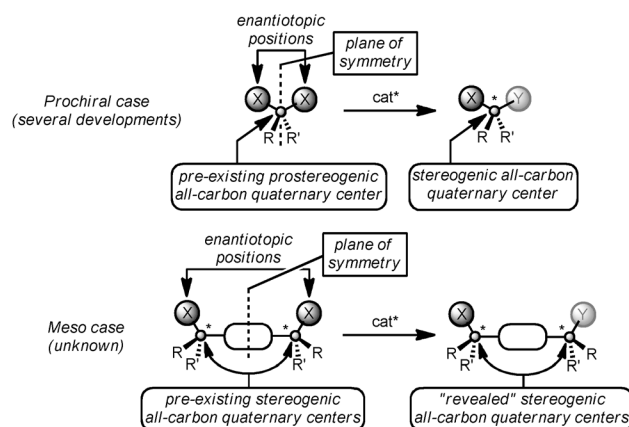


Stereocontrol of All-Carbon Quaternary Centers through Enantioselective Desymmetrization of *Meso* Primary Diols by Organocatalyzed Acyl Transfer**

Christèle Roux, Mathieu Candy, Jean-Marc Pons, Olivier Chuzel,* and Cyril Bressy*

Abstract: The symmetry breaking of *meso* primary diols bearing a tetrahydropyran ring was employed, using catalytic asymmetric acyl transfer, to control all-carbon quaternary stereocenters. The planar chiral Fu DMAP catalyst was used in this reaction to reach a high degree of enantioselectivity (up to 97:3 e.r.) through a synergic effect combining a desymmetrization step and a kinetic resolution. Moreover, a beneficial effect was exhibited by C_6F_6 solvent, yielding the first example of an organocatalyzed asymmetric acyl transfer. The desymmetrized monoesters were then used to obtain, after a straightforward ring opening sequence, complex polyketide building blocks bearing all-carbon quaternary stereocenters.

Enantioselective access to all-carbon quaternary centers has been clearly identified as a challenging area of research,^[1] particularly for acyclic systems. Among the catalytic processes used to reach this goal, the classic approach consists of the creation of the quaternary center concomitant with its stereocontrol. An alternative to this approach is the enantioselective desymmetrization of molecules bearing the pre-existing all-carbon quaternary center(s). Indeed, this powerful strategy separates the task of quaternary center generation from the task of its enantiocontrol. In this field, two types of achiral molecules could then be envisioned: prochiral precursors or *meso* compounds^[2] (Scheme 1). Whereas prochiral molecules hold a unique quaternary center in their plane of symmetry, *meso* compounds possess several stereogenic centers out of their symmetrical element. As a consequence, the level of complexity reached through desymmetrization of *meso* molecules is much higher than that from prochiral molecules. Surprisingly, although several studies have been published on the catalytic enantioselective desymmetrization of prochiral precursors to control all-carbon quaternary stereocenters,^[3–5] none, to the best of our knowledge, has



Scheme 1. Comparison of desymmetrizing approaches using prochiral or *meso* compounds in the stereocontrol of all-carbon quaternary centers.

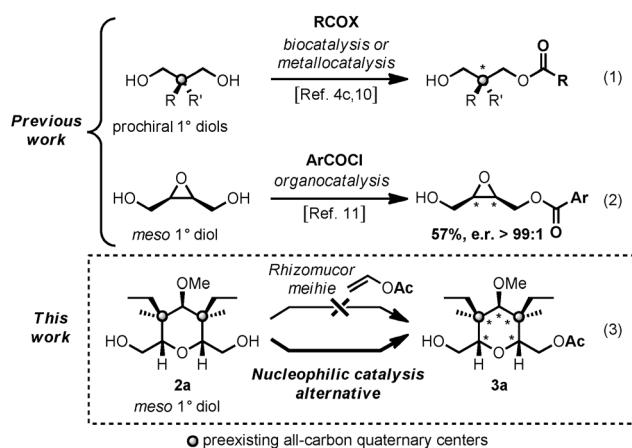
been reported starting from *meso* compounds bearing quaternary centers out of the plane of symmetry.^[6]

