Difunctional Pyrazole Derivatives − Key Compounds en Route to Multidentate Pyrazolate Ligands

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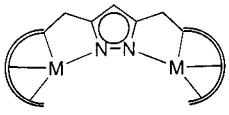
Straightforward syntheses for some basic functional pyrazole derivatives are reported. These compounds serve as starting materials for the preparation of a series of new 3,5-donor-substituted multifunctional pyrazole compounds, which may act as compartmental dinucleating ligand scaffolds for the controlled assembly of bimetallic complexes. The thp-protected 3,5-bis(chloromethyl)pyrazole (**1**), and in particular the more reactive 3,5-bis(bromomethyl) analogue **3**, permit efficient attachment of various N-donor side arms through nucleophilic substitution reactions. The preparation of the enantiomerically pure (methoxymethyl)pyrrolidine derivative **2e** by this route makes use of the intrinsic C_2 symmetry of the pyrazole-based framework, and a dizinc complex **2e**·(ZnCl$_2$)$_2$ has been characterized crystallographically. The thp-protected pyrazoledicarbaldehyde **6** affords access to pyrazole derivatives bearing aldimine donor side arms, which may be viewed as coupled dinucleating versions of α-diimine ligands. DIBAH reduction of thp-protected dimethyl 1H-pyrazole-3,5-dicarboxylate **4** yields the unsymmetrically functionalized methyl 3-hydroxymethyl-1H-pyrazole-5-carboxylate **8**, which has been analyzed by X-ray crystallography. Compound **8** is shown to provide a route to unsymmetrical pyrazole ligands with different chelating side arms in the heterocycle 3- and 5-positions, such as the thioether/amine system **11**.

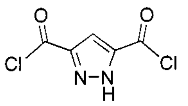
Introduction

The pyrazole heterocycle has found widespread use as a ligand in transition metal coordination chemistry.[1] It has proven particularly valuable as a building block for the assembly of di- and multinuclear complexes when acting as a bidentate bridging ligand in its deprotonated (i.e., anionic) form. Preorganization of pyrazolate-based bimetallic complexes can be significantly enhanced by attachment of chelating side arms to the 3- and 5-positions of the heterocycle, thus forming compartmental dinucleating type **A** systems.[2−8] In such complexes, variation of the side arm chain length or the donor functions of the ligand scaffold allows for fine-tuning of the metal−metal separation, as well as of the individual metal coordination spheres.[6−8] In contrast to the many dinuclear complexes based on compartmental phenolate ligand matrices,[9,10] however, examples of type **A** compounds have remained relatively scarce. A major reason for this is the lack of readily available functional pyrazole derivatives that might provide a straightforward and high-yielding route for the attachment of various donor side arms. This is even more true for unsymmetrical systems bearing distinct substituents in the 3- and 5-positions of the heterocycle,[8] despite their being attractive targets for a controlled synthesis of heterobimetallic complexes.[10]

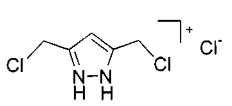


A

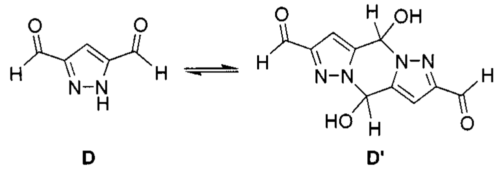
Some established symmetrically functionalized pyrazole starting materials are the diacid dichloride **B**,[3] the bis(chloromethyl)-substituted compound **C** reported by Bosnich and co-workers,[2] and the dialdehyde **D** described recently by Navarro and co-workers.[11] For the purposes outlined above, use of **B** is mainly restricted to the formation of its corresponding diamide derivatives. However, subsequent reduction of these amides by (for example) LiAlH$_4$ often results in cleavage of the newly formed amide bonds and concomitant loss of the side arm substituents. More general use of **C** and **D** is hampered by the presence of the *N*-bound proton: Treatment of **C** with primary or secondary amines suffers from competing nucleophilic substitution reactions by the pyrazole N, which yield considerable amounts of oligomeric side products. In **D**, which is almost insoluble in most common solvents, the pyrazole NH even attacks a formyl group in an intermolecular reaction to form **D′**.[11]



B



C



D **D'**

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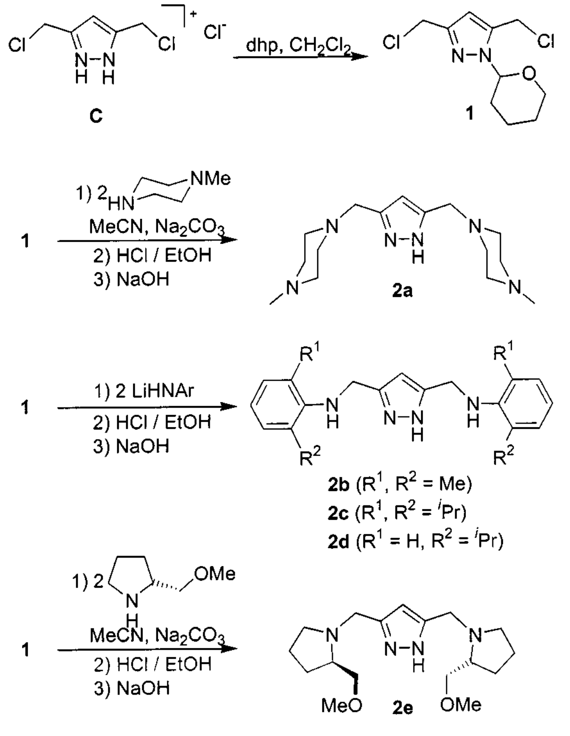
In order to explore the rich chemistry of type **A** bimetallic complexes further, new synthetic routes to difunctional pyrazole derivatives − in particular to *N*-protected analogues of **B**−**D** − would therefore be highly desirable. In this contribution we report the preparation of several *N*-protected pyrazole compounds related to **B**−**D** and their suitability for the attachment of various side arm substituents bearing potential donor atoms. The more reactive dibromo derivative of **C** is also described, together with a novel and simple route to systems bearing different functional substituents in the 3- and 5-positions of the heterocycle.

Results and Discussion

Bis(chloromethyl)pyrazole **C** is accessible through a four-step synthesis starting from 3,5-dimethylpyrazole.[2] We have recently shown that the thp moiety is a suitable NH protecting group for this pyrazole system, and is readily introduced by treatment of **C** with 3,4-dihydro-2*H*-pyran (dhp).[12] In *N*-protected **1**, substitution reactions by N-nucleophiles are straightforward and the acid-labile thp group can be conveniently removed in the final step. This is demonstrated here by the synthesis of a series of potentially dinucleating ligands **2a**−**e** (Scheme 1). All new compounds **2a**−**e** have been fully characterized by NMR spectroscopy, mass spectrometry, and elemental analyses.

Because of the prototropic equilibrium of the pyrazole ring, the ^{1}H and ^{13}C NMR spectra of pyrazole derivatives often display simple symmetric signal patterns,[11,13] as is also observed for **2b**−**e**. The pyrazole quaternary carbon atoms C(3) and C(5) thus appear as one signal, although this is very broad and sometimes even disappears in the baseline of the spectrum. In the case of **2a**, the room-temperature ^{1}H NMR spectrum in $CDCl_3$ features a single broad signal at $\delta = 2.48$ for all of the piperazino CH_2 protons, indicating a second fluxional process: chair-chair inversion of the piperazine six-membered rings.[14] The two dynamic processes are evident from variable-temperature ^{1}H and ^{13}C NMR spectra collected in the −60 °C to +50 °C range in $CDCl_3$ (Figure 1). Slow piperazine chair-chair interconversion at low temperatures gives rise to separate broad singlets, at $\delta = 2.13$ and 2.77, for the axial and equatorial CH_2 protons of the six-membered rings. The two different types of CH_2 groups in the unsymmetrically substituted piperazine moieties are not resolved, however, and any geminal coupling between the axial and equatorial protons also remains unresolved. These two signals broaden upon warming and coalesce at ca. 0 °C to give the single broad resonance (at $\delta = 2.48$ at room temperature), which at +50 °C splits into two multiplets centered at $\delta \approx 2.52$ and 2.46, corresponding to the CH_2 groups closer to and more distant from the pyrazole moiety. From the experimental data, the following parameters can be deduced for the piperazine ring inversion of **2a** at the coalescence temperature: $k_{273} = 568\ (\pm\ 20)\ \mathrm{s}^{-1}$ and $\Delta G^{\ddagger}_{273} = 52.3\ (\pm\ 0.2)\ \mathrm{kJ{\cdot}mol^{-1}}$. This is in reasonable agreement with previous findings for *N*,*N*′-disubstituted piperazine compounds.[14]



