Recent progress in cobalt-mediated [2 + 2 + 2] cycloaddition reactions

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For many years, our research group has been interested in the new developments of cobalt-mediated cyclizations. In this article, our recent achievements in the field of inter- and intramolecular [2 + 2 + 2] cyclizations are compiled.

Introduction

Since the discovery of benzene formation by thermal cyclization of three molecules of acetylene by Berthelot[1] and the pioneering work of Reppe in transition metal-mediated cyclizations,[2] catalysts based on no less than seventeen early to late transition metals have been developed for the cyclotrimerization of acetylenic compounds. In addition to alkynes, a large variety of other unsaturated partners such as alkenes, nitriles, aldehydes, ketones, imines, isocyanates, isothiocyanates, *etc.*[3] can take part in related cyclizations to give products with four-, five-, six- or eight-membered rings. Many of these cyclizations proceed with good chemo-, regio- and stereoselectivities and have found applications in the synthesis of complex polycyclic molecules. In the last three decades, this reaction has been extensively investigated and the topic has been thoroughly reviewed.[4]

Among all the available catalysts, cobalt complexes have proved versatile reagents for the selective formation of multiple carbon–carbon bonds in a single chemical step.[5] Numerous applications of cobalt-catalyzed cyclizations have been reported by Vollhardt and co-workers, who achieved very elegant and efficient total syntheses of various natural products and compounds of theoretical interest.[6]

For many years, our research group has also been interested in the development of new cobalt-mediated transformations. We anticipated that the potential of cobalt catalysis could be spectacularly displayed by designing cascade reactions aimed at the preparation of complex and highly functionalized molecules starting from simple acyclic polyunsaturated precursors.[7] In this article, we wish to review our recent achievements in the field of [2 + 2 + 2] cycloadditions involving alkynes, alkenes and new unsaturated partners. We will focus on the chemo- and regioselectivity of the cyclizations and their applications in synthesis.

Cyclotrimerization of alkynes

Contribution to the chemo- and the regioselectivity

The selective synthesis of polysubstituted benzenes and pyridines from intermolecular transition metal-catalyzed [2 + 2 + 2] cycloaddition reactions is a challenging problem. Indeed, the cyclotrimerization of a single monosubstituted alkyne

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Vincent Gandon

Vincent Gandon was born in Soissons, France. He obtained his PhD in 2002 from the University of Champagne-Ardennes, Reims under the supervision of Professor Jan Szymoniak (zirconium-mediated organic transformations). After a one year post-doctoral stay in the group of Professor Guy Bertrand in Riverside, California, he joined the laboratory of Professor Max Malacria in Paris as an Assistant Professor, working in collaboration with Dr C. Aubert. His main research interests are the development of new synthetic methods using group 9 transition metals and boron chemistry.

Corinne Aubert was born in Les Ardennes, France. After having studied chemistry at the University of Champagne-Ardennes, Reims, she attended the Ecole Nationale Supérieure de Chimie de Strasbourg. She received her PhD in 1985 under the supervision of Drs J. F. Biellmann and J. P. Bégué from the University of Paris-Sud, Orsay. She was appointed by the CNRS in 1985 as Chargée de Recherches in the laboratory of Dr J. P. Bégué and worked on fluorine chemistry. After doing two years of postdoctoral research at the University of California, Berkeley with Professor K. P. C. Vollhardt, she joined the team of Professor Max Malacria at the Université Pierre et Marie Curie, Paris. In 2001, she was appointed Directeur de Recherches. Her research interests concern new developments in transition metal-mediated cyclizations and applications in synthesis, asymmetric catalysis and boron chemistry.

Corinne Aubert

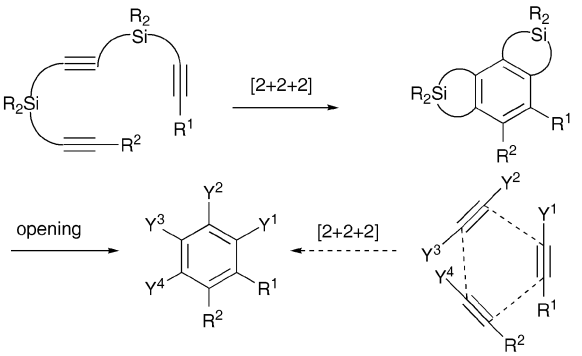
usually leads to regioisomeric 1,2,4- and 1,3,5-trisubstituted benzenes. Moreover, the cyclization of two different monosubstituted alkynes may give up to nine isomers, and that of three monosubstituted alkynes up to 38 different ones. A few methods have been proposed to overcome this crucial issue, but despite their impressive efficiency, these strategies remain restricted to specific cases.[8–11] For instance, a calixarene bound titanium complex allowed the highly selective cyclization of monosubstituted alkynes into 1,2,4-trisubstituted benzenes.[9] Chemoselective assembly of terminal alkynes with DMAD *via* iridium and ruthenium catalysis was also reported, yet with moderate levels of regioselectivity.[10] Although limited to 1,2-diynes, the palladium-catalyzed homodimerization of terminal alkynes and subsequent [4 + 2] benzannulation gave tetra- and pentasubstituted benzenes from three different alkynes with excellent levels of regio- and chemoselectivity.[11] Stepwise strategies involving stoichiometric amounts of zirconium and titanium complexes were also proposed for the selective formation of benzenes and pyridines.[12] In the cobalt series, examples remain rare and specific. For instance, Sugihara *et al.* reported that methylidynetricobalt nonacarbonyl is able to catalyze the cyclotrimerization of phenylacetylene with total regioselectivity.[13]

In this context, we proposed an unusual approach to the [2 + 2 + 2] cycloaddition of alkynes based on the use of disposable linkers.[14] The formal chemo- and regioselective intermolecular [2 + 2 + 2] cyclizations of three different alkynes were achieved *via* the judicious implementation of a temporary silylated tether (TST).[15] The general concept is presented in Scheme 1.

Under refluxing conditions, visible light irradiation and in the presence of 5 mol% of η^5-cyclopentadienyldicarbonyl cobalt [$CpCo(CO)_2$], silicon-tethered triynes **1** and **3** led to the corresponding cycloadducts **2** and **4** in good yields, regardless of the steric hindrance induced by the *iso*-propyl groups at the internal triple bond and of the substitution of the external triple bonds (Scheme 2).[16] Displacement of the silylated

Max Malacria

Max Malacria was born in 1949 in Marseille, France. He obtained his PhD from the University of Aix-Marseille III with Professor Marcel Bertrand in 1974. He was appointed Assistant in 1974 at the University of Lyon I with Professor J. Goré. After almost two years as a post-doctoral fellow with Professor K. P. C. Vollhardt at Berkeley, he went back to the University of Lyon as a Maître de Conférences in 1983. In 1988, he was appointed Full Professor at the UPMC. In 1991, he was elected junior member of the Institut Universitaire de France and promoted to senior member in 2001. His research interests include the development of new domino processes in both organometallic and radical chemistry, and applications in the synthesis, asymmetric synthesis and new stereoselective reactions involving heteroelements and platinum-catalyzed reactions.

