26.65° of sample B3 is also consistant with the (101) reflection of quartz, and also with a preferred orientation of silicalite crystals. Under the reaction conditions used an oxidation of the Si-library substrate can be excluded, which is supported by the lack of such a reflection in the rest of the library. Examination of the dot areas after the experiment by light microscopy shows no signs of attack of the single crystal–wafer surface after removal of the crystal layers. For detailed characterization of the individual materials formed the interesting reactions identified by X-ray diffraction would have to be repeated and investigated by conventional means in the laboratory.

Our reaction system combined with analyses has an enormous potential for increased efficiency in the development of new materials and the automatization of characterization of samples obtained by combinatorial methods, and it is certainly not limited to the synthesis under hydrothermal conditions. Currently, the lower limit of 50 μm for the focussing of the X-ray beam restricts the miniaturization of the diameter of the microreactors. The material selected for the reactor walls limits reaction temperatures up to 300 °C; much higher temperatures may become possible through the selection of different polymeric materials. An increase in the library dimension to 10 cm diameter as well as a decrease in the drilling distance can readily be realized without technical problems.

Minimization of the manual efforts for the preparation of starting solutions as well as for the filling of the microreactors can be achieved readily with commercially available pipetting robots. Even the direct synthesis in the reactor by the direct use of ultrasound for proper mixing of the tiny probe volumes is realizable. In general, every solid synthesis in liquid phase under pressure and temperature should be possible. Such a reactor should be ideal for the combinatorial screening of new microcrystalline or amorphous solids, especially since the reactor bottom can be exchanged and libraries can be prepared directly on the substrate of choice.

Experimental Section

Our standard experimental conditions for the preparation of this material library have been described in the original literature of Taramasso et al.[7] Since only very small amounts are necessary to fill of the microreactors, the reaction volumes were reduced by a factor of 200 and mixed in 10-mL flasks. The reaction mixtures have been modified as described in Table 1. A1 and F1 each contain the original recipe as described in the patent.

The reaction was carried out in a sealed autoclave at a temperature of 200 °C for 36 h. After reaction the mother liquor was separated from the microreactor and the remaining crystals in the microreactor were washed several times with 2 μL of destilled water. The removal of the liquid was achieved by the capillary forces of porous rods directly in the microreactors. The compounds were then dried in the open microreactors at 100 °C. After removal of the teflon and steel mask the Si wafer with the dried-on crystal products were calcined at 600 °C for 10 h.

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Chiral C_2-Symmetric Cu^{II} Complexes as Catalysts for Enantioselective Hetero-Diels–Alder Reactions**

David A. Evans,* Edward J. Olhava,
Jeffrey S. Johnson, and Jacob M. Janey

Previous reports from this laboratory have demonstrated that C_2-symmetric Cu^{II}–bis(oxazoline) complexes **1**–**3**[1] (Tf = trifluoromethanesulfanyl) are efficient chiral Lewis acid catalysts for Diels–Alder,[2] pyruvate aldol,[3] and glyoxylate–ene reactions.[4] Each of these processes exhibits behavior consistent with previously proposed chelation models for asymmetric induction. In a further extension of this methodology, we recently reported that α,β-unsaturated acyl phosphonates undergo enantioselective hetero-Diels–Alder

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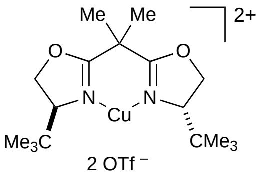

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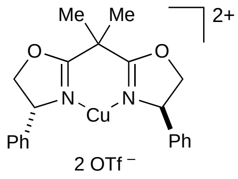

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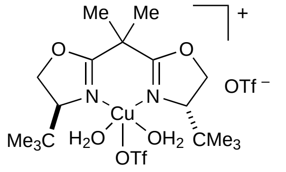
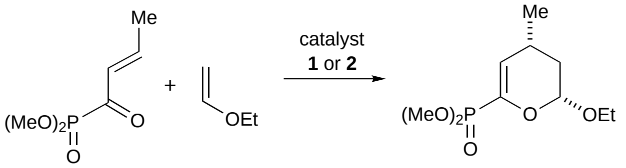