Scheme 1

Slowed N−H tautomerism gives rise to distinct ^{13}C NMR resonances for the C(3) (b) and C(5) (b′) pyrazole ring atoms: at $\delta = 148.8$ and $\delta = 139.9$ at low temperatures (instead of a single, very broad resonance at $\delta \approx 146$ at +50 °C). N−H tautomerism also causes broadening and finally decoalescence of the high-temperature signal for the pyrazole-bound CH_2 groups at $\delta = 55.0$, giving separate resonances at $\delta = 56.1$ and 53.4 upon cooling to −60 °C (coalescence temperature ca. −10 °C). In addition, the high-temperature ^{13}C NMR resonance at $\delta = 53.4$ for the d/d′ piperazine CH_2 groups splits into two signals ($\delta = 53.2$ and 53.5 at −60 °C), due to abolition of the magnetic equivalence of the pyrazole 3- and 5-environments. In the ^{1}H NMR spectrum this process results in decoalescence of the signals for the c/c′ CH_2, and two closely spaced signals at $\delta = 3.45$ and 3.50 are observed at temperatures below −40 °C. Below ca. 0 °C the NH proton also becomes discernible, sharpening and shifting to lower field upon further cooling. It is known that the dynamic exchange rate of the pyrazole prototropic equilibrium depends on the nature of the pyrazole C substituents.[11,13] For **2a**, N···H···N hydrogen bonding interactions between the pyrazole sp^2 nitrogen atoms and the aliphatic sidearm nitrogen atoms can be assumed to counteract rapid N−H tautomerism, thus making observation of distinct resonances for the 3- and 5-environment of the pyrazole heterocycle possible at comparatively high temperatures.

The enantiomerically pure compound **2e**, bearing two (*R*)-2-(methoxymethyl)pyrrolidine side arms, was intended to take advantage of the inherent twofold symmetry of a

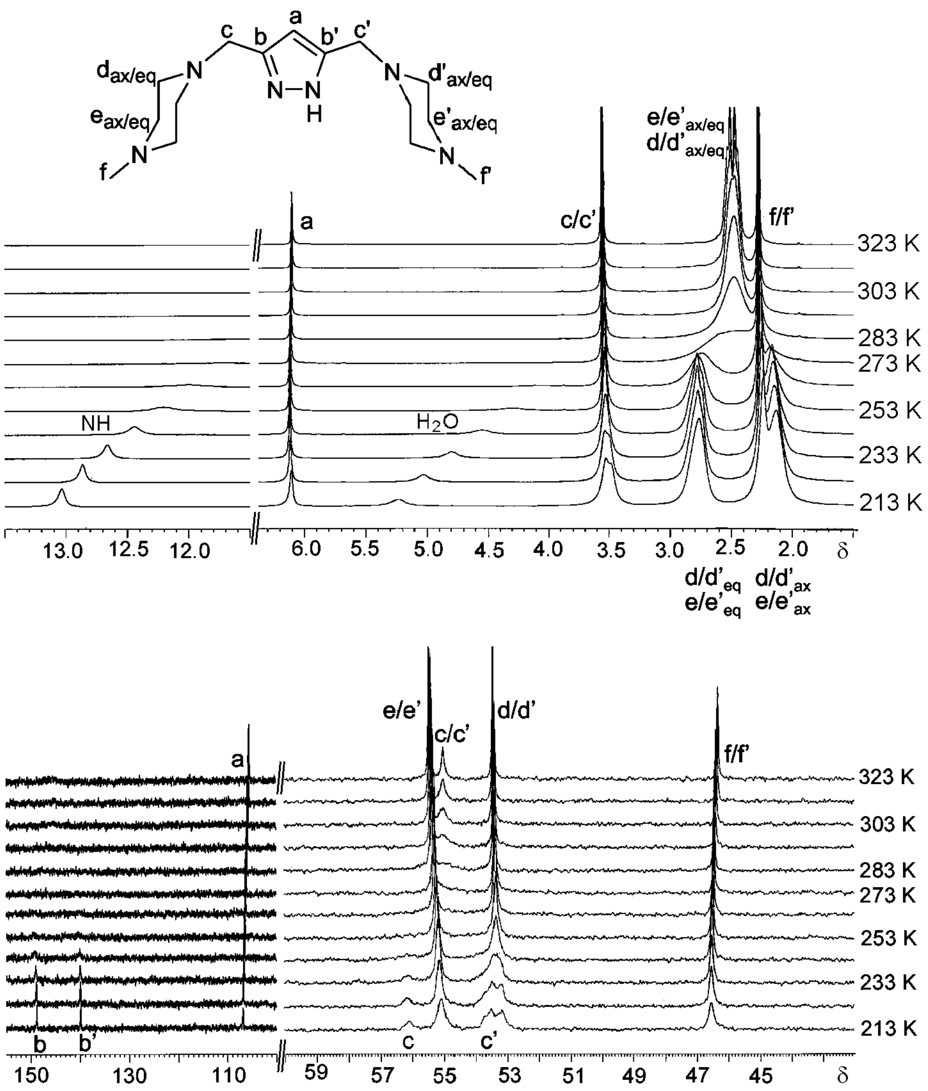


Figure 1. Temperature-dependent dynamic ^{1}H (top) and ^{13}C (bottom) NMR spectra of **2a** in $CDCl_3$ at 200.13 (^{1} H) and 50.32 (^{13}C) MHz; the signal for H_2O is not observed if the $CDCl_3$ solvent is condensed onto the sample and the NMR tube flame-sealed under vacuum

bimetallic type **A** scaffold. Although C_2-symmetric ligand systems have proven extremely valuable in asymmetric synthesis, the potential of C_2-symmetric *dinuclear* metal complexes has hardly been explored and has not as yet found widespread application.[15,16] Because of their rather rigid frameworks, pyrazolate-based type **A** systems with stereogenic centers in close proximity to the coordination sphere appear particularly promising in this regard, and compound **2e**, to the best of our knowledge, represents the first enantiomerically pure C_2-symmetric pyrazole ligand of that kind. As a preliminary test of its coordination potential, **2e** was treated with 2 equiv. of $ZnCl_2$. The bimetallic complex **2e**·$(ZnCl_2)_2$ was obtained in crystalline form, and its molecular structure was elucidated by X-ray crystallography (Figure 2). The **2e**·$(ZnCl_2)_2$·0.5 acetone complex crystallizes in the chiral space group $P2_1$ with two independent (but similar) bimetallic entities in the unit cell.

As anticipated, the pyrazolate spans two zinc ions in a μ-η^1:η^1-bidentate fashion, and a chloride ion is found as a secondary bridging ligand. While Zn(3) [and likewise Zn(1)] is five-coordinate with all side arm donors of its respective ligand compartment and one terminal Cl bound to the metal ion, the second zinc ion [Zn(2) and Zn(4)] is in a near-tetrahedral "NCl_3" environment, with its respective ligand side arm uncoordinated. In view of the overall charge of the system, this dangling side arm presumably picks up the surplus proton formerly bound to the pyrazole N in the free ligand. Although this H atom could not be located in the crystallographic analysis, rather short O···N [2.826/2.840 Å], Cl···N [3.308/3.273 Å], and Cl···O [3.393/3.475 Å] distances all point towards its involvement in some type of H-bonding situation, as indicated in Scheme 2. The structure of **2e**·$(ZnCl_2)_2$ underlines the high tendency of the pyrazole group to adopt a bridging coordination mode in its deprotonated form and confirms the general ability of the present system **2e** to form discrete bimetallic complexes. Complex **2e**·$(ZnCl_2)_2$ appears well suited to give a C_2-symmetric bimetallic type **A** complex upon addition of base and abstraction of "HCl" – this chemistry is soon to be studied.