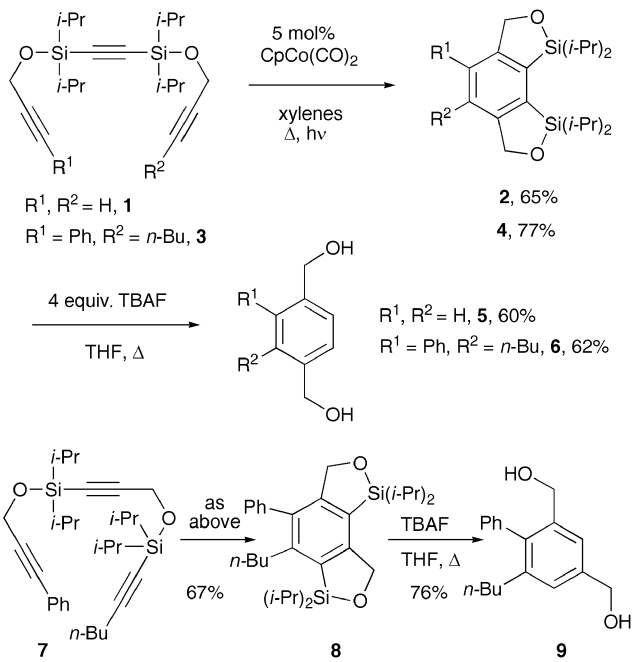


Scheme 1

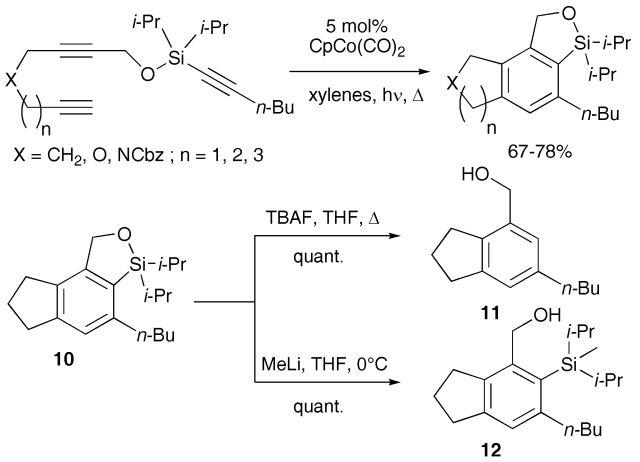
moieties was achieved using 4 equiv. of TBAF, giving diols **5** and **6** in *ca.* 60% yield. Similarly, cyclotrimerization of unsymmetrical triyne **7** followed by protodesilylation afforded diol **9** in 51% yield over the two steps.

This overall sequence led to di- or tetrasubstituted benzenes, formally arising from the cyclotrimerization between two molecules of propargyl alcohol and a third alkyne unit, which in the case of **5**, would be acetylene itself. In contrast, direct reactions between propargyl alcohol and alkynes gave us intractable mixtures of all feasible benzenic derivatives.

The reaction of silicon-tethered α,ω-diynes and alkynes also gave the corresponding cycloadducts in good yields (Scheme 3). The opening of the silylated ether was achieved either with TBAF or methyllithium to deliver quantitatively the bicyclic benzenic derivatives **11** and **12**, which formally originate from the totally chemo- and regioselective bimolecular [2 + 2 + 2] cyclizations between octa-2,7-diyne-1-ol and hex-1-yne or 1-((di-isopropyl)methyl)silylhexyne, respectively.



Scheme 2 Cyclization of silylated tethered triynes and displacement of silicon.



Scheme 3 Formal bimolecular [2 + 2 + 2] cyclotrimerization of α,ω-diynes with alkyne.

Synthetic applications: access to the taxane framework by sequential [2 + 2 + 2]/[4 + 2] cycloadditions

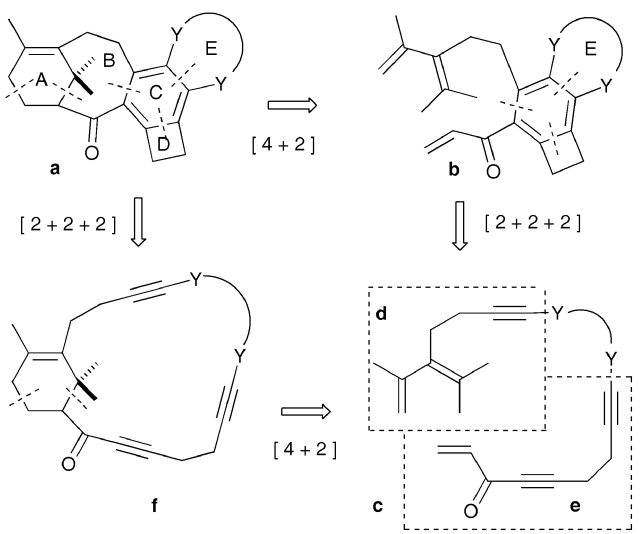
Our interest in the development of cobalt-mediated [2 + 2 + 2] cyclizations for synthetic purposes brought us to develop reaction cascades. We disclosed some years ago that cobalt(I) complexes catalyze formal Alder ene reactions of allenynes and enynes[17], and also Conia ene type reactions of ω-acetylenic β-ketoesters to form functionalized methylenecyclopentanes in a stereocontrolled manner.[18] After designing new polyunsaturated substrates, we combined these reactions with cyclotrimerizations, [4 + 2] cyclizations, or Pauson–Khand reactions, and proposed different approaches to the basic skeletons of natural tetracyclic diterpenes of the phyllocladane, kaurane and triquinane families.[19] Recently, we investigated stereoselective routes to the ABC core of taxane, starting from simple acyclic polyunsaturated precursors.

In the past ten years, taxane diterpenoids have been one of the most challenging synthetic targets due to their unique structural features as well as their considerable therapeutic potential.[20] The taxane framework **a**, depicted in Scheme 4, exhibits an aryl C-ring, an all-carbon D-ring and an additional E-ring. We reasoned that this skeleton could be obtained from an intramolecular [4 + 2] cycloaddition of triene **b**. The benzocyclobutene unit of **b** could arise from the [2 + 2 + 2] cyclization of the three alkyne units of enyne **c**. The link between both unsaturated moieties **d** and **e** could be either an alkylated or silylated tether, which might ensure the chemo- and the regioselectivity (*vide supra*).

