# ChemInform Abstract: Highly Enantioselective Conjugate Additions of Aldehydes to Vinyl Sulfones

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# Highly Enantioselective Conjugate Additions of Aldehydes to Vinyl Sulfones

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Given the vast chemistry of the aldehyde and the sulfone groups,[1] a combination of both functionalities through stereoselective C–C bond-forming reactions is highly appealing. Towards this goal, the 1,4-addition of aldehydes to unsaturated sulfones is a highly valuable tool. Unfortunately, catalytic and enantioselective variations of the reaction are seemingly elusive.[2] First reports of catalytic enantioselective conjugate additions of aldehydes to vinyl sulfones involve secondary/tertiary 1,2-diamine organocatalysts **1** and **2**,[3] which activate the aldehyde component through enamine formation.[4,5] The behaviour of these catalysts is significant, but the method holds important limitations with regards to substrate scope and enantioselectivity: a large excess (10 equivalents) of the aldehyde is usually required and modest selectivities (typically 70% *ee*) are obtained. On the other hand, while the direct catalytic and asymmetric 1,4-addition of aldehydes to certain electron-deficient olefins,[6,7] most particularly nitroolefins,[7,8] have met success recently, one accompanying problem to the reaction with vinyl sulfone acceptors is the retroaddition, which causes formation of undesired dimeric side products.[3] Herein we report the use of less basic chiral amine catalysts (see Figure 1) to provide a solution to these problems thus considerably expanding the utility of vinyl sulfones in organic synthesis.

In an initial screen, commercially available prolinol silyl ethers **3** and **4**,[9] and analogue **5**, recently disclosed from our laboratory,[10] were tested for the reaction between aldehydes **6** and vinyl bis(sulfone) **7**. At the outset, it was not clear whether each catalyst would be equally effective. Besides the above problems, there is the fact that diaryl prolinol ethers may exhibit certain substrate specificity.[11]

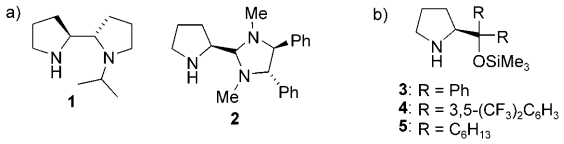
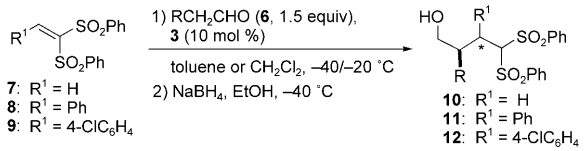



Figure 1. Amine catalysts explored for the conjugate addition of aldehydes to vinyl sulfones: a) Previous studies; b) this work.

To our delight, by using catalyst **3**, products **10** were obtained (Table 1), after reduction of the 1,4-addition adduct, in yields typically over 90% and enantioselectivities greater than 95% for both linear as well as β-branched aldehydes. For example, propionaldehyde, which provides racemic adducts with catalyst **1**, affords **10a** with 95% *ee*. Similarly,

Table 1. Addition of aldehydes 6 to vinyl sulfones promoted by **3**.




| Aldehyde **6**, R | Sulfone | Product | Yield [%][a] | *syn*/*anti*[b] | *ee* [%][c] |
|---|---|---|---|---|---|
| **a**, $CH_3$ | **7** | **10a** | 95 | – | 95 |
| | **8** | **11a** | 60 | 85:15 | 99(99)[d] |
| **b**, $CH_3CH_2$ | **7** | **10b** | 93 | – | 98 |
| | **9** | **12b** | 49 | 70:30 | 99(n.d.) |
| **c**, $CH_3(CH_2)_2$ | **7** | **10c** | 94 | – | 97 |
| **d**, $CH_3(CH_2)_3$ | **8** | **11d** | 52 | 70:30 | 99(99)[d] |
| | **9** | **12d** | 51 | 70:30 | 99(n.d.) |
| **e**, $CH_3(CH_2)_4$ | **7** | **10e** | 95 | – | 96 |
| **f**, $PhCH_2$ | **7** | **10f** | 92 | – | 95 |
| **g**, $(CH_3)_2CH$ | **7** | **10g** | 91 | – | 99 |

[a] Isolated yield of product alcohol after column chromatography (hexanes/EtOAc 60:40). [b] Determined by $^1H/^{13}C$ NMR and chiral HPLC. [c] Determined by chiral HPLC. [d] *ee* of the minor diastereomer. n.d.: not determined.

