Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8507–8510

The first organocatalytic addition of 2-trimethylsilyloxyfuran to carbonyl compounds: hydrogen-bond catalysis in γ-butenolides synthesis

Margherita De Rosa, Lucia Citro and Annunziata Soriente*

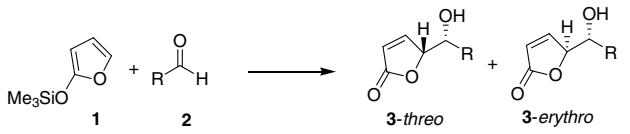
Dipartimento di Chimica, Università degli Studi di Salerno, via Ponte don Melillo, 84084 Fisciano, Salerno, Italy

Received 27 July 2006; revised 26 September 2006; accepted 27 September 2006
Available online 17 October 2006

Abstract—This letter describes the first example of diastereoselective 'organocatalyzed' synthesis of the butenolide products substituted at the γ-position by a chain bearing hydroxyl groups. The urea-derivative **4** has proved to be an efficient catalyst for the addition of the commercial TMSOF to carbonyl compounds under solvent-free conditions. The reaction conditions and generality of the procedure have been examined.

The butenolide moiety substituted at the γ-position by a chain bearing hydroxyl groups is an important structural subunit in many natural products and biologically active compounds.[1] The catalytic coupling of the commercial 2-trimethylsilyloxyfuran (TMSOF) **1** with aldehydes by means of aldol reaction has emerged as a pre-eminent strategy for butenolide synthesis (Scheme 1).[2]

In a pioneering work Yoshii et al.[3] reported the catalytic coupling of **1** with aldehydes for the preparation of a variety of butenolide-like compounds using Lewis acids as catalysts. The approach was expanded to various electrophiles[4] and the regiochemical behavior[5] was investigated. The corresponding vinylogous adducts were obtained as a mixture of racemic stereoisomer and the stereochemical behavior of the process began to be investigated later.[6,7] In recent years, a very great number of papers[8] report the diastereoselective addition



Scheme 1.

of variously substituted furan-based silyloxy diene synthons to a variety of achiral aldehydes and acetals using Lewis acids as catalysts.

In the past few years an attractive alternative to metal-catalyzed reactions is the organocatalysis[9] and surprisingly, a single organocatalytic approach to butenolide synthon is known. In fact, in 2003 MacMillan and co-workers[10] reported the first enantioselective organocatalytic 1,4-addition of TMSOF to unsaturated aldehydes with high enantioselectivties but no examples of 'organocatalyzed' aldol addition reaction of 2-trimethylsilyloxyfuran to aldehydes are known.

During our investigation on the reactivity of silyloxydienes[11] we chose to study the possibility to catalyze the reaction by using an urea-derivative catalyst. Ureas and thioureas, employing hydrogen bonding for substrate activation, have recently emerged as highly efficient catalysts[9i,12] in a wide variety of transformations. The choice of these neutral hydrogen-bond donors was dictated by their known ability to coordinate to carbonyl group via double hydrogen-bond motif lowering the LUMO energy and activating it.[13]

We describe herein the results of our preliminary study on the reactivity of the urea-derivative/TMSOF system with carbonyl electrophiles.

The reaction has been first explored with benzaldehyde **2a** and urea-derivative **4** as catalyst (Fig. 1).

Keywords: Organocatalysis; 2-Trimethylsilyloxyfuran; Urea-type catalyst; Aldehydes addition; Solvent-free reactions.
* Corresponding author. Tel.: +39 899 69584; fax: +39 899 69603; e-mail: titti@unisa.it

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.143

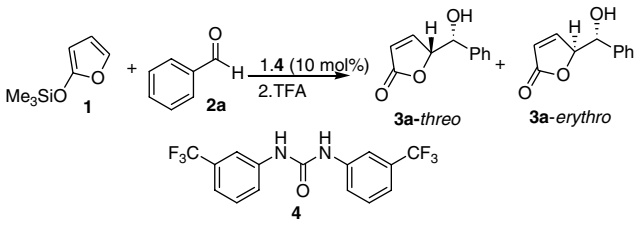


Figure 1.

