

Superbase promoted synthesis of dienamides as useful intermediates for the synthesis of α -ketoamides, γ -lactams and cyclic imino ethers†Marco Blangetti,^a Annamaria Deagostino,^a Giuliana Gervasio,^b Domenica Marabello,^b Cristina Prandi^{*a} and Paolo Venturello^a

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Alkoxydienamides **2** have been synthesized exploiting the reactivity of α,β -unsaturated acetals **1** with isocyanates in the presence of Schlosser's superbase LIC–KOR. In a mild acidic medium, **2** can then be promptly converted both into α -ketoamides **3** and into substituted 2-pyrrolidinones **4** or imino ethers **5** by choosing the appropriate experimental conditions.

Introduction

Dienamides are widely occurring structural features in a number of pharmacologically relevant natural products, as well as taste active substances.^{1–5} Moreover, these compounds can be undoubtedly considered as key intermediates with high and versatile synthetic potential, and their use both as electron rich and electron poor dienes in Diels–Alder reactions or in asymmetric cycloaddition is, as a matter of fact, well documented.^{6–9} Even though dienamides can be in principle used in electrophilic cyclization to afford unusual and interesting heterocyclic frameworks, very few references appear in the literature concerning this kind of application.¹⁰ Recently Xi and co-workers published an attractive approach to cyclic imino ethers starting from conjugate dienamides.¹¹ Several methods are reported in the literature for the stereoselective preparation of dienamides, among them Wittig-type approaches,^{12–14} transformation of dienic sulfones^{15,16} photochemical electrocyclic reaction from cyclobutenes,¹⁷ or cross-coupling reactions have all been used.^{18–22} Moreover, stereodefined multisubstituted dienamides can be concisely prepared in high yields by reaction of 1-lithiobutadienyl derivatives with *N*-alkyl or *N*-aryl isocyanates.¹¹ Very recently we reported an original synthesis of alkoxydienylamines obtained starting from α,β -unsaturated acetals in superbasic medium and their use as substrates for aminopalladation reactions to obtain pyrroles.²³ In this paper we describe an alternative way to prepare conjugate (*E*)-alkoxydienamides **2** and their utilization in the synthesis of β,γ -unsaturated α -ketoamides **3**, that represent an attractive

functionality both for enhanced reactivity in Michael type additions and for the occurrence in several natural products.^{24–26} Nevertheless, general and efficient approaches to this class of compound are still scarce.²⁷ Furthermore, (*E*)-alkoxydienamides can be exploited in the synthesis of functionalized 1*H*-pyrrol-2(5*H*)-ones (**4**) or *N*-(3-ethoxy-furan-2(5*H*)-ylidene)-1-amines (**5**) through an electrophilic cyclization that takes place selectively according to an *O*- or *N*-5-*exo*-attack pathway, depending on the substrate.

Results and discussion

Metalation of acetals **1** with LIC–KOR (equimolar mixture of *n*BuLi and *t*BuOK) superbase^{28–33} afforded the corresponding 1-metalated-1,3-dienes³⁴ whose treatment *in situ* with isocyanates produced stereodefined α -alkoxydienamides **2** in good yields after mild acidic work-up (see Experimental Section). As reported in Table 1, both *N*-alkyl (entry 1) and *N*-aryl (entries 2–11) isocyanates can be used in this reaction to obtain **2**. *N*-Cyclohexyl isocyanate smoothly reacted with metalated diene to afford the corresponding (*E*)-*N*-cyclohexyl-2-ethoxypenta-2,4-dienamide in 79% yield after purification. Aromatic phenyl, tolyl, *m*-methoxyphenyl, *p*-bromophenyl and α -naphthyl isocyanates all gave good yields of the corresponding dienamides, while slightly lower yields are obtained in the case of acetal **1b** (*R*¹ = Me, entries 8–10). Acetal **1c** (*R*¹ = H, *R*² = Me, entry 11) affords the corresponding dienamide **2k** in 65% yield. The *E* stereochemistry of the double bond has been assessed by ROESY experiments, thus confirming that the conjugate elimination reaction takes place according to a stereoselective process, as previously reported.³⁵

