Study on the reaction mechanism of Heck-oxyarylation of 2*H*-chromenes

Gábor Kerti,[a] Tibor Kurtán,[a] and Sándor Antus[a,b]*

[a]*Department of Organic Chemistry, University of Debrecen, P.O.Box 20, H-4010 Debrecen, Hungary*
[b]*Research Group for Carbohydrates of the Hungarian Academy of Sciences, P.O.Box 94, H-4010 Debrecen, Hungary*
E-mail: antuss@tigris.unideb.hu

Dedicated to Professor Henk van der Plas on his 80th birthday

Abstract

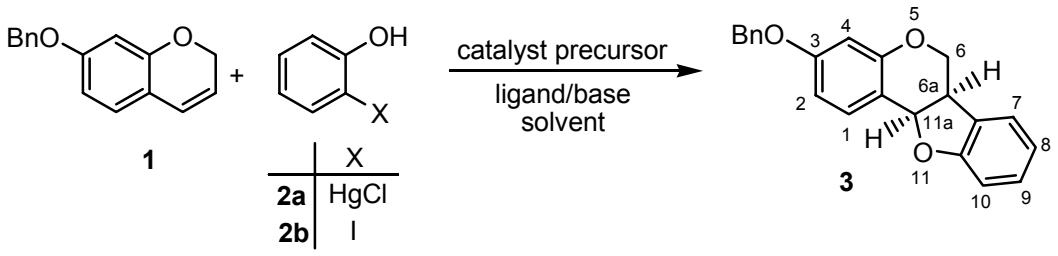
The Heck-oxyarylation reaction of deuterium labeled 2*H*-chromenes (**12**,**15**) has been studied whose synthesis was achieved in four steps starting from the readily available 7-benzyloxychromane (**9**). Since the deuterium label was not affected in the course of the oxyarylation, the formation of the neutral achiral intermediate **7** could be ruled out as a possible reaction pathway and a reason for the lack of enantioselectivity in asymmetric Heck-oxyarylations. This also allowed the simple synthesis of 6a- and 11a-deutero-3-benzyloxypterocarpanes (**13a**,**b**).

Keywords: Pterocarpan, Heck-oxyarylation, mechanism

Introduction

Pterocarpans are naturally occurring plant products carrying a *cis*-fused benzofuranyl-benzopyran ring system. Many of them are phytoalexins, which are produced in plants during infections by fungi, bacteria or viruses and subsequently act as protective agents for plants[1]. While some pterocarpans have antifungal[2] and oestrogenic activity[3] others have been reported to inhibit HIV-1 in cell cultures[4] and to possess significant snake or spider inhibition venom activity[5].

Among the wide variety of synthetic routes to pterocarpans,[6-14] one of the most commonly used approaches[14] involves the Heck-oxyarylation of 2*H*-chromenes (**1**) with 2-chloromercuriophenols (**2a**) using equimolar amount of $Li_2[PdCl_4]$ as catalyst (Scheme 1).



Scheme 1

Recently, we have described a convenient modification of this Heck-oxyarylation step by the replacement of the toxic chloromercuriophenol derivatives (**2a**) with 2-iodophenols (**2b**), which allowed to considerably decrease the amount of the expensive palladium (II) salt (from 100 mol% to 10 mol%) in the presence of triphenylphosphine and silver carbonate in acetone[15] or in ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate [[bmim] $[PF_6]$][16]. We have also published[17] that the extension of this reaction to a practical asymmetric Heck-oxyarylation affording enantiomerically enriched pterocarpans using different chiral bidentate phosphins or (+)-α-pinene as a ligand as well as a chiral ionic liquid could not be accomplished.

