Asymmetric Catalysis

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Catalytic Asymmetric Mannich Reactions of Sulfonylacetates**

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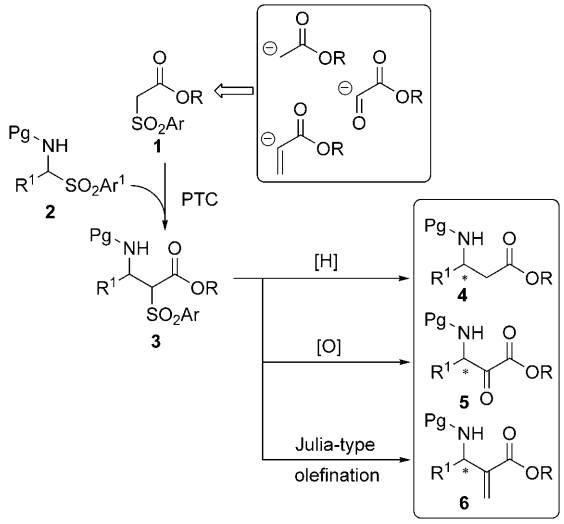
Aryl and heteroaryl sulfones are very versatile intermediates in organic chemistry.[1] Owing to their strong electron-withdrawing properties, sulfonyl moieties are able to stabilize a carbanion at the α position, as well as to activate a conjugated double bond for nucleophilic addition. After conferring the desired reactivity, the sulfonyl moiety can be removed by reduction or transformed into another useful functionality, such as a C–C double bond or a ketone, through simple synthetic manipulations.[2] For these reasons, the development of catalytic asymmetric transformations that lead to enantiomerically enriched sulfonyl compounds has received much attention.[3] In particular, vinyl sulfones[4] have been used as electron-deficient olefins, and α-substituted sulfones have been used for the generation of various nucleophilic species or carbenes.[5] In contrast, the employment of arylsulfonylacetates **1** in a catalytic asymmetric setting has to our knowledge never been reported, although these readily enolizable compounds could conceivably be used as convenient synthetic equivalents of α anions of carboxylic acid derivatives (Scheme 1).



Scheme 1. Catalytic asymmetric Mannich reaction of sulfonylacetates. Pg = *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz).

We considered the possibility of using phase-transfer catalysis (PTC) for the mild deprotonation of arylsulfonylacetates **1**[6] with the aim of exploring their enantioselective Mannich[7] addition to highly reactive *N*-carbamoyl imines generated in situ from α-amidosulfones **2** (Scheme 1).[8] The use of PTC with α-amidosulfones **2** as imine surrogates should guarantee broad substrate scope, user-friendly conditions, as well as useful *N*-carbamoyl protecting groups (Pg) on the nitrogen atom which would further enhance the versatility of the approach..[9] Our efforts were motivated by the various possible transformations of the Mannich adducts **3**. For example, the reductive removal of the sulfonyl moiety would lead to N-protected β^3-amino acid esters **4** in one step, whereas an oxidative desulfonylation would give α-keto-β-aminoesters **5** (Scheme 1). Optically active α-alkylidene β-aminoesters **6**, generally referred to as aza-Morita–Baylis–Hillman (aza-MBH) adducts, could instead be accessed through a Julia-type olefination process. Owing to their various applications and biological properties, the preparation of β-amino acid derivatives of type **4**–**6** in enantiomerically enriched form has been the focus of tremendous effort in the last few years;[10] remarkably, organocatalytic Mannich reactions with acetate donors equipped with removable activating groups are amongst the most attractive approaches reported to date.[11]

At the outset of our studies on the reaction between arylsulfonylacetates **1** and α-amidosulfones **2** under PTC conditions, we invariably observed the formation of a nearly equimolar mixture of two diastereoisomers **3** with almost identical *ee* values. This observation was accounted for in terms of an epimerization of the stereogenic center bonded to the sulfonyl group in adducts **3** under the basic reaction conditions. As this stereogenic center is lost in the final products **4**–**6**, the real goal of our catalytic transformation, we proceeded to optimize the reaction conditions and catalyst structure (Table 1). Commercially available methyl phenylsulfonylacetate (**1a**) was chosen as the Mannich donor for some preliminary experiments, which showed that it was possible to carry out the catalytic transformation with moderate enantioselectivity in toluene at −30 °C with aqueous K_3PO_4 (50 % w/w) as the base and a quaternary ammonium salt derived from inexpensive quinidine as the catalyst.[12] We screened catalysts **7a**–**e** (Table 1, entries 1–5), all of which contain *ortho* substituents in the benzylic moiety attached to the quinuclidine N atom,[9c,13] and found that the 2,6-difluoro derivative **7e** was the most efficient in terms of enantioinduction in the reaction with α-amidosulfone **2a**

