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Invited Review

Chromium(II)-based methods for carbon–carbon bond formation *

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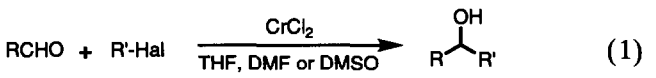
1. Introduction

Chromium(II)-based methods have been developed for a wide range of important carbon–carbon bond forming reactions [1]. The emphasis in this review is on the more significant methodological developments, common mechanistic themes and the most recent research. The main thrust of research in this area has been to develop reactions which have no counterpart in conventional organometallic chemistry, or which show increased chemo-, regio- and stereo-selectivity over known transformations. The review is organized according to the particular type of functional group that is reduced to an active organometallic agent. Much of the carbon–carbon bond forming reactions developed using chromium(II) chemistry can be broadly summarized as involving the coupling of an organic halide (or equivalent) with a carbonyl compound (eqn. (1)).



(1)

The carbonyl component is normally present *in situ*, because of the presumed instability of the intermediate organometallic species, and so the closest analogy with classical chemistry is found in the Barbier reaction [2]. The reducing power of chromium(II) salts is not as strong as with metals like Li, Mg and Zn, and some exquisite chemoselectivity with chromium(II) salts can be observed between different types of halide and exploited in synthesis. The usual source of chromium(II) is commercially available $CrCl_2$ although, less commonly, *in situ* reduction procedures from $CrCl_3$ have been applied. $CrCl_2$ does not generally reduce carbonyl groups to, for example alcohols or pinacols to any significant extent in the solvents in which these reactions are most often conducted, *i.e.* THF or DMF (in which $CrCl_2$ is a stronger reducing agent) [3]. Recently however, Stevenson *et al.* have reported that certain α,β-unsaturated aldehydes are converted directly to cyclopropanols when treated with $CrCl_2$ in DMF in the presence of small quantities of $NiCl_2$ [4].

A particular advantage inherent in using low-valent metal halides to generate organometallic species directly from organic halides, rather than by transmetallation from, for example, an organolithium and the metal(III) halide, relates to the greatly enhanced range of compatible functional groups allowed in the starting organic halide. The chemistry is ideally suited to intramolecular reactions where the halide and electrophilic site (usually a carbonyl group) are present in the same molecule. Chromium(II) salts are single electron transfer reducing agents in which the metal normally ends up in the +3 oxidation state at the end of the reaction. Therefore, to form an organochromium species, the stoichiometry of the reaction dictates that a minimum of two equivalents of the starting metal halide are required per halide atom removed from the organic component.

2. Allyl halides

Low-valent chromium salts have traditionally been widely used as reducing agents for a range of functional groups under aqueous conditions [5]. In 1976, Hiyama *et al.* in Japan first had the insight to examine the reduction of organic halides with $CrCl_2$ in aprotic solvents in the presence of a carbonyl compound, on

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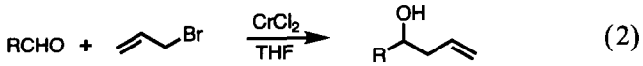
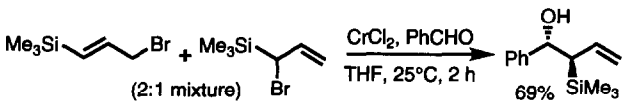
the basis that in the absence of water a transient organochromium intermediate might persist and undergo useful carbon–carbon bond forming reactions [6]. With allyl halides this has proven to be one of the most useful ways of preparing homoallyl alcohols (eqn. (2) [1]).



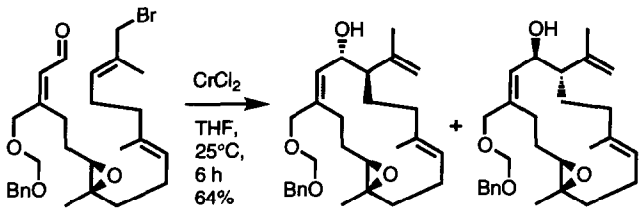
(2)

A wide variety of substituted allyl halides have since been examined. The reaction shows high chemoselectivity, for example, ester and cyano groups are tolerated in the coupling step, and aldehydes react preferentially in the presence of ketones. This chemoselectivity is a hallmark of most organochromium-mediated transformations. High regio- and stereo-selectivity is also evident in the coupling step. Reaction usually occurs through the most substituted end of the putative allylchromium species with high *anti* simple diastereoselectivity (*e.g.* eqn. (3) [7]).