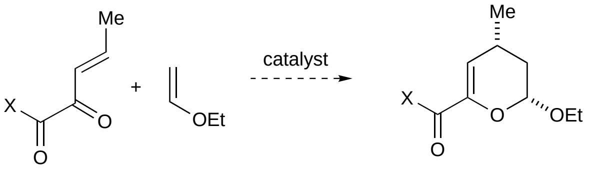
3

reactions[5] with enol ethers in the presence of chiral Cu^{II} complexes **1** and **2** [Eq. (1)].[6] We now disclose the analogous cycloaddition reactions of *β,γ*-unsaturated *α*-keto esters [Eq. (2)], reactions of established utility in the construction of enantiomerically enriched dihydropyrans.[7, 8] A similar study has been recently reported by Jørgensen et al.[9] The present work expands the scope of this process providing significant operational simplifications including lower catalyst loadings, convenient reaction temperatures that facilitate short reaction times, and a catalyst recycling procedure. An X-ray crystallographic study is also provided in support of a proposed model for asymmetric induction.



(1)

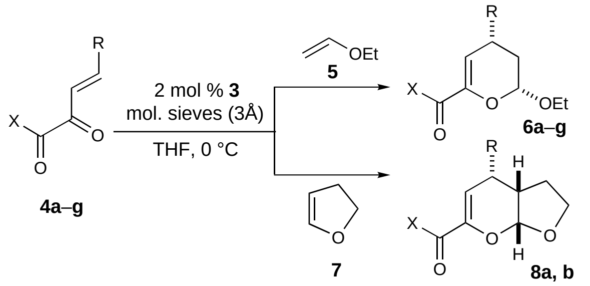
catalyst **1**: *endo*:*exo* = 99:1, 99% *ee*
catalyst **2**: *endo*:*exo* >99:1, 94% *ee*



(2)

Unsaturated keto esters **4a**–**4f** and keto amide **4g**[10] undergo highly enantioselective cycloaddition reactions with enol ethers in the presence of complexes **1** and **3** (Table 1). The reaction of ethyl vinyl ether with unsaturated keto ester **4a** in the presence of [Cu{(*S,S*)-*t*Bu-box}][OTf]$_2$ (**1**; 2 mol%, THF, 0 °C; box = bis(oxazoline)) provided cycloadduct **6a** in 93% yield, with an *endo*:*exo* selectivity of over 20:1, and with 97% *ee*. The same reaction in the presence of [Cu(OTf)(OH$_2$)$_2${(*S,S*)-*t*Bu-box}][OTf] (**3**) and molecular sieves (3 Å) afforded identical results.[11] Complex **3**, a readily prepared blue powder that may be stored indefinitely without special precaution, is an attractive alternative to the hygroscopic anhydro complex **1**. While enantioselectivities of greater than 99% may be obtained for these cycloadditions at lower temperatures, we have found that these reactions may be conveniently carried out at 0 °C with little loss in stereoselectivity (95–99% *ee*).

Table 1. Cycloaddition of heterodienes **4a**–**g** and enol ethers catalyzed by **3**.



Diene	X	R	Enol ether[a]	Product[b, c]	Yield [%][d]	*ee* [%][b]
4a	OEt	Ph	**5**	**6a** (>20:1)	93	97
4b	OEt	*i*Pr	**5**	**6b** (22:1)	95	96
4c	OEt	Me	**5**	**6c** (24:1)	87	97
4d	OEt	OMe	**5**	**6d** (59:1)	90	98
4e	OEt	OEt	**5**	**6e** (55:1)	98	98
4f	OEt	SBn	**5**	**6f** (>20:1)	97	99
4a	OEt	Ph	**7**	**8a** (16:1)	96	97
4b	OEt	*i*Pr	**7**	**8b** (16:1)	94	95
4g	N(OMe)Me	Me	**5**	**6g** (64:1)	99	99

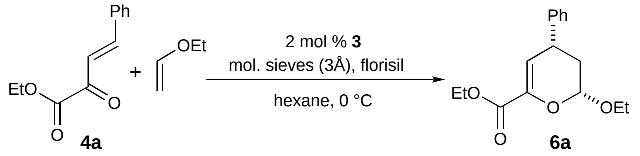
[a] The reactions were conducted with 3 equiv of enol ether (relative to the diene). [b] Determined by capillary GLC or chiral HPLC. [c] The *endo*:*exo* ratio is given in parentheses. [d] Yield of isolated product. Bn = benzyl.

