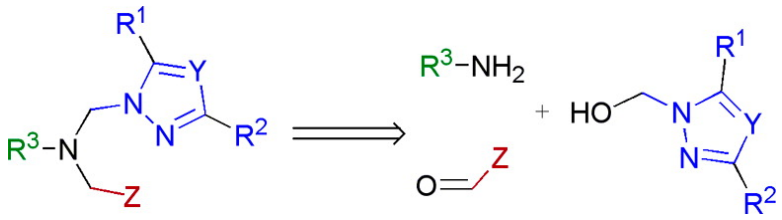
JOURNAL OF combinatorial CHEMISTRY

Article

Efficient Solution Phase Combinatorial Access to a Library of Pyrazole- and Triazole-Containing Compounds

Rachid Touzani, Stefania Garbacia, Olivier Lavastre, Veejendra K. Yadav, and Bertrand Carboni

J. Comb. Chem., **2003**, 5 (4), 375-378• DOI: 10.1021/cc030100b • Publication Date (Web): 04 June 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Efficient Solution Phase Combinatorial Access to a Library of Pyrazole- and Triazole-Containing Compounds

Rachid Touzani,[†] Stefania Garbacia,[†] Olivier Lavastre,*[,†] Veejendra K. Yadav,[‡,§] and Bertrand Carboni*[,‡]

Institut de chimie, UMR 6509 CNRS and UMR 6510 CNRS, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France

Received February 6, 2003

An efficient method for the synthesis of multidentate molecules, with various building blocks, such as pyrazolyl, triazolyl, pyridyl, furyl, or bispinidyl derivatives, is reported. This approach is based on the condensation of easily available *N*-alkyl heteroarylamines with *N*-hydroxymethyl pyrazoles or triazoles.

The development of new methods for the synthesis of heterocyclic compound libraries is an ever-expanding area in combinatorial chemistry. Neutral tripodal N-donor compounds have found wide applications as models for bioinorganic systems and novel efficient homogeneous catalysts.[1] For a number of them, the pyrazole ring has emerged as one of the key structural units.[2] For example, polypyrazolyl compounds have been used as mimics of active sites in copper oxidases,[3] while tris(pyrazolyl)borates **I** have been involved in the discovery of new activation processes and new catalytic reactions.[4] The bis(pyrazolyl)amines **II** also constitute another class of attractive 6-electron-donating ligands with two different types of nitrogen atoms (Figure 1).[5]

Of particular appeal to medicinal and coordination chemists is the ease with which the electronic richness of the donor atoms and the steric bulk of the substituents can be changed. In this context, we report herein a general and flexible method for the synthesis of a diversity of tripodal compounds **6** (Figure 2) using readily available, if not purchasable, starting materials. This method offers the opportunity to change, à la carte, one, two, or all of the three building blocks.

Recently, the use of specific equipment for high-throughput experiments in combinatorial chemistry has shown great impact for creating molecular diversity.[6] The main advantage of such an approach is that all the steps, including the mixing of starting products, the control of the experimental conditions, and the purification of the products, were fully automated. However, because all molecules are prepared simultaneously and under the same conditions, it is necessary to involve truly efficient reactions and use fast and simple purification techniques.

According to these specifications and as described in Scheme 1, our approach for the synthesis of compounds

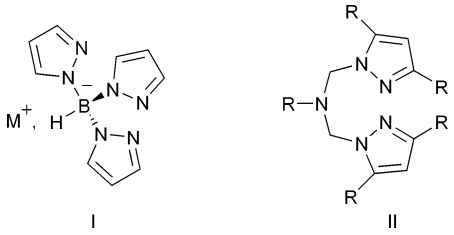


Figure 1. Some pyrazole-based chelating ligands.