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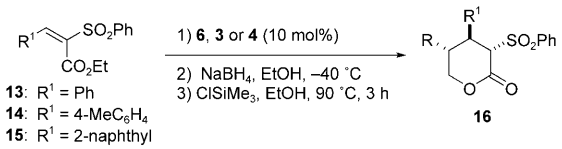
valeraldehyde affords **10c** with 97% *ee*, whilst only 54% *ee* is obtained with catalyst **1** (74% *ee* with **2**). Among the solvents methylene chloride and toluene gave the best results. No reaction was observed in protic solvents such as ethanol, methanol or isopropyl alcohol, whilst in DMF—a typical solvent for other enamine-based reactions—low *ee* values are obtained. Catalyst **4** behaved similarly, but **5**, which performs very well in other 1,4-addition reactions,[10] gave rise to 60–75% *ee* at best.[12] Formation of dimeric side product was determined to be below the limit of detection of $^1$H NMR spectroscopy. On the other hand, β-substituted sulfones **8** and **9** were also good electrophiles, giving rise adducts **11** and **12** with good yields, diastereomeric ratios in the range from 70:30 to 80:20, and essentially complete enantioselectivity.[13]

Table 2. Aldehyde addition to *E*-α-ethoxycarbonyl vinyl sulfones promoted by **3**/**4**.[a]




**13**: $R^1$ = Ph
**14**: $R^1$ = 4-$MeC_6H_4$
**15**: $R^1$ = 2-naphthyl

**16**

| | Product **16** | | | | | |
|---|---|---|---|---|---|---|
| R | $R^1$ | Cat. | *t* [h] | Yield [%][b] | dr[c] | *ee* [%][d] |
| **a** Me | Ph | **3** | 3 | 85 | 80:20 | 99 |
| | | **4** | 3 | 54 | 80:20 | 98 |
| **b** Me | 2-naphthyl | **3** | 3 | 75 | 75:25 | 97 |
| **c** Pr | 4-$MeC_6H_4$ | **3** | 20 | 60 | 75:25 | 99 |
| | | **4** | 20 | 30 | 70:30 | 97 |
| **d** Pn | Ph | **3** | 16 | 78 | 75:25 | 98 |
| | | **4** | 16 | 35 | 75:25 | n.d. |

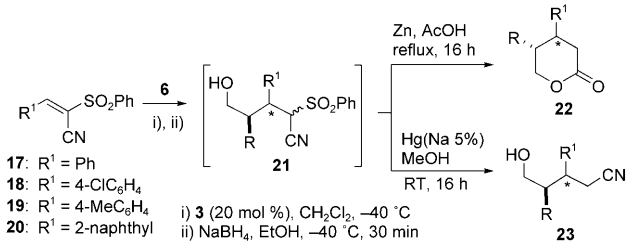
[a] Reactions conducted at 0.5 mmol scale in $CH_2Cl_2$ at RT overnight. Aldehyde/vinyl sulfone 3:1 ratio. [b] Isolated yield of lactone product after column chromatography (Hex/EtOAc 90:10). [c] Determined by $^{13}$C NMR; relative and absolute configuration of the minor diastereomer not determined. [d] Determined by chiral HPLC. n.d.: not determined.

