molybdate adds to the C-2 carbonyl of the ester and then displaces the ethanol leaving group resulting in a labile cyclic acyl molybdate ester. The rapid first-order production of pyruvate (no detectable lag in the presence of 0.45 M MoO_4^{2-}, k_{obs} = 0.12 min^{-1}) indicates that the half-life of this acyl molybdate intermediate must be <6 s. This can be compared to an estimate of $t_{1/2} < 0.5$ s for the hydrolysis of the 1-molybdo-3-phosphoglycerate at pH 7.3.[14]

The results presented here show that molybdate is an effective nucleophilic catalyst for the hydrolysis of a variety of substrates.

Acknowledgment. We thank Dr. Harry Ensley for obtaining the NMR spectra.

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Homolytic Substitution Reactions of Electron-Rich Pentatomic Heteroaromatics by Electrophilic Carbon-Centered Radicals. Synthesis of α-Heteroarylacetic Acids

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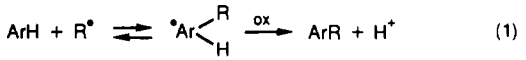
Efficient and selective homolytic substitutions (yields between 55 and 90%) of pyrrole, indole, and some pyrrole derivatives have been carried out using ambiphilic and electrophilic carbon centered radicals, generated in DMSO by Fe^{2+}/H_2O_2 and α-cyano-, α-carbonyl-, and α,α'-dicarbonylalkyl iodides. The reaction is highly successful also with pyrroles substituted by electron-withdrawing groups, which has allowed an efficient synthesis of Tolmetin. A few extensions of this reaction to furan and thiophene are described.

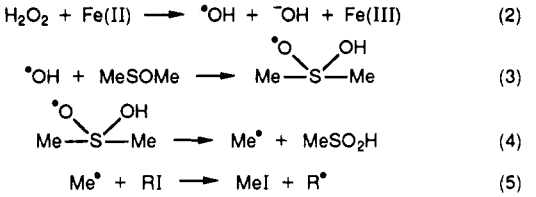
The last decade has witnessed an exceptional development of the synthetic aspects of free radical chemistry. However, as far as we know, few applications of this chemistry to the synthesis of pyrrole derivatives have been carried out.[1]

Recent studies have shown that efficient homolytic substitution of aromatic and electron-rich heteroaromatic substrates can be accomplished using electrophilic carbon-centered radicals generated by oxidation of 1,3-dicarbonyl compounds with cerium(IV) or manganese(III) salts.[2] The exploitation of these reactions for the synthesis of pyrrole derivatives would seem straightforward since pyrrole is an electron-rich heteroaromatic compound; however, all attempts in this direction have so far failed since pyrrole itself is preferentially oxidized under the reaction conditions.[3] On the other hand, when electrophilic carbon-centered radicals are formed under reductive conditions (i.e. by the atom-transfer method), no homolytic aromatic substitution has been observed,[4] presumably because there is no possibility that the intermediate σ radical is oxidized to products (eq 1).



$$ArH + R^{\bullet} \rightleftharpoons {}^{\bullet}Ar\begin{matrix}R\\H\end{matrix} \xrightarrow{ox} ArR + H^{+} \qquad (1)$$

We wish now to report that the homolytic substitutions of pyrrole and indole and some pyrrole derivatives by both ambiphilic[5] and electrophilic carbon-centered radicals is a highly efficient and selective process, if the radicals are generated by the corresponding alkyl iodides, H_2O_2, and catalytic Fe^{2+} in DMSO[6] (eqs 2–5).



$$H_2O_2 + Fe(II) \longrightarrow {}^{\bullet}OH + {}^{-}OH + Fe(III) \qquad (2)$$

$$^{\bullet}OH + MeSOMe \longrightarrow Me{-}S(O^{\bullet})(OH){-}Me \qquad (3)$$

$$Me{-}S(O^{\bullet})(OH){-}Me \longrightarrow Me^{\bullet} + MeSO_2H \qquad (4)$$