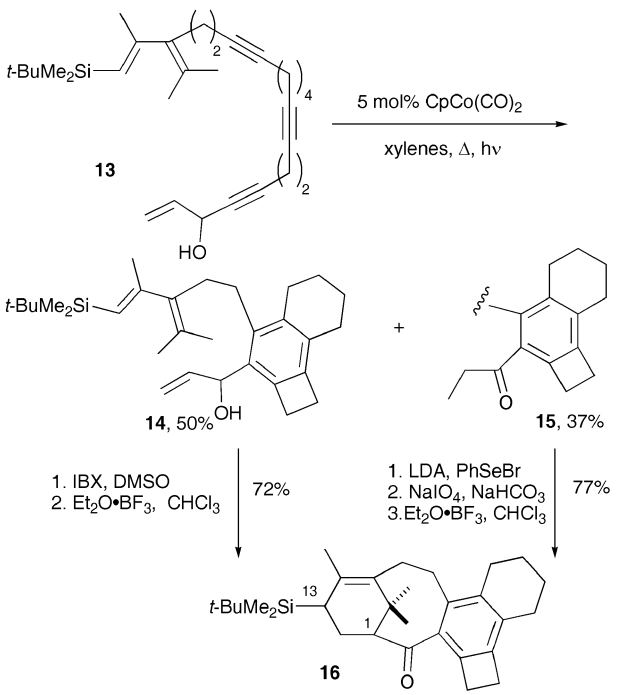
We first tried the sequential [2 + 2 + 2] and then [4 + 2] approach to the core of taxanes.[21] Compound **13**, which displays a *tert*-butyldimethylsilyl group, was submitted to standard [2 + 2 + 2] cyclization conditions. The presence of a sterically demanding substituent at the terminal position of the 1,3-butadiene moiety was revealed as necessary to avoid the competitive formation of cyclohexadienes.

Benzocyclobutenes **14** and **15** were obtained in 50 and 37% yield, respectively (Scheme 5). Compound **15** probably arose from a 1,3-migration of the double bond leading to an enol, which subsequently undergoes tautomerization to give the corresponding ketone. Despite this unexpected side reaction, both tautomers could be efficiently transformed into the same compound. The oxidation of **14** was carried out using IBX, and [4 + 2] cyclization was then promoted by $Et_2O{\cdot}BF_3$, leading to the formation of pentacycle **16** as a single diastereomer of unidentified stereochemical configuration. On the other hand, compound **15** was oxidized *via* selenation–oxidation–elimination and converted in good yield into **16**, as above.

The presence of the additional alkylated E-ring precludes further functionalization of the aromatic C-ring. In order to obtain an intermediate with latent functionalities, we carried out the TST strategy. Besides, so as to avoid the 1,3-migration, the monosubstituted double bond was removed.



Scheme 4 Retrosynthetic approach to the ABC core of taxoids.



Scheme 5 [2 + 2 + 2]/[4 + 2] approach to the ABC core of taxoids.

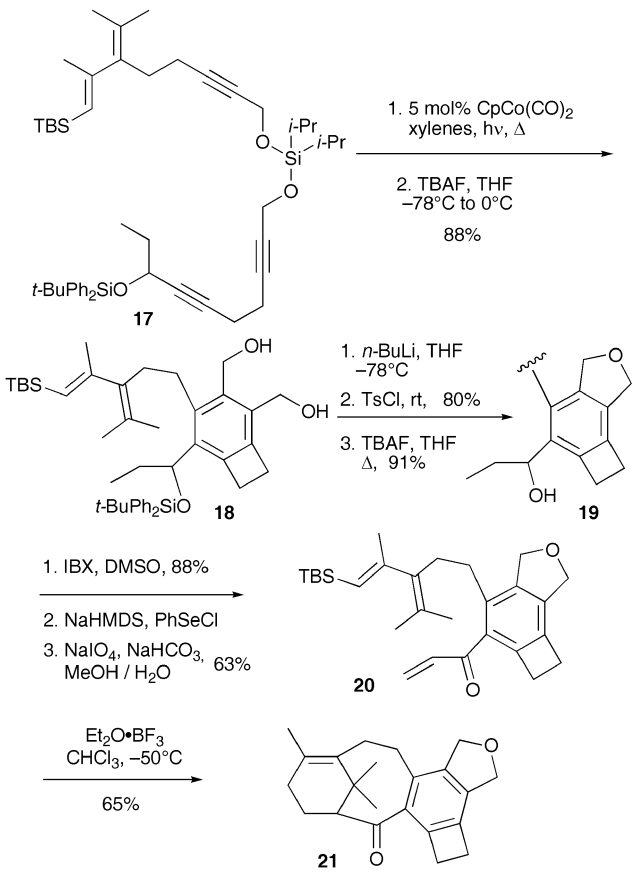
Polyunsaturated precursor **17**, which exhibits a di-*iso*-propylsilaketal linker, was submitted to the reaction sequence depicted in Scheme 6.

[2 + 2 + 2] Cyclization followed by fluoride-mediated desilylation furnished the corresponding diol **18** in 88% overall yield. After the protection of the diol, deprotection of the silylether, oxidation of the resulting alcohol into the ketone and its transformation into enone **20**, the Diels–Alder reaction was carried out as above, affording cycloadduct **21**, desilylated at C13, in 65% yield. This unexpected protodesilylation should not be troublesome because an allylic oxidation, leading to the alcohol precursor of the lateral chain of the taxoid, could be envisaged. Thus, the [2 + 2 + 2]/[4 + 2] approach to the core of taxoids was validated successfully. The functionalization of the aromatic C-ring of product **21** is now under investigation.

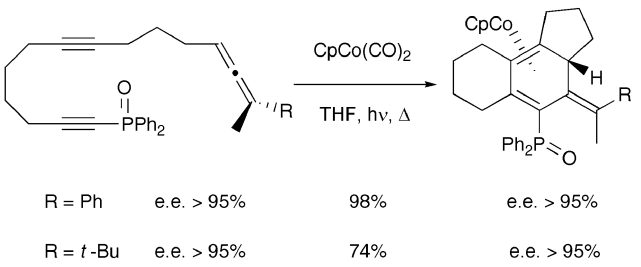
[2 + 2 + 2] cyclizations with new unsaturated partners

Allenediynes and their application to the synthesis of steroid skeletons

We previously reported that allenes are relevant partners for intramolecular [2 + 2 + 2] cocyclizations leading to alkynes. For instance, upon treatment with $CpCo(CO)_2$, allenediynes of yne–yne–allene type furnished the corresponding cycloadducts in high yields and in a completely chemo-, regio- and diastereoselective manner. Moreover, with optically-active



Scheme 6 Access to the taxane framework *via* the use of the silaketals.



