EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201201427

Asymmetric Organocatalytic 1,4-Addition Reactions Starting from Enals with *gem*-Difluoroalkyl Side Chains

Ali Khalaf,[a,b] Danielle Grée,[a] Hassan Abdallah,[b] Nada Jaber,[b] Ali Hachem,*[b] and René Grée*[a]

Keywords: Asymmetric synthesis / Organocatalysis / Michael addition / Fluorine / Enals

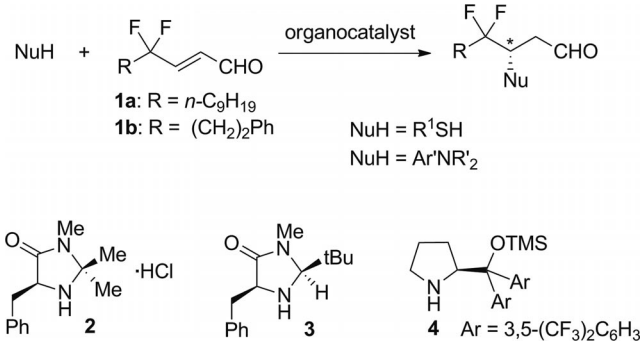
gem-Difluoroenals are excellent substrates for asymmetric organocatalytic 1,4-additions of thiols and anilines. By using diarylsilylprolinol ether as a catalyst, good to excellent yields with *ee* values in the same range (up to 98 %) were obtained. The CF_2R group strongly activates the enals towards these organocatalytic additions.

Introduction

Asymmetric organocatalysis has been strongly developing over the last 10 years, and a number of remarkable synthetic applications have been documented.[1] Fluorine chemistry has also become a major topic, especially in the realms of bioorganic and medicinal chemistry.[2] Therefore, the use of asymmetric organocatalysis for the preparation of optically pure fluorine-containing molecules appears to be of much interest, even if relatively few examples have been published to date. Most representative are the asymmetric monofluorination[3] and trifluoromethylation[4] reactions, as well as the additions on trifluoromethylcrotonates and the corresponding amides.[5] Very recently, an elegant study was reported on the preparation of trifluorocrotonaldehyde and its use in various asymmetric organocatalytic reactions.[6] Notably, the fluorine–iminium *gauche* effect can also be used to control the enantioselectivity in organocatalytic epoxidation reactions.[7] However, to the best of our knowledge, no examples of asymmetric organocatalysis has been reported for derivatives containing *gem*-difluoromethyl or *gem*-difluoroalkyl systems. As part of our program dealing with the use of propargylic systems for the synthesis of fluorine-containing building blocks,[8] we designed short and efficient routes to enals **1** bearing *gem*-difluoroalkyl side chains.[9] Therefore, we became interested in the use of such intermediates in asymmetric organocatalysis.

Results and Discussion

The purpose of this communication is to establish that, after proper selection of the organocatalyst, highly enantioselective Michael additions of thiols and aniline derivatives can be performed on *gem*-difluoroenals **1** (Scheme 1). We will also demonstrate that introduction of fluorine atoms in the chain has a positive effect on the efficiency of these reactions relative to the efficiencies of reactions performed with hydrogenated analogues.

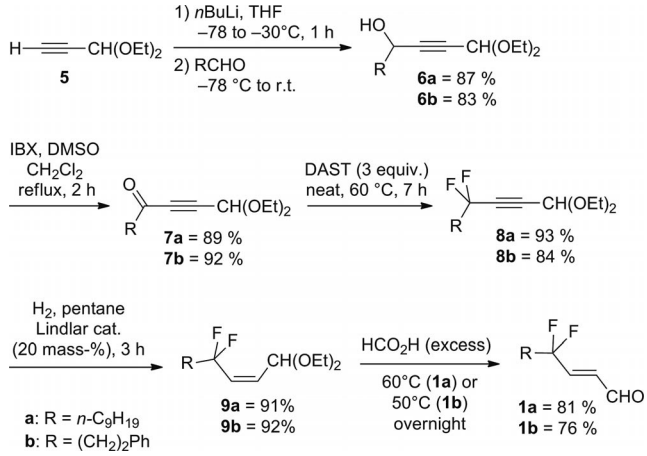


Scheme 1. Designed asymmetric organocatalysis starting from *gem*-difluoroenals **1** and catalysts selected for this study.

