JOC The Journal of Organic Chemistry

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Enantioselective Allylation of α,β-Unsaturated Aldehydes with Allyltrichlorosilane Catalyzed by METHOX

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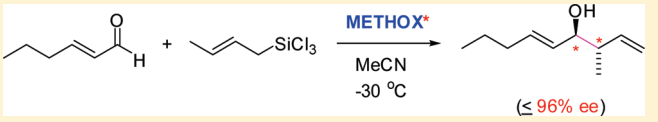
Supporting Information

ABSTRACT: α,β-Unsaturated aldehydes **6a**−**j** undergo an enantioselective allylation with allylic trichlorosilanes **2a,b** in the presence of METHOX (**4**) as a Lewis basic catalyst (≤10 mol %) to produce the homoallylic alcohols **7a**−***l*** at good to high enantioselectivity (83−96% ee). This study shows that the reactivity scope of METHOX can be extended from aromatic to nonaromatic aldehydes.

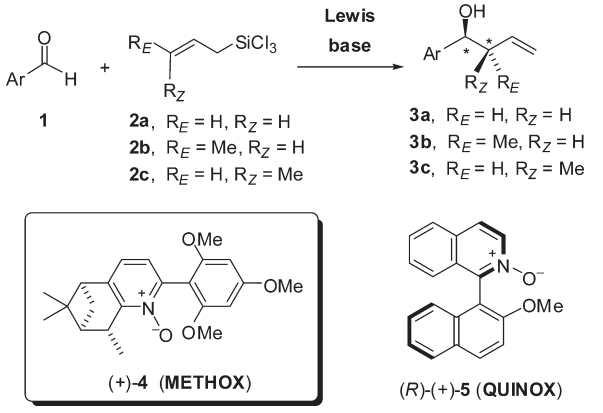


Allylation of aldehydes **1** with allylsilanes constitutes a powerful methodology that can create up to two chiral centers (Scheme 1). Its classical version, using allylic trialkylsilanes, requires a Lewis acid as catalyst and in the case of crotyl-type silanes produces *syn*-configured homoallylic alcohols **3c**, irrespective of the *E*/*Z*-configuration of the reagent. The latter outcome is believed to originate from an open transition state, in which a deliberate control of diastereoselectivity is difficult to attain.[1] Furthermore, the Me_3SiX, being released during the reaction, can itself act as a Lewis acid and compete with the chiral Lewis acidic catalyst, which has a negative effect on the enantioselectivity.[1,2] By contrast, the more recently developed allylation/crotylation with allylic trichlorosilanes **2a**−**c** requires catalysis by a Lewis base,[3] proceeds via a cyclic transition state, and as a result exhibits high levels of stereocontrol,[3] mimicking the allylation with allylboranes and boronates.[4] Another positive feature of this allylation is the aqueous workup with $NaHCO_3$, which generates innocuous, readily separable inorganic byproducts (SiO_2 and NaCl).[3] Therefore, this new methodology[3] can be viewed as a robust alternative to the existing and well-established protocols, which require stoichiometric chiral auxiliaries or metal-based Lewis acids.[4]

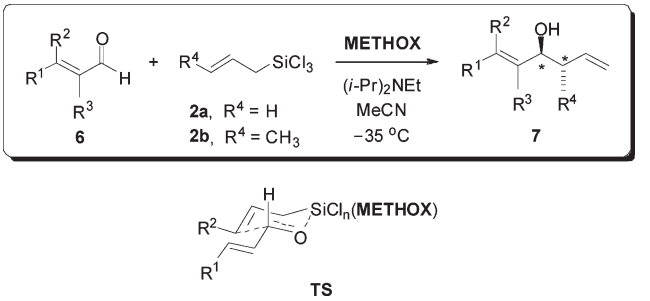
In the past few years, we have developed novel pyridine *N*-oxides,[5−7] such as METHOX (**4**),[6] which can be regarded as one of the most successful organocatalysts for the asymmetric allylation of aromatic aldehydes **1** with allylic trichlorosilanes **2** (≤99% ee at 1−5 mol % catalyst loading).[8−10] However, to date, the scope of METHOX (**4**) and related *N*-monoxides, such as QUINOX (**5**),[7] was limited to aromatic aldehydes. We have now endeavored to extend this methodology to the realm of α,β-unsaturated aldehydes **6** (Scheme 2), which in view of the previous experience was expected to proceed via the transition state TS. To this end, we have selected representative aldehydes with one or two conjugated double bonds **6a**−**e**, α-branched aldehydes **6f,g**, and α-methylene aldehydes **6 h**−**j** (Chart 1).

