JOC*Article*

New Flexible Synthesis of Pyrazoles with Different, Functionalized Substituents at C3 and C5

Douglas B. Grotjahn,* Sang Van, David Combs,† Daniel A. Lev, Christian Schneider,‡ Marc Rideout,‡ Christoph Meyer,‡ Genaro Hernandez,‡ and Lupe Mejorado‡

Department of Chemistry, San Diego State University, 5500 Campanile Drive, San Diego, California 92182-1030

grotjahn@chemistry.sdsu.edu

Received June 19, 2002

Syntheses of pyrazoles featuring a functionalized side chain attached to carbon 3 and varying alkyl and aryl substituents attached to carbon 5 are presented. Installation of R = methyl, isopropyl, *tert*-butyl, adamantyl, or phenyl groups at C5 is reported here, starting by coupling protected alkynols with acid chlorides RCOCl, forming alkynyl ketones, which are reacted with hydrazine to form the pyrazole nucleus. Alcohol deprotection and conversion to a chloride gave 5-substituted 3-(chloromethyl)- or 3-(2-chloroethyl)pyrazoles. This sequence can be done within 2 d on a 30 g scale in excellent overall yield. Through nucleophilic substitution reactions, the chlorides are useful precursors to other polyfunctional pyrazoles. In the work here, derivatives with side chains LCH_2- and LCH_2CH_2- at C3 (L = thioether or phosphine) were made as ligands. The significance of the ligands made here is that by placing a ligating side chain on a ring *carbon* (C3), rather than on a ring *nitrogen*, the ring nitrogen not bound to the metal and its attached proton will be available for hydrogen bonding, depending on the steric environment created by R at C5.

Introduction

It is clear that we can learn much about ligand and catalyst design by looking to Nature and some of its catalysts, the enzymes. For example, the active site of the enzyme carboxypeptidase[1] is typical of many metalloenzymes,[2] containing a Lewis acidic transition-metal center [a Zn(II) ion] bound tightly to the protein and several nearby organic functional groups capable of accepting or donating a proton or a hydrogen bond. It is thought that the combined effects (cooperativity) of the metal ion and nearby Brønsted−Lowry acids and bases are responsible for facilitating the addition of a water molecule to a carboxylic acid amide, accelerating amide hydrolysis by a factor of more than 10^{11}.[3,4]

In simplified systems, the effects of cooperativity have been studied using a variety of metal ions and organic functional groups such as phenol,[5] imidazole or imidazolium,[6] and alkylamine or -ammonium moieties.[7,8] The pK_a of the phenol, imidazolium, and alkylammonium moieties used is in the range of 7−10. Recently, organometallic examples of bifunctional catalysis have featured systems in which a transition-metal hydride and an electronically coupled N−H or O−H[9−14] act in concert to catalyze addition of hydrogen to polar functional groups (aldehydes, ketones, imines), in some cases with very high enantioselectivity.

Metal complexation to the pyrazole heterocycle[15−18] could offer a straightforward way to couple the effect of a metal bound to one heterocyclic nitrogen with the ability of the N−H to donate a proton or hydrogen bond (see Chart 1, structures **A** and **B**). The ability of metal-coordinated pyrazole to donate a hydrogen bond intramolecularly to a halide, hydroxide, carboxylate, or peroxo ligand is well-documented.[19] Literature data on *proton* donation of metal-coordinated pyrazoles is much more

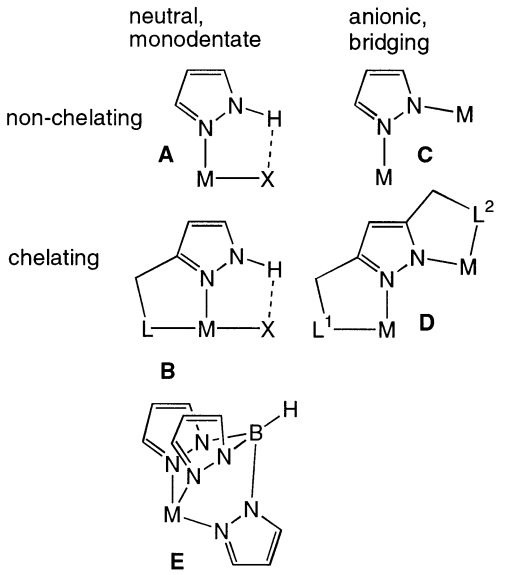
† Current address: Trilink Biotechnologies, San Diego, CA.