The *gem*-difluoroenals were prepared by using methodology that we reported previously for the synthesis of a difluoro analogue of 13 HODE.[9a] Both **1a** and **1b** were obtained, as described in Scheme 2, from commercially available propionaldehyde diethyl acetal (**5**) in four steps in 53 and 45% overall yield, respectively. In this synthesis, only the *E* isomer of enals **1** was obtained.

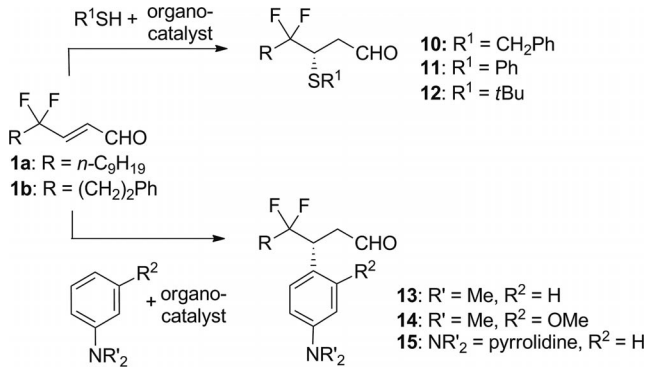
[a] Université de Rennes 1, Institut des Sciences Chimiques de Rennes, CNRS UMR 6226,
Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax: +33-2-23236978
E-mail: rene.gree@univ-rennes1.fr
[b] Laboratory for Medicinal Chemistry and Natural Products, Lebanese University, Faculty of Sciences (1) and PRASE-EDST,
Hadath, Beyrouth, Lebanon
Fax: +961-5-460-301
E-mail: ahachem@ul.edu.lb
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201427.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Synthesis of *gem*-difluoroenals **1a** and **1b**.

To develop the use of **1** in asymmetric 1,4-additions of thiols and aniline derivatives, the first problem was the selection of the organocatalyst and the optimization of the reaction conditions. We chose **1a** as a model, and considered three derivatives as catalysts: MacMillan's imidazolidones **2** and **3**[10] and Jørgensen's diarylprolinol silyl ether **4**.[11] We screened different reaction conditions, and the results are reported in Scheme 3 and Tables 1–3.



Scheme 3. Asymmetric organocatalytic 1,4-additions to *gem*-difluoroenals **1a** and **1b**. For conditions and results, see Tables 1–3.

For benzylthiol addition, hydrochloride salt catalyst **2** alone at room temperature gave good conversion but a low *ee* value (Table 1, entry 1). It is well known that water and some acids can enhance the reactivity in organocatalysis.[1e,12] Therefore, this reaction was performed with 10 mol-% water at –15 °C, but a very low conversion was obtained (Table 1, entry 2). An improvement in reactivity was observed at 0 °C (Table 1, entry 3) and room temperature (Table 1, entry 4) but the *ee* values still remained low. Then, catalyst **3** was tested in the presence of 0.1 equiv. of benzoic acid (Table 1, entry 5) and in the additional presence of 0.1 equiv. of water (Table 1, entry 6). After 24 h at –15 °C, conversions were only moderate and the *ee* values remained low (16–26%).

Table 1. Asymmetric organocatalyzed 1,4-addition of benzylthiol to *gem*-difluoroenal **1a** by using catalysts **2** and **3**.[a]

Entry	Cat.	H_2O [equiv.]	*T* [°C]	Time [h]	Conv. **10a** [%]	**10a** *ee*[c] [%]
1	**2**	–	r.t.	24	87	20
2	**2**	0.1	–15	46	<5	n.d.
3	**2**	0.1	0	44	71	14
4	**2**	0.1	r.t.	24	92	26
5[b]	**3**	–	–15	48	49	16
6[b]	**3**	0.1	–15	24	47	26
7	–	0.1	–15	46	0/0	–
8	–	0.1	0	44	46	0

[a] Reactions were performed in toluene. [b] Reaction performed with addition of benzoic acid (10 mol-%). [c] The *ee* value was established by analysis of the corresponding imidazolidines by ^{19}F NMR spectroscopy (see text); n.d.: not determined.

Therefore, these imidazolidine-type catalysts are not appropriate for the reaction under study. This could be due, at least in part, to the competition between catalyzed and uncatalyzed nucleophilic additions, as well as racemization processes at room temperature.[13] We performed control experiments without any catalyst and established that no reaction occurred at –15 °C (Table 1, entry 7), whereas after 44 h at 0 °C the conversion was 46% and adduct **10a** was afforded in racemic form (Table 1, entry 8).

