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Applications of organocopper reagents in organic synthesis

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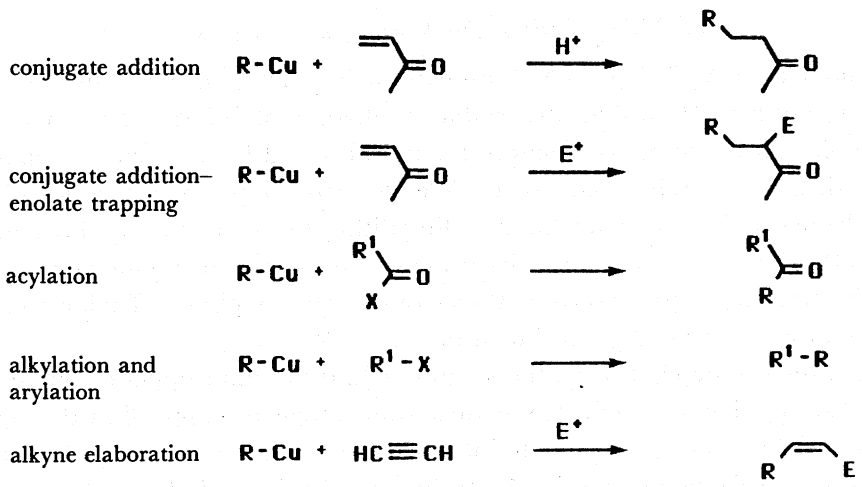
The importance of organocopper reagents in organic synthesis is highlighted and the different types of organocopper reagents available are briefly reviewed. Applications of organocopper reagents in the synthesis of natural products and related compounds of biological interest are then discussed commencing with synthetic approaches to thia-thromboxane analogues based on the organocopper conjugate addition–enolate alkylation reaction. The extension of this methodology to the preparation of 2,3-disubstituted cyclopentenones, illustrated by the synthesis of the antimicrobial natural product, tetrahydrodicranenone B, is then discussed. Finally, synthetic applications of the organocopper alkyne addition reaction are described with emphasis on the use of double acetylene carbocupration for the stereospecific preparation of *Z,Z*-dienes. The use of this methodology for the synthesis of the Navel Orangeworm pheromone is discussed.

1. Introduction

Organometallic reagents are invaluable in organic synthesis, particularly for carbon–carbon bond forming reactions. 'Organocopper reagents' (Posner 1980; Normant 1972, 1976, 1978; Jukes 1974; Erdik 1984; Lipshutz *et al.* 1984*b*; Alexakis *et al.* 1984; Yamomoto 1986; Lipshutz 1987) are particularly useful for conjugate addition (Posner 1972), conjugate addition–enolate trapping (Taylor 1985; Suzuki *et al.* 1985; Suzuki & Noyori 1984), alkylation, arylation, acylation (Posner 1975) and alkyne elaboration (Normant & Alexakis 1981) reactions as illustrated in scheme 1.



Scheme 1. Carbon–carbon bond forming reactions with organocopper reagents.

The term 'organocopper reagent' ('RCu') is used to encompass all copper-containing organometallic preparations ranging from copper-catalysed Grignard reagents to higher-order organocuprates, as shown in table 1. For simplicity, the stoichiometric formulae of the various 'organocopper reagents' have been employed in table 1 and throughout this paper, although the actual structures of 'organocopper reagents' are considerably more complex (Bertz & Gibson 1986; Lipshutz *et al.* 1984*a*, 1985; Hope *et al.* 1985; Pearson & Gregory 1976). Table 1 also includes outline preparative details; full experimental procedures are readily found in the literature cited. It should be emphasized that it is often necessary to try a range of organocopper reagents and/or experimental conditions to optimize the yield for a particular conversion.

TABLE 1. TYPES OF ORGANOCOPPER REAGENT

copper-catalysed Grignard reagents	$RMgX + z\ \%\ CuX$
organocopper reagents	$RM + CuX \rightarrow RCu$
homocuprate reagents	$2RM + CuX \rightarrow R_2CuM$
mixed homocuprate reagents	$RM + CuR^1 \rightarrow RR^1CuM$
heterocuprate reagents	$RM + CuZ \rightarrow RCu(Z)M$
higher-order cuprates, e.g.	$2RM + CuCN \rightarrow R_2Cu(CN)M_2$

R = alkyl, aryl, vinyl, etc. RM is usually RLi or RMgX. CuX is usually CuI or CuBr.SMe_2. R^1Cu is often 1-pentynylcopper. CuZ is usually CuCN or CuSPh. Ether or THF are usually used as solvents. Reactions usually carried out at −78 °C to 0 °C under N_2 or Ar. Solubilizing ligands (e.g. Me_2S or Bu_3P) are often added. Addition of Me_3SiCl or BF_3 often enhances reactivity.

