Hydroxylation

DOI: 10.1002/anie.200804476

A Dynamic Kinetic Asymmetric Transformation in the α-Hydroxylation of Racemic Malonates and Its Application to Biologically Active Molecules**

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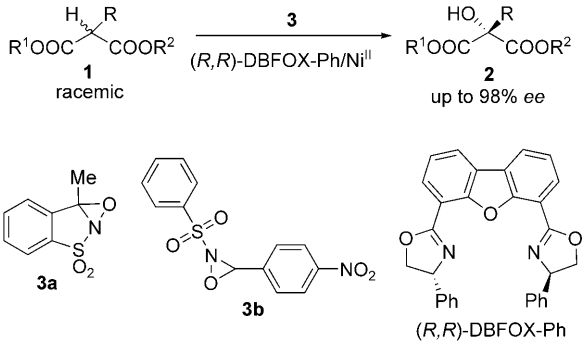
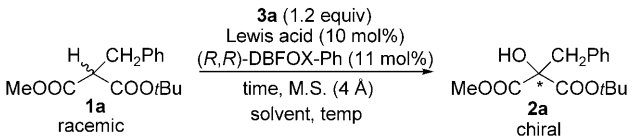
Chiral α-hydroxy malonates and their equivalents are a valuable class of compounds utilized in the synthesis of drug candidates such as chlozolinate and bicalutamide.[1] The synthesis of these compounds has been achieved by the enzymatic desymmetrization of prochiral malonate derivatives,[1a,d,2] or by the enzymatic and chemical desymmetrization of prochiral glycerols.[1b,c,3] Although in recent years significant progress has been made in the development of the catalytic asymmetric α-hydroxylation reaction of carbonyls,[4–6] there have been no reports of catalytic enantioselective hydroxylation of malonate derivatives in the literature, and the reaction remains a challenge. Recently we reported the desymmetrization-like enantioselective fluorination of malonate derivatives in the presence of an (*R*,*R*)-DBFOX-Ph/Zn^{II} complex,[7,8] where chiral α-fluorinated malonate derivatives[9] were obtained in high yields with high enantioselectivities. Herein, we present the first dynamic kinetic asymmetric transformation in the α-hydroxylation of racemic malonate **1** using the (*R*,*R*)-DBFOX-Ph/Ni^{II} complex with oxaziridine **3a** to provide the chiral α-hydroxy malonate **2**, which has a quaternary stereocenter, in high yield with a high enantioselectivity of up to 98% *ee* (Scheme 1). Application of this reaction to the synthesis of biologically attractive molecules illustrates the efficiency of this strategy.

First, we attempted the direct α-hydroxylation of racemic 2-benzyl-*tert*-butyl methyl malonate (**1a**) with oxaziridine **3a** under the best reaction conditions previously reported for the enantioselective fluorination of malonate derivatives:[7] the reaction was carried out in the presence of $Zn(OAc)_2$ and molecular sieves (M.S. 4 Å) in CH_2Cl_2 at room temperature. However, even after 24 hours, the reaction did not proceed (Table 1, entry 1). Under reflux the corresponding 2-hydroxy-2-benzyl-*tert*-butyl methyl malonate (**2a**) was obtained in 15% yield with 92% *ee* (Table 1, entry 2). When the reaction was performed in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$ in CH_2Cl_2 at reflux, the yield was improved to 60% with 91% *ee* (Table 1, entry 3). The addition of 1 equivalent of 2,6-lutidine as base dramatically improved the yield of **2a** (83–91% yield),



Scheme 1. A dynamic kinetic asymmetric transformation in the α-hydroxylation of racemic malonate using (*R*,*R*)-DBFOX-Ph/Ni^{II} complex with oxaziridine.