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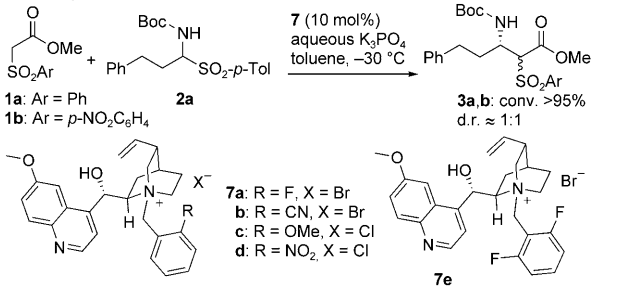
Supporting information for this article (including additional optimization results, experimental details, and copies of the ^{1}H and ^{13}C NMR spectra) is available on the WWW under http://dx.doi.org/10.1002/anie.200900701.

Table 1: Optimization studies.[a]

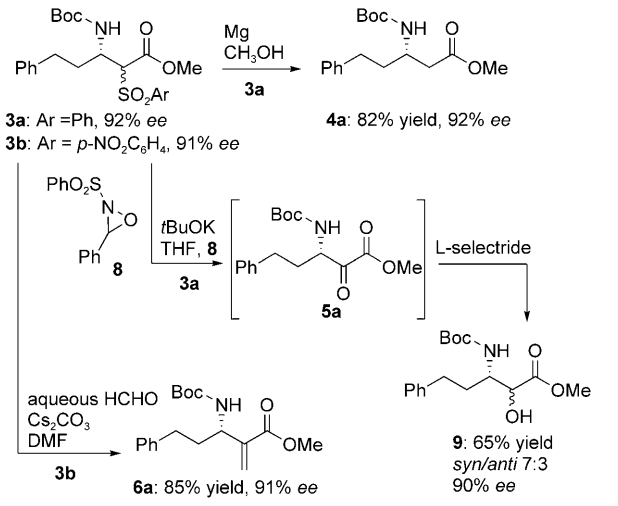


Entry	1	Catalyst	3	*ee* [%][b]
1	**1a**	**7a**	**3a**	63
2	**1a**	**7b**	**3a**	72
3	**1a**	**7c**	**3a**	76
4	**1a**	**7d**	**3a**	76
5	**1a**	**7e**	**3a**	92
6[c]	**1a**	**7e**	**3a**	92
7[c]	**1b**	**7e**	**3b**	80
8[c,d]	**1b**	**7e**	**3b**	91

[a] Reactions were carried out with **2a** (19 mg, 0.05 mmol), **1a** or **1b** (0.075 mmol), catalyst **7** (10 mol%), and aqueous K_3PO_4 (50% w/w, 70 μL, 0.25 mmol) in toluene (0.5 mL) at −30°C for 24–48 h. [b] The *ee* value was determined by HPLC on a chiral stationary phase and is the average value for the two diastereoisomers. [c] The reaction was carried out in 1 mL of toluene with 5 mol% of **7**. [d] The reaction was carried out with 0.125 mmol of aqueous K_3PO_4 (50% w/w, 35 μL).

(Table 1, entry 5). Finally, under more dilute conditions, a lower catalyst loading was possible (Table 1, entry 6).

At this point, we investigated the feasibility of synthetic transformations of the Mannich adducts **3** as envisaged in Scheme 1. On the basis of literature precedent for the reductive desulfonylation of phenylsulfonyl groups,[2,5b] crude **3a** was treated overnight with Mg powder in methanol to afford the corresponding β^3-aminoester **4a** in 82% yield (calculated over two steps; Scheme 2). Most importantly, the *ee* value of the product **4a** was identical to that observed for both diastereoisomers of **3a**, thus corroborating our assumption that adducts **3** undergo epimerization at the stereogenic center bonded to the sulfonyl group under the basic reaction conditions. We next investigated oxidative desulfonylation and used the phenylsulfonyloxaziridine **8** described by Davis et al.[14] for the conversion of the Mannich adduct **3a** into the β-amino-α-ketoester **5a** (Scheme 2).[15] This presumably configurationally unstable ketone was reduced in situ with L-selectride[16] to afford the corresponding N-protected β-amino-α-hydroxyester **9** with *syn* selectivity.