The synthetic utility of organocopper reagents has been extensively demonstrated by a large number of research groups over the past 20 or so years. The aim of this paper is to describe some recent research with organocopper reagents carried out at the University of East Anglia, starting with the use of the organocopper conjugate addition reaction for the synthesis of sulphur-containing analogues of thromboxane A_2.†

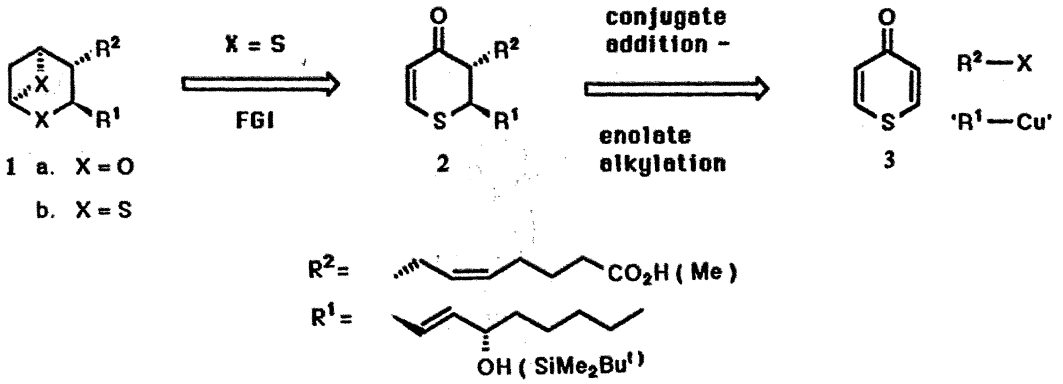
2. ORGANOCOPPER CONJUGATE ADDITION REACTIONS

(*a*) *The synthesis of thiathromboxane analogues*

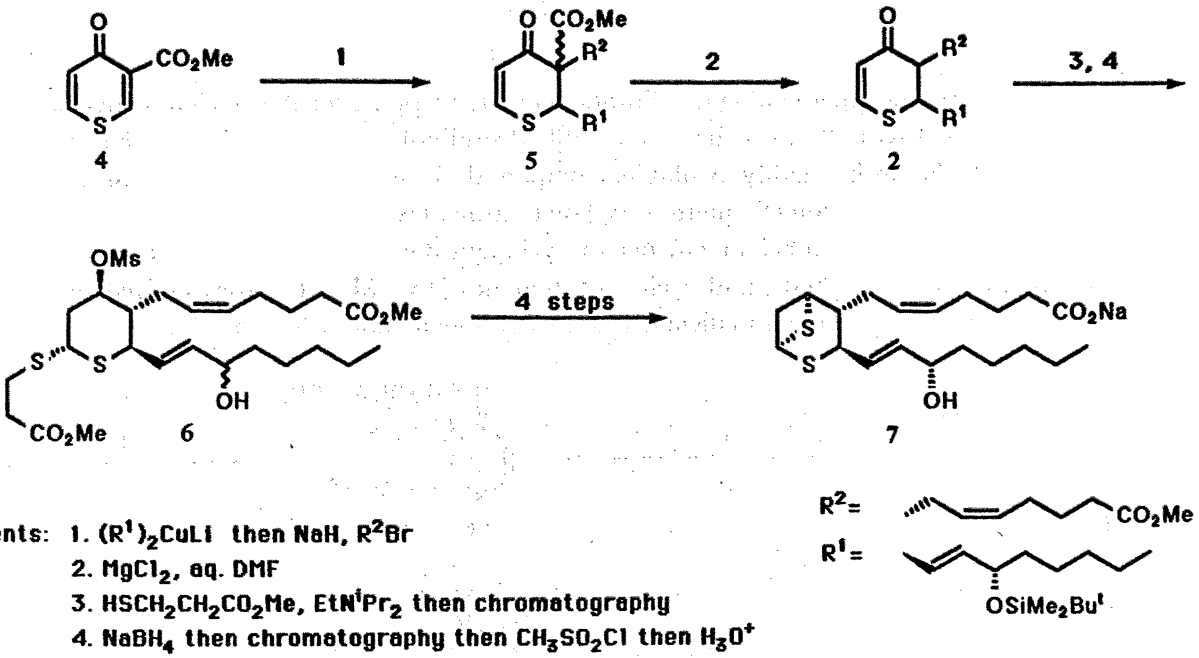
Natural thromboxane A_2 (TXA_2, **1a**) is an extremely potent cardiovascular agent with a short biological half-life. Hydrolytically stable analogues of TXA_2 (**1a**) that mimic or antagonize the biological action of the natural material would have potential applications as cardiovascular drugs (Newton *et al.* 1984). We decided to prepare a series of sulphur-containing analogues of thromboxane A_2, including dithia-thromboxane A_2 (**1b**), for bioassay (Casy *et al.* 1986). The original synthetic strategy was based on organocopper conjugate addition–enolate trapping (also known as three-component coupling) (Taylor 1985; Suzuki *et al.* 1985; Suzuki & Noyori 1984) as shown in scheme 2.

