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Highly Enantio- and Diastereoselective Synthesis of β-Methyl-γ-monofluoromethyl-Substituted Alcohols

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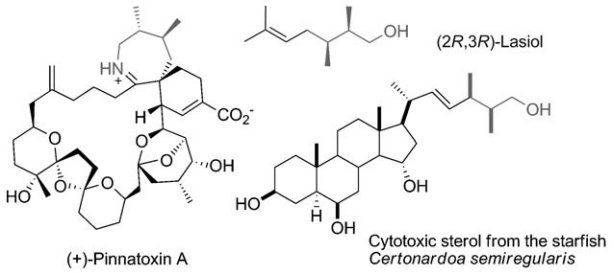
Abstract: Enanatiopure β-methyl-γ-monofluoromethyl alcohols were prepared from the allylic alkylation between fluorobis(phenylsulfonyl)methane with Morita–Baylis–Hillman carbonates. The reaction was catalyzed by using the *Cinchona* alkaloid derivative, $(DHQD)_2AQN$. The origin of the stereoselectivity was verified by DFT methods. Calculated geometries and relative energies of various transition states strongly support the observed stereoselectivity.

Keywords: alcohols · asymmetric catalysis · FBSM · Morita–Baylis–Hillman reactions · organocatalysis

Introduction

The highly polarized C–F bond has unique properties that are understood by considering its stereoelectronic interactions with neighboring bonds or lone pairs of electrons.[1] Monofluorinated analogues of biologically active compounds are often evaluated as bioisosteres of their parent molecules.[2] Fluorinated compounds containing a monofluoromethyl group have been utilized for important applications in biological systems.[2] Thus, there is a strong demand to increase synthetic capabilities to construct building blocks containing a monofluoromethyl group, particularly enantiopure ones.[3]

Alcohols bearing β,γ-dimethyl groups are important structural features in a large number of biologically active natural products and drugs.[4] For instance, (+)-pinnatoxin A (Scheme 1) was reported to be an activator of calcium channels.[4g] Other examples include, (2*R*,3*R*)-lasiol, which was one of new monoterpene alcohols isolated from mandibular glands of the male ants (*Lasius meridionalis*).[4h] Also, one of the cytotoxic sterols extracted from starfish *Certonardoa semiregularis* exhibited unique biological activity.[4d] Methods to introduce a fluorine atom on the 'naked' methyl group of β,γ-dimethyl-substituted alcohols in a stereoselective and diastereoselective manner will be highly desirable. The established protocol for the preparation of β,γ-dimethyl substituted alcohols utilized tandem conjugate addition/α-alkylation reactions employing chiral auxiliaries or chiral reagents.[5] Other methods include the use of baker's yeast to mediate the reduction of the trisubstituted double bonds in cinnamaldehydes[6] and silylated biarylprolinol-catalyzed enantioselective Michael addition of aldehydes to vinyl sulfones.[7] However, these methods cannot be easily modified for the preparation of monofluorinated derivatives.



Scheme 1. Biologically active natural products containing the β,γ-dimethyl moiety.

We recently reported the formation of chiral C–F bonds by using fluorocarbon nucleophiles in highly enantio- and diasteroselective conjugate-addition and Mannich reac-

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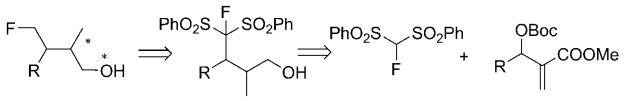
tions.[8] Herein, we would like to report the first highly enantio- and diastereoselective synthesis of β-methyl-γ-monofluoromethyl-substituted alcohols based on the allylic alkylations between bis(phenylsulfonyl)methane (BSM) or fluorobis(phenylsulfonyl)methane (FBSM) with Morita-Baylis–Hillman (MBH) carbonates.