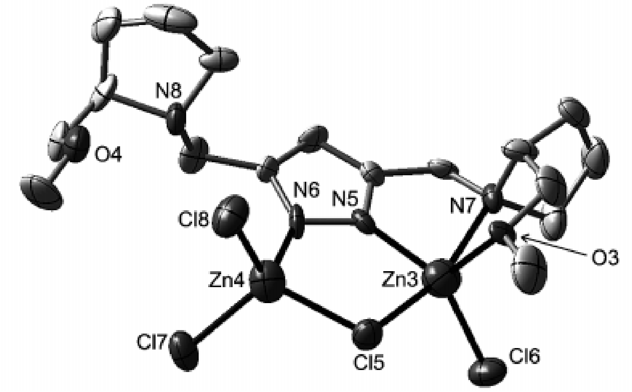
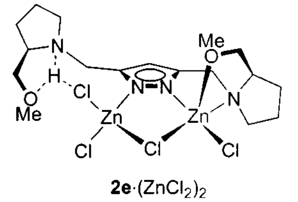
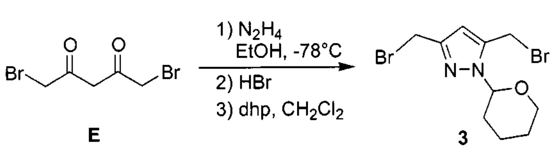


Figure 2. View of the molecular structure of **2e**·$(ZnCl_2)_2$; in the interests of clarity all hydrogen atoms have been omitted; selected interatomic distances [Å] and bond angles [°] [values for the second independent molecule in brackets]: Zn(3)−N(5) 1.981(9) [1.949(9)], Zn(3)−O(3) 2.150(6) [2.118(6)], Zn(3)−N(7) 2.239(9) [2.201(9)], Zn(3)−Cl(5) 2.543(3) [2.589(3)], Zn(3)−Cl(6) 2.217(3) [2.213(3)], Zn(4)−N(6) 1.974(10) [1.979(9)], Zn(4)−Cl(5) 2.287(3) [2.299(3)], Zn(4)−Cl(7) 2.255(3) [2.246(3)], Zn(4)−Cl(8) 2.258(3) [2.247(4)], N(5)−N(6) 1.386(12) [1.373(12)], Zn(3)···Zn(4) 3.701(1) [3.696(1)], Cl(8)···N(8) 3.273(6) [3.308(6)], Cl(8)···O(4) 3.393(8) [3.475(7)]; Zn(3)−Cl(5)−Zn(4) 99.9(1) [98.1(1)].

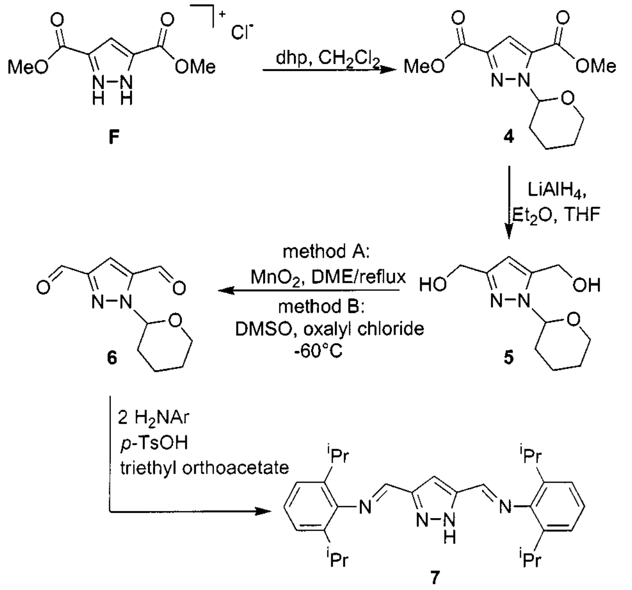


Scheme 2

While employing weak nucleophiles in synthetic procedures as outlined in Scheme 1, we observed that the dichloro derivative **1** was in several cases insufficiently reactive, only giving monosubstituted products at best. The corresponding dibromo compound thus appeared an attractive target, but previous attempts to synthesize 3,5-bis(bromomethyl)-1*H*-pyrazole have been unsuccessful.[17] This was attributed to the instability of such compounds due to their high reactivity, and only *N*-alkyl derivatives could later be obtained.[17,18] We have now devised a new procedure starting from dibromoacetylacetone **E**[19] (Scheme 3), in which the 3,5-bis(bromomethyl)-1*H*-pyrazole is not isolated but is directly treated with dhp to give the perfectly stable *N*-protected thp derivative **3**. As shown above for **1**, removal of the thp unit may conveniently be carried out after nucleophilic substitution of the side arm halides, and so the very reactive dibromo compound **3** might prove a valuable synthon for the preparation of a wide variety of type **A** systems.



Scheme 3

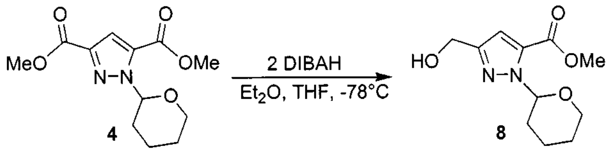


Scheme 4

Diimino-substituted pyrazole derivatives should in general be much better chelating ligands than diamino-substituted pyrazoles such as **2b**−**d**, in particular towards "soft" transition metals. As mentioned in the introduction, conversion of dialdehyde **D** into various diimines is hampered by its low solubility, due to its existence in equilibrium with dimers **D′**.[11] We therefore set out to develop a route to the thp-protected 3,5-pyrazoledicarbaldehyde **6** (Scheme 4), which was expected to exhibit improved solubility and to exist in monomeric form. The synthetic pathway starts from diester **F**,[2] and the thp group was introduced in the first step, yielding **4**. The thp-protected **4** was then reduced to the corresponding dialcohol **5**, which was finally reoxidized to give **6**. A Swern procedure[20] proved superior to oxidation by MnO_2 in the last step.

Compound **6** may serve as a suitable starting material for the sought-after compartmental diimine pyrazole ligand systems, as demonstrated by its reaction with 2,6-diisopropylaniline to afford the diimine relative of **2c**: compound **7** (Scheme 4). The potential ligand **7** may be viewed as a dinucleating analogue of the heavily used α-diimine ligands; these have proven particularly valuable, when bearing bulky N substituents, in olefin polymerization chemistry by late transition metal complexes.[21] The bimetallic coordination chemistry of the new pyrazole compound **7** will be reported in due course.

Several unsuccessful experiments were carried out in attempts to convert thp-protected diester **4** directly into the key dialdehyde **6**. Unexpectedly, when **4** was treated with 2 equiv. of diisobutylaluminium hydride (DIBAH), the unsymmetrically reduced compound **8** was obtained as the sole well-defined product (Scheme 5). No other product was observed even on varying the reaction temperature or the stoichiometry of the reagents. NMR spectroscopically pure **8** was isolated as colorless crystalline material in 81% yield. As the regiochemistry of the reduction could not be elucid-



Scheme 5

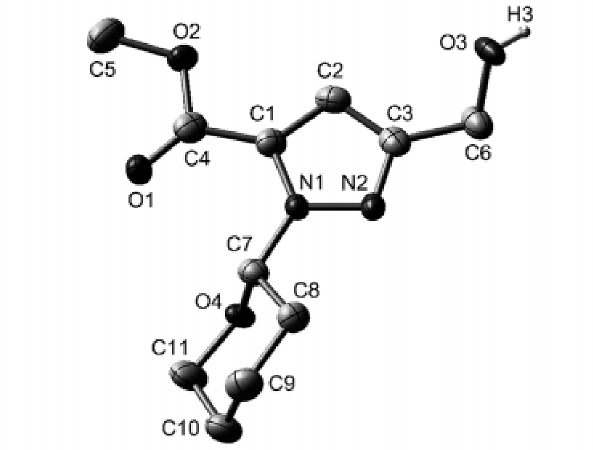
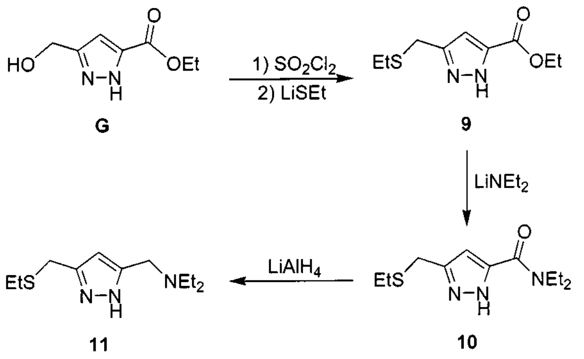


Figure 3. View of the molecular structure of **8**; in the interests of clarity most of the hydrogen atoms have been omitted; selected interatomic distances [Å] and bond angles [°]: N(1)−N(2) 1.354(2), N(1)−C(1) 1.368(2), C(1)−C(2) 1.374(3), C(2)−C(3) 1.395(3), C(3)−N(2) 1.337(3), N(1)−C(7) 1.463(3), C(1)−C(4) 1.474(3), C(4)−O(1) 1.204(3), C(4)−O(2) 1.338(3); N(2)−N(1)−C(1) 111.7(2), C(1)−N(1)−C(7) 128.4(2), C(7)−N(1)−N(2) 119.9(2)

ated unambiguously by NMR methods (NOESY etc.), a single-crystal X-ray analysis was performed. The molecular structure of **8** is displayed in Figure 3, together with selected interatomic distances and bond angles.