Unfortunately, the key step in this synthetic approach, the organocopper conjugate addition to thiin-4-one (**3**) could not be effected with a wide range of copper-based reagents and reaction conditions. An alternative route to intermediate **2** was therefore required and success was achieved when 3-carbomethoxythiin-4-one (**4**) was employed (scheme 3).

† All synthetic compounds are racemic mixtures although only one enantiomer is depicted in the schemes.



SCHEME 2. Retrosynthesis for dithiathromboxane A_2 (1b).

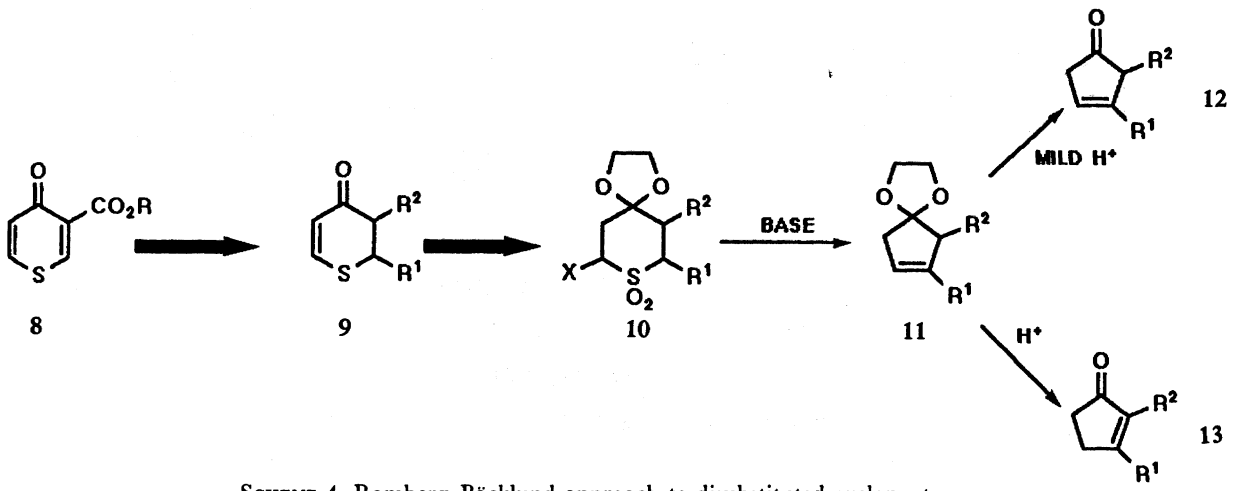


SCHEME 3. Synthesis of dithiathromboxane A_2, sodium salt (7).