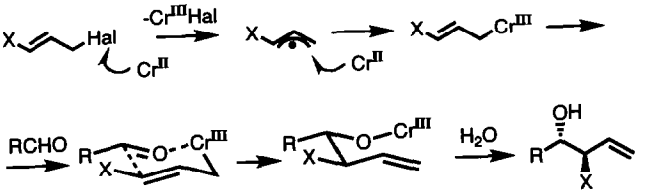
(3)

An example of the utility of this reaction, which exemplifies many of the points discussed so far, is Still's and Mobilio's elegant synthesis of the marine cembranoid antitumour agent Asperdiol (eqn. (4) [8]). Noteworthy aspects are the regio- and stereo-selectivity observed, and compatibility with the epoxide functional group which also serves to induce impressive diastereoselective macrocyclic conformational control in the cyclization. This example also ushered in the powerful strategy of intramolecular chromium(II)-mediated reactions.



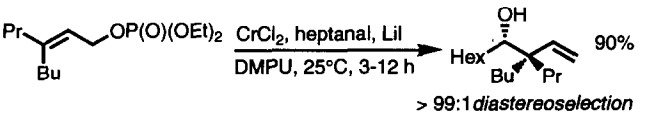
(4)

By comparison with Kochi's extensive mechanistic studies on the reduction of organic halides using chromium(II) salts in a mixture of an organic solvent and water [9], it seems likely that the formation of the allylchromium species in these reactions proceeds by halogen atom transfer to chromium(II) (an inner-sphere process) followed by rapid reduction of the intermediate allyl radical by a second chromium(II) species (eqn. (5)).



(5)

The high regio- and stereo-selectivity in the reaction of an allylchromium with an aldehyde has been explained by allylic transposition through a chair transition state in which the chromium atom is located at the least sterically demanding end of the allylic system. The aldehyde coordinates to the metal centre through the oxygen atom lone pair of electrons which is *trans* to the aldehyde R group [10] and this R group assumes an equatorial position to avoid interactions with ligands on the metal centre. The metal centre is likely to be hexa-coordinate, with the remaining four sites occupied by two halide ions and two solvent (usually THF) molecules or bridging halide ions from other chromium atoms. The γ-monosubstituted organochromium reagents usually react through the *E*-allyl organometallic form regardless of the starting alkene geometry [11]. It is also inconsequential which regioisomeric allyl halide is used as they both converge to the same product. This loss of stereo- and regio-chemical integrity could occur at the allyl radical stage and/or by η^1–η^3 interconversion at the organochromium stage. Interestingly, recent work by Knochel *et al.* indicates that 3,3-dialkyl substituted allylchromium reagents retain geometrical integrity in the coupling step (eqn. (6) [12]).

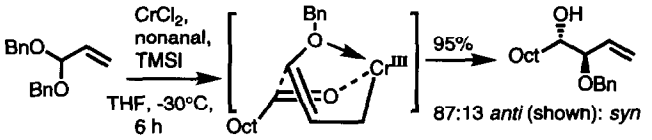


(6)

As the two alkyl groups have similar steric and electronic demands, there will be little preference for one allyl radical or organochromium. For these 3,3-disubstituted allyl systems, reduction of the allyl radical is faster than isomerization and also reaction of the resulting allylchromium with an aldehyde is faster than η^1-η^3 interconversion.

Whilst normal *anti* simple diastereoselectivity is observed with acrolein dialkyl acetals, these results have been explained by a boat transition state with alkoxy-coordination to the metal centre in the allylchromium (eqn. (7) [13]). A similar coordination has been invoked

to explain stereoselectivity in the reaction of 1,4-diene monoepoxides (eqn. (8) [14]).