The present catalytic reaction can also be applied to other vinyl sulfones with maintained levels of stereoselectivity. For example, as shown in Table 2, α-ethoxycarbonyl vinyl sulfones **13**, **14**, and **15** reacted with aldehydes in the presence of catalysts **3**/**4** (10 mol%) to give, after reduction and cyclisation, the corresponding lactone adducts **16** with three contiguous stereocenters. Nearly perfect enantiocontrol is observed in most cases for both catalysts, but catalyst **3** provided better yields (up to 85% yield over three steps) than **4**. It is particularly noteworthy the fact that the sulfone group is key for the 1,4-addition reaction to proceed satisfactorily. For instance, whilst vinyl sulfones **13a** and **13c**, upon reaction with propanal and pentanal, respectively, afforded products **16a** and **16c** in 85 and 60% yield, the respective arylidene ethyl malonates, which would generate analogous δ-lactones, were unreactive regardless of the reaction conditions employed.[14] In this respect, δ-lactones are common structural units of natural products as well as versatile building blocks of several classes of biologically active compounds.[15]

A third variation concerns α,β-unsaturated nitriles, a recalcitrant class of Michael acceptors[16] that remain completely unreactive under the present catalytic conditions. However, addition of aldehydes to α-cyano vinyl sulfones **17**–**20** took place smoothly at −40 °C (Table 3) to give, after reduction of the resulting adduct, alcohols **21**. The latter compounds are versatile intermediates which allow, for example, access to lactones **22** or cyano alcohols **23** in good yields, diastereomeric ratio, and again essentially perfect enantioselectivity. This approach constitutes a new enantioselective entry to building blocks otherwise difficult to access from unsaturated nitriles.[16] In the above reactions a threefold excess of aldehyde substrate is employed regularly, but nearly equimolar amounts suffice for achieving equal efficiency. Configuration of the products was established by X-ray analyses of *syn*-**12b**, **16a**, and *trans*-**22b**,[17] and by assuming a uniform reaction mechanism.[18]

The potential of this catalytic methodology can further be shown by the reductive double desulfonation of **10f** and *syn*-**11d** to afford alcohols **24** and **25** (Scheme 1). This achievement represents a formal catalytic enantioselective α-alkylation of aldehydes with secondary alkyl halides, a process that still bears a considerable challenge.[19] When the desulfonation step is preceded with a prior alkylation reaction under standard conditions, as in the transformation of **10f** into alcohols **26**, the above approach serves to access to

Table 3. Addition to *E*-α-cyano vinyl sulfones promoted by **3**.[a]

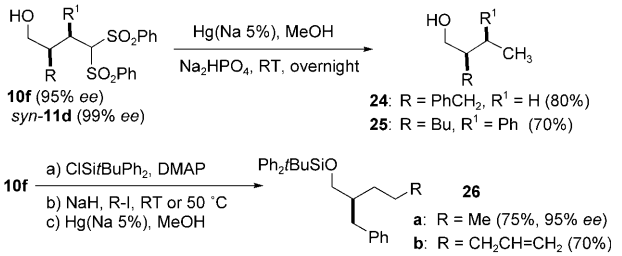



**17**: $R^1$ = Ph
**18**: $R^1$ = 4-$ClC_6H_4$
**19**: $R^1$ = 4-$MeC_6H_4$
**20**: $R^1$ = 2-naphthyl

| Compound | | | Product **22** | | | Product **23** | | |
|---|---|---|---|---|---|---|---|---|
| | R | $R^1$ | Yield[b] [%] | dr[c] *trans/cis* | *ee*[d] [%] | Yield[b] [%] | dr[c] *syn/anti* | *ee*[d] [%] |
| **a** | Me | Ph | 57 | 75:25 | 99(99) | 70 | 75:25 | 99(98) |
| **b** | | 4-$ClC_6H_4$ | 59 | 80:20 | 99(99) | – | – | – |
| **c** | | 4-$MeC_6H_4$ | 65 | 80:20 | 99(n.d.) | 70 | 75:25 | 99(97) |
| **d** | | 2-naphthyl | 65 | 70:30 | 99(99) | 52[e] | 80:20 | 99(90) |
| **e** | Et | Ph | 65 | 70:30 | 99(99) | 65 | 60:40 | 99(99) |
| **f** | Pr | Ph | 72 | 70:30 | 99(99) | 70 | 85:15 | 99(n.d.) |
| **g** | Bu | Ph | 70 | 75:25 | 99(99) | – | – | – |

