Note

Pauson–Khand reaction of 2-ethynyl aniline: Synthesis of fused ring indoles by organocuprate conjugate addition followed by spontaneous dehydration

Michael P. Coogan *, Li-ling Ooi, Derek S. Wilkins

Department of Chemistry, Cardiff University, Park Place, Cardiff, CF10 3 TB, Cymru/Wales, UK

Abstract

The Pauson–Khand reaction of 2-ethynyl aniline gives the expected cyclopentenone product, with the aniline alpha to the ketone. Treatment with organocuprates gives not the simple conjugate addition product, but the indole derived from an addition–cyclisation–nucleophilic attack sequence.
© 2005 Published by Elsevier B.V.

*Keywords:* Pauson Khand; Cuprate; Indole

1. Introduction

The Pauson–Khand (PK) reaction [1], the $Co_2(CO)_8$-mediated cyclisation of an alkyne and alkene and CO, is of interest due to easy carbon–carbon bond formation, often with high regio- and stereo-control. Many variations have been developed including the use of catalytic cobalt, [1b] other cobalt sources, [1c] other metals, [1d] heterometallic clusters [1e] and asymmetric variations based on either chiral ligands on metals [1f] or chiral auxiliaries on the substrates [1g]. This group has been interested in the PK reactions of alkynes bearing unusual structural features [1h] and in other reactions of cobalt carbonyls [1i] with unsaturated species, and was interested to investigate the PK reactions of alkynes bearing other groups which may potentially coordinate to cobalt and thus influence the stereo- or regio-chemistry of the PK. For instance, it has been demonstrated that certain alkynyl thiols are effective chiral auxiliaries in the PK [1g] as the sulphur acts as a hemilabile donor influencing the diastereoselectivity of the reaction. 2-Alkynyl anilines seemed interesting substrates for the PK as if the reaction were to proceed in the expected manner the products would contain an aniline nitrogen which would seem well positioned for condensation with the cyclopentenone carbonyl to give products which could tautomerise to alkenyl indoles (Scheme 1).

There appears to be only one reference to the PK reactions of alkynyl anilines [2]. In these systems the nitrogens were protected, which could explain the lack of both unusual reactivity and product self-condensation. However, there has recently [3] been a report of some unexpected and unusual products derived from the dicobalthexacarbonyl complexes of alkynyl anilines, and so it was difficult to predict the reactivity of such species.

2-Ethynyl aniline [4] **1** reacted smoothly with dicobaltoctacarbonyl to give the dicobalt hexacarbonyl adduct, with no evidence from IR or NMR (^{1}H and ^{13}C) of the aniline nitrogen acting as a donor. This complex upon treatment with norbornadiene (4 mol. equvi.) in DCM at reflux for 3 h gave the expected PK product **2** as a single regio- and diastereo-isomer in 67% yield after
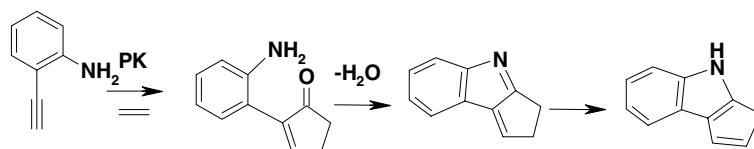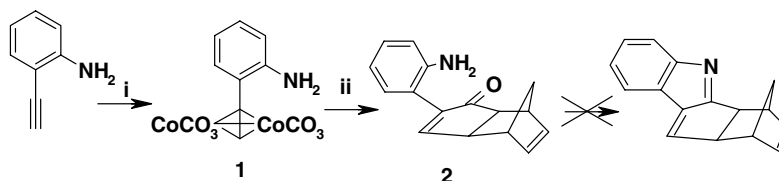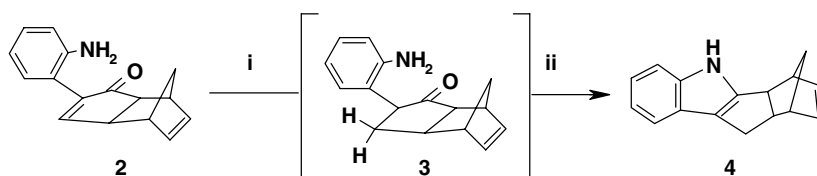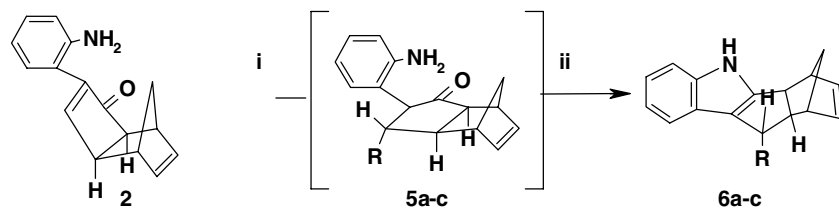
Scheme 1.