To fill this gap, we targeted the desymmetrization of *meso* diols bearing revealable stereocenters. Among the enantioselective catalytic methods of desymmetrization of *meso* diols, asymmetric acyl transfer takes a central place with a long hegemony of biocatalysis.^[7] This transformation furnished several valuable building blocks for total synthesis.^[8] We recently reported the desymmetrization of *meso* primary diols with a high level of enantioselection using an enzyme, *Rhizomucor meihei* lipase.^[9] However, this catalyst was not effective with hindered *meso* compounds bearing all-carbon quaternary stereocenters, such as **2a** (Scheme 2). To circumvent this absence of reactivity, we envisioned a chemical alternative requiring a nucleophilic organocatalysis approach as a valuable answer to the major drawbacks encountered with enzymes, namely the lack of tolerance towards substrates and the access to only one out of two enantiomers. Nevertheless, few studies have been conducted on prochiral primary diols bearing a quaternary center^[10] (Scheme 2, Eq. (1)). As for the organocatalyzed desymmetrization of *meso* primary diols by acyl transfer, a unique case was reported by Oriyama et al.^[11] (Scheme 2, Eq. (2)). We assume that the difficulty in reaching a good level of enantioselection^[12] mainly explains this lack of studies on *meso* primary diols. As a consequence, these substrates can be considered as challenging ones for non-enzymatic desymmetrization by acyl transfer.^[13] In this paper, we aim to report the first efforts towards the stereocontrol of all-carbon quaternary centers by desymmet-

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Scheme 2. Desymmetrization with prochiral or *meso* primary diols.

rization of *meso* primary diols using nucleophilic organocatalysis (Scheme 2, Eq. (3)).

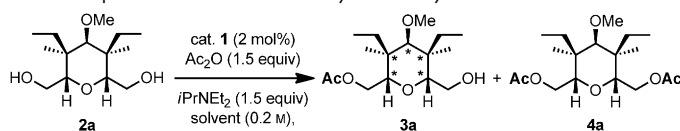
Among the variety of organocatalysts able to desymmetrize *meso* diols,^[14] chiral dialkylaminopyridines derivatives^[15] are very popular for enantioselective acyl transfer, owing to their efficiency.^[16] The commercially available and versatile ferrocenyl Fu catalysts^[17] exhibited a single excellent result with a *meso* secondary diol,^[18] but no study was reported on *meso* primary diols with these catalysts. Moreover, this catalyst is known to be highly selective in the case of enantioselective acyl transfer on secondary alcohols bearing β substituents with π substituents, such as aromatic rings or multiple bonds in the vicinity of the hydroxy group.^[17]

Based on these considerations, we started the optimization^[19] with catalysts **1a** and **1b**, using **2a** as model substrate. The first attempts, using catalyst **1a** under the conditions described by Fu and using 2-methyl-2-butanol (*tert*-amyl alcohol, *t*-AmOH) as solvent gave encouraging results. Indeed, monoacetate **3a** was obtained in 57% yield with a very good enantioselection (e.r. = 92:8; Table 1, entry 1) accompanied by a significant amount of diacetate **4a**. Catalyst **1b** led to a racemic mixture (entry 2), thus showing the strong influence of the cyclopentadienyl (Cp) ring substituents. Replacing Et₃N as the base by *i*PrNEt₂ slightly improved the yield and the enantioselectivity up to 94:6 e.r. (entry 3). A solvent screen highlighted the high selectivity obtained for monoacetate **3a** in CHCl₃ (88%), but also it revealed a drop in enantioselectivity for this solvent (entry 4). Hexafluorobenzene gave monoacetate **3a** with excellent enantioselectivity (e.r. = 95:5), but poor conversion (entry 5).

