B. Marini Bettolo on the occasion of his 75th birthday.

Registry No. 1, 38768-81-9; 2, 61330-61-8; 3, 37776-25-3; 4, 54623-25-5; 5, 132201-25-3; 6, 132201-26-4; 7a, 82064-64-0; 7b, 82110-05-2; 8a, 82110-04-1; 8b, 82110-06-3; 9, 132126-98-8; 10, 132126-99-9; 11, 132127-00-5; 12a, 132127-01-6; 12b, 82064-66-2; 13a, 132127-02-7; 13b, 82064-65-1; 14, 120090-21-3; 15, 110116-79-5.

Supplementary Material Available: Complete list of assigned signals in the ^1H NMR spectra recorded at 500 MHz of compounds 5–14 (6 pages). Ordering information is given on any current masthead page.

Substituted Oxazoles: Syntheses via Lithio Intermediates

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Reactions of 2-α-, 2-, 4-, and 5-lithiooxazoles are used to prepare various substituted derivatives. Previously unrecognized time dependence for the reaction of a 2-lithiooxazole with benzaldehyde is described, and a rationale for this behavior is offered. Competitive reactions occur when the readily available 2,5-diphenyloxazole is treated with *n*-butyllithium. Deprotonation of the ortho position of the 2-phenyl group and addition of *n*-butyl to the 2-position of the oxazole compete with the desired 4-lithiation. The use of *sec*-butyllithium/catalytic lithium tetramethylpiperidide allows preferential formation of 4-lithio-2,5-diphenyloxazole. This intermediate has been converted to the 4-bromo, -methyl, -hydroxybenzyl, -benzoyl, and -trialkylsilyl derivatives. Lithiation of 2,4-diphenyloxazole and subsequent trimethylsilylation occur readily at the 5-position. Deprotonation of 2-alkyloxazoles occurs at the α-carbon in preference to ring sites. Further reaction of an α-phenyl-2-oxazolemethanol methoxymethyl ether with base and acetyl chloride leads to an acyloin derivative. Chromic acid oxidation is used to prepare both 2- and 4-benzoyloxazoles. The formation of a 2-ethoxyoxazole from the 2-oxazolone vis Meerwein salt chemistry is described.

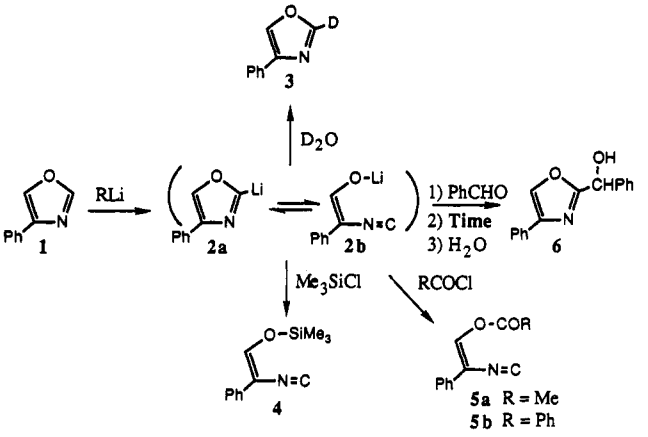
The reaction of oxazoles with benzyne provides a novel approach to the study of substituent effects on both Diels–Alder and (nonreverse) retro-Diels–Alder processes, in addition to affording a mild neutral method for the synthesis of isobenzofurans (IBFs).[1] The present paper describes the syntheses of several oxazoles needed for such studies, with emphases on new precedures and unusual findings.

Considerable effort has been devoted to the development of methods of synthesis of substituted oxazoles, but many specific examples remain difficult to prepare. Among several reviews of oxazole chemistry, that of Turchi is the most recent (1986), and it provides easy access to tabular information dealing with substituent patterns and related synthetic methods.[2]

We were especially interested in the use of metalated oxazoles to introduce substituents. The three C–H groups in oxazole itself differ considerably in acidity. It is generally believed that the 2-H is the most acidic, and a $pK_a = 20 \pm 2$ for this site has been suggested.[1b] This relatively high acidity prevents the use of base-induced methods for generating benzyne in the presence of these materials. Thus 4-phenyloxazole (1) (Scheme I) fails to give benzyne adduct when treated with PhCl/LTMP or with *o*-dibromobenzene/RLi. Instead, deprotonation occurs, as shown by quenching with D_2O to give the deuterated derivative **3**. The formation of **3** might be due to simple deuteration of the 2-lithiooxazole **2a**, but a more circuitous mechanism may be involved, analogous to the reaction with benzaldehyde discussed below.

A similar deprotonation problem arises in attempts to use LTMP induced benzyne methods with IBF ($pK_a \leq 33$) and even furan ($pK_a = 36$), but can be circumvented in these heterocycles by trimethylsilylation of the acidic sites. However, efforts to prepare 2-(trimethylsilyl)-4-phenyloxazole appear to result instead in the formation of the ring-opened isonitrile **4**; this material could not be isolated in pure form, but the structure is inferred from spectral evidence (^1H NMR 9:1 singlets at 0.22 and 6.95 ppm) and from the observation that very facile hydrolysis returns the starting oxazole. These attempts included mixing the intermediate organolithium species with Me_3SiCl at various temperatures, as well as treatment of a mixture of **1** and Me_3SiCl at −78 °C with LTMP. Distillation of crude **4** from a catalytic amount of KOH was also explored. This procedure has been reported[4] to yield the 2-$SiMe_3$ derivative from the analogous ring-opened *O*-$SiMe_3$ derivative

Scheme I



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0022-3263/91/1956-3058$02.50/0

Table I. Effect of Time Prior to Aqueous Quench on Yield of 6[a]

time, h	yield, %	time, h	yield, %
0.25	34	4.0	63
0.5	40	8.0	65
1.0	53	24.0	75
2.0	59		

[a] The yield was determined by NMR analysis of aliquots removed at the indicated times and then quenched by addition of water. Hexamethylbenzene was used as an internal standard; the amount of **6** was obtained by integration of the benzylic proton peak at 5.8 ppm. Unreacted **1** was the major residual component.

of 4-methyloxazole, but the method does not appear to be general and in our hands with **4** caused only decomposition or no change.