Reduction of the ester function only occurred at the substituent distant from the thp group. A space-filling model of **4** reveals clear differences in steric shielding of its two ester functions, due to the thp group attached to one of the N atoms. However, we assume the regioselectivity of DIBAH reduction to be largely dictated by electronic effects. A map of the electrostatic potential calculated for **4**[22] shows that (negative) electrostatic potential is predominantly located at the two-coordinate N atom of the pyrazole ring and at the adjacent carbonyl ester function, that is, at the particular site at which reduction occurs. It is tempting to assume that precoordination of the aluminium reagent at this accessible pyrazole N atom is responsible for the observed regiochemistry.

The unusual DIBAH reduction of **4** now opens a convenient route to the unsymmetrically functionalized pyrazole synthon **8**. Its unprotected ethyl ester analogue **G** was recently introduced as a versatile starting material for the construction of a variety of unsymmetrical dinucleating ligand systems.[8] This is demonstrated here by the synthesis of the new ligand **11**, which bears one pendant thioether and one amine side arm and which thus provides both a bidentate "SN" and a bidentate "N_2" coordination compartment (Scheme 6). The hydroxymethyl group of **G** was first transformed into a chloromethyl function by $SOCl_2$,[8] followed by treatment with LiSEt to attach the first donor side arm in **9**. Subsequent treatment with lithiated diethylamine gave amide **10**, which was finally reduced with $LiAlH_4$ to yield **11**.



Scheme 6

Conclusions

The collection of *N*-protected 3,5-difunctionalized pyrazole derivatives reported here − the dichloro compound **1**, the even more reactive dibromo compound **3**, the dialdehyde **6**, and the unsymmetrically substituted pyrazole **8** − have proven to be valuable synthons for straightforward synthesis of, for example, a variety of different compartmental type **A** pyrazole ligands. This is demonstrated here by the synthesis of various amine-substituted pyrazoles **2a−d**, the first example of an enantiomerically pure, C_2-symmetric, pyrazole-based multidentate ligand **2e**, a bulky diimine system **7** that can be viewed as a coupled dinucleating version of the heavily studied α-diimine ligands, and of a multidentate pyrazole **11**, providing both a bidentate "SN" and a bidentate "N_2" binding pocket. These new systems are expected to give rise to some rich and versatile coordination chemistry, which is presently under investigation.

Experimental Section

General Procedures and Methods: All manipulations involving organolithium or organoaluminium compounds were carried out under dry argon by standard Schlenk techniques. Solvents were dried according to established procedures. Compounds **C**, **E**, and **F** were synthesized according to the reported methods,[2,19] all other chemicals were used as purchased. Microanalyses: Mikroanalytische Laboratorien des Organisch-Chemischen Instituts der Universität Heidelberg. IR spectra: Perkin−Elmer 983G; recorded as KBr pellets. FAB/EI-MS spectra: Finnigan MAT 8230. HR EI-MS spectra: Jeol JMS 700. NMR spectra: Bruker AC 200 at 200.13 (^{1} H) and 50.32 (^{13}C) MHz, or Bruker DRX 300 at 300.13 MHz (^{1} H) and 75.47 (^{13}C) MHz; where necessary, assignments are based on a series of 2D experiments.

3,5-Bis(4-methylpiperazin-1-ylmethyl)-1*H*-pyrazole (2a): Na_2CO_3 (21 g, 0.2 mol) was dried by heating to 100 °C under vacuum. Dry acetonitrile (200 mL), 1-methylpiperazine (5 mL, 45 mmol), and **1** (5 g, 20 mmol) were then added and the reaction mixture was heated to reflux for 15 h. After filtration, all volatile material was removed under reduced pressure. The residue was taken up in ethanol (30 mL), treated with ethanolic hydrochloric acid, and left stirring overnight. Addition of diethyl ether caused precipitation of the hydrochloride salt of **2a**, which was separated by filtration, washed twice with diethyl ether, and dried under vacuum. This material was treated with aqueous NaOH (3.75 M) and the solution was extracted several times with dichloromethane. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness to yield crude **2a** (4.2 g, 14.4 mmol, 72%). Purification was achieved by recrystallization from dichloromethane/light petroleum ether. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.24 (br. s, 6 H, NCH_3), 2.44 (br. s, 16 H, NCH_2), 3.52 (br. s, 4 H, NCH_2), 6.07 (br. s, 1 H, CH^{pz}). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 46.4 (CH_3), 53.4 (CH_2), 55.0 (CH_2), 55.4 (CH_2), 105.7 ($C^{pz,4}$), 145.6 ($C^{pz,3/5}$). MS (FAB): *m/z* (%) = 292 (85) [M^+], 222 (100) [$M^+ - NC_4H_8$], 193 (90) [$M^+ - N_2C_5H_{11}$]. $C_{15}H_{28}N_6$ (292.43): calcd. C 61.61, H 9.65, N 28.74; found C 61.37, H 9.78, N 28.57.

3,5-Bis[(2,6-dimethylphenyl)aminomethyl]-1*H*-pyrazole (2b), 3,5-Bis[(2,6-diisopropylphenyl)aminomethyl]-1*H*-pyrazole (2c), and 3,5-Bis[(2-isopropylphenyl)aminomethyl]-1*H*-pyrazole (2d). − General Procedure: The aniline compound (**2b**: 2,6-dimethylaniline, 1.18 g, 10 mmol; **2c**: 2,6-diisopropylaniline, 1.77 g, 10 mmol; **2d**: 2-isopropylaniline, 1.35 g, 10 mmol) was dissolved in tetrahydrofuran (50 mL), and the solution was cooled to −78 °C and treated with *n*-butyllithium in hexane (2.5 M, 4 mL, 10 mmol). After 1 h, a solution of **1** (1.00 g, 4 mmol) in THF (10 mL) was added by syringe and the solution was left stirring overnight at room temperature. After hydrolysis with aqueous sodium bicarbonate, drying of the organic phase with magnesium sulfate and removal of the solvent, the crude product was dissolved in ethanol (20 mL) and stirred overnight with ethanolic hydrogen chloride (10 mL). Addition of diethyl ether (100 mL) gave the hydrochloride salt as a colorless solid. This was separated by filtration, neutralized with aqueous sodium bicarbonate, and extracted with dichloromethane. After the organic layer had been dried with magnesium sulfate, removal of the solvent under reduced pressure yielded the product **2b** (1.11 g, 3.3 mmol, 82.5%) as a light brown solid, **2c** (1.56 g, 3.5 mmol, 87.5%) as a colorless solid, and **2d** (1.24 g, 3.4 mmol, 85.0%) as a pale brown solid.

Compound 2b: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.29 (s, 12 H, CH_3), 4.17 (s, 4 H, CH_2), 6.07 (s, 1 H, CH^{pz}), 6.87 (t, ^3J = 7.2 Hz, 2 H, $CH^{Ph,4}$), 7.03 (d, ^3J = 7.2 Hz, 4 H, $CH^{Ph,3/5}$). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 18.1 (CH_3), 44.6 (CH_2), 101.9 ($CH^{pz,4}$), 122.3 ($CH^{Ph,4}$), 128.6 ($CH^{Ph,3/5}$), 130.0 ($C^{Ph,1}$), 144.9 ($C^{Ph,2/6}$), ($C^{pz,3/5}$) not observed. IR (KBr): $\tilde{\nu}_{max}$ = 3323 vs, 3183 vs, 3097 vs, 2961 vs, 2906 vs, 2862 vs, 1587s, 1564s, 1500s, 1463 vs, 1374 s, 1345 s, 1334 s, 1262 s, 1193 s, 1150 s, 1094 vs, 999 s, 845 s, 789 vs, 767 vs cm^{-1}. M.p. 69−71 °C. MS (FAB): *m/z* (%) = 335 (75) [MH^+], 214 (65) [$M^+ - H_2NC_6H_3Me_2$-2,6]. $C_{21}H_{26}N_4$ (334.46): C 75.41, H 7.83, N 16.75; found C 74.59, H 7.78, N 16.75.

