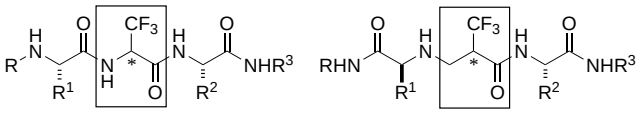
Fluorinated Peptidomimetics

Highly Stereoselective Tandem Aza-Michael Addition–Enolate Protonation to Form Partially Modified Retropeptide Mimetics Incorporating a Trifluoroalanine Surrogate**

Monica Sani, Luca Bruché, Gema Chiva, Santos Fustero, Julio Piera, Alessandro Volonterio,* and Matteo Zanda**

Poor bioavailability and rapid in vivo degradation are the two main drawbacks to the use of peptides as drugs.[1] Peptide-backbone modification has emerged as a powerful tool for overcoming these disadvantages, while retaining specific and potent bioactivity.[2] A number of modifications have been proposed, many of which have proved successful, such as the replacement, addition, or deletion of one or more amino acids in the parent sequence, the replacement of peptide bonds with surrogates, and the incorporation of synthetic scaffolds (often cyclic) into the backbone. We recently described novel peptidomimetic structures that incorporate a trifluoromethyl group,[3] within the frame of a research project aimed at the development of fluorine-containing protease inhibitors. The current project stems from the belief that the beneficial pharmacological effect of introducing fluorine substituents into a druglike molecule could be extended to peptides and peptidomimetics. Little information on the synthesis or the structural, conformational, and biological properties of fluorinated peptidomimetics is available in the literature.[4]

Recently, we became interested in the development of peptide mimetics that incorporate a stereochemically defined 3,3,3-trifluoroalanine (TF-Ala) unit. Unfortunately, the incorporation of TF-Ala into a peptide sequence to give a modified peptide **A** is a challenging endeavor,[5] as such peptides have low chemical and configurational stability at pH > 6.[6] To the best of our knowledge, no mimetics of TF-Ala-containing peptides have been described to date. For this reason, we planned the synthesis of partially modified retro (PMR) ψ[$NHCH_2$] peptide mimetics[7] **1**, which incorporate a chemically stable and stereodefined $CH_2CH(CF_3)CO$ surrogate for TF-Ala.



A **1**

Retrosynthetic analysis suggested that the asymmetric conjugate N-addition of α-amino esters to *N*-(α-trifluoromethyl)acryloyl-α-amino esters could represent a viable entry to the target structures **1**. However, surprisingly few studies have been dedicated to the asymmetric conjugate addition of nitrogen nucleophiles (such as amines, hydroxylamines, or amino acid derivatives) to α-substituted acryloyl acceptors, formally a tandem nonstereoselective aza-Michael reaction–stereoselective enolate protonation.[8] None of the previous studies addressed the issue of double stereoinduction. In our case, further challenges were expected because of the presence of the stereoelectronically demanding trifluoromethyl group and the strongly acidic nature of the $CH(CF_3)CO$ proton, which could lead to epimerization of the stereogenic center under the basic reaction conditions.

Herein we describe the smooth and general synthesis of PMR-ψ[$NHCH_2$]-tripeptides **4** (Scheme 1) by tandem asymmetric aza-Michael addition–enolate protonation of α-amino esters **2** with *N*-(α-trifluoromethyl)acryloyl-α-amino esters **3**. This sequence takes place with good to excellent 1,4-asymmetric induction (up to 95% *de*) depending on the substrate. Very high stereocontrol was observed upon the fine-tuning of key reaction parameters, such as the solvent and the base used. Side chains (R and R^1) and chirality (matched/mismatched pairs) of both reaction partners **2** and **3** were also found to have a strong influence on the diastereoselectivity.

Michael acceptors **3** (Scheme 2) were obtained by treatment of the appropriate α-amino ester H-AA-OX^1 with (α-trifluoromethyl)acryloyl chloride **6**,[9] which was prepared in turn from the acid **5**. Yields were generally high and the substrates **3** could be readily purified by flash chromatography (FC).