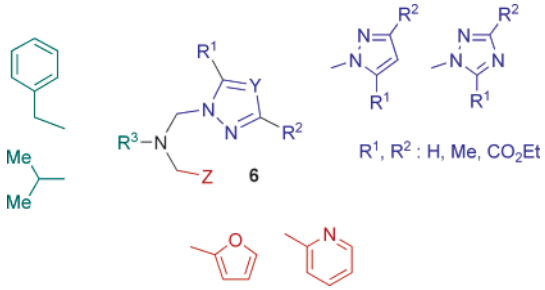
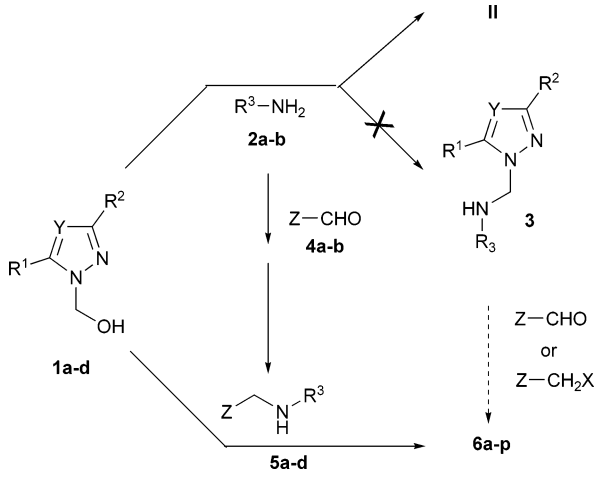


Figure 2. Tripodal molecules with three modular building blocks.

Scheme 1. Lego Construction of Compounds **6a**−**p**



6a−**p** is based on the condensation of 1-hydroxymethyl pyrazoles **1a**−**c**[7] or 1-hydroxymethyl triazole **1d**[8] with heterocyclic secondary amines **5a**−**d**. The latter are easily obtained from the corresponding amines and aldehydes by

* Address correspondence to either author. Lavastre phone: 33 223235630. E-mail: olivier.lavastre@univ-rennes1.fr. Carboni phone: 33 223236747. E-mail: bertrand.carboni@univ-rennes1.fr.

[†] UMR 6509 CNRS, Université de Rennes 1.

[‡] UMR 6510 CNRS, Université de Rennes 1.

[§] On leave from Indian Institute of Technology, Kanpur 208016, India.

10.1021/cc030100b CCC: $25.00
Published on Web 06/04/2003

Table 1. Tridentate *N,N,N-* or *N,N,O* Compounds **6a**−**p**

product	Y	R^1	R^2	R^3	Z	yield (%)
6a	CH	H	H	$C_6H_5CH_2$	2-furyl	90
6b	CH	H	H	$(CH_3)_2CH$	2-furyl	90
6c	CH	Me	Me	$(CH_3)_2CH$	2-furyl	60
6d	CH	Me	Me	$(CH_3)_2CH$	2-furyl	70
6e	CH	Me	$CO_2C_2H_5$	$C_6H_5CH_2$	2-furyl	90
6f	CH	Me	$CO_2C_2H_5$	$(CH_3)_2CH$	2-furyl	90
6g	N	H	H	$C_6H_5CH_2$	2-furyl	85
6h	N	H	H	$(CH_3)_2CH$	2-furyl	90
6i	CH	H	H	$C_6H_5CH_2$	2-pyridyl	75
6j	CH	H	H	$(CH_3)_2CH$	2-pyridyl	60
6k	CH	Me	Me	$C_6H_5CH_2$	2-pyridyl	90
6l	CH	Me	Me	$(CH_3)_2CH$	2-pyridyl	55
6m	CH	Me	$CO_2C_2H_5$	$C_6H_5CH_2$	2-pyridyl	75
6n	CH	Me	$CO_2C_2H_5$	$(CH_3)_2CH$	2-pyridyl	56
6o	N	H	H	$C_6H_5CH_2$	2-pyridyl	85
6p	N	H	H	$(CH_3)_2CH$	2-pyridyl	52