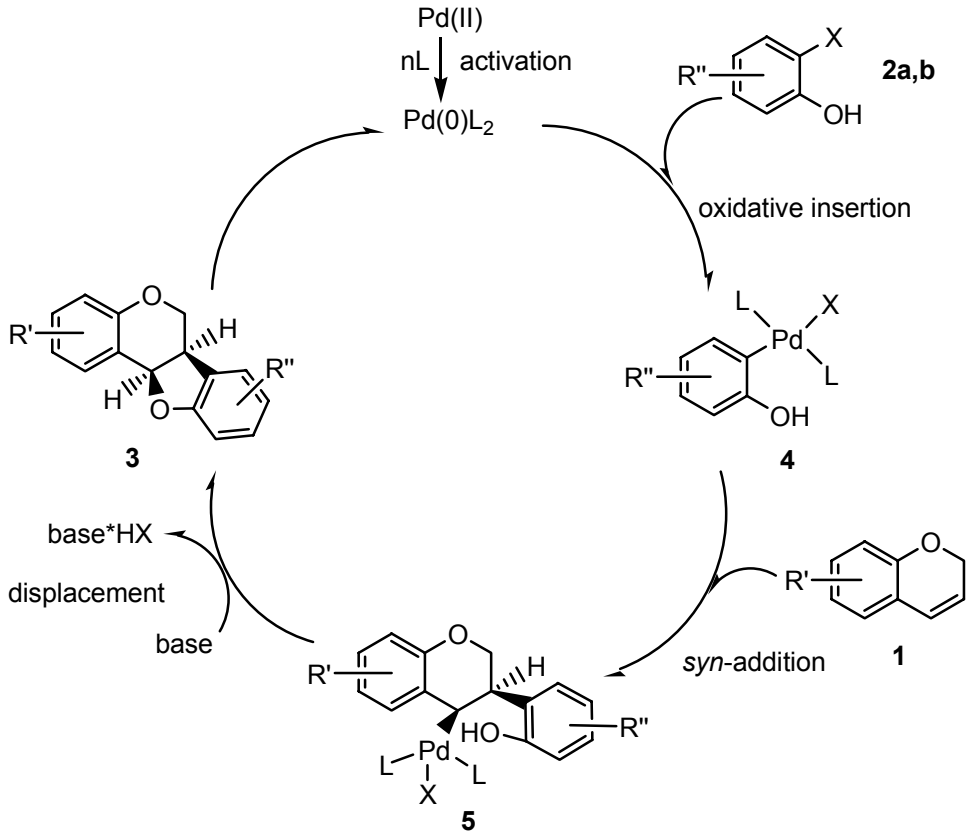


Figure 1. Proposed sequence of Pd-catalyzed oxyarylation.

Although intramolecular Heck-oxyarylation is widely used in the synthesis of racemic pterocarpans,[14,18-22] in contrast to the conventional Heck reaction,[23-25] its mechanism is not fully understood.

It presumably also proceeds *via* the generation of active Pd(0), oxidative addition of aryliodide (**2b**) or chloromercuriophenol (**2a**) to Pd(0), followed by regioselective *syn*-addition of **4** to 2*H*-chromenes (**1**) and palladium displacement by phenolic oxygen whose details are not known (Figure 1).

On the basis of data published in the literature,[26] the displacement step may take place *via* (i) cationic (**5**→**6**) (ii) neutral (**5**→**7**) or a palladium containing cyclic intermediate (**5**→**8**) as shown in Figure 2.