In an attempt to combine the excellent conversions in *t*-AmOH or CHCl₃ with the high enantioselectivity in C₆F₆, we found that a mixture of these solvents in a 1:1 ratio was effective (entries 6 and 7), and avoided the production of diester **4a**. Increasing the equivalents of base and acylating reagent allowed to improve the yield and retain the level of enantioselectivity. Various acylating reagents were also tested in this reaction, but they did not improved both the reactivity and the enantioselectivity.^[19]

Interestingly, control experiments without catalyst (entries 9 and 10) exhibited the formation of significant

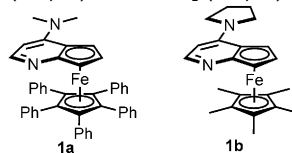
Table 1: Optimization of the non-enzymatic desymmetrization of **2a**.



Entry	Cat.	Solvent	Conv. [%] ^[a]	3a [%] ^[b]	4a [%]	e.r. ^[c]
1 ^[d]	1a	<i>t</i> -AmOH	90	60 (57)	30	92:8
2 ^[d]	1b	<i>t</i> -AmOH	53	41 (23)	12	50:50
3	1a	<i>t</i> -AmOH	96	72 (68)	24	94:6
4	1a	CHCl ₃	98	93 (88)	5	77:23
5	1a	C ₆ F ₆ ^[e]	7	7 (5)	0	95:5
6	1a	C ₆ F ₆ / <i>t</i> -AmOH ^[f]	60	57 (53)	3	91:9
7	1a	C ₆ F ₆ /CHCl ₃ ^[f]	65	65 (58)	0	90:10
8 ^[g]	1a	C ₆ F ₆ /CHCl ₃ ^[f]	90	83 (75)	7	90:10
9	none	<i>t</i> -AmOH	50	32	18	—
10	none	C ₆ F ₆ /CHCl ₃ ^[f]	0	0	0	—
11 ^[g]	none	C ₆ F ₆ /CHCl ₃ ^[f]	7	7	0	—

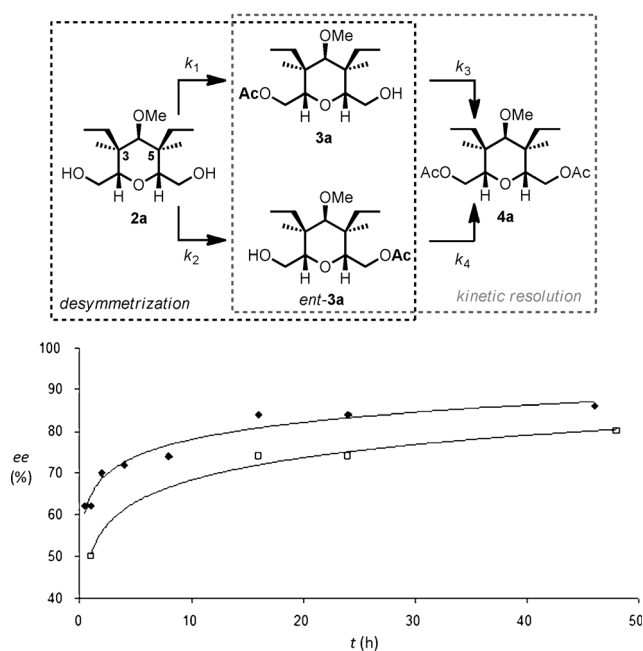
[a] Determined by ¹H NMR analysis of the crude reaction mixture.

[b] Yields of isolated products are given in parentheses. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS-3), *n*-hexane/isopropanol 80:20, 1 mL min⁻¹, DAD and polarimeter. [d] Et₃N was employed as base. [e] Performed at 4 °C. [f] 1:1 ratio. [g] Ac₂O (3 equiv) and *i*PrNEt₂ (3 equiv) were employed.



amounts of monoacetate **3a** and diacetate **4a** after 16 h in *t*-AmOH, but no acylation reaction occurred in the C₆F₆/CHCl₃ solvent system, except when increasing the amount of acylating reagent and base (entry 11).