work-up and crystallisation from ethanol–water. The anticipated condensation, however, proved elusive and no evidence of condensation was observed under a variety of conditions (neutral, acids, CSA, TsOH, reflux in EtOH, PhMe, Dean and Stark) only decomposition to an intractable material believed to be polymeric due to low solubility and very broad NM resonances. It seemed likely that the α–β unsaturated ketone was either not sufficiently electrophilic to react with the aniline, or that the unsaturated system was simply too strained for the required angle of attack at the carbonyl to be achieved (Scheme 2).

Removal of the alpha–beta unsaturation of the ketone was expected to release the putative reactants from limiting ring strain and simultaneously increase the electrophilicity of the carbonyl carbon, and so the selective conjugate reduction of the α–β unsaturated ketone with Stryker's reagent (hydrido (triphenylphosphine) copper(I) hexamer [PPh$_3$CuH]$_6$) was examined. After some initial failures with commercial preparations of Stryker's reagent, a recent synthesis of Stryker's reagent [5] using silane reducing agents was followed. The freshly prepared material was used to reduce the PK product **2**, and the indole **4** derived from spontaneous condensation was isolated after column chromatography in 68% yield as a white crystalline solid (Scheme 3).
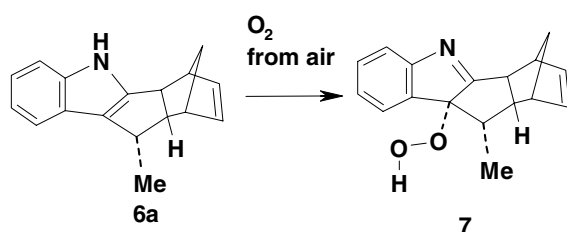
The indole portion of the molecule gave characteristic signals in the proton and carbon NMR and the totality gave a molecular ion at *M/Z* 221 (confirmed by HRMS), leaving no doubt as to the structure of the product.

In order to probe the generality of this combined PK-conjugate addition route to fused bicyclic indoles a small range of other soft nucleophiles were added to the cyclopentenone alkene. Gilman-type cuprates prepared by the addition of methyl, butyl and phenyl lithium to copper iodide successfully gave the corresponding indoles **6a–c** in essentially quantitative yield. These compounds were isolated as single diastereoisomers, of high purity, which could be further purified by recrystallisation from the reaction mixture without chromatography (Scheme 4). In no cases was the uncyclised product **5** observed, and examination of the crude reaction mixtures by NMR showed no trace of signals which could be assigned to the minor diastereoisomers. The stereochemistry of the indoles **6a–c** was initially assigned as illustrated (Scheme 4) from the vicinal coupling of the proton at the new chiral centre. Although many of the resonances are unassignable multiplets, as is common in such systems due to the large number of small couplings broadening many peaks, and the new chiral centre itself is complicated by coupling to the cuprate-derived chain, the proton at the ring fusion adjacent to the site of addition (H10a) has one ca. 7 Hz coupling (in **6a** and **6b**) to it is mutually *cis*-axial neigbor (H4a) and only shows a small (ca. 2 Hz) coupling to any other protons, thus indicating an approximate 90° relationship to the proton at the new chiral centre, consistent with endo-attack. This stereochemistry is easily explicable by considering the overall cup-shaped conformation of **2** (exaggerated for illustrative purposes in Scheme 4)

Scheme 2. (i) Co$_2$CO$_8$, (1.1 equvi.). (ii) Norbornadiene 5 equvi. DCM (4 ml/mol) 40 °C, 3 h 67%.

Scheme 3. (i) [Ph$_3$PCuH]$_6$ 3 equvi. PhMe (25 ml/mmol)/H$_2$O (5 equvi.) RT 24 h. (ii) Spontaneous. 68% overall.