Organocuprate conjugate addition to activated enone **4** followed by enolate trapping gave the 2,3-dialkylated dihydrothiinone **5**. Removal of the ester activating group gave compound **2** as a mixture of diastereomers.Further elaboration readily produced mesylate **6**, which has been converted into dithiathromboxane A_2, sodium salt (**7**) in four steps by the Ono Pharmaceutical Company (Ohuchida *et al.* 1983). It should be noted that the organocopper conjugate addition–enolate alkylation methodology (Casy *et al.* 1986) provides a much shorter and more efficient route to the key thiathromboxane precursor **6** than was possible using a more linear synthetic route (Ohuchida *et al.* 1983).

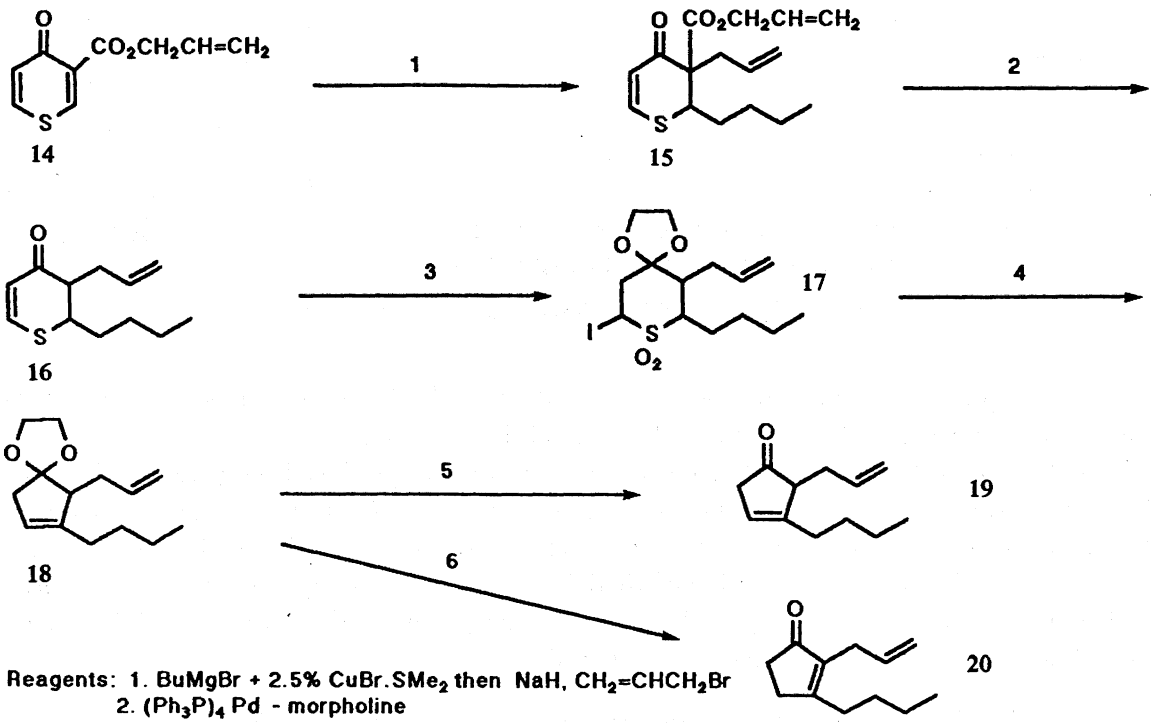
(*b*) *The synthesis of* 2,3-*disubstituted cyclopentenones and tetrahydrodicranenone B*

The methodology outlined in §2*a* has been developed into a versatile procedure for the synthesis of disubstituted cyclopentenones (scheme 4).