Scheme 7 [2 + 2 + 2] Cyclizations of allenediynes of yne–yne–allene type.

allenes, the process can be performed with a total transfer of chirality (Scheme 7).[22]

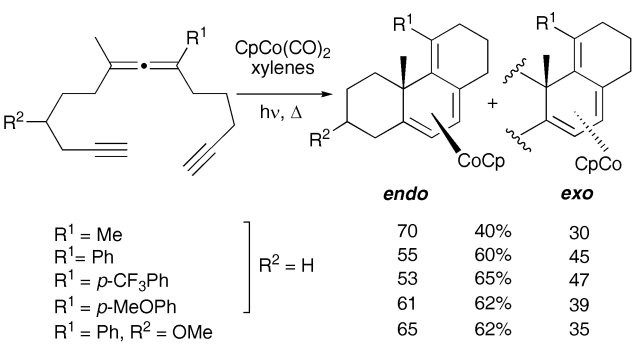
Although still chemo- and regioselective, the cyclization of yne–allene–yne compounds showed moderate to low diastereoselectivities. η^4-Complexed tricyclic (6,6,6) compounds were obtained in moderate to good yield as mixtures of *endo*/*exo* diastereomers that are independent of the substitution on the allene. The cyclization is also compatible with an oxy-functionality at C3 (Scheme 8).

Nevertheless, the resulting free ligands of the cyclizations may be regarded as constituting the BCD and ABC moieties of steroids, prompting us to explore the feasibility of building steroid frameworks starting from a judiciously-substituted allenediyne.

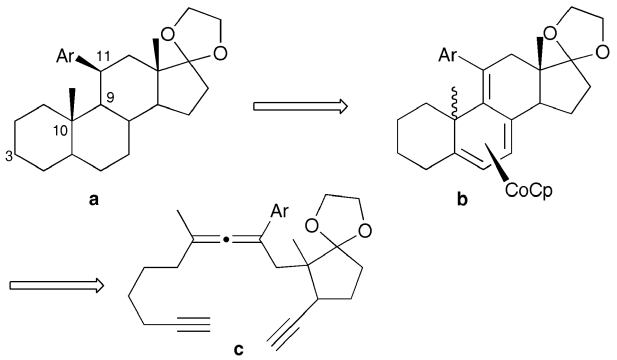
In the past 20 years, a new class of antiprogestational steroids that present an 11β-aryl unit have emerged due to their relevant pharmacological properties. However, the synthesis of such steroids still needs the development of new synthetic methods.

The strategy depicted in Scheme 9 would allow the creation in one step of the ABC ring system, and most interestingly, the simultaneous introduction of substituents at both C11 and C10. Indeed, tetracyclic complex **b** could be reached from the intramolecular [2 + 2 + 2] cyclization of allenediyne **c**, incorporating a pre-existing D-ring. Subsequent transformations of **b** might lead to 11β-aryl steroid **a**. At least for the time being, no oxygenated function has been introduced at C3.

We observed that, depending on the stereochemical relationship (*cis* or *trans*) between the ethynyl group on the five-membered ring and the chain incorporating the allene, two different trends occurred in the cobalt(I)-mediated



Scheme 8 [2 + 2 + 2] Cyclizations of allenediynes of yne–allene–yne type.

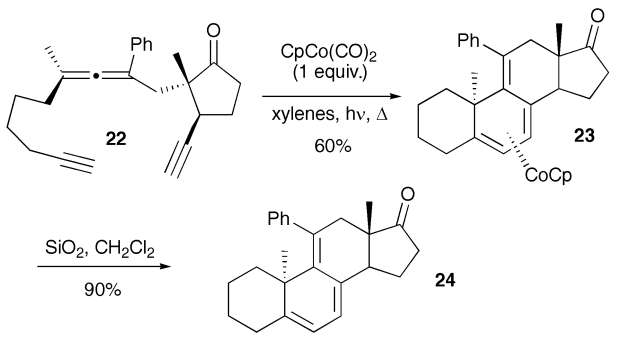


Scheme 9 Retrosynthetic approach to 11β-aryl steroid frameworks.

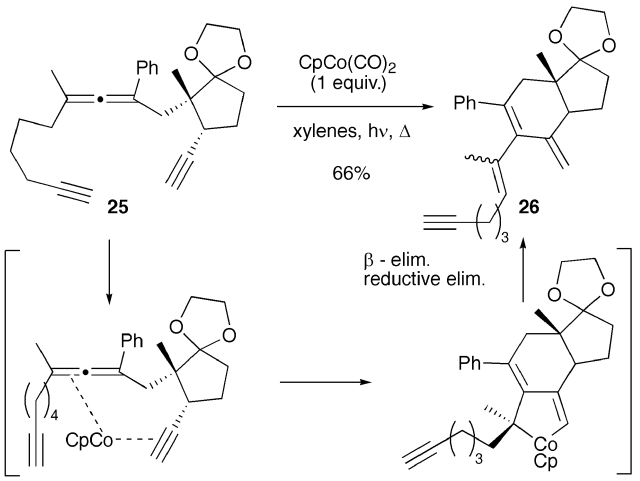
cyclizations.[23] If *trans*, the allenediyne **22** in the presence of a stoichiometric amount of $CpCo(CO)_2$ in boiling xylenes under irradiation gave the expected fused tetracyclic complex **23** in 60% yield as a single diastereomer. The structure of **23** was established by a single crystal X-ray analysis which showed an *endo* stereochemistry between CpCo and the vicinal methyl group, and a *trans* relationship between the two angular methyl groups (Scheme 10). The free ligand **24** could be readily obtained in 90% yield upon treatment of complex **23** with silica gel. The cyclization and decomplexation sequence could also be carried out without purifying the complex and allowed the formation of the 11β-aryl steroid skeleton in 48% overall yield. Functionalization of either complex **23** or the free ligand **24** are being investigated.

In contrast, allenediyne **25**, which displays a *cis* relationship between the ethynyl group on the five-membered ring and the allenic chain, furnished the bicyclic yne-trienic compound **26** in 66% yield under the same experimental conditions (Scheme 11).

This compound results from a formal Alder ene reaction between the ethynyl group and the double bond of the allene bearing the methyl group. Such an Alder ene reaction, which had already been observed by our group,[17] occurs competitively with the [2 + 2 + 2] cyclization when the latter is disfavored for geometrical reasons. In the present case, molecular models show that, on the contrary to **22**, both of these unsaturated moieties can be easily brought closer together, thus allowing a straightforward complexation to cobalt. After oxidative coupling, β-elimination followed by reductive elimination furnished compound **26**.