We then considered diarylprolinol silyl ether **4**,[13] and better results were obtained (Table 2). The reactions were performed at –15 °C. Catalyst **4** alone gave low conversion (Table 2, entry 1). In the presence of 0.1 equiv. of benzoic acid, the reaction was complete after 16 h and gave **10a** with an excellent *ee* value (Table 2, entry 2). Similar results were obtained after further addition of water (0.1 equiv.; Table 2, entry 3). This gave us the optimized reaction conditions to be used later, and they were extended to thiophenol additions (compound **11a**; Table 2, entry 5). Similarly, *tert*-butylthiol gave good conversion to **12a** with an excellent *ee* value (Table 2, entry 6). Finally, these optimized conditions were used with **1b** to afford desired adduct **10b** in excellent yield and *ee* (Table 2, entry 7). So this catalyst is well suited for such 1,4-additions to enals **1**, which is in agreement with literature results with nonfluorinated enals,[13] as well as with trifluorocrotonaldehyde.[6]

The next step was extension of the reaction to aniline derivatives (Scheme 3 and Table 3).[14] Starting from **1a** and using catalyst **2**, the reaction gave desired adduct **13a**; however, only a moderate *ee* value was obtained (42%; Table 3, entry 1). On changing to catalyst **3** in the presence of benzoic acid, the addition product was obtained in lower yield but with excellent *ee* (98%; Table 3, entry 2). In contrast, with the use of catalyst **4** and the addition of benzoic acid (0.1 equiv.) and water (0.1 equiv.) at 35 °C, good to excellent conversions and high *ee* values were obtained for adducts **13a**–**15a** (87–98%; Table 3, entries 3–6). The same result was obtained in the case of adduct **14b** starting from enal **1b** (Table 3, entry 7).

An important point to note is the method used for the measurement of the enantiomeric excess (Scheme 4). As a result of the presence of an aldehyde in the final product,

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Asymmetric organocatalyzed 1,4-addition of thiols to *gem*-difluoroenals **1** by using catalyst **4**.

Entry	Enal	R^1	Conditions[a]	Time [h]	Product	Conv./yield [%]	*ee*[b] [%]
1	**1a**	Bn	A	16	**10a**	40/nd	35
2	**1a**	Bn	B	16	**10a**	100/nd	96
3	**1a**	Bn	C	16	**10a**	100/98	98
4	**1a**	Ph	B	24	**11a**	84/nd	70
5	**1a**	Ph	C	21	**11a**	92/88	95
6	**1a**	*t*Bu	C	40	**12a**	76/71	94
7	**1b**	Bn	C	16	**10b**	100/94	96

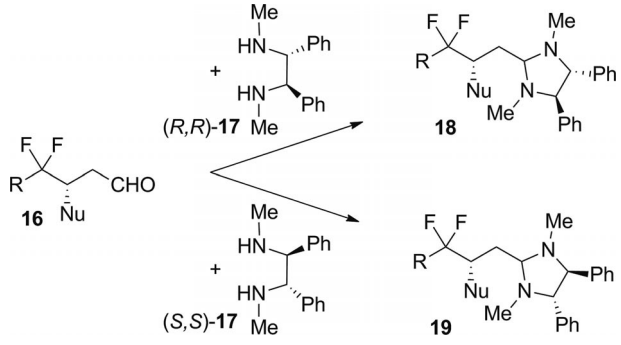
[a] Reactions performed in toluene at –15 °C. Conditions A: Catalyst (10 mol-%) alone; conditions B: catalyst (10 mol-%) and benzoic acid (10 mol-%); conditions C: catalyst (10 mol-%), H_2O (10 mol-%), and benzoic acid (10 mol-%); nd = not determined. [b] The *ee* value was established by analysis of the corresponding imidazolidines by ^{19}F NMR spectroscopy (see text).

Table 3. Asymmetric organocatalyzed 1,4-addition of aniline derivatives to *gem*-difluoroenals **1a** and **1b**.