Results and Discussion

Sulfone reagents, such as BSM, are sufficiently acidic to be activated by mild bases and can give terminal 'naked' alkyl groups with the removal of sulfonyl groups through reduction with Mg or Hg/Na.[9,10] FBSM, a fluorocarbon nucleophile derived from BSM, was demonstrated as an efficient precursor of the monofluoromethyl group.[10] Retrosynthetic analysis revealed that FBSM is a viable synthon to prepare enantiopure β-methyl-γ-monofluoromethyl-substituted alcohols from asymmetric allylic alkylation (Scheme 2).[11]



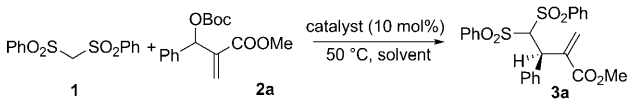
Scheme 2. Retrosynthetic analysis of β,γ-dimethyl-substituted alcohols.

BSM is commercially available and its reactivity is similar to FBSM.[10a–b] For the initial investigation, we selected BSM as a model for FBSM. *Cinchona* alkaloids were investigated as catalysts as they have been shown to be excellent chiral Lewis bases.[12] The allylic alkylation between BSM **1** and MBH carbonate **2a** was shown to work well with quinidine and hydroquinine, providing moderate reactivities and enantioselectivies (Table 1, entries 1–3). C_2-Symmetric (bis)cinchona alkaloid derivatives, such as $(DHQD)_2AQN$,[11g–h,k] improved the *ee* (*ee* = enantiomeric excess) values significantly (entries 3–7). Their rigid enzyme-like pockets help to increase the enantioselectivities.[12b] Catalyst loading can also be lowered to 5 mol% (entry 7). Next, we investigated the effects of solvent and temperature (entries 8–13). Mesitylene was found as the most suitable solvent, giving **3a** in 95% *ee* at 50°C after 72 h (entry 11). By lowering the reaction temperature to 30°C, the *ee* of **3a** was improved to 97% (entry 13).

By using the established conditions, allylic alkylations of BSM **1** with various MBH carbonates (**2b–m**) was found to afford the products **3b–m** with excellent *ee* values (Table 2). MBH carbonates (Table 2, **2b–d**, **f–i**) with electron-withdrawing groups appended on the aromatic rings were more active than those (Table 2, **2j–k**, **m**) with electron-neutral and donating groups. However, the fluorinated **2e** deviated from this trend. The absolute configurations of the allylic alkylation products were assigned based on X-ray crystallographic analysis of a single crystal of **3j**.[13]

With the excellent results in hand, we conducted the asymmetric allylic alkylation between FBSM **4** and MBH carbonate **2** in the presence of 10 mol% of $(DHQD)_2AQN$ in mesitylene at 30°C (Table 3, entry 1). The reaction was very slow and it indicated that the reactivity of FBSM **4** was lower than BSM **1** in this reaction. When the temperature was increased to 50°C, the desired product **5a** was obtained with 52% yield and 91% *ee* (entry 2). Subsequently, mesitylene-like solvents were screened under the same reaction conditions (entries 2–7). The best solvent was found to be

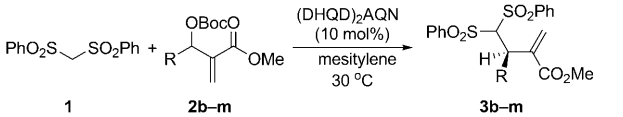
Table 1. Allylic alkylation of BSM **1** with MBH carbonate **2a**.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	quinidine	toluene	60	99	57
2	hydroquinine	toluene	63	75	57
3	$(DHQ)_2PYR$[d]	toluene	26	88	−65
4	$(DHQ)_2AQN$[d]	toluene	26	83	−55
5	$(DHQD)_2PHAL$[d]	toluene	26	93	53
6	$(DHQD)_2PYR$[d]	toluene	26	81	80
7	$(DHQD)_2AQN$[d]	toluene	20	90	91 (93)[e]
8	$(DHQD)_2AQN$[d]	DCE	33	66	80
9	$(DHQD)_2AQN$[d]	$PhCF_3$	20	87	89
10	$(DHQD)_2AQN$[d]	xylene	33	68	84
11	$(DHQD)_2AQN$[d]	mesitylene	72	74	95
12[f]	$(DHQD)_2AQN$[d]	toluene	43	60	95 (97)[g]
13[f]	$(DHQD)_2AQN$[d]	mesitylene	79	76	97

[a] Unless otherwise noted, reactions were performed with 0.05 mmol of **1**, 0.075 mmol of **2a**, and 0.005 mmol of catalyst in 0.5 mL solvent. [b] Yield of isolated product. [c] Determined by HPLC methods. [d] $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether. [e] 5 mol% catalyst, 24 h, 99% yield. [f] Reaction was conducted at 30°C. [g] 0.2 mmol scale, 96 h, 73% yield.

