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Registry No. Catechol 1,2-dioxygenase, 9027-16-1; pyrogallol, 87-66-1; oxygen, 7782-44-7.

Enamidines. Versatile Vehicles for Homologation of Carbonyl Compounds

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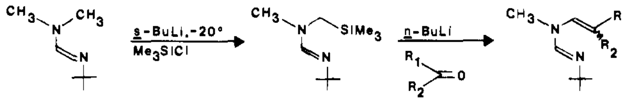
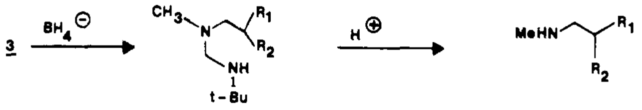
Enamidines **3** are rare in the literature, and their chemical behavior is virtually unexplored.[1] Yet, they possess a unique functional array since they may be considered as enamines containing an N-dipole stabilizing substituent,[2] i.e., formamidine. We report herein a simple route to enamidines but, more importantly, a preliminary study on their chemical properties which indicate that they indeed possess rich chemistry in areas of current synthetic interest, namely, homologation of carbonyl compounds.[3] The enamidines are readily prepared, in quantity, by metalation–silylation of **1**[4] to give the α-trimethylsilyl derivative **2**[5], which is metalated again and treated with various aldehydes or ketones in the Peterson olefination[6] to afford excellent yields of the enamidines **3**, as a mixture of geometric isomers. However, this lack of stereoselectivity is of no consequence in the carbonyl homologations to follow. The carbonyl compounds employed to prepare **3** were transformed, from this versatile intermediate, to homologated amines (**5**), aldehydes (**6**), and ketones (**10**) by simple changes in procedure. The technique utilized[7] to prepare the *N*-methylamines involved addition of sodium borohydride in ethanol (−10 °C) under slightly acidic conditions (pH 6). This resulted in reduction of both the C═N link and the vinylamine moiety, producing the aminal **4** which was hydrolyzed with dilute acid to the amine **5**. It is also possible to carry out this entire homologation from **1** without isolation of the intermediate silylformamidine **2** or purification of enamidine **3**[6] and aminal **4**. The intermediate silylformamidine, formed in situ, was immediately treated with *n*-butyllithium and the carbonyl compound to give enamidines **3** in 70–85%. Table I describes a number of examples which were examined. It is important to note that this procedure leads to *N*-methylamines as well as other *N*-alkylamines[8]

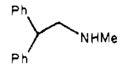
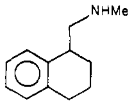
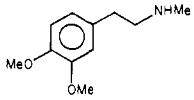
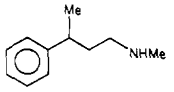
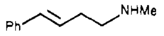
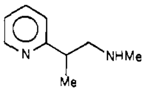


1 2 3



4 5

Table I. Homologation of Carbonyls to Amines 5 (Isolated Pure Material)

carbonyl	amine	% yield (from 2)	HCl salt[a] mp, °C
benzaldehyde		66	156–158
benzophenone		65	181–182
α-tetralone		66	202–205
veratraldehyde		67	138–140
α-(methylphenyl)-acetaldehyde		61	108–110
cinnamaldehyde		52	185–187[b]
α-acetylpyridine		70	*c*

[a] Mp of hydrochlorides agree with literature values where reported. [b] New compound; C, H, N analyses agree within ±0.4%. [c] Analyzed as free base.

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(1) Cook, L. S.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2392. Huffman, K. R.; Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1962**, *27*, 551. Arnold, R. J.; Gattuso, M. J. U.S. Patent 3 919 225, 1975; *Chem. Abstr.* **1976**, *84*, 43368C.

(2) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, 275. Krief, A. *Tetrahedron* **1980**, *36*, 2531.

(3) For a review on homologation of carbonyl compounds, see: Martin, S. F. *Synthesis* **1979**, 633.