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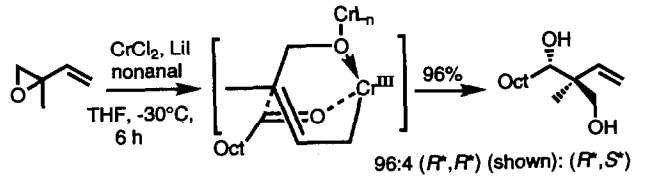
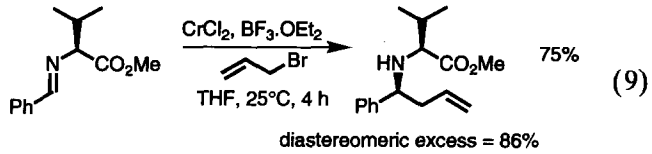


(8)

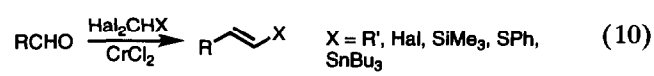
Tadei *et al.* have recently shown that allylchromiums can also be induced to react with imines if BF_3 is present [15]. Simple diastereoselectivity was poor with crotylchromiums, however a promising diastereomeric excess was observed with allylchromium and the imine derived from benzaldehyde and (*S*)-valine (eqn. (9)).



(9)

3. *Gem*-dihalides

Whilst the homologation of aldehydes to *E*-1,2-difunctionalized alkenes can often be accomplished using Wittig-type chemistry, certain substitution patterns are impossible to prepare using this strategy. In addition, the stereoselectivity obtained may not be satisfactory or functional groups elsewhere in the starting aldehyde may not be tolerated in the coupling step. For these cases, *gem*-dichromium reagents derived from *gem*-dihalides have provided some useful solutions [1]. *E*-1,2-Dialkyl-substituted alkenes, alkenyl halides, sulphides, silanes and stannanes can all be prepared using this chemistry, usually with good-to-excellent *E*-stereoselectivity (eqn. (10)). 1,2-Addition is observed with α,β-unsaturated aldehydes, however stereoselectivity for the *E*-isomer is usually slightly lower than that seen with aliphatic and aromatic aldehydes. The reactions have found widespread use in natural product synthesis [16].



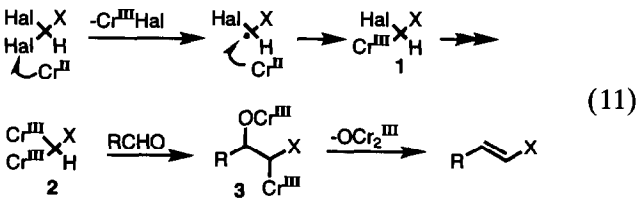
(10)

The *E*-1,2-dialkyl-substituted alkenes prepared using this chemistry require *gem*-diiodides [17] or 1-acetoxy-1-bromides [18] to partner the aldehyde. The reactions are generally run in THF; small quantities of DMF are often added to facilitate reductive removal of the halogen atoms and sonication has also been used in difficult cases. Yields are usually excellent (80–95%). *E* : *Z* Stereoselection is in the region of 90 : 10 to 95 : 5.

The conditions used to prepare alkenyl halides depend upon the specific halide required [19]. This reaction is the most popular of the chromium-mediated olefination procedures and is most often used to prepare alkenyl iodides because of the greater reactivity of the carbon–iodine bond for subsequent reactions. Alkenyl iodides are prepared in good yields (70–90%, with stereoselectivity (85 : 15–95 : 5) dependent on the nature of the aldehyde) using iodoform with $CrCl_2$ in THF. Stereoselectivity can be enhanced using 1,4-dioxane as a co-solvent [20].

Alkenyl silanes are produced exclusively as the *E*-isomers from aldehydes and $Br_2CHSiMe_3$ in THF in good yields (70–85%) [21]. Alkenyl stannane formation uses $CrCl_2$ with $Br_2CHSnBu_3$ and requires LiI and additional DMF as a co-solvent with the THF [22].

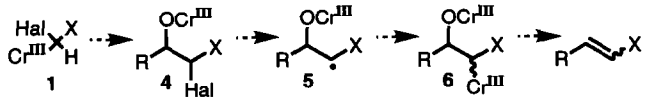
Mechanistically, the reactions are thought to proceed *via* two successive halogen atom transfers [9] to $CrCl_2$ where the intermediate radicals are immediately reduced to give ultimately a *gem*-dichromium species **2** which adds to the aldehyde to give **3** (eqn. (11)). β-Elimination from **3** then occurs to provide predominantly or exclusively the *E*-alkene.