Consistent with previous observations,[2c, 3b, 5] complex **3** can be employed as an effective catalyst over a broad range of temperatures and solvents. Adduct **6a** was produced stereoselectively from unsaturated ester **4a** and ethyl vinyl ether in the presence of **3** at temperatures ranging from −40 °C to 25 °C.[12] An enantioselectivity/solvent profile with substrate **4c** and complex **3** (0 °C) demonstrates that excellent results may be obtained in a number of solvents (THF, *endo*:*exo* = 24:1, 97% *ee*; Et$_2$O, *endo*:*exo* = 24:1, 97% *ee*; toluene, *endo*:*exo* = 28:1, 98% *ee*; dioxane, *endo*:*exo* = 24:1, 93% *ee*; CH$_2$Cl$_2$, *endo*:*exo* = 19:1, 89% *ee*).

The reaction tolerates a broad range of substituents R at the unsaturated ester terminus. Alkyl (**4b**, **c**), aryl (**4a**), alkoxy (**4d**, **e**), and thiobenzyl substituents (**4f**) afford cycloadducts in excellent yields and stereoselectivities (Table 1). In addition, under identical reaction conditions, the Weinreb amide **4g** underwent a highly stereoselective reaction (*endo*:*exo* = 64:1, 99% *ee*) to yield **6g**. This adduct is particularly versatile in view of the malleability of the amide functionality.[13] To demonstrate the preparative utility of this reaction, 2 mol% of catalyst **3** was used to prepare 6.7 g (98%) of cycloadduct **6a** from 5.0 g of heterodiene **4a** (*endo*:*exo* > 99:1, 99% *ee*).[14] Cyclic enol ethers are also effective reaction partners. In the presence of **3** and molecular sieves (3 Å), 2,3-dihydrofuran reacted with the unsaturated esters **4a** and **4b** to provide bicyclic unsaturated esters **8a** and **8b** in good diastereo- and enantioselectivity (Table 1).

The cycloaddition to form **6c** was conducted with as little as 0.5 mol% of catalyst **3**; there was only a slight decrease in stereoselectivity (*endo*:*exo* = 19:1, 96% *ee*). Preliminary studies indicate that complex **3** can be reused in multiple reaction cycles (Table 2).[15] When the catalyzed cycloaddition is

Table 2. Enantioselective cycloaddition with catalyst recycling.

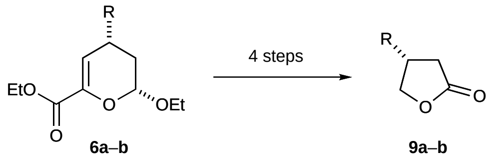


Cycle[a]	*endo*:*exo*	Yield [%]	*ee* [%]
1	> 99:1	89	96
2	> 99:1	98	96
3	> 99:1	91	96
4	> 99:1	98	93
5	> 99:1	92	95

[a] See text.

conducted in hexane in the presence of an adsorbent (florisil), conditions under which complex **3** is apparently insoluble, the product solution may be decanted at the end of the reaction and the catalyst reused. A series of five catalyst recycling experiments (Table 2) demonstrates that the catalyst/adsorbent mixture may be reused without significant diminution in yield or selectivity.[16]

The absolute configuration for structures **6a** and **6b** was unambiguously proven by chemical correlation with lactones **9a** and **9b** of known configuration [Eq. (3)].[17] The remaining cycloadducts are assigned the indicated configuration by analogy.



