Sequential Catalysis

Access to High Levels of Molecular Complexity by One-Pot Iridium/Enamine Asymmetric Catalysis**

Adrien Quintard, Alexandre Alexakis,* and Clément Mazet*

The introduction of high levels of molecular complexity in a minimal number of operations by sustainable approaches is a contemporary goal in asymmetric catalysis that has recently attracted much interest in the synthetic community. The successful combination of at least two organic and/or organometallic catalysts has enabled remarkable architectural complexity to be created in some cases.^[1,2] Acyclic α,β -chiral aldehydes are particularly attractive targets owing to their high prevalence as pivotal synthetic building blocks and to the challenge associated with their preparation with modular diastereoselectivity and perfect enantioselectivity, especially when stereolabile aldehydes with α -alkyl substituents are targeted. The synthesis of α,β -chiral aldehydes by standard intermolecular enamine catalysis [Eq. (1), Scheme 1] does not necessarily permit modulation of the

enamine catalysis

$$\mathbb{R}^{1} \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{1} \xrightarrow{\mathbb{R}^{2}} \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{1} \xrightarrow{\mathbb{R}^{2}} \xrightarrow$$

iminium/enamine organocascade

$$R^{1} \longrightarrow O^{+} Nu^{-} + E^{+} \longrightarrow Im \qquad En \longrightarrow R^{1} \longrightarrow R^{1} \longrightarrow O^{-} (2)$$

Ir-catalyzed asymmetric isomerization

$$\underset{R^{1}}{\overset{R^{2}}{\underset{R^{3}}{\longleftarrow}}}OH \xrightarrow{r} \underset{R^{1}}{\overset{R^{2}}{\underset{R^{3}}{\longleftarrow}}}O \qquad (3)$$

this study sequential Ir-catalyzed isomerization / enamine catalysis

$$R^{2} \longrightarrow OH^{+} E^{+} \prod_{r} P^{r} \bigoplus_{r} R^{1} \bigoplus_{r} Q^{r} (4)$$

Scheme 1. Complementary strategies to access acyclic α,β -chiral aldehydes.

[*] A. Quintard, Prof. Dr. A. Alexakis, Dr. C. Mazet
Département de chimie organique, Université de Genève
Quai Ernest Ansermet 30, 1211 Genève 4 (Switzerland)
Fax: (+41) 22-379-3215
E-mail: alexandre.alexakis@unige.ch
clement.mazet@unige.ch

- [**] This research was supported by the State Secretariat for Education and Research and the Swiss National Science Foundation.
- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007001.

of this approach.^[3] In contrast, the combination of iminium and enamine catalysis [Eq. (2), Scheme 1] enables valuable transformations, such as hydrohalogenation, hydrooxidation, and aminooxidation, to take place with modular diastereoselectivity along with virtually perfect enantioselectivity.^[4,5] Nonetheless, the large amount of waste generated and, more importantly, the limited scope of these reactions are severe limitations to the development of sustainable and general processes. From this point of view, the atomeconomical and waste-free asymmetric isomerization of tetrasubstituted primary allylic alcohols constitutes a valuable strategy to readily access α,β -chiral aldehydes [Eq. (3), Scheme 1]. Mazet and co-workers recently reported the highly enantioselective iridium-catalyzed asymmetric isomerization of 3,3-disubstituted primary allylic alcohols to β-chiral aldehydes.^[6] Preliminary attempts to promote the corresponding isomerization of primary allylic alcohols with a tetrasubstituted olefin proved unsuccessful.^[7] We hypothesized that a combination of the iridium-catalyzed asymmetric isomerization of 3,3-disubstituted primary allylic alcohols with enamine catalysis in either a sequential or a tandem approach would be a viable alternative, provided that compatibility issues between the organometallic and organic catalysts could be overcome [Eq. (4), Scheme 1].