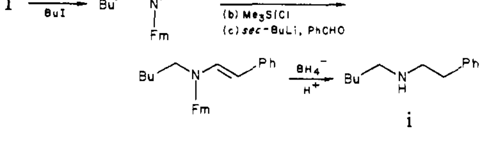
(4) Meyers, A. I.; Ten Hoeve, W. *J. Am. Chem. Soc.* **1980**, *102*, 7125.

(5) Preparation of **2**: *N*,*N*-dimethyl-*N'*-*tert*-butylformamidine (0.20 mol) in 400 mL of THF was treated with *sec*-butyllithium (0.22 mol) at −75 °C and the solution was allowed to warm to −20 °C over 30 min. After 1 h, the solution was recooled to −78 °C, and trimethylsilyl chloride (0.22 mol) was added and the mixture allowed to warm to the ambient temperature. The mixture was quenched in 600 mL of ice water and the organic layer removed by extraction with dichloromethane. Drying (Na_2SO_4), concentration, and distillation [bp 78–80° (7 mm)] gave 35.7 g of pure **2**; yield 89.2%; IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (s, 1 H), 2.80 (s, 3 H), 2.67 (s, 2 H), 1.12 (s, 9 H), 0.08 (s, 9 H).

(6) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 781. Preparation of **3** ($R_1 = R_2 =$ Ph, typical procedure: A solution of 5 mmol of **2** in 10 mL of THF was cooled to −78 °C and treated with 5.75 mmol of *n*-butyllithium or *sec*-butyllithium and the solution allowed to warm to -20 ± 5 °C, stirred for 2 h, and recooled to −78 °C. A solution of benzophenone (5.75 mmol) in 4 mL of THF was added and the solution slowly allowed to warm to 0 °C. Quenching was performed in 20 mL of cold 10% bicarbonate and 40 mL of dichloromethane and the organic layer separated, washed (brine), dried (Na_2SO_4), and concentrated. The enamidines, thus obtained, may be used in the subsequent reactions described or may be purified by bulb-to-bulb distillation. For **3** ($R_1 = R_2 =$ Ph) the distilled material, 5.41 g (93%), was recrystallized (pentane); mp 56–57 °C; IR (neat) 1642, 1614, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) 7.42 (s, 1 H), 7.30 (s, 5 H), 7.25 (s, 5H), 6.57 (s, 1 H), 2.91 (s, 3 H), 1.03 (s, 9 H). Anal. ($C_{20}H_{24}N_2$) C, H, N.

(7) Procedure for conversion of **3** to amines **5**. The crude enamidine **3** (5 mmol) is dissolved in 15 mL of 80% ethanol and treated with 10% HCl until the pH of the solution is ~6. A solution of 600 mg of (15.9 mmol) sodium borohydride in 15 mL of ethanol is added dropwise between −5 and −15 °C, interrupted by dropwise addition of 10% HCl to maintain the pH at ~6. After stirring for 1 h at 0 °C, the mixture is made strongly alkaline (pH >12) by addition of NaOH pellets, diluted with 50 mL of water, extracted with ether, and then concentrated. The residue is redissolved in 30 mL of THF and treated with 5 mL of 10% HCl and the solution stirred at ambient temperature for 2 h. The solution is again made strongly alkaline (NaOH pellets), extracted with ether, dried (K_2CO_3), and then concentrated to provide the amine. Purification is accomplished by distillation or dry HCl (ether) to form the hydrochloride.

(8) Starting from **1**, it is possible to introduce, via metalation and alkylation, an alkyl group prior to metalation–silylation and then proceed to form *N*-alkylethylamines, i.e (Fm = formamidine),



This sequence was carried out without isolation or purification of any of the intermediates to give i in 55% overall yield.