Compound 2c: ^1H NMR (200 MHz, $CDCl_3$): δ = 1.27 (d, ^3J = 6.8 Hz, 24 H, CH_3), 3.33 (sept, ^3J = 6.8 Hz, 4 H, CH^{iPr}), 4.13 (s, 4 H, CH_2), 6.19 (s, 1 H, CH^{pz}), 7.15 (m, $6H^{Ph,3/4/5}$). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.0 (CH_3), 27.5 (CH^{iPr}), 47.9 (CH_2), 101.9 ($CH^{pz,4}$), 123.4 ($CH^{Ph,3/5}$), 124.2 ($CH^{Ph,4}$), 142.1, 142.5 ($C^{Ph,1/2/6}$), ($C^{pz,3/5}$) not observed. IR (KBr): $\tilde{\nu}_{max}$ = 3368 s, 3180 s, 2954 vs, 2931 vs, 2861 vs, 1453 vs, 1443 vs, 1379 s, 1358 s, 1252 s, 1192 s, 1100 w, 1051 s, 801 s, 749 s cm^{-1}. M.p. 37−39 °C. MS (FAB): *m/z* (%) = 447 (45) [MH^+], 269 (100) [$M^+ - H_2NC_6H_3iPr_2-2,6$]. $C_{29}H_{42}N_4$ (446.67): calcd. C 77.98, H 9.47, N 12.54; found C 77.55, H 9.53, N 12.47.

Compound 2d: ^1H NMR (200 MHz, $CDCl_3$): δ = 1.27 (d, ^3J = 6.7 Hz, 12 H, CH_3), 2.91 (sept, ^3J = 6.7 Hz, 2 H, CH^{iPr}), 4.39 (s, 4 H, CH_2), 6.22 (s, 1 H, CH^{pz}), 6.69 (d, ^3J = 7.4 Hz, 2 H, $CH^{Ph,6}$), 6.81 (t, ^3J = 7.4 Hz, 2 H, $CH^{Ph,4}$), 7.16 (m, 4 H, $CH^{Ph,3/5}$). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22.1 (CH_3), 26.9 (CH^{iPr}), 41.1 (CH_2), 101.8 ($CH^{Pz,4}$), 110.6 ($CH^{Ph,6}$), 117.9 ($CH^{Ph,4}$), 124.8 ($CH^{Ph,5}$), 126.5 ($CH^{Ph,3}$), 132.4 ($C^{Ph,2}$), 144.1 ($C^{Ph,1}$),146.9 ($C^{pz,3/5}$). IR (KBr): $\tilde{\nu}_{max}$ = 3377 vs, 2955 vs, 2860 vs, 1697 vs, 1580s, 1507 vs, 1448 vs, 1432 s, 1311 s, 1285 vs, 1259 s, 1036 w, 746 vs cm^{-1}. − M.p. 74 °C. MS (EI): *m/z* (%) = 363 (100) [M^+], 227 (80) [$M^+ - H_2NC_6H_4iPr_2-2$]. $C_{23}H_{30}N_4$ (362.51): calcd. C 76.20, H 8.34, N 15.45; found C 75.65, H 8.40, N 14.83.

3,5-Bis[(*R*)-(2-methoxymethyl)pyrrolidin-1-ylmethyl]-1*H*-pyrazole (2e): Na_2CO_3 (4.2 g, 40 mmol) was dried by heating to 100 °C under vacuum. Dry acetonitrile (100 mL), (*R*)-(2-methoxymethyl)pyrrolidine (1.0 mL, 8.8 mmol), and **1** (1.00 g, 4.0 mmol) were then added and the reaction mixture was heated to reflux for 15 h. After filtration, all volatile material was removed under reduced pressure. The residue was taken up in ethanol (25 mL), treated with ethanolic hydrochloric acid, and left stirring overnight. Addition of diethyl ether caused precipitation of the hydrochloride salt of **2e**, which was separated by filtration, washed twice with diethyl ether, and dried under vacuum. This material was treated with aqueous NaOH (3.75 M) and the solution was extracted several times with dichloromethane. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness to yield crude **2e** (1.07 g, 3.3 mmol, 83%). Impurities were removed by kugelrohr distillation. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.57−1.87 (m, 8 H, CH_2), 2.36 (pseudo-q, *J* = 8.2 Hz, 2 H, NC*H*H), 2.70 (pseudo-quint, *J* = 6.1 Hz, 2 H, NCH*H*), 2.98 (m, 2 H, NCH), 3.34 (s, 6 H, OCH_3), 3.37 (m, 4 H, OCH_2), 3.69 (d, ^2J = 14.0 Hz, 2 H, NC*H*H), 3.97 (d, ^2J = 14.0 Hz, 2 H, NCH*H*), 6.06 (s, 1 H, CH^{pz}). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22.2 (CH_2), 28.0 (CH_2), 49.8 (br, NCH_2), 54.0 (NCH_2), 58.8 (OCH_3), 61.7 (CH), 76.2 (OCH_2), 104.6 ($C^{pz,4}$), 144.5 (br, $C^{pz,3/5}$). MS (FAB): *m/z* (%) = 323 (100) [M + H^+], 321 (62) [$M^+ - 1$], 277 (60) [$M^+ - H_3COCH_2$], 208 (93) [$M^+ - C_6H_{12}NO$]. $C_{17}H_{30}N_4O_2$ (322.45): calcd. C 63.32, H 9.38, N 17.38; found C 62.41, H 9.57, N 16.83.

Complex 2e·(ZnCl$_2$)$_2$: A solution of **2e** (0.15 g, 0.47 mmol) in THF (15 mL) was treated with $ZnCl_2$ (0.24 mL of a 1.0 M solution in diethyl ether). After this had been stirred for 2 h, the solvent was removed under reduced pressure and the residue was taken up in acetone (20 mL). The solution was filtered and layered with light petroleum ether and gradually afforded colorless crystals of **2e**·$(ZnCl_2)_2$·0.5 acetone (0.18 g, 0.28 mmol, 59%). MS (FAB): *m/z* (%) = 523 (28) [**2e**·$Zn_2Cl_2H^+$], 421 (62) [**2e**·$ZnClH^+$]. IR (KBr): $\tilde{\nu}_{max}$ = 3441 br m, 3014 s, 2937 s, 2834 m, 1707m (acetone), 1521 w, 1485 m, 1447 s, 1435 s, 1392 m, 1374 m, 1329 s, 1206 m, 1128 m, 1106 m, 1062 s, 1032 s, 944 s, 817 m, 805 m cm^{-1}. $C_{17}H_{30}N_4Cl_4O_2Zn_2$·0.5 acetone (624.08): calcd. C 35.60, H 5.33, N 8.98; found C 35.83, H 5.45, N 8.96.