Aldehydes **6a**−**g** are either commercially available or were prepared by standard routes, involving Wittig-type chemistry (**6b**). The α-methylene-aldehydes **6h**−**j** were synthesized from the corresponding aldehydes via the aldol condensation with formaldehyde, catalyzed by pyrrolidine and benzoic acid, following the Pihko protocol.[11]

Scheme 1. Allylation of Aromatic Aldehydes



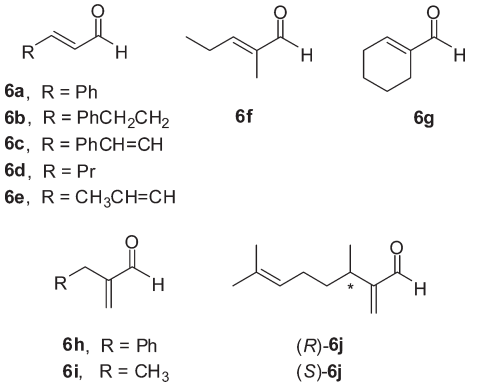
Scheme 2. Allylation of α,β-Unsaturated Aldehydes[a]



[a] For R^1−R^3, see Charts 1 and 2.

Received: April 6, 2011
Published: May 02, 2011

Chart 1. α,β-Unsaturated Aldehydes



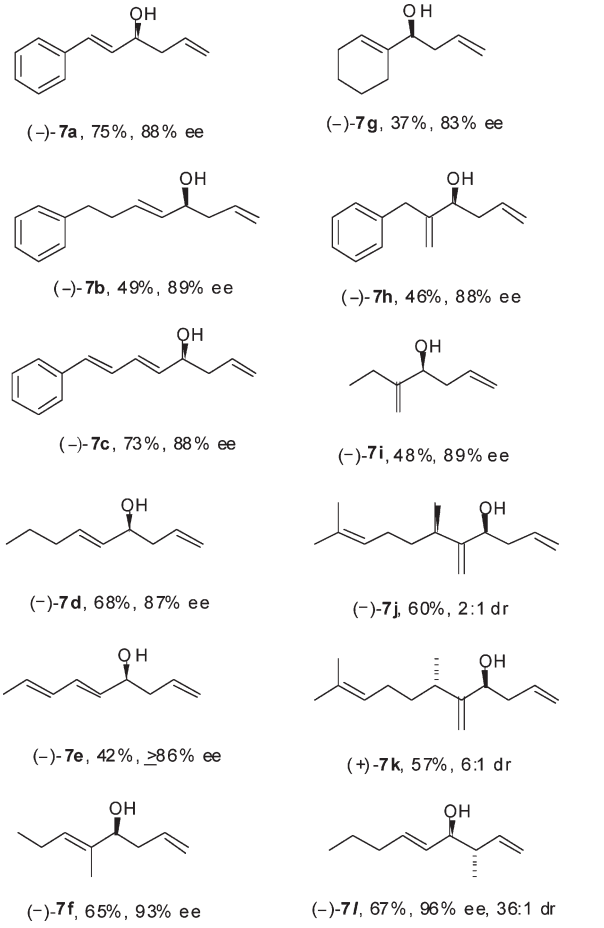
Allylation of the α,β-unsaturated aldehydes **6** with **2a** followed our optimized protocol: MeCN as solvent, 1.5 equiv of **2a**, −30 °C, 10 mol % of METHOX (+)-(**4**), and an excess of Hünig base.[12] Under these conditions, all of the aldehydes were found to react with a practically full conversion within 3−5 days, as shown by the ^{1}H NMR spectra of the crude products.[13] However, due to the volatility of some of the products and the small scale of these experiments, which did not allow efficient recovery of the products on the removal of the solvent, the isolated yields turned out not to be as high as expected from the conversions. Nevertheless, the enantiopurities of the products **7a**−**i** (Chart 2)[14] proved to be high (≤93% ee), on average only ca. 5% below those attained with aromatic aldehydes **1**. Neither the α-branching (**7f,g**) nor the α-methylene pattern (**7h,i**) was detrimental to the enantioselectivity.[15] In the case of the α-methylene derivative of citronellal **6j**, the mismatched (*R*)-enantiomer afforded mainly the *syn*-configured **7j** as a ∼2:1 mixture of diastereoisomers, whereas (*S*)-**6j** furnished the *anti*-diastereoisomer **7k** (6:1 dr), as revealed by the ^{1}H NMR spectra of the crude product.[16] The same reaction catalyzed by DMF[17] afforded a ∼1:1 *anti/syn* mixture. Crotylation of aldehyde **6d** with **2b**, carried out under the same conditions, gave rise to the expected *anti*-diastereoisomer **7*l*** as the only product with the highest enantiomeric excess (96% ee). It is pertinent to note that METHOX was always recovered almost quantitatively by chromatography in all these reactions.[18]