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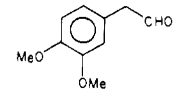
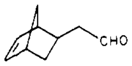
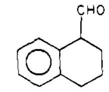
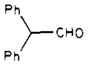
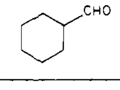
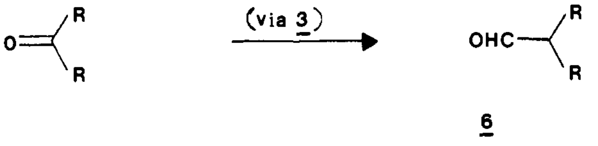
Table II. Homologation of Carbonyls to Aldehydes 6 (Isolated Pure Material)

carbonyl	aldehyde	% yield (from 2)
veratraldehyde		55
5-norbornene-2-carboxaldehyde		72[a]
α-tetralone[b]		60[a]
benzophenone		84[c]
cyclohexanone[b]		62[a]

[a] Precursor enamidines 3 were cleaved to product aldehydes by hydrazinolysis with 1,1-dimethylhydrazine (see procedure of ref 9) followed by acid hydrolysis of methiodides obtained from the intermediate dimethylhydrazones (Corey, E. J.; Enders, D. *Tetrahedron Lett.* 1976, 3). [b] Prior to addition to lithiated 2, 2 equiv of HMPA were added at −78 °C. This procedure was found advantageous when any enolizable ketone was employed. [c] Enamidine 3 ($R_1 = R_2$ = Ph) was cleaved to diphenylacetaldehyde by using aluminum amalgam in moist ether (Meyers, A. I.; Durandetta, J. *J. Org. Chem.* 1975, *40*, 2021), giving the corresponding *N*-methyl enamine, which was cleaved in aqueous acid.

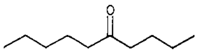
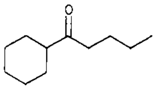
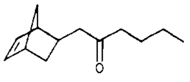
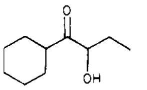
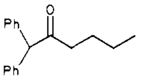
and should complement the traditional route of reaching *primary* ethylamines via the carbonyl–nitromethane–$LiAlH_4$ route. Furthermore, the reduction, using aqueous borohydride, circumvents the use of $LiAlH_4$ in the nitromethane method and allows for the presence of sensitive groups (e.g., conjugated dienes, pyridines, esters, etc.).

Instead of reduction of the enamidines 3, it is also feasible to release the homologated aldehyde 6 by either hydrazinolysis or aluminum amalgam reduction[9] in good yields. This technique



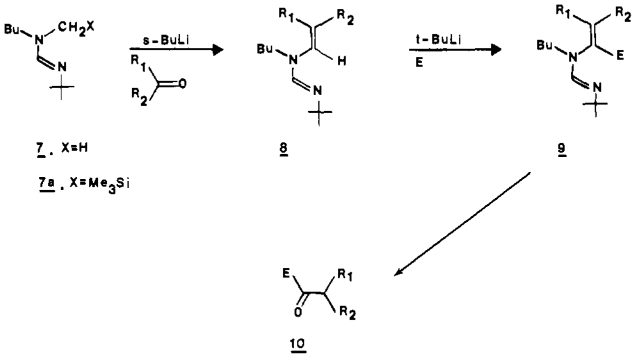
for homologating aldehydes or ketones to aldehydes by one additional carbon competes well with previous methods[3] in its simplicity and efficiency, using readily available reagents, such as 1.[3,10] Once again the entire process can be carried out starting from 1 and sequentially transforming it to the enamidine 3.[11] Only solvent removal of the latter is required prior to hydrazinolysis or reduction to aldehydes 6. Table II depicts several examples of this method.

Table III. Homologation of Carbonyls to Ketones, 10

carbonyl	E	ketone 10	% yield (from 2)[a,b]
valeraldehyde	*n*-BuI		71
cyclohexanone[c]	*n*-BuI		64
5-norbornene-2-carboxaldehyde	*n*-BuI		74
cyclohexanone[c]	EtCHO		50
benzophenone	*n*-BuI		61[d]

[a] All yields are for pure, isolated materials. [b] All compounds were analyzed to within ±0.3% of calculated values, unless previously reported. [c] See footnote *b* to Table II. [d] In the enamidine metalation step, 2 equiv of *t*-BuLi were employed.

