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Journal of Organometallic Chemistry 692 (2007) 1812–1816
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

From chiral and prochiral *N*-allylpyrroles to stereodefined pyrrole fused architectures: A particular application of the rhodium-catalyzed hydroformylation

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Received 30 August 2006; received in revised form 14 November 2006; accepted 14 November 2006
Available online 19 November 2006

This paper is dedicated to Professor Gyula Palyi on the occasion of his 70[th] birthday.

Abstract

We review our recent results on the rhodium-catalyzed hydroformylation of chiral and prochiral *N*-allylpyrroles as a synthetic route to stereodefined 5,6-dihydro- and 5,6,7,8-tetrahydroindolizines. The indolizine nucleus at different degrees of unsaturation is a building block of natural and synthetic target compounds; thus new approaches, especially if stereoselective and/or stereospecific, are highly desirable. The construction of the indolizine architectures reported here occurs by formation of a C8–C9 bond through intramolecular cyclization of the 4-pyrrolylbutanal intermediate.

Keywords: Hydroformylation; Synthesis; Chiral indolizines; Diastereoselectivity

1. Introduction

The indolizine building block at different degrees of unsaturation is a very common skeleton for many types of active natural and synthetic compounds (see Fig. 1).

Among the fully hydrogenated substrates [1a,1b], polyhydroxylated indolizidines mimic monosaccharides in their structure and ability to function as glycosidase inhibitors [1c,1e]; 5- or 3,5-alkylsubstituted indolizidines are also quite important biologically active derivatives [1f]. Partially hydrogenated systems have also been prepared and characterized. They are used as intermediates in the synthesis of indolizines or indolizidines but they themselves also constitute target molecules, as illustrated by the extensive literature on 5,6,7,8-tetrahydroindolizines [2a,2b,2c]. Among these, 7-aminotetrahydroindolizines are dopaminergic ligands [2d] while 8-hydroxytetrahydroindolizines possess antiTNF and antithrombotic activities [2e,2f]. Tetrahydroindolizine was first obtained by catalyzed hydrogenation of indolizine [3]. More recently, 8-substituted tetrahydroindolizines, bearing an electron-donating group on the α-position of the pyrrole ring, have been prepared via a C7–C8 bond disconnection, where an iodine atom constitutes a good leaving group [4]; 7-amino and 8-aminomethyl-5,6,7,8-tetrahydroindolizines have also been obtained by stereoelectronically controlled cationic cyclization [2b,2c,2d].

Some investigations of the biological activity of 5,6-dihydroindolizines have been reported mainly in patents [5,6]; in particular, the basic 5,6-dihydroindolizine nucleus appears to be very useful for the treatment and prevention of diseases in which viruses of the herpes family and/or cytokines, in particular TNFα, are involved [7]. 5,6-Dihydroindolizines were first obtained by reducing indolizines with metals. Subsequently different synthetic approaches have been explored, e.g., electrochemically induced cycloaddition of

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doi:10.1016/j.jorganchem.2006.11.020

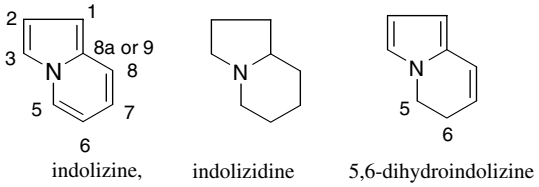


Fig. 1. Indolizine bicyclic core at different degree of unsaturation.

enamines (N–C5 and C6–C7 bond formation) [8], Dieckmann type condensation (C7–C8 bond formation) [9], or Pt(IV)-catalyzed hydroarylation (C8–C9 bond formation) [10]. A C7–C8 bond-forming nucleophilic substitution has been exploited by Katritzky and co-workers [11]. A masked aldehydic group is involved in the synthesis of the highly substituted 5,6-dihydroindolizine precursors of natural myrmicarins [12], where the cyclization and the double bond formation occur in the same step.