(11)

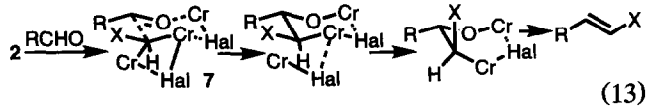
As alkylchromium reagents are known to add to aldehydes (Section 5), one may question the intermediacy of *gem*-dichromium reagents and instead consider it possible that addition of the intermediate **1** to an aldehyde occurs to give the alkoxide **4** (eqn. (12)). Halogen atom transfer from the alkoxide **4** to chromium(II) would then be followed by trapping of the intermediate radical **5** by another chromium(II) species to give **6**. However, deoxygenations of both *E*- and *Z*-2-butene epoxides with chromium complexes gave the same *E* : *Z* ratio of 2-butene (~ 55 : 45) [23], and treatment of 1,1-diiodo-2-tridecanol with $CrCl_2$ produced a 1 : 1 mixture of *E*- and *Z*-1-iodo-1-tridecenes [19]. As these reactions are likely to proceed through intermediates **5** and **6** (R = X = Me for 2-butene preparation; $R = C_{11}H_{23}$, X = I for 1-iodo-1-tridecene preparation), it follows that *E*-alkene forma-

tion is not inherently favoured in the β-elimination step, but must be dependent on the relative *vic*-stereochemistry in **6**. That is, the carbon–chromium linkage in **6** is sufficiently stable to maintain stereochemical integrity until stereospecific β-elimination occurs. This β-elimination is likely to be a *syn* process [23]. The $E:Z$ alkene ratio is then dependent on stereoselectivity in the addition of a particular *gem*-dichromium species to an aldehyde.



(12)

Given the importance of bridging halide ions in chromium chemistry [5], a reasonable mechanism for the olefination reaction is shown in eqn. (13). The minor *Z*-alkene arises from a less favourable transition state **7** (X and H interchanged).

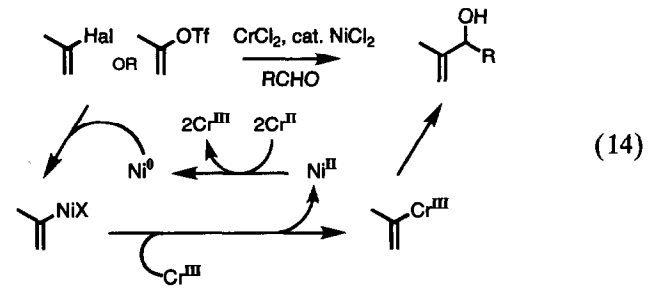


(13)

A remaining question relates to the lack of reaction between the monoalkyl chromium intermediate **1** and an aldehyde. It seems that the stability of the halide-substituted monoalkylchromium **1** renders it a poor species to react with an aldehyde and activation as the *gem*-dichromium reagent is required.

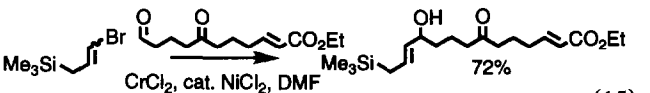
4. Alkenyl and aryl halides (and enol triflates)

Activation of the (sp^2)C–Hal bond and (sp^2)C–O bond of enol triflates for reaction with an aldehyde using $CrCl_2$ requires DMF or DMSO as a solvent and trace amounts of a nickel(II) or palladium(II) catalyst [24]. The mechanistic cycle that has been suggested for this process is shown in eqn. (14).



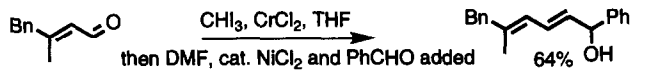
(14)

The reaction has found extensive application in natural product synthesis. Kishi in particular [25] has used the reaction to dramatic effect in the landmark syntheses of Palytoxin, the Halichondrins (in which *five* of the key C–C bonds were constructed using this chemistry [26]) and more recently towards the taxane class of anticancer agents [27]. A recent example of this type of reaction, which illustrates the excellent chemoselectivity often found in organochromium-mediated processes, is found in the elegant approach of Parsons *et al.* towards the histrionicotoxins (eqn. (15) [28]).