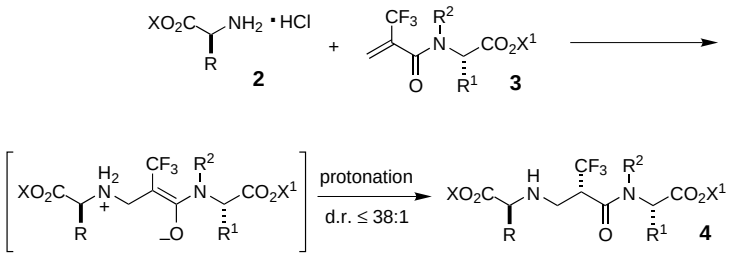
The reactions of α-amino esters (generated in situ by the treatment of commercially available hydrochlorides **2** with a tertiary amine) with Michael acceptors **3** were operationally very straightforward, quite fast, and efficient. Thus, **2**, **3**, and the amine base were simply mixed in the appropriate solvent, and at the end of the reaction (usually after 2 h at RT) the solvent was evaporated. The PMR-tripeptides **4** were isolated in yields of 75–98% (Scheme 3 and Table 1).

[*] Dr. M. Zanda, M. Sani
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare (ICRM)
Sezione "A. Quilico"
via Mancinelli 7, 20131 Milano (Italy)
Fax: (+39) 02-2399-3080
E-mail: matteo.zanda@polimi.it
Dr. A. Volonterio, Prof. Dr. L. Bruché
Dipartimento di Chimica, Materiali ed
Ingegneria Chimica "Giulio Natta"
Politecnico di Milano
via Mancinelli 7, 20131 Milano (Italy)
Fax: (+39) 02-2399-3080
E-mail: alessandro.volonterio@polimi.it
Prof. Dr. S. Fustero, G. Chiva, J. Piera
Departamento de Química Orgánica
Facultad de Farmacia, Universidad de Valencia
46100-Burjassot, Valencia (Spain)
Fax: (+34) 96-386-4939
E-mail: santos.fustero@uv.es

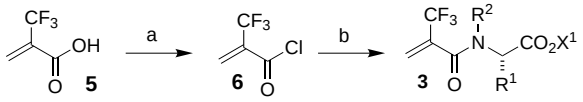
[**] We thank the European Commission (IHP Network grant "FLUOR MMPI" HPRN-CT-2002-00181), MIUR (Cofin 2002, Project "Peptidi Sintetici Bioattivi"), CNR (Italy), and MCYT (PPQ2000–0824) (Spain) for financial support. We are indebted to Prof. Takeo Taguchi and Prof. Takashi Yamazaki for useful experimental information on the preparation of (α-trifluoromethyl)acryloyl chloride.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

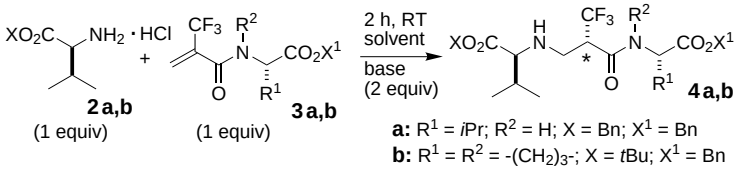
  DOI: 10.1002/ange.200250711



Scheme 1. Tandem reaction to produce PMR-ψ[$NHCH_2$]-tripeptides **4**.



Scheme 2. Preparation of the chiral Michael acceptors **3**. a) Phthaloyl chloride, 140 °C; b) HCl·H-AA-OX^1, TMP (2 equiv), CH_2Cl_2, 0–25 °C, 75–95 %. AA = Gly, Val, Pro, Ala, Phe, Leu, etc.



Scheme 3. Reaction optimization: influence of base and solvent on stereoselectivity.

renders the experimental procedure less practical. Surprisingly, the *de* dropped when the chiral bases quinidine and cinchonine were used (54 % and 9 % *de* for **4b**, respectively Table 1, entries 19 and 20).

Reaction temperature was not a major factor in the range −40 °C to RT (Table 1, entries 1, 3 and 4). Concentration had negligible effect on the stereocontrol, but we qualitatively observed (TLC monitoring) a clear-cut increase in the reaction rate with increasing concentrations of **2** and **3**. This effect was particularly pronounced with the Pro-derived acceptor **3b**.[11] Ancillary control experiments demonstrated that, as expected, the reaction is kinetically controlled, and that under the optimized conditions (DABCO, CCl_4, RT) the CF_3-substituted stereogenic center of the products **4** is configurationally stable.

The full scope of the methodology in the synthesis of PMR-peptides **4** and the effect of the structure and stereochemistry of the reactants **2** and **3** on diastereoselectivity were investigated next. To this end, a variety of amino ester hydrochlorides **2a–j** were treated with acceptors **3a–h** under the optimized conditions (DABCO, CCl_4, RT) to provide a library of molecules **4d–u**, in generally good to excellent yields (Scheme 4 and Table 2).