At this point, the choice of a suitable acidic catalyst may direct further synthetic elaborations of **2**, hence allowing the selective hydrolysis of the vinyl ether moiety to α -ketoamides **3** from one side or an electrophilic cyclization to heterocyclic frameworks **4** and **5** from the other. Accordingly, when dienamides **2** were treated with a stoichiometric amount of PTSA monohydrate in CH₂Cl₂–MeOH the unmasking process leads to α -ketoamides **3** with good

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Table 1 Superbase promoted synthesis of stereodefined dienamides from acetals

Entry	R ¹	R ²	R	Product 2	Yield (%) ^a
1	H	H	Cy	2a	79
2	H	H	Ph	2b	74
3	H	H	<i>p</i> -Tol	2c	71
4	H	H	MMP ^b	2d	77
5	H	H	<i>p</i> -BrPh	2e	64
6	H	H	α -Naph	2f	72
7	H	H	<i>o</i> -ClPh	2g	72
8	Me	H	Ph	2h	52
9	Me	H	<i>p</i> -Tol	2i	59
10	Me	H	α -Naph	2j	68
11	H	Me	Ph	2k	65

^a Yields refer to isolated purified products. ^b MMP *meta*-methoxyphenyl.

Table 2 Synthesis of α -ketoamides **3**

Entry	R ¹	R ²	R	Product 3	Yield (%) ^a
1	H	H	Cy	3a	93
2	H	H	Ph	3b	88
3	H	H	<i>p</i> -Tol	3c	84
4	H	H	<i>p</i> -BrPh	3e	79
5	Me	H	Ph	3h	81
6	Me	H	<i>p</i> -Tol	3i	86

^a Yields refer to isolated purified products.

to excellent yields as reported in Table 2. Several attempts to convert alkoxydienamides **2** into α -ketoamides **3** in the presence of Amberlyst-15[®], CSA in CH₂Cl₂ or triflic acid in CH₂Cl₂ were unsuccessful.

Besides, **2** can be used as substrates for electrophilic cyclization. Among the experimental conditions reported in the literature that may promote an intramolecular electrophilic process,³⁶ we found that the use of neat TFA at 0 °C allows to selectively obtain pure products. Substrates **2b–2e** underwent an electrophilic cyclization, namely the *N*-5-*exo* attack leading to 1*H*-pyrrol-2(5*H*)-ones **4** (as depicted in Table 3). Direct cyclization of α -ketoamides **3** into compounds **4** or **5** have been attempted in the presence of protic or Lewis acids or under organocatalytic conditions (proline in CH₂Cl₂) with discouraging results.

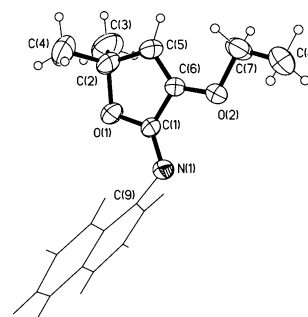
The structures of lactams **4c** and **4d** have been confirmed by ROESY experiments (diagnostic is the cross peak between methyl at 1.40 ppm for **4c**, 1.33 ppm for **4d** and *o*-aromatic protons, see the ESI[†]). Conversely, when substrates **2h–2j** were subjected to the same reaction conditions the electrophilic cyclization takes place according to an *O*-*exo* attack affording imino ethers **5h–j**

Table 3 Electrophilic cyclization of **2**

Entry	R ¹	R	Product	Yield (%) ^a
1	H	Ph	4b	91
2	H	<i>p</i> -Tol	4c	93
3	H	MMP	4d	94
4	H	<i>p</i> -BrPh	4e	96
5	H	α -Naph	5f	81
6	H	<i>o</i> -ClPh	5g	88
7	Me	Ph	5h	95
8	Me	<i>p</i> -Tol	5i	92
9	Me	α -Naph	5j	83