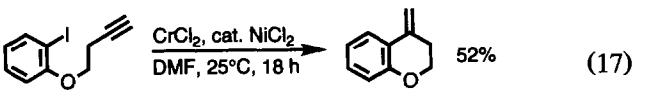
(15)

The different conditions required to activate *gem*-dihalides and alkenyl halides using $CrCl_2$ can be exploited in 'one-pot' syntheses of allyl alcohols [19] and have been applied in a model study towards the dienyl alcohol unit of the maytansinoids (eqn. (16) [29]). Iodoform functions as a methine trianion in the reaction sequence.



(16)

Recently, the $CrCl_2$-mediated $NiCl_2$-catalysed method of (sp^2)C–Hal bond activation has been extended to carbometallation reactions (eqns. (17) and (18) [30]).



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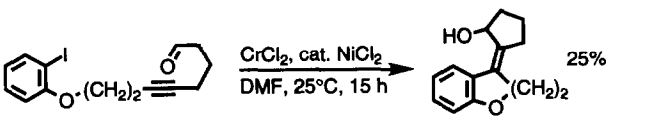


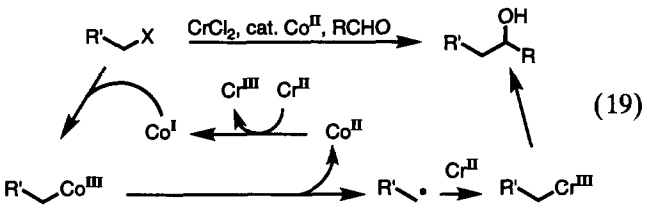
(18)

Mechanistically, the tandem cyclization process (eqn. (18)) could proceed *via* oxidative addition into the C–I bond by a nickel(0) (or nickel(I)) species, followed by intramolecular *syn*-arylnickelation of the triple bond prior to transmetallation to chromium(III) (or chromium(II)) with retention of geometry and then attack on the pendant electrophilic aldehyde. Conceptually, the metal 'switch', which allows a carbometallation followed by an intramolecular reaction with an aldehyde, complements Heck-style chemistry where the reaction can be terminated by an organic 'anion' (or hydride) *via* transmetallation from, for example, an organostannane [31].

5. Alkyl halides

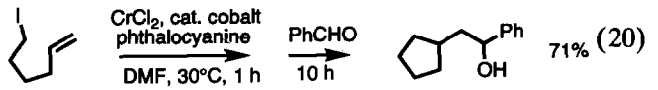
Alkyl halides (and tosylates) can be coupled with aldehydes using $CrCl_2$ in DMF under Co catalysis

(eqn. (19) [32]). The reaction has been postulated as passing through an organocobalt intermediate which cleaves to an alkyl radical.



(19)

Support for this process is found in an elegant tandem carbon–carbon bond-forming process (eqn. (20)) which can be envisaged as proceeding *via* 5-exo-trig radical cyclization, and reduction of the resulting new radical to an alkylchromium prior to coupling to an aldehyde. The sequencing of free-radical steps and organometallic chemistry in a single operation is likely to be a rich source of tandem C–C bonding forming reactions in the future [33].



71% (20)