Table 1: Catalytic enantioselective hydroxylation of racemic **1a**: optimization of the reaction conditions.[a]



Entry	Lewis acid	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$Zn(OAc)_2$	CH_2Cl_2	RT	24	trace	–
2	$Zn(OAc)_2$	CH_2Cl_2	reflux	36	15	92
3	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	reflux	42	60	91
4[d]	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	RT	24	91	82
5[d]	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	−20	48	83	84
6	$Ni(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	reflux	48	82	91
7	$Zn(OAc)_2$	$ClCH_2CH_2Cl$	reflux	80	trace	–
8	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	reflux	48	77	89
9	$Ni(OAc)_2{\cdot}4H_2O$	$ClCH_2CH_2Cl$	reflux	48	0	–
10	$Sc(OTf)_2$	$ClCH_2CH_2Cl$	reflux	60	trace	53
11	$Mg(ClO_4)_2$	$ClCH_2CH_2Cl$	reflux	60	trace	7
12	$Mg(OTf)_2$	$ClCH_2CH_2Cl$	reflux	60	19	0
13	$Ni(ClO_4)_2{\cdot}6H_2O$	EtOH	reflux	60	0	–
14	$Ni(ClO_4)_2{\cdot}6H_2O$	toluene	85	60	20	85
15[e]	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	reflux	62	28	87
16[e]	$Zn(OAc)_2$	CH_2Cl_2	reflux	48	41	49

[a] Reaction conditions: Lewis acid (10 mol%), (*R*,*R*)-DBFOX-Ph (11 mol%), and molecular sieves (4 Å) in solvent. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] 2,6-Lutidine (1 equiv) was added. [e] **3b** was used instead of **3a**.

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[**] Support was provided by KAKENHI (19390029), by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science, and Technology Japan (19020024).

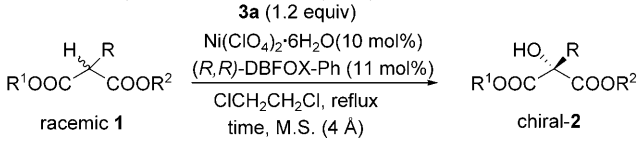
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804476.

even at a lower temperature, but the enantioselectivity was not excellent (82–84% *ee*; Table 1, entries 4–5). Optimization experiments for both the Lewis acid and the solvent were carried out to improve both the yield and enantioselectivity of the transformations (Table 1, entries 6–14), and the combination of $Ni(ClO_4)_2 \cdot 6H_2O$ in 1,2-dichloroethane at reflux was very effective for the dynamic kinetic asymmetric transformation in the α-hydroxylation of malonate derivatives (Table 1, entry 6). The structure of the oxidant slightly affected the yield and enantioselectivity of **2a**. Changing the oxidant from cyclic oxaziridine **3a** to acyclic 3-(4-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine (**3b**) resulted in lower yields with lower *ee* values (Table 1, entries 15–16).