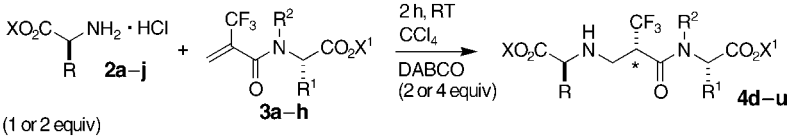
The R side chain of **2** has a strong influence, as was clearly demonstrated in the addition of **2b–g** to

We first investigated the effect of the tertiary amine base on the diastereoselectivity of the reaction by conducting model reactions in CH_2Cl_2 between L-Val ester hydrochlorides **2a** (X = Bn) and **2b** (X = *t*Bu), and acceptors **3a** (derived from L-Val) and **3b** (derived from L-Pro), respectively (Scheme 3, Table 1, entries 1–10). These experiments showed that the amine base has a profound influence. Modest stereocontrol was observed with TMP, DMAP, TEA, and DIPEA (Table 1, entries 1–6). Of these, the best result was obtained with DIPEA (65 % *de* for **4a**, Table 1, entry 6). Considerably higher diastereocontrol was obtained with DABCO, which promoted the formation of **4a** and **4b** in 77 % and 83 % *de*, respectively (Table 1, entries 7 and 8). Lower *de* (70 %) was observed in the absence of an amine (Table 1, entry 9). The effect of solvent, which is the other main factor in this reaction, was investigated next in the presence of DABCO as the base (Table 1, entries 10–17). We found that the use of low-polarity or apolar solvents resulted in much higher diastereocontrol. Thus, acetonitrile (Table 1, entry 10) promoted modest *de* (63 % for **4b**), lower than that observed for CH_2Cl_2, whereas use of the less polar solvent THF increased the *de* to 88 % (Table 1, entry 11). Even better results were obtained with toluene, in which **4a** and **4b** were formed in 89 % and 90 % *de*, respectively (entries 12 and 14).[10] Use of the apolar solvent CCl_4 gave the best diastereoselectivity with **4a** and **4b** formed in 94.9 % and 94.6 % *de*, respectively (Table 1, entries 16 and 17). Very good *de* was also observed in the presence of Me_3N as the base (94.3 % *de* for **4a**, Table 1, entry 18), but its high volatility

Table 1: Influence of base and solvent.

Entry	Product	Base[a]	Solvent	Yield [%]	d.r.[b]
1[c]	**4a**	TMP	CH_2Cl_2	> 98	3.7:1.0
2	**4a**	DMAP	CH_2Cl_2	90	3.8:1.0
3	**4a**	TEA	CH_2Cl_2	86	4.0:1.0
4[d]	**4a**	TEA	CH_2Cl_2	84	4.2:1.0
5	**4b**	TEA	CH_2Cl_2	77	3.0:1.0
6[c]	**4a**	DIPEA	CH_2Cl_2	95	4.7:1.0
7	**4a**	DABCO	CH_2Cl_2	> 98	7.6:1.0
8	**4b**	DABCO	CH_2Cl_2	84	10.5:1.0
9[c,e]	**4a**	–	CH_2Cl_2	94	5.7:1.0
10	**4b**	DABCO	CH_3CN	91	4.4:1.0
11	**4b**	DABCO	THF	95	15.0:1.0
12	**4a**	DABCO	toluene	83	17.4:1.0
13[f]	**4a**	DABCO (cat.)	toluene	75	13.3:1.0
14	**4b**	DABCO	toluene	95	18.0:1.0
15[g]	**4a**	–	toluene	85	3.3:1.0
16	**4a**	DABCO	CCl_4	90	38.0:1.0
17	**4b**	DABCO	CCl_4	90	36.0:1.0
18[h]	**4a**	TMA	CCl_4	94	34.0:1.0
19[g]	**4b**	quinidine	toluene	79	3.3:1.0
20[g]	**4b**	cinchonine	toluene	84	1.2:1.0

[a] TMP = 2,4,6-trimethylpyridine (*sym*-collidine), DMAP = 4-dimethylaminopyridine, TEA = triethylamine, DIPEA = diisopropylethylamine, DABCO = 1,4-diazabicyclo[2,2,2]octane, TMA = trimethylamine. [b] Determined by ^{19}F NMR spectroscopy and/or HPLC analysis. [c] Reaction carried out at 0 °C. [d] Reaction carried out at −40 °C. [e] Hydrochloride **2a** was treated prior to reaction with aqueous $NaHCO_3$. [f] DABCO (0.1 equiv) was used after treatment of **2a** with aqueous $NaHCO_3$. [g] Reaction time: 48 h. [h] Reaction carried out at −10 °C.