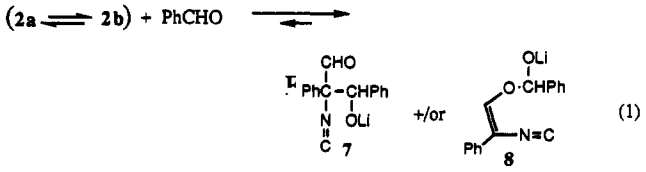
Ring-opened products were also formed when acid chlorides were used as electrophiles. Thus, treatment of the 2-lithiated species with acetyl chloride gave only ring-opened product **5a**; benzoyl chloride likewise gave **5b**.

The existence of facile ring–chain tautomerism of 2-lithiooxazoles was first proposed by Schoellkopf and coworkers for the 5-phenyl and 4,5-diphenyl derivatives.[5] Our results are entirely analogous to theirs with D_2O, Me_3SiCl, and AcCl as the quenching agents, i.e., exclusive isolation of deuterated oxazole with D_2O, and ring-opened products with the latter two electrophiles.

Although foiled in the use of Me_3Si as a protecting group, we were encouraged by Schoellkopf's observation that benzaldehyde afforded the "normal" ring-closed products analogous to **6**. Similar behavior has been reported for other oxazoles and aromatic aldehydes by Kozikowski and Ames,[6] and this reaction thus appears to have some generality. Carbinols may also serve as removable proton surrogates for substrates that form reasonably stable carbanions, as amply demonstrated by the work of Cram et al.[7] We therefore examined the reaction of the lithiated intermediate **2** with benzaldehyde and were disappointed to obtain only low yields of **6**, with major amounts of recovered **1**.

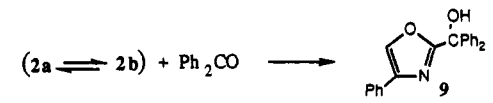
Curiously, the yield of **6** was significantly improved simply by allowing more time to pass between the addition of benzaldehyde and the aqueous acid quench. The best yields were obtained when this elapsed time was ca. 18–24 h (room temperature), as shown in Table I.

We believe that such a slow direct reaction between a formal carbanion and an aldehyde is unprecedented and that a more complex mechanism must be involved. This behavior can be rationalized by invoking a reversible reaction between **2b** and benzaldehyde to form either the aldol salt **7** or the hemiacetal salt **8** as shown in eq 1. This equilibrium must lie far to the right in order to diminish the availability of ring lithiated form **2a** (and benzaldehyde) needed to form **6**.



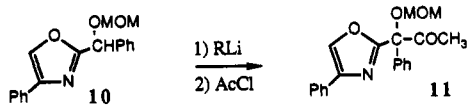
(1)

The delayed-quenching technique was also used to carry out the reaction of **2** with benzophenone, to give the tertiary carbinol **9** in good yield. Diphenylcarbinols are traditionally used in Haller–Bauer type cleavage reactions to generate carbanions.[7]



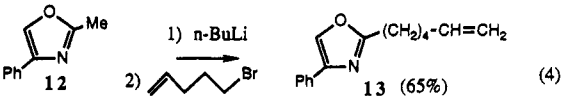
(2)

Tertiary derivatives such as **9** may in fact be needed for such cleavage processes in oxazoles, since the well-known acidity[8] of 2-α-methyl protons could interfere with these reactions. The sequence shown in eq 3 illustrates this point. The methoxymethyl (MOM) ether **10** was prepared from **6** by standard methods and was used to determine if deprotonation at the C-5 position of the protected oxazole could be effected. Instead, the 2-α-proton was removed, perhaps reflecting activation by the MOM group[9] in addition to the two aromatic rings. Treatment of the intermediate organometallic species with AcCl gave the novel acyloin derivative **11**. McGarvey and Kimura have previously commented on the enhanced nucleophilicity of α-alkoxyorganolithium reagents and reported similar acyloin derivative formation upon treatment with *N,N*-dimethylcarboxamides.[10]



(3)

Almost all 2-α-methyl anion reactions described in the literature have been carried out on trisubstituted oxazoles. An exception is the reaction of **12** with *n*-butyllithium followed by D_2O, which gave the 2-α-deuterio product.[8a] This suggests that the 2-α-proton is more acidic than the 5-proton in this substrate. In contrast, the 5-proton is preferentially removed when 2-methyloxazole-4-carboxylic acid is treated with base, as shown by reactions with several different electrophiles.[11] This outcome appears to be associated with enhanced reactivity of the 5-proton caused by the carboxylate group and does not reflect the normal oxazole acidity difference (2-α > 5). To test the generality of the earlier observation with **12**, we carried out the reaction shown in eq 4. The success of this alkylation with an unactivated bromide speaks to the nucleophilicity of this simple anion and provides a substrate for prospective intramolecular IBF cycloaddition.



(4)

Turning again to ring-lithiated materials, the possibility of forming aliphatic tertiary carbinol analogues of **9** from **2** was explored by treatment with acetone. Starting oxazole **1** was recovered in high yield. Repetition of this experiment with (excess) acetone-d_6 as the electrophile gave the 2-deuterated oxazole **3**, showing that protons α

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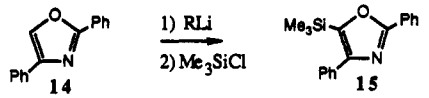
to a carbonl group are sufficiently acidic to transfer to 2, although this reaction may be driven by further condensation of the acetone enolate.

In contrast to the complex behavior of 2-lithiooxazoles, the acidity of the 5-position of oxazole is reflected in the straightforward lithiation/derivatization of the 2,4-diphenyl derivative 14. The 5-$SiMe_3$ product (15) was formed in good yield upon addition of Me_3SiCl.

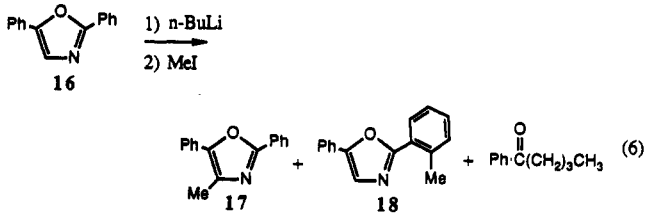


14 15 (5)

This outcome was anticipated on the basis of the work of Levin and Weinreb, who found that deprotonation of 2-phenyloxazole occurred exclusively at the 5-position.[12] The absence of 4-deprotonation in this monosubstituted example is particularly informative regarding the relative acidity, 5 > 4.