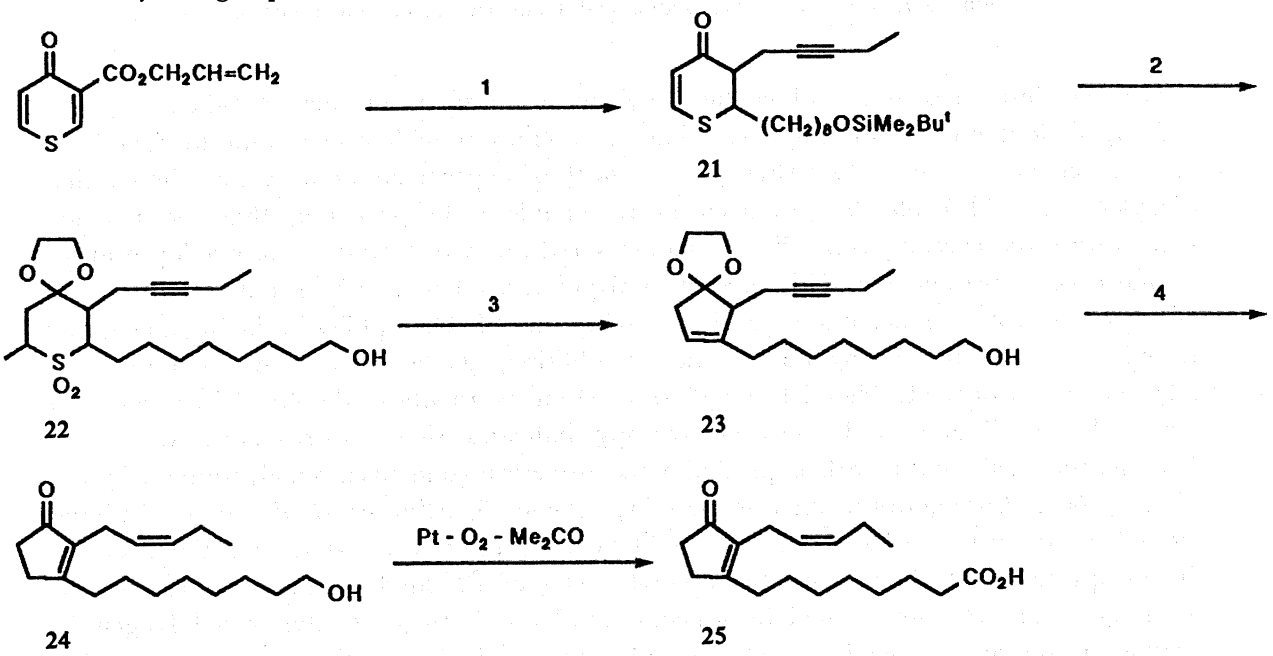
SCHEME 4. Ramberg–Bäcklund approach to disubstituted cyclopentenones.

The use of organocopper conjugate addition–enolate trapping for the efficient conversion of thiin-4-one derivatives (**8**) into dialkylated dihydrothiin-4-ones (**9**) indicated that α-iodosulphones (**10**) should be readily available. Compounds **10** would be expected to undergo the Ramberg–Bäcklund reaction (Paquette 1977) on treatment with base to produce cyclopentenes **11**, which would be the ideal precursors to cyclopent-3-enones (**12**), which are relatively inaccessible by other methods, and cyclopent-2-enones (**13**). Model studies showed that this sequence did indeed provide an efficient route to cyclopentenones (scheme 5).



SCHEME 5. Ramberg–Bäcklund model studies.

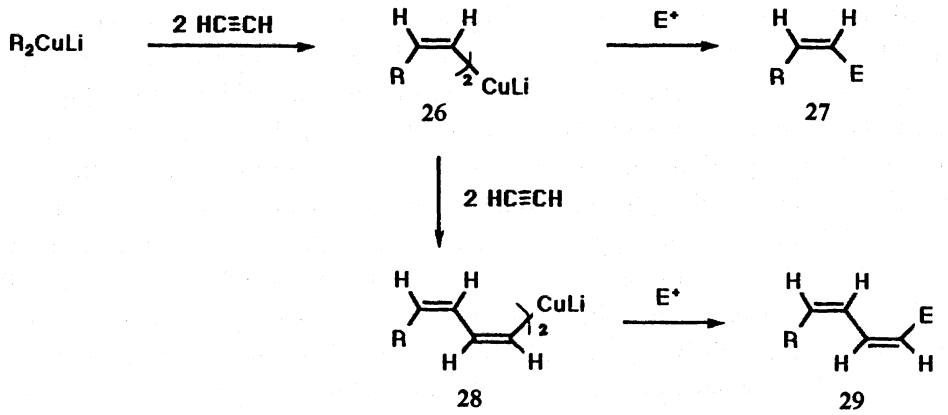
Allyl ester **14** was used in place of methyl ester **4** in order to expedite decarboxyalkylation. Conjugate addition with a copper-catalysed Grignard reagent, followed by enolate alkylation gave adduct **15**, which was efficiently decarboxyallylated by using a palladium catalyst and morpholine (Kunz & Waldmann 1984) to produce the dialkylated dihydrothiinone **16**. Oxidation of sulphide **16** to the corresponding sulphone followed by treatment with trimethylsilyl iodide and ethylene glycol gave α-iodosulphone **17**, which, on exposure to strong base, underwent an efficient and facile Ramberg–Bäcklund reaction to produce cyclopentene **18** in 78% yield. In contrast to related procedures (Matsuyama *et al.* 1987), this Ramberg–Bäcklund approach to cyclopentenones proceeds rapidly at low temperatures and can be employed to prepare disubstituted derivatives. Acidic hydrolysis of compound **18** produced either Δ^3-cyclopentenone (**19**) or Δ^2-cyclopentenone (**20**) depending on the conditions employed (Matsuyama *et al.* 1987). This methodology was applied to a new synthesis of tetrahydrodicranenone B (**25**), an antimicrobial natural product isolated from Japanese mosses (Sakai *et al.* 1985) as shown in scheme 6 (Casy & Taylor 1988). The conjugate addition–enolate alkylation–decarboxyallylation sequence was used to transform the same starting material **14** into adduct **21**. Oxidation of sulphide **21** followed by treatment of the resulting sulphone with trimethylsilyl iodide and ethylene glycol effected iodo-dioxolane formation and desilylation to give compound **22**. Treatment of compound **22** with base produced Ramberg–Bäcklund product **23**, further treatment with acid followed by catalytic hydrogenation giving cyclopentenone (**24**), which has previously been oxidized to tetrahydrodicranenone B (**25**) (Moody *et al.* 1986). Further applications of this procedure for cyclopentenone synthesis are currently being explored.