Finally, the homologation of eneamidines to ketones 10 via an acyl anion equivalent was shown by forming the vinyllithium intermediate and subsequently alkylating to 9. Thus, starting with *N*-butylformamidine 7,[13] transforming it to the α-silyl derivative 7a, as described earlier, and following by metalation to 8, alkylation to 9, and cleavage gave the ketones 10.[14] The electrophiles used were *n*-butyl iodide and propionaldehyde to afford either the monofunctional ketones or α-hydroxy ketones (Table III). This efficient route to ketones may, as before, be carried through without isolation of 7a and 8 and only solvent



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(9) Procedure for transforming 3 to aldehydes 6: A typical example is given for homologation of veratraldehyde. The crude enamidine 3 (5.5 mmol), after removal of solvent,[6] is heated with a mixture of hydrazine or dimethylhydrazine–acetic acid–ethanol–water (1.4:1.0:10.6:6.7 v/v) for 6 h and diluted with water, extracted with chloroform, dried (Na_2SO_4), and concentrated to the hydrazone. The latter is dissolved in 30 mL of THF, treated with 2.5 equiv of $Cu(OAc)_2$[11] in 30 mL of water, and heated to reflux (30 min). The THF is removed in vacuo, and the aqueous solution treated with 800 mg of pyridine and extracted with dichloromethane. The organic phase is washed with brine, dried (Na_2SO_4), filtered through fluorisil (ether eluent), and concentrated to give the aldehyde.

(10) Several recent methods to carry out this type of carbonyl homologation have been reported. Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091. Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535. Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.

(11) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667.

(12) It was found convenient to prepare large quantities (~100 g) of 2 and carry out all the reported homologations with various carbonyl compounds starting from 2; thus yields in the tables are based on 2. They will be slightly lower when based on 1.

(13) Prepared from commercially available *N*-methyl-*N*-butylformamide with 1.0 equiv of dimethyl sulfate (80–90 °C, 3 h, N_2); the reaction mixture is cooled to 0 °C followed by addition of 1.05 equiv of *tert*-butylamine in CH_2Cl_2 under 15 °C. It is then heated to reflux (16 h) and worked up as in ref 4; bp 74–75 °C (8 mm), 90% yield.

(14) General procedure for ketones 10: The formamidine 7 was transformed into its α-silyl derivative 7a according to the procedure given in ref 5. 7a: bp 60–65 °C (0.2 mm); IR (neat) 1638 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (s), 3.10 (t), 2.69 (s), 1.15 (s), 0.8–1.7 (m), 0.10 (s). The enamidine was prepared according to the procedure given in ref 6 and not purified, only the solvent was removed and redissolved in THF. Thus, 2.0 mmol of enamidine in 5 mL of THF is cooled to −75 °C and then treated with 2.6 mmol of *tert*-butyllithium. The solution was allowed to warm to −25 °C and stirred at this temperature for 1.5 h to form lithio anion 8 (*sec*-butyllithium may be used but requires ~3 h for complete anion formation). After cooling to −78 °C, a solution of 2.4 mmol of the electrophile in THF was added and the mixture allowed to reach ambient temperature, quenched in water, extracted with methylene chloride, dried, and concentrated to give crude enamidine 9. Hydrazinolysis to the hydrazone and subsequent cleavage to ketone 10 was performed as described in ref 9. Alternatively, the hydrazone is cleaved to 10 using the method of Fuchs.[15]

(15) Sacks, C. E.; Fuchs, P. L. *Synthesis* **1976**, 456.

removal of **9** so it may be cleaved to the ketones. Further work on these interesting enamidines is in progress.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this work.

