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Organometallic reagents and protocols for synthesis

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Abstract

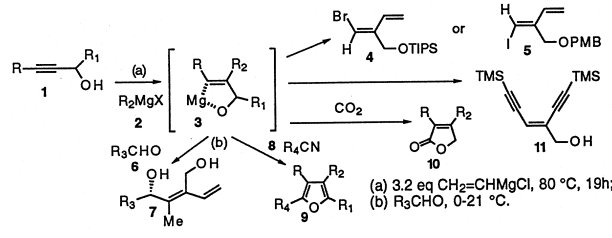
The addition of vinyl, aryl and alkynyl Grignard reagents to propargyl alcohols for the direct synthesis of dihydroxydienes (**7**), furans (**9**), butenolides (**10**) and enediyne alcohols (**11**) from a one-pot reaction involving a putative magnesium chelate intermediate (**3**) is described. Treatment of 5-bromo-1,3-pentadiene with indium metal in the presence of carbonyl compounds resulted in γ-pentadienylation to generate 1,4-dienes (**30**). Dehydration afforded cross-conjugated trienes (**31**) for tandem Diels–Alder reactions, while the alcohol product (**34**) from an unsaturated aldehyde after oxy-Cope rearrangement afforded the 1,4-diene product (**35**) and ultimately hydrindane (**36**).

Keywords: Cycloadditions; Dienes; Indium; Magnesium; Trienes

Our interest in the synthesis of taxoids required the development of diverse organometallic reagents and protocols for the preparation of key intermediates and building blocks [1–3]. This included routes to stereodefined dienes by the direct addition of vinyl Grignard reagents to propargyl alcohols (**1**) [4–14]. Thus generation of the magnesium chelate (**3**) (or a closely related species) provides a direct synthesis of the family illustrated in Scheme 1. This includes the halodienes (**3**, **4**) [15], plus diene-diols (**7**), furans (**9**), 2(5*H*)-furanones (butenolides) (**10**) and enediynes (**11**) [16,17].

Direct condensation of the diene unit with carbonyl compounds was more efficient in cyclohexane due to the increased nucleophilicity of the Grignard complex in a less polar solvent. Table 1 lists representative examples for the preparation of compound **7**. It is of interest that the presence of the silyl ether is sufficient to inhibit the reaction of compound **14** (Table 1, entry e).

Furans comprise an important class of oxygen heterocycles for which new preparative routes continue to be developed [18–21]. Following the protocol developed above, substituted furans (**9**) can be synthesized directly upon reaction of (**3**) with dimethylformamide (DMF) followed by acidification. Alternatively, reaction with aryl nitriles provides C-2 substitution. The vinyl furan systems contain useful functionality for the construction of more complex skeletons



Scheme 1. Compounds from carbometallation of compound **1**.

Table 1
Synthesis of dihydroxydienes (**7**)

Entry	Substrate R—≡—CH_2OH	Reactant	Yield (%)	
			C_6H_{12}	THF
a	**12**, R = Me	PhCHO	80	50
b	**12**, R = Me [a]	PhCHO	68	44
c	**12**, R = Me [b]	PhCHO	100	
d	**13**, R = TMS	PhCHO	78	94
e	**14**, R = CH_2OTBS	PhCHO	0	0

[a] 2.1 equiv. CH_2=CHMgCl.
[b] 0.5 equiv. MeCCCH_2OH plus PhCHOHCH=CH_2.

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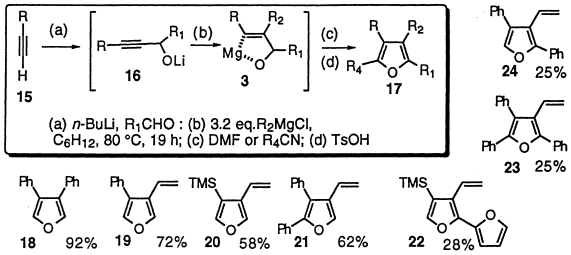
via a double Diels–Alder strategy and also may be used as monomers. The versatility and scope of this furan synthesis was extended by in situ generation of the intermediate chelate compound **3** via lithium–magnesium transmetallation, as illustrated in Scheme 2. Thus, modification of the standard protocol permitted the control of the substitution pattern at all the ring positions. Various examples are listed, including the bis-furanyl system (**23**). Thus, depending upon the substrate–reagent–reactant combination selected, a large number of substituted furans can be prepared in a straightforward manner.