Scheme 10

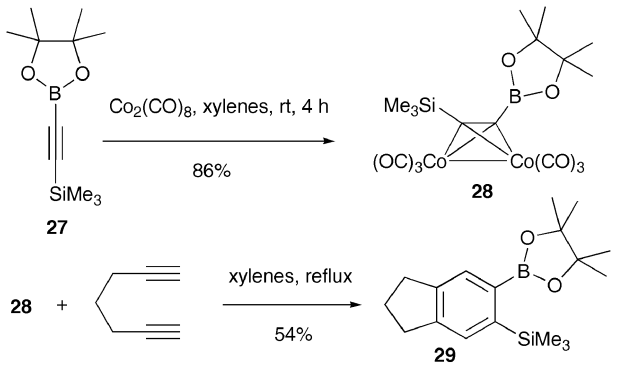


Scheme 11

Alkynyl boronic esters: synthesis of fused arylboronic esters and diboryl-1,3-cyclohexadienes

Introduction of main group heteroelements to unsaturated partners such as olefins, acetylenes, allenes and 1,3-dienes may have a dramatic influence on the product distribution of the cycloadditions.[24] For instance, they can control the chemo- and regioselectivities. Besides, they can confer kinetic stabilization and allow the preparation of structural moieties which would be hardly accessible in the unsubstituted series. They can be replaced under electrophilic substitution conditions and thus be considered as latent functional groups. Of particular interest are the substrates incorporating group 13 or 14 heteroatoms, such as boron, silicon, germanium or tin. These elements can provide useful disposable tethers (*vide supra*) or give rise to transition metal-mediated couplings. Cycloadditions and cycloisomerizations of alkynylboranes lead to compounds of synthetic value, in which the newly formed C_{sp^2}–B bond can be subjected to coupling reactions[25] or to the plethora of known functional group transformations.[26] We will now focus on our recent contribution in this area.

The synthesis of arylboronic esters is usually accomplished by metal–halogen exchange of haloarenes followed by the addition of trialkoxyborates.[27] However, this strategy is not compatible with many functional groups, and to address this issue, new methods involving alkynylboronic esters have been developed. In this respect, the Dötz benzannulation with Fischer carbenes allows the preparation of quinone boronic esters.[28] Siebert *et al.* have shown that alkynyl catechol, thiocatechol and dithiocatechol boronic esters undergo facile catalytic cyclotrimerization with $Co_2(CO)_8$ or $CpCo(CO)_2$, giving 1,2,4- and 1,3,5-triborylbenzene derivatives, and up to hexaborylbenzene when starting from diborylacetylenes.[29] On the other hand, under the same experimental conditions, we found that alkynyl pinacol boronic esters did not give cyclotrimerization adducts. They instead proved to be much better candidates for cocyclization reactions such as the cobalt(0)-mediated [2 + 2 + 2] cycloaddition with α,ω-diynes.[30] Mixing the borylalkynes, such as **27**, with a stoichiometric amount of cobalt carbonyl in xylenes at room temperature led

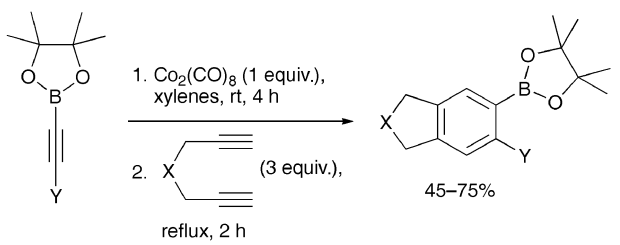


Scheme 12 Preparation of pinacolboryldicobaltatetrahedrane complex and its cocyclization with α,ω-diyne.

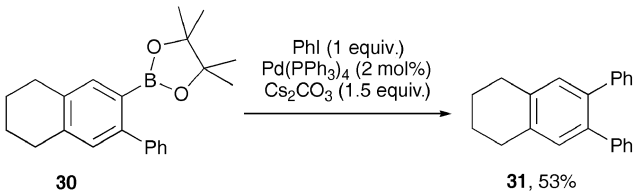
to the corresponding dicobaltatetrahedrane derivatives **28** in good yields after column chromatography (Scheme 12). Treatment of complex **28** (1 equiv.) with 1,6-heptadiyne (1 equiv.) in refluxing xylenes gave the cycloadduct **30** in an isolated yield of 50%.

Because the dicobaltatetrahedrane complexes derived from our substrates proved to be very light sensitive and therefore hard to handle, we decided to avoid their isolation and to treat them *in situ* with α,ω-diynes, leading to the results compiled in Scheme 13. Using this sequence, an excess of diyne is needed to reach the same yields as those obtained in the stepwise procedure. Unreacted cobalt–carbonyl might be responsible for some depletion of diyne by oligomerization, affecting the yields of the cycloaddition reaction. Alkyl-, aryl- and silyl-substituted alkynylboronic esters were successfully converted into arylboronates by following this one-pot procedure: A xylenes solution of $Co_2(CO)_8$ is added all at once to the alkyne in the same solvent. The dark solution is stirred in the absence of light until no more CO evolution is visible. The neat diyne is then added and the mixture refluxed until the conversion is complete. The product is then purified by column chromatography on silica gel. In this way, a variety of indan, tetralin and benzocycloheptene derivatives become accessible starting from 1,6-hepta-, 1,7-octa- and 1,8-nonadiyne.

To demonstrate the utility of the products, compound **30** was treated with phenyl iodide in the presence of 2 mol% of $Pd(PPh_3)_4$ to furnish the cross-coupling product **31** in an unoptimized 53% yield (Scheme 14).



Scheme 13 One-pot procedure for the preparation of fused arylboronic esters.