diastereoselectivity and consequently prevents generalization

To evaluate the feasibility of the overall process, we conducted preliminary experiments with the isomerization catalyst 1a (the Crabtree catalyst), (E)-4-methyl-3-phenylpent-2-enol (3a) as a model substrate, the Hayashi-Jørgensen enamine catalyst 2a, and one equivalent of vinyl sulfone 4 as the electrophilic partner.^[8,9] The reaction was performed in a sequential manner. First, the organometallic precatalyst was converted into the highly reactive dihydride intermediate by applying the standard activation protocol using molecular hydrogen, followed by degassing and subsequent addition of the allylic alcohol at room temperature. After completion of the isomerization reaction, the organic catalyst and the electrophile were added directly to the same reaction vessel (Scheme 2). Initially, 5 was obtained in low yield when the reaction was conducted exclusively in THF. The addition of CHCl₃ and acetic acid had a beneficial effect on the efficiency of the second step of the sequence.^[10] Satisfyingly, under optimized conditions, the sequential use of the organometallic and organic catalysts proved to be feasible. As expected from a parallel kinetic resolution under catalyst control, a 1:1 mixture of two diastereoisomers, syn-5a and anti-5a, was obtained quantitatively, with 92 % ee for syn-5a and 96 % ee for anti-5a (Scheme 2, entry 1).^[11] Whereas similar results were obtained with substrate **3b** (*syn*-**5b**/*anti*-**5b** 1:1; *syn*-**5b**: 91% ee, anti-5b: 91% ee), use of the more biased allylic



Scheme 2. Parallel kinetic resolution on the basis of an isomerization/ α -alkylation sequence. [a] Yield of **5** as determined by ¹H NMR spectroscopy. [b] Determined by supercritical-fluid chromatography (SFC). Absolute configurations as shown. BAr^F = tetrakis[3,5-bis(trifluoro)phenyl]borate, Cy = cyclohexyl, TMS = trimethylsilyl.

alcohol **5c** ($\mathbb{R}^1 = \mathbb{M}e$, $\mathbb{R}^2 = t\mathbb{B}u$) led to an increase in diastereoselectivity (*syn-***5c**/*anti-***5c** 1:4) along with a substantial erosion in enantioselectivity for both diastereoisomers (*syn-***5c**: 66% *ee*, *anti-***5c**: 47% *ee*). This last result indicates that catalyst **2a** and the transient racemic β -chiral aldehyde act oppositely in the formation of the Michael adducts **5c** (catalyst control versus substrate control).

This observation prompted us to explore the possibility of developing a kinetic resolution with the achiral iridium

catalyst **1a** in combination with an appropriate chiral enamine catalyst to access enantiomerically enriched β -chiral and α,β -chiral aldehydes in a single operation.^[9h,12] Because examples of kinetic resolution in enamine catalysis are scarce, we anticipated that this study might also provide useful mechanistic information on the C–C bond-formation step at the α position in the second part of the sequence.^[13]

Initial investigations were conducted at room temperature with a lower stoichiometry of vinyl sulfone 4 (0.5 equiv), with allylic alcohol 3c, and with catalysts 1a and 2a (Table 1, entry 1). The corresponding α,β -chiral aldehydes **5c** and the enantiomerically enriched β-chiral aldehyde 6c were obtained in a 60:40 ratio with anti-5c as the major diastereoisomer (syn-5c/ anti-5c 1.0:4.9; syn-5c: 95% ee, anti-5c: 62% ee). An ee value of 45% was measured for 6c. The reaction was attempted at lower temperatures, and the best results were obtained at 0°C (compare entries 1–3 in Table 1). α , β -Chiral aldehydes **5c** and the β -chiral aldehyde **6c** were obtained in a similar ratio (58:42) but with an increased diastereoisomeric ratio (*syn*-**5c**/*anti*-**5c** 1.0:9.0; *syn*-**5c**: 95% *ee*, *anti*-**5c**: 65% *ee*) as well as an improved level of enantioselectivity for the enriched aldehyde **6c** (80% *ee*). Catalyst **2b**^[9f] displayed similar reactivity and slightly higher selectivity (Table 1, entry 4) and was subsequently used for all other substrates surveyed. Not surprisingly, when the less biased allylic alcohol **3b** was employed (**R**¹ = Cy, **R**² = Ph), aldehydes