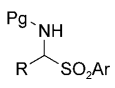
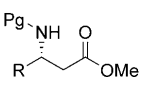
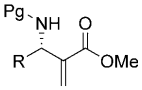
Scheme 2. Transformation of the Mannich adducts **3a** and **3b**. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

We next focused on the synthesis of enantiomerically enriched aza-MBH adducts **6**. As the classical Julia–Lythgoe olefination with phenyl sulfones requires three steps, that is, an aldol reaction followed by acylation and reductive elimination,[17] we turned our attention to a different type of sulfone, namely, π-electron-deficient aryl sulfonyl derivatives, which are known to undergo a mechanistically distinct olefination (modified Julia or Julia–Kocienski reaction).[18] In this transformation, which proceeds through a Smiles rearrangement, the C=C double bond is formed in one step from the sulfone. Among the different possible substrates, we chose the *p*-nitrophenylsulfonylacetate **1b**, which we prepared and tested in the catalytic reaction (Table 1, entries 7 and 8).[19] Although this more acidic sulfonylacetate was converted under the previously optimized reaction conditions into the desired adduct with lower enantioselectivity than that observed with **1a**, high enantioinduction was restored simply by decreasing the amount of base used (Table 1, entry 8). The Mannich product **3b** was transformed into the aza-MBH adduct **6a** in one step as expected by treating crude **3b** with formaline and Cs_2CO_3 in DMF (Scheme 2).[19,20]

We next verified the possibility of using different α-amidosulfones **2** in catalytic asymmetric Mannich reactions of sulfonylacetates **1a** and **1b** (Table 2). The crude products **3** obtained from the catalytic reactions were subjected directly to reductive desulfonylation in the case of **1a**, or to the modified Julia olefination in the case of **1b**, to facilitate HPLC analysis and to demonstrate the generality of our methods. A range of α-amidosulfones, **2a**–**m**, derived from linear, α- or β-branched, and aromatic aldehydes, were converted into the corresponding *N*-Boc- or *N*-Cbz-protected β^3-aminoesters **4a**–**l** (from **1a**) and aza-MBH adducts **6a**–**m** (from **1b**) in moderate to good yields (over two steps) and with good enantioselectivities. During our investigations, we found that the *N*-(2-nitrobenzyl)quinidine catalyst **7d** afforded consistently higher enantioselectivities than those observed with **7e** in the case of the aromatic or more sterically demanding substrates **2g**–**m** (Table 2, entries 7–13). Our protocol proved to be efficient even in the case of very readily enolizable imines derived from linear, unbranched aldehydes (Table 2, entries 1–6). Furthermore, a chloride substituent was tolerated in the desulfonylation process (Table 2, entry 12). In contrast, a bromide substituent did not survive treatment with Mg powder; the α-amidosulfone **2m** could thus be used only for the preparation of the aza-MBH adduct **6m** (Table 2, entry 13).

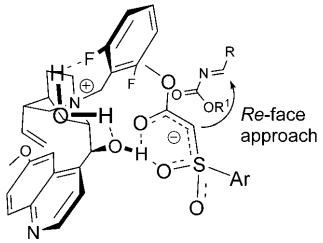
The absolute configuration of several products **4** and **6** was determined by comparison of the specific optical rotation with known values (Table 2).[12] In all cases, the observed configuration derives from the Mannich addition of the

Table 2: Catalytic enantioselective Mannich reactions of sulfonylacetates **1**, followed by reductive desulfonylation or a modified Julia olefination.[a]

Entry				Cat.						
	2, Ar	R	Pg		**4**[b]	Yield [%][c]	*ee* [%][d]	**6**[e]	Yield [%][c]	*ee* [%][d]
1	**2a**, *p*-Tol	$Ph(CH_2)_2$	Boc	**7e**	**4a**	82	92	**6a**	85	91
2	**2b**, *p*-Tol	$Ph(CH_2)_2$	Cbz	**7e**	**4b**	70	77	**6b**	74	78
3	**2c**, *p*-Tol	Me	Boc	**7e**	**4c**	88	78[f,g,h]	**6c**	88	90[h]
4	**2d**, Ph	*i*Bu	Cbz	**7e**	**4d**	71	87	**6d**	76	84
5	**2e**, Ph	*n*-pentyl	Cbz	**7e**	**4e**	62	85	**6e**	79	88
6	**2f**, Ph	*n*-hexyl	Boc	**7e**	**4f**	68	95[g]	**6f**	91	96
7	**2g**, Ph	*i*Pr	Boc	**7d**	**4g**	65[i]	80[g,h]	**6g**	74	87
8	**2h**, Ph	cyclohexyl	Boc	**7d**	**4h**	78	91[g]	**6h**	84[j]	92
9	**2i**, Ph	Ph	Boc	**7d**	**4i**	75	92[h]	**6i**	85	91[h]
10	**2j**, Ph	2-naphthyl	Boc	**7d**	**4j**	76	85	**6j**	84	84
11	**2k**, *p*-Tol	*p*-$MeOC_6H_4$	Boc	**7d**	**4k**	70	90[g]	**6k**	63	89
12	**2l**, Ph	*p*-ClC_6H_4	Boc	**7d**	**4l**	89	83	**6l**	70	80
13	**2m**, Ph	*o*-BrC_6H_4	Cbz	**7d**	–	–	–	**6m**	75[j]	94