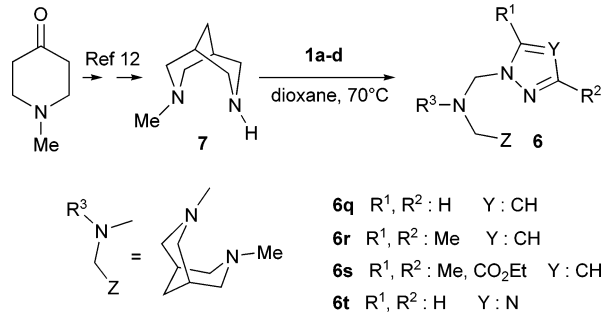
reductive amination. It is worthy to note that the inverse sequence, that is, synthesis of secondary amine **3** then reductive amination of Z-CHO or alkylation with ZCH_2X, was not retained because of the difficulty in directly obtaining potential precursors **3** in pure form and good yields. Direct reaction between reagents **1** and **2** leads indeed to the major formation of symmetrical compounds of type II, as previously reported by several groups.[9]

The starting compounds **5a**−**c** were first separately synthesized in 80−90% yields using a two-step protocol. Condensation of 2-furylaldehyde **4a** or 2-pyridylaldehyde **4b** with benzylamine **2a** or isopropylamine **2b** in THF for 16 h was followed by the reduction of the resulting imine by $NaBH_4$ in ethanol for 1 h and purification by Kugelrohr distillation.[10] Hydroxyalkylation of pyrazole, its 3,5-disubstituted derivatives, or triazole with formaldehyde afforded the other set of reagents **1a**−**d**.[7,8] A library of 16 new compounds **6a**−**p** were then prepared simultaneously using an automated solution-phase parallel chemistry by simply stirring the two components at 70 °C for 24 h in dioxane. Transfer of the crude material to a silica gel column for filtration gave **6a**−**p** in good to moderate yields and good purity (Table 1).

The structures were established by ^{1}H NMR spectroscopy, mainly in view of two singlets of equal intensity in the range of δ 4.85−5.05 for the pyrazolyl-C*H*$_2$ or δ 4.99−5.10 for triazolyl-C*H*$_2$ and in the range of δ 3.67−3.85 for the 2-furyl-C*H*$_2$ or δ 3.90−4.00 for 2-pyridyl-C*H*$_2$. ^{13}C chemical shifts and IR and mass spectra were also in good agreement with the proposed structures. Yields were not optimized, and minor amounts of starting materials (≈5%) were detected by ^{1}H NMR spectroscopy. Differences in yields could be probably explained by the application of the same purification protocol to all crude products **6**.

To vary the spatial environment of the donor atoms and following the same approach, we also prepared four other new compounds possessing a bispinidine framework.[11] The starting amine **7** was first prepared according to the literature[12] and coupled with the pyrazolyl or triazolyl unit, as previously described, to afford the corresponding compounds **6q**−**t** in almost quantitative yields (Scheme 2). The structures of these new compounds were ascertained by ^{1}H NMR (δ 4.68−4.98 for azolyl-C*H*$_2$−N), ^{13}C NMR (δ 69.5−72.8 for azolyl-*C*H$_2$−N), and mass spectroscopy.

Scheme 2. Synthesis of Bispinidine Derivatives **6q**−**t**



In conclusion, we have developed an efficient access to tripodal compounds with the opportunity to change easily one, two, or all three of the building blocks. This method takes advantage of the vast number of commercially available heterocycles containing aldehydes and aliphatic or aromatic amines. Such a structural and electronic diversity makes this approach well suited to the production of large arrays of compounds for potential applications in medicinal or coordination chemistry. Further developments on this subject are currently in progress.

Experimental Section

General Details. Commercially available reagents were used without further purification, and solvents were dried by standard procedures. Reactions were performed using a Chemspeed ASW 1000 under an atmosphere of dry nitrogen. Infrared spectra were recorded in the range of 4000−600 cm^{-1} on a IRFT BIORAD 175C spectrometer, and they are reported in centimeters^{-1}. NMR spectra were recorded using a Bruker ARX 200 instrument operating at 200 MHz for ^{1}H spectra and 50 MHz for ^{13}C spectra. *J* values were recorded in Hz, and multiplicities were expressed by the usual conventions. HRMS were obtained with a Varian MAT 311 mass spectrometer (Centre Régional de Mesures Physiques de l'Ouest, Rennes, France).