	$R^{2} \xrightarrow{R^{1}} OH \xrightarrow{5 \text{ mol% } 1a} H_{2} (1 \text{ min}) \xrightarrow{\text{then degassed}} THF, 23^{\circ}C, 22 \text{ h}$			a () 22 h 22 h 22 h	$\begin{array}{c} \text{SO}_2\text{Ph} \\ \text{SO}_2\text{Ph} \\ \text{D.5 equiv}) \\ \text{ol% 2a or 2b} \\ \text{a, AcOH,} \\ \text{2h} \\ \end{array} \xrightarrow{\text{R}^2} \begin{array}{c} \text{R}^1 \\ \text{H} \\ \text{H} \\ \text{anti-5b} \end{array}$	$ \begin{array}{c} & & \\ & & \\ & \\ & \\ & \\ -\mathbf{e} \end{array} + \begin{array}{c} & & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ $	
Entry	5/6	2	R ¹	R ²	5/6 (yield of 5 [%]) ^[a]	syn-5/anti-5 (ee (syn-5)/ ee (anti-5) [%]) ^[b]	ee (6) [%] ^[c]
1 ^[d]	5c/6c	2a	Me	<i>t</i> Bu	60:40	1.0:4.9	45
					(nd)	(95/62)	
2	5c/6c	2a	Me	<i>t</i> Bu	58:42	1.0:9.0	80
					(43)	(95/65)	
3 ^[e]	5c/6c	2a	Me	tBu	47:53	1.0:6.1	52
					(31)	(50/85)	
4	5c/6c	2 b	Me	<i>t</i> Bu	54:46	1.0:9.0	86
					(32)	(95/65)	
5	5b/6b	2 b	Су	Ph	58:42	2.0:1.0	46 (32) ^[f]
					(43)	(94/90)	
6	5 d/6 d	2 b	Me	SiMe ₂ Ph	62:38	1.0:8.7	63 (32) ^[f,g]
					(38)	(nd/66)	
7	5e/6e	2b	Me	SiMe₃	63:37	1.0:7.3	63 (15) ^[f,g]
					(42)	(91/73)	. ,

Table 1: Resolution by sequential isomerization/enantioselective α alkylation.

[a] The ratio was determined by ¹H NMR spectroscopy. The yield given was determined after chromatography on the basis of **4**. [b] The diastereoisomeric ratio was determined by ¹H NMR spectroscopy of the crude reaction mixture. The *ee* values were determined by SFC or GC. [c] The *ee* value was determined by SFC or GC. [d] The reaction was performed at 23 °C. [e] The reaction was performed at -20 °C. [f] In parenthesis is the yield after chromatography. [g] In the reaction mixture, 5–10% of desilvlated **6** was observed. nd = not determined.

Communications

5b were isolated in good yield (43% yield, i.e. max. 50%) with reduced diastereoselectivity and increased enantioselectivity (*syn*-**5c**/*anti*-**5c** 2.0:1.0; *syn*-**5c**: 94% *ee*, *anti*-**5c**: 90% *ee*). Aldehyde **6b** was isolated in 32% yield with only 46% *ee* (Table 1, entry 5). Allylic alcohols with a large silyl substituent ($R^2 = SiMe_2Ph$ or $SiMe_3$) exhibited higher levels of performance, approaching that of **3b** (compare entries 4, 6, and 7 in Table 1). Additional preliminary experiments with other electrophilic sources suggested that C–C bond formation might be both the rate- and enantiodetermining step.^[14]

In an effort to access high levels of molecular complexity with exquisite diastereo- and enantioselectivity, we next turned our attention to the combination of a chiral isomerization catalyst with a chiral enamine catalyst. In initial experiments on our model substrate 3a, the serine-derived chiral isomerization catalyst 1b^[6c] was combined with 2a in a similar procedure to that developed with the achiral catalyst 1a (Table 2). When 1.0 equivalent of electrophile 4 was used, anti-5c was obtained virtually as the sole product in 46% yield with 99% ee (Table 2, entry 1). Adjustment of the stoichiometry of vinyl sulfone 4 to better match the incomplete conversion of the iridium-catalyzed isomerization step facilitated the isolation and purification of product anti-5a without affecting the outcome of the catalytic sequence (Table 2, entry 2).^[6] This approach was systematically followed in subsequent experiments. Under these conditions, when the mismatched catalyst ent-2b was used, excellent results were still observed (syn-5c/anti-5c 16:1; syn-5c: 99% ee).