To explain the high level of enantioselection during this non-enzymatic symmetry breaking, we proposed that the present desymmetrization belongs to a particular class of reactions characterized by the synergic combination of a true desymmetrization reaction and a kinetic resolution (Scheme 3),^[20] with the nucleophilic catalyst being involved in both processes. The formation of the initially undesired diacetate **4a** could be beneficial, if it arises from the consumption of the minor enantiomer of **3a**. Typically, the case where $k_1 > k_2$ and $k_4 > k_3$ represents a favorable scenario to obtain monoacetate **3a** with high enantioselectivity. To experimentally underscore this synergic connection, a following of the enantioselectivity of the product **3a** versus time was conducted using **1a** as catalyst (Scheme 3). Under conditions A (using *t*-AmOH as solvent) the enantiomeric ratio increased over the course of the reactions from 81:19 after 30 min to 93:7 after 46 h. The same tendency was observed under conditions B (with a solvent system combining C₆F₆ and CHCl₃) starting from an e.r. of 75:25 after 30 min to 90:10 ratio after 48 h. These observations validated our hypothesis in both solvent systems (Scheme 3). It is important to notice that the enantioselectivity obtained under conditions A (Table 1, entry 3) results from a desymmetrization reaction/kinetic resolution process, whereas the enantioselectivity in C₆F₆ (e.r. = 95:5) comes from a true desymmetrization

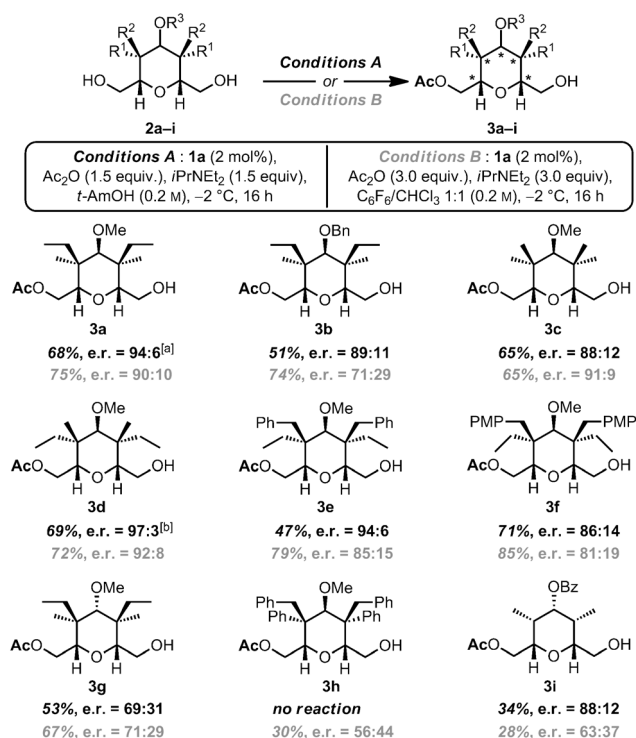


Scheme 3. Experimental evidence for the combination of a desymmetrization reaction coupled to a kinetic resolution by monitoring of the enantioselectivity over time. Conditions A (♦), conditions B (□).

reaction (Table 1, entry 5). Owing to the aromatic structure of the catalyst **1a**, π - π complexation(s) could be postulated between C_6F_6 and the chiral DMAP derivative **1a** (DMAP = dimethylaminopyridine).^[21] The role of this solvent remains unclear, but it seems that the observed enhancement in enantioselectivity would result from a hindered supramolecular entity more discriminating than the catalyst without C_6F_6 . This hypothesis could also explain the lower conversion. Additionally, no evolution of the enantiomeric ratio of monoacetate **3a** was observed under conditions A without acetic anhydride, which demonstrates the irreversibility of the acylation reaction (thus avoiding an eventual racemization process during the transformation).