Preliminary exploratory experiments revealed that **4** (10 mol %) promoted the addition of aldehyde to TMSOF at room temperature under 'solvent-free conditions' with good results (Table 1, entry 1) providing it as the good catalyst candidate for further optimization of the reaction conditions. It is noteworthy that in a blank experiment no reaction was observed under similar reaction conditions in the absence of **4.**

When the reaction was carried out at room temperature with 5 mmol of benzaldehyde (Table 1, entry 2) enhanced the yield and the diastereoselectivity. By lowering the reaction temperature to −20 °C (Table 1, entry 3) resulted in a much longer reaction time and the diastereoselectivity was not improved.

Therefore, from the results in Table 1, the reaction conditions indicated in entry 2 are evidently the best choice for the present reaction system in terms of reactivity and diastereoselectivity. With optimal reaction conditions established, several aldehydes were evaluated as substrates (Table 2).

A variety of aromatic aldehydes (Table 2, entries 1–5) were found to be suitable coupling partners with TMSOF. Electron-donating, electron-withdrawing substrates underwent reaction in isolated yields ranging from 40% to 90% and with moderate to good diastereoselectivities. Moreover, variation in the electronic nature of the substituent on the aromatic ring has apparently no influence on the efficiency and diastereoselectivity of the reaction. These reaction conditions seem to be efficient also for α,β-unsaturated cinnamaldehyde (Table 2, entry 6) while the result from entry 7 (Table 2) suggests that aromatic aldehydes are superior to aliphatic ones. Moreover, it is worthwhile to note that the activated ketone (Table 2, entry 8) has also been transformed in a moderate yield and moderate diastereoselectivity.

In agreement with the data of the literature,[17] the *anti* isomers are predominantly observed in all cases. The

Table 1. Addition of silyloxyfuran **1** to benzaldehyde **2a** catalyzed by urea-derivative **4**

Entry	Equivalent of **2a**	*T*/*t* (°C/h)	Yield (%)[a]	*erythro*/*threo*[b]
1	1	rt/24	67	61/39
2	5	rt/24	81	66/34
3	5	−20/72	73	66/34

[a] Yields refer to isolated compounds **3**, obtained as diastereomeric mixtures after chromatographic purification.

[b] The diastereoisomeric ratio was calculated by ^{1}H NMR data according to the literature data.[14]

Table 2. Addition of silyloxyfuran **1** to different aldehydes under optimized conditions

Entry	RCHO	Product	Yield (%)	d.r.[a]
1[b,c]	*p*-O_2N–C_6H_5	**3b**	90[d]	65/35
2	*p*-CF_3–C_6H_5	**3c**	49[d]	57/43
3[c]	*p*-Br–C_6H_5	**3d**	40[e]	64/36
4	*p*-CH_3–C_6H_5	**3e**	90[d]	66/34
5	*p*-OCH_3–C_6H_5	**3f**	64[e]	50/50
6	C_6H_5CH=CH	**3g**	46[e]	61/39
7	C_7H_{15}	**3h**	25[e]	60/40
8	$CH_3COCOOEt$	**3i**	47[d]	55/45

[a] The reported values refer to *erythro*/*threo* diastereoisomeric ratios and were calculated by ^{1}H NMR data according to the literature data.[14,15]

[b] The reaction was completed after only 1 h.

[c] Toluene (0.5 mL) was used to dissolve the aldehydes.