(3)

The absolute configuration of the cycloadducts is consistent with our previously proposed model for asymmetric induction, in which the Cu^{II} complex and vicinal carbonyl functionalitiies form a well-defined reactive complex **11**. Stereoregular behavior has been observed with substrates which can engage in chelation with **1**, for example, *N*-acylimides,[2a] pyruvate and glyoxylate esters,[3b, 4] acyl phosphonates,[5] and now β,γ-unsaturated α-keto esters. In conjunction with the construction of a suitable catalyst – substrate model, the X-ray crystal structure of the bis(aquo) complex **3** was obtained (Figure 1). The crystallographic data for **3** reveal a distorted square pyramidal geometry, in which one of the triflate ligands is weakly bound to the metal center in the apical position (Cu–OTf 2.624 Å) while the other is fully dissociated (Cu–OTf 3.667 Å). The two water molecules occupy the equatorial positions and are distorted by approximately 26° out of the plane of the ligand. Replacement of the water molecules with the chelating substrate generates reactive complexes **10** and **11.** Semiempirical calculations (PM3) have been employed to model these catalyst – substrate complexes. For simplicity, the triflate counterions are omitted from the calculations. The cationic complexes [Cu(*t*Bu-box)(acyl phosphonate)]$^{2+}$ (**10**) and [Cu(*t*Bu-box)(β,γ-unsaturated α-keto ester)]$^{2+}$ (**11**) generated at the PM3 level are illustrated in Figure 1. In both cases, the heterodiene α-*Si* face of the heterodiene is blocked by the bulky *tert*-butyl substituent on the ligand, leaving the α-*Re* face accessible to the dienophile.

In summary, the stereoselective hetero-Diels – Alder reaction of β,γ-unsaturated α-keto esters and amides with enol ethers catalyzed by C_2-symmetric Cu^{II} – bis(oxazoline) complexes provides a general and practical entry into enantioenriched dihydropyrans. Application to complex target synthesis will be reported in due course.

Experimental Section

3: To an oven-dried round-bottom flask containing a magnetic stir bar was added, in an inert-atmosphere glove box, 2,2-bis{2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]}propane[1] (163 mg, 0.554 mmol) and copper(II) trifluoromethanesulfonate (200 mg, 0.554 mmol). The flask was fitted with a serum cap,

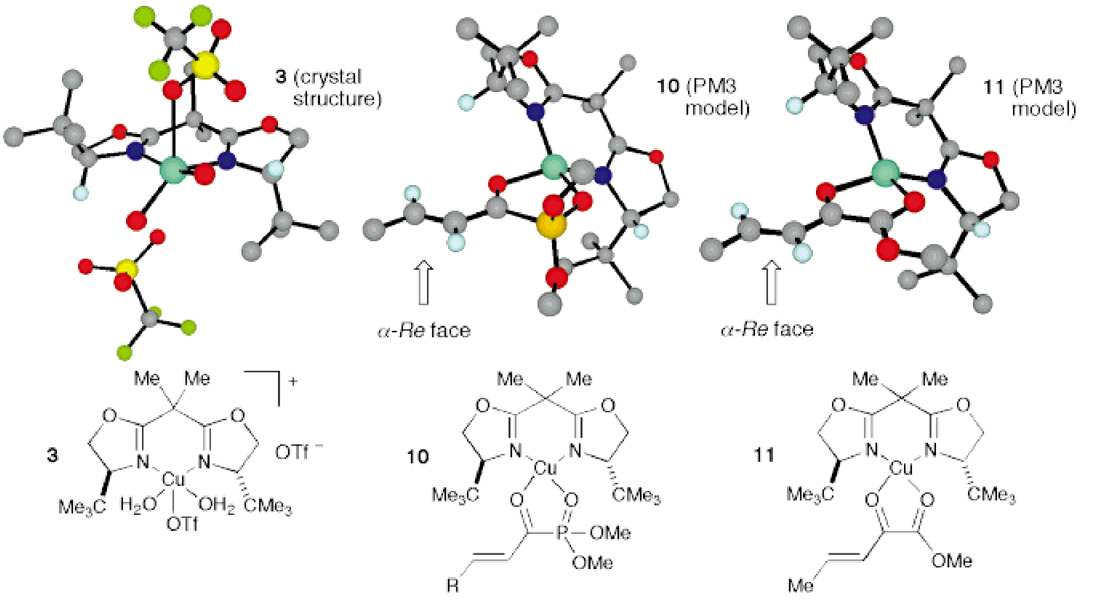


Figure 1. Crystal structure of bis(oxazoline) catalyst **3** and model structures calculated at the PM3 level for catalyst – substrate complexes **10** and **11**.