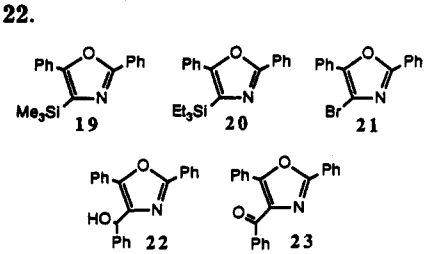
The 2,5-diphenyl derivative 16 is one of the few inexpensive commercially available oxazoles. The cycloaddition of 16 with benzyne is complicated by further reactions of the initially formed cycloadduct.[1b] Work in progress indicates that this problem is largely or completely avoided by the presence of any 4-substituent other than H. We were therefore especially interested in the use of 16 as a starting material for the preparation of a series of 4-substituted oxazoles.

The 4-deprotonation of 16 with *n*-butyllithium was complicated by two competing reactions, identified by product analysis after methylation with MeI. Ortho deprotonation of one of the phenyl groups occurs to some extent, as shown by the isolation of 4% of a monomethylated isomer. This was tentatively identified as the 2-*o*-tolyl derivative 18, based on parallels with oxazolidine ortho directing effect chemistry and ^1H NMR chemical shift features. Another side reaction leads to the formation, after addition of water, of valerophenone (12%); this product can be accounted for by addition of *n*-BuLi to the "imine" carbon of the oxazole ring to give an intermediate aminal, which is hydrolyzed to the ketone on workup.



16 17 18 (6)

The yield of the desired material (17 in this instance) was significantly improved by the use of *sec*-butyllithium and catalytic LTMP, and this base combination was subsequently employed for the preparation of silylated products 19 and 20, the 4-bromo derivative 21, and the carbinol 22.


19 20 21 22 23

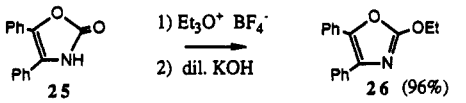
Formation of 4-lithio-2,5-diphenyloxazole has previously been accomplished by metal–halogen exchange of the bromide 21.[13] Interestingly, this 4-metallooxazole undergoes ring–chain tautomerism analogous to that exhibited by the 2-lithio derivatives, although more forcing conditions (70 °C, hexane/HMPA) are required for the 4-lithio example.[13b] Our results show that simpler acid/base reactions are suitable for 4-deprotonation and that the ring remains intact for coupling with a variety of electrophiles, in ethereal solvents at or below room temperature.

The 4-benzoyloxazole 23 was prepared from the 4-lithio intermediate by addition of the organometallic to excess benzoyl chloride. Interestingly, chromic acid (Jones) oxidation of 22 can also be used for the preparation of 23. We were encouraged by this observation to examine the Jones oxidation of 6, even though an earlier attempt to use Swern oxidation on this substrate had failed. Jones oxidation gave the 2-benzoyl derivative 24 as outlined in eq 7, in 79% yield. A search of the literature revealed one other example of sucessful chromic acid oxidation of an oxazole derivative. Rinehart et al. prepared a 2-acetyl derivative in 33% yield in this manner.[14]


6 24 (7)

This (limited) demonstration of the generality of chromic acid oxidation is potentially useful because 2-ketooxazoles have been relatively inaccessible. Recently Pridgen and Shilcrat reported direct aroylation via reaction of 2-lithio-5-phenyloxazole with *N*-methyl-*N*-(2-pyridinyl)carboxamides.[15] The only other 2-acyloxazole preparations in the literature involve the addition of Grignard reagents to rare 2-cyanooxazoles[16] and Dondoni's reaction of acid chlorides with the 2-$SiMe_3$ derivative of 4-methyloxazole, which as already noted lacks generality in preparation of the precursor.[4]

Alkoxy substituents suitably placed on the diene component have been useful in some instances to enhance Diels–Alder reactivity, and 2-alkoxyoxazoles are of interest from this perspective. The literature approach to these materials utilizes the reaction of 2-oxazolones with $POCl_3$, to form the 2-chlorooxazole.[17] Subsequent reaction with sodium alkoxide furnishes the 2-alkoxyoxazole, presumably by an addition/elimination mechanism. An alternative synthetic method is described here. Alkylation of the 2-oxazolone 25 with Meerwein's salt occurs readily, and exposure of the intermediate salt to dilute aqueous base leads to efficient formation of the 2-ethoxyoxazole 26.



25 26 (96%) (8)

This method has also been applied to the preparation of the previously unknown 2-ethoxy-4,5-dimethyloxazole (27). The overall yield from commercial acetoin is low, but the procedure can be carried out on a large scale and uses readily available materials.

The reactions described here provide access to a number of oxazoles that are either difficult to obtain or less effi-

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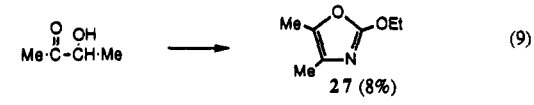

27 (8%) (9)

ciently prepared by other methods. These and several additional oxazoles prepared by traditional methods have been used in a study of cycloaddition with benzyne that will be reported shortly.

Experimental Section

^1H and ^{13}C NMR spectra were taken on $CDCl_3$ solutions at 500 and 125 MHz, respectively. MS data were obtained by Dr. Hugh Webb. Melting points were taken in open capillary tubes and are uncorrected. THF was distilled from Na benzophenone ketyl, and ether from $LiAlH_4$, immediately before use. DMF was distilled under vacuum from P_2O_5 and stored over 3A molecular sieves. Me_3SiCl was distilled from CaH_2 and stored over poly(2-vinylpyridine). Benzaldehyde was washed with saturated aqueous sodium carbonate and distilled under vacuum from CaH_2. Commercial alkyllithium reagents, standardized by periodic titration, were employed. All reactions were carried out under dry N_2.