[d] Yields refer to isolated compounds **3**, obtained as diastereomeric mixtures after chromatographic purification whose structures were confirmed by spectroscopic data.[16]

[e] Yields refer to isolated compounds **3**, obtained as diastereomeric mixtures after chromatographic purification whose structures were confirmed by ^{1}H NMR and ^{13}C NMR data according to the literature data.[14,15]

diastereoselective behavior of the reaction can be tentatively explained from an open-chain transition state (**B**) (Fig. 2) with a synclinal arrangement of the reagents. In fact, the *anti*-diastereoselectivity has to be attributed to the unfavorable steric interaction between the R group of the aldehyde and the furanic ring (conformer **A**). An antiperiplanar arrangement of the reagents (**C** and **D**) reveals steric congestions in both conformers. In particular the transition state depicted by **D**, which would have to carry to the same configurated *erythro*-aldol

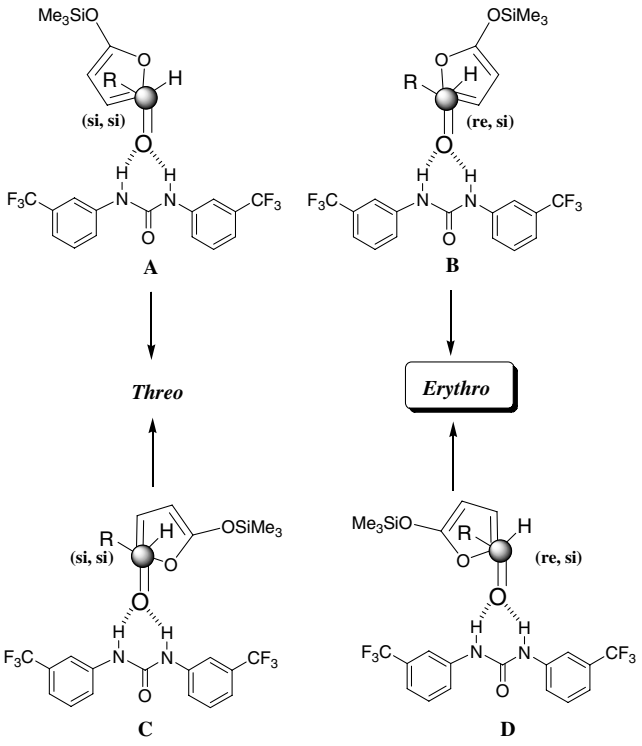


Figure 2. The open transition state structures.

adduct obtained from **B**, possesses the same steric crowding of **A** and the examination of **C** also reveals steric congestion between the bulky trimethylsilyl group and the trifluoromethyl-phenyl ring of the catalyst.

In summary, the collected data show the broad potential for hydrogen-bond catalysis in the diastereoselective addition of **1** to carbonyl compounds. The simplicity of the experimental procedure and the ready accessibility of catalyst **4** renders this an experimentally attractive method for the preparation of butenolides substituted at the γ-position by a chain bearing hydroxyl groups.

Future work in our laboratory will be addressed to extend this survey and to examine chiral urea-derivatives in order to produce chiral products.

General procedure for the addition of aldehydes to 2-trimethylsilyloxyfuran catalyzed by urea-derivative. A mixture of catalyst **4** (0.05 mmol) and aldehyde (2.5 mmol) was stirred at room temperature for 30 min. The TMSOF (84 μl, 0.5 mmol) was then added dropwise and the resulting solution was stirred at room temperature for the times reported in Table 1. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled at −30 °C and TFA (0.2 mL) was added. The solution was then warmed to rt and stirred for 1 h after which the desilylation was complete. The reaction mixture was diluted with ethyl acetate and a saturated aqueous solution of $NaHCO_3$ (2 mL) was added dropwise. The mixture was stirred until the evolution of gas ceased (30 min), then the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography ($CHCl_3$) to afford a mixture of the corresponding diastereomeric butenolides. The diastereomeric ratio was determined by ^1H NMR (400 MHz) analysis.

Acknowledgments

This work was supported by the Italian Ministry of Education (MIUR).