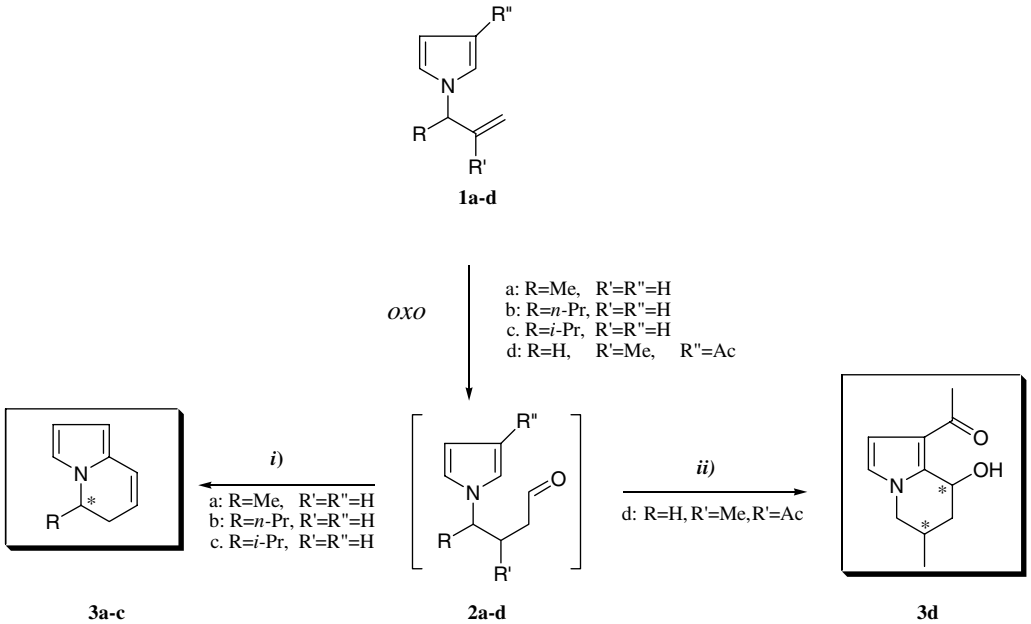
In all cases, the 5,6-dihydroindolizine structure, like the tetrahydro- one, is not a target molecule but one product together with many other, useful for testing new synthetic methodologies.

Despite the variety of preparative approaches cited above, there has so far been no report on the use of the *oxo* process as a possible synthetic alternative route to 5,6-dihydro- or 5,6,7,8-tetrahydroindolizines. Nevertheless, hydroformylation, i.e., the formal addition of CO and H_2 to an olefinic double bond to give aldehydes, has many attractive features: the reaction needs only catalytic amounts of a metal complex, it introduces the reactive aldehyde functionality, and all atoms of the starting materials remain incorporated into the product in a very economical C–C-bond forming reaction. However possible criticisms are that it provides only a one carbon chain elongation (low synthetic efficiency) and it requires control of both the regio- and the enantioselectivity.

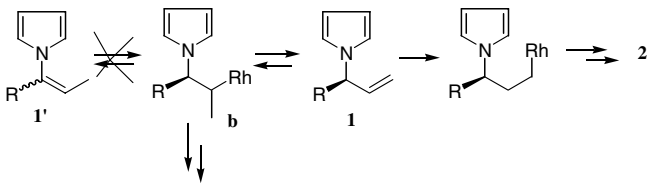
We recently solved these troublesome problems in a new hydroformylation-based domino process for the formation of indolizines (Scheme 1).We elaborated the sequential rhodium-catalyzed hydroformylation of the *N*-allylpyrroles **1a**–**d**/intramolecular cyclization of the pyrrolylbutanal **2a**–**d** produced, which may or may not be followed by water elimination. In the former case (i) the optically active 5,6-dihydroindolizines **3a**–**c** having the same e.e. as the starting olefins were prepared stereospecifically. In the latter case (ii), where no water is eliminated, the 8-hydroxy-5,6,7,8-tetrahydroindolizine **3d** having the same configuration at both C6 and C8 chiral centers was obtained in a stereoselective manner.

