. Finch, D. R. Kelly and S. M. Roberts, *Tetrahedron Lett.*, 1979, **20**, 3981–3982.
24 (*a*) D. J. Cram and J. M. Bram, *Acc. Chem. Res.*, 1971, **4**, 204–213; (*b*) M. A. Grundl and D. Trauner, *Org. Lett.*, 2006, **8**, 23–25; (*c*) J. H. Jeong and S. M. Weinreb, *Org. Lett.*, 2006, **8**, 2309–2312; (*d*) K. C. Nicolaou, T. Montagnon, G. Vassilikogiannakis and C. J. N. Mathison, *J. Am. Chem. Soc.*, 2005, **127**, 8872–8888.
25 B. A. Laurent and S. M. Grayson, *J. Am. Chem. Soc.*, 2006, **128**, 4238–4239.
26 C. Stern, F. Franceschi, E. Solari, C. Floriani, N. Re and R. Scopelliti, *J. Organomet. Chem.*, 2000, **593–594**, 86–95.
27 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95–102.
28 (*a*) J. T. M. Carlock, *Tetrahedron Lett.*, 1978, **19**, 5153–5156; (*b*) D. B. R. Guianvarc'h and J. L. Fourrey, *Tetrahedron Lett.*, 2001, **42**, 647–650; (*c*) K. C. Nicolaou, J. Li, J. Pastor and M. Winssinger, *Angew. Chem., Int. Ed.*, 1998, **37**, 1559–1561.
29 (*a*) A. Rudi, Y. Benayahu and Y. Kashman, *Org. Lett.*, 2004, **6**, 4013–4016; (*b*) B. S. Olson and D. Trauner, *Synlett*, 2005, 700–702; (*c*) M. Bruder and C. J. Moody, *Synlett*, 2008, 575–577.