‡ Undergraduate research participant.

(1) Creighton, T. E. *Proteins: Structures and Molecular Properties*, 2nd ed.; W. H. Freeman: New York, 1993.
(2) Sadler, P. J. *Metal Sites in Proteins and Models*; Springer: Heidelberg, Germany, 1997; Vol. 89.
(3) Bryant, R. A. R.; Hansen, D. E. *J. Am. Chem. Soc.* **1996**, *118*, 5498−5499.
(4) Radzicka, A.; Wolfenden, R. *J. Am. Chem. Soc.* **1996**, *118*, 6105−6109.
(5) Schepartz, A.; Breslow, R. *J. Am. Chem. Soc.* **1987**, *109*, 1814−1826.
(6) Breslow, R.; Berger, D.; Huang, D. *J. Am. Chem. Soc.* **1990**, *112*, 3687−3688.
(7) Kövári, E.; Krämer, R. *J. Am. Chem. Soc.* **1996**, *118*, 12704−12709.
(8) Wall, M.; Linkletter, B.; Williams, D.; Lebuis, A.-M.; Hynes, R. C.; Chin, J. *J. Am. Chem. Soc.* **1999**, *121*, 4710−4711.
(9) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102.
(10) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045−2061.
(11) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478.
(12) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7473−7474.
(13) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.
(14) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090−1100.
(15) Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, pp 1−75.
(16) Sadimenko, A. P.; Basson, S. S. *Coord. Chem. Rev.* **1996**, *147*, 247−297.
(17) Garnovskii, A. D.; Sadimenko, A. P. *Adv. Heterocycl. Chem.* **1999**, *72*, 1−77.
(18) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151−218.

10.1021/jo026083e CCC: $22.00
Published on Web 11/27/2002

CHART 1. Pyrazole Derivatives as Ligands

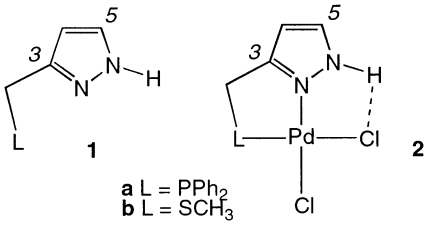


rare, but it appears that the acidity of pyrazole itself (pK_a = 14.2)[20] moves into the range 5.98−7.21 (similar to that of protonated imidazole) upon coordination to $[M(NH_3)_5]^{3+}$ (M = Cr, Co, Ru).[21,22]

Surprisingly, we are unaware of attempts to use pyrazole proton or hydrogen bond donation properties in catalysis or enzyme modeling until recently. In 1998, as we began our work,[19e,23] Deters and Krämer reported that Cu(II) complexes of type **B** underwent deprotonation and dimerization (forming structures similar to **C** or **D**) rather than catalyzing phosphate ester hydrolysis.[24] This result shows one of the potential difficulties in maintaining structures such as **A** and **B**: deprotonation of pyrazole produces a pyrazolate, a monoanionic ligand, usually bridging two metals by coordination of both nitrogens as in **C** or **D**.[25,26] We felt that if we could hinder the *intermolecular* approach of hydrogen bond acceptors, bulky metal fragments, or bases to the pyrazole N−H, we would be able to focus our studies on the *intramolecular* hydrogen-bonding interactions schematically illustrated in structures **A** and **B**.