2. Stereospecific rhodium-catalyzed hydroformylation of chiral *N*-allylpyrroles to optically active bicylic 5,6-dihydroindolizines

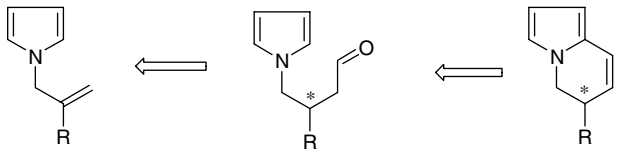
The hydroformylation of the optically active **1a**–**c** [13] is a case of a highly selective reaction [14]. In fact, when **1a**–**c** were submitted to hydroformylation conditions which favor the linear isomer (30 atm, 125 °C), the aldehydes **2a**–**c** were the predominant products (85% with respect to 15% branched isomers). The aldehydes **2a**–**c** are not stable under the experimental conditions and cyclize as soon as they form to the dihydroindolizines **3a**–**c**. An evaluation of the optical purity of both unconverted **1a**–**c** and the produced **3a**–**c** showed, at all conversions, around the same enantiomeric excess, i.e., the starting e.e. value (>92%). Taking into account the generally accepted mechanism of



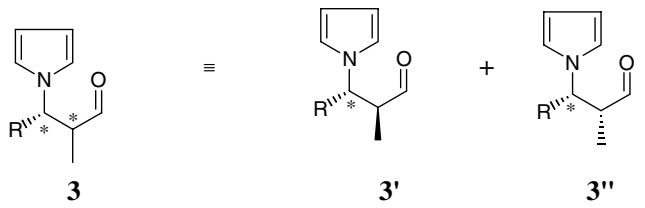
Scheme 1. *oxo*: $Rh_4(CO)_{12}$ (substrate/Rh = 100–200), CO/H_2 (1:1) 30–100 atm, 100–125 °C, toluene, 25 ml stainless-steel autoclave under magnetic stirring. (i) the same conditions as *oxo*, with water elimination. (ii) the same conditions as *oxo*, CO atmosphere only, after CO and H_2 removal.



Scheme 2.



Scheme 3.



Scheme 4.

hydroformylation [15], we can affirm that, under the above conditions, unlike the behavior observed with other olefins, e.g. allylbenzene [16], the branched alkyl-rhodium intermediate **b** undergoes a β-hydride elimination process that does not involve the chiral center, generating the olefin **1** but not **1′** (Scheme 2).

In fact, no traces of the internal olefin **1′** were observed in the crude reaction mixture either at partial or at total conversion. As a consequence of the electron-withdrawing heteroaromatic effect, the methynic hydrogen bonded to the carbon vicinal to the annular nitrogen in **b** does not have enough hydridic character to take part in β-hydride elimination. This very interesting result indicates that hydroformylation conditions are perfectly compatible with the optically active pyrrolyl-olefins employed and allow complete configurational stability even under forcing conditions that would favor isomerization (high temperature and low pressure).

Interestingly, when the R group was on the β- instead of the α-position of the exocyclic chain i.e., the starting substrate was a vinylidenic olefin (Scheme 3), the corresponding linear aldehyde was obtained as the exclusive product, the hydroformylation being completely regioselective [17]. This aldehyde, as it forms, immediately cyclizes and eliminates water, chemoselectively giving 6-alkyl-5,6-dihydroindolizines. As a new stereogenic center is generated when the aldehyde forms, the use of a catalyst precursor modified with chiral ligands could lead to enantiodifferentiated indolizines.

3. Diastereoselective rhodium-catalyzed hydroformylation of chiral *N*-allylpyrrole to N-protected β-aminoaldehydes

The above experimental conditions are able to enhance the formation of the linear aldehyde and hence the yield of the corresponding 5,6-dihydroindolizine. Indeed, an inversion of regioselectivity (up to 70/30 in favor of the branched aldehyde **3**) (Scheme 4) was obtained by carrying out the hydroformylation of **1a**–**c** at lower temperatures (25–60 °C). In generating the aldehyde a new stereogenic center is formed; significant diastereodifferentiation was observed in the case of R = *i*-Pr (**3′**/**3″** = 85/15 evidenced by NOE experiments of relative configuration assignement carried out on the corresponding olefin) (Scheme 4). This is one of the few cases reported in the literature of substrate-directed 1,2-asymmetric induction under *oxo* conditions [18,19]. As the pyrrole ring is known to be a useful protecting group for primary amines [20], the process reported above represents a new access to N-protected, optically active β-aminoaldehydes [21a,21b], which are important building blocks in the biosynthesis and total synthesis of various alkaloids [21c], and confirms that *N*-allylpyrroles are versatile synthetic precursors.