General Procedure for the Automated Synthesis of 6a−**p.** Stock solutions of **1a**−**d** (0.39 M in dioxane) and **5a**−**d** (0.39 M in dioxane) were prepared. These solutions were selectively dispatched in 16 tubes to generate the 16 possible combinations [1500 μL of **1a**−**d** (0.6 mmol) and 1500 μL of **5a**−**d** (0.6 mmol)]. After stirring at 70 °C for 24 h, the solvent was removed under vacuum. The crude products were dissolved in MeOH/CH_2Cl_2 1:19 (2 mL) and transferred to silica gel columns (2.5 × 1 cm). Elution using the same solvent combination (2 mL × 5) was performed. The solvents were removed, and the residues were dried in vacuum to give oils, which were kept under nitrogen in the freezer for storage.

***N*-Benzyl-*N*-(2-furylmethyl)-*N*-(1*H*-pyrazol-1-ylmethyl)amine 6a.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.67 (d, 1H, J = 1.6 Hz), 7.50−7.30 (m, 7H), 6.42−6.32 (m, 3H), 5.05 (s, 2H), 3.84 (s, 2H), 3.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.6, 142.8, 140.0, 138.7, 130.6, 129.2, 128.7, 127.8, 110.7, 109.4, 105.8, 68.3, 55.8, 48.8. IR (KBr): υ 1508, 1452, 1393, 1292, 1081, 737 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{13}NO$ $[M - C_3H_4N_2]^+$ 199.0997, found 199.099.

***N*-(2-Furylmethyl)-*N*-isobutyl-*N*-(1*H*-pyrazol-1-ylmethyl)-amine 6b.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.54−7.48 (m, 2H), 7.42−7.39 (m, 1H), 6.40−6.34 (m, 1H), 6.30−6.25 (m, 2H), 5.00 (s, 2H), 3.85 (s, 2H), 3.18 (hept, 1H, J = 6.6 Hz), 1.05 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.8, 142.0, 139.0, 129.0, 110.2, 108.3, 105.5, 66.8, 50.9, 44.4, 19.5. IR (KBr): υ 1508, 1465, 1393, 1261, 1166, 1083 cm^{-1}. HRMS (EI) calcd for $C_9H_{13}NO$ [M − $C_3H_4N_2$]$^+$ 151.0997, found 151.100.

***N*-Benzyl-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-*N*-(2-furylmethyl)amine 6c.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45−7.20 (m, 6H), 6.38−6.32 (m, 1H), 6.30−6.25 (m, 1H), 5.85 (s, 1H), 4.85 (s, 2H), 3.80 (s, 2H), 3.75 (s, 2H), 2.30 (s, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.8, 147.0, 141.8, 139.8, 138.4, 128.5, 128,0, 126.8, 109.9, 108.7, 105.4, 65.9, 54.7, 47.4, 13.3, 10.6. IR (KBr): υ 1508, 1452, 1393, 1292, 1147, 1081, 1046, 738 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{13}NO$ [M − $C_5H_8N_2$]$^+$ 199.0997, found 199.100.

***N*-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]-*N*-(2-furylmethyl)-*N*-isobutylamine 6d.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35−7.29 (m, 1H), 6.34−6.25 (m, 1H), 6.22−6.15 (m, 1H), 5.80 (s, 1H), 4.81 (s, 2H), 3.71 (s, 2H), 3.10 (hept, 1H, J = 6.7 Hz), 2.22 (s, 3H), 2.19 (s, 3H), 1.05 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.8, 147.8, 142.1, 140.2, 110.6, 108.4, 106.2, 64.8, 49.9, 44.0, 19.0, 13.9, 11.4. IR (KBr): υ 1556, 1461, 1381, 1316, 1174, 778 cm^{-1}. HRMS (EI) calcd for $C_9H_{13}NO$ [M − $C_5H_8N_2$]$^+$ 151.0997, found 151.098.