$$Me^{\bullet} + RI \longrightarrow MeI + R^{\bullet} \qquad (5)$$

As alkyl iodides we have used $ICH(CH_3)CO_2Et$, ICH_2CO_2Me, ICH_2CO_2Et, ICH_2CN, $IC(CH_3)(CO_2Et)_2$, and $ICH(CO_2Me)_2$ which provide the radicals $^{\bullet}CH(CH_3)CO_2Et$, $^{\bullet}CH_2CO_2Me$, $^{\bullet}CH_2CO_2Et$, $^{\bullet}CH_2CN$, $CH_3C^{\bullet}(CO_2Et)_2$, and $^{\bullet}CH(CO_2Me)_2$, respectively, whose properties from ambiphilic or borderline to clearly electrophilic should increase in the same order. Some experiments carried out using furan and thiophene as the substrates are also described.

Results and Discussion

Reactions were carried out, at room temperature, in DMSO by adding 35% H_2O_2 to a solution of substrate, alkyl iodide, and $FeSO_4{\cdot}7H_2O$. The substrate was in large excess with respect to both alkyl iodide and $FeSO_4{\cdot}7H_2O$ (at least 15:1 and 75:1, respectively) whereas the substrate:H_2O_2 molar ratio was 1.5–4. These conditions turned out to be the most suitable for obtaining only monosub-

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(2) (a) Baciocchi, E.; Dell'Aira, D.; Ruzziconi, R. *Tetrahedron Lett.* **1986**, 2763. Baciocchi, E.; Ruzziconi, R. In *Free Radicals in Synthesis and Biology*; Minisci, F.; Ed.; NATO ASI Series; Kluwer Academic Publisher: Dordrecht, 1989; Chapter 14. (b) Santi, R.; Tiziana, F.; Citterio, A.; Strologo, S. *J. Org. Chem.* **1989**, *54*, 2703.

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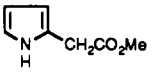
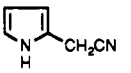
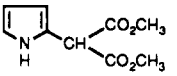
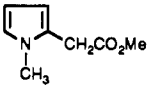
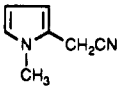
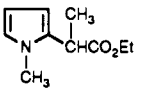
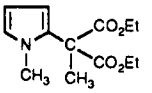
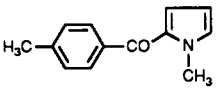
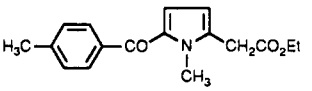
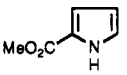
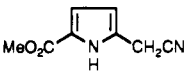
Table I. Homolytic Substitution of Pyrrole Derivatives by α-Carbonyl-, α,α'-Dicarbonyl- and α-Cyanoalkyl Iodides Promoted by H_2O_2 and Fe^{2+} in DMSO

entry	substrate	radical source	product	yield (%)[a]
1		ICH_2CO_2Me		59
2		ICH_2CN		73
3		$ICH(CO_2Me)_2$		55
4		ICH_2CO_2Me		87
5		ICH_2CN		88
6		$ICH(CH_3)CO_2Et$		55
7		$IC(CH_3)(CO_2Et)_2$		89
8		ICH_2CO_2Et		90
9		ICH_2CN		74[b]

[a] Yield of isolated product with respect to the alkyl iodide. [b] 9% of 3-(methoxycarbonyl)-2-pyrroleacetonitrile was also isolated.

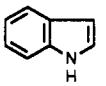
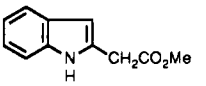
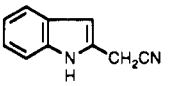
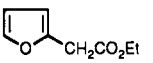
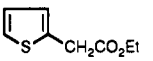
stitution products. With less substrate or a larger amount of alkyl iodide, formation of disubstituted products (α,α') was observed. After 15–40 min the reaction mixture was worked up as usual and the structure of the products established on the basis of spectral (^1H NMR, GC–MS) and elemental analysis (details in the Experimental Section).

The results, which are displayed in Tables I (pyrroles) and II (indole, furan, and thiophene), clearly show that the method is highly efficient. The yields of the substituted products range from 55 to 90%. Probably, the success of these reactions is due to the relatively mild conditions used and to the fact that Fe^{3+}, produced in (eq 2), is a weak oxidant and can oxidize the σ-radical to the substituted product (eq 1), without significantly affecting the substrate.