3,5-Bis(bromomethyl)-1-(tetrahydropyran-2-yl)-1*H*-pyrazole (3): 1,5-Dibromo-2,4-pentanedione (**E**) (10.94 g, 42 mmol) was dissolved in ethanol (150 mL). The solution was cooled to −78 °C and hydrazine hydrate (2.12 g, 42 mmol) was added. After this had been stirred for 1 h, hydrobromic acid in acetic acid (7.4 mL of a 5.7 M solution) was added and the suspension was stirred for a further 1 h at low temperature. The mixture was allowed to warm to room temperature, the solvent was evaporated to dryness, and the crude residue was suspended in dichloromethane (500 mL). 3,4-Dihydro-2*H*-pyran (10.59 g, 126 mmol) was then added. After stirring overnight, the reaction mixture was extracted with a solution of sodium bicarbonate (25 g) in water (400 mL) and the organic phase was dried with magnesium sulfate. Removal of the solvent and purification by column chromatography [silica; light petroleum ether/diethyl ether, 9:1; R_f (light petroleum ether/diethyl ether, 1:1) = 0.45] yielded **3** (4.85 g, 14 mmol, 33%) as colorless crystals. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.61−1.77 (m, 3 H, $\mathrm{CH_2^{thp,4/5}}$), 1.98−2.13 (m, 2 H, $\mathrm{CH_2^{thp,3/4}}$), 2.39 (m, 1 H, $\mathrm{CH_2^{thp,3}}$), 3.69 (dt, ^3J = 10.0/3.2 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 4.03 (d, ^3J = 10.0 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 4.44 (s, 2 H, $\mathrm{CH_2^{BrCH2-C-3-pz}}$), 4.50 (s, 1 H, $\mathrm{CH_2^{BrCH2-C-5-pz}}$), 4.53 (s, 1 H, $\mathrm{CH_2^{BrCH2-C-5-pz}}$), 5.45 (dd, ^3J = 9.4/2.3 Hz, 1 H, $\mathrm{CH^{thp,2}}$), 6.40 (s, 1 H, $\mathrm{CH^{pz}}$). ^{13}C NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 19.9 ($\mathrm{CH_2^{BrCH2-C-5-pz}}$), 22.1 ($\mathrm{CH_2^{thp,4}}$), 24.5, 24.7 ($\mathrm{CH_2^{BrCH2-C-3-pz/thp,5}}$), 29.0 ($\mathrm{CH_2^{thp,3}}$), 67.4 ($\mathrm{CH_2^{thp,6}}$), 84.8 ($\mathrm{CH^{thp,2}}$), 93.7 ($\mathrm{CH^{pz,4}}$), 139.7 ($\mathrm{C^{pz,5}}$), 148.2 ($\mathrm{C^{pz,3}}$). IR (KBr): $\tilde{\nu}_{max}$ = 3023 w, 2947 s, 2841 s, 1461 s, 1204 vs, 1078 vs, 1055 s, 1039 vs, 999 vs, 917 s, 888 s, 806 s, 727 s, 691 s, 573 s cm^{-1}. M.p. 68 °C. MS (EI): *m*/*z* (%) = 338 (2) [$\mathrm{M^+}$], 258 (10) [$\mathrm{M^+}$ − Br], 173 (50) [$\mathrm{M^+}$ − Br − dhp], 85 (100) [dhp + $\mathrm{H^+}$]. $\mathrm{C_{10}H_{14}Br_2N_2O}$ (338.04): calcd. C 35.53, H 4.17, N 8.28, Br 47.27; found C 35.66, H 4.17, N 8.28, Br 47.56.

Dimethyl 1-(Tetrahydropyran-2-yl)-1*H*-pyrazole-3,5-dicarboxylate (4): Dimethyl pyrazole-3,5-dicarboxylate hydrochloride (**F**) (18.8 g, 85 mmol) was suspended in 500 mL of dichloromethane, and 1,2-dihydropyran (14.33 g, 170 mmol) was added. The stirred suspension turned clear after 1 h. After stirring overnight, the mixture was extracted with a solution of sodium bicarbonate (25 g) in water (400 mL) and the organic phase was dried with magnesium sulfate. The solvent was evaporated and the residue was washed with light petroleum ether to give **4** (19.15 g, 71.4 mmol, 84%) as a white solid. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.61−1.77 (m, 3 H, $\mathrm{CH_2^{thp,4/5}}$), 1.97−2.11 (m, 2 H, $\mathrm{CH_2^{thp,3/4}}$), 2.45 (m, 1 H, $\mathrm{CH_2^{thp,3}}$), 3.74 (dt, ^3J = 10.9/3.0 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 3.91 (s, 3 H, $\mathrm{CH_3}$), 3.92 (s, 3 H, $\mathrm{CH_3}$), 4.06 (dd, ^3J = 10.9/3.0 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 6.33 (dd, ^3J = 9.8/1.8 Hz, 1 H, $\mathrm{CH^{thp,2}}$), 7.38 (s, 1 H, $\mathrm{CH^{pz}}$). ^{13}C NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 22.2 ($\mathrm{CH_2^{thp,4}}$), 24.5 ($\mathrm{CH_2^{thp,5}}$), 28.9 ($\mathrm{CH_2^{thp,3}}$), 52.0 ($\mathrm{CH_3}$), 67.5 ($\mathrm{CH_2^{thp,6}}$), 85.5 ($\mathrm{CH^{thp,2}}$), 114.4 ($\mathrm{CH^{pz,4}}$), 133.4 ($\mathrm{C^{pz,5}}$), 145.0 ($\mathrm{C^{pz,3}}$), 159.0, 161.7 ($\mathrm{C^{C=O}}$). IR (KBr): $\tilde{\nu}_{max}$ = 3423 w, 3155 w, 2980 w, 2949 s, 2932 s, 1735 vs, 1717 vs, 1529 s, 1469 s, 1439 s, 1265 vs, 1241 vs, 1221 vs, 1200 s, 1099 s, 1081 vs, 1052 s, 1038 vs, 1010 s, 1003 s, 910 s, 848 s, 763 s cm^{-1}. M.p. 78−81 °C. MS (FAB): *m*/*z* (%) = 269 (60) [$\mathrm{MH^+}$], 185 (100) [$\mathrm{MH^+}$ − dhp]. $\mathrm{C_{12}H_{16}N_2O_5}$ (268.26): calcd. C 53.72, H 6.01, N 10.44; found C 53.51, H 6.16, N 10.46.

3,5-Bis(hydroxymethyl)-1-(tetrahydropyran-2-yl)-1*H*-pyrazole (5): A suspension of $\mathrm{LiAlH_4}$ (10 g, 263 mmol) in diethyl ether (1.0 l) was prepared, and a solution of compound **4** (12 g, 45 mmol) in tetrahydrofuran (100 mL) was slowly added. After completion of the addition, the reaction mixture was left stirring for 1 h and water (50 mL) was then added dropwise to the cooled suspension (0 °C). The solvent was removed under reduced pressure and the resulting white cake was suspended in methanol (1.0 l), treated with $\mathrm{CO_2}$(g) for 10 min, and finally refluxed for 6 h. The solid was filtered off and the filtrate was concentrated and dried under vacuum to give the wax-like colorless product **5** (8.0 g, 37 mmol, 82%), from which solvent could not be removed completely. ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 1.61−1.78 (m, 3 H, $\mathrm{CH_2^{thp,4/5}}$), 1.87−2.08 (m, 2 H, $\mathrm{CH_2^{thp,3/4}}$), 2.19 (m, 1 H, $\mathrm{CH_2^{thp,3}}$), 3.52 (dt, ^3J = 9.9/3.0 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 3.86 (d, ^3J = 9.9 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 4.40 (s, 2 H, $\mathrm{CH_2OH}$), 4.45 (s, 2 H, $\mathrm{CH_2OH}$), 5.28 (dd, ^3J = 8.5/1.6 Hz, 1 H, $\mathrm{CH^{thp,2}}$), 6.04 (s, 1 H, $\mathrm{CH^{pz}}$). ^{13}C NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 22.3 ($\mathrm{CH_2^{thp,4}}$), 24.6 ($\mathrm{CH_2^{thp,5}}$), 29.4 ($\mathrm{CH_2^{thp,3}}$), 54.7 ($\mathrm{CH_2OH}$), 58.3 ($\mathrm{CH_2OH}$), 67.7 ($\mathrm{CH_2^{thp,6}}$), 85.1 ($\mathrm{CH^{thp,2}}$), 105.1 ($\mathrm{CH^{pz,4}}$), 143.3 ($\mathrm{C^{pz,5}}$), 151.3 ($\mathrm{C^{pz,3}}$). IR (KBr): $\tilde{\nu}_{max}$ = 3329 vs, 2929 vs, 2860 vs, 1647 w, 1546 w, 1461 vs, 1401 vs, 1377 vs, 1316 vs, 1258 vs, 1204 s, 1133 s, 1080 vs, 1036 vs, 999 vs, 916s, 880 s, 844 s, 810 s cm^{-1}. M.p. 47−48 °C. MS (EI, HR): *m*/*z* (%) [Err(mmu)] = 212.1143 (20) [−1.8] [$\mathrm{C_{10}H_{16}N_2O_3}$ [$\mathrm{M^+}$], 129.0656 (40) [−0.8] [$\mathrm{C_5H_9N_2O_2}$ ($\mathrm{M^+}$ − dhp)], 85.0673 (100) [+2.0] [$\mathrm{C_5H_9O}$ (dhp + $\mathrm{H^+}$)]. $\mathrm{C_{10}H_{16}N_2O_3}$ (212.24): calcd. C 56.59, H 7.59, N 13.19; found C 55.07, H 7.37, N 12.99 (product contains unremovable traces of solvent).