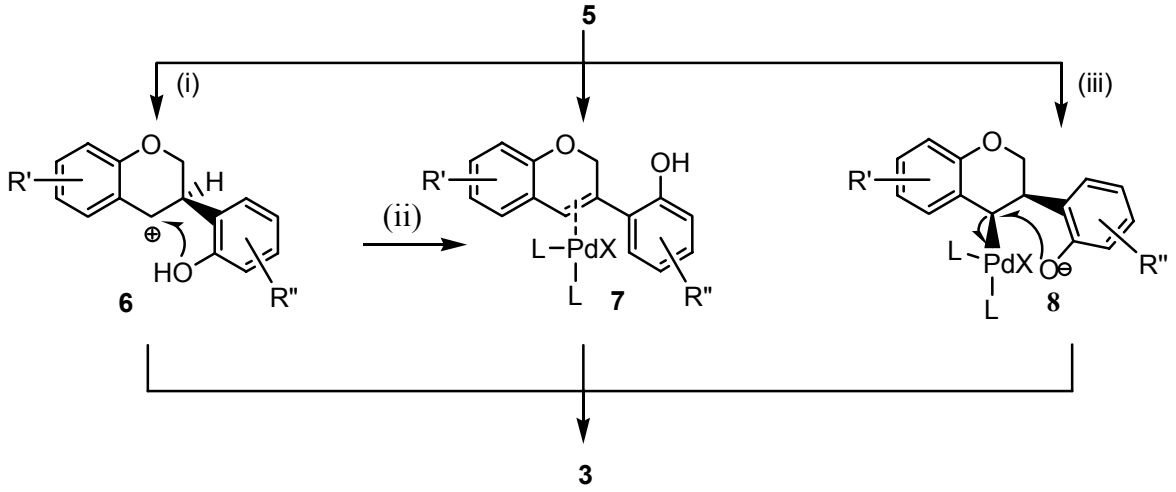


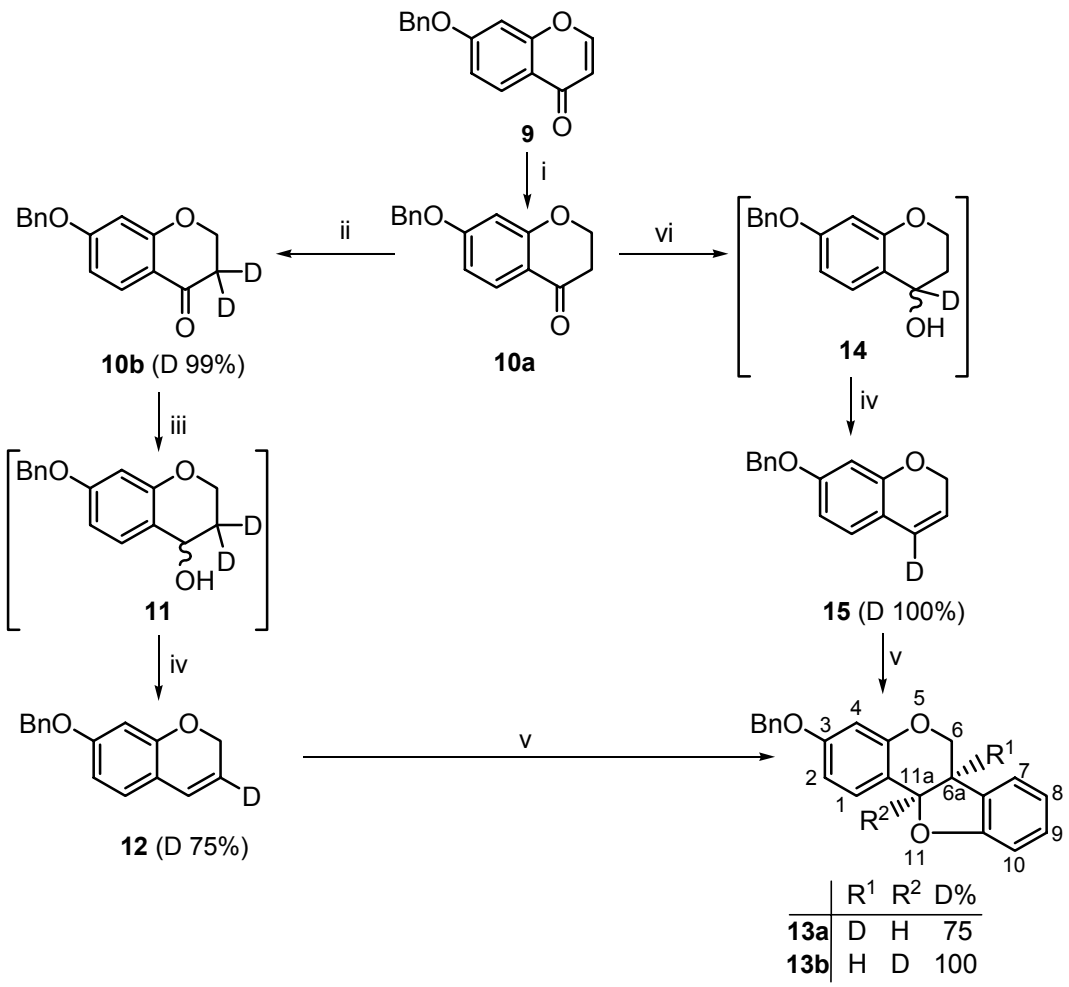
Figure 2. Possible pathways of the displacement step.