^a Yields refer to isolated purified products

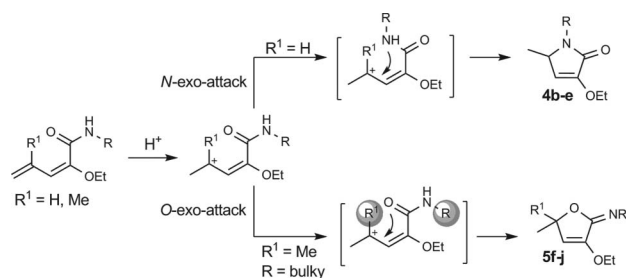
(Table 3). In this case the structure of the imino ether has been confirmed by single crystal X-ray analysis (Fig. 1).

**Fig. 1** ORTEP plot (thermal ellipsoids at 30% of probability) of **5j** showing the atom labeling.

The asymmetric unit contains two molecules, A and B, with different conformations: in molecule A the naphthalene moiety forms an angle of 87° with the penta-atomic ring, in the other molecule B the angle value is 40°. This fact demonstrates the possibility of a free rotation around the N(1)–C(9) bond in the isolated molecule and therefore its single bond feature. The C(1)–N(1) bond values agree with a double bond value (1.263(2) Å av.), and the angle around N(1) is that of an sp² hybridization. The C(1)–O(1) and C(6)–O(2) bond values agree with a Csp²–O distance (1.349(2) Å av.), while the C(5)–C(6) bond length corresponds to a double bond (1.318(2) Å av.). The crystal packing shows only weak C–H⋯N and C–H⋯O intermolecular hydrogen bonds.

Our results seem then to confirm the hypothesis that the 4 position is crucial in determining the *N*- or the *O*-cyclization pathway (Scheme 1).^{10,11,37} According to this assumption, the attack of the less bulky O atom (leading to imino ethers **5**) is favoured when the 4-position is substituted, on the other hand the encumbered N atom of the amide group is more likely to attack an unsubstituted 4 position (leading to lactams **4**, Scheme 1).

Intrigued by these results, we decided to investigate if the increase in bulkiness of the *N*-substituent would lead to an *O*-cyclization pathway even in the case of an unsubstituted C4 position of the starting dienamide. To this purpose we synthesized



Scheme 1 Electrophilic cyclization of dienamides **2**.

compounds **2f** and **2g**, unsubstituted on C4 and with a naphthyl group (**2f**) or *o*-chlorophenyl (**2g**) on nitrogen (entries 6 and 7, Table 1) and subjected them to electrophilic cyclization under the usual conditions. In this case we obtained imino ethers **5f** and **5g** (entries 5 and 6, Table 3) as the only product in excellent yield. Single crystal X-ray structure of **5f** is herein reported (Fig. 2).³⁸

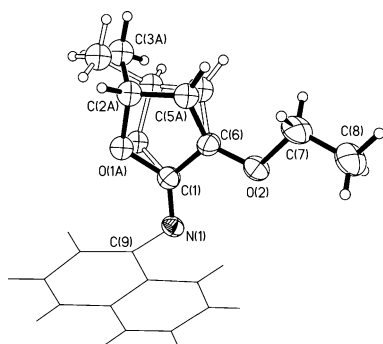


Fig. 2 ORTEP plot (thermal ellipsoids at 30% of probability) of **5f** showing the atom labeling. The two disordered rings are shown: the ring with open bonds corresponds to the occupancy factor 0.38 (ring B).

Owing to the disorder of the molecule and to the great thermal motion the data have been collected at 153 K. The disorder of the penta-atomic ring (Fig. 2) may be described as a reflection with respect to the plane defined by the N(1), C(1) and C(6) atoms. The two penta-atomic rings have an asymmetric carbon atom (C(2A) and C(2B)) and the two faced rings are enantiomerically related. The naphthalene moiety and the planes of the penta-atomic ring form angles of 143° and 110° respectively (A ring, B ring). Also in **5f** C(1)–N(1) and C(5)–C(6) bonds are formal double bonds (1.247(4) Å and 1.35(1) Å av.), while C(1)–O(1) and C(6)–O(2) distances are in keeping with a Csp²–O distance (1.413(6) Å av. and 1.321(4) Å, respectively). As in **5j** the crystal structure shows only weak C–H···N and C–H···O intermolecular hydrogen bonds.