Registry No. 1, 23314-06-9; **2**, 80376-66-5; **3** (R_1 = Ph; R_2 = H), 80376-67-6; **3** (R_1R_2 = Ph), 80376-68-7; 3 (R_1R_2 = α-tetralin), 80376-69-8; **3** (R_1 = 3,4-$(MeO)_2C_6H_3$; R_2 = H), 80376-70-1; **3** (R_1 = PhCH-(CH_3); R_2 = H), 80376-71-2; **3** (R_1 = PhCH=CH; R_2 = H), 80376-72-3; **3** (R_1 = 2-pyridyl; R_2 = Me), 80376-73-4; **3** (R_1 = 5-norbornen-2-yl; R_2 = H), 80376-74-5; **4** (R_1 = Ph; R_2 = H), 80376-75-6; **4** (R_1, R_2 = Ph), 80376-76-7; **4** (R_1R_2 = α-tetralin), 80376-77-8; **4** (R_1 = 3,4-$(MeO)C_6H_3$; R_2 = H), 80376-78-9; **4** (R_1 = $PhCH(CH_3)$; R_2 = H), 80376-79-0; **4** (R_1 = PhCH=CH; R_2 = H), 80376-80-3; **4** (R_1 = 2-pyridyl; R_2 = Me), 80376-81-4; **5** (R_1 = Ph; R_2 = H), 589-08-2; **5** (R_1 = Ph; R_2 = H) HCl, 4104-43-2; **5** (R_1, R_2 = Ph), 80376-82-5; **5** (R_1, R_2 = Ph) HCl, 80376-83-6; **5** (R_1, R_2 = α-tetralin), 80376-84-7; **5** (R_1, R_2 = α-tetralin) HCl, 80376-85-8; **5** (R_1 = 3,4-$(MeO)_2C_6H_3$; R_2 = H), 3490-06-0; **5** (R_1 = 3,4-$(MeO)_2C_6H_3$; R_2 = H) HCl, 13078-76-7; **5** (R_1 = $PhCH(CH_3)$; R_2 = H), 40192-26-5; **5** (R_1 = $PhCH(CH_3)$; R_2 = H) HCl, 80376-86-9; **5** (R_1 = PhCH=CH; R_2 = H), 24316-73-2; **5** (R_1 = PhCH=CH; R_2 = H) HCl, 80376-87-0; **5** (R_1 = 2-pyridyl; R_2 = Me), 26832-29-1; **6** (R_1 = 3,4-$(MeO)_2C_6H_3$; R_2 = H), 5703-21-9; **6** (R_1 = 5-norbornen-2-yl; R_2 = H), 80376-88-1; **6** (R_1, R_2 = α-tetralin), 18278-24-5; **6** (R_1, R_2 = Ph), 947-91-1; **6** (R_1, R_2 = $(CH_2)_5$), 2043-61-0; **7**, 80376-89-2; **7a**, 80376-90-5; **8** (R_1 = Bu; R_2 = H), 80376-91-6; **8** (R_1, R_2 = $(CH_2)_5$), 80376-92-7; **8** (R_1 = 5-norbornen-2-yl; R_2 = H), 80376-93-8; **8** (R_1, R_2 = Ph), 80376-94-9; **9** (R_1, E = Bu; R_2 = H), 80376-95-0; **9** (E = Bu; R_1, R_2 = $(CH_2)_5$), 80376-96-1; **9** (E = Bu; R_1 = 5-norbornen-2-yl; R_2 = H), 80376-97-2; **9** (E = CH_3CH_2CHOH; R_1, R_2 = $(CH_2)_5$), 80376-98-3; **9** (E = Bu; R_1, R_2 = Ph), 80376-99-4; **10** (E = $CH_3(CH_2)_4$; R_1 = Pr; R_2 = H), 820-29-1; **10** (E = *c*-C_6H_{11}; R_1 = Pr; R_2 = H), 5445-35-2; **10** (E = 5-norbornen-2-ylmethyl; R_1 = Pr; R_2 = H), 80377-00-0; **10** (E = *c*-C_6H_{11}; R_1 = OH; R_2 = Et), 80377-01-1; **10** (E = $(Ph)_2CH$; R_1 = Pr; R_2 = H), 22117-90-4; *i*, 80377-02-2; benzaldehyde, 100-52-7; benzophenone, 119-61-9; α-tetralone, 529-34-0; veratraldehyde, 120-14-9; α-methylphenylacetaldehyde, 93-53-8; cinnamaldehyde, 104-55-2; α-acetylpyridine, 1122-62-9; 5-norbornene-2-carboxaldehyde, 5453-80-5; cyclohexanone, 108-94-1; valeraldehyde, 110-62-3; *N*-methyl-*N*-pentyl-*N'*-*tert*-butylformamidine, 80377-03-3; *N*-pentyl-*N*-phenylethenyl-*N'*-*tert*-butylformamidine, 80377-04-4; *N*-methyl-*N*-butylformamidine, 80377-05-5.