These results show that the scope of METHOX (**4**) as organocatalyst is not limited to aromatic aldehydes and that it can be successfully employed in the allylation and crotylation of α,β-unsaturated aldehydes. The latter catalyst thus supplements the bipyridine-type *N,N′*-dioxides, recently developed by Kotora (≤97% ee), whose synthesis is rather more complicated.[9j,l,m] Of particular importance is the finding that the α-branching, as in **6f,g**, is not detrimental to the enantioselection, which was not observed in the previous studies.[9j,l,m]

EXPERIMENTAL SECTION

General Methods and Materials. Melting points were determined on a Kofler block and are uncorrected. The NMR spectra were recorded for $CDCl_3$ solutions, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) or TMS as internal standard unless otherwise indicated. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film of $CHCl_3$ solutions between NaCl plates. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with the nitrogen. Solvents and solutions were transferred by syringe-septum technique. THF was obtained from Pure-Solv Solvent Purification System (Innovative Technology); acetonitrile, dichloromethane, and Hünig base were freshly distilled from CaH_2. Petroleum ether (PE) refers to the fraction boiling in the range of 40−60 °C, AcOEt refers to ethyl acetate, MeOH refers to methanol. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. Allyltrichlorosilane (**2a**) is commercially available. Trichlorocrotylsilane **2b** was prepared from the commercial *trans*-crotyl chloride (6:1) as a 6:1 *trans/cis* mixture,[5−7] which was not separated, as METHOX is known to exhibit strong kinetic preference for the *trans*-isomer **2b**.[5−7] Aldehydes **6h**−**j** were prepared according to Pihko's protocol.[11]

Chart 2. Products of Allylation of Aldehydes 6a−j with 2a,b Catalyzed by METHOX (4)



General Procedure for the Reaction of Allyltrichlorosilane (2a) and Crotyltrichlorosilane (2b) with Aldehydes 6. An oven-dried flask was filled with argon and charged with Methox (+)-**4** or Quinox (*R*)-(+)-**5** (0.075 mmol), followed by acetonitrile (5 mL, in the case of Methox) or dichloromethane (5 mL, in the case of Quinox), diisopropylethylamine (478 mg, 3.7 mmol), and aldehyde **6** (0.75 mmol). The mixture was then cooled to −45 °C, and allyltrichlorosilane or crotyltrichlorosilane (1.10 mmol) was added dropwise. The mixture was stirred at −45 °C for 4 h and then kept in a freezer at −30 °C for 5 days. The reaction was quenched with aqueous satd $NaHCO_3$, the product was extracted with ethyl acetate, and the organic solution was dried with

dx.doi.org/10.1021/jo200712p |*J. Org. Chem.* 2011, 76, 4800–4804

$MgSO_4$ and evaporated The crude product was purified by chromatography on a column of silica gel (15 cm × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5). In all cases the conversions were ≥95%, as revealed by GC and NMR analysis of the crude mixtures. The isolated yields of **7** and ee are given in Chart 2. The enantiopurity of the resulting alcohol was determined by chiral GC, or HPLC, or by Mosher derivatization (see below).

(*S*,*E*)-(−)-1-Phenyl-hexa-1,5-dien-3-ol (7a). Obtained as a yellowish oil (445 mg, 75%): $[\alpha]_D$ −25.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (br d, *J* = 4.0 Hz, 1H), 2.27−2.41 (m, 2H), 4.29 (m, 1H), 5.08−5.15 (m, 2H), 5.74−5.84 (dddd, *J* = 17.1, 10.2, 7.4, 6.9 Hz, 1H), 6.17 (dd, *J* = 15.9 and 6.3 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 7.15−7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.0 (CH_2), 71.7 (CH), 118.5 (CH_2), 126.5 (2 × CH), 127.7 (CH), 128.6 (2 × CH), 130.4 (CH), 131.6 (CH), 134.1 (CH), 136.7C); IR ν 3371, 3070, 3026, 2926, 2850, 1495, 1449, 1217, 1030, 997, 966, 916, 748 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 157 (100, M−OH), 133 (24); HRMS (CI/isobutane) 157.1016 ($C_{12}H_{13}$ requires 157.1017), all identical to the data of an authentic sample of the (+)-enantiomer;[5a] chiral HPLC (Chiralcel IB column, hexane/2-propanol = 97:3, 0.75 mL min^{-1}) showed 88% ee (t_R = 18.5 min, t_S = 27.7 min).