Next, to probe the general applicability of the method, the substituents at C3 in the primary allylic alcohols **3** were varied

systematically with both enantiomers of 2a. Aromatic primary allylic alcohols 3a,b,f were converted into the desired α,β -chiral aldehydes **5a,b,f** in acceptable yields with constantly high diastereoselectivity (even in the mismatched case) and with virtually perfect enantioselectivity for the major isomer (Table 2, entries 2-9). Substrate 3g, with a combination of primary and secondary alkyl substituents, was converted into the corresponding adduct 5g in reasonable yield with excellent enantioselectivity, but with decreased diastereoselectivity regardless of which enantiomer of catalyst 2a was used (Table 2, entries 8 and 9). For the highly biased substrates 3c and 3d, the corresponding α,β -chiral aldehydes 5c,d could only be obtained with high levels of diastereoselectivity with the matched catalyst 2a. When the mismatched catalyst ent-2a was employed, the α -alkylation reaction did not proceed at all. Interestingly, a substantial erosion in enantioselectivity was observed when the tert-butyl group was replaced with a much larger (dimethyl)phenylsilyl or trimethylsilyl substituent (Table 2, entries 10, 12, and 13).^[15] The use of catalyst **2b** led to slightly diminished diastereoselectivity along with a net increase in the enantioselectivity of the major diastereoisomer (Table 2, entry 14). These last results provide additional evidence for conflicting interactions between the enamine catalyst and the large β substituents of the chiral intermediate during the installation of the second stereogenic center in the α position.

The scope of the sequential reaction was next investigated placing emphasis on the electrophilic component.^[16] Under optimized reaction conditions, a variety of C–X bonds could be formed during the enamine-catalyzed step of the reaction sequence. The reaction products were obtained in moderate

Table 2: Scope of the sequential isomerization/enantioselective α alkylation with a chiral iridium catalyst in combination with a chiral organocatalyst.^[a]

R ¹ R ² 3a-f	`он	5 mol% 1b H ₂ (1 min) then degassed THF, 23°C	$\frac{20 \text{ mol}\% 23^{\circ}\text{C}, 2 \text{ h}}{23^{\circ}\text{C}, 2 \text{ h}}$	R ² <i>R</i> ² <i>c</i>	[≷] O + R H(SO₂Ph)₂ f	2 ² CH(SO anti- 5a-f	(Bu, /, N=4) (Bu, P., N=4)	⊃ ⁺ - BAr ^E Ph
Entry	5	R ¹	R ²	4 [equiv]	2	Yield [%] ^[b]	syn- 5 /anti-5 ^[c]	ee [%] ^[d]
1	5 a	<i>i</i> Pr	Ph	1.0	2 a	46 (46)	1:19	99
2	5 a	<i>i</i> Pr	Ph	0.5	2 a	32 (63)	1:49	99
3	5 a	<i>i</i> Pr	Ph	0.5	ent- 2 a	34 (68)	16:1	99
4	5 b	Су	Ph	0.7	2 a	66 (94)	1:32	98
5	5 b	Су	Ph	0.7	ent- 2 a	61 (87)	13:1	98
6	5 f	<i>i</i> Pr	p-OMeC ₆ H ₄	0.8	2 a	64 (80)	1:13	99
7	5 f	<i>i</i> Pr	p-OMeC ₆ H ₄	0.8	ent- 2 a	55 (69)	9:1	99
8	5 g	Me	Су	0.7	2 a	54 (78)	1:5	99
9	5 g	Me	Су	0.7	ent- 2 a	45 (60)	4:1	99
10	5 c	Me	<i>t</i> Bu	0.6	2 a	30 (49)	1:49	99
11	5 c	Me	<i>t</i> Bu	0.6	ent- 2 a	nd	nd	nd
12	5 d	Me	SiMe ₂ Ph	0.5	2 a	41 (82)	1:24	75
13	5 d	Me	$SiMe_2Ph$	0.7	2 a	44 (64)	1:24	75
14	5 d	Me	$SiMe_2Ph$	0.5	2 b	28 (55)	1:13	88