In fact, in our pursuit of structure **B** in which a N−H bond is retained, we have reported the preparation of pyrazole ligands **1** (Chart 2) featuring a soft thioether or phosphine group.[19e] (For clarity in this paper, in all cases where two tautomeric forms of a pyrazole are possible

CHART 2. Ligands and Complexes Made Previously



and probable, e.g., **1**, only one form will be shown.) In the crystal structures of Pd(II) species of type **B** (e.g., **2**, Chart 2) it was obvious that a lack of steric hindrance at the pyrazole N−H allowed multiple hydrogen-bonding interactions, both the desired intramolecular one shown and undesired intermolecular ones. Because we wanted to study the cooperative effects of intramolecular hydrogen bonding, our synthetic tactic, the fruits of which are reported here, has been to increase steric hindrance at the NH by introducing alkyl or aryl groups at C5. We now report a versatile synthesis of pyrazoles which allows us to vary the steric environment of the pyrazole ring as well as the length of the side chain spacer between L and C3 of the heterocycle. The crystal structures of several $PdCl_2$ complexes show that changing these groups allows control of the structure of the complexes and their intermolecular hydrogen bonding.[27] The ability to create pyrazole-containing ligands with different steric and electronic properties will facilitate future studies of pyrazole−metal complexes. These synthetic advances should have application not only to the field of ligand and catalyst design, but also in pharmaceutical chemistry, since hundreds of pyrazole derivatives have already been made as drugs, herbicides, etc.[28]

Results and Discussion

Synthesis Design. We sought a general route which would allow one to vary systematically both the steric and electronic properties of the pyrazole ligand system.

(19) For leading references, see: (a) Kitajima, N.; Osawa, M.; Tamura, N.; Moro-oka, Y.; Hirano, T.; Hirobe, M.; Nagano, T. *Inorg. Chem.* **1993**, *32*, 1879−1880. (b) Esteruelas, M. A.; García, M. P.; Martín, M.; Nürnberg, O.; Oro, L. A.; Werner, H. *J. Organomet. Chem.* **1994**, *466*, 249−257. (c) Komatsuzaki, H.; Icikawa, S.; Hikichi, S.; Akita, M.; Moro-oka, Y. *Inorg. Chem.* **1998**, *37*, 3652−3656. (d) Esteruelas, M. A.; Oliván, M.; Oñate, E.; Ruiz, N.; Tajada, M. A. *Organometallics* **1999**, *18*, 2953−2960. (e) Grotjahn, D. B.; Combs, D.; Van, S.; Aguirre, G.; Ortega, F. *Inorg. Chem.* **2000**, *39*, 2080−2086.

(20) Yagil, G. *Tetrahedron* **1967**, *23*, 2855−2861.

(21) Johnson, C. R.; Henderson, W. W.; Shepherd, R. E. *Inorg. Chem.* **1984**, *23*, 2754−2763.

(22) Winter, J. A.; Caruso, D.; Shepherd, R. A. *Inorg. Chem.* **1988**, *27*, 1086−1089.

(23) Grotjahn, D. B.; Van, S.; Combs, D.; Kassel, W. S.; Rheingold, A. L. *J. Inorg. Biochem.* **2001**, *85*, 61−65.

(24) Deters, R.; Krämer, R. *Inorg. Chim. Acta* **1998**, *269*, 117−124.

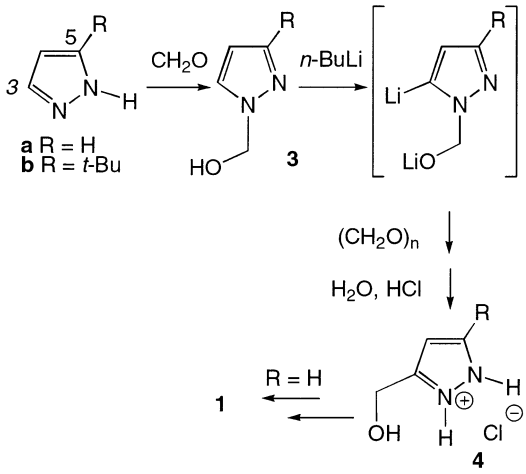
(25) la Monica, G.; Ardizzoia, G. A. *Prog. Inorg. Chem.* **1997**, *46*, 151−238.