(*S*,*E*)-(−)-8-Phenylocta-1,5-dien-4-ol (7b). Obtained as a light yellow oil (78 mg, 49%): $[\alpha]_D$ −12.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13−2.25 (m, 2H), 2.24−2.31 (m, 2H), 2.62 (dd, *J* = 8.1, 7.4 Hz, 2H), 4.03 (br q, *J* = 6.3 Hz, 1H), 5.02−5.07 (m, 2H), 5.42 (tdd, *J* = 15.4, 6.7, 1.3 Hz, 1H), 5.63 (dtd, *J* = 15.4, 6.7, 0.9 Hz, 1H), 5.70 (dddd, *J* = 18.0, 10.6, 7.3, 6.8 Hz, 1H), 7.09−7.13 (m, 3H), 7.17−7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9 (CH_2), 34.5 (CH_2), 40.9 (CH_2), 70.7 (CH), 117.1 (CH_2), 124.8 (CH), 127.3 (2 × CH), 127.4 (2 × CH), 130.1 (CH), 131.8 (CH), 133.3 (CH), 140.7 (C); IR ν 3315, 3055, 2932, 1435, 1265, 972, 918, 708 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 185 (M − OH, 100), 161 (43), 142 (81), 117 (19), 91 (16), 81 (9); HRMS (CI/isobutane) 185.1327 ($C_{14}H_{17}$ requires 185.1330); HPLC analysis (Chiralcel OJ-H, hexane/2-propanol 95:5, 0.75 mL min^{-1}) showed 89% ee (t_R = 14.8 min, t_S = 17.1 min).

(4*S*,5*E*,7*E*)-(−)-8-Phenyl-1,5,7-octatrien-4-ol (7c). Obtained as a yellowish oil (183.7 mg, 73%): $[\alpha]_D$ −23.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 1.65 (d, *J* = 4.0 Hz, 1H), 2.23−2.37 (m, 2H), 4.19−4.25 (m, 1H), 5.08−5.14 (m, 2H), 5.72−5.82 (m, 2H), 6.35 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.70 (dd, *J* = 15.5, 10.6 Hz, 1H), 7.13−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.0 (CH_2), 71.4 (CH), 118.5 (CH_2), 126.4 (2 × CH), 127.6 (CH), 128.2 (CH) 128.6 (2 × CH), 130.8 (CH), 132.8 (CH), 134.0 (CH), 135.6 (CH), 137.2 (C); IR ν 3364, 3078, 3024, 2905, 1641, 1492, 1447, 1297, 1071, 1026, 986, 914, 746, 691 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 183 (100, M − OH), 159 (10), 107 (15), 81 (10), 73 (10); HRMS (CI/isobutane) 183.1172 ($C_{14}H_{15}$ requires 183.1168), all in accordance with the literature data given for the racemate;[19] HPLC analysis (Chiralcel OD-H, hexane/propan-2-ol, 96:4, 0.75 mL min^{-1}) showed 88% ee (t_R = 18.54 min, t_S = 22.78 min).

(4*S*,5*E*)-(−)-1,5-Nonadien-4-ol (7d). Obtained as a yellowish oil (244 mg, 68%): $[\alpha]_D$ −14.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.40 (sext, *J* = 7.4 Hz, 2H), 1.63 (br s 1H), 1.95 (q, *J* = 7.1 Hz, 2H), 2.23−2.36 (m, 2H), 4.12 (q, *J* = 6.3 Hz, 1H), 5.10−5.16 (m, 2H), 5.48 (ddd, *J* = 15.4, 6.7, 1.4 Hz, 1H), 5.61 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.80 (dddd, *J* = 17.1, 10.4, 7.4, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 22.3 (CH_2), 34.3 (CH_2), 42.1 (CH_2), 71.9 (CH), 118.0 (CH_2), 132.1 (CH), 132.2 (CH), 134.5 (CH); IR ν 3433, 3414, 3333, 2960, 2930, 2911, 2873, 1436, 1261, 1027, 995, 968, 914 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 123 [(M − OH)$^+$, 100], 113 (5), 99 (45), 81 (20), 67 (10) in agreement with the literature;[20] HRMS (CI/isobutane) 123.1160 (C_9H_{15} requires 123.1174); ^{19}F NMR of the corresponding Mosher ester showed 87% ee (δ_R = −71.46, δ_S = −71.51).