No trend in the yields is observed, which can reasonably be attributed to differences in the degree of the electrophilic character of the radical. As a matter of fact, the product yield is significantly smaller in the reaction of pyrrole with malonyl radical (entry 3, Table I) than with cyanomethyl radical (entry 2, Table I), in spite of the fact that the former radical should be more electrophilic than the second. Probably, other factors play a role in this respect, i.e. the reversibility of the free radical attack which should be more important with the more stable malonyl radical. Interestingly, since pyrrole is a very electron rich compound, good yields are also observed when an electron-withdrawing substituent is present (entries 8 and 9, Table I). The procedure is suitable as well for the functionalization of furan and thiophene, as clearly shown by the entries 3 and 4 in Table II. Oxidative malonylation of these two compounds has already been described,[2a] but under conditions which are unsuitable for the alkoxycarbonylmethylation reactions reported here.

With pyrrole and *N*-methylpyrrole, as well as with 2-(*p*-methylbenzoyl)-*N*-methylpyrrole, furan, and thiophene, exclusive substitution at the α-position was observed.

Table II. Homolytic Substitution of Pentatomic Heteroaromatic Derivatives by α-Carbonyl- and α-Cyanoalkyl Iodides Promoted by H_2O_2 and Fe^{2+} in DMSO

entry	substrate	radical source	product	yield (%)[a]
1		ICH_2CO_2Me		66[b,c]
2		ICH_2CN		60[b,d]
3		ICH_2CO_2Et		65
4		ICH_2CO_2Et		62

[a] Yield of isolated product with respect to the alkyl iodide. [b] Determined by NMR. [c] Also the β-substituted isomer was formed in a 6% yield (GC–MS analysis). [d] Also the β-substituted isomer was formed in a 10% yield (GC–MS analysis).

Some attack at the β-position was detected for the reaction of indole and methyl 2-pyrrolecarboxylate. Attempts to change the direction of the attack in pyrrole by the use of the bulky triisopropylsilyl group as N-substituent have been unsuccessful so far.

Very low yields of product (10% or less) have been obtained in the reaction of *N*-(triisopropylsilyl)pyrrole with $\cdot CH_2CO_2Me$ (not reported in Table I; see Experimental Section), but the orientation remains unchanged. In this respect, electrophilic C-centered radicals behave quite differently than electrophilic ionic reagents, which instead attack the 3-position of 1-(triisopropylsilyl)pyrrole.[7]

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Clearly, this finding confirms the low sensitivity of homolytic aromatic substitutions to steric effects,[2a] but it cannot also be excluded that the relative reactivity of α and β positions in pyrrole is higher in homolytic than in electrophilic aromatic substitutions. Studies aimed at clarifying this interesting point would be desirable.

In the reaction of indole, the α:β reactivity ratio is ca. 11 in the reaction with $^{\bullet}CH_2CO_2C_2H_5$ (entry 1, Table II) and ca. 6 in the reaction with $^{\bullet}CH_2CN$ (entry 2, Table II).

Finally, it is important to remark that the products obtained by this procedure are of considerable practical interest, since all of them can easily be converted, by simple hydrolysis or, in the case of the malonates, by decarboxylation, into the corresponding heteroarylacetic or 2-heteroarylpropanoic acids, which are potential antiinflammatory drugs.[8]

As an example of a possible application, we have carried out the synthesis of the ethyl ester of Tolmetin (a commercial antiinflammatory drug)[9] by reaction of 2-(*p*-methylbenzoyl)-*N*-methylpyrrole with $^{\bullet}CH_2CO_2Et$ (entry 8, Table I). An excellent yield of product (90%) was obtained and, since 2-(*p*-methylbenzoyl)-*N*-methylpyrrole can be prepared with a yield of 70% by the Vilsmeier–Haack aroylation of *N*-methylpyrrole,[10] the overall yield of this novel synthetic approach[11] to the ethyl ester of Tolmetin from *N*-methylpyrrole and *p*-methylbenzoyl chloride is 63%.