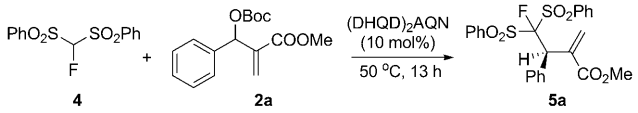
Table 2. Highly enantioselective allylic alkylation between BSM **1** and MBH carbonates **2b–m**.[a]



Entry	R^1	R^2	**2**	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_5$	CO_2Me	**2b**	48	**3b**	99	94
2	3-$NO_2C_6H_5$	CO_2Me	**2c**	47	**3c**	96	90
3	4-$CF_3C_6H_5$	CO_2Me	**2d**	47	**3d**	80	92
4[d]	4-FC_6H_5	CO_2Me	**2e**	75	**3e**	84	90
5	2-ClC_6H_5	CO_2Me	**2f**	44	**3f**	80	92
6	3,4-$Cl_2C_6H_5$	CO_2Me	**2g**	47	**3g**	96	95
7	4-BrC_6H_5	CO_2Me	**2h**	47	**3h**	83	96
8	3-BrC_6H_5	CO_2Me	**2i**	59	**3i**	97	93
9[d]	4-*i*PrC_6H_5	CO_2Me	**2j**	48	**3j**	97	94
10[d]	4-$MeOC_6H_5$	CO_2Me	**2k**	36	**3k**	99	94
11[d]	3-thiophenyl	CO_2Me	**2l**	20	**3l**	71	92
12[d]	2-naphthyl	CO_2Me	**2m**	75	**3m**	85	94

[a] Reactions were performed with 0.1 mmol of **1**, 0.15 mmol of **2b–m**, and 0.01 mmol of catalyst in 1.0 mL mesitylene. [b] Yield of isolated product. [c] Determined by HPLC methods. [d] Reaction was conducted at 50°C.

Table 3. Allylic alkylation of FBSM **4** with MBH carbonate **2a**.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1[d]	mesitylene	n.d.[e]	n.d.[e]
2	mesitylene	52	91
3	$PhCF_3$	64	89
4	xylene	43	91
5	*o*-xylene	67	90
6	*p*-xylene	68	90
7	toluene	58	91
8[f]	toluene	72	>99.9

[a] Unless otherwise noted, reactions were performed with 0.05 mmol of **4**, 0.075 mmol of MBH **2a**, and 0.005 mmol of catalyst in 0.5 mL solvent. The reactions were stopped after 13 h. [b] Yield of isolated product. [c] Determined by HPLC methods. [d] 30 °C. [e] n.d. = not determined. [f] 0.5 mmol scale, reaction was stopped after 72 h. Filtration yield. The reaction was repeated three times.

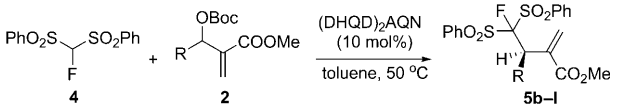
toluene as the reaction was faster in this solvent (entry 7). Recently, a filtration approach was used by List et al. to achieve enantiopure products in a convenient manner.[14] The product **5a** precipitated progressively from the initial homogenous reaction mixture of starting materials consisting of FBSM **4**, MBH carbonate **2**, and $(DHQD)_2AQN$ (Figure 1).

Figure 1. Allylic alkylation of MBH carbonate **2a** and FBSM **4** in the presence of 10 mol% $(DHQD)_2AQN$ in toluene. Left: picture of homogenous reaction mixture after mixing all components. Right: picture of reaction mixture after completion of the reaction (72 h).

After a simple filtration, the product **5a** was rinsed with cold toluene/petroleum ether (60–90 °C) 1:10 and **5a** was obtained with >99.9% *ee* (entry 11).[15] Different MBH carbonates were investigated under the optimal reaction conditions and enantiopure products **5b–l** were obtained with excellent *ee* values by using the filtration protocol (Table 4).