(26) For leading references to the many excellent uses of anionic pyrazolate ligands, see reviews of poly(pyrazolyl)borate complexes: (a) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943−980. (b) Kitajima, N.; Tolman, W. B. *Prog. Inorg. Chem.* **1995**, *43*, 419−531. Further, for some uses of bridging pyrazolates (**C** and **D**) in studying bimetallic reactivity, cooperativity, and electronic communication between metals, to name a few properties of interest in coordination, bioinorganic, and organometallic chemistry, see: (c) Bode, R. H.; Bol, J. E.; Driessen, W. L.; Hulsbergen, F. B.; Reedijk, J.; Spek, A. L. *Inorg. Chem.* **1999**, *38*, 1239−1243. (d) Yu, Z.; Wittbrodt, J. M.; Heeg, M. J.; Schlegel, H. B.; Winter, C. H. *J. Am. Chem. Soc.* **2000**, *122*, 9338−9339. (e) Cámpora, J.; López, J. A.; Maya, C. M.; Palma, P.; Carmona, E. *Organometallics* **2000**, *19*, 2707−2715. (f) Carmona, D.; Ferrer, J.; Arilla, J. M.; Reyes, J.; Lahoz, F. J.; Elipe, S.; Modrego, F. J.; Oro, L. A. *Organometallics* **2000**, *19*, 798−808. (g) Meyer, F.; Jacobi, A.; Zsolnai, L. *Chem. Ber./Recl.* **1997**, *130*, 1441−1447. (h) Meyer, F.; Kaifer, E.; Kircher, P.; Heinze, K.; Pritzkow, H. *Chem.−Eur. J.* **1999**, *5*, 1617−1630.

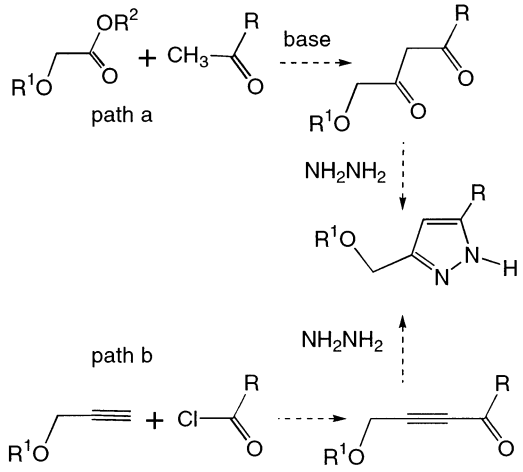
(27) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D.; Schneider, C.; Meyer, C.; Rideout, M.; Hernandez, G.; Mejorado, L.; Incarvito, C.; Lam, K.-C.; Rossi, G.; Rheingold, A. L. *Inorg. Chem.*, submitted for publication.

(28) For recent leading references, see Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787−6791, especially ref 1 therein. Pinto, D. J. P.; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E.; Cacciola, J.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Luettgen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knabb, R. M. *J. Med. Chem.* **2001**, *44*, 566−578. Donohue, B. A.; Michelotti, E. L.; Reader, J. C.; Reader, V.; Stirling, M.; Tice, C. M. *J. Comb. Chem.* **2002**, *4*, 23−32.

SCHEME 1. Attempt To Extend Previously Used Chemistry



SCHEME 2. 1,3-Electrophiles as Pyrazole Precursors



We wanted to avoid using reducing or oxidizing reagents, so as to increase the variety of functional groups tolerated. Many pyrazoles have been made as ligands, but virtually all of these feature a substituent on one of the ring nitrogens. Perhaps the most common type of pyrazole-containing ligands are poly(pyrazolyl)borates (e.g., structure **E**).[26a] Because substitution at one of the ring nitrogens is such a facile reaction, virtually all pyrazole ligands have been made by one of two routes, alkylation at one ring nitrogen with either aldehydes or alkyl halides or tosylates[29] or attachment of a boron.[26a,b] These strategies result in blockage of the substituted nitrogen to coordination and loss of the critical NH group, which we required.