As represented in Scheme 1, the cyclization pathways selectively follow a 5-*exo*-trig mechanism, as a matter of fact products coming from an *endo* attack have never been detected. The choice between N or O as nucleophilic attacking atom is determined by both electronic and steric reasons. In the absence of bulky substituents on C4 of the diene or on the nitrogen the cyclization is prompted by the more nucleophilic N atom, otherwise, in the presence of encumbered substituents it is the less sterically demanding oxygen that acts as attacking nucleophile.

Conclusions

In this work a convenient synthesis of stereodefined alkoxydienamides has been developed, and both their hydrolysis to α -ketoamides, and electrophilic cyclization to heterocyclic frameworks have been described. The cyclization occurs according to a 5-*exo*-attack by either the O or the N depending on the substrate structure, thus allowing the selective synthesis of pyrrol-2(5*H*)-ones or cyclic imino ethers. The worthwhile and synthetically useful aspects involved in this approach are that the formation of either 2-pyrrolidinones or imino ethers can be easily tuned by a suitable choice of the substrate. We have demonstrated that the cyclization pathway is determined both by steric and electronic parameters, and that not only the C4 position on the dienyl moiety, but also the bulkiness of the substituent on the nitrogen atom is responsible for the product outcome. This approach should prove quite useful for a rapid access to dienamides and their further synthetic elaboration to heterocyclic derivatives.

Experimental

General procedure for the syntheses of pentadienamides **2**

A solution of freshly sublimated *t*BuOK (5 mmol, 560 mg, 2.5 equiv.) in THF (7 mL) was cooled to –78 °C. 1,1-Diethoxybut-2-ene (2 mmol, 288 mg) in THF (2 mL) and *n*BuLi (1.6 M in hexanes, 5 mmol, 3.13 mL) were added in quick succession and the mixture was stirred for 2 h during which time the temperature was raised to –40 °C. Afterwards the reaction was cooled back to –78 °C and the appropriate isocyanate (2.2 mmol) in THF (2 mL) was added. After stirring the mixture at –78 °C for 2 h, a saturated NH₄Cl solution (10 mL) was added. The resulting mixture was extracted with Et₂O (3 × 10 mL), washed with water (10 mL) and brine (2 × 10 mL), and dried with anhydrous K₂CO₃. After filtration and evaporation of the solvent, the crude products were purified by flash column chromatography.

(*E*)-N-Cyclohexyl-2-ethoxypenta-2,4-dienamide 2a. Purified by flash chromatography (Et₂O:petroleum ether 3:7, 1% Et₃N, *R_f* 0.45) to give **2a** (356 mg, 79%). ¹H NMR (200 MHz, CDCl₃). δ ppm 7.69 (dt, *J* = 17.2, 10.7 Hz, 1H), 6.53 (br, 1H), 5.68 (d, *J* = 10.7 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.7 Hz, 1H), 3.83 (q, *J* = 6.9 Hz, 2H) superimposed to 3.92–3.78 (m, 1H), 2.00–1.82 (m, 2H), 1.79–1.54 (m, 4H), 1.36 (t, *J* = 6.9 Hz, 3H) superimposed to 1.27–1.07 (m, 4H). ¹³C NMR (50.2 MHz, CDCl₃). δ 162.0 (s), 145.9 (s), 132.4 (d), 117.6 (t), 111.9 (d), 63.5 (t), 47.4 (d), 32.7 (t), 25.3 (t), 24.6 (t), 14.3 (q). MS *m/z* 223 (M⁺, 26), 193 (100), 111 (98), 67 (50), 55 (39). Anal. Calcd for C₁₃H₂₁NO₂: C, 69.92; H, 9.48. Found C, 69.84; H, 9.29.