Since no or very moderate (ee%<10) asymmetric induction could be observed by us[17] in the presence of chiral bidentate phosphine ligands, such as CHIRAPHOS, NORPHOS, TRIPHOS and R-(+)-BINAP, it could be assumed that this reaction takes place through parallel pathways and the main pathway involves an achiral intermediate **7**, where the chirality introduced by chiral ligands of Pd(0) is lost.

In order to obtain aunambiguous evidence about this assumption, 2*H*-chromenes (**12**,**15**) labeled with deuterium at C-3 or C-4 have been synthesized and their transformation to the corresponding pterocarpans were studied.

Results and Discussion

According to the proposed mechanism shown in Figure 1 and 2, it seemed reasonable to prepare compounds in which a D atom was introduced at C-3 or at C-4 of the 2*H*-chromene skeleton (**1**).



Scheme 2. (i) LAH/THF, Et_2O, -60 °C, (ii) $CDCl_3$/TBD, r.t, (iii) LAH/Et_2O, r.t, (iv) acetone, 10% HCl, 56 °C, (v) $Pd(C_6H_5CN)_2Cl_2$, Ag_2CO_3, Ph_3P/THP, 65 °C or [bmim] [PF_6], 100 °C or $Li_2[PdCl_4]$ in acetone, r. t. Deuterium abundance is indicated in brackets as determined by ^{1}H-NMR.

For this purpose 7-benzyloxychromone (**9**) was reduced by lithium aluminium hydride in tetrahydrofuran at – 60 ºC resulting in 7-benzyloxychromanone (**10a**)[18] in 70% yield, whose hydrogens at C-3 could be exchanged (**10a**→**10b**) using the method published by Mioskowski et al[27] (Scheme 2). Since the ^{1}H NMR monitoring of **10a** in $CDCl_3$ at room temperature has clearly indicated that in the presence 10 mol% triazabicyclo [4.4.0] dec-5-ene (TBD) the deuterium incorporation has reached 99% in 12h, then the target molecule (**10b**) could be simply isolated in 88% yield. Subsequently, **10b** was reduced by lithium aluminium hydride in ether at room temperature resulting in the corresponding chromane-4-ol (**11**), whose dehydratation was performed by some drops of diluted hydrochloric acid in acetone at 56 ºC affording the C-3 deuterium labeled 2*H*-chromene **12** in an overall yield 46%. The deuterium content of **12** has been determined by ^{1}H NMR as 75%. The Heck-oxyarylation of **12** was performed with **2a** or **2b**

under the standard conditions [in case of **2a**: $PdCl_2$/LiCl, acetone, r.t.; in case of **2b**: $Pd(C_6H_6CN)_2Cl_2$, Ag_2CO_3, Ph_3P, THF, at 65 ºC or [bmim] [PF_6], at 100 ºC] to result in 3-benzyloxypterocarpan (**13a**) in 30-40% yield whose ^{1}H NMR spectrum has clearly indicated the presence of the C-6a deuterium with 75% abundance. Since the deuterium incorporation of the chromene ring did not change in the course of the oxyarylation, contrast to our earlier assumption, the formation of the neutral achiral intermediate **7** must have been ruled out as a possible reaction pathway. It is also noteworthy that the oxyarilation of C-4 labeled **15** possessing 100% deuterium incorporation with **2a** or **2b** (R'=H) took place in a similar manner to give **13b** with unchanged deuterium incorporation. The ^{1}H NMR spectra of **13a** and **13b** has also been found identical with those of compounds prepared by us in different synthetic route.[28] Since the absence of an asymmetric Heck-oxyarylation can not be attributed to the formation of achiral intermediate **7**, further efforts are required to find suitable chiral inductor and to optimize circumstances. It is also noteworthy that our efforts to increase the yield of the oxyarylation carried out in DMF or NMP in the presence of a palladacycle, such as *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) prepared according to the literature[29] were unsuccessful. Surprisingly, no transformation could be observed in these solvents, although palladacycletes have been found highly efficient catalysts for Heck vinylation of aryl halides under these conditions.[30] Moreover the yield of the oxyarylation described in general procedure b of the experimental section could not be improved by microwave irradiation either. Work on this project is in progress in our laboratory.