Scheme 4. (i) R$_2$CuLi 1.5 equvi. Et$_2$O (6 ml/mmol) THF (3 ml/mmol) −78 °C, 12 h. (ii) Spontaneous R = (a) Me (92%), (b) Bu (70%) (c) Ph (74%).

Scheme 5.

Fig. 1. ORTEP view of 9 (50% probability).

which hinders attack from the *endo* face and leads to the *trans* geometry illustrated. Thus the fused ring indoles are obtained with defined relative stereochemistry at all the chiral centres, and, as an enantioselective PK procedure could provide a single enantiomer of **2**, a route to single enantiomers of **6**[1] is conceivable.

Upon exposure to air indoles **4**, **6a**–**c** degrade slowly, and a peak in the mass spectrum at (M + 32) is observed, indicating the formation of a dioxygen adduct, although further degradation makes characterisation of these adducts difficult. Slow evaporation of an ether-petrol solution of **6a** gave crystals suitable for X-ray determination, and these proved to be the hydroperoxide **7** formed by dioxygen addition to the indole 3 position, followed by tautomerisation to the imino-hydroperoxide form (Scheme 5).

That the C2–N bond order has increased to a full double bond is indicated by the measured bond length of 1.27 Å compared to the C(Ph)–N bond length of 1.44 Å, and a typical indole C2–N bond length of 1.38 Å [6]. Although autooxidation of indoles is common, only one such adduct has previously been characterised crystallographically [7] itself also the product of inadvertent oxidation. The structure of **7** allows confirmation of the relative stereochemistry of the conjugate
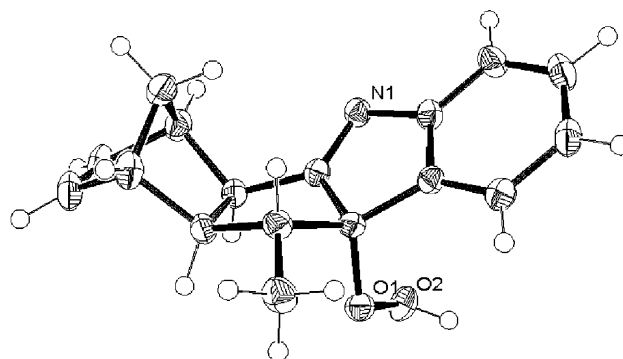
addition product, as it is unlikely that the stereochemistry is labile under aerobic oxidation (see Fig. 1).

As indicated by NMR studies, the methyl group added from the less hindered *exo* face of the cup-shaped polycyclic system, and it can also be seen that, as expected, the initial PK reaction[2] was *exo* selective with respect to norbornadiene. Analogously, the addition of dioxygen takes face from the less hindered face of the indole (although this places it *cis* to the neighbouring methyl group), and it could be expected that other electrophiles would be similarly directed by the norbornadiene bulk.

The fused ring indoles obtained by this route are of interest as these constrained bridged bicyclic indoles themselves have known biological activity [6], and there are a wealth of indole-containing natural products and unnatural compounds of interesting biological activity [7].

We are now investigating the use of catalytic cobalt [1b] in this synthesis, the extension to other alkenes and substituted ethynyl anilines, and addressing the

---

[2] PK reaction products often contain problematical paramagnetic cobalt residues which are difficult to separate chromatographically as they 'smear'. We find these can be removed by an aerobic oxidation catalysed by finely powdered charcoal, (commonly used to oxidise cobalt species in coordination chemistry). Typically the crude product of the PK will be evaporate to dryness and treated with high vacuum to remove excess alkene, then re-dissolved in DCM, treated with approximately 5% by weight of both finely powdered charcoal and silica, and stirred under air for 16 h. At the end of this time filtration of the inorganics and evaporation provides the unadulterated organic product.

application of this synthetic sequence to specific target molecules.