General procedure for the syntheses of α -ketoamide derivatives **3**

A solution of the appropriate pentadienamide (0.5 mmol) in CH₂Cl₂–MeOH (3 mL) was stirred in the presence of PTSA·H₂O (0.5 mmol, 95 mg, 1 equiv.) and the reaction progress monitored by TLC. After 0.5 h the reaction was complete, the reaction was quenched with water. After extraction with CH₂Cl₂ (3 × 10 mL), the collected organic layers were washed with water (10 mL) and brine (2 × 10 mL), and dried with anhydrous K₂CO₃. After filtration and evaporation of the solvent, the crude products were purified by column flash chromatography.

(E)-N-Cyclohexyl-2-oxopent-3-enamide 3a. Purified by flash chromatography (Et₂O:petroleum ether 3:7, 1% Et₃N, *R_f* 0.40) to give **3a** (91 mg, 93%). ¹H NMR (200 MHz, CDCl₃). δ ppm 7.41–7.24 (m, 1H), 7.14 (dd, *J* = 15.7, 1.4 Hz, 1H), 7.03 (br, 1H), 4.19–4.01 (m, 1H), 3.88–3.69 (m, 1H), 2.02 (dd, *J* = 6.8, 1.4 Hz, 3H), 1.99–1.87 (m, 4H), 1.82–1.60 (m, 6H), 1.45–1.31 (m, 4H), 1.33–1.12 (m, 6H). ¹³C NMR (50.2 MHz, CDCl₃). δ 185.3 (s), 160.0 (s), 149.1 (d), 124.4 (d), 48.1 (d), 32.4 (t), 24.5 (t), 18.8 (q). MS *m/z* 195 (M⁺, 8), 180 (12), 126 (15), 83 (72), 69 (100), 55 (58). Anal. Calcd for C₁₁H₁₇NO₂: C, 67.66; H, 8.78. Found C, 67.32; H, 8.75.

General procedure for the syntheses of *N*-aryl pyrrolidinones **4** and cyclic imino ethers **5**

A 20-mL sealed tube fitted with a rubber septum cap and connected to a nitrogen filled balloon was charged with the appropriate pentadienamide (0.5 mmol) and cooled to 0 °C. Then TFA (5 ml) was added dropwise, and the resulting mixture was stirred for 1 h. Afterwards the reaction was cooled back to 0 °C and a solution of NaOH (10%) was added, and the resulting mixture was extracted with several portions of Et₂O. The combined organic layers were washed twice with NaHCO₃, water and brine, and dried over anhydrous K₂CO₃. After filtration and evaporation of the solvent, the crude products were purified by column flash chromatography.

(E)-3-Ethoxy-5-methyl-1-phenyl-1H-pyrrol-2(5H)-one 4b. Purified by flash chromatography (Et₂O:petroleum ether 7:3, 1% Et₃N, *R_f* 0.50) to give **4b** (98 mg, 91%). ¹H NMR (200 MHz, CDCl₃). δ ppm 7.36–7.20 (m, 4H), 7.12–7.02 (m, 1H), 5.70 (d, *J* = 1.9 Hz, 1H), 5.13 (qd, *J* = 6.2, 1.9 Hz, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 6.2 Hz, 3H). ¹³C NMR (50.2 MHz, CDCl₃). δ 156.1 (s), 148.6 (s), 146.1 (s), 128.2 (d), 123.6 (d), 123.2 (d), 111.5 (d), 78.7 (d), 66.6 (t), 20.9 (q), 14.0 (q). MS *m/z* 217 (M⁺, 11), 202 (38), 174 (19), 120 (24), 83 (100), 77 (34). Anal. Calcd for C₁₃H₁₅NO₂: C, 71.87; H, 6.96. Found C, 71.46; H, 6.73.