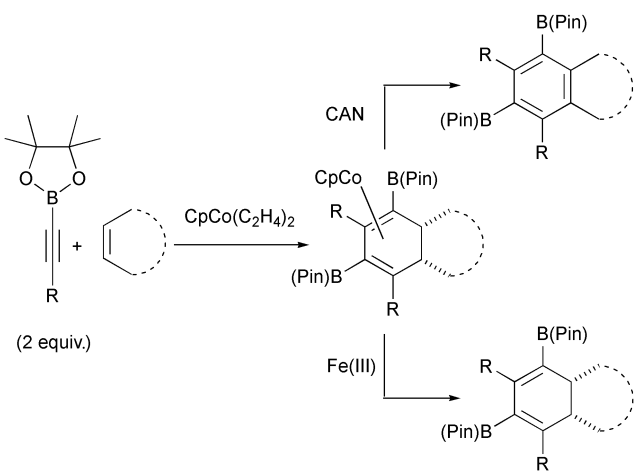


Scheme 14

Recently, and complementary to our investigations, the [2 + 2 + 2] cocyclotrimerization of tethered alkynylboronic esters with alkynes catalyzed by Ru(II) was reported by Yamamoto and co-workers.[31] In this work, the product arylboronates could not be isolated but were converted directly by Suzuki–Miyaura coupling reactions. The synthesis of bi- and tricyclic arylboronates *via* Ru(II)-catalyzed cycloaddition of α,ω-diynes to alkynylboronates was also accomplished by the same team. Because internal alkynes proved to be inefficient substrates for such cyclizations, this reaction was limited to ethynylboronates.[32]

In addition to this novel one-pot method for the preparation of arylboronic esters *via* the Co(0)-mediated cycloaddition of alkynylboronates to α,ω-diynes, we also performed Co(I)-mediated [2 + 2 + 2] cycloadditions of alkynyl boronates to alkenes.[33] This strategy, which proved compatible with various substrates, allowed the rapid and efficient construction of highly functionalized 1,3-cyclohexadienes and arenes after oxidative demetallation (Scheme 15). Extensive chemo-, regio- and diastereoselective assembly of mono-, bi- and tricyclic 1,3- and 1,4-diboryl-1,3-cyclohexadienes was accomplished by means of the CpCo-mediated cycloaddition of alkynyl pinacolboronates to alkenes. The method produces a rapid entry route to highly functionalized 1,3-cyclohexadiene synthons of potential use in complex molecule synthesis.

Alkenylboranes are useful intermediates for the preparation of a wide range of important organic molecules. Specifically, mono- and diborylated 1,3-dienes have found various applications as dienylation reagents,[34] Diels–Alder partners[35] and in the synthesis of α,β- or γ,δ-unsaturated ketones.[36] Their cyclic counterparts, namely boryl-1,3-cyclohexadienes, were

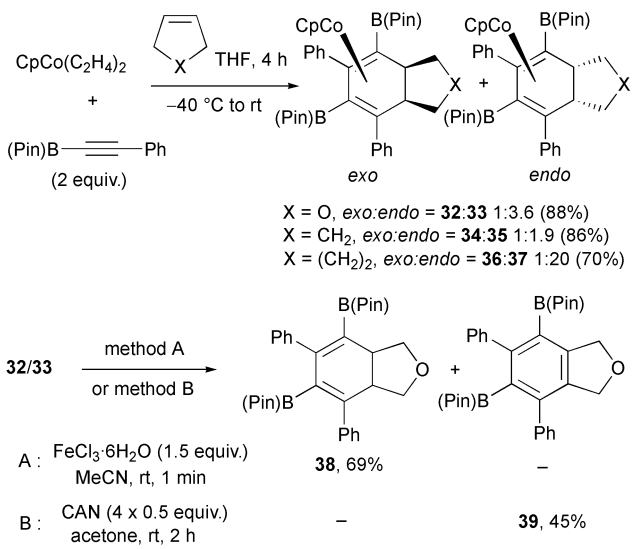


Scheme 15

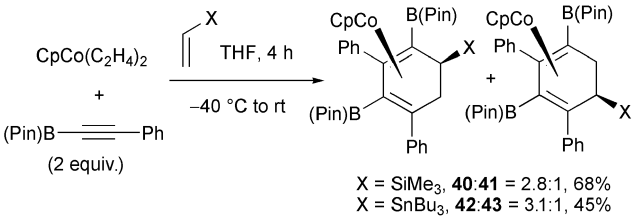
unreported. Considering that the 1,3-cyclohexadiene nucleus is a key sub-unit of many natural and/or biologically active compounds, including those of the didehydroretinol and -carotene families,[37] borylated 1,3-cyclohexadienes constitute valuable reagents by which to introduce this synthon directly. The latter task had been accomplished in the past by using 1,3-cyclohexadienyl–metals,[38] –triflates,[39] or –phosphates,[40] but these reagents had to be generated in several steps from enolizable cyclohexenone derivatives, and the methodology has not been applied to dimetallated 1,3-cyclohexadienes. Our strategy allowed us to prepare 1,3- and 1,4-diboryl-1,3-cyclohexadienes regioselectively. The success of the present study was predicated by the employment of η^5-cyclopentadienylbis(ethene)cobalt,[41] which has previously been exploited as an active source of CpCo for the cooligomerization of alkynes with alkenes.[6] With 2,5-dihydrofuran, cyclopentene and cyclohexene, the reactions proceeded completely regioselectively in very good overall yields, with moderate to excellent stereoselectivity (Scheme 16). In all cases, the *endo* diastereomer was favored (**33**, **35** and **37**). The free dienes could be liberated through rapid oxidative demetallation using iron(III) chloride in acetonitrile. For instance, both complexes **32** and **33** furnished the same cyclohexadiene **38** after treatment with $FeCl_3 \cdot 6H_2O$. Aromatization was accomplished, albeit in only moderate yields so far, using ceric ammonium nitrate, either starting from the free ligand or directly from the complex. In that respect, **32** and **33** were converted into arene **39** in 45% yield.

Terminal alkenes revealed interesting stereo- and regioselectivities (Scheme 17). For instance, a preference for placing the substituted ethene carbon adjacent to the boron-bearing terminus was found with vinyltrimethylsilane and vinyl(tributyl)tin, respectively. The stereochemistry of addition was exclusively *exo*, an outcome that is most likely to be of steric origin.

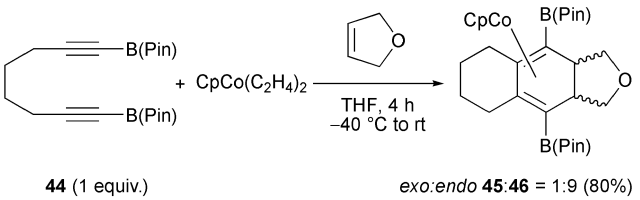
The scope of the reaction was expanded to the cycloaddition of various α,ω-diboryldiynes to alkenes (Scheme 18). These substrates enforced the 1,4-orientation of the boryl substituents in the resulting diene and granted access to the first



Scheme 16



Scheme 17



Scheme 18

polycyclic 1,4-diborylcyclohexa-1,3-diene derivatives. The reactions proceeded in good yield and, in the case of **44**, with high stereoselectivity, boding well for its synthetic application to more complex structures.

Thus, the cyclization of alkynyl pinacolboronates to alkenes produces a rapid entry into highly functionalized 1,3-cyclohexadiene synthons of potential use in complex molecule synthesis. Applications of such syntheses and the mechanistic rationale for the selective outcome of these cyclizations are being investigated.