With the reaction conditions now optimized, we next explored the range of substrates that could be tolerated during the hydroxylation reaction (Table 2). First we examined the malonate derivatives and looked at the effect that substitutents on the stereogenic center at the α position had on the hydroxylation reaction. The results showed that the aryl and alkyl substitutents at the α position of **1** have less of an effect on the yields and enantioselectivities, and they were indeed good substrates to afford **2a–e** in high enantioselectivity (91–98% *ee*; Table 2, entries 1–5). The hydroxylation of **1f** with a sterically demanding *i*Bu group also proceeded nicely to give **2f** with 88% *ee* (Table 2, entry 6). We next investigated the scope, limitation, and ability of the present method to discriminate between ester moieties of different steric bulk. As shown in Table 2, the (*R*,*R*)-DBFOX/Ni^{II} catalyst efficiently discriminated between the Me/*t*Bu ester system (Table 2, entries 1–6), the Et/*t*Bu ester system (Table 2, entries 7–10), as well as the Pr/*t*Bu ester system (Table 2, entry 11), and gave at least 90% *ee*. Notably, the discrimination between both sterically hindered *i*Pr and *t*Bu esters was possible, and gave **2l** with 82% *ee* (Table 2, entry 12). We then attempted the discrimination between Me and Et ester substituents using **1m**. However, the desired product **2m** was obtained in 98% yield with only 12% *ee* (Table 2, entry 13). These results indicate that the *t*Bu ester moiety in **1** is responsible for the enantioselective transformation. Discrimination between the Ph and Et esters of **1n** was also possible with the (*R*,*R*)-DBFOX/Ni^{II} catalyst, and gave **2n** with 66% *ee* (Table 2, entry 14), however, the *ee* value was not satisfactory. When oxazoline **3b** was used, **2n** was obtained with 60% *ee* (Table 2, entry 15). To improve the enantioselectivity, we attempted the same reaction of **1n** using 2 equivalents of **3a** or **3b**, but the results were slightly worse (Table 2, entries 16 and 17). This outcome could be explained in light of the "matched/mismatched" concept between two chiral molecules, namely, (*R*,*R*)-DBFOX-Ph and the oxaziridine derivatives. To identify the "matched/mismatched" effect of **3** more clearly, we investigated the reaction of **1n** with an alternative oxaziridine **3c**, which is available in both enantiomeric forms. Although the reactivity of **3c** was very low, the reaction of **1n** with (+)-**3c** proceeded with a high enantioselectivity of 81% *ee* to produce **2n** in the matched case (Table 2, entry 18). The mismatched case using (−)-**3c** provided a trace amount of product (Table 2, entries 19). We next carried out the reaction with aryl ethyl malonate derivatives having larger substituents on the benzene ring to overcome the poor discrimination between Ph and Et esters. It should be noted that the enantioselectivity was finally improved to 88% and 90% *ee* by the use of larger aryl substituents, *o*-fluorophenyl ester **1o** and 1-naphthyl ester **1p**, respectively (Table 2, entries 20 and 21). The configuration of the resulting α-hydroxy malonate **2** can be explained by the preferential approach of the hydroxylating agent **3** from the less hindered *Si* face of the complex formed between the substrates, a Ni^{II} ion, and (*R*,*R*)-DBFOX-Ph—based on the mechanism outlined previously for the enantioselective fluorination of malonate derivatives by (*R*,*R*)-DBFOX-Ph/Zn^{II} catalysis (Figure 1).[7] The octahedral complex of **1c**/(*R*,*R*)-DBFOX-Ph/Ni^{II} containing a water molecule was optimized by using the PM3 program (Spartan 06)[8b] in light of the reported X-ray structure of the (*R*,*R*)-DBFOX-Ph/Ni^{II} complex[10] (Figure 2).

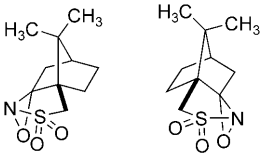
The utility of α-hydroxy malonate **2** was next demonstrated by the synthesis of chlozolinate (**4**; Scheme 2), an important antifungal agent.[1a,11] Previously, (*R*)-**4** was synthe-

Table 2: Catalytic enantioselective hydroxylation of racemic **1a–p**.



Entry	1	R	R^1	R^2	*t* [h]	2	Yield [%]	*ee* [%][a]
1	**1a**	CH_2Ph	Me	*t*Bu	48	**2a**	82	91
2	**1b**	Ph	Me	*t*Bu	12	**2b**	83	93
3	**1c**	Me	Me	*t*Bu	16	**2c**	84	98
4	**1d**	Et	Me	*t*Bu	36	**2d**	74	95
5	**1e**	Bu	Me	*t*Bu	36	**2e**	80	94
6	**1f**	*i*Bu	Me	*t*Bu	48	**2f**	65	88
7	**1g**	CH_2Ph	Et	*t*Bu	48	**2g**	71	91
8	**1h**	Ph	Et	*t*Bu	16	**2h**	74	90
9	**1i**	Me	Et	*t*Bu	14	**2i**	72	94
10	**1j**	Et	Et	*t*Bu	62	**2j**	52	90
11	**1k**	CH_2Ph	Pr	*t*Bu	48	**2k**	63	90
12	**1l**	CH_2Ph	*i*Pr	*t*Bu	62	**2l**	48	82
13	**1m**	CH_2Ph	Me	Et	14	**2m**	98	12
14	**1n**	Me	Et	Ph	3	**2n**	80	66
15[b]	**1n**	Me	Et	Ph	2	**2n**	55	60
16[c]	**1n**	Me	Et	Ph	3	**2n**	79	54
17[b,c]	**1n**	Me	Et	Ph	1	**2n**	59	47
18[d]	**1n**	Me	Et	Ph	16	**2n**	24	81
19[e]	**1n**	Me	Et	Ph	24	**2n**	trace	–
20	**1o**	Me	Et	*o*-FPh	2	**2o**	91	88
21	**1p**	Me	Et	1-naphthyl	2	**2p**	93	90