(E)-N-(3-Ethoxy-5-methylfuran-2(5H)-ylidene)naphthalen-1-amine 5f. Purified by flash chromatography (EtOAc:petroleum ether 1:1, 1% Et₃N, *R_f* 0.50) to give **5f** (108 mg, 81%). ¹H NMR (200 MHz, CDCl₃). δ ppm 8.13–7.94 (m, 1H), 7.75–7.69 (m, 1H), 7.53–7.45 (m, 1H), 7.42–7.28 (m, 3H), 7.18–7.10 (m, 1H), 5.63 (d, *J* = 1.9 Hz, 1H), 4.98 (qd, *J* = 6.4, 1.9 Hz, 1H), 3.96 (q, *J* = 7.0, 1H), 1.43 (t, *J* = 7.0 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 1H). ¹³C NMR (50.2 MHz, CDCl₃). δ 155.6 (s), 147.6 (s), 142.4 (s), 133.1 (s), 126.8 (s), 126.7 (d), 124.7 (2C, d), 123.9 (d), 123.3 (d), 122.5 (d), 116.0 (d), 111.2 (d), 77.7 (d), 65.8 (t), 20.1 (q), 13.3 (q). MS *m/z* 267 (M⁺, 100), 252 (34), 168 (76), 143 (27), 69 (91). Anal. Calcd for C₁₇H₁₇NO₂: C, 76.38; H, 6.41. Found C, 76.11; H, 6.38. m.p. 102–103 °C.