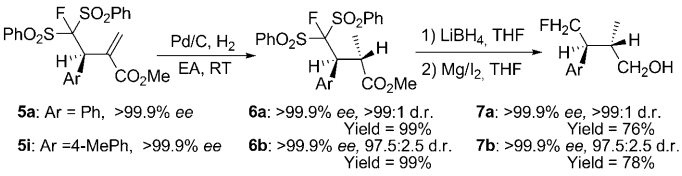
We then proceeded to synthesize the β-methyl-γ-monofluoromethyl alcohols from the monofluorinated allylic alkylation adducts (Scheme 3). After attempting several reductive protocols, hydrogen gas on Pd/C in ethyl acetate at room temperature was found as the most effective method; only one diastereoisomer **6a** was obtained with 99% yield.[15] The structure of **6a** was confirmed by using X-ray crystallographic analysis.[16] Diastereoisomer **6a** was subjected to $LiBH_4$ reduction and desulfonation with magnesium/iodine in THF. Enantiopure monofluoromethylated **7a** was obtained (>99.9% *ee* and >99:1 d.r. (d.r. = diastereomeric ratio)) in good overall yield.

Table 4. Highly enantioselective allylic alkylation between FBSM **4** and MBH carbonates **2**.[a]



Entry	R^1	**2**	*t* [h]	**5**	Yield [%][b]	*ee* [%][c]
1[d]	4-$NO_2C_6H_5$	**2b**	24	**5b**	67	>99.9
2	4-$CF_3C_6H_5$	**2d**	94	**5c**	60	>99.9
3	4-FC_6H_5	**2e**	72	**5d**	71	>99.9
4	2-FC_6H_5	**2n**	46	**5e**	69	>99.9
5[e]	2-ClC_6H_5	**2f**	48	**5f**	72	>99.9
6[f]	3,4-$Cl_2C_6H_5$	**2g**	48	**5g**	65	>99.9
7	4-BrC_6H_5	**2h**	42	**5h**	70	>99.9
8	4-MeC_6H_5	**2o**	71	**5i**	59	>99.9
9	4-*i*PrC_6H_5	**2j**	48	**5j**	58	>99.9
10[g]	4-$MeOC_6H_5$	**2k**	94	**5k**	68	>99.9
11	3-thiophenyl	**2l**	48	**5l**	60	>99.9

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **4**, 0.15 mmol of **2**, and 0.01 mmol of catalyst in 1.0 mL toluene. The reactions were repeated more than twice. [b] Filtration yield. [c] Determined by HPLC methods. [d] FC yield = 81%, *ee* = 86%. [e] FC yield = 85%, *ee* = 90%. [f] FC yield = 83%, *ee* = 90%. [g] Flash chromatography yield = 85%, *ee* = 95%.



Scheme 3. Synthesis of the β-methyl-γ-monofluoromethyl alcohols.

To shed light on the origin of the enantioselectivity of the alkylation reaction of FBSM **1**/BSM **4** with MBH carbonates catalyzed by $(DHQD)_2AQN$, computational modeling was conducted by using DFT at the B3LYP level of theory[17] to investigate the transition states for the generation of *R* and *S* enantiomers through the nucleophilic attack from the *si* (CS1) or *re*-face (CS2) rotamers of the catalyst–MBH substrate adduct, respectively, by the BSM nucleophile in either *cis* or *trans* forms (Figure 2).[18] Preliminary results indicate that the transition state for the generation of the *R* product is lower than those for the *S* product by 11.4 to 13.8 kcal mol^{-1}, owing to the increased steric interaction in the *re*-face approach in which both MBH substrate and nucleophile are buried internally within the anthraquinone backbone. The observation that the *cis*-BSM attack to afford the *R* enantiomer is preferred may be attributed to the stabilization effect of the π–π orbital interaction between the two phenyl rings on the nucleophile.[18] Since the calculated species are charge-separated zwitterions, solvent effects on the structures by using toluene were also evaluated by single-point calculations on the optimized gas-phase structures by employing a polarizable continuum model with the default integral equation formalism variant (IEFPCM).[19] It was found that the computed energy of the transition state leading to the *R* enantiomer was more stable than those leading