Ethyl 1-{[Benzyl(2-furylmethyl)amino]methyl}-5-methyl-1*H*-pyrazole-3-carboxylate 6e. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43−7.15 (m, 6H), 6.61 (s, 1H), 6.38−6.32 (m, 1H), 6.30−6.24 (m, 1H), 5.00 (s, 2H), 4.41 (q, 2H, J = 7.1 Hz), 3.80 (s, 2H), 3.75 (s, 2H), 2.25 (s, 3H), 1.45 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.6, 151.3, 142.3, 142.1, 149.5, 136.9, 128.7, 128.2, 127.1, 110.1, 109.2, 108.6, 67.4, 60.6, 54.8, 47.6, 14.2, 10.8. IR (KBr): υ 1716, 1601, 1552, 1450, 1367, 1102, 1073 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{13}NO$ [M − $C_7H_{10}N_2O_2$]$^+$ 199.0997, found 199.098.

Ethyl 1-{[(2-Furylmethyl)(isobutyl)amino]methyl}-5-methyl-1*H*-pyrazole-3-carboxylate 6f. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32−7.28 (m, 1H), 6.51 (s, 1H), 6.29−6.25 (m, 1H), 6.20−6.15 (m, 1H), 4.94 (s, 2H), 4.35 (q, 2H, J = 7.1 Hz), 3.67 (s, 2H), 3.05 (hept, 1H, J = 6.7 Hz), 2.20 (s, 3H), 1.35 (t, 3H, J = 7.1 Hz), 1.02 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.6, 152.7, 141.9, 141.6, 140.6, 110.1, 108.8, 108.0, 65.9, 60.5, 49.6, 43.5, 18.4, 14.2, 10.9. IR (KBr,): υ 1719, 1553, 1445, 1213, 1075, 780 cm^{-1}. HRMS (EI) calcd for $C_9H_{13}NO$ [M − $C_7H_{10}N_2O_2$]$^+$ 151.0997, found 151.100.

***N*-Benzyl-*N*-(2-furylmethyl)-*N*-(1*H*-1,2,4-triazol-1-ylmethyl)amine 6 g.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.10 (s, 1H), 8.04 (s, 1H); 7.47−7.25 (m, 6H), 6.40−6.34 (m, 2H), 5.06 (s, 2H), 3.85 (s, 2H), 3.78 (s, 2H).^{13}C NMR ($CDCl_3$, 50 MHz): δ 151.8, 151.3, 143.9, 142.4, 135.6, 128.8, 128.4, 127.5, 110.2, 109.2, 65.4, 55.4, 48.3. IR (KBr): 3116, 1501, 1452, 1366, 1074, 739 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{13}$-NO [M − $C_2H_2N_3$]$^+$ 199.0997, found 199.096.

***N*-(2-Furylmethyl)-*N*-isobutyl-*N*-(1*H*-1,2,4-triazol-1-ylmethyl)amine 6h.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.20 (s, 1H), 7.98 (s, 1H), 7.45 (d, 1H, J = 1 Hz), 6.39−6.32 (m, 2H), 5.10 (s, 2H), 3.85 (s, 2H), 3.20 (hept, 1H, J = 6.6 Hz), 1.10 (d, 6H, J = 6.6 Hz).^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.5, 152.1, 143.6, 142.9, 110.8, 109.2, 65.5, 51.9, 45.3, 20.2. IR (KBr): υ 1720, 1534, 1463, 1565, 1272, 1081, 708 cm^{-1}. HRMS (EI) calcd for $C_9H_{13}NO$ [M − $C_2H_2N_3$]$^+$ 151.0997, found 199.099.

***N*-Benzyl-*N*-(1*H*-pyrazol-1-ylmethyl)-*N*-(pyridin-2-ylmethyl)amine 6i.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.55−8.60 (m, 1H), 7.72−7.15 (m, 10H), 6.33 (t, 1H, J = 2 Hz), 5.03 (s, 2H), 3.91 (s, 2H), 3.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.9, 149.1, 139.3, 138.3, 136.4, 130.3, 128.8, 128.4, 127.2, 123.1, 122.1, 105.2, 67.9, 57.4, 55.9. IR (KBr): 3062, 1590, 1570, 1452, 1257, 1084, 749 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{14}N_2$ [M − C_6H_6N]$^+$ 210.1157, found 210.117.