removed from the glove box, and charged with THF (20 mL). The reaction mixture was stirred under argon for 1 h, affording a clear green solution to which distilled water (20 mg, 1.11 mmol) was added. The resulting blue solution was concentrated in vacuo to afford a blue solid. Hexane (5 mL) was added, and the solvent was removed in vacuo to provide **3** as a light blue powder (372 mg, 0.538 mmol, 97 % yield). Elemental analysis calcd for $C_{19}H_{34}CuF_6N_2O_{10}S_2$: C 32.97, H 4.95, N 4.05; found: C 33.22, H 5.03, N 3.95.

6c: A dry round-bottom flask with magnetic stirrer was charged with **3** (4.8 mg, 0.007 mmol; 0.02 equiv) and powdered molecular sieves (3 Å; 25 mg). To this was added THF (1.75 mL) by syringe. The mixture was stirred for 1 h to produce a heterogeneous light green solution that was then cooled to 0 °C. The mixture was treated sequentially with ester **4c** (48 μL, 50 mg, 0.35 mmol) and freshly distilled ethyl vinyl ether (101 μL, 75.7 mg, 1.05 mmol). After 15 min the reaction solution was applied to a silica gel column and eluted with EtOAc/hexanes (15/85) to afford **6c** as a clear oil (65 mg, 0.30 mmol, 87 %). Analysis by GC (DB-1701, 110 °C for 10 min, then increased by 10 °C min^{-1}, 0.48 bar; $t_r = 17.0$ (minor product), 17.4 (major product) and HPLC (Chiralpak OD-H, EtOAc/hexanes (4/96), flow rate 1 mL min^{-1}, 254 nm; $t_r = 7.9$ (major product), 10.6 (minor product)) gave the isomeric composition of the product: d.r. 96:4, 97 % *ee*. Analytical data for **6c**: $[\alpha]_D = -77.3°$ ($c = 0.44$, $CHCl_3$); IR (KBR): $\tilde{\nu} = 2978$, 2932, 2874, 1734, 1648, 1458, 1377, 1297, 1256, 1208, 1175, 1124, 1102, 1090, 1053, 1026, 982 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.98$ (d, $J = 3.0$ Hz, 1 H, $\mathit{H}C{=}CCO_2CH_2CH_3$), 5.67 (dd, $J = 6.9$, 2.4 Hz, 1 H, $C\mathit{H}O_2$), 4.27 (dq, $J = 10.8$, 7.1 Hz, 1 H, $CO_2C\mathit{H}HCH_3$), 4.23 (dq, $J = 10.8$, 7.1 Hz, 1 H, $CO_2CH\mathit{H}CH_3$), 3.97 (dq, $J = 9.6$, 7.1 Hz, 1 H, $CH_3C\mathit{H}HOCCHO$), 3.60 (dq, $J = 9.6$, 7.1 Hz, 1 H, $CH_3CH\mathit{H}OCCHO$), 2.50 (m, 1 H, $=CHC\mathit{H}CH_3$), 2.03 (dddd, $J = 13.5$, 6.9, 2.4, 0.7 Hz, 1 H, $CH(CH_3)C\mathit{H}HCHO_2$), 1.59 (m, 1 H, $CH(CH_3)CH\mathit{H}CHO_2$), 1.32 (t, $J = 7.1$ Hz, 3 H, $CO_2CH_2C\mathit{H}_3$), 1.24 (t, $J = 7.1$ Hz, 3 H, $CHOCH_2C\mathit{H}_3$), 1.14 (d, $J = 7.2$ Hz, 3 H, $=CHCH_2C\mathit{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.0$, 140.8, 117.0, 99.4, 64.5, 61.0, 34.8, 26.1, 20.6, 15.1, 14.2; TLC (hexanes/CH_2Cl_2 10/90): $R_f = 0.27$; HR-MS (CI, NH_3): m/z calcd for $C_{11}H_{22}NO_4$: 232.1549 $[M{+}NH_4]^+$, found: 232.1555; elemental analysis calcd for $C_{11}H_{18}O_4$: C 61.66, H 8.47; found: C 61.39, H 8.56.