Experimental Section

General Procedures. All reagents and organic compounds were purchased from Sigma Aldrich. 7-Benzyloxychromane (**9**), *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]- dipalladium (II) and 2-chloromercuriophenol (**2a**, R'=H) were prepared according to the known procedures.[29,31,32]

7-Benzyloxychromanone (10a)

To a stirred solution of **9** (2 g, 7.9 mmol) in 40 ml dry THF and Et_2O (1:1) at –60 °C a solution of $LiAlH_4$ (600 mg, 15.8 mmol) in dry THF (15 ml) was added under N_2 atmosphere. After 3 hours the reaction was quenched by addition of saturated aqueous NH_4Cl (20 ml) and extracted with Et_2O (3x20 ml). The organic layer was washed with brine, water, dried (Na_2SO_4), filtered and concentrated. The resulting product was purified by column chromatography on silica gel resulting in **10a** of m.p.101-103 °C (1.41 g, 70%) as a colorless solid. Lit.[33] m.p 102-103 °C. ^{1}H-NMR: δ 2.69 (t, *J* = 6.6 Hz, 2H, 3-H), 4.44 (t, *J* = 6.6 Hz, 2H, 2-H), 5.03 (s, 2H, OCH_2Ph), 6.44 (d, *J* = 2.4 Hz, 1H, 8-H), 6.61 (dd, *J* = 8.8, 2.4 Hz, 1H, 6-H), 7.25-7.40 (m, 5H, Ph), 7.80 (d, *J* = 8.8 Hz, 1H, 5-H).

7-Benzyloxy-3,3-dideutero-chromanone (10b)

To the stirred solution of TBD (33 mg, 0.24 mmol) in deutero chloroform (8 ml) **10a** (388 mg, 1.53 mmol) was added at room temperature. After 12 h the reaction mixture was quenched with 1N HCl (2 ml). The organic layer was washed with water (2x15 ml), brine (15 ml), dried (Na_2SO_4) and filtered. Evaporation of the solvent afforded **10b**, whose deuterium incorporation has been found as 99% by ^{1}H-NMR. ^{1}H-NMR: δ 4.51 (s, 2H, 2-H), 5.09 (s, 2H, OCH_2Ph), 6.49 (d, *J* = 2.4 Hz, 1H, 8-H), 6.66 (dd, *J* = 8.8, 2.4 Hz, 1H, 6-H), 7.25-7.40 (m, 5H, Ph). 7.85 (d, *J* = 8.8 Hz, 1H, 5-H).

7-Benzyloxy-4-deutero-2*H*-chromene (15)