The absolute configuration of the desymmetrized monoacetate *ent*-**3a**, obtained using (*R*)-ferrocenyl-DMAP *ent*-**1a** as catalyst, was determined by X-ray diffraction of the corresponding crystalline tosylate^[23] (see the Supporting Information).

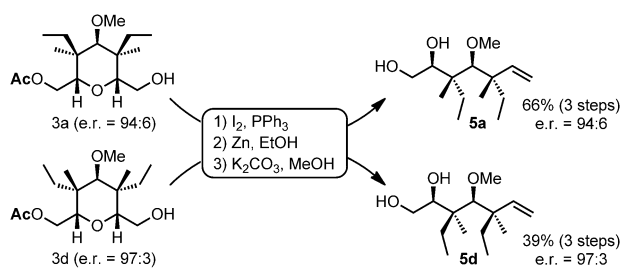
With these optimized conditions, several *meso* primary diols were submitted to both desymmetrization conditions A and B (Scheme 4). Generally, slightly better enantioselectivity was observed under conditions A than under conditions B, but higher yields were obtained with the latter. The substitution pattern on the α -face of the two quaternary centers has a significant effect on the stereoselectivity. Indeed, when this face was blocked by methyl groups in the 3 and 5 positions of the tetrahydropyran (THP) ring (**3a**, **3b**, and **3c**) very good selectivities (up to 94:6 e.r.) were observed. The level of enantioselectivity was improved by exchanging the methyl groups for ethyl groups, as in **3d**, **3e**, and **3f**, reaching up to 97:3 e.r. This transformation also tolerates several hydroxy protecting groups on the prostereogenic 4 position, such as methylether (**3a**), benzylether (**3b**), or benzoate (**3i**). The



Scheme 4. Scope and limitation of the non-enzymatic desymmetrization. Unless otherwise specified, reactions performed with **2** on a 0.2 mmol scale. [a] Performed on a 600 mg scale. [c] Performed on a 300 mg scale. Ac = acetyl, Bn = benzyl, Bz = benzoate.

inversion of the prostereogenic center in the 4 position of the THP ring of diol **2g** led to a significant loss of enantioselectivity for monoester **3g**, as compared to its diastereomer **3a**, which was formed from **2a**. The lower reactivity and selectivity for **2h** could be explained by a dramatic increase in steric hindrance around the quaternary centers bearing here phenyl and benzyl groups. Interestingly, the desymmetrization conditions also gave good results with substrate **2i**, which was successfully employed in reactions with *Rhizomucor meihei* lipase.^[9] Lower yields were obtained under both conditions owing to the higher reactivity of diol **2i** with less steric hindrance in the 3 and 5 positions of the THP ring, which gave larger amounts of diester. Additionally, the desymmetrizations of *ent*-**3a** and **3d** were performed on larger scales (respectively on 600 mg and 300 mg) under conditions A with reproducible yields and enantioselectivities.

With these building blocks in hand, we decided to convert the two diastereomeric enantioenriched monoacetates **3a** and **3d**, which contain the THP systems in acyclic stereotetrads (Scheme 5). The three-step sequence (iodination of the hydroxy group, Zn-mediated reductive ring opening, and mild hydrolysis) provided diastereomeric diols **5a** and **5d** from **3a** and **3d**, respectively, without erosion in enantioselectivity. This global transformation offers privileged access to stereotetrads using an enantioselective organocatalytic method. A high level of complexity was obtained with building blocks bearing three differentiable hydroxy functions, and four contiguous stereogenic centers, including two



Scheme 5. Access to complex polyketides through ring-opening reactions of desymmetrized THPs **3a** and **3d**.

all-carbon quaternary ones. In both cases, the quaternary stereocenters bear methyl and ethyl groups, which are quite difficult to discriminate through other approaches.^[23]