[a] Reactions were carried out with **2a–m** (0.15 mmol), **1a** or **1b** (0.225 mmol), **7** (5 mol%), and aqueous K_3PO_4 (50% w/w, 210 μL, 0.75 mmol for **1a**; 105 μL, 0.37 mmol for **1b**) in toluene (3.0 mL) at −30 °C for 16–60 h. [b] After plug filtration, the crude products of the catalytic reaction were treated with Mg powder (109 mg, 4.5 mmol) in CH_3OH (1.5 mL) overnight. [c] Yield of the isolated product (two steps) after chromatography on silica gel. [d] The *ee* value was determined by HPLC on a chiral stationary phase. [e] After plug filtration, the crude products of the catalytic reaction were treated with aqueous HCHO (37% w/w, 57 μL, 0.75 mmol) and Cs_2CO_3 (123 mg, 0.37 mmol) in DMF (1.5 mL) overnight. [f] Catalyst **7d** was used. [g] The *ee* value was determined after conversion into the Cbz derivative.[12] [h] The absolute configuration was assigned by comparison of the optical rotation with a known value.[12] [i] Acetate **1b** was used. [j] Reaction time for the olefination step: 48 h.

sulfonylacetate **1** to the *Re* face of the intermediate *N*-carbamoyl imine. The inefficiency of O-alkylated and O-acylated catalysts in this[12] and related transformations[9] suggests a crucial hydrogen-bond interaction between the hydrogen atom of the hydroxy group of the catalyst and one of the reagents; such an interaction was rationalized very convincingly for the related aza-Henry reaction by a computational study.[21] On the basis of these considerations, we tentatively propose an intermediate in which the catalyst coordinates the deprotonated sulfonylacetate through the hydrogen atom of the hydroxy group to give the tight ionic couple depicted in Scheme 3. Additional hydrogen-bond interactions between the incoming imine and the hydrogen atoms α to the quaternary nitrogen atom in the catalyst (not shown)[21] force the imine to approach from the back side and thus favor selective addition to its *Re* face. The superior efficiency of catalysts containing an *ortho*-substituted benzylic moiety in these reactions, when used in combination with aqueous inorganic bases, can be interpreted by considering a possible hydrogen-bond network involving the *ortho* substituent, the oxygen atom of the hydroxy group, and a molecule of water (Scheme 3), as observed in the solid state.[13] This interaction can help to rigidify the system and thus augment its effectiveness in discriminating the two prochiral faces of the imine.



Scheme 3. Proposed reaction intermediate.

In summary, arylsulfonylacetates **1** have been used for the first time in a catalytic asymmetric reaction, namely, an enantioselective Mannich addition to *N*-carbamoyl imines. Reductive removal of the sulfonyl group of the Mannich adducts gave a range of β^3-amino-ester derivatives **4** through a very simple two-step procedure in which the hydrolytic, oxidative, or thermal conditions typically used in previously reported related transformations were avoided.[7a–c,11] Similarly, an oxidative desulfonylation furnished a β-amino-α-hydroxyester **5**, whereas a Julia-type olefination provided access to aza-MBH products **6**. In contrast to the more common aza-MBH approach,[10] in which preformed *N*-tosyl imines are typically employed, this procedure enables the use of highly unstable imines through their generation in situ; furthermore, the enantiomerically enriched products contain a readily removable protecting group on the nitrogen atom.

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[1] a) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**; b) *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**.
[2] C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547.
[3] J. C. Carretero, R. Gómez Arrayás, J. Adrio in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, p. 291.
[4] For example, for conjugate additions, see: a) L. Hongming, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123, and references therein; c) P. Mauleón, I. Alonso, M. R. Rivero, J. C. Carretero, *J. Org. Chem.* **2007**, *72*, 9924, and references therein; for reductions, see: d) T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem.* **2007**, *119*, 3393; *Angew. Chem. Int. Ed.* **2007**, *46*, 3329; e) J.-N. Desrosiers, A. B. Charette, *Angew. Chem.* **2007**, *119*, 6059; *Angew. Chem. Int. Ed.* **2007**, *46*, 5955; for cycloadditions, see: f) A. López-Pérez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 10084.