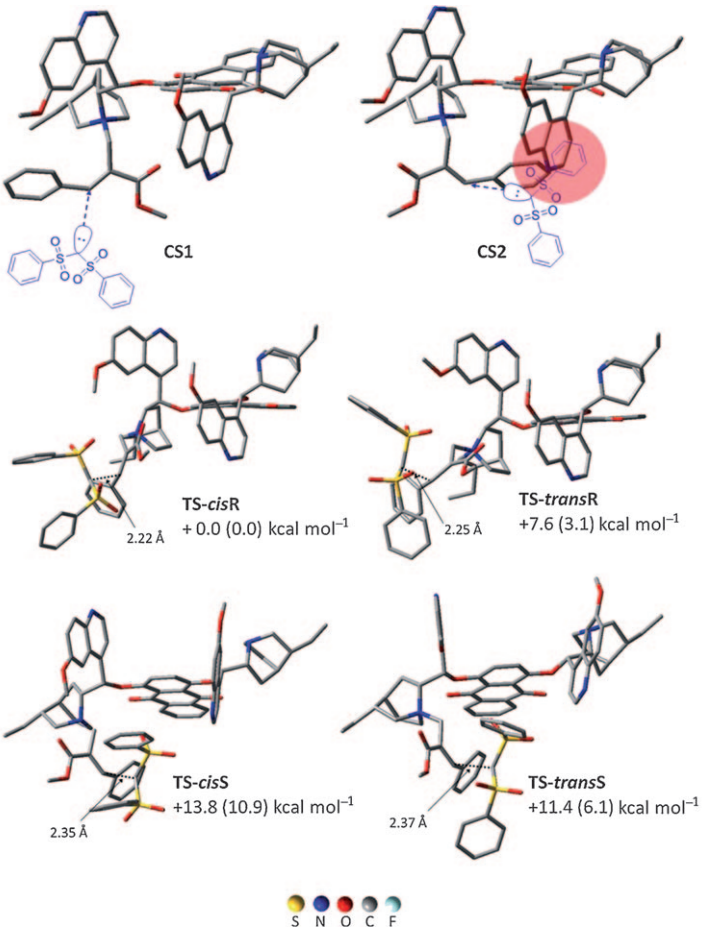


Figure 2. Optimized geometries of catalyst–substrate adduct, CS1 and CS2 (top), with the addition of BSM nucleophile leading to four transition states, TS-*cis*R, TS-*trans*R, TS-*cis*S and, TS-*trans*S (bottom). Free energies with ZPE and single-point energies in parenthesis are reported relative to their most stable conformers.

to the *S* enantiomer by 3.1 to 10.9 kcal mol^{-1}, in good agreement with the gas-phase DFT calculations and experimental results.

Conclusion

We have successfully developed practical and highly enantioselective allylic alkylations to construct enantiopure β-methyl-γ-monofluoromethyl-substituted alcohols. The origin of stereoselectivity was elucidated by DFT calculations. Further work is ongoing to illustrate a more coherent picture of the reaction mechanism and to extend the scope of applications.

Experimental Section

Representative procedure for the synthesis of 5a: FBSM **4** (157.2 mg, 0.5 mmol, 1.0 equiv), MBH carbonate **2a** (219.2 mg, 0.75 mmol, 1.5 equiv), and $(DHQD)_2AQN$ (95% purity) (45.1 mg, 0.05 mmol, 0.1 equiv) were dissolved in toluene (5.0 mL). The reaction mixture was stirred at 50 °C and monitored by using TLC analysis. After 72 h, the reaction was completed and cooled down to 0 °C. Then the precipitate was filtered through a Buchner funnel and washed with a cooled solvent (toluene/petroleum ether (60–90 °C) 1:10, 0 °C). Finally, **5a** (176.1 mg, 72% yield) was obtained as a white solid after drying.

Acknowledgements

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[1] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.
[2] a) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, New York, **2009**; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
[3] For reviews on asymmetric fluorination, see: a) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558–568; b) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708–2732; c) V. A. Brunet, D. O'Hagan, *Angew. Chem.* **2008**, *120*, 1198–1201; *Angew. Chem. Int. Ed.* **2008**, *47*, 1179–1182; d) N. Shibata, T. Ishimaru, S. Nakamura, T. Toru, *J. Fluorine Chem.* **2007**, *128*, 469–483; e) C. Bobbio, V. Gouverneur, *Org. Biomol. Chem.* **2006**, *4*, 2065–2075; f) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558–561; *Angew. Chem. Int. Ed.* **2006**, *45*, 544–547; g) M. Oestreich, *Angew. Chem.* **2005**, *117*, 2376–2379; *Angew. Chem. Int. Ed.* **2005**, *44*, 2324–2327; h) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147–1155; i) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146.
[4] a) N. Ferro, J. E. Tacoronte, T. Reinard, P. Bultinck, L. A. Montero, *J. Mol. Struct.: THEOCHEM* **2006**, *758*, 263–274; b) T. Ohnishi, T. Nomura, B. Watanabe, D. Ohta, T. Yokota, H. Miyagawa, K. Sakata, M. Mizutani, *Phytochemistry* **2006**, *67*, 1895–1906; c) A. Yokosuka, Y. Mimaki, C. Sakuma, Y. Sashida, *Steroids* **2005**, *70*, 257–265; d) W. Wang, J. Hong, C.-O. Lee, K. S. Im, J. S. Choi, J. H. Jung, *J. Nat. Prod.* **2004**, *67*, 584–591; e) H. Shigemori, Y. Sato, T. Kaga, J. Kobayashi, *J. Nat. Prod.* **1999**, *62*, 372–374; f) E. Palagiano, F. Zollo, L. Minale, M. Iorizzi, P. Bryan, J. McClintock, T. Hopkins, *J. Nat. Prod.* **1996**, *59*, 348–354; g) D. Uemura, T. Chou, T. Haino, A. Nagatsu, S. Fukuzawa, S. Zheng, H. Chen, *J. Am. Chem. Soc.* **1995**, *117*, 1155–1156; h) T. Kasai, H. Watanabe, K. Mori, *Bioorg. Med. Chem.* **1993**, *1*, 67–70.
[5] a) S. Nakamura, F. Kikuchi, S. Hashimoto, *Angew. Chem.* **2008**, *120*, 7199–7202; *Angew. Chem. Int. Ed.* **2008**, *47*, 7091–7094; b) C. E. Stivala, A. Zakarian, *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776; c) S. Nakamura, F. Kikuchi, S. Hashimoto, *Tetrahedron: Asymmetry* **2008**, *19*, 1059–1067; d) S. Mitra, S. R. Gurrala, R. S. Coleman, *J. Org. Chem.* **2007**, *72*, 8724–8736; e) K. Fujiwara, J. Naka, T. Katagiri, D. Sato, H, Kawai, T. Suzuki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1173–1186; f) C. E. Stivala, A. Zakarian, *Tetrahedron Lett.* **2007**, *48*, 6845–6848; g) E. Reyes, J. L. Vicario, L. Carrillo, D. Badía, A. Iza, U. Uria, *Org. Lett.* **2006**, *8*, 2535–2538; h) S. Hanessian, G. J. Reddy, N. Chahal, *Org. Lett.* **2006**, *8*, 5477–5480; i) E. Reyes, J. L. Vicario, L. Carrillo, D. Badía, U. Uria, A. Iza, *J. Org. Chem.* **2006**, *71*, 7763–7772; j) S. Sakamoto, H. Sakazaki, K. Hagiwara, K. Kamada, K. Ishii, T. Noda, M. Inoue, M. Hirama, *Angew. Chem.* **2004**, *116*, 6667–6672; *Angew. Chem. Int. Ed.* **2004**, *43*, 6505–6510.
[6] G. Fronza, C. Fuganti, S. Serra, *Eur. J. Org. Chem.* **2009**, 6160–6171.
[7] Q. Zhu, Y. Lu, *Org. Lett.* **2008**, *10*, 4803–4806.
[8] a) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2010**, *16*, 779–782; b) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. Wong, C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681–3685; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627–3631; for selected examples to the synthesis of chiral C–F bonds

from fluorocarbon derivatives, see: c) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.* **2010**, *352*, 2778–2782; d) H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.* **2010**, *75*, 117–122; e) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem.* **2009**, *121*, 7740–7743; *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607; f) H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun.* **2009**, 2136–2138; g) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044–2046; h) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090–4094; i) C. Ding, K. Maruoka, *Synlett* **2009**, 664–666; j) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608–9610; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466–9468.

[9] For recent examples, see: a) Q. Zhu, Y.-X. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756; b) A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, *16*, 5354–5361.

[10] For reviews, see: a) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jørgensen, *Angew. Chem.* **2010**, *122*, 2726–2738; *Angew. Chem. Int. Ed.* **2010**, *49*, 2668–2679; b) A.-N. R. Alba, X. Companyó, R. Rios, *Chem. Soc. Rev.* **2010**, *39*, 2018–2033; c) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547–10658; d) N. S. Simpkins, *Tetrahedron* **1990**, *46*, 6951–6984; for selected examples, see: e) W.-B. Liu, S.-C. Zheng, H. He, X.-M. Zhao, L.-X. Dai, S.-L. You, *Chem. Commun.* **2009**, 6604–6606; f) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 8171–8174; *Angew. Chem. Int. Ed.* **2008**, *47*, 8051–8054; g) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.* **2007**, *129*, 6394–9395; h) G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew, G. A. Olah, *Angew. Chem.* **2007**, *119*, 5021–5024; *Angew. Chem. Int. Ed.* **2007**, *46*, 4933–4936; i) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem.* **2006**, *118*, 5095–5099; *Angew. Chem. Int. Ed.* **2006**, *45*, 4973–4977; j) S. Zhang, Y. Zhang, Y. Ji, H. Li, W. Wang, *Chem. Commun.* **2009**, 4886–4888.

[11] For selected examples on allylic alkylation reactions, see: a) W. Sun, L. Hong, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 3914–3917; b) L. Hong, W. Sun, C. Liu, D. Zhao, R. Wang, *Chem. Commun.* **2010**, *46*, 2856–2858; c) J. Peng, X. Huang, H.-L. Cui, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 4260–4263; d) H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 720–723; e) Z. Chen, J. Zhang, *Chem. Asian J.* **2010**, *5*, 1542–1545; f) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5847–5850; *Angew. Chem. Int. Ed.* **2009**, *48*, 5737–5740; g) H.-L. Cui, J. Peng, X. Feng, W. Du, K. Jiang, Y.-C. Chen, *Chem. Eur. J.* **2009**, *15*, 1574–1577; h) K. Jiang, J. Peng, H.-L. Cui, Y.-C. Chen, *Chem. Commun.* **2009**, 3955–3957; i) D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, *349*, 281–286; j) Y. Du, X. Han, X. Lu, *Tetrahedron Lett.* **2004**, *45*, 4967–4971; k) J. N. Kim, H. J. Lee, J. H. Gong, *Tetrahedron Lett.* **2002**, *43*, 9141–9146.

[12] For a review on *Cinchona* alkaloids as Lewis base catalysts, see: a) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584–1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638; b) S.-K. Tian, Y. Chen, J. Huang, L. Tang, P. Mcdaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; For selected examples, see: c) Y. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543; d) S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; e) S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; f) M. Shi, L.-H. Chen, C.-Q. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800; g) J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296; h) H. Li, X. Liu, F. Wu, L. Tang, L. Deng, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20625–20629.

[13] CCDC-806254 (**3j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, *119*, 615–617; *Angew. Chem. Int. Ed.* **2007**, *46*, 609–611.

[15] See the Supporting Information for details.

[16] CCDC-806255 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] a) Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**; b) Full computational data are summarized in the Supporting Information.

[18] G. K. S. Prakash, F. Wang, N. Shao, T, Mathew, G. Rasul, R. Haiges, T, Stewart, G. A. Olah, *Angew. Chem.* **2009**, *121*, 5462–5466; *Angew. Chem. Int. Ed.* **2009**, *48*, 5358–5362.

[19] a) S. Miertuš, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117–29; b) S. Miertuš, J. Tomasi, *Chem. Phys.* **1982**, *65*, 239–245.

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