In conclusion, in this preliminary communication we have described the first cases of catalytic enantioselective non-enzymatic desymmetrizations of *meso* compounds bearing all-carbon quaternary centers. This was achieved through a challenging transformation, an asymmetric acyl transfer to primary diols, with an enantioselective ratio of up to 97:3. This is the first example of the use of a chiral Fu DMAP to desymmetrize *meso* primary diols. From a mechanistic point of view, we showed that this symmetry breaking was in fact the result of the combination of a desymmetrization reaction and a kinetic resolution. Moreover, it was shown that building blocks containing up to five stereogenic centers can be easily converted into complex polyketide fragments, which could be useful in the synthesis of analogues of natural products. During this study, important solvent effects were noted with C₆F₆ which, we assume, interacts with the catalyst to produce a supramolecular entity that is more efficient, in terms of enantioselectivity, than the catalyst alone. This hypothesis will be examined in further detail in due course.

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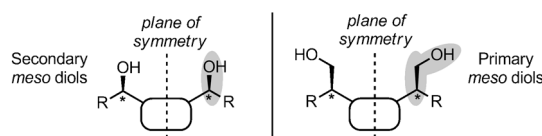
Published online: December 6, 2013

Keywords: desymmetrization · *meso* compounds · organocatalysis · quaternary centers · tetrahydropyranes

- [1] For reviews, see: a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745; b) J. Prakash Das, I. Marek, *Chem. Commun.* **2011**, 47, 4593; c) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, 46, 7295; d) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583.
- [2] Confusion between *meso* compounds and prochiral molecules exists and is persistent in current literature. In the “*Basic Terminology of Stereochemistry*”, IUPAC defines a *meso* compound as “the achiral member(s) of a set of diastereomers which also includes one or more chiral members” (G. P. Moss, *Pure Appl. Chem.* **1996**, 68, 2193). This definition is not applicable to prochiral compounds such as the 2-methylpropane-1,3-diol, for example.
- [3] For selected references, see: a) T. Honda, T. Koizumi, Y. Komatsuzaki, R. Yamashita, K. Kanai, H. Nagase, *Tetrahedron: Asymmetry* **1999**, 10, 2703; b) S. Akai, T. Tsujino, E. Akiyama, K. Tanimoto, T. Naka, Y. Kita, *J. Org. Chem.* **2004**, 69, 2478; c) V.

Iosub, A. R. Haerl, J. Leung, M. Tang, K. Vembaiyan, M. Parvez, T. G. Back, *J. Org. Chem.* **2010**, 75, 1612.

- [4] For selected references, see: a) E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, 131, 943; b) D. H. T. Phan, K. G. M. Kou, V. M. Dong, *J. Am. Chem. Soc.* **2010**, 132, 16354; c) A. K. Mourad, J. Leutzow, C. Czekelius, *Angew. Chem.* **2012**, 124, 11311; *Angew. Chem. Int. Ed.* **2012**, 51, 11149.
- [5] For selected references, see: a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615; b) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem.* **2010**, 122, 9669; *Angew. Chem. Int. Ed.* **2010**, 49, 9479; c) F. Liu, X. Bugaut, M. Schedler, R. Fröhlich, F. Glorius, *Angew. Chem.* **2011**, 123, 12834; *Angew. Chem. Int. Ed.* **2011**, 50, 12626; d) M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc, U. Hennecke, *J. Am. Chem. Soc.* **2013**, 135, 8133.
- [6] We have found a couple of examples of catalytic enantioselective desymmetrization of *meso* compounds bearing an all-carbon quaternary center in the plan of symmetry; see: a) M. H. Wu, K. B. Hansen, E. N. Jacobsen, *Angew. Chem.* **1999**, 111, 2167; *Angew. Chem. Int. Ed.* **1999**, 38, 2012; b) A. C. Spivey, S. J. Woodhead, M. Weston, B. I. Andrews, *Angew. Chem.* **2001**, 113, 791; *Angew. Chem. Int. Ed.* **2001**, 40, 769.
- [7] E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2011**, 111, PR110.
- [8] Recent applications in total synthesis by our group: for Crocacin C, see: M. Candy, G. Audran, H. Bienaymé, C. Bressy, J.-M. Pons, *J. Org. Chem.* **2010**, 75, 1354; for a synthetic approach to Callystatin A, see: M. Candy, L. Tomas, S. Parat, V. Heran, H. Bienaymé, J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2012**, 18, 14267.
- [9] M. Candy, G. Audran, H. Bienaymé, C. Bressy, J.-M. Pons, *Org. Lett.* **2009**, 11, 4950.
- [10] J. Y. Lee, Y. S. You, S. H. Kang, *J. Am. Chem. Soc.* **2011**, 133, 1772.
- [11] D. Terakado, T. Oriyama, *Org. Synth.* **2006**, 83, 70.
- [12] Two factors seem to be the origins of the lower enantioselectivity: first, the higher nucleophilicity of primary alcohols, compared to secondary ones, which is partially due to the higher accessibility of the reactive center; second, lower asymmetric induction with *meso* primary diols could be expected than with secondary *meso* diols because of the distance between the preexisting stereogenic centers and the reactive ones.