***N*-Isobutyl-*N*-(1*H*-pyrazol-1-ylmethyl)-*N*-(pyridin-2-ylmethyl)amine 6j.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.52−8.61 (m, 1H), 7.68−7.40 (m, 4H), 7.15−7.09 (m, 1H), 6.21 (t, 1H, J = 2 Hz), 4.95 (s, 2H), 3.92(s, 2H), 3.15(hept, 1H, J = 6.6 Hz), 1.00 (d, 6H, J = 6.6 Hz). IR (KBr): 3031, 1591, 1471, 1435, 1235, 1085, 617 cm^{-1}. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9, 148.8, 138.7, 136.3, 129.2, 122.5, 122.0, 105.4, 67.2, 52.9, 51.0, 19.3. IR (KBr): 3031, 1591, 1471, 1435, 1235, 1085, 617 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{15}N_2$ [M − $C_3H_3N_2$]$^+$ 163.1235, found 163.125.

***N*-Benzyl-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-*N*-(pyridin-2-ylmethyl)amine 6k.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.55−8.63 (m, 1H), 7.65(t, 1H, J = 7.6 Hz), 7.45−7.12 (m, 7H), 5.80 (s, 1H), 4.86 (s, 2H), 3.90 (s, 2H); 3.80 (s, 2H), 2.23 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 148.8, 147.2, 139.8, 138.5, 136.2, 128.7, 128.1, 126.9, 122.8, 121.8, 105.3, 65.8, 57.3, 55.8, 13.4, 10.7. IR (KBr): 3208, 1555, 1432, 1383, 1251, 1073, 762 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{14}N_2$ [M − $C_5H_8N_2$]$^+$ 210.1157, found 210.117.

***N*-Isobutyl-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-*N*-(pyridin-2-ylmethyl)amine 6l.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.48−8.56 (m, 1H), 7.62 (dt, 1H, J = 7.7 and 1.8 Hz), 7.38−7.32 (m, 1H), 7.18−7.14 (m, 1H), 5.78 (s, 1H), 4.85 (s, 2H), 3.90 (s, 2H), 3.10 (hept, 1H, J = 6.7 Hz), 2.20 (s, 6H), 1.10 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.9, 148.7, 147,0, 139.5, 136.2, 122.5, 121.6, 105.8, 65.0, 53.1, 50.3, 18.7, 13.4, 11.1. IR (KBr): 3143, 1589, 1463, 1381, 1069, 756 cm^{-1}. HRMS (EI) calcd for $C_9H_{13}N_3$ [M − C_6H_6N]$^+$ 166.1344, found 166.135.

Ethyl 1-{[Benzyl(pyridin-2-ylmethyl)amino]methyl}-5-methyl-1*H*-pyrazole-3-carboxylate 6m. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.52−8.58 (m, 1H), 7.65 (dt, 1H, J = 7.7 and 1.8 Hz), 7.40−7.10 (m, 7H), 6.55 (s, 1H), 5.02 (s, 2H), 4.40 (q, 2H, J = 7.1 Hz), 3.90 (s, 2H), 3.78 (s, 2H), 2.10 (s, 3H), 1.38 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.5, 158.4, 148.9, 142.3, 140.7, 137.9, 136.3, 128.7, 128.1, 127.1, 122.7, 122.0, 108.4, 67.0, 60.5, 57.2, 55.7, 14.2, 10.8. IR (KBr): 1716, 1583, 1435, 1216, 1106, 763 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{16}N_4O_2$ [M − C_7H_7]$^+$ 272.1273, found 272.129.

Ethyl 1-{[Isobutyl(pyridin-2-ylmethyl)amino]methyl}-5-methyl-1*H*-pyrazole-3-carboxylate 6n. ^{1}H NMR ($CDCl_3$,

200 MHz): δ 8.45−8.52 (m, 1H), 7.55 (dt, 1H, J = 7.6 and 1.7 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.10−7.04 (m, 1H), 6.45-(s, 1H), 4.95(s, 2H), 4.31 (q, 2H, J = 7.1 Hz), 3.84 (s, 2H), 3.10 (hept, 1H, J = 6.6 Hz), 2.20 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz), 1.10 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.4, 159.9, 148.5, 141.95, 140.2, 136.1, 122.39, 121.6, 108.6, 67.4, 66.0, 60.4, 53.0, 50.3, 18.5, 14.1, 11.0. IR (KBr): 1716, 1590, 1435, 1216, 1030, 779 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{18}N_3O_2$ [M − C_6H_6N]$^+$ 224.1399, found 224.140.