2. Experimental

Numbering scheme for ring systems
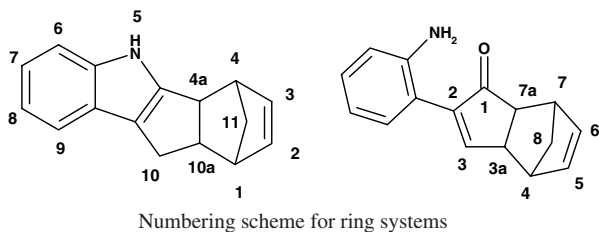
2.1. 2-(2-Aminophenyl)-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (2)

To a flame dried (200 ml) Schlenk flask equipped with a reflux condenser was added dicobaltoctacarbonyl (8.71 g, 25.48 mmol) and 2-ethynyl aniline [4] (2.714 g, 23.17 mmol) and dry, degassed dichloromethane (100 ml) under an inert atmosphere. The mixture was stirred at room temperature until the dicobalthexacarbonyl alkyne complex was formed as indicated by a high running red T.L.C spot (ca. 30 min). To the mixture was then added 2-5-norbornadiene (12.5 ml, 116 mmol) and the reaction mixture heated at reflux for 3 h. The reaction mixture was then evaporated to dryness (black/brown solid), dissolved in DCM (50 ml) treated with activated charcoal (1 g) silica (ca. 1 g) and stirred under an atmosphere of air for 16 h. Column chromatography (1:1 ether: 40–60 petroleum ether) gave **2** as a yellow solid (R_f = 0.3) (3.71 g, 67%); m.p. 103–105 °C (EtOH/H_2O). v_{max} (Nujol) 3398–3327, 3056, 1692 cm^{-1}; δ H (400 MHz, CDCl$_3$), 7.58 (1H, d, J = 3.0 Hz, H3) 7.10 (2H, m, 2 × ArH) 6.70 (2H, m, 2 × ArH) 6.30 (1H, dd, J = 5.5, 3.0 H6) 6.20 (1H, dd, J = 5.5, 3.0 H5) 3.98 (2H, bs, NH$_2$) 2.95 (1H, bs, H7) 2.85 (1H, bm, H7a) 2.78 (1H, bs, H4) 2.40 (1H, d, J = 3 H3a) 1.40 (H, d, J = 16.0, 1/2 × 8-CH$_2$) 1.33 (1H, d, J = 16.0, 1/2 × 8-CH$_2$); δC (100 MHz, CDCl$_3$), 209.0, 163.9, 149.4, 144.8, 138.5, 137.1, 130.1, 129.8, 118.9, 118.8, 117.0, 53.0, 48.2, 44.1, 43.1, 41.4; m/z (%) (APCI) 238.7 (100) (M + H$^+$); HRMS C$_{16}$H$_{15}$NO requires [M + H] 238.1231 found 238.1226. C$_{16}$H$_{15}$NO requires C, 80.98; H, 6.37; N, 5.90. Found: C, 80.72; H, 6.37; N, 5.82%.

2.2. 1,4,4a,5,10,10a-Hexahydro-1,4-methanoindeno [1,2b] indole (4)

To a flame dried (50 ml) Schlenk flask containing Stryker's reagent (0.334 g, 0.17 mmol) under an inert atmosphere was added toluene (5 ml) and the mixture was stirred during the addition of 2-(2-aminophenyl)-

3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (0.1 g, 0.421 mmol) and water (0.15 ml) then sealed and stirred for a further 16 h. Column chromatography (1:1 ether: 40–60 petroleum ether) gave **4** (R_f = 0.37) as a white solid 0.0621 g, 66.7%); m.p. 76–78 °C (EtOH). v_{max} (Nujol) 3397–3053 cm^{-1}; δH (400 MHz, CDCl$_3$), 7.70 (1H, bs, NH) 7.30 (1H, dd, J = 7.0, 2.0, H6) 7.20 (1H, dd, J = 7.0, 2.0 H9) 7.00 (2H, m, H7,H8) 6.10 (2H, m, H2, H3) 3.00 (1H, d, J = 7.0, H4a) 2.95 (2H, m, H10) 2.80 (1H, bs, H1) 2.68 (1H, bs, H4) 2.40 (1H, m, H10a) 1.35 (2H, m, 11-CH$_2$); δC (100 MHz, CDCl$_3$), 143.4, 140.8, 137.6, 137.2, 124.9, 121.5, 120.7, 119.5, 118.6, 111.4, 50.2, 48.3, 45.7, 45.6, 42.5, 29.2; m/z (APCI) (%) 222 (M + H$^+$) (100) HRMS C$_{16}$H$_{16}$N [M + H] requires 222.128 found 222.1277.