4. Diastereoselective rhodium-catalyzed hydroformylation of a prochiral *N*-allylpyrrole to a tricyclic 5,6,7,8-tetrahydroindolizine

The hydroformylation of the prochiral substrate **1d**, shown in Scheme 1, constitutes a new example of complete linear regioselectivity and 1,3-substrate-induced diastereoselectivity [22]. The aldehyde **2d** was formed as the sole isomer and the derivative **3d** was obtained from it as the sole diastereomer having the same relative configuration at carbon atoms C6 and C8. While 4-(pyrrol-1-yl)butanals unsubstituted or substituted with electron-donor groups on the pyrrole ring immediately give the corresponding 5,6-dihydroindolizines [17], e.g., the case of **1a**–**c**, cyclization of the aldehyde **2d** containing an electron-withdrawing group, occurs much more slowly. Only after 70 h under 15 atm of CO had the aldehyde **2d** disappeared in favor of the alcohol **3d**. As shown by NMR and IR measurements, the six membered ring in **3d** has a half chair conformation with the methyl group in an equatorial position, and the hydroxyl and methyl groups being mutually anti. In particular, the ^{13}C and ^{1}H NMR spectra show only one resonance for every carbon and every proton, indicating that the intramolecular cyclization produces only one diastereomer, namely, that having chiral centers at carbon atoms C_6 and C_8 with the same relative configuration (6*S*,8*S*; 6*R*,8*R*). The structure of **3d** obtained from spectroscopic measurements (^{1}H NMR, IR) is in perfect agreement with the structure shown in Fig. 2 for the *R*,*R* antipode of **3d** determined by DFT calculations, at the B3LYP/6-31G*

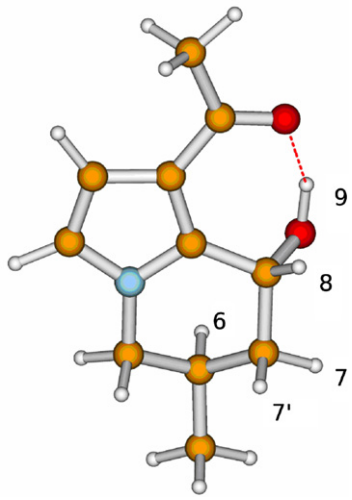


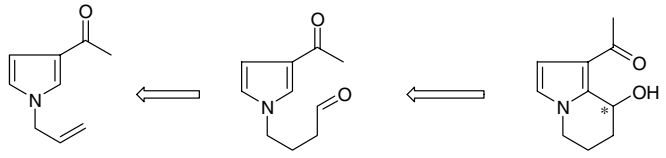
Fig. 2. B3LYP/6-31G* gas-phase optimized structure of **3d**.

level (Gaussian 03 system of programs), the geometry in the gas phase being fully relaxed.

It is noteworthy that quantum mechanical calculations indicate the two diastereomers (**3d** *RR*,*SS* and **3d** *RS*,*SR*) to have essentially the same thermodynamic stability; therefore, the complete diastereoselectivity of the reaction is likely to be due to the lower activation energy for the formation of the *R*,*R*; *S*,*S* diastereomer.

Interestingly, IR and ^{1}H NMR measurements strongly support the formation of an intramolecular hydrogen bond between the hydroxyl group and the acetyl group at the 3-position of the pyrrole ring. In principle, this hydrogen bond may be responsible for the unusual resistance of the hydroxyl group to dehydration under the experimental conditions, making **3d** a tricyclic stabilized structure. This is one of the few cases reported in the literature of complete 1,3-asymmetric induction under hydroformylation conditions [23].

Thus, when a simple allyl group is bonded to the nitrogen atom (Scheme 5), a tetrahydroindolizine with a sole chiral center susceptible of enantiodifferentiation under asymmetric catalysis is obtained [24].



Scheme 5.

5. Mechanistic aspects of the cyclization

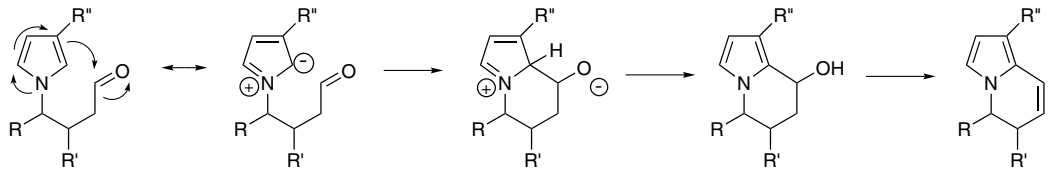
The key step of the reported sequences probably consists of an intramolecular electrophilic aromatic substitution promoted by the carbon atom of the carbonyl group on the electron-rich carbon atom C2 of the pyrrole ring. Then a bicyclic alcohol should form, which can either undergo water elimination to give a double bond conjugated with the pyrrole ring or be stabilized by an intramolecular hydrogen bond (Scheme 6), depending on the nature of substituent *R*″.