(4*S*,5*E*,7*E*)-(−)-1,5,7-Nonatrien-4-ol (7e). Obtained as a yellowish oil (151 mg, 42%): $[\alpha]_D$ −7.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, *J* = 3.9, 1H), 1.76 (dd, *J* = 6.7, 1.2 Hz, 3H), 2.25−2.38 (m, 2H), 4.16−4.22 (m, 1H), 5.11−5.17 (m, 2H), 5.57 (dd, *J* = 15.2, 6.6 Hz, 1H). 5.71 (dd, *J* = 15.0, 6.8 Hz, 1H), 5.80 (dddd, *J* = 17.0, 10.3, 7.4, 6.8 Hz, 1H), 6.04 (ddd, *J* = 15.1, 10.5, 1.5 Hz, 1H), 6.20 (dd, *J* = 15.1, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 42.0 (CH_2), 71.5 (CH), 118.3 (CH_2), 130.2 (CH), 130.7 (CH), 131.0 (CH), 132.3 (CH), 134.2 (CH); IR ν 3362, 3078, 3018, 2916, 1435, 1261, 1025, 985, 913 cm^{-1}; MS (EI$^+$) *m*/*z* (%) 138 (M$^+$, 23), 97 (100), 79 (41); HRMS (EI$^+$) 138.1048 ($C_9H_{14}O$ requires 138.1045), all consistent with the literature data.[21,22] ^{19}F NMR of the corresponding Mosher ester showed ≥86% ee (δ_R = −71.47, δ_S = −71.53).[22]

(4*S*,5*E*)-(−)-5-Methyl-1,5-octadien-4-ol (7f)[23]. Obtained as a colorless oil (196 mg 65%): $[\alpha]_D$ −11.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.61 (s, CH_3 and OH), 2.03 (quintet, *J* = 7.4 Hz, 2H), 1.99−2.38 (m, 2H), 4.01−4.05 (m, 1H), 5.07−5.15 (m, 2H), 5.40 (dt, *J* = 7.1, 1.1 Hz, 1H), 5.76 (dddd, *J* = 17.2, 10.2, 7.3, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 14.0 (CH_3), 20.8 (CH_2), 39.9 (CH_2), (CH), 117.6 (CH_2), 128.5 (CH), 134.9 (CH), 135.7 (C); IR ν 3369, 2963,2934, 2874, 1641, 1125, 1066 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 123 [(M − OH)$^+$, 100], 99 (15), 81 (10), 69 (10); HRMS (CI/isobutane) 123.1167 (C_9H_{15} requires 123.1168); GC analysis (Supelco γ-DEX 120 column, oven: 70 °C, then 0.5 °C min^{-1} to 90 °C) showed 93% ee (t_R = 32.52 min, t_S = 33.62 min).

(*S*)-(−)-(1′-Cyclohexen-1′-yl)but-3-en-1-ol (7g). Obtained as a colorless oil (73 mg, 37%): $[\alpha]_D$ −17.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.50−1.71 (m, 4H + 1H (OH)), 1.89−1.96 (m, 1H)], 1.98−2.11 (m, 3H), 2.25−2.38 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 1H), 5.02−5.08 (m, 2H), 5.61 (br s, 1H), 5.72 (dddd, *J* = 17.1, 10.2, 7.4, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.62 (CH_2), 22.63 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 39.9 (CH_2), 75.2 (CH), 117.7 (CH_2), 123.1 (CH), 135.0 (C), 139.2 (CH); IR ν 3347, 2926 2858, 2837, 1641, 1298, 1269, 1137, 1030 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 135 (M − OH, 35), 113 (57), 107 (90), 97 (40), all consistent with the literature data;[24] HRMS (CI/isobutane) 135.1177 ($C_{10}H_{15}$ requires 135.1174); ^{19}F NMR of the corresponding Mosher's ester showed 83% ee (δ_R = −71.32, δ_S = −71.57).

(*S*)-(−)-2-Benzylhexa-1,5-dien-3-ol (7h). Obtained as a colorless oil (68 mg, 46%): $[\alpha]_D$ −3.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 3.8 Hz, 1H), 2.23 (dt, *J* = 14.2, 7.7 Hz, 1H), 2.32−2.38 (m, 1H), 3.27 (d, *J* = 15.6 Hz, 1H), 3.41 (d, *J* = 15.6 Hz, 1H), 4.04−4.08 (m, 1H), 4.73 (d, *J* = 1.2 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 5.05 (br s, 1H), 5.07−5.10 (m, 1H), 5.09 (d, *J* = 1,2 Hz, 1H), 5.67−5.77 (m, 1H), 7.12−7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2 (CH_2), 40.4 (CH_2), 73.2 (CH), 112.4 (CH_2), 118.4 (CH_2), 126.4 (CH), 128.5 (2 × CH), 129.3 (2 × CH), 134.6 (CH), 139.3 (C), 150.6 (C); IR ν 3321, 3055, 2924, 1435, 1265, 910, 740 cm^{-1}; MS (CI/isobutane) *m*/*z* (%) 171 (47, M$^+$−OH), 129 (20), 113 (21), 97 (27); HRMS (CI/isobutane) 171.1177 ($C_{13}H_{15}$ requires 171.1174); chiral GC analysis (Supelco β-DEX 120 column, oven at 100 °C for 2 min then 1 °C min^{-1}) showed 88% ee for the Methox experiment carried out at −45 °C, 70% ee for the Methox experiment carried out at −30 °C, and 80% ee (opposite enantiomer) for the (*R*)-(+)-Quinox experiment carried out at −30 °C (t_R = 50.14 min, t_S = 50.49 min).