Scheme 4. Synthesis of an array of PMR-ψ[$NHCH_2$]-tripeptides (**4**).

Table 2: Validation of the methodology and influence of R, R^1, R^2, and configuration on diastereoselectivity.

Entry	2	3	4	R[a]	X	R^1[a]	R^2	X^1	Yield [%]	d.r.[b]
1	**c**	**a**	**d**	H	Et	*i*Pr	H	Bn	98	7.0:1.0
2	**d**	**a**	**e**	*i*Bu	Bn	*i*Pr	H	Bn	80	10.6:1.0
3	**e**	**a**	**f**	Bn	Me	*i*Pr	H	Bn	85	13.0:1.0
4	**f**	**a**	**g**	Me	Me	*i*Pr	H	Bn	82	14.0:1.0
5	**g**	**a**	**h**	*s*Bu	Me	*i*Pr	H	Bn	80	23.0:1.0
6	**b**	**c**	**i**	*i*Pr	*t*Bu	*i*Pr	H	*t*Bu	90	33.0:1.0
7	**e**	**b**	**j**	Bn	Me	-$(CH_2)_3$-		Bn	84	12.5:1.0
8	**f**	**b**	**k**	Me	Me	-$(CH_2)_3$-		Bn	85	24.0:1.0
9	**g**	**b**	**L**	*s*Bu	Me	-$(CH_2)_3$-		Bn	83	29.0:1.0
10	**h**	**e**	**m**	Bn	Bn	Bn	H	Bn	70	6.0:1.0
11	**a**	**f**	**n**	*i*Pr	Bn	Me	H	*t*Bu	71	29.2:1.0
12	**i**	**f**	**o**	Me	*t*Bu	Me	H	*t*Bu	76	17.0:1.0
13	D-**i**	**f**	**p**	D-Me	*t*Bu	Me	H	*t*Bu	70	3.2:1.0[c]
14	D-**j**	D-**g**	**q**	D-Ph	Me	D-Ph	H	Me	73	2.8:1.0
15	**j**	D-**g**	**r**	Ph	Me	D-Ph	H	Me	87	1.0:1.0[c]
16	**e**	**h**	**s**	Bn	Me	H	H	Bn	85	2.0:1.0
17	**g**	**h**	**t**	*s*Bu	Me	H	H	Bn	82	3.0:1.0
18	**a**	**h**	**u**	*i*Pr	Bn	H	H	Bn	89	6.0:1.0

[a] L-Configured amino esters were used unless otherwise indicated. [b] Determined by ^{19}F NMR spectroscopy and/or HPLC analysis. [c] The stereochemistry at the carbon center α to the CF_3 group was not assigned.

the L-Val acceptors **3a** and **3c** (Table 2, entries 1–6). The *de* of the products **4d–i** increased in the sense R = H < *i*Bu < Bn < Me < *s*Bu < *i*Pr, such that the best stereocontrol was achieved with the bulkiest R groups. This trend was confirmed with the other acceptors **3b** (L-Pro-derived, Table 2, entries 7–9), **3f** (L-Ala-derived, entries 11 and 12), and **3h** (Gly-derived, entries 16–18). The R^1 side chain of the acceptors **3** also had a strong influence, as shown by the fact that L-Phe amino esters such as **2e** and **2h** (R = Bn) reacted with **3h** (Gly acceptor, Table 2, entry 16), **3e** (L-Phe acceptor, entry 10), **3b** (L-Pro acceptor, entry 7), and **3a** (L-Val acceptor, entry 3) with progressively higher diastereocontrol (d.r. of products increased from 2.0:1.0 to 13.0:1.0). The effect of R^1 on the *de* followed the same trend observed for R. The configuration of the reaction partners **2** and **3** also had a profound effect, as demonstrated by the use of matched/mismatched pairs of the L- and D-Ala methyl esters **2i** and the L-Ala acceptor **3f** (Table 2, entries 12 and 13), and the D- and L-phenylglycine methyl esters **2j** and the D-phenylglycine acceptor **3g** (Table 2, entries 14 and 15). In both cases the "like" combination (D/D or L/L) resulted in higher diastereoselectivity, with the striking case of like-**2i**/**3f**, which gave an excellent 17.0:1.0 ratio in favor of the **4o** diastereomer (Table 2, entry 12), whereas a modest 3.2:1.0 diastereomeric ratio was found in the case of unlike-**2i**/**3f** (Table 2, entry 13). The X and X^1 ester groups had minor (if any) influence on stereoselectivity.