The cyclization of **2d** is likely to be rhodium-promoted. Indeed, a pure sample of **2d** does not cyclize when heated at high temperature for a long time in the absence of the rhodium catalyst; this last, likely acting as a Lewis acid, makes the carbonyl carbon atom more available for an electrophilic attack on the 2-pyrrole position allowing the intramolecular cyclization. In the case of **2a**–**c** the cyclization could be spontaneous owing to the absence of any electron-withdrawing group on the pyrrole ring.

6. Final remarks

In the context of our studies on the influence of substrate structure on hydroformylation selectivity, *N*-allylpyrroles have played, and still play, a crucial role. While vinylpyrroles "simply" hydroformylate with almost exclusive α-regioselectivity [25], *N*-allylpyrroles give rise to a domino process in which the linear aldehyde intermediate gives access to differently hydrogenated indolizines which are very important, biologically active compounds that are widespread in nature. It is known that the pyrrole α-carbon atoms are nucleophilic but we were the first to point out that these carbon atoms can attack an aldehyde carbonyl group. Another interesting aspect concerns the poor hydridic character of the hydrogen atoms bonded to the carbon adjacent to the nitrogen atom. This property undoubtedly accounts for the absence of substrate isomerization, even under drastic conditions (low pressure, high temperature). It is also responsible for the configurational stability of the substrate, the formation of only two aldehyde isomers, and the possibility of modulating the regioselectivity of the reaction itself.

Domino reaction sequences are of great interest because they enable the atom-economic formation of C–C bonds, thus providing relatively easy access to complex molecular architectures [26,23a]. In this light, and considering the importance of the indolizines as biologically



Scheme 6.

active compounds, the sequential hydroformylation/cyclization reported here promises to be a useful protocol for fine chemistry.

Acknowledgements

Financial support by MIUR – Programma di Ricerca Scientifica di Rilevante Interesse Nazionale is gratefully acknowledged. We thank Professor Martin A. Bennett, Australian National University, Canberra (Australia), for fruitful discussions.

References

[1] (a) J.P. Michael, Nat. Prod. Rep. 22 (2005) 603, and references cited therein;
(b) J.W. Daly, J. Med. Chem. 46 (2003) 445;
(c) E.W. Baxter, A.B. Reitz, J. Org. Chem. 59 (1994) 3175;
(d) L.M. Sinnot, Chem. Rev. 90 (1990) 1171;
(e) A.D. Elbein, R.J. Molyneux, in: S.W. Pelletier (Ed.), Alkaloids: Chemical and Biological Perspectives, vol. 5, Wiley, New York, 1987, p. 1;
(f) S. Leclerq, J.C. Braekman, D. Daloze, J.M. Pasteels, Prog. Chem. Org. Nat. Prod. 79 (2000) 115.

[2] (a) M. Bergauer, H. Huebner, P. Gmeiner, Tetrahedron 60 (2004) 1197;
(b) T. Lehmann, H. Huebner, P. Gmeiner, Bioorg. Med. Chem. Lett. 11 (2001) 2863;
(c) T. Lehmann, P. Gmeiner, Heterocycles 53 (2000) 1371;
(d) P. Gmeiner, J. Mierau, G. Hoefner, Arch. Pharm. (Weinheim) 325 (1992) 576;
(e) J.C. Carry, S. Mignani, Eur. Pat. Appl. EP 118 321, EP 147 317, EP 124 384, 1997;
(f) J.C. Carry, S. Mignani, French Appl. 2 539 417, 1997.

[3] A. Galbright, T. Small, R.A. Barnes, V. Boekelheide, J. Am. Chem. Soc. 83 (1961) 453.

[4] H. Carpio, E. Galeazzi, R. Greenhouse, A. Guzmán, S. Belaverde, Y. Antonio, F. Franco, A. Leon, V. Pérez, R. Salas, D. Valdés, J. Ackrell, D. Cho, O. Halpern, R. Koeeler, M.L. Maddox, J.M. Muchowski, A. Prince, D. Tegg, T.C. Thurber, A.R. van Horn, D. Wren, Can. J. Chem. 60 (1982) 2295.