Experimental Section

^1H NMR spectra were recorded on a Bruker instrument at 80 MHz in $CDCl_3$ solution, and ^{13}C NMR were recorded on a Varian XL 300 in $CDCl_3$. Mass spectra were obtained on a Hewlett-Packard 5970 mass selective detector, operating at 70 eV, coupled with a 5890 GC. MS data are reported as *m/z* (relative intensity). Yields were calculated with respect to the alkyl iodide and in all cases the mass balance was 90–95%.

Starting Materials. Ethyl iodoacetate and iodoacetonitrile are commercially available (Aldrich). Dimethyl iodomalonate and diethyl methyliodomalonate were prepared according to the literature.[12] Ethyl α-iodopropionate[13] was obtained by halogen exchange from ethyl α-bromopropionate (Aldrich) with NaI in acetone[14] (yield 87%): mass spectrum 228 (M^+, 100), 183 (M^+ – OEt, 29), 155 (M^+ – CO_2Et, 88), 101 (M^+ – I, 93). Methyl iodoacetate and methyl 2-pyrrolecarboxylate were obtained by esterification with diazomethane of the corresponding carboxylic acids (Aldrich). *N*-(Triisopropylsilyl)pyrrole was obtained from pyrrole, according to the literature.[15] Pyrrole, 1-methylpyrrole (Aldrich), furan (C. Erba), thiophene, indole (Janssen), and all solvents (C. Erba) were used as purchased, without any further purification.

General Procedure for the Alkylation Reactions. H_2O_2 (35%) (4–12 mmol) was added dropwise to a stirred mixture of the substrate (15–20 mmol), the alkyl iodide (1 mmol), and $FeSO_4 \cdot 7H_2O$ (0.2–0.6 mmol) in 15–30 mL of DMSO, while the solution was kept at room temperature with a water bath. The mixture was then diluted with brine and extracted with diethyl ether. The organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The residue was finally purified by column chromatography on silica gel (eluent: petroleum ether (bp 40–70 °C)–diethyl ether). The yields are reported in Table I. Characterization of the products was carried out as described below.

For the following compounds NMR, mass spectra, and, for solids, melting points were compared with those of authentic specimens, commercially available (Aldrich): methyl 1-methyl-2-pyrroleacetate, 1-methyl-2-pyrroleacetonitrile, ethyl 2-thiopheneacetate, methyl 3-indoleacetate, 3-indoleacetonitrile; or with the corresponding literature data: methyl 2-pyrroleacetate,[16] 2-pyrroleacetonitrile,[17] ethyl 1-methyl-2-*p*-toluoyl-5-pyrroleacetate (ethyl ester of Tolmetin),[9] ethyl 2-furanacetate,[18] methyl 2-indoleacetate,[19] and 2-indoleacetonitrile.[20]

Ethyl α-methyl-*N*-methyl-2-pyrroleacetate was obtained as an oil. Mass spectrum: 181 (M^+, 17); 108 (M^+ – CO_2Et, 100), 93 (10). ^1H NMR δ (ppm): 1.22 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.52 (d, J = 7.2 Hz, 3 H, CH_3CH), 3.57 (s, 3 H, NCH_3), 3.72 (q, J = 7.2 Hz, 1 H, CH_3CH), 4.12 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.05 (m, 2 H, 3-H and 4-H pyrrole); 6.54 (m, 1 H, 5-H pyrrole). Anal. Found for $C_{10}H_{15}NO_2$ (Calcd): C, 66.27 (66.98); H, 8.41 (8.34); N, 7.78 (7.73).

Dimethyl 2-pyrrolemalonate was obtained as an oil. Mass spectrum: 197 (M^+, 52), 138 (M^+ – CO_2Me, 93), 106 (100). ^1H NMR δ (ppm): 3.75 (s, 3 H, 2 CO_2CH_3), 4.78 (s, 1 H, $CH(CO_2Me)_2$), 6.13–6.15 (m, 2 H, 3-H and 4-H pyrrole), 6.79–6.83 (m, 1 H, 5-H pyrrole), 9.1 (bs, 1 H, NH). Anal. Found for $C_9H_{11}NO_4$ (Calcd): C, 54.22 (54.82); H, 5.36 (5.62); N, 7.50 (7.10).