2.3. 10-Methyl-1,4,4a,5,10,10a-hexahydro-1,4-methano-indeno[1,2b]indole (6a)

To a dried Schlenk tube under an inert atmosphere containing a slurry of copper iodide (0.218 g, 1.145 mmol) in dry diethyl ether (2 ml) at 0 °C was added a solution of methyl lithium in ether (1.6 M, 2.29 mmol) and stirred with cooling for 1 h. After this time, **2** (0.181 g, 0.763 mmol) was added as a solution in ether/THF (2 ml/2 ml), the reaction mixture was allowed to warm to room temperature and stirred under an inert atmosphere for 12 h. The mixture was added to ether (50 ml) and washed with NH$_4$Cl (saturated, aqueous, 3 × 50 ml), dried over MgSO$_4$, evaporated to dryness and crystallised from ethanol/water to give **5a** (0.25 g, 92.4%) as brown crystals; m.p. 170–173 °C. v_{max} (Nujol) 3382–3053 cm^{-1}; δH (400 MHz, CDCl$_3$), 7.63 (1H, bs, NH) 7.36 (1H, dd, J = 7.0, 2.0 H6) 7.22 (1H, dd, J = 7.0, 2.0 H9) 7.00 (2H, m, H7,H8) 6.10 (2H, m, H2,H3) 3.00 (1H, d, J = 7.0 H4a) 2.80 (1H, m, H10) 2.79 (1H, bs, H1) 2.68 (1H, bs, H4) 2.30 (1H, dd, J = 7.0, 2.0 H10a) 1.30 (5H, overlapped m and s, 11-CH$_2$ + 10-CH$_3$); ^{13}C NMR δ (100 MHz, CDCl$_3$), 142.6, 140.8, 137.6, 137.2, 126.6, 124.5, 120.7, 119.4, 118.4, 111.4, 60.1, 47.5, 45.7, 45.4, 43.0, 38.0, 22.5; m/z (EI) (%) 235.2 (M$^+$) (100) HRMS C$_{17}$H$_{17}$N requires 235.1361, found 235.1353.

2.4. 10-Butyl-1,4,4a,5,10,10a-hexahydro-1,4-methano-indeno[1,2b]indole (6b)

To a dried Schlenk tube under an inert atmosphere containing a slurry of copper iodide (0.152 g, 0.80 mmol) in dry diethyl ether (2 ml) at 0 °C was added a solution of butyl lithium in ether (1.6 M, 1.6 mmol) and stirred with cooling for 1 h. After this time **2** (0.1 g, 0.421 mmol) was added as a solution in ether/THF (2 ml/2 ml), the reaction mixture was allowed to warm to room temperature and stirred under an inert atmosphere for 12 h. The mixture was added to ether

(50 ml) and washed with NH_4Cl (saturated aqueous, 3×50 ml) dried over $MgSO_4$ evaporated to dryness and crystallised from ethanol/water to yield **6b** (81 mg, 0,29 mmol, 70%) as brown crystals mp, 236–238 °C. v_{max} (Nujol)/cm^{-1} 3404 (NHR$_2$) 3045 (sp^{2}CH); ^{1}H NMR δ (400 MHz, CDCl$_3$), 7.70 (1H, bs, NH) 7.42 (1H, dd, $J = 7.0$, 2.0, H6) 7.25 (1H, dd, $J = 7.0$, 2.0, H9) 7.00 (2H, m, H7,H8) 6.10 (2H, m, H2,H3) 3.45 (2H, d, $J = 5.0$, H4a) 3.05 (1H, t, $J = 6.6$, H10) 2.78 (2H, m, H1) 2.68 (1H, bs, H4) 2.40 (1H, dd, $J = 5.0$, 2.0, H10a) 1.80 (2H, m, BuCH$_2$-α) 1.48–1.3 (9H, m, Bu, $2 \times CH_2 + CH_3 + 11CH_2$); ^{13}C NMR δ (100 MHz, CDCl$_3$), 143.0, 140.8, 137.8, 137.1, 126.5, 124.9, 120.6, 119.4, 118.9, 111.4, 57.6, 48.0, 45.5, 45.4, 43.7, 42.9, 37.1, 30.1, 23.1, 14.2; m/z (EI) (%) 309.3 ([M + O$_2$]$^+$) (100).