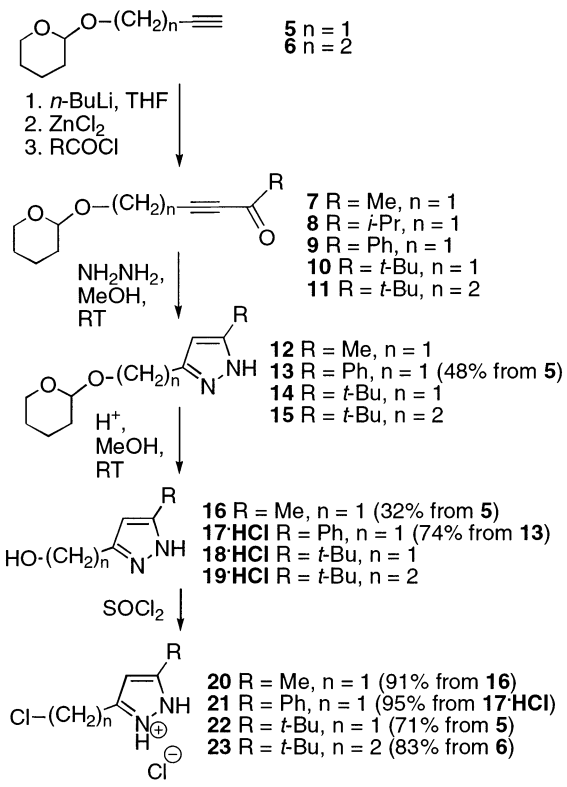
The number of pyrazole-containing ligands in which both ring nitrogens are unsubstituted and a side chain is attached at a ring carbon is rather small,[30] probably because it is relatively difficult to make such systems. In our reported approach to **1** and **2** (Scheme 1),[19e] we overcame this problem by attaching a functionalized side chain at the pyrazole 3-position starting with pyrazole itself, which was converted to its *N*-hydroxymethyl derivative **3a** with formaldehyde. The ring of **3a** was lithiated using *n*-BuLi, and the resulting species treated with formaldehyde. After *N*-deprotection, the hydrochoride salt of pyrazole-3-methanol (**4a**) resulted; subsequent conversions of **4a** led to **1**. In early stages of this work, we treated 3(5)-*tert*-butylpyrazole[31] with formaldehyde, isolating a single *N*-hydroxymethyl derivative, **3b**. The structure shown is tentatively assigned on the basis of ample literature precedents involving the reaction of sterically biased 3(5)-substituted pyrazoles under thermodynamic control, which show that *N*-substitution is preferred on the less-hindered nitrogen.[29,32] However, limited attempts at lithiation of **3b** and trapping with electrophiles suggested that alternative routes were desirable. Even if the chemistry proceeded smoothly, if we were to use lithiation of preformed pyrazole derivatives, for each desired pyrazole 5-substituent we would have to first make the pyrazole itself and then its *N*-hydroxymethyl derivative **3**.

Perhaps the most common route to construction of pyrazoles with different substituents at C3 and C5 is condensation of hydrazine with an unsymmetrical 1,3-diketone [path a in Scheme 2, in equilibrium with its tautomeric enol form(s)].[15,33−35] For our purposes, formation of the requisite 1,3-diketone would require selective, directed Claisen condensation between compounds such as those shown in path a. Initial experiments in this direction were not promising, so another kind of 1,3-bis(electrophile) was sought.

There are scattered but increasingly frequent literature reports that pyrazoles can be made by adding hydrazine (as a double nucleophile) to other three-carbon units featuring two electrophilic carbons in a 1,3-relationship. Vinyl ketones with a potential leaving group β to the carbonyl are one candidate.[36−38] However, a century ago it was discovered that acetylenic ketones can react with hydrazine derivatives to give pyrazoles.[39−41] Until recently, there have only been a few reports of this reaction,[33,42−48] though in recent years it has assumed