The configurations of the PMR-peptides **4j** and **4n** were determined by X-ray diffraction,[12] and the configurations of the other main diastereomers **4** were tentatively assigned by analogy with **4j** and **4n**, based on their spectroscopic and physical data.

The striking effects of the amine catalyst and the solvent on the diastereoselectivity of the reaction had not been described in previous studies on the asymmetric addition of nitrogen nucleophiles to α-substituted acryloyl acceptors,[8] in which the best stereocontrol was often achieved in protic solvents, in the absence of an amine base. Although detailed kinetic and computational studies will be necessary before we can draw a reliable mechanistic picture of this process, the body of experimental evidence discussed above suggests that the amino ester **2**, Michael acceptor **3**, and DABCO might form a tight termolecular ion-pair transition state, which is energetically favored and not disrupted in nonpolar solvents.[13]

In conclusion, we have described a highly stereoselective synthesis of PMR-ψ[$NHCH_2$]-peptides that incorporate a stereochemically defined and stable TF-Ala mimetic by means of a novel tandem asymmetric aza-Michael addition–enolate protonation reaction. The process is operationally very simple, makes use of readily available and cheap reagents, occurs under very mild conditions, and produces compounds suitable for combinatorial applications, all of which are of interest for potential industrial development. Additional interest in this reaction stems from its peculiar mechanism and the underlying stereochemical implications, such as the high double stereoinduction and the strong stereodirecting solvent and base effects, which deserve further in-depth mechanistic investigations.

Received: December 6, 2002 [Z50711]

Keywords: diastereoselectivity · Michael addition · peptidomimetics · protonation · solvent effects

[1] A. Loffet, *J. Pept. Sci.* **2002**, *8*, 1–7.
[2] a) G. L. Olson, D. R. Bolin, M. P. Bonner, M. Bös, C. M. Cook, D. C. Fry, B. J. Graves, M. Hatada, D. E. Hill, M. Kahn, V. S. Madison, V. K. Rusiecki, R. Sarabu, J. Sepinwall, G. P. Vincent, M. E. Voss, *J. Med. Chem.* **1993**, *36*, 3039–3049; b) J. Gante, *Angew. Chem.* **1994**, *106*, 1780–1802; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1720; c) D. Leung, G. Abbenante, D. P. Fairlie, *J. Med. Chem.* **2000**, *43*, 305–341.
[3] a) A. Volonterio, P. Bravo, M. Zanda, *Org. Lett.* **2000**, *2*, 1827–1830; b) A. Volonterio, P. Bravo, M. Zanda, *Tetrahedron Lett.* **2001**, *42*, 3141–3144; c) A. Volonterio, S. Bellosta, P. Bravo, M.