Entry	Cat./enal	R′	R^2	Time [h][a]	Product	Conv./yield [%]	*ee*[d] [%]
1[c]	**2/1a**	Me	H	26	**13a**	90/n.d.	42
2	**3/1a**	Me	H	48	**13a**	38/n.d.	98
3[c]	**4/1a**	Me	H	48	**13a**	58/n.d.	94
4	**4/1a**	Me	H	48	**13a**	82/77	98
5	**4/1a**	Me	OMe	24	**14a**	95/87	98
6	**4/1a**	–[b]	H	51	**15a**	53/40	87
7	**4/1b**	Me	OMe	24	**14b**	88/84	98

[a] Reactions were performed in $CHCl_3$ at 35 °C; nd = not determined. [b] NR'_2 = 1-pyrrolidino. [c] Reaction was performed without water. [d] The *ee* value was established by analysis of the corresponding imidazolidines by ^{19}F NMR spectroscopy (see text).

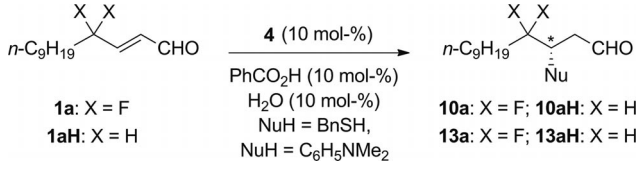
it is possible to use diastereoisomeric imidazolidines to determine the *ee* values, and these derivatives are easily analyzed by NMR spectroscopy. Condensation of enantiopure aldehyde **16** with enantiopure diamine (*R*,*R*)-**17**[15] gives single diastereoisomer **18**. The same condensation performed with the racemic diamine gives a mixture of **18** and **19**, and this mixture produces well-separated signals in the ^{19}F NMR spectrum.



Scheme 4. NMR method used to measure the *ee* values of the 1,4-adducts.

Therefore, starting from the crude reaction mixtures, condensation reactions performed with racemic diamines will give two set of signals corresponding to the two diastereoisomers, whereas condensation with enantiopure diamines will give the stereoisomers in a ratio (*de*) that will transfer directly to the *ee* of the starting aldehyde. A key advantage of this very simple and efficient method is that it avoids any purification step.[16]

An interesting point is the effect of the *gem*-difluoro group in the asymmetric catalytic process. Thus, we have compared the reactivity and selectivity of our compounds with the same derivatives with two hydrogen atoms in the allylic position (Scheme 5 and Table 4). The results clearly indicate that the presence of the two fluorine atoms strongly accelerates the reactions in both cases. In the addition of BnSH, complete conversion of **1a** was observed after 16 h, whereas after the same amount of time, conversion of hydrogeno analogue **1aH** was only 44% complete (Table 4, entries 1 and 2). The *ee* value was also slightly lower in the latter case (82 vs. 98% *ee*). In the addition of *N*,*N*-dimethylaniline (Table 4, entries 3 and 4), the difference was even more striking, as there was no reaction at all starting from hydrogeno analogue **1aH**, whereas addition was highly successful with **1a**.



Scheme 5. Reactivity comparison between *gem*-difluoroenal **1a** and hydrogeno analogue **1aH** during representative asymmetric organocatalyzed 1,4-additions.

Table 4. Comparison of asymmetric organocatalyzed 1,4-addition to *gem*-difluoroenal **1a** and non-fluorinated molecules **1aH**.

Entry	Enal	NuH	Time [h]	Product	Conv./yield [%]	*ee*[c] [%]
1[a]	**1a**	BnSH	16	**10a**	100/98	98
2[a]	**1aH**	BnSH	16	**10aH**	44/40	82
3[b]	**1a**	$C_6H_5NMe_2$	48	**13a**	82	98
4[b]	**1aH**	$C_6H_5NMe_2$	48	**13aH**	0/nd	nd

[a] Reactions were performed in toluene at –15 °C. [b] Reactions were performed in $CHCl_3$ at 35 °C. [c] The *ee* values was established by analysis of the corresponding imidazolidines by ^{19}F NMR and ^1H NMR spectroscopy (see text).

In-depth mechanistic studies have been performed on these types of asymmetric organocatalytic reactions.[1,17] On the basis of these data, it is possible to propose an explanation for the effect of the CF_2R groups: The increase in reactivity with enals **1** is likely connected to the electronegativity of the fluorine atoms, which should increase the electrophilicity of the iminium intermediates. Moreover, the larger size of F as compared to that of H should also increase the steric effects during these reactions and improve the enantioselectivity. Further, electronic effects, for instance through repulsions as a result of the electron pairs of fluorine, could also participate to the improved selectivity of **1a** versus **1aH**.