(*S*)-(−)-2-Ethyl-1,5-hexadien-3-ol (7i). Obtained as a yellowish oil (215 mg, 48%): $[\alpha]_D$ −30.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.4 Hz, 3H), 1.68 (d, *J* = 3.9 Hz, 1H), 2.02 (dq, *J* = 16.5, 7.4 Hz, 1H), 2.13 (dq, *J* = 16.3, 7.5 Hz, 1H), 2.28 (dt, *J* = 14.2, 7.7 Hz, 1H), 2.37−2.44 (m, 1H), 4.12−4.16 (m, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 5.05 (t, *J* = 1.1 Hz, 1H), 5.11−5.18 (m, 2H), 5.80 (dddd, *J* = 17.1, 10.2, 7.4, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2 (CH_3), 24.4 (CH_2), 40.4 (CH_2), 74.0 (CH), 108.5 (CH_2), 118.1 (CH_2), 134.7 (CH),

152.7 (C); IR ν 3380, 3078, 3025, 2931, 1641, 1434, 1297, 989, 915, 748, 692 cm^{-1}; MS (CI/isobutane) m/z (%) 1109 (M^+−OH, 100), 95 (19), 85 (30); HRMS (CI/isobutane) 109.1019 (C_8H_{13} requires 109.1017); **GC** analysis (Supelco γ-DEX 120 column, oven: 50 °C for 2 min, then 0.5 °C min^{-1} to 70 °C) showed 89% ee (t_R = 36.06 min, t_S = 36.44 min).

(4*S*,6*R*)-(−)-6,10-Dimethyl-5-methyleneundeca-1,9-dien-4-ol (7j). Obtained as a yellowish oil (46 mg, 60%): $[\alpha]_D$ −27.6 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, main diastereoisomer) δ 1.05 (d, *J* = 6.9 Hz, 3H), 1.30−1.40 (m, 1H), 1.45−1.50 (m, 1H), 1.52 (s, 3H), 1.56 (d, *J* = 3.8 Hz, 1H), 1.61 (s, 3H) 1.87−1.93 (m, 2H), 2.01−2.08 (m, 1H), 2.15−2.22 (m, 1H), 2.30−2.37 (m, 1 H), 4.00−4.04 (m, 1H), 4.84 (s, 1H), 5.00−5.10 (m, 4H), 5.71−5.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; major diastereoisomer) δ 17.7 (CH_3), 21.6 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 35.6 (CH), 36.5 (CH_2), 40.9 (CH_2), 73.1 (CH), 108.0 (CH_2), 117.9 (CH_2), 124.6 (CH), 131.5 (C), 134.9 (CH), 157.1 (C); IR ν 3335, 3055, 2924, 1442, 1381, 1265, 1049, 995, 733 cm^{-1}; MS (CI/isobutane) m/z (%) 191 (M − OH, 80), 167 (17), 149 (20), 135 (39), 109 (29), 81 (69), 69 (100); HRMS (CI/isobutane) 191.1797 ($C_{14}H_{23}$ requires 191.1800).

(4*S*,6*S*)-(+)-6,10-Dimethyl-5-methyleneundeca-1,9-dien-4-ol (7k). Obtained as a colorless oil (55 mg, 57%): $[\alpha]_D$ +7.5 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, main diastereoisomer) δ 1.08 (d, *J* = 6.9 Hz, 3H), 1.30−1.40 (m, Hz, 1H), 1.49 (ddt, *J* = 15.7, 8.9, 6.7 Hz, 1H), 1.59 (s, 3H), 1.69 (br s, 4H), 1.84−1.92 (m, 2H), 2.02 (sxt, *J* = 6.9 Hz, 1H), 2.18 (br pent, *J* = 6.9 Hz, 1H), 2.31−2.38 (m, 1H), 4.01−4.05 (m, 1H), 4.85 (s, 1H), 5.00−5.12 (m, 4H), 5.75 (dddd, *J* = 17.0, 10.3, 7.5, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ 17.7 (CH_3), 20.7 (CH_3), 25.7 (CH_3), 25.9 (CH_2), 35.4 (CH), 37.4 (CH_2), 40.8 (CH_2), 73.3 (CH), 107.8 (CH_2), 118.1 (CH_2), 124.4 (CH), 131.6 (C), 134.8 (CH), 157.1 (C); IR ν 3389, 3077, 2965, 2916, 2857, 1642, 1452, 1437, 1377, 1109, 1047, 901 cm^{-1}; MS (CI/isobutane) m/z (%) 209 (M + H, 9), 191 (M − OH, 100), 167 (16) 149 (24), 135 (58), 124 (15), 109 (31), 95 (41), 81 (28); HRMS (CI/isobutane) 209.1901 ($C_{14}H_{25}O$ requires 209.1905).