[a] Ratio of aldehyde/vinyl sulfone 3:1. [b] Combined yield of diastereomers over the three steps. [c] Determined by $^1$H NMR and/or HPLC. [d] Determined by HPLC. *ee* values in brackets refer to the minor diastereomer *cis*-**22** and *anti*-**23**, respectively. n.d.: not determined.




Scheme 1. Elaboration of adducts via desulfonation/alkylation standard protocols.

longer chain alkylated products in a practical way. These examples demonstrate how the present organocatalytic conjugate addition to vinyl bis(sulfone)s, in conjunction with a subsequent alkylation step, opens up new opportunities for the asymmetric synthesis of α-branched aldehydes and products thereof.

In summary, although further optimisation is needed to improve reaction diastereocontrol,[20] the present catalytic system introduces an operationally simple protocol for accessing a variety of structural motifs from readily available vinyl sulfones and unmodified aldehydes as starting materials. The trick of success is the use of a diarylprolinol silyl ether as reaction promoter that leads to the highest enantioselectivity reported to date for this class of Michael acceptors. Further investigations on the utility of *gem*-disulfone adducts as alkyl carbanion surrogates are currently underway in our laboratory and will be reported in due course.

## Experimental Section

**Catalytic conjugate addition of aldehydes to vinyl sulfones**: To a mixture of the catalyst **3** or **4** (10–20 mol%) and vinyl sulfone (1 mmol) in toluene (1 mL) (for sulfones **7**–**9**) or $CH_2Cl_2$ (1 mL) (for **13**–**15** and **17**–**20**) at −40 °C was added aldehyde **6** (1.5–3.0 equiv), and the mixture stirred overnight (16 h) at the same temperature. The resulting solution was diluted with EtOH (1 mL) and a suspension of $NaBH_4$ (2 equiv) in EtOH (2 mL) was then added drop-wise. The mixture was stirred at −40 °C for 30 min and quenched with $H_2O$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and the crude product purified by flash column chromatography (hexane/EtOAc 60:40).

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**Keywords:** alkylation · asymmetric catalysis · Michael addition · organocatalysis · vinyl sulfones

[1] N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, **1993**.

[2] Enantioselective additions of active methylenes to vinyl sulfones: a) H. Li, J. Song, Z. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; b) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097–2099.

[3] a) S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361–4364; b) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562; c) A. Quintard, C. Bournaud, A. Alexakis, *Chem. Eur. J.* **2008**, *14*, 7504–7507.

[4] Reviews on enamine catalysis: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; c) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001–2011; d) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492.

[5] Reviews on asymmetric organocatalysis: a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* Wiley-VCH, Weinheim, **2005**.

[6] Enones: a) P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151–4157; b) Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253–4256; c) T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599; d) M. T. Hechevarria Fonseca, B. List, B. *Angew. Chem.* **2004**, *116*, 4048–4050; *Angew. Chem. Int. Ed.* **2004**, *43*, 3958–3960. Benzoquinones: e) J. Aleman, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 5616–5619; *Angew. Chem. Int. Ed.* **2007**, *46*, 5520–5523. Maleimides: f) G.-L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayah, A. Córdova, *Chem. Commun.* **2007**, 734–735. Vinyl phosphonates: g) S. Sulzer-Mossé, M. Tissot, A. Alexakis, *Org. Lett.* **2007**, *9*, 3749–3752. Alkylidene malonates: h) G.-L. Zhao, J. Vesely, J. Sun, K. E. Christensen, C. Bonneau, A. Córdova, *Adv. Synth. Catal.* **2008**, *350*, 657–661; i) α-keto-α,β-unsaturated esters: J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 2561–2564; α-cyanoacrylates: j) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2008**, *14*, 4788–4791.