The (*S*) absolute configuration at the new stereogenic center of the 1,4-adducts was attributed by analogy with previous results from the literature with related enals. Start-

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ing from catalyst **4**, the same configuration was obtained in the series of enals with alkyl chains[13] and in the series of enals with the CF_3 group.[6] These data are also in agreement with the mechanism proposed for these reactions.

Conclusions

We have shown that *gem*-difluoroenals are excellent substrates for asymmetric organocatalyzed 1,4-additions by using Jørgensen's catalyst **4**.[18] The desired adducts were obtained in fair to good yields with good to excellent *ee* values. It was also established that the CF_2R group strongly activates the enals towards these organocatalytic 1,4-additions. Further, a very simple and efficient method based on NMR spectroscopy was used to establish the *ee* values directly on the crude reaction mixtures. Taking into account the large number of reactions that can be used in asymmetric organocatalysis, these enals could be of much interest for the preparation of various types of bioactive molecules with *gem*-difluoroalkyl side chains. Corresponding studies are ongoing in our groups and will be reported in due course.

Experimental Section

Preparation of 3-Benzylsulfanyl-4,4-difluorotridecanal (10a) as a Representative Procedure for the Addition of Thiols: In a glass vial equipped with a magnetic stirring bar, aldehyde **1a** (100 mg, 0.43 mmol, 1.5 equiv.), catalyst **4** (17 mg, 10 mol-%), benzoic acid (3.5 mg, 10 mol-%), and water (0.5 M in dioxane, 57 μL, 10 mol-%) were dissolved in toluene (1 mL). The mixture was cooled to –15 °C before benzyl mercaptan (34 μL, 1 equiv.) was added. The mixture was stirred at this temperature for 16 h and then subjected to silica gel flash column chromatography to afford **10a** as a colorless oil (100 mg, 98%, 98% *ee*). $[a]_D^{22}$ = +5.1 (*c* = 0.25, $CHCl_3$). R_f = 0.41 (pentane/diethyl ether = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.49 (dd, *J* = 0.8, 2.0 Hz, 1 H, C*H*O), 7.28–7.16 (m, 5 H, CH_{arom}), 3.77 (s, 2 H, CH_2S), 3.27 (dddd, *J* = 4.5, 9.4 Hz, J_{HF} = 7.1, 19.4 Hz, 1 H, CF_2CH), 2.82 (ddd, *J* = 0.8, 4.4, 17.8 Hz, 1 H, CH_2CHO), 2.61 (ddd, *J* = 2.0, 9.4, 17.8 Hz, 1 H, CH_2CHO), 1.91–1.78 (m, 2 H, CH_2CF_2), 1.36–1.20 (m, 14 H, 7 CH_2), 0.82 (t, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7 (*C*HO), 137.2 (*C*CH_2), 129.2 (2 *C*H_{arom}), 128.7 (2 *C*H_{arom}), 127.5 [C(CH)$_2$*C*H], 125.7 (t, *J* = 245.9 Hz, *C*F_2), 43.4 (dd, *J* = 1.5, 4.1 Hz, *C*H_2CHO), 42.9 (t, *J* = 27.2 Hz, CF_2CH), 36.8 (*C*H_2S), 33.7 (t, *J* = 24.6 Hz, *C*H_2CF_2), 31.9, 29.4, 29.3, 29.28, 29.26, 22.7, 21.5 (dd, *J* = 3.8, 4.6 Hz, *C*$H_2CH_2CF_2$), 14.1 (CH_3) ppm. ^{19}F NMR (376 and 282 MHz, $CDCl_3$): δ = –98.78 (dddd, J_{HF} = 7.1, 15.7, 23.0 Hz, J_{FF} = 244.6 Hz), –101.81 (dtd, J_{HF} = 12.6, 19.4 Hz, J_{FF} = 244.6 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{30}OF_2NaS$ $[M + Na]^+$ 379.1883; found 379.1890.