1-(Tetrahydropyran-2-yl)-1*H*-pyrazole-3,5-dicarbaldehyde (6). − Method A: A suspension of **5** (8 g, 37 mmol) and activated $\mathrm{MnO_2}$ (65 g, 747 mmol) in 1,2-dimethoxyethane (500 mL) was refluxed for 3 h and then filtered whilst hot. The solvent was removed in vacuo and the residue was recrystallized from light petroleum ether to give **6** (1.54 g, 7.4 mmol, 20%) as colorless crystals. − **Method B:** Oxalyl chloride (12.7 g, 100 mmol) was dissolved in dichloromethane (500 mL) and cooled to −60 °C. Dimethyl sulfoxide (15 g, 192 mmol) was added to the stirred solution by syringe. After 2 min, a solution of **5** (5 g, 23.6 mmol) in dimethyl sulfoxide (50 mL) was added over 5 min. Stirring was continued for an additional 15 min, still at low temperature. Triethylamine (48.8 g, 726 mmol) was then added and the reaction mixture was stirred for further 5 min and finally allowed to warm to room temperature. The mixture was hydrolyzed with ice and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed twice with cold hydrochloric acid (2%), twice with concentrated sodium bicarbonate solution, and once with brine. The organic phase was dried with magnesium sulfate. Removal of the solvent and purification by column chromatography [silica; light petroleum ether/diethyl ether, 1:1; R_f (diethyl ether) = 0.58] yielded **6** (2.81 g, 13.5 mmol, 57%) as a colorless solid. ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 1.64−1.80 (m, 3 H, $\mathrm{CH_2^{thp,4/5}}$), 2.00−2.08 (m, 2 H, $\mathrm{CH_2^{thp,3/4}}$), 2.37 (m, 1 H, $\mathrm{CH_2^{thp,3}}$), 3.77 (dt, ^3J = 9.5/3.2 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 4.07 (d, ^3J = 9.5 Hz, 1 H, $\mathrm{CH_2^{thp,6}}$), 6.21 (dd, ^3J = 9.5/2.4 Hz, 1 H, $\mathrm{CH^{thp,2}}$), 7.42 (s, 1 H, $\mathrm{CH^{pz}}$), 9.96 (s, 1 H, HC=O), 10.03 (s, 1 H, HC=O). ^{13}C NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 21.9 ($\mathrm{CH_2^{thp,4}}$), 24.4 ($\mathrm{CH_2^{thp,5}}$), 29.2 ($\mathrm{CH_2^{thp,3}}$), 67.9 ($\mathrm{CH_2^{thp,6}}$), 86.5 ($\mathrm{CH^{thp,2}}$), 113.7 ($\mathrm{CH^{pz,4}}$), 140.4 ($\mathrm{C^{pz,5}}$), 150.3 ($\mathrm{C^{pz,3}}$), 179.4, 185.6 (HC=O). IR (KBr): $\tilde{\nu}_{max}$ = 3117 s, 2935 s, 2849 s, 1684 vs, 1458 s, 1439 s, 1317 s, 1250 vs, 1205 s, 1135 s, 1118 s, 1086 vs, 1057 vs, 1040 vs, 1001 s, 914 s, 843 s, 811 s, 771 s, 752 vs cm^{-1}. M.p. 55 °C. MS (EI): *m*/*z* (%) = 208 (20) [$\mathrm{M^+}$], 85 (100) [$\mathrm{dhpH^+}$]. $\mathrm{C_{12}H_{12}N_2O_3}$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.56, H 5.82, N 13.32.

3,5-Bis[(2,6-diisopropylphenyl)iminomethyl]-1*H*-pyrazole (7): 2,6-Diisopropylaniline (3.2 g, 18 mmol), triethyl orthoacetate (3.2 g, 20 mmol), and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of **6** (1.66 g, 8 mmol) in toluene (100 mL), and the solution was refluxed overnight. After removal of the solvent, the red, oily residue was redissolved in diethyl ether, washed with aqueous ammonia, and dried with magnesium sulfate. The solvents were evaporated to dryness. Purification was achieved by column chromatography [silica; light petroleum ether/diethyl ether, 9:1; R_f (light petroleum ether/diethyl ether, 1:1) = 0.63] and subsequent recrystallization from light petroleum ether to yield **7** (1.1 g, 2.4 mmol, 31%) as a pale brown solid. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.23 (d, ^3J = 6.8 Hz, 24 H, $\mathrm{CH_3}$), 3.01 (sept, ^3J = 6.8 Hz, 4 H, $\mathrm{CH^{iPr}}$), 7.20 (s, $\mathrm{6H^{Ph,3/4/5}}$), 7.30, 7.36 (s, 1 H, $\mathrm{CH}^{\mathrm{pz,4}\ [\mathit{syn/anti}\ \mathrm{isomers}]}$), 8.29 (s, 2 H, N=CH). ^{13}C NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 23.4 ($\mathrm{CH_3}$), 27.8 ($\mathrm{CH^{iPr}}$), 107.4 ($\mathrm{CH^{pz,4}}$), 122.9

($CH^{Ph,3/5}$), 124.9 ($CH^{Ph,4}$), 137.4 ($C^{Ph,1/2/6}$), 155.3 (br, N=CH), ($C^{pz,3/5}$) not observed. IR (KBr): $\tilde{\nu}_{max}$ = 3425 s, 3147 s, 3094 s, 3063 s, 2954 vs, 2862 s, 1642 vs, 1625 vs, 1584 w, 1455 vs, 1427 s, 1378 s, 1358 s, 1324 s, 1179 w, 1142 vs, 994 s, 931 w, 859 vs, 789 vs, 745 vs, 684 w, 621 w cm^{-1}. M.p. 146−148 °C. MS (FAB): *m*/*z* (%) = 443 (100) [MH^+], 400 (40) [$MH^+ - i$Pr]. $C_{29}H_{38}N_4$ (442.63): calcd. C 78.68, H 8.65, N 12.65; found C 78.29, H 8.69, N 12.28.

Methyl 3-Hydroxymethyl-1-(tetrahydropyran-2-yl)-1*H*-pyrazole-5-carboxylate (8): Compound **4** (11 g, 41 mmol) was dissolved in 1.0 L of a 1:2 mixture of tetrahydrofuran and diethyl ether and the solution was cooled to −78 °C. A solution of DIBAH in cyclohexane (1 M, 90 mL, 90 mmol) was then added by syringe. After completion of the addition, stirring was continued for 1 h and water (50 mL) was added dropwise to the cooled suspension (0 °C). The solvent was removed under reduced pressure and the resulting white cake was suspended in methanol (1.0 l), treated with CO_2(g) for 10 min, and finally refluxed for 6 h. The solid was filtered off and the filtrate was concentrated to give the crude, colorless product **8** (7.95 g, 33 mmol, 81%). Crystalline material could be obtained by recrystallization from dichloromethane/light petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58−1.81 (m, 3 H, $CH_2^{thp,4/5}$), 1.94−2.07 (m, 2 H, $CH_2^{thp,3/4}$), 2.36 (m, 1 H, $CH_2^{thp,3}$), 3.71 (dt, ^3J = 10.9/2.7 Hz, 1 H, $CH_2^{thp,6}$), 3.85 (s, 3 H, CH_3), 4.07 (dd, ^3J = 10.9/2.7 Hz, 1 H, $CH_2^{thp,6}$), 4.67 (s, 2 H, CH_2OH), 6.25 (dd, ^3J = 9.5/1.6 Hz, 1 H, $CH^{thp,2}$), 6.86 (s, 1 H, CH^{pz}). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 22.7 ($CH_2^{thp,4}$), 24.8 ($CH_2^{thp,5}$), 29.7 ($CH_2^{thp,3}$), 51.9 (CH_3), 58.7 (CH_2OH), 68.3 ($CH_2^{thp,6}$), 85.0 ($CH^{thp,2}$), 110.5 ($CH^{pz,4}$), 133.0 ($C^{pz,5}$), 151.7 ($C^{pz,3}$), 159.8 (C=O). IR (KBr): $\tilde{\nu}_{max}$ = 3323 s, 3216 s, 2947 s, 2847 s, 1731 vs, 1449 s, 1429 s, 1392 s, 1259 vs, 1240 vs, 1197 s, 1091 s, 1079 s, 1041 vs, 1005 s, 913 s, 765 s cm^{-1}. M.p. 78 °C. MS (EI): *m*/*z* (%) = 240 (1) [M^+], 156 (20) [M^+ − dhp], 84 (100) [dhp^+]. $C_{11}H_{16}N_2O_4$ (240.25): calcd. C 54.99, H 6.71, N 11.66; found C 55.10, H 6.75, N 11.68.