The preparation of 4-phenyloxazole (1) has been described previously.[1b] The 2,5-diphenyloxazole (16) was purchased from the Aldrich Chemical Co. and used as received. The general method of Davidson et al.[18] was used to prepare 2,4-diphenyloxazole (14, 27%), mp 105–106.5 °C (lit.[19] mp 104–105 °C). The reaction of α-bromoacetophenone with acetamide, modeled after a procedure developed by Bredereck and Gompper,[20] was employed to obtain 2-methyl-4-phenyloxazole (12) in 69% yield: bp 100–104 °C (3 Torr); lit.[21] bp 97–99 °C (3 Torr); ^1H NMR δ 2.51 (s, 3 H), 7.29 (t, 1 H, J = 7.5 Hz), 7.38 (t, 2 H, J = 7.5 Hz), 7.70 (d, 2 H, J = 7.5 Hz), and 7.80 (s, 1 H).

2-Deuterio-4-phenyloxazole (3). This material was prepared by treatment of 1 with *n*-butyllithium, followed by addition of D_2O. It had ^1H NMR spectral features identical with those of 1 except for the integral of the singlet at ca. 8.0 ppm, which was halved. The 2- and 5-protons of 1 are distinguishable only with careful instrument tuning.

(*Z*)-2-Isocyano-*O*-acetyl-2-phenylethenol (5a). A flask containing 635 mg (4.38 mmol) of 4-phenyloxazole and 20 mL of THF was cooled in a dry ice bath, and *n*-butyllithium (4.8 mmol, 3.5 mL of a 1.4 M solution in hexane) was added dropwise by syringe, followed within minutes by similar addition of acetyl chloride (0.50 mL, 7.0 mmol). The bath was removed, and 20 mL of water was added. After thawing, the mixture was extracted with 3 × 25 mL of CH_2Cl_2. The combined organic phase was dried over K_2CO_3 and vacuum evaporated to give 773 mg (94%) of nearly pure **5a** as a pale yellow solid. Recrystallization from hexanes (−10 °C) gave 655 mg of material with mp 54–56 °C: ^1H NMR δ 2.33 (s, 3 H), 7.32–7.43 (m, 3 H), 7.51 (d, 2 H, J = 7.5 Hz), 7.98 (s, 1 H); ^{13}C NMR δ 20.48, 124.56, 128.94, 129.27, 129.28, 134.20, 166.42, 170.54; IR (neat) 3070 (w), 2950 (w), 2220 (w), 2075 (m), 1750 (s), 1470 (w), 1350 (m), 1260 (w), 1170 (s), 1125 (s), 990 (m), 890 (s) cm^{-1}; MS m/z (relative intensity) 187 (16), 146 (9), 145 (85), 117 (43), 91 (7), 90 (54), 89 (36), 63 (21), 62 (9), 43 (100); HRMS calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0627.

(*Z*)-2-Isocyano-*O*-benzoyl-2-phenylethenol (5b). The enol benzoate analogue was similarly prepared by substituting benzoyl chloride for acetyl chloride. This product (71% after recrystallization from ether/petroleum ether) had mp 115–116 °C: ^1H NMR δ 7.38–7.45 (m, 3 H), 7.52 (t, 2 H, J = 7.5 Hz), 7.57 (d, 2 H, J = 7.5 Hz), 7.67 (t, 1 H, J = 7.5 Hz), 8.22–8.25 (overlapping s and d, 3 H); ^{13}C NMR δ 124.57, 127.30, 128.81, 129.00, 129.22, 129.34, 130.42, 134.50, 161.88, 170.75; IR (KBr) 3095 (w), 2115 (m), 1735 (s), 1600 (w), 1445 (m), 1200 (s), 1100 (s), 1060 (s), 1020 (m); MS 249 (3), 145 (3), 106 (8), 105 (100), 77 (36), 51 (11); HRMS calcd for $C_{16}H_{11}NO_2$ 249.0790, found 249.0771.

α,4-Diphenyl-2-oxazolemethanol (6). A mixture of 4-phenyloxazole (1.45 g, 10.00 mmol), 2,2,6,6-tetramethylpiperidine (TMP, 0.169 mL, 1.00 mmol), and 20 mL of THF was cooled under N_2 in a dry ice/acetone bath. Dropwise addition of *sec*-butyllithium (9.23 mL of a 1.3 M solution in cyclohexane) over 15 min caused the colorless solution to turn orange. The dry ice bath was replaced after 0.5 h with an ice/water bath, and freshly distilled benzaldehyde (1.525 mL, 15.00 mmol) was added by syringe. In this experiment stirring was continued for 18 h before 40 mL of 5% HCl was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phase was washed with brine and then dried over Na_2SO_4. Vacuum evaporation of the solvent gave 2.58 g of an orange semisolid, which was chromatographed (silica gel, 70% petroleum ether, 30% CH_2Cl_2) to provide 1.89 g (75%) of 6 as a white solid; a sample recrystallized from methanol had mp 99.5–101 °C: ^1H NMR δ 3.27 (d, 1 H, J = 5 Hz), 5.93 (d, 1 H, J = 5 Hz), 7.31–7.36 (m, 2 H), 7.38–7.42 (m, 4 H), 7.50 (d, 2 H, J = 7.5 Hz), 7.74 (d, 2 H, J = 7.5 Hz), 7.87 (s, 1 H); ^{13}C NMR δ 70.04, 125.55, 126.66, 128.19, 128.52, 128.63, 128.70, 130.46, 134.06, 139.10, 140.53, 164.83; IR (KBr) 3220 (br, OH), 3040 (w), 2920 (w), 1585 (m), 1500 (m), 1460 (m), 1420 (m), 1340 (m), 1300 (w), 1280 (m), 1255 (s), 1200 (m), 1130 (s), 1100 (s), 1080 (s), 1040 (m), 995 (m), cm^{-1}; MS 252 (5.4), 251 (M, 30), 146 (11), 145 (100), 117 (34), 107 (27), 90 (26), 89 (17), 79 (37), 63 (9), 51 (12); HRMS calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0934.