(3*S*,4*R*,*E*)-(−)-3-Methylnona-1,5-dien-4-ol (7*l*). Obtained as a colorless oil (103 mg, 67%): $[\alpha]_D$ −3.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.34−1.47 (m, 2H), 1.73 (br s, 1H), 1.96−2.10 (m, 2H), 2.17−2.26 (m, 1H), 3.79 (t, *J* = 7.3 Hz, 1H), 5.05−5.10 (m, 2H), 5.42 (tdd, *J* = 15.4, 7.5, 1.3 Hz, 1H), 5.60 (dt, *J* = 15.4, 6.7, 1H), 5.69 (ddd, *J* = 16.7, 10.8, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 16.3 (CH_3), 22.4 (CH_2), 34.5 (CH_2), 44.7 (CH), 76.5 (CH), 116.5 (CH_2), 130.8 (CH), 133.8 (CH), 140.8 (CH); IR ν 3385, 2957, 2925, 2855, 1639,1260, 1015 cm^{-1}; MS (CI/isobutane) m/z (%) 137 (M − OH, 35), 91 (49), 69 (100); HRMS (CI/isobutane) 137.1307 ($C_{10}H_{17}$ requires 137.1330); GC analysis (Supelco α-DEX 120 column, oven: 50 °C, then 1 °C min^{-1}) showed 36:1 dr and 96% ee for the major enantiomer ($t_{3S,4R}$ = 43.21 min, $t_{3R,4S}$ = 43.62 min).

■ ASSOCIATED CONTENT

Supporting Information. General experimental methods and ^1H and ^{13}C NMR spectra for new allylation products (**7b**, **7f**, **7h**, **7i**, and **7*l***) and chiral HPLC/GC traces (**7a**−**c**, **7f**, **7h**, **7i**, and **7*l***) and ^{19}F NMR spectra of the Mosher derivatives (**7d**, **7e**, and **7g**). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the EPSRC for grant No. EP/E011179/1 and the Erasmus Exchange Program for support to J.M.

■ REFERENCES

(1) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Denmark, S. E.; Almstead, N. G. *J. Mex. Chem. Soc.* **2009**, *53*, 174. (c) For the experimental and computational study of the origin of *syn/anti* diastereoselectivity in the aldehyde and ketone crotylation, see: Tietze, L. F.; Kinzel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483.

(2) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.

(3) Kočovský, P.; Malkov, A. V. Chiral Lewis Bases as Catalysts., In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 255.

(4) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol 2, p 1. (b) Hall, D. G.; Lachance, H. *Org. React.* **2008**, *73*, 1.

(5) (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. (b) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659. (c) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179. (d) Malkov, A. V.; Westwater, M.-M.; Kadlčíková, A.; Gutnov, A.; Hodačová, J.; Rankovic, Z.; Kotora, M.; Kočovský, P. *Tetrahedron* **2008**, *64*, 11335. (e) Malkov, A. V.; Kabeshov, M. A.; Barłóg, M.; Kočovský, P. *Chem.—Eur. J.* **2009**, *15*, 1570. (f) Malkov, A. V.; Kysilka, O.; Edgar, M.; Kadlčíková, A.; Kotora, M.; Kočovský, P. *Chem.—Eur. J.* **2011**, *17*, in press (DOI: 10.1002/chem.201100513). For a different application of the *N*-oxides, see: (g) Malkov, A. V.; Gordon, M. R.; Stončius, S.; Hussain, J.; Kočovský, P. *Org. Lett.* **2009**, *11*, 5390. For an overview, see: (h) Kočovský, P.; Malkov, A. V. *Pure Appl. Chem.* **2008**, *80*, 953.

(6) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219.

(7) (a) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674. (b) Malkov, A. V.; Ramírez-López, P.; Bendová, L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský, P. *J. Am. Chem. Soc.* **2008**, *130*, 5341.

(8) For other pyridine *N*-monoxide catalysts, see: (a) Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, *47*, 8611. (b) Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006**, *71*, 1458. (c) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574. (d) Boyd, D. R.; Sharma, N. D.; Sbircea, L.; Murphy, D.; Malone, J. F.; James, S. L.; Allen, C. C. R.; Hamilton, J. T. G. *Org. Biomol. Chem.* **2010**, *8*, 1081.