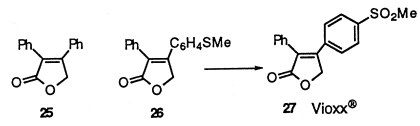
The study and synthesis of enyne and enediyne chromophores are of current interest because of their challenging structures and biological activity as antibiotics and antitumor agents [22–24]. An additional application of the synthetic utility of this carbometallation method is the facile preparation of these building blocks [25–28]. Thus the enediyne alcohol (**11**) [29] was prepared easily with trimethylsilylacetylene magnesium chloride.

Early examples of dialkyl butenolides from the condensation of species related to compound **3** with carbon dioxide have been reported [30,31], and other methods are available [32,33]. However, there is medicinal interest in preparing 3,4-diaryl-2(5*H*)-furanones. Thus, phenylpropargyl alcohol plus phenylmagnesium chloride or 4-thiomethylphenylmagnesium chloride followed by carbon dioxide afforded lactones **25** and **26** (Scheme 3). Oxidation of the sulfide with *m*-chloroperoxybenzoic acid gave the new Merck anti-inflammatory drug Vioxx® (**27**) in quantitative yield.

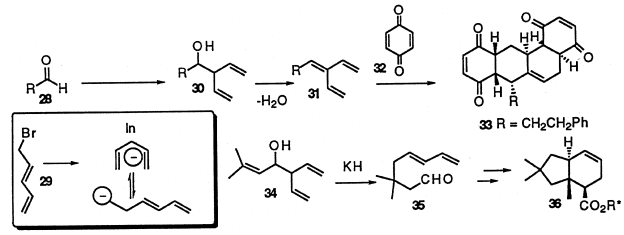
Li and Chan [34] have demonstrated the utility of allylindium species for addition to carbonyl compounds where the tin and zinc reagents failed [35–37]. For many metal pentadienyl systems condensation is not regioselective, and the delocalized anion may react at either the α or γ position (Scheme 4). However, the reagent generated from 5-bromo-1,3-pentadiene [38] and indium metal adds in a regioselective manner to give non-conjugated compounds of type **30** [39]. During our investigations, Araki and co-workers [40] reported related studies. Recently, Chan and Yang [41] have established that allylindium additions to ketones proceed via



Scheme 2. Synthesis of furans.



Scheme 3. Butenolide products.



Scheme 4. Pentadienyl indium addition and [4+2] cycloadditions.

the formation of an indium(I) species rather than indium(III). A parallel process involving metal surface-mediated allyl radical anions is also possible. In view of the close structural similarity between pentadienyl and allylindium species, the mechanisms are probably closely related.

Dehydration of these diene products (**30**) under Mitsunobu-type conditions (Ph_3P, diethylazodicarboxylate (DEAD), C_6H_6, 80°C) generated the corresponding trienes (**31**). These trienes facilitate diene-transmissive tandem Diels–Alder reactions [42] such as the reaction with compound **32** to give compound **33**. The alcohol product (**34**) from an unsaturated aldehyde is a surrogate for the Michael addition product. Thus oxy-Cope rearrangement afforded the 1,4-diene product (**35**). Subsequent cycloaddition with the Oppolzer chiral auxiliary [43,44] completed an enantioselective route to the hydrindane (**36**) [45].

In summary, the carbometallation protocols described above provide direct access to a number of useful unsaturated systems that can be employed for a variety of synthetic objectives. In addition, the organoindium reagent derived from 5-bromo-1,3-pentadiene and indium metal reacts with excellent regioselectivity and after further manipulation affords rapid entry to complex multicyclic skeletons from various [4+2] cycloadditions.

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References

[1] A.G. Fallis, Acc. Chem. Res. 32 (1999) 464.
[2] A.G. Fallis, Can. J. Chem. 77 (1999) 159.
[3] A.G. Fallis, Pure Appl. Chem. 69 (1997) 495.
[4] H.G. Richey Jr., F.W. Von Rein, J. Organomet. Chem. 20 (1969) 32.
[5] F.W. Von Rein, H.G. Richey Jr., Tetrahedron Lett. (1971) 3777.