α,α,4-Triphenyl-2-oxazolemethanol (9). When procedures were carried out as described for the preparation of 6 but with benzophenone, 9 was obtained in 71% yield. An improved yield was obtained with the following variation. A mixture of 1 (1.451 g, 10.0 mmol) and tetramethylpiperidine (0.169 mL, 1.0 mmol) in 20 mL of THF was cooled in a dry ice bath, and *sec*-butyllithium (12.0 mmol, 9.23 mL of a 1.30 M solution) was added by syringe over a period of 15 min. After the dark red mixture was stirred for an additional 15 min, solid benzophenone (2.722 g, 15.0 mmol) was added in one portion. The benzophenone dissolved slowly, as the solution turned from red to green and eventually orange. Stirring was continued for 6 h at 0 °C and then for 10 h at room temperature. Aqueous HCl (5%, 40 mL) was added, and the resulting mixture was extracted with three 50-mL portions of CH_2Cl_2. Workup as above gave 4.4 g of crude product, which by NMR analysis included benzophenone. Column chromatography (silical gel, 40% CH_2Cl_2 in petroleum ether) gave 3.159 g (96%) of essentially pure 9 as a white solid. Recrystallization from methanol gave material with mp 129–130 °C: ^1H NMR δ 4.41 (s, 1 H), 7.31–7.41 (m, 13 H), 7.75 (d, 2 H, J = 7.5 Hz), 7.92 (s, 1 H); ^{13}C NMR δ 78.19, 125.57, 127.18, 128.00, 128.09, 128.26, 128.68, 130.38, 134.42, 140.40, 143.27, 166.83; IR (KBr) 3110 (br), 3080 (w), 1600 (w), 1560 (m), 1490 (m), 1450 (m), 1350 (s), 1280 (m), 1180 (m), 1120 (s), 1100 (m), 1070 (s), 1040 (m), 1010 (w), 990 (m), 955 (m), 915 (m), 895 (m) cm^{-1}; HRMS calcd for $C_{22}H_{17}NO_2$ 327.1259, found 327.1254.

MOM Ether 10. NaH (0.16 g of a 60% dispersion in mineral oil) was washed with hexanes; 15 mL of THF was added, followed by 0.505 g (2.01 mmol) of 6 in 5 mL of THF. After 0.5 h, chloromethyl methyl ether (0.33 mL, 4.4 mmol) was added to the ice-cooled mixture, and stirring was continued for 2 h. Water was then added, and the organic material was extracted into CH_2Cl_2. The usual workup and chromatography gave 0.502 g (84%) of a colorless solid, mp 73.5–75 °C: ^1H NMR δ 3.40 (s, 3 H), 4.78 (AB q, 2 H, J_{app} = 6.5 Hz), 5.92 (s, 1 H), 7.28 (t, 1 H, J = 7 Hz), 7.3–7.4 (m, 5 H), 7.55 (d, 2 H, J = 7 Hz), 7.73 (d, 2 H, J = 7 Hz), 7.85 (s, 1 H); ^{13}C NMR δ 55.83, 72.79, 94.52, 125.57, 127.35, 128.04, 128.58, 130.71, 133.99, 136.90, 140.81, 162.67; IR (KBr) 3065 (w), 2950 (m), 2900 (m), 1570 (m), 1450 (m), 1155 (s), 1100 (s), 1040 (s), 940 (s), 920 (s) cm^{-1}; MS 295 (6), 235 (8), 234 (7), 189 (11), 159 (18), 151 (13), 77 (13), 45 (100); HRMS calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1222.

Acetoin Derivative 11. A sample of 10 (389 mg, 1.32 mmol) in 10 mL of THF at −78 °C was treated with 1.5 mmol of *n*-BuLi. After 15 min, MeCOCl (140 μL, 2.0 mmol) was added, the bath was replaced by ice water, and stirring was continued for 0.5 h. The usual workup gave 473 mg of yellow orange viscous oil, which by NMR analysis consisted of starting material 10 and product 11, with the latter present in ca. 30% yield. Compounds 10 and 11 were difficult to separate, but a sample of nearly pure 11 was

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obtained by chromatography (silica gel, 15% ether in petroleum ether), as a colorless viscous liquid: ^{1}H NMR δ 2.33 (s, 3 H), 3.28 (s, 3 H), 4.88 (AB q, 2 H, J_{appar} = 7 Hz), 7.31 (t, 1 H, J = 7 Hz), 7.40 (m, 5 H), 7.62 (d, 2 H, J = 7 Hz), 7.76 (d, 2 H, J = 7 Hz), 7.97 (s, 1 H); ^{13}C NMR δ 25.94, 56.11, 85.93, 93.63, 125.65, 127.61, 128.18, 128.46, 128.66, 128.89, 130.60, 134.33, 135.61, 141.04, 160.86; IR (film) 3060 (w), 2955 (w), 1730 (s), 1450 (m), 1265 (s), 1160 (m), 1030 cm^{-1}; MS 295 (7), 294 (16), 264 (10), 250 (24), 105 (31), 77 (25), 45 (100), 43 (12); HRMS(CI) calcd for (P + H) $C_{20}H_{20}NO_4$ 338.1393, found 338.1371.