Conclusions

Over the last few years, we have made continuous contributions to the development of cobalt-mediated [2 + 2 + 2] cyclizations and have tried to solve the chemo- and regioselective problems of the cyclotrimerization reactions of alkynes. By using temporary silylated tethers, we could efficiently produce di- or tetrasubstituted benzenic derivatives starting from up to three different unsymmetrical alkynes. This TST strategy allowed us to propose a rapid entry route to the core of taxanes starting from acyclic polyunsaturated precursors by combining a cobalt(I)-catalyzed cyclotrimerization and a Diels–Alder reaction. The resulting pentacyclic compounds exhibit latent functionalities for further transformations.

We have also expanded the arsenal of unsaturated partners which can be involved in these cyclizations. Allenes are relevant partners for intramolecular cycloadditions to alkynes. Depending on the position in the chain and the substitution of the allene, different patterns can be prepared. By carefully designing an allenediyne having a pre-existing D-ring, we succeeded in building skeletons of steroids in one step, with the simultaneous introduction of an angular methyl group at C10 and an aryl substituent at C11.

Finally, pinacol alkynylboronates have been revealed as exciting unsaturated partners in such cyclizations. We have developed a novel one-pot method for the synthesis of fused arylboronic esters *via* the Co(0)-mediated cycloadditions of alkynylboronates to α,ω-diynes. We have also described extensively the chemo-, regio- and diastereoselective assembly

of mono-, bi- and tricyclic 1,3- and 1,4-diboryl-1,3-cyclohexadienes by means of the CpCo-mediated cycloaddition of alkynyl pinacolboronates to alkenes. We believe that the synthetic applications of this newly developed cyclization will be very fruitful.

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Notes and references

1 M. Berthelot and C. R. Hebd, *C. R. Hebd. Seances Acad. Sci.*, 1866, **62**, 905.
2 W. Reppe and W. J. Schweckendiek, *Justus Liebigs Ann. Chem.*, 1948, **560**, 104.
3 N. E. Schore, *Chem. Rev.*, 1988, **88**, 1081; N. E. Schore, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, Oxford, 1991, vol. **5**, pp. 1129; D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone, G. Wilkinson and L. Hegedus, Pergamon Press, Oxford, 1995, vol. **12**, pp. 741; D. F. Harvey, B. M. Johnson, C. S. Ung and K. P. C. Vollhardt, *Synlett*, 1989, 15; J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787; H. A. Duong, M. J. Cross and J. Louie, *J. Am. Chem. Soc.*, 2004, **126**, 11438; Y. Yamamoto, H. Takagishi and K. Itoh, *J. Am. Chem. Soc.*, 2002, **124**, 28.
4 M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635; S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; Y. Yamamoto, *Curr. Org. Chem.*, 2005, **9**, 503; S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741.
5 K. P. C. Vollhardt, *Acc. Chem. Res.*, 1977, **10**, 1; K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 536; M. Malacria, C. Aubert and J. L. Renaud, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. M. Lautens and B. M. Trost, Georg Thieme Verlag, Stuttgart, 2001, vol. **1**, pp. 439.
6 K. P. C. Vollhardt, *Pure Appl. Chem.*, 1985, **57**, 1819; E. J. Johnson and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1991, **113**, 381; J. Germanas, C. Aubert and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1991, **113**, 4006; M. J. Eichberg, R. L. Dorta, D. B. Grotjahn, K. Lamottke, M. Schmidt and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 2001, **123**, 9324; D. L. Mohler and K. P. C. Vollhardt, in *Advances in Strain in Organic Chemistry*, ed. B. Halton, JAI Press, London, 1996, pp. 121; S. Han, A. D. Bond, R. L. Disch, D. Holmes, J. M. Schulman, S. J. Teat, K. P. C. Vollhardt and G. D. Whitener, *Angew. Chem., Int. Ed.*, 2002, **41**, 3223; S. Kumaraswamy, S. S. Jalisatgi, A. J. Matzger, O. S. Miljanic and K. P. C. Vollhardt, *Angew. Chem., Int. Ed.*, 2004, **43**, 3711 and pertinent references cited therein.
7 M. Malacria, *Chem. Rev.*, 1996, **96**, 289.
8 K. Tanaka, K. Toyoka, A. Wada, K. Shirasaka and M. Hirano, *Chem.–Eur. J.*, 2005, **11**, 1145; S. Saito, T. Kawasaki, N. Tsuboya and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 796; N. Mori, S.-i. Ikeda and K. Odashima, *Chem. Commun.*, 2001, 181; Y. Yamamoto, T. Arakawa, R. Ogawa and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143.
9 O. V. Ozerov, B. O. Patrick and F. T. Ladipo, *J. Am. Chem. Soc.*, 2000, **122**, 6423.
10 R. Takeuchi and Y. Nakaya, *Org. Lett.*, 2003, **5**, 3659; Y. Ura, Y. Sato, M. Shiotsuki, T. Kondo and T.-a. Mitsudo, *J. Mol. Catal. A: Chem.*, 2004, **209**, 35.
11 V. Gevorgyan, U. Radhakrishnan, A. Takeda, M. Rubina, M. Rubin and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 2835; M. Rubin, A. W. Sromek and V. Gevorgyan, *Synlett*, 2003, 2265.
12 T. Takahashi, *Pure Appl. Chem.*, 2001, **73**, 271; T. Takahashi, Y. Li, T. Ito, F. Xu, K. Nakajima and Y. Liu, *J. Am. Chem. Soc.*, 2002, **124**, 1144; D. Suzuki, H. Urabe and F. Sato, *J. Am. Chem. Soc.*, 2001, **123**, 7925; D. Suzuki, K. Tanaka, H. Urabe and F. Sato, *J. Am. Chem. Soc.*, 2002, **124**, 3518.
13 T. Sugihara, A. Wakabayashi, Y. Nagai, H. Takao, H. Imagawa and M. Nishizawza, *Chem. Commun.*, 2002, 576.
14 Several reviews have compiled different aspects of the chemistry of silicon linkers, see: M. Bols and T. Skrydstrup, *Chem. Rev.*, 1995, **95**, 1253; L. Fensterbank, M. Malacria and S. M. Sieburth, *Synthesis*, 1997, 813; D. R. J. Gauthier, K. S. Zandi and K. J. Shea, *Tetrahedron*, 1998, **54**, 2289; T. Skrydstrup, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. I. Fleming, Georg Thieme Verlag, Stuttgart, 2001, vol. **4**, pp. 439; J. D. White and R. G. Carter, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. I. Fleming, Georg Thieme Verlag, Stuttgart, 2001, vol. **4**, pp. 371. Concerning the [2 + 2 + 2] cyclization, Eckenberg and Groth described the preparation of 1,9,10-trihydroxyoctahydroanthracene, which represents the ABC core of many anthracyclin antibiotics. Prior to the cobalt-mediated [2 + 2 + 2] cyclization, a diyne and an alkene were connected through a TST, which was cleaved afterwards either by oxidation or hydrolysis, see: P. Eckenberg and U. Groth, *Synlett*, 2003, 2188.
15 G. Chouraqui, M. Petit, C. Aubert and M. Malacria, *Org. Lett.*, 2004, **6**, 1519.
16 M. Petit, G. Chouraqui, C. Aubert and M. Malacria, *Org. Lett.*, 2003, **5**, 2037.
17 D. Llerena, C. Aubert and M. Malacria, *Tetrahedron Lett.*, 1996, **37**, 7027; D. Llerena, C. Aubert and M. Malacria, *Tetrahedron Lett.*, 1996, **37**, 7353.
18 R. Stammler and M. Malacria, *Synlett*, 1994, 92; P. Cruciani, R. Stammler, C. Aubert and M. Malacria, *J. Org. Chem.*, 1996, **61**, 2699.
19 P. Cruciani, C. Aubert and M. Malacria, *J. Org. Chem.*, 1995, **60**, 2664; P. Cruciani, C. Aubert and M. Malacria, *Synlett*, 1996, 105; J. L. Renaud, C. Aubert and M. Malacria, *Tetrahedron*, 1999, **55**, 5113.
20 D. G. I. Kingston, *Chem. Commun.*, 2001, 867 and references therein.
21 M. Petit, G. Chouraqui, P. Phansavath, C. Aubert and M. Malacria, *Org. Lett.*, 2002, **4**, 1027.
22 D. Llerena, O. Buisine, C. Aubert and M. Malacria, *Tetrahedron*, 1998, **54**, 9373; O. Buisine, C. Aubert and M. Malacria, *Synthesis*, 2000, 985.
23 M. Petit, C. Aubert and M. Malacria, *Org. Lett.*, 2004, **6**, 3937.
24 V. Gandon, C. Aubert and M. Malacria, *Curr. Org. Chem.*, 2005, **9**, 1699.
25 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; N. Miyaura, *Top. Curr. Chem.*, 2002, **219**, 11; N. Miyaura in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, vol. **1**, pp. 41.
26 For representative examples, see: C. Thiebes, G. K. Surya Prakash, N. A. Petasis and G. A. Olah, *Synlett*, **1998**, 141; K. S. Webb and D. Levy, *Tetrahedron Lett.*, 1995, **36**, 5117; T. D. Quach and R. A. Batey, *Org. Lett.*, 2003, **5**, 4397.
27 M. Vaultier and B. Carboni, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon Press, Oxford, 1995, vol. **11**, pp. 191.
28 M. W. Davies, C. N. Johnson and J. P. A. Harrity, *J. Org. Chem.*, 2001, **66**, 3525.
29 A. Maderna, H. Pritzkow and W. Siebert, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1501; C. Ester, A. Maderna, H. Pritzkow and W. Siebert, *Eur. J. Inorg. Chem.*, 2000, 1177; Y. Gu, H. Pritzkow and W. Siebert, *Eur. J. Inorg. Chem.*, 2001, 373; A. Goswami, C.-J. Maier, H. Pritzkow and W. Siebert, *Eur. J. Inorg. Chem.*, 2004, 2635.