[a] Determined by HPLC on a chiral stationary phase. The absolute configuration of **2n** was determined to be *S* by comparison with the optical rotation of the known (*S*)-1-ethyl 3-phenyl-2-hydroxy-2-methylmalonate,[1a] and the configuration of **2** was tentatively assumed to be the same by analogy. [b] **3b** was used instead of **3a**. The reaction was performed at RT. [c] 2 equivalents of **3a** or **3b** was used. [d] (+)-**3c** was used instead of **3a**. [e] (−)-**3c** was used instead of **3a**.


(−)-**3c**

(+)-**3c**

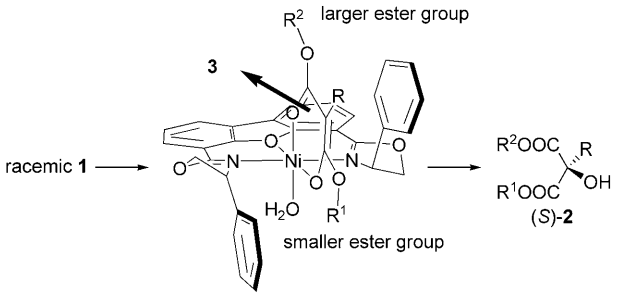


Figure 1. Transition-state structure for the (*R*,*R*)-DBFOX-Ph/Ni^{II}-catalyzed enantioselective hydroxylation of **1** to (*S*)-**2**.

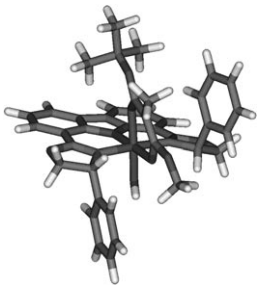
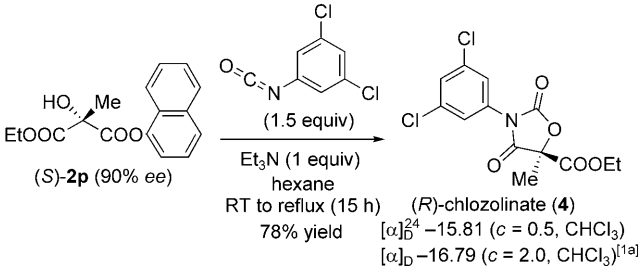


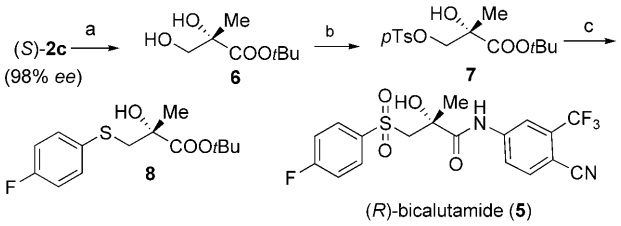
Figure 2. Optimized structure of the **1c**/(*R*,*R*)-DBFOX-Ph/Ni^{II} complex.

sized based on enzymatic desymmetrization,[1a] However, the synthesis requires multiple-step transformations. Our method allowed access to **4** in only two steps from the racemic malonate **1p** via chiral **2p**. Namely, treatment of (*S*)-**2p** (90% *ee*) with 3,5-dichlorophenyl isocyanate in the presence of triethylamine afforded enantiomerically enriched (*R*)-chlozolinate **4**.



Scheme 2. Synthesis of (*R*)-chlozolinate (**4**).