2-(5-Hexenyl)-4-phenyloxazole (13). A solution of **12** (318 mg, 2.00 mmol) in 20 mL of THF was treated at −78 °C with *n*-BuLi (2.40 mmol), to give an orange-red mixture. After an additional 5 min, 5-bromo-1-pentene (1.42 mL, 12.0 mmol) was added, the cooling bath was replaced by ice water, and the mixture was stirred while coming to ambient temperature overnight. Aqueous HCl (5%, 20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was washed with brine, dried over K_2CO_3, and vacuum evaporated to give an orange oil, which was chromatographed (5% ether in petroleum ether) to give 279 mg (61%) of **13** as a colorless oil: ^{1}H NMR δ 1.51 (p, 2 H, J = 7 Hz), 1.83 (p, 2 H, J = 7 Hz), 2.11 (q, 2 H, J = 7 Hz), 2.83 (t, 2 H, J = 7 Hz), 4.96 (dd, 1 H, J = 10, 1 Hz), 5.02 (dd, 1 H, J = 17, 1 Hz), 5.81 (ddt, 1 H, J = 17, 10, 7 Hz), 7.29 (t, 1 H, J = 7.5 Hz), 7.39 (t, 2 H, J = 7.5 Hz), 7.71 (d, 2 H, J = 7.5 Hz), 7.81 (s, 1 H); ^{13}C NMR δ 26.55, 28.10, 28.31, 33.28, 114.70, 125.41, 127.79, 128.64, 131.23, 132.93, 138.35, 140.47, 165.20; IR (neat) 3090 (m), 2940 (s), 2870 (m), 1685 (s), 1640 (w), 1455 (s), 1120 (s), 1085 (s), 1005 (m), 955 (s), 925 (s) cm^{-1}; MS 227 (38), 226 (35), 199 (19), 198 (56), 173 (38), 172 (100), 159 (74), 130 (29), 119 (12), 105 (10), 104 (74), 103 (20), 95 (44), 91 (24), 90 (64), 89 (82), 77 (36), 67 (30), 64 (15), 63 (35), 62 (11), 55 (29), 54 (20), 53 (19), 51 (20); HRMS calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1327.

5-(Trimethylsilyl)-2,4-diphenyloxazole (15). A dry ice cooled mixture of **14** (1.106 g, 5.00 mmol) and tetramethylpiperidine (0.084 mL, 0.50 mmol) in 20 mL of THF was treated with *sec*-BuLi (5.50 mmol) over a period of 15 min. The dark red solution was transferred to an ice bath, and Me_3SiCl (0.76 mL, 6.0 mmol) was added. After 1 h the contents were poured into a separatory funnel containing 100 mL of 5% HCl. The usual extraction, drying, and evaporation gave 1.51 g of a pale yellow oil, which was chromatographed on silica gel with 5% ether in petroleum ether to give 1.29 g (88%) of **15** as a colorless solid, mp 58–61 °C: ^{1}H NMR δ 0.35 (s, 9 H), 7.35 (t, 1 H, J = 7.5 Hz), 7.40–7.48 (m, 5 H), 7.67 (d, 2 H, J = 7.5 Hz), 8.13 (d, 2 H, J = 7.5 Hz); ^{13}C NMR δ −1.07, 126.26, 127.73, 128.06, 128.22, 128.62, 130.16, 133.10, 149.78, 151.28, 164.15 ppm; IR (KBr) 3040 (w), 2970 (m), 2890 (w), 1550 (m), 1482 (m), 1450 (m), 1340 (m), 1260 (s), 985 (m), 850 (s) cm^{-1}; MS(CI) 294 (P + H, 65), (100), 278 (31), 175 (22), 73 (11), 69 (18); HRMS calcd for $C_{18}H_{19}NOSi$ 293.1236, found 293.1207.

4-Methyl-2,5-diphenyloxazole (17). Commercial 2,5-diphenyloxazole (**16**) (2.21 g, 10.0 mmol) was placed in a flask containing tetramethylpiperidine (0.17 mL, 1.0 mmol) and 40 mL of THF. The dry ice cooled mixture was treated with *sec*-BuLi (11.0 mmol) with an addition time of 0.5 h, to give an intensely red-black colored solution. The bath was replaced by ice water, and CH_3I (0.72 mL, 11.5 mmol) was added via syringe, causing the mixture to turn to a clear orange color. After 1 h, the ice bath was removed and the mixture was quenched by the addition of 5% HCl. Extraction with ether (3 × 50 mL) and the usual drying and rotary evaporation gave 2.49 g of an orange solid. Chromatography (silica gel, 15% ether in petroleum ether, R_f = 0.26) afforded 1.94 g (85%) of the known colorless solid **17**. A sample recrystallized from methanol had mp 76–78 °C (lit.[22] mp 82 °C): ^{1}H NMR δ 2.50 (s, 3 H), 7.32 (t, 1 H, J = 7.5 Hz), 7.42–7.48 (m, 5 H), 7.68 (d, 2 H, J = 7.5 Hz), 8.08 (d, 2 H, J = 7.5 Hz).

5-Phenyl-2-*o*-tolyloxazole (18). An attempt to prepare **17** by using *n*-BuLi alone as the base led to the isolation of a small amount of a side product identified as **18** on the basis of NMR characteristics: ^{1}H NMR δ 2.76 (s, 3 H), 7.30–7.37 (m 4 H), 7.45 (t, 2 H, J = 7.5 Hz), 7.48 (s, 1 H), 7.72 (d, 2 H, J = 7.5 Hz), 8.09 (d, 1 H, J = 7.5 Hz); MS(CI) 237 (13), 236 (81), 235 (P, 100), 163 (26), 130 (11), 120 (11), 105 (32), 97 (11), 83 (11), 77 (13), 71 (12), 69 (15).

4-(Trimethylsilyl)-2,5-diphenyloxazole (19). The general conditions used to prepare **17** were employed, with Me_3SiCl used as the electrophile. The product (83%) was isolated by chromatography (silica gel, petroleum ether) as a colorless solid, mp 81.5–82.5 °C: ^{1}H NMR δ 0.35 (s, 9 H), 7.37–7.47 (m, 6 H), 7.66 (d, 2 H, J = 7.5 Hz), 8.11 (d, 2 H, J = Hz); ^{13}C NMR δ −0.77, 126.45, 127.39, 127.73, 128.38, 128.60, 129.70, 129.91, 135.59, 157.02, 161.08; IR (KBr) 3080 (w), 2962 (w), 1546 (m), 1488 (s), 1451 (m), 1252 (s), 1095 (m), 1079 (m), 1038 (m), 860 (s) cm^{-1}; MS 294 (23), 293 (P, 90), 292 (16), 279 (25), 278 (100), 204 (33), 178 (21), 135 (16), 105 (56), 77 (52), 73 (16), 51 (12), 45 (11), 43 (17); HRMS calcd for $C_{18}H_{19}NOSi$ 293.1236, found 293.1245.