30 V. Gandon, D. Leca, T. Aechtner, K. P. C. Vollhardt, M. Malacria and C. Aubert, *Org. Lett.*, 2004, **6**, 3405.
31 Y. Yamamoto, J.-i. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2004, **126**, 3712; Y. Yamamoto, J.-i. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 9625; Y. Yamamoto, J.-i. Ishii, H. Nishiyama and K. Itoh, *Tetrahedron*, 2005, **61**, 11501.
32 Y. Yamamoto, K. Hattori, J.-i. Ishii, H. Nishiyama and K. Itoh, *Chem. Commun.*, 2005, 4438.
33 V. Gandon, D. Leboeuf, S. Amslinger, K. P. C. Vollhardt, M. Malacria and C. Aubert, *Angew. Chem., Int. Ed.*, 2005, **44**, 7114.
34 A. B. Smith, G. K. Friestad, J. Barbosa, E. Bertunesque, J. J.-W. Duan, K. G. Hull, M. Iwashima, Y. Qiu, P. G. Spoors and B. A. Salvatore, *J. Am. Chem. Soc.*, 1999, **121**, 10478; S. A. Frank and W. R. Roush, *J. Org. Chem.*, 2002, **67**, 4316; G. N. Maw, C. Thirsk, J.-L. Toujas, M. Vaultier and A. Whiting, *Synlett*, 2004, 1183.
35 G. Hilt and P. Bolze, *Synthesis*, 2005, 2091 and references cited therein.
36 A. Hassner and J. A. Soderquist, *J. Organomet. Chem.*, 1977, **131**, C1; G. Zweifel, M. R. Najafi and S. Rajagopalan, *Tetrahedron Lett.*, 1988, **29**, 1895; G. Desurmont, S. Dalton, D. M. Giolando and M. Srebnik, *J. Org. Chem.*, 1996, **61**, 7943 and references therein.
37 For representative examples, see: M. B. Ksebati and F. J. Schmitz, *J. Org. Chem.*, 1985, **50**, 5637; R. D. Dawe and J. L. C. Wright, *Tetrahedron Lett.*, 1986, **23**, 2559; X. Fu, E. P. Hong and F. J. Schmitz, *Tetrahedron*, 2000, **56**, 8989.
38 E. Piers and H. E. Morton, *J. Org. Chem.*, 1979, **44**, 3437; E. J. Corey and H. Kigoshi, *Tetrahedron Lett.*, 1991, **32**, 5025; K. Morihira, T. Nishimori, H. Kusama, Y. Horiguchi, I. Kuwajima and T. Tsuruo, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2977; K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama and I. Kuwajima, *J. Am. Chem. Soc.*, 1998, **120**, 12980; S. Aoyagi, R. Tanaka, M. Naruse and C. Kibayashi, *J. Org. Chem.*, 1998, **63**, 8397.
39 A. S. E. Karlström, M. Rönn, A. Thorarensen and J.-E. Bäckvall, *J. Org. Chem.*, 1998, **63**, 2517.
40 A. S. E. Karlström, K. Itami and J.-E. Bäckvall, *J. Org. Chem.*, 1999, **64**, 1745.
41 K. Jonas, E. Deffense and D. Habermann, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 716; J. K. Cammack, S. Jalisatgi, A. J. Matzger, A. Negron and K. P. C. Vollhardt, *J. Org. Chem.*, 1996, **61**, 4798.