2.5. 10-Phenyl-1,4,4a,5,10,10a-hexahydro-1,4-methano-indeno[1,2b]indole (6c)

To a dried Schlenk tube under an inert atmosphere containing a slurry of copper iodide (0.218 g, 1.145 mmol) in dry diethyl ether (2 ml) at 0 °C was added a solution of phenyl lithium in dibutylether (1.6 M, 2.29 mmol) and stirred with cooling for 1 h. After this time **2** (0.181 g, 0.763 mmol) was added as a solution in ether/THF (2 ml/2 ml), the reaction mixture was allowed to warm to room temperature stirred under an inert atmosphere for 12 h. The mixture was added to ether (50 ml) and washed with NH_4Cl (saturated aqueous, 3×50 ml) dried over $MgSO_4$ evaporated to dryness and crystallised from ethanol/water to give **6c** (0.168 g, 94.0%) as brown crystals; m.p. 224–226 °C. v_{max} (Nujol) 3335 3062 cm^{-1}; δH (400 MHz, CDCl$_3$), 8.55 (1H, bs, NH) 7.89 (1H, d, $J = 8.0$, H6) 7.12–6.70 (8H, m, $5 \times$ Ph–H + H7,H8,H9) 6.42 (1H, d,d $J = 7$, 1, H10) 6.19 (1H, d,d $J = 5.0$, 3.0, H2) 6.08 (1H, d,d $J = 5.0$, 3.0, H3) 3.02 (2H, d, $J = 8.0$, H4a) 2.76 (1H, bs, H1) 2.52 (2H, m, overlapped H4, H10a) 1.9 (1H, d, $J = 8.0$, 1/2 $\times$ 11-CH$_2$) 1.45 (1H, d, $J = 8.0$ 1/2 $\times$ 11-CH$_2$); ^{13}C NMR δ (100 MHz, CDCl$_3$), 167.3, 147.5, 146.5, 137.0, 136.5, 135.2, 134.6, 129.8, 127.3, 127.1, 126.6, 123.4, 122.6, 121.1, 85.9, 55.0, 52.0, 43.1, 41.7, 41.7, 23.5; m/z (EI) (%) 297.3 ([M + O$_2$]$^+$).

References

[1] (a) P.L. Pauson, Tetrahedron 41 (1985) 5855;
(b) For reviews see: A.J. Fletcher, S.D.R. Christie, J. Chem. Soc., Perkin Trans. 1 (2000) 1657;
M.E. Welker, Curr. Org. Chem. 5 (2001) 785;
K.M. Brummond, J.L. Kent, Tetrahedron 55 (2000) 3263;
N.E. Schore, in: E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Comprehensive Organometallic Chemistry II, vol. 12, Pergamon, Oxford, UK, 1995, p. 703;
(c) e.g.: J. Cassayre, S. Zard, J. Orgmet. Chem 624 (2001) 316;
M.E. Krafft, Y.-Y. Cheung, K.A. Abboud, J. Org. Chem. 66 (2001) 7443;
(d) e.g.: D.R. Carbery, S. Reignier, J.W. Myatt, N.D. Miller, J.P.A. Harrity, Angew. Chem., Int. Ed. Eng. 41 (2002) 2584;
(e) S.E. Gibson, A. Stevenazzi, Angew. Chem., Int. Ed. Eng. 42 (2003) 1853;
(f) A.R. Kennedy, W.J. Kerr, D.M. Lindsay, J.S. Scott, S.P. Watson, J. Chem. Soc., Perkin Trans. 1 (2000) 4366;
(g) S. Fonquerna, A. Moyano, M. Pericas, A. Riera, J. Am. Chem. Soc. 119 (1997) 10225;
(h) M.P. Coogan, T. Walther, L.S. Stanton, J. Organomet. Chem. 677 (2003) 125;
(i) M.P. Coogan, E. Nutz, R.L. Jenkins, J. Organomet. Chem. 689 (2004) 694.
[2] M. Ishizaki, Y. Kasama, M. Zyo, Y. Niimi, O. Hoshino, Heterocycles 55 (2001) 1438.
[3] F.-E. Hong, Y.-L. Huang, H.-L. Chen, J. Organomet. Chem. 689 (2004) 3449.
[4] A. Acardi, S. Cacchi, F. Marinelli, Tetrahedron Lett. 30 (1989) 2581.
[5] P. Chiu, Z. Li, K.C.M. Fung, Tetrahedron Lett. 44 (2003) 455.
[6] N. Okabe, A. Yu, Acta Crystallogr., Sect. C 54 (1998) 386.
[7] G.A. Morales, F.R. Fronczek, Acta Crystallogr., Sect. C 52 (1996) 1266.