4-(Triethylsilyl)-2,5-diphenyloxazole (20). A similar reaction with Et_3SiCl gave **20** as a pale yellow oil, in 71% yield: ^{1}H NMR δ 0.86 (q, 6 H, J = 7 Hz), 0.96 (t, 9 H, J = 7 Hz), 7.37–7.47 (m, 6 H), 7.64 (d, 2 H, J = 7 Hz), 8.11 (d, 2 H, J = Hz); ^{13}C NMR δ 3.79, 7.47, 126.47, 127.49, 127.90. 128.36, 128.61, 128.67, 129.83, 130.00, 133.49, 157.67, 161.19; IR (neat) 3065 (w), 2965 (s), 2895 (s), 1550 (m), 1485 (m), 1075 (m), 1020 (m) cm^{-1}; MS 336 (9), 336 (P, 31), 308 (12), 307 (46), 306 (100), 278 (22), 204 (41), 105 (48); HRMS calcd for $C_{21}H_{25}NOSi$ 335.1705, found 335.1731.

4-Bromo-2,5-diphenyloxazole (21). Bromine was added dropwise to the lithiated intermediate prepared as described above. Purification was effected by silica gel chromatography (10% ether in petroleum ether), to give 58% of the known compound **21**, mp 70.5 °C (lit.[13b] mp 70–72 °C): ^{1}H NMR δ 7.39 (t, 1 H, J = 7.5 Hz), 7.46–7.50 (m, 5 H), 8.00 (d, 2 H, J = 7.5 Hz), 8.07–8.10 (m, 2 H); MS 302 (63), 301 (100), 300 (65), 299 (94), 192 (20), 165 (10), 105 (20).

α,2,5-Triphenyl-4-oxazolemethanol (22). Benzaldehyde (1.5 equiv) was used as the electrophile, with the 4-lithio intermediate prepared as above. One hour after addition of PhCHO, 5% HCl was added. The usual workup gave a nearly colorless solid, which was recrystallized from methanol (two crops) to give 94% of fluffy colorless crystals, mp 154–155 °C: ^{1}H NMR δ 3.31 (d, 1 H, J = Hz), 6.06 (d, 1 H, J = 7 Hz), 7.30 (t, 1 H, J = 7.5 Hz), 7.36 (t, 2 H, J = 7.5 Hz), 7.42–7.49 (m, 5 H), 7.54 (d, 2 H, J = 7.5 Hz), 7.63 (d, 2 H, J = 7.5 Hz), 8.10–8.13 (m, 2 H); ^{13}C NMR δ 68.72, 126.21, 126.48, 126.92, 127.07, 127.82, 127.98, 128.54, 128.74, 128.84, 130.51, 138.04, 141.95, 146.18, 160.24; IR (KBr) 3280, (br, OH), 3060 (w), 2940 (w), 2840 (w), 1590 (m), 1545 (m), 1485 (s), 1450 (s), 1190 (m), 1045 (s), 1010 (m), 1000 (m) cm^1; MS(CI) 328 (22), 327 (P, 63), 326 (12), 313 (16), 312 (69), 311 (76), 310 (100), 250 (15), 222 (13), 105 (76), 91 (17), 79 (12), 77 (27), 51 (10), 43 (29), 42 (13); HRMS calcd for $C_{22}H_{17}NO_2$ 327.1259, found 327.1272.

4-Benzoyl-2,5-diphenyloxazole (23). Method A. A solution of 4-lithio-2,5-diphenyloxazole was prepared as described above (10 mmol in 15 mL of THF, −78 °C) and cannulated into a dry ice cooled solution of benzoyl chloride (25 mmol) in 25 mL of THF. The mixture was stirred and allowed to warm to room temperature (2.5 h) and then treated with 50 mL of 1 M NaOH; stirring was continued overnight. The product was extracted into CH_2Cl_2. The usual workup gave 4.1 g of a viscous yellow orange oil, which was chromatographed (10% ether in petroleum ether) to give 2.37 g (73%) of **23**. After recrystallization from methanol, it had mp 89–90 °C (lit.[23] mp 90 °C): ^{1}H NMR δ 7.41–7.52 (m, 8 H), 7.58 (t, 1 H, J = 7.5 Hz), 8.06 (d, 2 H, J = 7.5 Hz), 8.14–8.16 (m, 2 H), 8.18 (d, 2 H, J = 7.5 Hz); ^{13}C NMR δ 126.57, 126.66, 127.30, 127.77, 128.12, 128.49, 128.80, 129.04, 129.51, 130.14, 130.51, 130.89, 132.98, 137.34, 154.48, 158.88, 188.63; MS 326 (16), 325 (P, 70), 324 (49), 296 (9), 165 (10), 105 (88), 77 (100), 54 (24).

Method B. A solution of **22** (491 mg, 1.50 mmol) in 15 mL of acetone was treated dropwise with Jones reagent until the orange color persisted. The organic layer was decanted from the chromium precipitates, added to $NaHCO_3$ solution, and extracted with CH_2Cl_2. Chromatography of the oily crude product gave 417 mg (87%) of **23**, with spectral properties identical with those described above.

2-Benzoyl-4-phenyloxazole (24). Jones oxidation of **6** (1.28 g, 5.11 mmol) in 25 mL of acetone gave, after chromatography

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(10% ether in petroleum ether), 1.01 g (79%) of **24** as a colorless solid, mp 126.5–128 °C: ^{1}H NMR δ 7.38 (t, 1 H, J = 7.5 Hz), 7.46 (t, 2 H, J = 7.5 Hz), 7.55 (t, 2 H, J = 7.5 Hz), 7.67 (t, 1 H, J = 7.5 Hz), 7.84 (d, 2 H, J = 7.5 Hz), 8.15 (s, 1 H), 8.59 (d, 2 H, J = 7.5 Hz); ^{13}C NMR δ 125.84, 128.48, 128.84, 128.90, 129.93, 131.03, 134.02, 134.96, 136.22, 142.70, 157.55, 178.70; IR (KBr) 3140 (w), 1660 (s), 1600 (m), 1520 (m), 1480 (s), 1450 (m), 1350 (s), 1280 (s), 1170 (s), 1130 (s), 970 (m), 940 (m), 910 (s) cm^{-1}; MS 250 (3), 249 (P, 18), 105 (100), 77 (42), 51 (13); HRMS calcd for $C_{16}H_{11}NO_2$ 249.0790, found 249.0765.