(29) Watson, A. A.; House, D. A.; Steel, P. J. *Aust. J. Chem.* **1995**, *48*, 1549−1572.
(30) See the eight publications cited in ref 10 of our previous paper.[19e]
(31) Trofimenko, S.; Calabrese, J. C.; Thompson, J. S. *Inorg. Chem.* **1987**, *26*, 1507−1514.
(32) Reger, D. L.; Collins, J. E.; Jameson, D. L.; Castellano, R. K. *Inorg. Synth.* **1998**, *32*, 63−65.
(33) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347−429, especially pp 366−368.
(34) Wiley, R. H. *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; Interscience Publishers: New York, 1967.
(35) Elguero, J. Pyrazoles and Derivatives. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, pp 167−303.
(36) Zelenin, K. N. *Org. Prep. Proc. Int.* **1995**, *27*, 521−540.
(37) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 225−314, esp. pp 253−258.
(38) Manferdini, M.; Morelli, C.; Veronese, A. C. *Heterocycles* **2000**, *53*, 2775−2780.
(39) Moureu, C.; Delange, R. *Bull. Soc. Chim. Fr.* **1901**, *25*, 302−313.
(40) Moureu, C.; Delange, R. *Ann. Chim. Phys.* **1902**, *25*, 239−268, esp. 252−255.
(41) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3664−3673.
(42) Bowden, K.; Jones, E. R. H. *J. Chem. Soc.* **1946**, 953−954.
(43) Coispeau, G.; Elguero, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1970**, 689−696.
(44) Coispeau, G.; Elguero, J. *Bull. Soc. Chim. Fr.* **1970**, 2717−2736.
(45) Tämnefors, I.; Claesson, A.; Karlsson, M. *Acta Pharm. Suec.* **1975**, *12*, 435−444.
(46) Baddar, F. G.; Al-Hajjar, F. H.; El-Rayyes, N. R. *J. Heterocycl. Chem.* **1976**, *13*, 257−268.

SCHEME 3



greater interest because better routes to the requisite alkynyl ketones have allowed functionalized or optically active compounds to be made.[49−54] Application of this chemistry to our study is shown schematically in Scheme 2, path b. We were especially attracted to a report that acetylenic ketones were readily available by addition of simple alkynylzinc reagents to carboxylic acid chlorides.[55] This chemistry, stoichiometric in lithium and zinc, was successful, as described in the following section, but toward the end of our study a further improvement, a Pd-catalyzed alkyne−acid chloride coupling, was used.[47]

Pyrazole Synthesis. We reasoned that readily available THP ethers **5** and **6** (Scheme 3) could be used as starting materials for our work. Deprotonation of **5** or **6** with *n*-BuLi and transmetalation with $ZnCl_2$,[56] followed by addition of the appropriate acid chloride,[55] gave ketones **7**−**11**. Addition of hydrazine to **7** or **9**−**11**[57] exothermically produced pyrazoles **12**−**15**, which were deprotected in acidic methanol−water or methanol to give hydrochloride salts of 5-substituted pyrazole-3-methanol or pyrazole-3-ethanol (**16**−**19**). Free bases **16** and **17** were known, having been made by other routes.[58−62] The hydroxyl group in **16**−**19** or their hydrochloride salts was converted to a chloride using thionyl chloride, as had been done previously for **4a**.[19e,63] Overall yields of the chloro compounds **20**−**23** as hydrochloride salts are good to excellent. Several of the intermediates were isolated and characterized, but this is not necessary to complete the synthesis. As an example, over 30 g of **22** was made from **5** in a matter of 2 days in overall 71% yield, with the only purification step being extraction, rotary evaporation, or precipitation.