Acknowledgements

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References and notes

1 Previous reviews: P. Cintas, *Synthesis*, (1992) 248; N.A. Saccomano, in B.M. Trost and I. Fleming (eds.), *Comprehensive Organic Synthesis*, Vol. 2, Pergamon Press, Oxford, 1991, p. 173; K. Utimoto and K. Takai, *J. Synth. Org. Chem. Jpn., 48* (1990) 962; K. Takai and K. Utimoto, *J. Synth. Org. Chem. Jpn., 46* (1988) 66.
2 C. Blomberg and F.A. Hartog, *Synthesis*, (1977) 18.
3 THF: S. Nakatsukasa, K. Takai and K. Utimoto, *J. Org. Chem., 51* (1986) 5045; DMF: see footnote e in Table I in ref. 32.
4 D. Montgomery, K. Reynolds and P. Stevenson, *J. Chem. Soc., Chem. Commun.*, (1993) 363.
5 J.R. Hanson, *Synthesis*, (1974) 1.
6 Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc., 99* (1977) 3179.
7 D.M. Hodgson and C. Wells, *Tetrahedron Lett., 33* (1992) 4761.
8 W.C. Still and D. Mobilio, *J. Org. Chem., 48* (1983) 4785.
9 J.K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, New York, 1978, p. 138.
10 M.T. Reetz, M. Hüllmann, W. Massa, S. Berger, P. Rademacher and P. Heymanns, *J. Am. Chem. Soc., 108* (1986) 2405.
11 T. Hiyama, Y. Okude, K. Kimura and H. Nozaki, *Bull. Chem. Soc. Jpn., 55* (1982) 561.
12 C. Jubert, S. Nowotny, D. Kornemann, I. Antes, C.E. Tucker and P. Knochel, *J. Org. Chem., 57* (1992) 6384.
13 K. Takai, K. Nitta and K. Utimoto, *Tetrahedron Lett., 29* (1988) 5263.
14 O. Fujimura, K. Takai and K. Utimoto, *J. Org. Chem., 55* (1990) 1705.
15 M. Giammaruco, M. Taddei and P. Ulivi, *Tetrahedron Lett., 34* (1993) 3635.
16 Recent examples: D.A. Evans, H.P. Ng and D.L. Rieger, *J. Am. Chem. Soc., 115* (1993) 11446; K.C. Nicolaou, P. Bertinato, A.D. Piscopio, T.K. Chakraborty and N. Minowa, *J. Chem. Soc., Chem. Commum.*, (1993) 619.
17 T. Okazoe, K. Takai and K. Utimoto, *J. Am. Chem. Soc., 109* (1987) 951.
18 M. Knecht and W. Boland, *Synlett*, (1993) 837.
19 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc., 108* (1986) 7408.
20 D.A. Evans and W. Cameron Black, *J. Am. Chem. Soc., 115* (1993) 4497. See also ref. 16.
21 K. Takai, Y. Kataoka, T. Okazoe and K. Utimoto, *Tetrahedron Lett., 28* (1987) 1443.
22 D.M. Hodgson, *Tetrahedron Lett., 33* (1992) 5603; D.M. Hodgson, L.T. Boulton and G.N. Maw, *Tetrahedron Lett., 35* (1994) 2231.
23 J.K. Kochi and D.M. Singleton, *J. Am. Chem. Soc., 90* (1968) 1582.
24 H. Jin, J. Uenishi, W.J. Christ and Y. Kishi, *J. Am. Chem. Soc., 108* (1986) 5644; K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto and H. Nozaki, *J. Am. Chem. Soc., 108* (1986) 6048.
25 Y. Kishi, *Pure. Appl. Chem., 64* (1992) 343.
26 T.D. Aicher, K.R. Buszek, F.G. Fang, C.J. Forsyth, S.H. Jung, Y. Kishi, M.C. Matelich, P.M. Scola, D.M. Spero and S.K. Yoon, *J. Am. Chem. Soc., 114* (1992) 3162.
27 M.H. Kress, R. Ruel, W H. Miller and Y. Kishi, *Tetrahedron Lett., 34* (1993) 5999; *34* (1993) 6003.
28 P.J. Parsons, R. Angell, A. Naylor and E. Tyrell, *J. Chem. Soc., Chem. Commun.*, (1993) 366.
29 D.M. Hodgson, PhD Thesis, University of Southampton, 1989.
30 D.M. Hodgson and C. Wells, *Tetrahedron Lett., 35* (1994) 1601.
31 E. Negishi, Y. Noda, F. Lamaty and E.J. Vawter, *Tetrahedron Lett., 31* (1990) 4393; B. Burns, R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson and T. Worakun, *Tetrahedron, 48* (1992) 7297 and refs. therein.
32 K. Takai, K. Nitta, O. Fujimura and K. Utimoto, *J. Org. Chem., 54* (1989) 4732.
33 D.P. Curran, T.L. Fevig, C.P. Jasperse and M.J. Totleben, *Synlett*, (1992) 943.