[a] Reactions were carried out with 20 mol% of **2a** or **2b** with respect to **4**. [b] Yield after chromatography based on **3**. The yield based on **4** is given in parenthesis. [c] The diastereoisomeric ratio was determined by ¹H NMR spectroscopy of the crude reaction mixture. [d] The *ee* value for the major diastereoisomer is given. Values were determined by SFC or GC.

levels of diastereoselectivity and remarkable enantioselectivity (Scheme 3). For example, a combination of the iridium-catalyzed isomerization step with catalyst 2c and N-fluorodi(benzenesulfonyl)amine (NFSI) delivered syn-7 smoothly as the major diastereoisomer (32:1) with 99% ee in 49% yield after reduction to the alcohol. Similarly, through the use of catalyst 2b and N-chlorosuccinimide (NCS) as a source of electrophilic chlorine, syn-8 was obtained with d.r. 24:1 and 99% ee. L-Proline (2d) was found to be the catalyst of choice for the reaction of 3a with diethyl azodicarboxylate (DEAD): anti-9 was obtained as the major product with d.r. 24:1 and 99% ee.

yields but with constantly high

In conclusion, we have developed a catalytic reaction sequence that exploits the compatibility between recently discovered cationic iridium catalysts for the isomerization of primary allylic alco-

2356 www.angewandte.org

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Scope of the sequential catalytic reaction with respect to the electrophile.

hols to aldehydes and well-established organocatalysts for the highly enantioselective α functionalization of aldehydes.^[17] When an achiral iridium catalyst was used in the first step of the sequence, we observed conflicting interactions between the β substituent of the transient aldehyde and the organic catalyst for sterically more demanding substrates. On the basis of this observation, we developed a resolution reaction to access enantiomerically enriched β -chiral and α , β -chiral aldehydes in a single operation. Although the diastereo- and enantioselectivities observed are not in the practical range, we believe our study will serve as a stepping stone for the design of improved catalysts in related kinetic resolutions. A chiral iridium isomerization catalyst was used in combination with a chiral enamine catalyst to access α,β -chiral aldehydes with excellent diastereo- and enantioselectivity. These products can be obtained with high levels of modular diastereocontrol if the appropriate catalyst combination is used. The generality of the reaction was addressed in terms of both the nucleophile and the electrophile. We have also shown that the modular diastereocontrol in these systems may be highly dependent upon the substitution pattern of the substrate. We anticipate that such observations may be useful in the context of total synthesis if organocatalyzed a-substitution reactions are attempted on relatively elaborate intermediates.

Received: November 8, 2010 Revised: December 12, 2010 Published online: February 3, 2011 **Keywords:** asymmetric catalysis · iridium · isomerization · one-pot reactions · organocatalysis