Ethyl 5(3)-Ethylthiomethyl-1*H*-pyrazole-3(5)-carboxylate (9): The pyrazole derivative **G** (0.85 g, 5.0 mmol) was treated with thionyl chloride (30 mL) and stirred for 3 h at 0 °C. After evaporation of the solvent in vacuum, ethyl 5-(chloromethyl)pyrazole-3-carboxylate remained as a white solid and was dissolved in THF (100 mL). In a second vessel, a solution of ethanethiol (0.37 mL, 5.0 mmol) in THF (50 mL) was cooled to −70 °C and treated with BuLi (2.0 mL of a 2.5 M solution in hexane). After stirring for 5 min, this cold reaction mixture was transferred by cannula to the cooled solution of ethyl 5-chloromethylpyrazole-3-carboxylate (−70 °C). The mixture was left stirring overnight while warming to room temperature, then treated with aqueous NH_4Cl and extracted several times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure to give the product **9** as a slightly yellow oil (0.9 g, 4.3 mmol, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.39 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.50 (q, ^3J = 7.4 Hz, 2 H, SCH_2), 3.79 (s, 2 H, CH_2), 4.39 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 6.78 (s, 1 H, CH^{pz}). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.7 (CH_3), 26.0 (SCH_2), 27.3 (SCH_2), 61.7 (OCH_2), 108.1 ($CH^{pz,4}$), 139.8/147.6 ($C^{pz,3/5}$), 161.3 (C=O). MS (EI): *m*/*z* (%) = 214 (14) [M^+], 154 (100) [M^+ −SEt], 108 (83) [M^+ −SEt −OEt]. $C_9H_{14}N_2O_2S$ (214.29): calcd. C 50.45, H 6.58, N 13.07; found C 50.56, H 6.80, N 12.92.

***N*,*N*-Diethyl-5(3)-ethylthiomethyl-1*H*-pyrazole-3(5)-carboxamide (10):** A solution of diethylamine (1.14 mL, 11.0 mmol) in THF (50 mL) was cooled to −70 °C and treated with BuLi (4.4 mL of a 2.5 M solution in hexane). After stirring for 5 min, this cold reaction mixture was slowly transferred by cannula to a precooled (−70 °C) solution of **9** (5 mmol) in THF (100 mL). The mixture was left stirring overnight while warming to room temperature, then treated with aqueous NH_4Cl and extracted several times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure to give the product **10** as a slightly yellow oil (1.1 g, 4.6 mmol, 92%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, ^3J = 7.5 Hz, 9 H, CH_3), 2.50 (q, ^3J = 7.5 Hz, 2 H, SCH_2), 3.44−3.70 (m, br, 4 H, *E*/*Z*-NCH_2), 3.77 (s, 2 H, CH_2), 6.49 (s, 1 H, CH^{pz}). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 13.1 (CH_3), 14.7 (CH_3), 25.9 (SCH_2), 27.8 (br, SCH_2), 41.5 (NCH_2), 43.3 (NCH_2), 106.0 ($CH^{pz,4}$), $C^{pz,3/5}$ not observed, 161.8 (C=O). MS (EI): *m*/*z* (%) = 241 (7) [M^+], 181 (100) [M^+ − SEt], 108 (32) [M^+ − SEt − NEt_2]. $C_{11}H_{19}N_3OS$ (241.36): calcd. C 54.74, H 7.94, N 17.41; found C 54.98, H 7.66, N 17.68.

3(5)-Diethylaminomethyl-5(3)-ethylthiomethyl-1*H*-pyrazole (11): A solution of **10** (5.0 mmol) in diethyl ether (50 mL) was added dropwise at room temperature to a suspension of $LiAlH_4$ (0.19 g, 5.0 mmol) in diethyl ether (100 mL). The reaction mixture was left stirring overnight and then heated to reflux for 30 min. After the mixture had been cooled to 0 °C, water (0.38 mL), aqueous NaOH (15%; 0.38 mL), and again water (0.38 mL) were carefully added. The precipitate formed was filtered off and washed several times with small portions of diethyl ether. The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure to give the product **11** as a slightly yellow oil (0.7 g, 2.9 mmol, 58%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, ^3J = 7.1 Hz, 6 H, CH_3), 1.24 (t, ^3J = 7.4 Hz, 3 H, CH_3), 2.49−2.60 (m, 6 H, CH_2), 3.63 (s, 2 H, CH_2), 3.73 (s, 2 H, CH_2), 6.10 (s, 1 H, CH^{pz}). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 11.5 (CH_3), 14.6 (CH_3), 25.6 (SCH_2), 27.9 (br, SCH_2), 46.8 (NCH_2), 48.9 (NCH_2), 104.6 ($CH^{pz,4}$), 143.5/148.6 (br, $C^{pz,3/5}$). IR (film): $\tilde{\nu}_{max}$ = 3179 vs, 3096 vs, 2963 vs, 2806 vs, 1567 m, 1452 s, 1370 s, 1351 m, 1288 w, 1163 m, 1127 m, 1058 m, 1001 m, 803 m cm^{-1}. MS (EI): *m*/*z* (%) = 228 (100) [M^+]. $C_{11}H_{21}N_3S$ (227.37): calcd. C 58.11, H 9.31, N 18.48; found C 58.66, H 9.52, N 17.68.

X-ray Crystallography. − Crystal Data for 2e·$(ZnCl_2)_2$·0.5 Acetone: $C_{17}H_{30}Cl_4N_4O_2Zn_2$·0.5 acetone (*M* = 624.1), *a* = 7.854(5), *b* = 13.916(5), *c* = 24.766(7) Å, β = 95.10(4), *V* = 2696(2) Å^3, *Z* = 4, *d* = 1.52 g·cm^{-3}, monoclinic, $P2_1$. Data collection: Bruker AXS CCD diffractometer, graphite-monochromated Mo-K_α radiation, crystal size 0.05 × 0.12 × 0.24 mm, *T* = 173 K, ω scan, 1.7° < 2Θ <57.1°, $-10 \le h \le 10$, $-18 \le k \le 18$, $-33 \le l \le 32$, 27887 reflections measured, 16929 reflections observed [$I > 2\sigma(I)$], μ = 2.198 mm^{-1}, no absorption correction. The crystal used for data collection was a nonmerohedral twin. Refinement was carried out with all reflections (overlapped and nonoverlapped) using batch scale factors for the groups of varying overlap (GEMINI, SHELXL97).[23,24] Atomic coordinates and thermal parameters of the non-hydrogen atoms were refined in anisotropic models by full-matrix, least-squares calculation based on F^2. The hydrogen atoms were included in calculated positions. The acetone molecule was found between the two independent molecules and is severely disordered. 566 parameters, *R* = 0.067, R_w = 0.209, residual electron density +1.16/−1.57 e·Å^{-3}. − **Crystal Data for 8:** $C_{11}H_{16}N_2O_4$ (*M* = 240.3), *a* = 4.676(1), *b* = 14.187(3), *c* = 17.716(4) Å, *Z* = 4, *d* = 1.358 g·cm^{-3}, orthorhombic, $P2_12_12_1$. Data collection: Nonius Kappa CCD diffractometer, graphite-monochromated Mo-K_α radiation, crystal size 0.40 × 0.08 × 0.08 mm, *T* = 200 K, ω scan, 3.7° < 2Θ <55.0°, $-6 \le h \le 6$, $-18 \le k \le 18$, $-23 \le l \le 22$, 2670 reflections measured, 2646 independent reflections, 2143 reflections observed [$I > 2\sigma(I)$], μ = 0.104 mm^{-1}, experimental absorption correction. Structural analysis and refinement: Atomic coordinates and thermal parameters of the non-hydrogen atoms were refined in anisotropic models by full-matrix, least-squares calculation based on F^2. The hydrogen atoms were located in the difference Fourier map and refined isotropically. 219 parameters, $R = 0.053$, $R_w = 0.094$, residual electron density $+0.16/-0.20$ e·Å^{-3}. Structures were solved by direct methods with SHELXS-97 and refined with the SHELXL-97 program.[23] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160612 [**2e**·$(ZnCl_2)_2$] and -156768 (**8**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44 1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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