- [13] For recent reviews see: a) C. E. Müller, P. R. Schreiner, *Angew. Chem.* **2011**, 123, 6136; *Angew. Chem. Int. Ed.* **2011**, 50, 6012; b) A. Enríquez-García, E. P. Kündig, *Chem. Soc. Rev.* **2012**, 41, 7803; c) M. D. Díaz-de-Villegas, J. A. Galvez, R. Badorrey, M. P. Lopez-Ram-de-Viu, *Chem. Eur. J.* **2012**, 18, 13920.
- [14] a) T. Oriyama, K. Imai, T. Hosoya, T. Sano, *Tetrahedron Lett.* **1998**, 39, 397; b) E. Vedejs, O. Daugulis, N. Tuttle, *J. Org. Chem.* **2004**, 69, 1389; c) V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, 9, 3237; d) P. E. Kündig, A. Enríquez García, T. Lomberger, P. Perez Garcia, P. Romanens, *Chem. Commun.* **2008**, 3519.
- [15] For a review, see: R. P. Wurz, *Chem. Rev.* **2007**, 107, 5570.
- [16] For mechanistic aspects, see: a) A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, 116, 5552; *Angew. Chem. Int. Ed.* **2004**, 43, 5436; b) A. C. Spivey, S. Arseniyadis, *Top. Curr. Chem.* **2010**, 291, 233; c) N. De Tycke, F. Couty, O. R. P. David, *Chem. Eur. J.* **2011**, 17, 12852.
- [17] a) G. C. Fu, *Acc. Chem. Res.* **2000**, 33, 412; b) G. C. Fu, *Acc. Chem. Res.* **2004**, 37, 542; c) S. Yunmi Lee, J. M. Murphy, A.

- Ukai, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 15149, and references therein.
- [18] J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794.
- [19] The optimization process is fully described in the Supporting Information.
- [20] S. L. Schreiber, M. T. Goulet, G. Schulte, *J. Am. Chem. Soc.* **1987**, *109*, 4718.
- [21] A similar amplification of enantioselectivity was recently observed in the organocatalytic Michael addition; see: A. Lattanzi, C. De Fusco, A. Russo, A. Poater, L. Cavallo, *Chem. Commun.* **2012**, 48, 1650.
- [22] CCDC 942839 contains the supplementary crystallographic data available at the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [23] For elegant diastereoselective approaches, see: a) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky, I. Marek, *Nature* **2012**, *490*, 522; b) P.-O. Delaye, D. Didier, I. Marek, *Angew. Chem.* **2013**, *125*, 5441; *Angew. Chem. Int. Ed.* **2013**, *52*, 5333.
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