***N*-Benzyl-*N*-(pyridin-2-ylmethyl)-*N*-(1*H*-1,2,4-triazol-1-ylmethyl)amine 6o.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.52 (m, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.62 (bt, 1H, J = 7.6 Hz), 7.41−7.10 (m, 7H), 4.99 (s, 2H), 3.80 (s, 2H), 3.68 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.5, 151.1, 148.6, 143.7, 137.0, 136.1, 128.3, 128.0, 127.0, 122.7, 121.9, 65.0, 56.7, 55.5. IR (KBr): 3117, 1590.2, 1570, 1473, 1297, 1188.8, 1016.1, 743.2 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{15}N_2$ [M − $C_2H_2N_3$]$^+$ 211.1235, found 221.123.

***N*-Isobutyl-*N*-(pyridin-2-ylmethyl)-*N*-(1*H*-1,2,4-triazol-1-ylmethyl)amine 6p.** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.60 (m, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.70 (dd, 1H, J = 7.7 and 1.8 Hz), 7.45(d, 1H, J = 7.7 Hz), 7.31−7.20 (m, 1H), 5.10 (s, 2H), 4.00 (s, 2H), 3.30−3.19 (heptet, 1H, J = 6.6 Hz), 1.12 (d, 6H, J = 6.6 Hz).^{13}C NMR ($CDCl_3$; 50 MHz): δ 159.2, 151.5, 149.2, 143.5, 136.7, 122.9, 122.3, 65.5, 53.4, 51.9, 19.8. IR (KBr): 3111.6, 1590.8, 1435.2, 1388.5, 1267.7, 1016.0, 796.2 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{15}N_2$ [M − $C_2H_2N_3$]$^+$ 163.1235, found 162.125.

3-Methyl-7-(1*H*-pyrazol-1-ylmethyl)-3,7-diazabicyclo-[3.3.1]nonane 6q. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55 (d, 1H, J = 1.7 Hz), 7.47 (d, 1H, J = 1.7 Hz), 6.30 (t, 1H, J = 2 Hz), 4.95 (s, 2H), 2.99 (t, 4H, J = 12.1 Hz), 2.66 (dd, 2H, J = 3.2 and 10.5 Hz), 2.26 (dd, 2H, J = 3.2 and 10.5 Hz), 2.24 (3H, s), 1.90−1.80 (m, 2H), 1.48 (dm, 1H, J = 11.7 Hz), 1.30 (dm, 1H, J = 11.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 130.0, 104.6, 72.8, 60.1, 54.0, 47.3, 30.1, 29.2. HRMS (FAB) calcd for $C_{12}H_{19}N_4$ [M − H]$^+$ 219.1610, found 219.161.

3-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]-7-methyl-3,7-diazabicyclo[3.3.1]nonane 6r. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.72 (s, 1H), 4.68 (s, 2H), 2.82 (t, 4H, J = 12.5 Hz), 2.60 (dd, 2H, J = 3.2 and 10.5 Hz), 2.17−2.23 (m, 2H), 2.22 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.90−1.80 (m, 2H), 1.45 (dm, 1H, J = 11.7 Hz), 1.30 (dm, 1H, J = 11.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.5, 139.9, 104.9, 69.5, 60.0, 54.4, 47.0, 29.9, 29.2, 13.4, 11.1. HRMS (FAB) calcd for $C_{14}H_{23}N_4$ [M − H]$^+$ 247.1923, found 247.191.