References and notes

1. Selected examples: (a) Cameron, J. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142–145; (b) Schuyler, A.; Caufield, C. E.; Hu, W.; Keeney, D.; Labthavikul, P.; Morris, K.; Naughton, S. M.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 176–180; (c) Li, R.-T.; Han, Q.-B.; Zheng, Y.-T.; Wang, R.-R.; Yang, L.-M.; Lu, Y.; Sang, S.-Q.; Zheng, Q.-T.; Zhao, Q.-S.; Sun, H.-D. *Chem. Commun.* **2005**, *23*, 2936–2938; (d) Dalpiaz, A.; Pavan, B.; Scaglianti, M.; Vitali, F.; Bortolotti, F.; Biondi, C.; Scatturin, A.; Manfredini, S. *Int. J. Pharm.* **2005**, *291*, 171–181.
2. Maulide, N.; Marko, I. E. *Org. Lett.* **2006**, *8*, 3705–3707.
3. Yoshii, E.; Koizumi, T.; Kitatsuji, E.; Kawazoe, T.; Kaneko, T. *Heterocycles* **1976**, *4*, 1663–1668.
4. (a) Asaoka, M.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1953–1956; (b) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 4611–4614; (c) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269–4270.
5. (a) Fiorenza, M.; Ricci, A.; Romanelli, M. N.; Taddei, M.; Dembech, P.; Seconi, G. *Heterocycles* **1982**, *19*, 2327–2329; (b) Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, *49*, 551–553.
6. (a) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037–4040; (b) Jefford, C. W.; Jaggi, D.; Bernardinelli, G.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4041–4044.
7. Brown, D. W.; Campbell, M.; Taylor, A. P.; Zhang, X.-A. *Tetrahedron Lett.* **1987**, *28*, 985–988.
8. (a) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hänsel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717–742; (b) Boukouvalas, J.; Maltais, F. *Tetrahedron Lett.* **1995**, *36*, 7175–7176; (c) Boukouvalas, J.; Maltais, F. *Tetrahedron Lett.* **1994**, *35*, 5769–5770; (d) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897–7900; (e) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett* **1998**, *39*, 7665–7668; (f) Xu, D.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 4685–4688; (g) Von der Ohe, F.; Brückner, R. *Tetrahedron Lett.* **1998**, *39*, 1909–1910; (h) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford, 1998; Vol. 3, pp 113–189.
9. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) List, B. *Synlett* **2001**, 1675; (c) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (d) Barbas, C. F.; Notz, W.; Tanaka, F. *Acc. Chem. Res.* **2004**, *37*, 580–591; (e) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296; (f) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763; (g) Pinko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064; (h) List, B. *Adv. Synth. Catal.* **2004**, *346*, 1021; (i) List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (j) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, 2005.
10. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.
11. (a) Soriente, A.; De Rosa, M.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2255–2258; (b) Soriente, A.; De Rosa, M.; Stanzione, M.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 959–963; (c) Villano, R.; De Rosa, M.; Salerno, C.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1949–1952; (d) De Rosa, M.; Acocella, M. R.; Villano, R.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2499–2502; (e) Villano, R.; Acocella, M. R.; De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *38*, 2421–2424.
12. (a) Mark, S. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543, and references therein; (b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032–4035; (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125; (d) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807–811; (e) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898–1900.
13. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.
14. Szlosek, M.; Figadére, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799–1801.
15. Acocella, M. R.; De Rosa, M.; Massa, A.; Palombi, L.; Villano, R.; Scettri, A. *Tetrahedron* **2005**, *61*, 4091–4097.
16. *Data for* **3b**: *Mixture of diastereoisomers*. Viscous yellow oil. Anal. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96.