- For recent reviews, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* 2009, *38*, 2745; b) C. Zhong, X. Shi, *Eur. J. Org. Chem.* 2010, 2999.
- [2] For recent examples of transition-metal/enamine asymmetric catalysis, see: a) F. Bihelovic, R. Matovic, B. Vulovic, R. N. Saicic, Org. Lett. 2007, 9, 5063; b) O. Abillard, B. Breit, Adv. Synth. Catal. 2007, 349, 1891; c) S. Chercheja, P. Eilbracht, Adv. Synth. Catal. 2007, 349, 1897; d) S. Chercheja, T. Rothenbücher, P. Eilbracht, Adv. Synth. Catal. 2009, 351, 339; e) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, Angew. Chem. 2009, 121, 9085; Angew. Chem. Int. Ed. 2009, 48, 8923; f) G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic, A. Córdova, Chem. Eur. J. 2010, 16, 1585; g) K. L. Jensen, P.T. Franke, C. Arroniz, S. Kobbelgaard, K. A. Jørgensen, Chem. Eur. J. 2010, 16, 1750; h) S. Belot, A. Quintard, N. Krause, A. Alexakis, Adv. Synth. Catal. 2010, 352, 667; i) D. A. Nicewicz, D. W. C. MacMillan, Science 2008, 322, 77; j) S. Chercheja, S. K. Nadakudity, P. Eilbracht, Adv. Synth. Catal. 2010, 352, 637; k) A. E. Allen, D. W. C. MacMillan, J. Am. Chem. Soc. 2010, 132, 4986; 1) T. Zweifel, D. Hollmann, B. Prüger, M. Nielsen, K. A. Jørgensen, Tetrahedron: Asymmetry 2010, 21, 1624; m) T. Sato, K. Tomioka, Heterocycles 2009, 77, 587; n) B. Vulovic, F. Bihelovic, R. Matovic, R. N. Saicic, Tetrahedron 2009, 65, 10485; o) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, J. Am. Chem. Soc. 2009, 131, 10875; p) M. Ikeda, Y. Miyake, Y. Nishibayashi, Angew. Chem. 2010, 122, 7447; Angew. Chem. Int. Ed. 2010, 49, 7289; q) A. Quintard, A. Alexakis, Adv. Synth. Catal. 2010, 352, 1856.
- [3] For selected reviews on enamine catalysis, see: a) S. Bertelsen, K. A. Jørgensen, Chem. Soc. Rev. 2009, 38, 2178; b) D. W. C. MacMillan, Nature 2008, 455, 304; c) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, Angew. Chem. 2008, 120, 6232; Angew. Chem. Int. Ed. 2008, 47, 6138; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, Chem. Rev. 2007, 107, 5471; e) P. I. Dalko, Enantioselective Organocatalysis, Wiley-VCH, Weinheim, 2007; f) S. Sulzer-Mossé, A. Alexakis, Chem. Commun. 2007, 3123.
- [4] For reviews, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* 2007, 119, 1590; *Angew. Chem. Int. Ed.* 2007, 46, 1570; b) G. Guillena, D. J. Ramon, M. Yus, *Tetrahedron: Asymmetry* 2007, 18, 693; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* 2010, 2, 167.
- [5] For pioneering contributions, see: a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* 2005, *127*, 15051; b) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* 2005, *127*, 15710; c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* 2005, *127*, 15036.
- [6] a) L. Mantilli, C. Mazet, *Tetrahedron Lett.* 2009, *50*, 4141; b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem.* 2009, *121*, 5245; *Angew. Chem. Int. Ed.* 2009, *48*, 5143; c) L. Mantilli, C. Mazet, *Chem. Commun.* 2010, *46*, 445; d) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Pure Appl. Chem.* 2010, *82*, 1461; e) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, C. Besnard, C. Mazet, *Chem. Eur. J.* 2010, *16*, 12736.
- [7] Allylic alcohols with tetrasubstituted olefins are much less reactive. Furthermore, a substituent on C2 implies that the tautomerization is the enantiodetermining step. If the metal is not involved, or if background tautomerization is substantially

Angew. Chem. Int. Ed. 2011, 50, 2354-2358

Communications

faster, the racemic product is obtained. For a relevant discussion, see: S. Bergens, B. Bosnich, J. Am. Chem. Soc. **1991**, 113, 958.