We also considered the synthesis of a key intermediate for the bicalutamide derivatives.[1b,c,12] Bicalutamide (**5**; Scheme 3), which is sold under the trade name of Casodex, is a leading antiandrogen used for the treatment of prostate cancer. Bicalutamide is a racemic mixture with most of its activity residing with the *R* isomer. The chemoselective reduction of (*S*)-**2c** was successfully achieved using LiAl(O*t*Bu)$_3$H[13] and gave (*S*)-*tert*-butyl-2-hydroxy-2-(hydroxymethyl)propanoate (**6**) in 66% yield. The primary hydroxy group of **6** was then protected using *p*-toluenesulfonyl chloride and pyridine in $CHCl_3$ to give the tosylate **7**. Nucleophilic substitution of **7** by sodium 4-fluorobenzenethiol furnished (*R*)-**8**, which should be useful as a common intermediate for the synthesis of (*R*)-bicalutamide as well as its derivatives.



Scheme 3. Reagents and conditions: a) LiAl(O*t*Bu)$_3$H (5 equiv), THF, −78 °C to reflux, 4 h, 66%; b) *p*TsCl (1.5 equiv), pyridine, $CHCl_3$, 0 °C to RT, 17 h, 49%; c) NaH (3 equiv), 4-fluorobenzenethiol (3 equiv), THF, 0 °C to RT, 3 h, 88%.

In conclusion, we have achieved the first highly enantioselective direct hydroxylation of α-hydroxy malonate **2** using the (*R*,*R*)-DBFOX/Ni^{II} complex. Based on this strategy, a dynamic kinetic asymmetric transformation in the α-functionalization of racemic malonate with other electrophiles is now under investigation.

Received: September 11, 2008
Revised: November 6, 2008
Published online: December 19, 2008

Keywords: asymmetric catalysis · desymmetrization · enantioselectivity · hydroxylation · synthetic methods

[1] a) G. Guanti, L. Banfi, K. Powels, M. Rasparini, C. Scolastico, N. Fossati, *Tetrahedron: Asymmetry* **2001**, *12*, 271–277; b) A. Fujino, M. Asano, H. Yamaguchi, N. Shirasaka, A. Sakoda, M. Ikunaka, R. Obata, S. Nishiyama, T. Sugai, *Tetrahedron Lett.* **2007**, *48*, 979–983; c) K. D. James, N. N. Ekwuribe, *Tetrahedron* **2002**, *58*, 5905–5908; d) M. Breznik, D. Kikelji, *Tetrahedron: Asymmetry* **1997**, *8*, 425–434; e) D. Kikelj, L. Povsic, A. Stalc, P. Pristovsek, J. Kidric, *Med. Chem. Res.* **1996**, *6*, 118–127; f) T. Harada, H. Nakajima, T. Ohnishi, M. Takeuchi, A. Oku, *J. Org. Chem.* **1992**, *57*, 720–724; g) P. Blundell, A. K. Ganguly, V. M. S.-P. Girijavallabhan, *Synlett* **1994**, 263–265; h) Y. Yasohara, K. Miyamoto, N. Kizaki, J. Hasegawa, T. Ohashi, *Tetrahedron Lett.* **2001**, *42*, 3331–3333.

[2] a) P. Mohr, N. W. Sarcewic, C. Tamm, K. Gawronska, J. K. Gawronski, *Helv. Chim. Acta* **1983**, *66*, 2501–2511; b) M. Breznik, S. G. Grdadolnik, G. Giester, I. Leban, D. Kikelj, *J. Org. Chem.* **2001**, *66*, 7044–7050; c) M. Breznik, V. Hrast, A. Mrcina, D. Kikelj, *Tetrahedron: Asymmetry* **1999**, *10*, 153–167; d) M. Breznik, V. Hrast, A. Mrcina, D. Kikelj, *Tetrahedron: Asymmetry* **1998**, *9*, 1115–1116; e) M. Breznik, D. Kikelj, *Tetrahedron: Asymmetry* **1997**, *8*, 425–434; f) P. Domínguez de Maria, C. A. Garcia-Burgos, G. Bargeman, R. W. van Gemert, *Synthesis* **2007**, 1439–1452.

[3] a) E. Garcia-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313–354; b) B. Jung, S. H. Kang, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1471–1475; c) B. Jung, M. S. Hong, S. H. Kang, *Angew. Chem.* **2007**, *119*, 2670–2672; *Angew. Chem. Int. Ed.* **2007**, *46*, 2616–2618; d) C. A. Lewis, B. R. Sculimbrene, Y. Xu, S. J. Miller, *Org. Lett.* **2005**, *7*, 3021–3023; e) Y. Yashonara, N. Kizaki, K. Miyamoto, J. Hasegawa, T. Ohashi, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 2044–2049.