Found: C, 56.26; H, 3.78; N, 5.87. *Erythro isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (2H, d, $J = 8.6$ Hz), 7.61 (1H, dd, $J = 1.3$, 5.8 Hz), 7.54 (2H, d, $J = 8.6$ Hz), 6.11 (1H, dd, $J = 1.6$, 5.8 Hz), 5.17 (1H, m), 4.83 (1H, d, $J = 4.2$ Hz), 3.18 (br s, OH). ^{13}C NMR ($CDCl_3$) δ: 173.1; 152.4; 147.3; 146.8; 127.9 (2C); 123.9 (2C); 123.8; 85.7; 74.0. *Threo isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (2H, d, $J = 8.6$ Hz), 7.54 (2H, d, $J = 8.6$ Hz), 7.29 (1H, dd, $J = 1.3$, 5.8 Hz), 6.18 (1H, dd, $J = 1.6$, 5.8 Hz), 5.17 (1H, m), 4.97 (1H, d, $J = 6.2$ Hz), 3.20 (br s, OH). ^{13}C NMR ($CDCl_3$) δ: 172.9; 152.0; 147.3; 146.8; 127.2 (2C); 124.0 (2C); 123.8; 85.8; 72.6.

Data for **3c**: *Mixture of diastereoisomers*. Viscous yellow oil. Anal. Calcd for $C_{12}H_9F_3O_3$: C, 55.82; H, 3.51; F, 22.07. Found: C, 56.72; H, 3.60; F, 21.99. *Erythro isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67–7.48 (4H, m), 7.29 (1H, dd, $J = 1.1$, 5.8 Hz), 6.17 (1H, dd, $J = 1.6$, 5.8 Hz), 5.15 (2H, m), 3.36 (br s, OH). ^{13}C NMR ($CDCl_3$) δ: 173.4; 152.9; 142.6; 128.8; 126.6 (2C); 125.7 (2C); 123.4; 122.7; 86.6; 72.4. *Threo isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67–7.48 (4H, m), 7.23 (1H, dd, $J = 1.5$, 5.8 Hz), 6.11 (1H, dd, $J = 1.8$, 5.8 Hz), 5.15 (1H, m), 4.86 (1H, d, $J = 6.1$ Hz), 3.36 (br s, OH). ^{13}C NMR ($CDCl_3$) δ: 172.9; 153.3; 142.1; 128.8; 127.2 (2C); 125.7 (2C); 123.2; 122.7; 86.5; 74.2.

Data for **3e**: *Mixture of diastereoisomers*. Viscous yellow oil. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.49; H, 6.00. *Erythro isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (1H, dd, $J = 1.4$, 5.8 Hz), 7.28–7.14 (4H, m), 6.10 (1H, dd, $J = 1.9$, 5.8 Hz), 5.11 (1H, m), 4.96 (1H, d, $J = 3.2$ Hz), 3.51 (br s, OH). 2.34 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 173.6; 153.5; 138.2; 135.7; 129.4 (2C); 126.2 (2C); 123.0; 87.0; 73.0; 21.2. *Threo isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.14 (m, 5H) 6.03 (1H, dd, $J = 1.9$, 5.8 Hz), 5.11 (1H, m), 4.64 (1H, d, $J = 6.8$ Hz), 3.51 (br s, OH), 2.32 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 173.2; 153.9; 138.6; 135.2; 129.4 (2C); 126.8 (2C); 122.8; 87.2; 75.1; 21.2.

Data for **3i**: *Mixture of diastereoisomers*. Viscous yellow oil. Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 54.08; H, 6.13. *Erythro isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (1H, dd, $J = 1.4$, 5.8 Hz), 6.19 (1H, dd, $J = 1.9$, 5.8 Hz), 5.17 (1H, d, $J = 1.4$ Hz), 4.26 (2H, q, $J = 7.1$ Hz), 3.54 (br s, OH), 1.52 (3H, s), 1.29 (3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$) δ: 173.4; 172.4; 151.6; 123.8; 86.1; 85.8; 63.0; 22.3; 14.1. *Threo Isomer* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (1H, dd, $J = 1.4$, 5.8 Hz), 6.17 (1H, dd, $J = 1.9$, 5.8 Hz), 5.10 (1H, d, $J = 1.4$ Hz), 4.26 (2H, q, $J = 7.1$ Hz), 3.41 (br s, OH), 1.49 (3H, s), 1.28 (3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$) δ: 173.0; 172.5; 152.5; 123.3; 86.3; 85.8; 62.8; 21.7; 14.2.

17. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109–118.