To stirred solution of **10a** (132 mg, 0.52 mmol) in dry Et_2O (10 ml) $LiAlD_4$ (28 mg, 0.66 mmol) was added at 0 °C. After 30 min. the reaction mixture was quenched with sat. aqueous NH_4Cl (20 ml) and the organic layer was separated and the water phase was extracted with Et_2O (3x10 ml). The combined organic phase was washed with brine and dried (Na_2SO_4), whose evaporation resulted in **14** as a colorless solid (132 mg). It was dissolved in acetone (5 ml) and heated in the presence of one drop 10% HCl for 3 hours. After neutralization with Et_3N, the reaction mixture was diluted with water and extracted with dichloromethane (3x5 ml). The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave an oil (70 mg), which was purified by preparative TLC (*n*-hexane:ethyl acetate = 3:1) to give **15** of m.p. 59-60 °C (55 mg, 44%), as a colorless solid incorporation has been determination by ^{1}H-NMR to be 99%.^{1}H-NMR: δ 4.77 (d, *J* = 3.2 Hz, 2H, 2-H), 5.01 (s, 2H, OCH_2Ph), 5.61 (t, *J* = 3.2 Hz, 1H, 3-H), 6.44 (d, *J* = 2.2 Hz, 1H, 8-H), 6.48 (dd, *J* = 8.2, 2.2 Hz, 1H, 6-H), 6.86 (d, *J* = 8.2 Hz, 1H, 5-H), 7.25-7.40 (m, 5H, Ph).

7-Benzyloxy-3-deutero-2*H*-chromene (12)

Starting from **10b** (170 mg, 0.66 mmol) **12** (73 mg, 46%) was obtained by a similar procedure described for **15**. On the basis of its ^{1}H-NMR the deuterium incorporation is 75%.

^{1}H-NMR: δ 4.78 (d, *J* = 1.8 Hz, 2H, 2-H), 5.02 (s, 2H, OCH_2Ph), 6.30-6.40 (m, 1H, 4-H), 6.44 (d, *J* = 2.4 Hz, 1H, 8-H), 6.49 (dd, *J* = 8.2, 2.4 Hz, 1H, 6-H), 6.86 (d, *J* = 8.2 Hz, 1H, 5-H), 7.30-7.45 (m, 5H, Ph).

General procedures for the Heck-oxyarylation reaction

a) Palladium chloride (89 mg, 0.48 mmol) and lithium chloride (45 mg, 1.06 mmol) were stirred in dry acetone (5 ml) for 15 min, 7-benzyloxy-2*H*-chromene (**12** or **15**) (120 mg, 0.50 mmol) was added, stirred further for 15 min, followed by dilution of the mixture with dry acetone (15 ml) and addition of *o*-chloromercuriophenol (**2a**) (181 mg, 0.55 mmol). Stirring was continued for 14 hours and then the reaction mixture was poured on brine (50 ml), extracted with dichloromethane, dried, and concentrated in *vacuo* to give a viscous crude product (180 mg), whose purification by column chromatography on silica gel (*n*-hexane:ethyl acetate = 7:1) resulted in (±)-**13a** or **13b** respectively (60-66 mg, 36-40%) as colorless prisms, m.p. 146-148 °C (MeOH).

b) To a stirred solution of **12** or **15** (100 mg, 0.42 mmol) in dry acetone or THF (6 ml), 2-iodophenol (93 mg, 0.42 mmol), silver carbonate (350 mg, 1.26 mmol), PPh_3 as ligand (220 mg, 0.84 mmol) and $Pd(C_6H_5CN)_2Cl_2$ palladium catalyst (16 mg, 0.042 mmol) were added at room temperature, and then the reaction mixture was stirred at 65 °C. After filtration, the solution was evaporated, and **13a** or **13b** respectively (40-45%) was isolated as given above.
c) 4.2×10^{-3} mmol Pd(II) catalyst and 8.4×10^{-3} mmol PPh_3 were stirred in [bmim][PF_6] (1 g) at 80 °C for 5 min, respectively. Then 100 mg (0.42 mmol) **12** or **15**, 93 mg (0.42 mmol) **2b** and Ag_2CO_3 (348 mg, 1.26 mmol) were added. Stirring was continued at 100 °C for 5 hours and then the reaction mixture was cooled, extracted with toluene and concentrated in *vacuo*. The crude product was purified by preparative TLC (dichloromethane:*n*-hexane=1:2) to give *rac*-**13a** or **13b** respectively (34-36 mg, 36-38%).