Ethyl 5-Methyl-1-[(7-methyl-3,7-diazabicyclo[3.3.1]non-3-yl)methyl]-1*H*-pyrazole-3-carboxylate 6s. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.42 (s, 1H), 4.71 (s, 2H), 4.10 (q, 2H, J = 7.1 Hz), 2.84−2.70 (4H, m), 2.53 (dd, 2H, J = 2.7 and 10.7 Hz), 2.25−2.00 (2H, m), 2.25 (3H, s), 2.02 (3H, s), 1.85−1.76 (m, 2H), 1.47 (dm, 1H, J = 11.7 Hz), 1.37 (t, 3H, J = 7.1 Hz), 1.35 (dm, 1H, J = 11.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.5, 141.6, 140.7, 107.9, 77.2, 70.7, 66.7, 60.3, 59.7, 54.2, 46.7, 29.9, 29.0, 14.1, 11.0. HRMS (FAB) calcd for $C_{16}H_{25}N_4O_2$ [M − H]$^+$ 305.1978, found 305.198.

3-Methyl-7-(1*H*-1,2,4-triazol-1-ylmethyl)-3,7-diazabicyclo-[3.3.1]nonane 6t. ^{1}H NMR ($CDCl_3$, 200 MHz,) δ 8.17 (s, 1H), 7.95 (s, 1H), 4.98 (s, 2H), 2.92 (t, 4H, J = 11.1 Hz), 2.65 (dd, 2H, J = 3.2 and 10.5 Hz), 2.23 (dd, 2H, J = 3.2 and 10.5 Hz), 2.13 (s, 3H), 1.85−1.75 (m, 2H), 1.50 (dm, 1H, J = 12.2 Hz), 1.32 (dm, 1H, J = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz,) δ 151.2, 143.6, 70.9, 60.1, 53.8, 47.2, 30.0, 29.2

Acknowledgment. We thank the CNRS, MJENR and the Region Bretagne for their support.

References and Notes

(1) For reviews of nitrogen-containing ligands for asymmetric catalysis, see: Fache, F.; Schultz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. Togni, A.; Venanzi, M. M. L. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 497.

(2) For a review, see: Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151.

(3) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376.

(4) Trofimenko, S.; *Chem. Rev.* **1993**, *93*, 943. Trofimenko, S. *Scorpionates: The coordination chemistry of polypyrazolylborate ligands*; Imperial College Press: London, 1999. Gunnoe, T. B.; Sabat, M.; Harman, W. D. *Organometallics* **2000**, *19*, 728.

(5) Sheu, S−C.; Tien, M.-J.; Cheng, M.-C.; Ho, T.-I.; Peng, S.-M.; Lin, Y.-C. *J. Chem. Soc., Dalton Trans.* **1995**, 3503. Gupta, R.; Lal, T. K.; Mukherjee, R. *Polyhedron* **2002**, *1*, 1245. Gamez, P.; Steensma, R. H.; Driessen, W. L.; Reedijk, J. *Inorg. Chim. Acta* **2002**, *333*, 51. Mathieu, R.; Esquius, G.; Lugan, N.; Pons, J.; Ros, J. *Eur. J. Inorg. Chem.* **2001**, 2683. Esquius, G.; Pons, J.; Yañez, R.; Ros, J. *J. Organomet. Chem.* **2001**, *619*, 14.

(6) Powers, D. G.; Coffen, D. L. *Drug Discov. Today* **1999**, *4*, 377. Doll, R. E. *Mol. Diversity* **1997**, *2*, 223. Gorden, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144.

(7) Katritzky, A. R.; Lue, P.; Akutagawa, K. *Tetrahedron* **1989**, *45*, 4253.

(8) Maier, L.; Kunz, W.; Rist, G. *Phosphor. Sulf.* **1987**, *33*, 41.

(9) Driessen, W. L. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 441. Touzani, R.; Ramdani, A.; Ben-Hadda, T.; El Kadiri, S.; Maury, O.; Le Bozec, H.; Dixneuf, P. H.; Pierre, H. *Synth. Commun.* **2001**, *31*, 1315.

(10) Zylber, I.; Tubul, A.; Brun, P. *Tetrahedron: Asymmetry* **1995**, *6*, 377. Spencer, D. J. E.; Johnson, B. J.; Tolman, W. B. *Org. Lett.* **2002**, *4*, 1391.

(11) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Commun*. **2002**, 673.

(12) Smissman, E. E.; Ruenitz, P. C. *J. Org. Chem.* **1976**, *41*, 1593.

CC030100B