[4] For a catalytic asymmetric hydroxylation of β-keto esters, see: a) M. R. Acocella, O. G. Mancheno, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2004**, *69*, 8165 – 8167; b) C. Bonaccorsi, M. Althaus, C. Becker, A. Togni, A. Mezzetti, *Pure Appl. Chem.* **2006**, *78*, 391 – 396; c) P. Y. Toullec, C. Bonaccorsi, A. Mezzetti, A. Togni, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5810 – 5814; d) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanamasa, *J. Am. Chem. Soc.* **2006**, *128*, 16488 – 16489.

[5] For an organocatalytic approach, see selected examples: a) M. Marigo, K. A. Jørgensen in *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**, pp. 56 – 76; b) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465 – 1492; c) B. Plietker, *Tetrahedron: Asymmetry* **2005**, *16*, 3453 – 3459, and references therein; d) D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, *10*, 1593 – 1595; e) M. Engqvist, J. Casas, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2053 – 2057; f) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914 – 8915; g) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129 – 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109 – 1112; h) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132 – 1135; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112 – 1115; i) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379 – 4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247 – 4250; j) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038 – 6039; k) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808 – 10809; l) M. Masui, A. Ando, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 2835 – 2838.

[6] For an enzymaric approach, see selected examples: a) L. DiMarco, L. Hochrein, C. R. Otey, A. Kasrayan, J-E. Bäckvall, F. H. Arnold, *J. Am. Chem. Soc.* **2006**, *128*, 6058 – 6059; b) W. Adam, W. Boland, J. Hartmann-Schreier, H.-U. Humpf, M. Lazarus, A. Saffert, C. R. Saha-Möller, P. Schreier, *J. Am. Chem. Soc.* **1998**, *120*, 11044 – 11048.

[7] D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanamasa, *Angew. Chem.* **2008**, *120*, 170 – 174; *Angew. Chem. Int. Ed.* **2008**, *47*, 164 – 168.

[8] a) N. Shibata, H. Yasui, S. Nakamura, T. Toru, *Synlett* **2007**, 1153 – 1157; b) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 4276 – 4279; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204 – 4207; c) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703 – 1706.

[9] a) G. Haufe, *J. Fluorine Chem.* **2004**, *125*, 875 – 894; b) E. Narisano, R. Riva, *Tetrahedron: Asymmetry* **1999**, *10*, 1223 – 1242; c) T. Kitazume, T. Kobayashi, *Synthesis* **1987**, 187 – 188; d) A. Sattler, G. Haufe, *Tetrahedron: Asymmetry* **1995**, *6*, 2841 – 2848.

[10] S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074 – 3088.

[11] a) V. Di Toro, G. Franco, M. Cecere, S. Lorusso, C. Garavaglia, DE 2906574, **1979**; b) C. Lentza-Rizos, E. J. Avramides, A. Argyropoulou, V. Papadimitriou, K. Kokkinaki, *J. Agric. Food Chem.* **2000**, *48*, 2522 – 2527; c) T. M. Stewart, P. G. Long, *N. Z. J. Exp. Agric.* **1987**, *15*, 97 – 103.

[12] a) G. Blackledge, G. Kolvenbag, A. Nash, *Anticancer Drugs* **1996**, *7*, 27 – 34; b) P. Iversen, M. A. Roder, *Expert Rev. Anticancer Ther.* **2008**, *8*, 361 – 369; c) H. Tucker, J. W. Crook, G. J. Chesterson, *J. Med. Chem.* **1988**, *31*, 954 – 959; d) T. Sugai, M. Ikunaka, H. Yamaguchi, JP 2007204420, **2007**; e) A. Bor, G. Orosz, F. Lukacs, G. Schneider, EP 1669347, **2006**.

[13] T. A. Ayers, *Tetrahedron Lett.* **1999**, *40*, 5467 – 5470.