[5] S. Mignani, C. Nemecek, PCT Int. Appl. WO 996 4419, 1998;
Chem. Abs. 132 (1999) 22870.

[6] J.C. Carry, S. Mignani, C. Nemecek, PCT Int. Appl. WO 982 5925, 1997;
Chem. Abs. 129 (1998) 81672.

[7] J.T. Kim, V. Gevorgyan, J. Org. Chem. 70 (2005) 2054.

[8] T. Peglow, S. Blechert, E. Steckhan, Chem. Eur. J. 4 (1998) 107.

[9] C.W. Ong, M.C. Lari, J.J. Jan, Y.A. Chang, Heterocycles 57 (2002) 1303.

[10] S.J. Pastine, S. Youn, D. Sames, Tetrahedron 59 (2003) 8859.

[11] A.R. Katrizky, C.N. Fali, J. Li, J. Org. Chem. 62 (1997) 4148.

[12] M. Movassaghi, A.E. Ondrus, Org. Lett. 7 (2005) 4423.

[13] R. Settambolo, G. Guazzelli, L. Mengali, A. Mandoli, R. Lazzaroni, Tetrahedron: Asymmetry 14 (2003) 2491.

[14] R. Settambolo, G. Guazzelli, A. Mandoli, R. Lazzaroni, Tetrahedron: Asymmetry 15 (2004) 1821.

[15] R. Lazzaroni, R. Settambolo, A. Caiazzo, Hydroformylation with unmodified rhodium catalysts, in: P. van Leeuwen, C. Claver (Eds.), Rhodium-Catalysed Hydroformylation, Kluwer CMC, Dortrecht, 2000, pp. 15–33.

[16] (a) L. Kollár, E. Farkas, J. Bâtiu, J. Mol. Catal. A 115 (1997) 283;
(b) C. Abu-Gnim, I. Amer, J. Organomet. Chem. 516 (1996) 235;
(c) I. Amer, H. Alper, J. Am. Chem. Soc. 112 (1990) 3674.

[17] R. Settambolo, A. Caiazzo, R. Lazzaroni, Tetrahedron Lett. 42 (2001) 4045.

[18] (a) T. Takahashi, S. Ebata, H. Yamada, Synlett 381 (1998);
(b) B. Breit, S.K. Zahn, J. Org. Chem. 66 (2001) 4870;
(c) B. Breit, S.K. Zahn, Tetrahedron Lett. 39 (1998) 1901.

[19] (a) A. Stefani, D. Tatone, P. Pino, Helv. Chim. Acta 59 (1976) 1639;
(b) P. Pino, S. Pucci, F. Piacenti, G. Dell' Amico, J. Chem. Soc. (C) 1640 (1971).

[20] (a) S.P. Bruekelman, S.E. Leach, G.D. Meakins, M.D. Tirel, J. Chem. Soc., Perkin Trans. I (1984) 2801;
(b) C. Kashima, T. Maruyama, Y. Fujioka, K. Harada, J. Chem. Soc., Perkin Trans. I (1989) 1041.

[21] (a) S.R. Angle, S.D. Belanger, J. Org. Chem. 69 (2004) 4361;
(b) X.-L. Hou, Y.-M. Luo, K. Yuan, L.-X. Dai, J. Chem. Soc., Perkin Trans. I (2002) 1487;
(c) A. Chesney, I.E. Marko, Synth. Commun. 20 (1990) 3167.

[22] R. Settambolo, S. Rocchiccioli, R. Lazzaroni, G. Alagona, Lett. Org. Chem. 3 (2006) 10.

[23] (a) B. Breit, Acc. Chem. Res. 36 (2003) 264, and references cited therein;
(b) B. Breit, W. Seiche, Synthesis (2001) 1.

[24] S. Rocchiccioli, R. Settambolo, R. Lazzaroni, J. Organomet. Chem. 690 (2005) 1866.

[25] R. Settambolo, A. Caiazzo, R. Lazzaroni, J. Organomet. Chem. 506 (1996) 337.

[26] P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B.E. Kitsos-Rzychon, C.L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, Chem. Rev. 99 (1999) 3329.