Canavesi, E. Corradi, S. V. Meille, M. Monetti, N. Moussier, M. Zanda, *Eur. J. Org. Chem.* **2002**, 428 – 438.
[4] a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**; for some recent examples of fluorine-containing peptidomimetics, see: b) G. S. Garrett, S. J. McPhail, K. Tornheim, P. E. Correa, J. M. McIver, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 301 – 306; c) M.-A. Poupart, G. Fazal, S. Goulet, L.-T. Mar, *J. Org. Chem.* **1999**, *64*, 1356 – 1361; d) M. Eda, A. Ashimori, F. Akahoshi, T. Yoshimura, Y. Inoue, C. Fukaya, M. Nakajima, H. Fukuyama, T. Imada, N. Nakamura, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 919 – 924, and references therein; e) R. V. Hoffman, J. Tao, *Tetrahedron Lett.* **1998**, *39*, 4195 – 4198; f) P. A. Bartlett, A. Otake, *J. Org. Chem.* **1995**, *60*, 3107 – 3111; g) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 7207 – 7219.
[5] a) E. Höss, M. Rudolph, L. Seymour, C. Schierlinger, K. Burger, *J. Fluorine Chem.* **1993**, *61*, 163 – 170, and references therein; b) S. N. Osipov, N. Sewald, A. F. Kolomiets, A. V. Fokin, K. Burger, *Tetrahedron Lett.* **1996**, *37*, 615 – 618; c) F. Bordusa, C. Dahl, H.-D. Jakubke, K. Burger, B. Koksch, *Tetrahedron: Asymmetry* **1999**, *10*, 307 – 313.
[6] a) *Fluorine-containing Amino Acids, Synthesis and Properties* (Eds.: V. P. Kukhar', V. A. Soloshonok), Wiley, Chichester, **1995**; b) N. Lebouvier, C. Laroche, F. Huguenot, T. Brigaud, *Tetrahedron Lett.* **2002**, *43*, 2827 – 2830; c) T. Sakai, F. Yan, S. Kashino, K. Uneyama, *Tetrahedron* **1996**, *52*, 233 – 244; d) S. Ayhan, A. S. Demir, S. Özge, G.-A. Zuhal, *Tetrahedron: Asymmetry* **2001**, *12*, 2309 – 2313; e) S. Fustero, A. Navarro, B. Pina, J. G. Soler, A. Bartolomé, A. Asensio, A. Simón, P. Bravo, G. Fronza, A. Volonterio, M. Zanda, *Org. Lett.* **2001**, *3*, 2621 – 2624.
[7] a) M. Chorev, M. Goodman, *Acc. Chem. Res.* **1993**, *26*, 266 – 273; b) M. Chorev, M. Goodman, *Trends Biotechnol.* **1995**, *13*, 438 – 445; c) M. D. Fletcher, M. M. Campbell, *Chem. Rev.* **1998**, *98*, 763 – 795.
[8] See, for example: a) L. M. Pratt, R. P. Beckett, S. J. Davies, S. B. Launchbury, A. Miller, Z. M. Spavold, R. S. Todd, M. Whittaker, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2585 – 2588; b) A. D. Lebsack, L. E. Overman, R. J. Valentekovich, *J. Am. Chem. Soc.* **2001**, *123*, 4851 – 4852; c) F. M. Martin, R. P. Beckett, C. L. Bellamy, P. F. Courtney, S. J. Davies, A. H. Drummond, R. Dodd, L. M. Pratt, S. R. Patel, M. L. Ricketts, R. S. Todd, A. R. Tuffnell, J. W. S. Ward, M. Whittaker, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2887 – 2892; d) L. A. Paquette, R. R. Rothhaar, M. Isaac, L. M. Rogers, R. D. Rogers, *J. Org. Chem.* **1998**, *63*, 5463 – 5472; e) B. Koksch, K. Mütze, S. N. Osipov, A. S. Golubev, K. Burger, *Tetrahedron Lett.* **2000**, *41*, 3825 – 3828, and references therein.
[9] a) Y. Hanzawa, M. Suzuki, Y. Kobayashi, T. Taguchi, Y. Iitaka, *J. Org. Chem.* **1991**, *56*, 1718 – 1725; b) T. Yamazaki, T. Ichige, S. Takei, S. Kawashita, T. Kitazume, T. Kubota, *Org. Lett.* **2001**, *3*, 2915 – 2918.
[10] In toluene the absence of an amine produced a dramatic drop in stereoselectivity (54% *de* for **4a**, Table 1, entry 15). The *de* also decreased when DABCO was used in a catalytic amount (86% for **4a**, Table 1, entry 13).
[11] Faster reactions were also observed when DABCO was used instead of TEA, DIPEA, or TMP.
[12] The crystal structures of **4j** and **4n** will be published in a full paper.
[13] The asymmetric addition of chiral alcohols to ketenes ("Merck reaction"), a conceptually related reaction, shows a very similar dependence on the polarity of the solvent and the structure of the catalyst (the amine base). See, for example: a) R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1989**, *111*, 7650 – 7651; see also: b) B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637 – 2638; c) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831 – 7832; d) M. Calmes, J. Daunis, N. Mai, *Tetrahedron* **1997**, *53*, 13719 – 13726. The tight zwitterionic termolecular (alcohol/ketene/amine) intermediate that was recently proposed to explain the high stereocontrol of the Merck reaction might also be a useful model for a mechanistic interpretation of the reaction presented herein. The latter reaction is probably more complex both from a mechanistic and a stereochemical point of view because of the presence of a double stereoinduction effect: e) C. E. Cannizzaro, T. Strassner, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 2668 – 2669.