Diethyl α-methyl-*N*-methyl-2-pyrrolemalonate was obtained as an oil. Mass spectrum: 253 (M^+, 22), 180 (M^+ – CO_2Et, 74), 106 (M^+ – (CO_2Et + HCO_2Et), 100). ^1H NMR δ (ppm): 1.25 (t, J = 7.1 Hz, 6 H, 2 $CO_2CH_2CH_3$), 1.87(s, 3 H, $CH_3C(CO_2Et)_2$), 3.57 (s, 1 H, NCH_3), 4.21 (q, J = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 6.05–6.07 (m, 2 H, 3-H and 4-H pyrrole), 6.57–6.61 (m, 1 H, 5-H pyrrole). ^{13}C NMR (300 MHz) δ (ppm): 13.91 (CH_2CH_3), 22.58 ($C(CH_3)(CO_2Et)_2$), 35.47 (NCH_3), 54.27 ($C(CH_3)(CO_2Et)_2$), 61.78 (CH_2CH_3), 106.44 and 108.29 (3-C and 4-C pyrrole), 124.72 (5-C pyrrole); 129.03 (2-C pyrrole), 170.92 (CO_2Et). The resulting compound was unstable, which prevented elemental analysis.

5-(Methoxycarbonyl)-2-pyrroleacetonitrile was obtained as a solid which was recrystallized from benzene–cyclohexane, mp 144.5–145.5 °C. Mass spectrum: 164 (M^+, 90), 133 (M^+ – OCH_3, 100), 132 (M^+ – CH_3OH, 41), 106 (M^+ – (CH_3OH+CN), 59), 104 (46), 78 (35); 51 (30). ^1H NMR, δ (ppm): 3.80 (s, 2 H, CH_2CN), 3.87 (s, 3 H, CO_2CH_3), 6.16–6.30 (m, 1 H, 3-H pyrrole), 6.84–6.94 (m, 4-H pyrrole), 10.1 (bs, 1 H, NH). Anal. Found for $C_8H_8N_2O_2$ (Calcd): C, 59.15 (58.53); H, 4.87 (4.91); N, 17.42 (17.06). Another product was also present, in very small amounts, which was assigned the structure of 2-(methoxycarbonyl-3-pyrroleacetonitrile on the basis of the following spectral data: mass spectrum: 164 (M^+, 54), 133 (M^+ – OCH_3, 52), 132 (M^+ – CH_3OH, 100), 106 (M^+ – (CH_3OH + CN), 11), 105 (M^+ – (CH_3OH + HCN), 25), 104 (59), 78 (29), 51 (29). ^1H NMR δ (ppm): 3.87 (s, 3 H, CO_2CH_3), 3.92 (s, 2 H, CH_2CN), 6.32–6.40 (m, 1 H, 4-H pyrrole), 6.85–6.95 (m, 1 H, 5-H pyrrole).

Acknowledgment. This work was carried out into the framework of the Progetto Finalizzato CNR Chimica Fine.

Registry No. ICH_2CO_2Me, 5199-50-8; ICH_2CN, 624-75-9; $ICH(CO_2Me)_2$, 123507-65-3; $ICH(CH_3)CO_2Et$, 31253-08-4; $IC(CH_3)(CO_2Et)_2$, 119368-33-1; ICH_2CO_2Et, 623-48-3; pyrrole, 109-97-7; *N*-methylpyrrole, 96-54-8; 2-(*p*-methylbenzoyl)-*N*-methylpyrrole, 62128-31-8; methyl 2-pyrrolecarboxylate, 1193-62-0; indole, 120-72-9; furan, 110-00-9; thiophene, 110-02-1; methyl 2-pyrroleacetate, 53912-79-1; 2-pyrroleacetonitrile, 50551-29-6; dimethyl 2-pyrrolemalonate, 68940-77-2; methyl 1-methyl-2-pyrroleacetate, 51856-79-2; 1-methyl-2-pyrroleacetonitrile,

(8) See, for example: Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*, John Wiley & Sons: New York, 1984; Vol. 3, pp 85–99; Vol. 2, 1980, pp 63–70; Vol. 1, 1977, pp 37–45. Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