[5] For example, for α-halosulfones, see: a) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem.* **2006**, *118*, 5095; *Angew. Chem. Int. Ed.* **2006**, *45*, 4973; b) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.* **2007**, *129*, 6394; c) S. Arai, T. Shioiri, *Tetrahedron* **2002**, *58*, 1407; for α-ketosulfones, see: d) J. Pulkkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077; for α-cyanosulfones, see: e) M. B. Cid, J. López-Cantarero, S. Duce, J. L. García Ruano, *J. Org. Chem.* **2009**, *74*, 431; for sulfenes, see: f) F. M. Koch, R. Peters, *Angew. Chem.* **2007**, *119*, 2739; *Angew. Chem. Int. Ed.* **2007**, *46*, 2685; for diazosulfones, see: g) M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 2860; h) S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042.

[6] Sulfonylacetates can be alkylated under PTC conditions; see, for example: a) D. A. Alonso, C. Nájera, M. Varea, *Helv. Chim. Acta* **2002**, *85*, 4287; for an overview of asymmetric PTC, see: b) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; c) *Asymmetric Phase Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, Weinheim, **2008**.

[7] Fluorobis(phenylsulfonyl)methane can react enantioselectively with α-amidosulfones under PTC conditions; see reference [5b]. For a recent review on organocatalytic enantioselective Mannich reactions, see: a) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29; for recent advances, see: b) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453; c) Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa, T. Uchimaru, *Angew. Chem.* **2008**, *120*, 9193; *Angew. Chem. Int. Ed.* **2008**, *47*, 9053; d) C. Gianelli, L. Sambri, A. Carlone, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8828; *Angew. Chem. Int. Ed.* **2008**, *47*, 8700.

[8] M. Petrini, *Chem. Rev.* **2005**, *105*, 3949.

[9] a) F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 8189; *Angew. Chem. Int. Ed.* **2005**, *44*, 7975; b) C. Palomo, M. Oiarbide, A. Laso, R. López, *J. Am. Chem. Soc.* **2005**, *127*, 17622; c) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338, and references therein.

[10] a) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed. (Eds.: E. Juaristi, V. A. Soloshonok), Wiley, New York, **2005**; for reviews on the aza-MBH reaction, see: b) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; c) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; d) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581.

[11] For the use of malonates: see reference [9c] and references therein; for the use of diazoacetates, see: a) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360; b) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054; for the use of nitroacetates, see: c) B. Shen, J. N. Johnston, *Org. Lett.* **2008**, *10*, 4397; for the use of phoshonium acetates, see: d) Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu, Y.-C. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 2456; for the use of malonic acid half thioesters, see: e) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herrera, V. Sgarzani, *Adv. Synth. Catal.* **2007**, *349*, 1037.

[12] See the Supporting Information.

[13] S.-s. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-g. Park, *Org. Lett.* **2002**, *4*, 4245.

[14] F. A. Davis, R. Jenkins, Jr., S. G. Yocklovich, *Tetrahedron Lett.* **1978**, *19*, 5171.

[15] a) D. R. Williams, L. A. Robinson, G. S. Amato, M. H. Osterhaut, *J. Org. Chem.* **1992**, *57*, 3740; b) L. A. Paquette, L. Barriault, D. Pissarnidski, J. N. Johnston, *J. Am. Chem. Soc.* **2000**, *122*, 619.

[16] K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420. Other reducing agents (e.g. borohydrides, BH_3·THF, catecholborane) gave the product **9** with reduced yield and/or stereoselectivity under these conditions.

[17] M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833.

[18] a) D. A. Alonso, M. Fuensanta, C. Nájera, M. Varrei, *J. Org. Chem.* **2005**, *70*, 6404; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563; c) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831.

[19] D. Mirk, J.-M. Grassot, J. Zhu, *Synlett* **2006**, 1255. Although widely used, 3,5-(bistrifluoromethyl)phenylsulfonylacetates are considerably more expensive. Heteroaromatic sulfones gave the product with low enantioselectivity (< 55% *ee*) under these conditions.

[20] All attempts to develop a one-pot procedure failed. Aldehydes more hindered than formaldehyde did not react under these conditions.

[21] E. Gomez-Bengoa, A. Linden, R. López, I. Múgica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955.