- [8] For reviews, see: a) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jørgensen, Angew. Chem. 2010, 122, 2726; Angew. Chem. Int. Ed. 2010, 49, 2668; b) Q. Zhu, Y. Lu, Aust. J. Chem. 2009, 62, 951; c) A.-N. R. Alba, X. Companyo, R. Rios, Chem. Soc. Rev. 2010, 39, 2018.
- [9] For the specific use of sulfone 4, see: a) S. Mossé, A. Alexakis, Org. Lett. 2005, 7, 4361; b) Q. Zhu, Y. Lu, Org. lett. 2008, 10, 4803; c) A. Quintard, C. Bournaud, A. Alexakis, Chem. Eur. J. 2008, 14, 7504; d) Q. Zhu, L. Cheng, Y. Lu, Chem. Commun. 2008, 6315; e) A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide, C. Palomo, Chem. Eur. J. 2009, 15, 1562; f) A. Quintard, S. Belot, E. Marchal, A. Alexakis, Eur. J. Org. Chem. 2010, 927; g) S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli, Y. Filinchuk, Chem. Eur. J. 2009, 15, 3204; h) A. Quintard, A. Alexakis, Chem. Commun. 2010, 46, 4085; i) Q. Zhu, Y. Lu, Chem. Commun. 2010, 46, 2235.
- [10] See the Supporting Information for details.
- [11] a) S. El-Baba, J.-C. Poulin, H. B. Kagan, *Tetrahedron* 1984, 40, 4275; b) H. B. Kagan, J.-C. Fiaud, *Top. Stereochem.* 1988, 18, 249; c) J. R. Dehli, V. Gotor, *Chem. Soc. Rev.* 2002, 31, 365.
- [12] a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, J. Am. Chem. Soc. 2005, 127, 18296; b) J. Yang, Z. Ding, Z. Shen, Y. Zhang, Org. Biomol. Chem. 2009, 7, 2208; c) A.-N. Alba, P. Gómez-Sal, R. Rios, A. Moyano, Tetrahedron: Asymmetry 2009, 20, 1314; d) R. D. Carpenter, J. C. Fettinger, K. S. Lam, M. J. Kurth, Angew. Chem. 2008, 120, 6507; Angew. Chem. Int. Ed. 2008, 47, 6407; e) L. Chen, S. Luo, Y. Li, X. Li, J.-P. Cheng, Org. Biomol. Chem. 2010, 8, 2627; f) M. Marigo, S. Bachmann, N. Halland, A. Braunton, K. A. Jørgensen, J. Am. Chem. Soc. 2005, 127, 18296; g) S. Luo, P. Zhou, J. Li, J.-P. Cheng, Chem. Eur. J. 2010, 16, 4457.
- [13] M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* 2011, 47, 632.

- [14] When N-chlorosuccinimide or N-fluorodi(benzenesulfonyl)amine (0.5 equiv) was used as a source of electrophilic chloride or fluoride, 5 was obtained in a 1.3:1.0 or 1.2:1.0 syn/anti diastereoisomeric ratio, respectively, along with aldehyde 6 in nearly racemic form. These observations suggest that in the present system, C-C bond formation, rather than enamine formation, is both the rate- and enantiodetermining step. For a relevant discussion, see reference [13].
- [15] A SiMe₃ substituent has a larger Charton value (v) than a *t*Bu group (1.40 versus 1.24). For recent discussions on the use of Charton values in the context of asymmetric catalysis, see: a) J. J. Miller, M. S. Sigman, *Angew. Chem.* 2008, *120*, 783; *Angew. Chem. Int. Ed.* 2008, *47*, 771; b) M. S. Sigman, J. J. Miller, *J. Org. Chem.* 2009, *74*, 7633; and reference [6e].
- [16] For pioneering enamine-catalyzed fluorination, see: a) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, K. A. Jørgensen, Angew. Chem. 2005, 117, 3769; Angew. Chem. Int. Ed. 2005, 44, 3703; b) T. D. Beeson, D. W. C. MacMillan, J. Am. Chem. Soc. 2005, 127, 8826; c) D. Enders, M. R. M. Hüttl, Synlett 2005, 991; d) D. D. Steiner, N. Mase, C. F. Barbas III, Angew. Chem. 2005, 117, 3772; Angew. Chem. Int. Ed. 2005, 44, 3706; for pioneering enamine-catalyzed chlorination, see: e) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, J. Am. Chem. Soc. 2004, 126, 4790; f) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, J. Am. Chem. Soc. 2004, 126, 4790; f, M. P. Brochu, S. P. Brown, D. W. C. MacMillan, J. Am. Chem. Soc. 2004, 126, 4108; for pioneering enamine-catalyzed amination, see: g) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, Angew. Chem. 2002, 114, 1868; Angew. Chem. Int. Ed. 2002, 41, 1790; h) B. List, J. Am. Chem. Soc. 2002, 124, 5656.
- [17] Preliminary attempts to carry out the catalytic reactions in a tandem rather than sequential manner were successful with the achiral catalyst **1a** but not with the chiral catalyst **1b**. These studies are ongoing.