(9) For bipyridine *N*,*N*′-dioxide catalysts, see: (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306. (c) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (d) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329. (e) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169. (f) Hrdina, R.; Stará, I. G.; Dufková, L.; Mitchell, S.; Císařová, I.; Kotora, M. *Tetrahedron* **2006**, *62*, 968. (g) Hrdina, R.; Kadlčíková, A.; Valterová, I.; Hodačová, J.; Kotora, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3185. (h) Hrdina, R.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2007**, *349*, 822–826. (i) Hrdina, R.; Dračínský, M.;

Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2008**, *350*, 1449. (j) Hrdina, R.; Boyd, T.; Valterová, I.; Hodačová, J.; Kotora, M. *Synlett* **2008**, 3141–3144. (k) Hrdina, R.; Opekar, F.; Roithová, J.; Kotora, M. *Chem. Commun.* **2009**, 2314. (l) Kadlčíková, A.; Hrdina, R.; Valterová, I.; Kotora, M. *Adv. Synth. Catal.* **2009**, *351*, 1279. (m) Kadlčíková, A.; Valterová, I.; Ducháčková, L.; Roithová, J.; Kotora, M. *Chem.—Eur. J.* **2010**, *16*, 9442. (n) Ducháčková, L.; Kadlčíková, A.; Kotora, M.; Roithová, J. *J. Am. Chem. Soc.* **2010**, *132*, 12660. (o) Vlašaná, K.; Hrdina, R.; Valterová, I.; Kotora, M. *Eur. J. Org. Chem.* **2010**, 7040. (p) For an overview, see: Kotora, M. *Pure Appl. Chem.* **2010**, *82*, 1813.

(10) For analogous *N*,*N*′,*N*″-trioxides, see: (a) Wong, W.-L.; Lee, C.-S.; Leung, H. K.; Kwong, H.-L. *Org. Biomol. Chem.* **2004**, 1967. For polymeric poly-*N*-oxides, see: (b) Müller, C. A.; Hoffart, T.; Holbach, M.; Reggelin, M. *Macromolecules* **2005**, *38*, 5375.

(11) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205.

(12) The higher reactivity of aromatic aldehydes allowed the use of as little as 1−5 mol% of METHOX. Here, the higher loading was required to attain reasonable reaction times.

(13) In the case of aldehyde **6h**, the reaction was carried out at −45 °C (approximately the freezing point of the mixture) for 5 h and then quenched. The conversion to **7h** was therefore rather low: the crude product was a ∼3:2 mixture of the unreacted aldehyde to alcohol, as revealed by NMR spectroscopy.

(14) The absolute configuration of alcohols **7** has not been rigorously established but is assumed to be (*S*) as shown, in analogy with their aromatic counterparts.[5−7]

(15) In the Methox-catalyzed reaction, **7h** was obtained in 88% ee at −45 °C and in 70% ee at −30 °C. With (*R*)-(+)-Quinox, an opposite enantiomer of **7h** was obtained in 80% ee at −30 °C.

(16) The relative configuration is proposed on the assumption that the allylations catalyzed by METHOX (+)-**4** afford the (*S*)-configured alcohols.[6]

(17) For activation of trichlorosilyl derivatives by DMF and other Lewis bases, see ref 3 and the following: (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. (c) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457. (d) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407. (e) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (f) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977. (g) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507. (h) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. (i) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610. (j) Massa, A.; Malkov, A. V.; Kočovský, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179. (k) Rowlands, G. J.; Barnes, W. K. *Chem. Commun.* **2003**, 2712.

(18) The recovered METHOX, collected from several experiments and combined, can be purified by crystallization and used again. No difference has been observed between the "new" and "second-hand" samples of METHOX, as will be fully demonstrated in a separate paper.

(19) Kostikov, R. R. *Zh. Org. Khim.* **1971**, *7*, 2297.

(20) (a) Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, *9*, 1507. (b) Kubota, K.; Leighton, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.

(21) Georgy, M.; Lesot, P.; Campagne, J. *J. Org. Chem.* **2007**, *72*, 3543.

(22) The starting aldehyde **6e** has to be stored at −20 °C to prevent partial *trans*/*cis* isomerization of the double bond. The NMR spectra of the samples of alcohol **7e** contained minor peaks corresponding to that isomerization. Inevitably, the ^{19}F NMR spectrum of the Mosher ester of racemic **7e** showed a pair of major peaks (1:1) and another pair of minor peaks. In the spectrum of the enantiomerically enriched **7e** one of the two major peaks remained, whereas its partner peak was very small and partly overlapped with one of the pair of the minor peaks. Therefore, the enantiomeric ratio could not be determined with the accuracy attained with other members of the series. Hence, the final figure (≥86% ee) represents a conservative estimate and might be actually slightly higher.

(23) For the corresponding racemate, see: Knorr, A. German Patent 544,388, 1930; *Chem. Abstr.* 1932, *26*, 2466.

(24) Kimura, M.; Shimizu, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2005**, *61*, 3709.