Notes and references

- 1 B. S. Siddiqui, S. Begum, T. Gulzar, Farhat and F. Noor, *Phytochemistry*, 1997, **45**, 1617–1619.
- 2 S. E. Binns, B. Purgina, C. Bergeron, M. L. Smith, L. Ball, B. R. Baum and J. T. Arnason, *Planta Med.*, 2000, **66**, 241–244 CAN 127: 202886.
- 3 J. P. Ley, J.-M. Hilmer, B. Weber, G. Krammer, I. L. Gatfield and H.-J. Bertram, *Eur. J. Org. Chem.*, 2004, 5135–5140.
- 4 Y. Chen, T. Fu, Tao, J. Yang, Y. Chang, M. Wang, L. Kim, L. Qu, J. Cassidy, R. Scalzo and X. Wang, *J. Nat. Prod.*, 2005, **68**, 773–776 CAN 143: 40911.
- 5 N. B. Cech, K. Tutor, B. A. Doty, K. Spelman, M. Sasagawa, G. M. Raner and C. A. Wenner, *Planta Med.*, 2006, **72**, 1372–1377 CAN: 147: 314136.
- 6 D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy and K. R. Campos, *J. Am. Chem. Soc.*, 1999, **121**, 7582–7594.
- 7 J. P. Morris, H. McAlonan, M. Nieuwenhuyzen, K. Reynolds, P. K. S. Sarma, P. J. Stevenson and N. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 69–79.
- 8 Y. Huang, T. Iwama and V. H. Rawal, *J. Am. Chem. Soc.*, 2000, **122**, 7843–7844.
- 9 L. E. Overman, D. Lesuisse and M. Hashimoto, *J. Am. Chem. Soc.*, 2002, **105**, 5373–5379.
- 10 K. Cherry, J. Thibonnet, A. Duchene, J. L. Parrain and M. Abarbri, *Tetrahedron Lett.*, 2004, **45**, 2063–2066.
- 11 (a) C. Y. Wang, J. Lu, G. L. Mao and Z. F. Xi, *J. Org. Chem.*, 2005, **70**, 5150–5156; (b) Q. F. Wang, W. X. Zhang and Z. F. Xi, *Organometallics*, 2008, **27**, 3627–3629; (c) Z. F. Xi, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 1021–1032; (d) Z. F. Xi, *Eur. J. Org. Chem.*, 2004, 2773–2781; (e) J. L. Chen, Q. L. Song, C. Y. Wang and Z. F. Xi, *J. Am. Chem. Soc.*, 2002, **124**, 6238–6239; (f) Q. L. Song, J. L. Chen, X. L. Jin and Z. F. Xi, *J. Am. Chem. Soc.*, 2001, **123**, 10419–10420.
- 12 S. Pachali, C. Hofmann, G. Rapp, R. Schobert, A. Baro, W. Frey and S. Laschat, *Eur. J. Org. Chem.*, 2009, 2828–2835.
- 13 Y. C. Shen and Y. J. Xiang, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2493–2494.
- 14 J. E. Mathieson, J. J. Crawford, M. Schmidtman and R. Marquez, *Org. Biomol. Chem.*, 2009, **7**, 2170–2175.
- 15 M. C. Bernabeu, R. Chinchilla and C. Najera, *Tetrahedron Lett.*, 1995, **36**, 3901–3904.
- 16 N. A. Plobeck and J. E. Backvall, *J. Org. Chem.*, 1991, **56**, 4508–4512.
- 17 N. Gauvry and F. Huet, *J. Org. Chem.*, 2001, **66**, 583–588.
- 18 I. Schwarz and A. Braun, *J. Prakt. Chem.*, 1999, **341**, 72–74.
- 19 T. Tanaka, S. Hirano, H. Urabe and F. Sato, *Org. Lett.*, 2003, **5**, 67–70.
- 20 H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T. Mitsudo and T. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 5160–5163.
- 21 A. B. Smith III, M. O. Duffey, K. Basu, S. P. Walsh, H. V. Suenemann and M. Frohn, *J. Am. Chem. Soc.*, 2008, **130**, 422–423.
- 22 A. B. Smith III, S. P. Walsh, M. Frohn and M. O. Duffey, *Org. Lett.*, 2005, **7**, 139–142.
- 23 M. Blangetti, A. Deagostino, C. Prandi, S. Tabasso and P. Venturello, *Org. Lett.*, 2009, **11**, 3914–3917.
- 24 N. Fusetani, S. Matsunaga, H. Matsumoto and Y. Takebayashi, *J. Am. Chem. Soc.*, 1990, **112**, 7053–7054.
- 25 D. A. James, K. Koya, H. Li, G. Q. Liang, Z. Q. Xia, W. W. Ying, Y. M. Wu and L. J. Sun, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1784–1787.
- 26 A. G. Montalban, E. Boman, C. D. Chang, S. C. Ceide, R. Dahl, D. Dalesandro, N. G. J. Delaet, E. Erb, J. T. Ernst, A. Gibbs, J. Kahl, L. Kessler, J. Lundstrom, S. Miller, H. Nakanishi, E. Roberts, E. Saiah, R. Sullivan, Z. J. Wang and C. J. Larson, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1772–1777.
- 27 C. Allais, T. Constantieux and J. Rodriguez, *Synthesis*, 2009, 2523–2530.
- 28 L. Lochmann, *Eur. J. Inorg. Chem.*, 2000, 1115.
- 29 A. Mordini, in *Advances in Carbanion Chemistry*, ed. V. Snieckus, JAI Press, Inc., Greenwich, CT, 1992, vol. 1, pp. 1–45.
- 30 M. Schlosser, *J. Organomet. Chem.*, 1967, **8**, 9.
- 31 M. Schlosser, in *Modern Synthetic Methods*, ed. R. Scheffold, VCH, Weinheim, Germany, 1992, p. 227.
- 32 P. Venturello, *Chem. Commun.*, 1992, 1032–1033.
- 33 A. Deagostino, C. Prandi, C. Zavattaro and P. Venturello, *Eur. J. Org. Chem.*, 2006, 2463–2483.
- 34 To review the reactivity of α,β-unsaturated acetals in the presence of organometallic reagents, see: S. Manna, C. Mioskowski and J. R. Falk, *Tetrahedron Lett.*, 1984, **25**, 519.
- 35 C. Canepa, C. Prandi, L. Sacchi and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1875–1878.
- 36 S. Robin and G. R. Rousseau, *Tetrahedron*, 1998, **54**, 13681–13736.
- 37 M. Abarbri, J. L. Parrain and A. Duchene, *Synth. Commun.*, 1998, **28**, 239–249.
- 38 **5g** has been recovered as an oil. NOESY spectra are reported in the ESI†.