Enantioselective Synthesis of Binaphthyls via Nucleophilic Aromatic Substitution on Chiral Oxazolines

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The extraordinary chiral recognition properties of axially dissymmetric binaphthyl derivatives has opened exciting new routes to enantiomerically enriched organic compounds. The elegant studies by Cram[1] using crown-type ethers containing chiral binaphthyl moieties has resulted in complete separation of racemic amino acids via selective complexation of one enantiomer. Transition metals, complexed with ligands derived from chiral binaphthyls, have catalyzed hydrogenations[2] and isomerizations[3] of prochiral olefins in high enantiomeric excess, whereas binaphthyl hydride[4] and binaphthyllithium[5] reagents have led to chiral alcohols by enantioselective reactions on carbonyl compounds. In spite of these highly useful properties, there is no viable synthetic route to chiral binaphthyls, and their acquisition relies only on resolution of racemic materials. Kumada[6] described the cross coupling of 1-bromo-2-methylnaphthalene via the Grignard reagent, catalyzed, ironically, by a chiral binaphthylnickel species, to give 2,2'-dimethyl-1,1'-binaphthyl in 12.5% ee. Wynberg[7] reports an oxidative binaphthyl coupling catalyzed by chiral amines in 16% ee. The best method to date is that of Miyano,[8] which involves an intramolecular Ullmann coupling of a bis(bromonaphthoic) ester derived from optically active, 1,1'-binaphthol. The latter route, which led to ~100% ee of binaphthoic ester, also required an optically pure binaphthyl as the starting material.

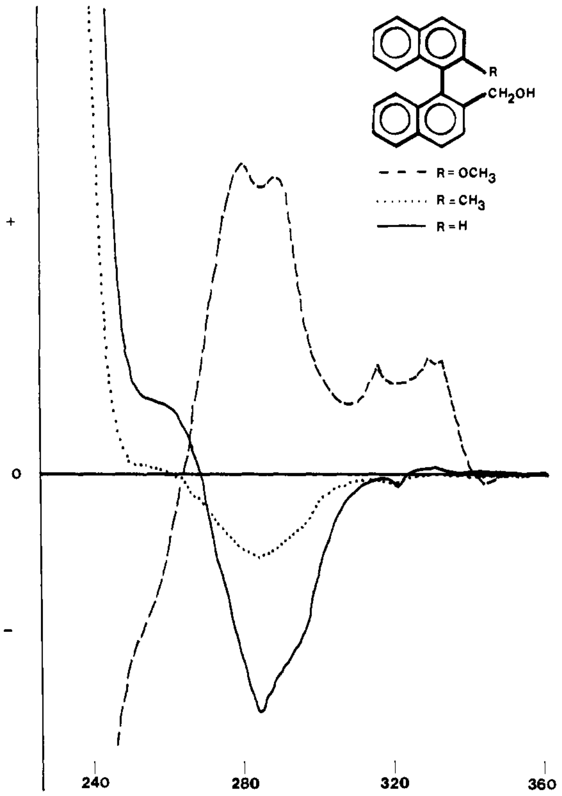

Figure 1. CD spectra in dioxane.

We now introduce a synthetic route to chiral binaphthyls **7** using nucleophilic aromatic displacement of an *o*-methoxy group[9] activated by chiral oxazoline **4**, furnishing these interesting substances in 87–96% ee.[10] The process is based on the addition of the Grignard reagent of 1-bromo-2-substituted naphthalenes to the 2-methoxy-1-oxazolinylnaphthalene **4** to afford the binaphthyl system **5** in 68–80% yields. The requisite chiral (methoxynaphthyl)oxazoline **4** was prepared from 2-methoxy-1-naphthoic acid[11] after conversion to its amide **2** (oxalyl chloride, NH_4OH, 83%, mp 155–158 °C) and treatment with (+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane[12] via its imidinium salt **3**.[13]

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