Preparation of 3-(4-Dimethylamino-2-methoxyphenyl)-4,4-difluoro-6-phenylhexanal (14b) as a Representative Procedure for the Addition of Anilines: In a glass vial equipped with a magnetic stirring bar, aldehyde **1b** (90 mg, 0.43 mmol), catalyst **4** (25.6 mg, 10 mol-%), benzoic acid (5.3 mg, 10 mol-%), water (0.5 M in dioxane, 86 μL, 10 mol-%), and 3-methoxy-*N*,*N*-dimethylaniline (94 μL, 1.5 equiv.) were dissolved in $CHCl_3$ (1 mL). The mixture was stirred at 35 °C for 24 h and then directly subjected to silica gel flash column chromatography to afford **14b** as a colorless oil (130 mg, 84%, 98% *ee*). $[a]_D^{22}$ = –10.9 (*c* = 1.53, $CHCl_3$). R_f = 0.33 (pentane/diethyl ether = 85:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (br. s, 1 H, C*H*O), 7.17–7.13 (m, 2 H, CH_{arom}), 7.09–7.00 (m, 4 H, CH_{arom}), 6.23 [dd, *J* = 2.5, 8.6 Hz, 1 H, $(CH_3)_2NCCHCH$], 6.12 [d, *J* = 2.5 Hz, 1 H, C*H*C(OCH$_3$)], 4.22 (dddd, *J* = 5.6, 9.1 Hz, J_{HF} = 5.4, 27.0 Hz, 1 H, CF_2CH), 3.74 (s, 3 H, OCH_3), 3.01 (ddd, *J* = 1.9, 5.6, 16.7 Hz, 1 H, CH_2CHO), 2.86 [s, 6 H, N(CH_3)$_2$], 2.81–2.59 (m, 2 H, PhCH_2), 2.71 (ddd, *J* = 2.4, 9.1, 16.7 Hz, 1 H, CH_2CHO), 2.02–1.79 (m, 2 H, CH_2CF_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1 (*C*HO), 157.9 [*C*(OCH$_3$)], 151.2 [*C*N(CH$_3$)$_2$], 141.0 (C$_{arom}$), 129.3 [d, *J* = 3.1 Hz, $(CH_3)_2NCCHCH$], 128.3 (2 *C*H$_{arom}$), 128.25 (2 *C*H$_{arom}$), 126.0 [C(CH)$_2$*C*H], 125.4 (dd, *J* = 245.7, 247.8 Hz, *C*F_2), 112.9 [d, *J* = 9.3 Hz, (CH$_3$O)C*C*], 105.4 [(CH$_3$)$_2$NC*C*HCH], 95.7 (*C*HCOCH$_3$), 55.5 (O*C*H$_3$), 43.4 (dd, *J* = 2.3, 3.6 Hz *C*H_2CHO), 40.5 [(*C*H$_3$)$_2$N], 36.8 (t, *J* = 24.8 Hz, *C*H_2CF_2), 36.7 (dd, *J* = 22.8, *J* = 25.7 Hz, CF_2CH), 28.1 (dd, *J* = 4.3, 5.9 Hz, Ph*C*H$_2$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –99.14 (dddd, J_{HF} = 5.4, 15.5, 21.5, J_{FF} = 239.1 Hz), –107.05 (dddd, J_{HF} = 10.2, 19.5, 27.0 Hz, J_{FF} = 239.1 Hz) ppm. HRMS (ESI): calcd. for $C_{21}H_{25}NO_2F_2Na$ $[M + Na]^+$ 384.1751; found 384.1750.

Supporting Information (see footnote on the first page of this article): Experimental procedures with spectral and analytical data for all compounds and copies of the ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products.

Acknowledgments

We thank the Centre National de la Recherche Scientifique (CNRS) and University of Rennes 1 for financial support. We thank the Centre Regional de Mesures Physiques (CRMPO, Rennes) for mass spectral analyses.

[1] For some recent reviews, see: a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; b) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; c) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; d) B. List, *Angew. Chem.* **2010**, *122*, 1774–1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734; e) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649; f) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264, and references cited therein.

[2] See, for instance: a) I. Ojima, J. R. McCarthy, J. T. Welch, *ACS Symposium Series 639: Biomedical Frontiers in Fluorine Chemistry*, American Chemical Society, Washington, DC, **1996**; b) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**; c) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123–3197; d) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; e) J.-P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–1012; f) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029, and references cited therein.

[3] a) D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991–993; b) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem.* **2005**, *117, 3772–3776*; *Angew. Chem. Int. Ed.* **2005**, *44*, 3706–3710; c) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828; d) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; e) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, *Angew. Chem.* **2005**, *117, 3769–3772*; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706; f) P. Kwiatowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741, and references cited therein.