Crystal data for **3** ($C_{19}H_{34}CuF_6N_2O_{10}S_2$): crystal dimensions 0.15 × 0.15 × 0.25 mm, orthorhombic, space group $P2_12_12_1$, $a = 9.562(2)$, $b = 12.166(2)$, $c = 25.753(4)$ Å, $\beta = 90°$; $V = 2996.0(9)$ Å^3, $\rho_{calcd} = 1.535$ mg mm^{-3}; Siemens SMART CCD diffractometer, $1.58 < \theta < 26.43°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $\theta/2\theta$ scans, $T = 213(2)$ K; of 14 840 measured reflections, 5889 were independent and 5005 were observed with $I > 2\sigma(I)$, $-11 \le h \le 6$, $-15 \le k \le 14$, $-27 \le l \le 22$; $R = 0.0468$, $wR = 0.1253$, GOF = 1.006 for 361 parameters, Flack parameter = $-0.004(15)$, $\Delta\rho_{max} = 0.845$ e Å^{-3}. The structure was solved by direct methods (SHELXTL Plus) and developed by least-squares refinement against $|F^2|$ (SHELXL93). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103312. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[10] Substrates **4a–c** were prepared by an aldol-elimination protocol: H. Sugimura, K. Yoshida, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3209–3211. Substrates **4d–e** were prepared by reaction of ethyl vinyl ether or methyl vinyl ether with ethyl chlorooxoacetate: L.-F. Tietze, H. Meier, E. Voss, *Synthesis* **1988**, 274–277. Substrate **4f** was prepared from **4e** and phenylmethanethiol in the presence of catalytic amounts of sodium bisulfate. Substrate **4g** was prepared by addition of 1-propenylmagnesium bromide to the bis(Weinreb amide) of oxalic acid: M. P. Sibi, M. Marvin, R. Sharma, *J. Org. Chem.* **1995**, *60*, 5016–5023. Details of the synthesis of these substrates will appear in a full account of this work.

[11] The use of bis(aquo) complex **3** without molecular sieves severely attenuated reactivity, indicating that the anhydrous complex **1** is generated in the presence of moleclar sieves (3 Å).

[12] At −40 °C: >99 % *ee*; at −20 °C: 98 % *ee*; at 0 °C: 97 % *ee*; at 25 °C: 94 % *ee*.

[13] For reviews on the synthetic utility of the Weinreb amide, see a) M. Mentzel, M. R. Hoffman, *J. Prakt. Chem.* **1997**, *339*, 517–524; b) M. P. Sibi, *Org. Prep. Proced. Int.* **1993**, *25*, 15–40.

[14] The ligand may also be recovered (50 %) by aqueous workup (3 M NH_4OH) and chromatographic separation of the adduct and ligand.

[15] For an example of catalyst recycling in an enantioselective reaction, see K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10 924–10 925.

[16] Catalyst activity is diminished slightly in subsequent runs. In the absence of florisil or in the presence of other adsorbents (SiO_2, Al_2O_3), lower enantioselectivity and/or reactivity is observed. Attempts to optimize this process and identify the role of the adsorbent are currently being actively studied.

[17] The lactones were generated by the following procedure: a) O_3, $MeOH/CH_2Cl_2$ (1/1), −78 °C; $NaBH_4$, 25 °C; b) 1 M HCl (aq), THF, 65 °C; c) tetrapropylammonium perruthenate (TPAP; cat.), 4-methylmorpholine *N*-oxide (NMO), molecular sieves (4 Å), CH_2Cl_2, 25 °C. **9a** (3*S*): $[\alpha]_D = +38°$ ($c = 0.34$, MeOH) (lit.: $[\alpha]_D = +51°$; G. Helmchen, G. Nill, *Angew. Chem.* **1979**, *91*, 66–68; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 65–66). **9b** (3*S*): $[\alpha]_D = -11°$ ($c = 0.52$, $CHCl_3$) (lit.: $[\alpha]_D = +14.7°$ (3*R*); C.-H. R. King, C. D. Poulter, *J. Am. Chem. Soc.* **1982**, *104*, 1413).

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