[7] Reviews on enantioselective organocatalytic conjugate additions: a) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065–2092.

[8] Review: a) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135. Selected, more recent examples: b) L.-q. Gu, G. Zhao, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632; c) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5610; d) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548; e) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874; f) P. García-García, A. Ladépeche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; g) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724.

[9] First reports documenting catalysts **3** and **4**: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215. For a review: d) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948.

[10] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583–8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.

[11] Diarylprolinol ethers such as **3** and **4** display considerable reaction- and substrate specificity (see ref. [9d]). For recent examples illustrating this behaviour, see: Conjugate addition to enals and enones:

  

a) see ref. [6d,k]; b) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 4664–4667; *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591; c) P. T. Franke, B. Richter, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 6317–6321. Other conjugate additions: d) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724; e) P. García-García, R. Ladépeche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721.

[12] For details, see Supporting Information. While still premature, the superior performance of diaryl catalysts **3** and **4**, with respect to the dialkyl catalyst **5**, might be indicative of π-π interactions between the catalysts **3**/**4** and the arylsulfonyl moiety of substrates being operative.

[13] During the preparation of this manuscript, a highly enantioselective conjugate addition of aldehydes to vinyl bis(sulfone)s catalysed by **3**/**4** has appeared wherein comparatively higher dr and opposite sense of enantioinduction are reported for the reactions involving β-substituted vinyl bis(sulfone)s; see: Q. Zhu, Y. Lu, *Org. Lett.* **2008**, *10*, 4803–4806.

[14] After 24 h of stirring with the corresponding aldehyde in either $CH_2Cl_2$ or $CH_3CN$ at room temperature in the presence of 10–20 mol% of catalyst **3**, both benzylidene and 4-methylbenzylidene ethyl malonates were recovered unchanged. Apparently, only electron deficient arylidene malonates react satisfactorily with aldehydes under enamine catalysis; see ref. [6h].

[15] For leading references, see: a) A. Habel, W. Boland, *Org. Biomol. Chem.* **2008**, *6*, 1601–1604; b) R. K. Dieter, F. Guo, *Org. Lett.* **2006**, *8*, 4779–4782; c) O. Pàmies, J.-E. Bäckvall, *J. Org. Chem.* **2002**, *67*, 1261–1265.

[16] For a review on unsaturated nitriles, see: F. F. Fleming, Q. Wang, *Chem. Rev.* **2003**, *103*, 2035–2077.

[17] CCDC-706443 (*syn*-**12b**), 706444 (**16a**), 706445 (*trans*-**22b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] For a theoretical study of enamine catalysis involving diaryl prolinol ethers, see: P. Dinér, A. Kjaersgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122–127.

[19] To the best of our knowledge, catalytic α-alkylation of unmodified aldehydes with concomitant generation of two stereocenters remains unsolved. For an organocatalytic entry to the asymmetric intramolecular α-alkylation of aldehydes with alkyl iodides, see: a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451. For emergent intermolecular approaches, see: b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80; c) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831–8834; *Angew. Chem. Int. Ed.* **2008**, *47*, 8707–8710.

[20] Current catalytic asymmetric Michael reaction protocols in which adducts with either *syn* or *anti* relative configuration can be formed tend to show, with few exceptions, moderate levels of diastereocontrol (see ref. [7]). While results in Tables 1 and 2 confirm this inherent problem, we have found that improved dr values are affordable by changing the nature of the sulfone group. For instance, starting from the respective *tert*-butyl sulfone analogue to **17** and **20**, respectively, and propanal, lactones **22a** and **22d** were obtained in 90:10 and 85:15 diastereomeric ratios.

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