SCHEME 6. The synthesis of tetrahydrodicranenone B (**25**).

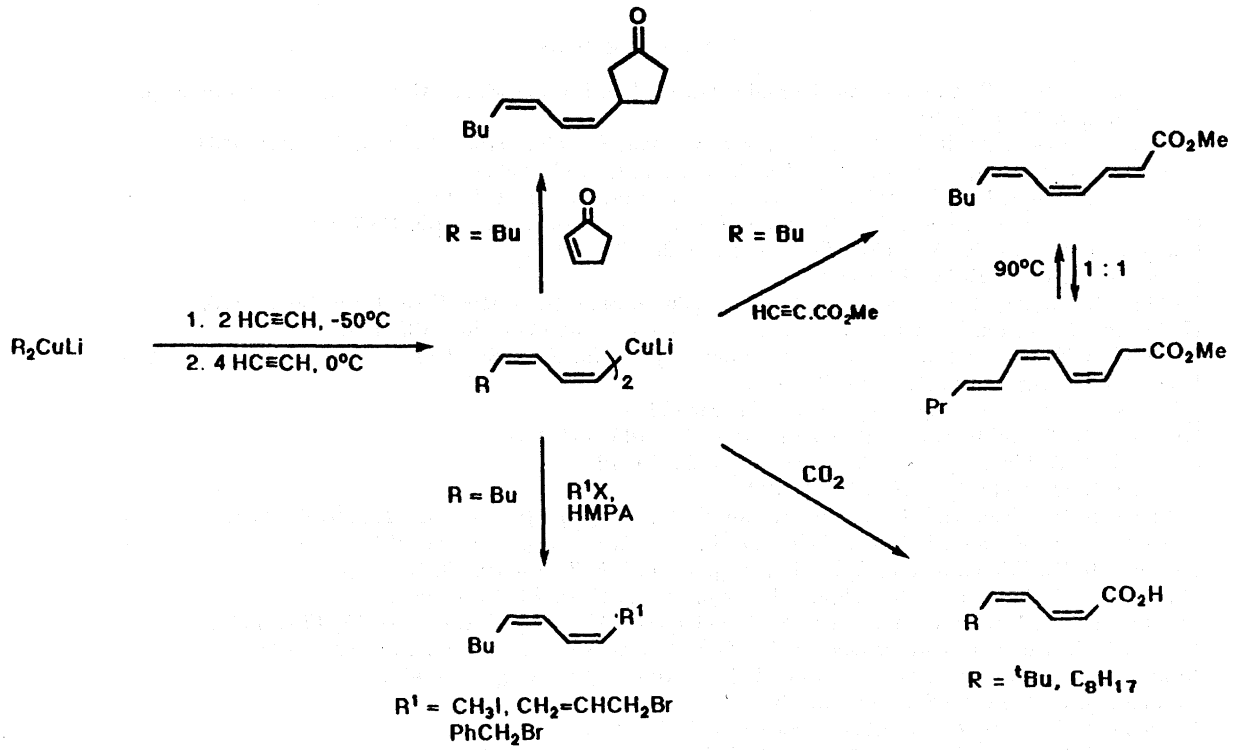
3. Acetylene carbocupration reactions: stereospecific synthesis of *Z,Z*-dienes including the Navel Orangeworm pheromone