[6] L. Labaundinière, J. Hanaizi, J.-F. Normant, J. Org. Chem. 57 (1992) 6903.
[7] I. Creton, I. Marek, J.-F. Normant, Tetrahedron Lett. 36 (1995) 7451.
[8] E. Negishi, Y. Zhang, F.E. Cederbaum, M.B. Webb, J. Org. Chem. 51 (1986) 4080.
[9] B. Jousseaume, J.-G. Duboudin, J. Organomet. Chem. 91 (1975) C1.
[10] J.G. Duboudin, B. Jousseaume, J. Organomet. Chem. 168 (1979) 1.
[11] J.G. Duboudin, B. Jousseaume, A. Bonakdar, J. Organomet. Chem. 168 (1979) 227.
[12] J.H. Merkley, J.E. Gallo, J. Org. Chem. 44 (1979) 587.
[13] J.J. Eisch, J.H. Merkley, J. Organomet. Chem. 20 (1969) 37.
[14] S. Ma, E. Negishi, J. Org. Chem. 62 (1997) 784.
[15] T. Wong, N.W. Tjepkema, H. Audrain, P.D. Wilson, A.G. Fallis, Tetrahedron Lett. 37 (1996) 755.
[16] P. Forgione, A.G. Fallis, Tetradedron Lett. 41 (2000) 11.
[17] P. Forgione, P.D. Wilson, A.G. Fallis, Tetrahedron 41 (2000) 17.
[18] T.L. Gilchrist, Contemp. Org. Syn. 1 (1994) 205.
[19] T.L. Gilchrist, J. Chem. Soc., Perkin Trans. I (1998) 615.
[20] E. Bures, P.G. Spinazze, G. Beese, I.R. Hunt, C. Rodgers, B.A. Keay, J. Org. Chem. 62 (1997) 8741.
[21] P. Wipf, L.T. Rahman, S.R. Rector, J. Org. Chem. 63 (1998) 7132.
[22] D.B. Borders, T.W. Doyle, Enediyne Antibiotics as Antitumor Agents, Marcel Dekker, New York, 1995.
[23] H. Lhermitte, D.S. Grierson, Contemp. Org. Syn. 3 (1996) 41.
[24] H. Lhermitte, D.S. Grierson, Contemp. Org. Syn. 3 (1996) 43.
[25] Y.F. Lu, C.W. Harwig, A.G. Fallis, J. Org. Chem. 58 (1993) 4202.
[26] Y.F. Lu, C.W. Harwig, A.G. Fallis, Can. J. Chem. 73 (1995) 2253.
[27] C.W. Harwig, S. Py, A.G. Fallis, J. Org. Chem. 62 (1997) 7902.
[28] S. Py, C.W. Harwig, S. Banerjee, D.L. Brown, A.G. Fallis, Tetrahedron Lett. 39 (1998) 6139.
[29] A.G. Meyers, P.M. Harrington, E.Y. Kuo, J. Am. Chem. Soc. 113 (1991) 694.
[30] R. Mornet, L. Gouin, Bull. Soc. Chim. Fr. (1977) 737.
[31] J.-G. Duboudin, B. Jousseaume, J. Organomet. Chem. 168 (1979) 233.
[32] S. Ma, Z. Shi, J. Org. Chem. 63 (1998) 6387.
[33] S. Ma, Z. Shi, Tetrahedron Lett. 40 (1999) 2393.
[34] C.J. Li, T.H. Chan, Tetrahedron Lett. 32 (1991) 7017.
[35] T.H. Chan, C.J. Li, M.C. Lee, Z.Y. Wei, Can. J. Chem. 72 (1994) 1181.
[36] C.J. Li, Chem. Rev. 93 (1993) 2023.
[37] P. Cintas, Synlett (1995) 1087.
[38] C. Prevost, P. Miginiac, L. Miginiac-Groizeleau, Bull. Soc. Chim. Fr. (1964) 2485.
[39] S. Woo, N. Squires, A.G. Fallis, Org. Lett. 1 (1999) 573.
[40] T. Hirashita, S. Inoue, H. Yamamura, M. Kawai, S. Araki, J. Organomet. Chem. 549 (1997) 305.
[41] T.H. Chan, Y. Yang, J. Am. Chem. Soc. 121 (1999) 3228.
[42] J.D. Winkler, Chem. Rev. 96 (1996) 167.
[43] W. Oppolzer, D. Dupuis, Tetrahedron Lett. 26 (1985) 5437.
[44] W. Oppolzer, D. Dupuis, G. Poli, T.M. Raynham, G. Bernardinelli, Tetrahedron Lett. 26 (1988) 5885.
[45] A.G. Melekhov, A.G. Fallis, Tetrahedron Lett. 40 (1999) 7862.