2-Ethoxy-4,5-diphenyloxazole (26). The method of Dziomko and Ivashchenko[24] was used to convert benzoin to 4,5-diphenyl-2(3*H*)-oxazolone (**25**), in 52% yield, mp 208–210 °C (lit.[17] mp 211 °C): ^{1}H NMR δ 7.29–7.34 (m, 3 H), 7.40–7.45 (m, 3 H), 7.50–7.53 (m, 4 H), 10.16 (s, 1 H).

A slurry of **25** (2.235 g, 9.42 mmol) in 15 mL of CH_2Cl_2 was treated with triethyloxonium tetrafluoroborate (3.58 g, 18.8 mmol) in 10 mL of CH_2Cl_2, and the mixture was stirred overnight, effecting conversion to a clear pale yellow solution. The pH was brought to ca. 9 by dropwise addition of 3 M KOH (ca. 14 mL), with stirring continued for an additional 15 min. This mixture was added to 100 mL of water and extracted with CH_2Cl_2 (3 × 50 mL). Washed with brine, dried over K_2CO_3, and evaporated, the crude product was obtained as a yellow oil (2.52 g). Silica gel chromatography (10% ether in petroleum ether, R_f = 0.23) returned 2.43 g (97%) of **26** as a colorless solid, mp 61–62.5 °C (lit.[17] mp 64–66 °C): ^{1}H NMR δ 1.48 (t, 3 H, J = 7 Hz), 4.54 (q, 2 H, J = 7 Hz), 7.25 (t, 1 H, J = 7.5 Hz), 7.31 (t, 3 H, J = 7.5 Hz), 7.36 (t, 2 H, J = 7.5 Hz), 7.52 (d, 2 H, J = 7.5 Hz), 7.63 (d, 2 H, J = 7.5 Hz).

2-Ethoxy-4,5-dimethyloxazole (27). Following the general procedure from the literature,[24] we heated a mixture of commercial acetoin (4.41 g, 50 mmol), KOCN (4.46 g, 55 mmol), and DMF (15 mL) to 120 °C, at which point a solution of concd HCL (6 mL) in DMF (10 mL) was slowly added. The internal temperature was increased to 135 °C, and this was maintained for 2 h. After brief cooling, the mixture was poured into water, extracted with CH_2Cl_2 (4 × 40 mL), and worked up in the usual manner. The residue in CH_2Cl_2 was passed through a short plug of silica gel to give 4.1 g of a light brown solid. This was taken up in CH_2Cl_2 and treated with triethyloxonium tetrafluoroborate followed by base as described above. The brown oil that resulted was chromatographed (20% ether in petroleum ether) to give 569 mg (8% based on acetoin) of this unknown oxazole as a colorless liquid: ^{1}H NMR δ 1.40 (t, 3 H, J = 7 Hz), 1.98 (s, 3 H), 2.12 (s, 3 H), 4.36 (q, 2 H, J = 7 Hz); ^{13}C NMR δ 9.36, 11.08, 14.13, 66.36, 128.59, 137.04, 159.62; IR (neat) 2995 (m), 2945 (m), 1600 (s), 1445 (m), 1380 (s), 1350 (s), 1320 (m), 1240 (s), 1140 (m), 1075 (m), 1030 (m) cm^{-1}; MS 142 (6), 141 (64), 114 (8), 113 (100), 112 (29), 84 (16), 69 (11), 43 (57); HRMS calcd for $C_7H_{11}NO_2$ 141.0790, found 141.0768.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **5a,b**, **6**, **9–11**, **13**, **15**, **19**, **20**, **22**, **24**, and **27** (26 pages). Ordering information is given on any current masthead page.

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Electroorganic Chemistry. 129. Electroreductive Synthesis of Chiral Piperazines and Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of the Chiral Piperazines

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Electroreduction of diimines, prepared from 1,2-diamines and aromatic aldehydes, in acidic media gave intramolecularly coupled products, 2,3-diarylpiperazines, stereoselectively. Chiral tri- and tetrasubstituted piperazines were synthesized effectively from chiral 1,2-diamines by the same electroreductive method. Chiral piperazines, prepared from 1(*R*),2(*R*)-diaminocyclohexane were effective chiral ligands of catalysts for the enantioselective addition of diethylzinc to aldehydes.

Chiral 1,2-diamines have been known to be effective ligands of catalysts for enantioselective synthesis of some chiral compounds.[1] The methods of synthesis of chiral 1,2-diamines were, however, rather limited. Reductive intermolecular coupling of imines promoted by metal reducing agents has been reported as one of the methods,[2] though complete stereoselectivity was not always achievable.

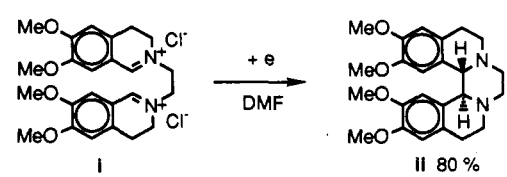
On the other hand, chiral piperazines also seem to be effective chiral ligands. The electroreduction of *N,N'*-dibenzylideneethylenediamine leading to the formation of *trans*-2,3-diphenylpiperazine **1** (R^1 = R^2 = H, 42% yield),[3,4]

(1) For recent studies on the enantioselective synthesis using chiral 1,2-diamine derivatives see: (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *Ibid.* **1989**, *111*, 5493. (c) Corey, E. J.; Yu, C.-M.; Kim, S. S. *Ibid.* **1989**, *111*, 5495. (d) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *Ibid.* **1990**, *112*, 878.

(2) (a) Smith, J. G. *Can. J. Chem.* **1966**, *44*, 59. (b) Smith, J. G.; Veach, C. D. *Ibid.* **1966**, *44*, 2497. (c) Smith, J. G.; Ho, I. J. *J. Org. Chem.* **1972**, *37*, 653. (d) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152. (e) Mangeneg, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. (f) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999.

(3) Koch, R. W.; Dessy, R. E. *J. Org. Chem.* **1982**, *47*, 4452.

(4) We have also found that the electroreduction of diisiquinolinium salt **i** gave the corresponding coupled product **ii** stereoselectively.[5]



I **II** 80 %

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