Acknowledgements

Authors thank the Hungarian Scientific Research Fund (OTKA, T-049436, NI-61336), National Office for Research and Technology (NKTH, K-68429), Bolyai János Foundation, and Pázmány Péter Programme (NKTH, RET 006/2004) for financial support.

References

1. Dewick, P. M. *Flavonoids, Advences in Research Since 1986*, Harborn J. B. Ed., Chapman and Hall: London 1994, p 166
2. Lane, G. A.; Sutherland, O. R. W.; Skipp, R. A. *J. Chem. Ecology* **1987**, *13*, 771
3. Perrin, D. R.; Cruickshank, A. M. *Phytochemistry* **1969**, *8*, 971
4. Engler, T. A.; Lynch, O. K.; Reddy, J. P.; Gregory, E. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1229
5. Nakagawa, M.; Nakanishi, K.; Darko, L. L.; Vick, J. A. *Tetrahedron Lett.* **1982**, *23*, 3855
6. Suginome, H.; Iwadare, T. *Bull. Chem. Soc. Jpn.* **1986**, *39*, 1535
7. Farkas, L.; Gottsegen, Á.; Nógrádi, M.; Antus, S. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 305
8. Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander-Velde, D. J. *J. Org. Chem.* **1990**, *55*, 1248
9. Gonzalez, L. J.; Munoz, S. G.; Corral, M. A.; Dorago, M. M.; Garcia, I. R. *Chem. Eur. J.* **2006**, *12*, 8762
10. Gopalsamy, A.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1988**, 28
11. Van Aardt, P. G.; van Heerden, P. S.; Ferreira, D. *Tetrahedron Lett.* **1998**, *39*, 3881
12. Ozaki, Y.; Mochida, K.; Kim, S.-W. *J. Chem. Soc. Chem. Commun.* **1988**, 374
13. Kiss, L.; Szilágyi, L.; Antus, S. *Z. Naturforsch.* **2002**, *57b*, 1165
14. Horino, H.; Inone, N. *J. Chem. Soc., Chem. Commun.* **1976**, 500

15. Kiss, L.; Antus, S. *Heterocycl. Commun.* **2000**, *6*, 309
16. Kiss, L.; Papp, G.; Joó, F.; Antus, S. *Heterocycl. Commun.* **2001**, *7*, 417
17. Kiss, L.; Kurtán, T.; Antus, S.; Brunner, H. *ARKIVOC* **2003**, *(v)*, 69
18. Breytenback, J. C.; Rall, G. J. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1804
19. Lichtenfels, R. A.; Coelho, A. L.; Costa, P. R. R. *J. Chem. Soc. Perkin Trans. 1* **1995**, 949
20. Narkhade, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* **1990**, *46*, 2031
21. Ishiguro, M.; Tatsuoka, T.; Nakatsuka, N. *Tetrahedron Lett.* **1982**, *23*, 3859
22. Tőkés, A. L.; Litkei, Gy.; Gulácsi, K.; Antus, S.; Baitz-Gács, E.; Szántay, Cs.; Darkó, L. L. *Tetrahedron* **1999**, *55*, 9283
23. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320
24. Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights* VCH,:Weinheim, 1991
25. DeMeijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379
26. Larock, R. *J. Organomet. Chem.* **1999**, *576*, 111
27. Sabor, C.; Kumar, K. A.; Antheaume, C.; Mioskowski, Ch. *J. Org. Chem.* **2007**, *72*, 5001
28. Tóth, E.; Dinya, Z.; Szilágyi, L.; Antus, S. *Heterocyclic Commun.* **2001**, *7*, 257
29. Hermann, W. A.; Brossmer, Ch.; Reisinger, C.-P.; Riermeier, Th. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357
30. Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev*. **2005**, *105*, 2527
31. Malkotra, S.; Sharma, V. K.; Parmar, V. S. *Chem. Research Synopses* **1988**, *b*, 179
32. Chapman and Hall, London *Org. Synth. Coll. Vol. I*. **1947**, pp 161-162
33. Antus, S. ; Gottsegen, A.; Nógrádi, M. *Synthesis* **1981**, *7*, 574