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24437-41-0; ethyl α-methyl-*N*-methyl-2-pyrroleacetate, 60730-15-6; diethyl α-methyl-*N*-methyl-2-pyrrolemalonate, 144194-94-5; ethyl 1-methyl-2-*p*-toluoyl-5-pyrroleacetate, 52074-58-5; 5-(methoxycarbonyl)-2-pyrroleacetonitrile, 144194-95-6; methyl 2-indoleacetate, 21422-40-2; 2-indoleacetonitrile, 7210-27-7; ethyl 2-furanacetate, 4915-21-3; ethyl 2-thiopheneacetate, 57382-97-5.

Supplementary Material Available: Copy of the ^{13}C NMR spectrum of diethyl α-methyl-*N*-methyl-2-pyrrolemalonate (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Solution Conformation of Two C_2-Symmetric Amino Derivatives of 1,1′-Binaphthalene by Circular Dichroism and Liquid Crystal Technique

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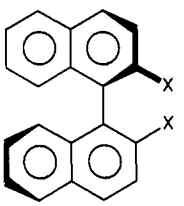
The solution conformation of two C_2-symmetric 1,1′-binaphthyl compounds (*N,N,N′,N′*-tetramethyl-[1,1′-binaphthalene]-2,2′-diamine (1) and *N,N′*-dimethyl-[1,1′-binaphthalene]-2,2′-diamine (2) has been studied by MMX calculations, analysis of the absorption and CD spectra, and induction of cholesteric mesophases in nematic liquid crystals. All these methods indicate that 1 prefers a ciscoid conformation and that 2 assumes a conformation where the two naphthyl moieties are quasi-perpendicular.

Introduction

Studies aimed at determining the structure of C_2-symmetric 1,1′-binaphthyl compounds have received considerable attention in the past years. Such studies have been carried out by circular dichroism (CD) spectroscopy,[1-3] X-ray diffraction,[4] or liquid crystal techniques.[5] C_2-symmetric binaphthyl compounds play an important role as chiral auxiliaries in asymmetric organic reactions.[6,7] Conformational studies on these molecules deserve attention because the studies can help to explain the stereochemical outcome of the reactions in which these substances are employed as chiral auxiliaries.

It is the aim of this paper to present a detailed conformational study of two diamines with the C_2-symmetric binaphthyl structure, i.e., *N,N,N′,N′*-tetramethyl-[1,1′-binaphthalene]-2,2′-diamine (1) and *N,N′*-dimethyl-[1,1′-binaphthalene]-2,2′-diamine (2) (Chart I). Optically active 1 has been recently introduced[8] as a chiral controller for the enantioselective addition of diethylzinc to aromatic aldehydes, and satisfactory enantiomeric excesses have been obtained. Although preliminary chiroptical data for 1 have been reported,[1] the CD spectrum of 1 has not been analyzed. No data about the chiroptical properties of 2 have appeared and to the best of our knowledge, it has been employed only as a chiral ligand for $LiAlH_4$ in the asymmetric reduction of aromatic ketones.[9] Binaphthyls of a given absolute configuration, for example R, can have conformations with opposite helicities, depending on the dihedral angle (ψ) (i.e., the angle C_9–C_1–$C_{1'}$–$C_{9'}$) between the naphthyl rings (see Figure 1). For $0 < \psi < 90$, the helicity between the planes containing the naphthyl moieties is M, and for $90 < \psi < 180$, the helicity is P.

Chart I



(R)–1, X = $N(CH_3)_2$

(R)–2, X = $NHCH_3$

Results and Discussion

Synthesis. The syntheses of compounds 1 and 2 require optically active [1,1′-binaphthyl]-2,2′-diamine as starting material. This compound was prepared and resolved into its antipodes according to the procedure of Miyano and co-workers.[10] The ee of the samples obtained was determined by HPLC analysis on a Pirkle (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine CSP column. (*R*)-1 was obtained from the reaction[11] of (*R*)-primary diamine with formaldehyde/formic acid (Eschweiler–Clarke reaction) and crystallization from toluene. The ee (>95%) of the product was established by ^1H-NMR spectroscopy in the

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