Acetylene carbocupration has proved to be an extremely useful procedure for the preparation of *Z*-alkenylcuprates **26**, which can be trapped with a wide range of electrophiles to produce *Z*-alkenes **27** in good yield with extremely high stereoselectivity (scheme 7) (Normant & Alexakis 1981). The corresponding reaction with monosubstituted alkynes is also of great synthetic value providing a stereospecific method of preparing trisubstituted alkenes (Marfat *et al.* 1979).

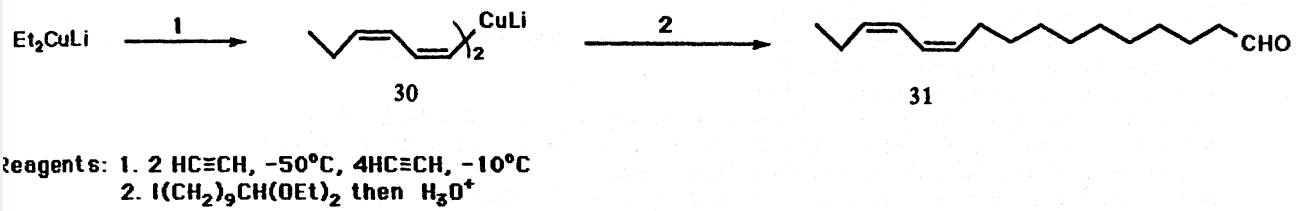


Scheme 7. Acetylene carbocupration and double carbocupration reactions.

We were interested in extending the acetylene procedure to produce *Z,Z*-dienylcuprates (**28**) by a 'double carbocupration' reaction and thereby provide a new route to *Z,Z*-dienes (**29**) as shown in scheme 7. After a good deal of experimentation, it was shown that dienylcuprates **28** could be produced in reasonable yield providing that the reaction temperature was carefully controlled and a measured excess of acetylene was employed in the second carbocupration step. This experimental procedure has now been published in detail (Furber *et al.* 1986). Scheme 8 shows the use of a range of electrophiles in the organocuprate trapping reaction illustrating further the 1,4-addition, alkylation and acylation reactions referred to in scheme 1. The yield for these reactions is usually in the 45–60% range after Kugelrohr distillation, and NMR spectroscopy indicates that the reactions are highly stereospecific. This double carbocupration procedure was used in an extremely simple synthesis of the Naval Orangeworm pheromone (**31**, scheme 9) (Furber *et al.* 1986). Lithium diethylcuprate was employed in the double carbocupration reaction and the resulting dienylcuprate **30** alkylated with the diethyl acetal of 10-iododecanal. Treatment of the resulting acetal with oxalic acid in aqueous tetrahydrofuran gave, after rapid Kugelrohr distillation, the pheromone **31** in 33% overall yield as a single stereoisomer according to ^{13}C NMR spectroscopy (Furber *et al.* 1986).



SCHEME 8. The synthesis of *Z,Z*-dienes.



SCHEME 9. The synthesis of the Navel Orangeworm pheronone (**31**).

4. CONCLUDING REMARKS

In this paper I have deliberately concentrated on synthetic applications of organocopper reagents and refrained from any mention of reaction mechanisms. This is for the simple reason that, although a great deal of valuable information has been gathered (Corey & Boaz 1985; Hallnemo *et al.* 1985; Ashby *et al.* 1982; Krauss & Smith 1981; House 1976), the actual reaction mechanisms are still not completely understood. I hope, however, that I have illustrated the potential of organocopper reagents in organic synthesis and persuaded at least some of the audience that these versatile reagents would be of use in their own research work.

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References

Alexakis, A., Chuit, C., Commercon-Bourgain, M., Foulon, J. P., Jabri, N., Mangeney, P. & Normant, J. F. 1984 *Pure appl. Chem.* **56**, 91–98.

Ashby, E. C., DePriest, R. N., Tuncay, A. & Srivastava, S. 1982 *Tetrahedron Lett.* **23**, 5251–5254.

Bertz, S. H. & Gibson, C. P. 1986 *J. Am. chem. Soc.* **108**, 8286–8288.

Casy, G. & Taylor, R. J. K. 1988 *J. chem. Soc. chem. Commun.*, pp. 454, 455.

Casy, G., Lane, S. & Taylor, R. J. K. 1986 *J. chem. Soc. Perkin Trans.* I, pp. 1397–1404.

Corey, E. J. & Boaz, N. W. 1985 *Tetrahedron Lett.* **26**, 6015–6018.

Erdik, E. 1984 *Tetrahedron* **40**, 641–657.

Furber, M., Taylor, R. J. K. & Burford, S. C. 1986 *J. chem. Soc. Perkin Trans.* I, pp. 1809–1815.

Hallnemo, G., Olsson, T. & Ullenius, C. 1985 *J. organometall. Chem.* **282**, 133–144.

Hope, H., Olmstead, M. M., Power, P. P., Sandell, J. & Xu, X. 1985 *J. Am. chem. Soc.* **107**, 4337–4338.

House, H. O. 1976 *Acct. chem. Res.* **9**, 59–67.

Jukes, A. E. 1974 *Adv. organometall. Chem.* **12**, 215–322.

Krauss, S. R. & Smith, S. G. 1981 *J. Am. chem. Soc.* **103**, 141–148.

Kunz, H. & Waldmann, H. 1984 *Angew. Chem.* **23**, 71–72.

Lipshutz, B. H. 1987 *Synthesis*, pp. 325–341.

Lipshutz, B. H., Kozlowski, J. A. & Breneman, C. M. 1985 *J. Am. chem. Soc.* **107**, 3197–3204.

Lipshutz, B. H., Kozlowski, J. A. & Wilhelm, R. S. 1984*a* *J. org. Chem.* **49**, 3943–3949.

Lipshutz, B. H., Wilhelm, R. S. & Kozlowski, J. A. 1984*b* *Tetrahedron* **40**, 5005–5038.

Marfat, A., McGuirk, P. R. & Helquist, P. 1979 *J. org. Chem.* **44**, 3888–3901.

Matsuyama, H., Miyazawa, Y., Takei, Y. & Kobayashi, M. 1987 *J. org. Chem.* **52**, 1703–1710.

Moody, C. J., Roberts, S. M. & Toczek, J. 1986 *J. chem. Soc. chem. Commun.*, pp. 1292–1293.

Newton, R. F., Roberts, S. M. & Taylor, R. J. K. 1984 *Synthesis*, pp. 449–478.

Normant, J. F. 1972 *Synthesis*, pp. 63–80.

Normant, J. F. 1976 *J. organometall. Chem. Libr.* **1**, 219–256.

Normant, J. F. 1978 *Pure appl. Chem.* **50**, 709–715.

Normant, J. F. & Alexakis, A. 1981 *Synthesis*, pp. 841–870.

Ohuchida, S., Hamanaka, N. & Hayashi, M. 1983 *Tetrahedron* **39**, 4273–4280.

Paquette, L. A. 1977 *Org. React.* **25**, 1–71.

Pearson, R. G. & Gregory, C. D. 1976 *J. Am. chem. Soc.* **98**, 4098–4104.

Posner, G. H. 1972 *Org. React.* **19**, 1–113.

Posner, G. H. 1975 *Org. React.* **22**, 253–400.

Posner, G. H. 1980 *An introduction to synthesis using organocopper reagents*. New York: Wiley.

Sakai, K., Fujimoto, T., Yamashita, M. & Kondo, K. 1985 *Tetrahedron Lett.* **26**, 2089–2092.

Suzuki, M. & Noyori, R. 1984 *Angew. Chem.* **23**, 847–876.

Suzuki, M., Yanagisawa, A. & Noyori, R. 1985 *J. Am. chem. Soc.* **107**, 3348–3349.

Taylor, R. J. K. 1985 *Synthesis*, pp. 364–392.

Yamamoto, Y. 1986 *Angew. Chem.* **25**, 947–959.

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