[4] D. A. Nagib, M. E. Scott, D. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[5] a) T. Konno, T. Tanaka, T. Miyabe, A. Morigaki, T. Ishihara, *Tetrahedron Lett.* **2008**, *49*, 2106–2110; b) Y. Huang, E. Tokunaga, S. Suzuki, N. Shibata, M. Shiro, *Org. Lett.* **2010**, *12*, 1136–1138; c) X.-Q. Dong, X. Fang, C.-J. Wang, *Org. Lett.* **2011**, *13*, 4426–4429; d) Q.-H. Li, M.-C. Tong, J. Li, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 11110–11112; e) K. Shibatomi, F. Kobayashi, A. Narayama, I. Fujisawa, S. Iwasa, *Chem. Commun.* **2012**, *48*, 413–415.

[6] K. Shibatomi, A. Narayama, K. Abe, S. Iwasa, *Chem. Commun.* **2012**, *48*, 7380–7382.

[7] a) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121, 3111–3114*, 42–47; *Angew. Chem.* **2009**, *121*, 3111; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; b) C. Sparr, J. Bahmann, E.-M. Tanzer, R. Gilmour, *Synthesis* **2010**, 1394–1397; c) C. Sparr, R. Gilmour, *Angew. Chem.* **2010**, *122*, 6670–6673; *Angew. Chem. Int. Ed.* **2010**, *49*, 6520–6523; d) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem.* **2011**, *123*, 12062–12074; *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871; e) E. M. Tanzer, L. E. Zimmer, W. B. Schweizer, R. Gilmour, *Chem. Eur. J.* **2012**, *18*, 11334–11342.

[8] a) A.-L. Blayo, S. Le Meur, D. Grée, R. Grée, *Adv. Synth. Catal.* **2008**, *350*, 471–476; b) P. Bannwarth, A. Valleix, D. Grée, R. Grée, *J. Org. Chem.* **2009**, *74*, 4646–4649; c) P. Bannwarth, D. Grée, S. Das, J. S. Yadav, R. Grée, *J. Fluorine Chem.* **2012**, *134*, 180–187.

[9] a) E. Kerouredan, M. Prakesch, D. Grée, R. Grée, *Lett. Org. Chem.* **2004**, *1*, 78–80; b) M. Prakesch, E. Kerouredan, D. Grée, R. Grée, J. De Chancie, K. N. Houk, *J. Fluorine Chem.* **2004**, *125*, 537–541; c) V. Manthati, D. Grée, R. Grée, *Eur. J. Org. Chem.* **2005**, 3825–3829; d) P. Bannwarth, D. Grée, R. Grée, *Tetrahedron Lett.* **2010**, *51*, 2413–2415; e) A. Khalaf, D. Grée, H. Abdallah, N. Jaber, A. Hachem, R. Grée, *Tetrahedron* **2011**, *67*, 3881–3886.

[10] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4245; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875; c) A. Erkillä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470 and references cited therein.

[11] a) M. Marigo, T. C. Wabntiz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.

[12] M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57.

[13] For previous examples of asymmetric organocatalytic 1,4-addition of thiols to enals by using catalyst **4**, see: M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.

[14] For previous examples of asymmetric organocatalytic 1,4-addition of anilines to enals by using catalyst **3**, see: a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895; b) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833–1835.

[15] A. Alexakis, I. Aujard, T. Kanger, P. Mangeney, *Org. Synth.* **1999**, *76*, 23–36.

[16] For representative examples of the use of this method, see: a) D. Cuvinot, P. Mangeney, A. Alexakis, J. F. Normant, J. P. Lellouche, *J. Org. Chem.* **1989**, *54*, 2420–2425; b) A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2431–2434; c) M. Prakesch, D. Grée, R. Grée, *J. Org. Chem.* **2001**, *66*, 3146–3151.

[17] D. Seebach, R. Gilmour, U. Groselj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Sisak, T. Uchimaru, *Helv. Chim. Acta* **2010**, *93*, 603–634, and references cited therein.

[18] Comparison of reactivities of organocatalysts is obviously structure/reaction dependent. For instance, in the case of Diels–Alder reactions, imidazolidinone derivatives **2** and **3** are more active catalysts than **4**, see: J. B. Brazier, G. P. Hopkins, M. Jirari, S. Mutter, R. Pommereuil, L. Samulis, J. A. Platts, N. C. O. Tomkinson, *Tetrahedron Lett.* **2011**, *52*, 2783–2785.

Received: October 26, 2012
Published Online: December 19, 2012

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim