Asymmetric Synthesis

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Asymmetric Synthesis of Spiroketals with Aminothiourea Catalysts

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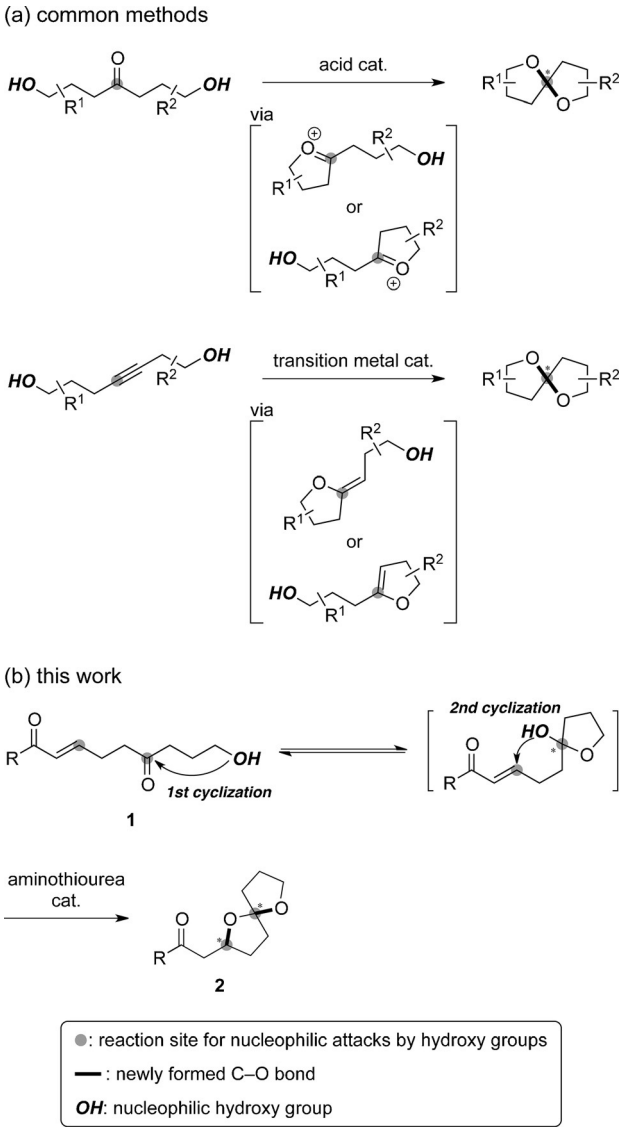
Abstract: *Chiral spiroketal skeletons are found as core structures in a range of bioactive compounds. These natural compounds and their analogues have attracted much attention in the field of drug discovery. However, methods for their enantioselective construction are limited, and easily available optically active spiroketals are rare. We demonstrate a novel catalytic asymmetric synthesis of spiroketal compounds that proceeds through an intramolecular hemiacetalization/oxy-Michael addition cascade mediated by a bifunctional aminothiourea catalyst. This results in spiroketal structures through the relay formation of contiguous oxacycles, in which multipoint recognition by the catalyst through hydrogen bonding imparts high enantioselectivity. This method offers facile access to spiroketal frameworks bearing an alkyl group at the 2-position, which are prevalent in insect pheromones. Optically active (2S,5S)-chalcogran, a pheromone of the six-spined spruce bark beetle, and an azide derivative could be readily synthesized from the bicyclic reaction product.*

Spiroketal structures are fundamental motifs found in a broad array of natural products and bioactive agents,[1] and even their analogous scaffolds exhibit unique biological activities.[2] The development of flexible synthetic methods would thus be beneficial for the discovery of new drugs and agricultural chemicals. Since the synthesis of optically active spiroketals has largely relied on chiral starting materials, enantioselective spiroketalization from achiral starting materials would be of significance, however, the stereocontrolled construction of contiguous oxacycles poses a formidable challenge, and the methodology has not been well investigated.

Spiroketal construction commonly involves the acid-catalyzed dehydration of dihydroxy ketones, and transition-metal-mediated cyclizations that make use of triple bonds as carbonyl surrogates have also become popular since Utimoto's pioneering work (Scheme 1a).[3] Although these approaches eventually construct the desired structures, the regioselectivity of the consecutive nucleophilic attacks by the two hydroxy groups in the substrates is difficult to control. This results in the generation of multiple intermediates during the course of the transformation, which is not compatible with asymmetric synthesis. Therefore, examples of enantioselective spiroketalizations effected by chiral organic and transition-metal catalysts by employing these reaction cascades are limited.[4] It would be desirable to develop an efficient method that exploits a more controlled pathway in order to realize the facile enantioselective construction of spiroketal rings from achiral starting materials and expand the library of synthetically available spiroketals.



Scheme 1. Strategies for spiroketalization.

Inspired by our recent studies of catalytic asymmetric cycloetherifications[5] mediated by bifunctional aminothiourea catalysts,[6] which achieve highly sophisticated stereocontrol through hydrogen-bonding interactions,[7] we envisioned the spiroketalization of substrate **1** through intra-

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molecular hemiacetal formation followed by intramolecular oxy-Michael addition promoted by a chiral aminothiourea (Scheme 1b). In this strategy, a unidirectional ring formation cascade takes place as the first nucleophilic attack by the hydroxy group in the substrate generates the second hydroxy group by relay,[8] and the nearly neutral conditions, like in biosynthesis, allow the unstable hemiacetal to act as the nucleophile for the subsequent Michael addition without elimination of the hydroxy group.[9] Consequently, there is no concern with respect to regioselectivity of the ring formation sequence. Furthermore, the resulting product **2** has a chiral spiroketal skeleton bearing an alkyl group at the 2-position.[10] Such potential pharmacophoric structures are prevalent in an extremely wide range of insect pheromones, although their catalytic asymmetric synthesis has thus far not been accomplished (Figure 1).[1a]

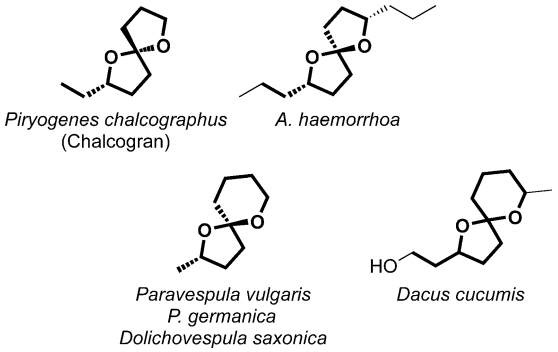
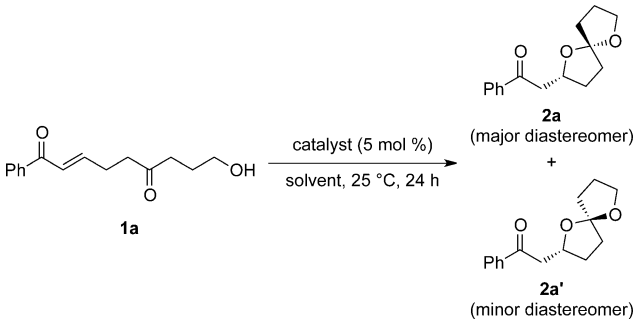


Figure 1. Spiroketal insect pheromones and their source organisms.

We initiated our investigation by using **1a** and 5 mol% of the quinidine-derived aminothiourea catalyst **3a** in CH_2Cl_2 at 25°C. As expected, the spiroketal product was obtained nearly quantitatively with high enantioselectivity (Table 1, entry 1). A solvent optimization study identified THF as affording the best stereoselectivity (Table 1, entry 6). Even when the catalytic loading was decreased to 1 mol% at ambient temperature, the enantioselectivity remained excellent, although the yield was reduced (Table 1, entry 7). A catalyst screen showed that catalyst **3e** further improves the diastereoselectivity while retaining the excellent yield and enantioselectivity (Table 1, entry 11).

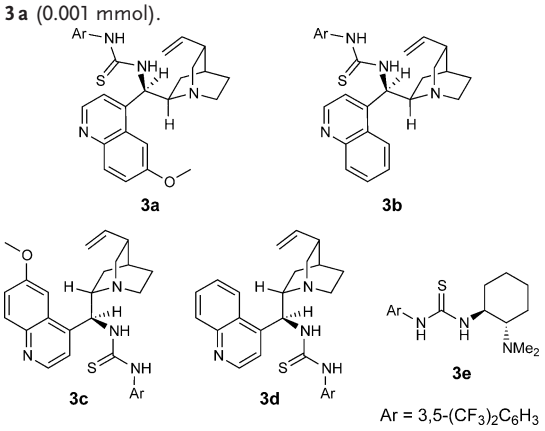
Subsequently, we explored the substrate scope with 5 mol% **3e** as the catalyst (Table 2).[11] Good to excellent yields and enantioselectivities were obtained with both electron-rich and electron-poor enones (**2b** and **2c**). In addition, substrates bearing *p*-bromophenyl and *p*-biphenyl groups afforded the corresponding products **2d** and **2e** in high yields with excellent enantioselectivities. Furthermore, an aliphatic enone was also applicable to provide spiroketal **2f** in high yield with good enantioselectivity under conditions with 10 mol% catalyst **3e** and a longer reaction time. A substrate bearing an α,β-unsaturated aldehyde provided the desired product **2g** in only modest yield and low enantioselectivity, in addition to a dimeric byproduct (see Supporting Information for details). Fortunately though, a substrate with an α,β-unsaturated thioester functionality, which is useful for various

Table 1: Optimization of conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c] (**2a**:**2a'**)	*ee* of **2a** [%][d]
1	**3a**	CH_2Cl_2	98	3.6:1	96
2	**3a**	benzene	99	3.4:1	97
3	**3a**	toluene	99	3.2:1	97
4	**3a**	Et_2O	92	3.0:1	96
5	**3a**	CPME[e]	97	3.7:1	98
6	**3a**	THF	97	4.8:1	98
7[f]	**3a**	THF	60	5.1:1	98
8	**3b**	THF	88	4.5:1	97
9	**3c**	THF	99	5.7:1	−95
10	**3d**	THF	81	5.5:1	−95
11	**3e**	THF	99	7.4:1	97

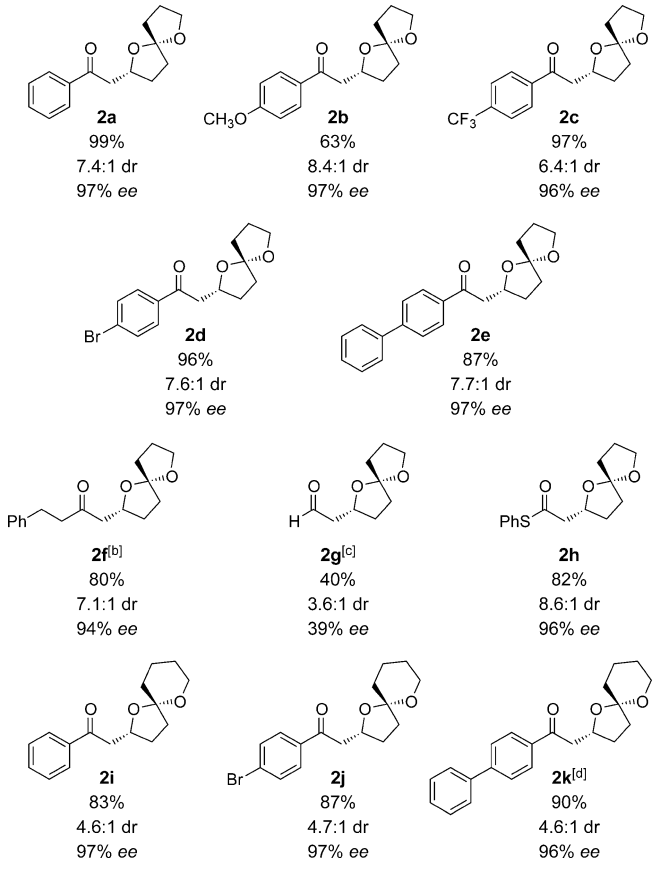
[a] Reactions were run with **1a** (0.1 mmol) and the catalyst (0.005 mmol) in the solvent (0.2 mL). [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR. [d] Values are for the major diastereomer **2a**. [e] CPME = cyclopentyl methyl ether. [f] Reaction was run with 1 mol% **3a** (0.001 mmol).



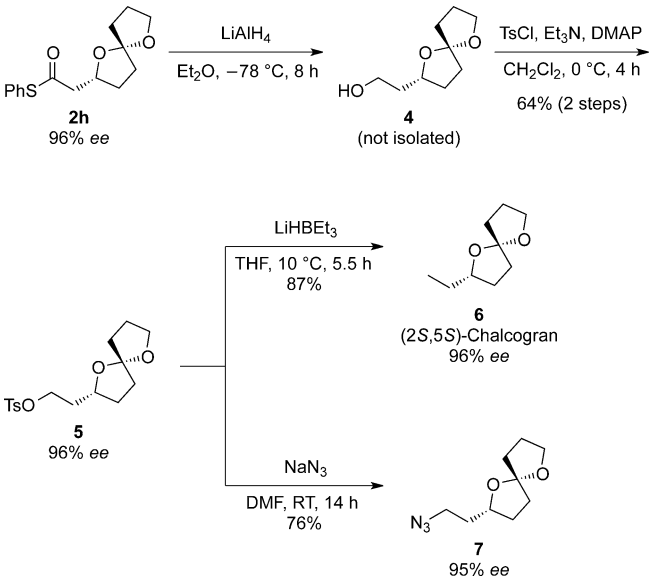
subsequent transformations including Fukuyama reduction for conversion into a formyl group,[12] underwent this reaction and yielded spiroketal product **2h** with high enantioselectivity.[5c] Furthermore, this method could also be applied to the construction of [4,5]-spiroketal ring systems with excellent enantioselectivity (**2i**, **2j**, and **2k**).[13] The absolute configurations of **2e** were determined by X-ray analysis (see the Supporting Information), and the configurations of all of the other examples were assigned analogously.

Using the obtained product **2h**, we carried out the asymmetric syntheses of chalcogran **6**, a pheromone of the six-spined spruce bark beetle *Pityogenes chalcographus*, and its azide derivative **7** (Scheme 2).[1j] Reduction of **2h** with lithium aluminium hydride followed by tosylation afforded the corresponding tosylate **5** without any erosion of enantiomeric excess in 64% yield for the two steps. Subsequent

Table 2: Substrate scope.[a]



[a] Reactions were run with **1** (0.1 mmol) and **3e** (0.005 mmol) in THF (0.2 mL) at 25 °C for 24 h. Yields represent material isolated after silica gel column chromatography. Diastereomeric ratios were determined by ^{1}H NMR. Values of *ee* are for major diastereomers. [b] Reaction was run on a 0.2 mmol scale with 0.02 mmol of **3e** for 7 d. [c] Reaction was run on a 0.2 mmol scale with 0.02 mmol of **3e** for 10 d. [d] Reaction was run on a 0.3 mmol scale.



Scheme 2. Synthesis of chalcogran (**6**) and its derivative **7**.

reduction with lithium triethylborohydride gave optically active (2*S*,5*S*)-chalcogran (**6**) in 87% yield. Compound **5** was also treated with sodium azide in DMF to afford **7**, which contains the pheromone framework with an azide tag. Such a transformation expands the utility of the bioactive structure by allowing its facile introduction into various compounds by means of well-established ligation methods based on click chemistry.[14]

To gain insight into the enantiodetermining step, the minor diastereomer **2e′** was also stereochemically analyzed (see the Supporting Information). The results strongly suggest that both product diastereomers have a consistent absolute configuration (the same (*R*)-configuration) at the β-position of the carbonyl group. These facts, as well as the knowledge obtained from our previous studies,[5] indicate that the enantioselectivity of this reaction can be attributed largely to the second step comprising the oxy-Michael addition from the hemiacetal intermediates. At this stage, we believe that the diastereoselectivity is determined through kinetic resolution of the chiral hemiacetal intermediates, which are generated even in the absence of any catalyst: the presence of the hemiacetal form of **1a** was observed by ^{1}H NMR analysis of a solution of pure **1a** in [D_8]THF ([open chain form]/[hemiacetal form] = 3.4:1, see the Supporting Information). In addition, when the isolated pure diastereomers of **2a** and **2a′** were resubjected to the reaction conditions, the other diastereomers were not generated, and the enantiomeric excesses were completely unchanged in both cases (see the Supporting Information). We can thus rule out any effects on the stereoselectivity of degradation of the formed spiroketals, such as isomerizations between the diastereomers and reverse reactions.

In summary, we have demonstrated a novel catalytic asymmetric spiroketal synthesis that allows direct access to synthetically challenging spiroketal structures from achiral substrates. This method affords spiroketal structures through the relay formation of contiguous oxacycles, in which multipoint recognition by the bifunctional catalyst through hydrogen bonding imparts high enantioselectivity. The product frameworks are found in various bioactive compounds, such as insect pheromones. Optically active (2S,5S)-chalcogran, a pheromone of the six-spined spruce bark beetle, and an azide derivative thereof were readily synthesized from the spiroketalization product. Further studies regarding expansion of the substrate scope and the application of this methodology to the synthesis of various biologically active compounds are currently ongoing in our laboratory and will be reported in due course.

Experimental Section

General procedure for asymmetric synthesis of 2-substituted spiroketals: Substrate **1** (0.1 mmol), THF (0.2 mL), and **3e** (0.005 mmol) were sequentially added to a 5 mL vial. The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1:1), passed through a short silica gel pad to remove **3e**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography with hexane/EtOAc (v/v = 1:1) as an eluent afforded the corresponding 2-alkylspiroketals **2**.

Acknowledgements

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Angew. Chem. **2015**, *127*, 15717–15720

[1] a) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617; b) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406; c) J. A. Palmes, A. Aponick, *Synthesis* **2012**, 3699; d) J. Sperry, Z. E. Wilson, D. C. K. Rathwell, M. A. Brimble, *Nat. Prod. Rep.* **2010**, *27*, 1117; e) M. Brasholz, S. Sörgel, C. Azap, H.-U. Reissig, *Eur. J. Org. Chem.* **2007**, 3801; f) K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227; g) M. T. Fletcher, W. Kitching, *Chem. Rev.* **1995**, *95*, 789; h) M. F. Jacobs, W. Kitching, *Curr. Org. Chem.* **1998**, *2*, 395; i) Y. K. Booth, W. Kitching, J. J. De Voss, *Nat. Prod. Rep.* **2009**, *26*, 490; j) J. A. Byers, H.-E. Högberg, C. R. Unelius, G. Birgersson, J. Löfqvist, *J. Chem. Ecol.* **1989**, *15*, 685.

[2] G. Zinzalla, L.-G. Milroy, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 1977.

[3] K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845.

[4] a) I. Čorić, B. List, *Nature* **2012**, *483*, 315; b) Z. Sun, G. A. Winschel, A. Borovika, P. Nagorny, *J. Am. Chem. Soc.* **2012**, *134*, 8074; c) P. Nagorny, Z. Sun, G. A. Winschel, *Synlett* **2013**, 661; d) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2012**, *51*, 936; *Angew. Chem.* **2012**, *124*, 960; e) H. Wu, Y.-P. He, L.-Z. Gong, *Org. Lett.* **2013**, *15*, 460; f) L. Cala, A. Mendoza, F. J. Fañanás, F. Rodríguez, *Chem. Commun.* **2013**, *49*, 2715; g) M. Wilsdorf, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2012**, *51*, 9486; *Angew. Chem.* **2012**, *124*, 9624; h) H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487; i) F. Wang, F. Chen, M. Qu, T. Li, Y. Liu, M. Shi, *Chem. Commun.* **2013**, *49*, 3360.

[5] a) K. Asano, S. Matsubara, *J. Am. Chem. Soc.* **2011**, *133*, 16711; b) K. Asano, S. Matsubara, *Org. Lett.* **2012**, *14*, 1620; c) T. Okamura, K. Asano, S. Matsubara, *Chem. Commun.* **2012**, *48*, 5076; d) Y. Fukata, R. Miyaji, T. Okamura, K. Asano, S. Matsubara, *Synthesis* **2013**, 1627; e) R. Miyaji, K. Asano, S. Matsubara, *Org. Biomol. Chem.* **2014**, *12*, 119; f) N. Yoneda, A. Hotta, K. Asano, S. Matsubara, *Org. Lett.* **2014**, *16*, 6264.

[6] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; c) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151; d) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; e) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.* **2012**, *77*, 9813.

[7] R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678.

[8] An analogous cascade reaction to afford spiroketals was previously reported, although this is not a catalytic reaction, and the stereoselectivity is only modest: M. Tiecco, L. Testaferri, L. Bagnoli, C. Scarponi, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2006**, *17*, 2768.

[9] Analogous biosynthetic reactions: a) A. Bhatt, C. B. W. Stark, B. M. Harvey, A. R. Gallimore, Y. A. Demydchuk, J. B. Spencer, J. Staunton, P. F. Leadlay, *Angew. Chem. Int. Ed.* **2005**, *44*, 7075; *Angew. Chem.* **2005**, *117*, 7237; b) A. R. Gallimore, C. B. W. Stark, A. Bhatt, B. M. Harvey, Y. Demydchuk, V. Bolanos-Garcia, D. J. Fowler, J. Staunton, P. F. Leadlay, J. B. Spencer, *Chem. Biol.* **2006**, *13*, 453; c) S. Takahashi, A. Toyoda, Y. Sekiyama, H. Takagi, T. Nogawa, M. Uramoto, R. Suzuki, H. Koshino, T. Kumano, S. Panthee, T. Dairi, J. Ishikawa, H. Ikeda, Y. Sakaki, H. Osada, *Nat. Chem. Biol.* **2011**, *7*, 461.

[10] For selected examples of synthesis of 2-alkylspiroketals, see Refs. [1j,3,8] and: a) S. J. Danishefsky, W. H. Pearson, *J. Org. Chem.* **1983**, *48*, 3865; b) C. Iwata, K. Hattori, S. Uchida, T. Imanishi, *Tetrahedron Lett.* **1984**, *25*, 2995; c) T. Capecchi, C. B. de Koning, J. P. Michael, *Tetrahedron Lett.* **1998**, *39*, 5429; d) H. Huang, C. Mao, S.-T. Jan, F. M. Uckun, *Tetrahedron Lett.* **2000**, *41*, 1699; e) O. Barun, S. Sommer, H. Waldmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 3195; *Angew. Chem.* **2004**, *116*, 3258; f) P. M. Pihko, J. E. Aho, *Org. Lett.* **2004**, *6*, 3849; g) D. Castagnolo, I. Breuer, P. M. Pihko, *J. Org. Chem.* **2007**, *72*, 10081; h) L. R. Takaoka, A. J. Buckmelter, T. E. LaCruz, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 528; i) J. S. Potuzak, S. B. Moilanen, D. S. Tan, *J. Am. Chem. Soc.* **2005**, *127*, 13796; j) S. B. Moilanen, J. S. Potuzak, D. S. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 1792; k) S. Chang, R. Britton, *Org. Lett.* **2012**, *14*, 5844; l) P. H. S. Paioti, J. M. Ketcham, A. Aponick, *Org. Lett.* **2014**, *16*, 5320.

[11] Starting materials **1** were prepared through the synthetic routes described in the Supporting Information. Although the shorter route was employed only for the synthesis of **1 f** and **1 g**, it would also be applicable to the synthesis of other substrates.

[12] a) T. Fukuyama, S. C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050; b) T. Fukuyama, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 87; c) T. Miyazaki, Y. Han-ya, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, 477.

[13] A substrate bearing a racemic secondary alcohol was also investigated to afford a disubstituted spiroketal; two diastereomers were preferentially obtained with high enantioselectivities (82%, d.r. = 11:9.2:2.2:1, 92% *ee*/73% *ee*/97% *ee*/33% *ee*), while the recovered starting material was nearly racemic (17%, 4% *ee*; see the Supporting Information).

[14] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; *Angew. Chem.* **2001**, *113*, 2056; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; *Angew. Chem.* **2002**, *114*, 2708; c) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

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