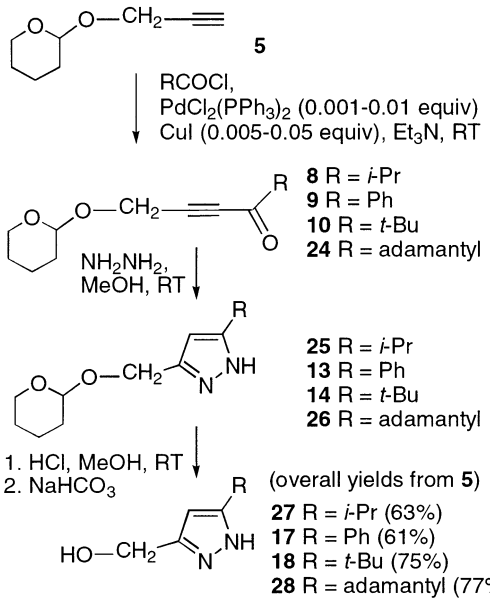
The proton NMR spectra of hydrochloride salts such as **20**−**23** showed a broad two-proton peak for the NH protons downfield of δ 10 ppm. Remarkably, the compounds with the *tert*-butyl group showed good solubility in $CDCl_3$ or CH_2Cl_2. Carbon NMR data showed three signals for the pyrazole ring carbons in the expected ranges, the one for C4 near 104 ppm and the two for C3 and C5 downfield, near 145 and 158 ppm.[64]

After showing the beneficial effects of varying the nature of the pyrazole ring substituents,[27] we decided to improve on the ligand synthesis by examining catalytic methods of constructing the carbon skeleton. Especially attractive was the report of Giacomelli et al.,[47] in which alkynyl ketones were constructed by Pd- and Cu-catalyzed addition of unfunctionalized terminal alkynes and acid chlorides in triethylamine solvent. Concerns that an oxygenated functional group at a propargylic position would interfere were quickly dispelled by successful use of Pd and Cu cocatalysts with a variety of acid chlorides (see Scheme 4). Although as little as 0.1% Pd catalyst is effective, with hindered acid chlorides such as *t*-BuCOCl complete reaction requires several days at ambient temperature. In distinct contrast, *i*-PrCOCl appeared to react completely within hours. The slower reactions can be accelerated so that consumption of alkyne is complete within 1 day by using 0.5−1.0% Pd, which is still a reasonably small amount. Overall yields of (hydroxymethyl)pyrazoles were excellent (61−77%).

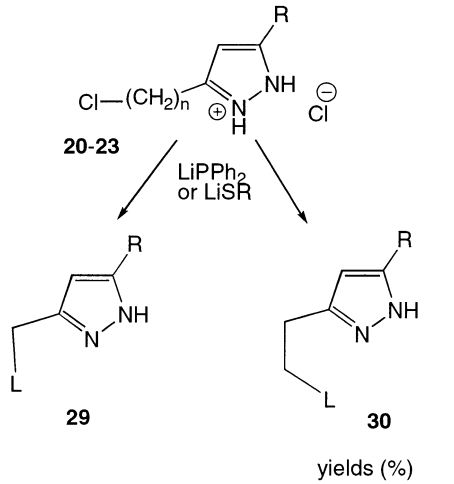
Finally (Scheme 5), the desired sulfur- or phosphorus-based ligand **29** or **30** was produced in 47−82% yield by nucleophilic substitution of the chloride. An excess of nucleophilic reagent ($LiPPh_2$ or lithium thioalkoxide) was applied because of the two acidic protons on the pyrazole ring (for comparison, the two pK_a values of protonated pyrazole are pK_{a1} = 2.5 and pK_{a2} = 14.2).[20] A variety of sulfur-based nucleophiles were employed, producing **29b**, **29d**, **29e**, **29f**, **29g**, and **30d**. Using excess lithium diphenylphosphide, ligands **29a** and **29c** were obtained as air-sensitive oils, whereas **30c** was a solid. From

(47) Giacomelli, G.; Rosini, C.; Caporusso, A. M.; Palla, F. *J. Org. Chem.* **1983**, *48*, 4887−4891.
(48) Falorni, M.; Lardicci, L.; Giacomelli, G. *Gazz. Chim. Ital.* **1987**, *117*, 7−10.
(49) Rycroft, A. D.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2667−2668 and references to previous work.
(50) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039−3046.
(51) Wang, X.-j.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107−3109.
(52) Cabarrocas, G.; Ventura, M.; Maestro, M.; Mahía, J.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2483−2493.
(53) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; J., P. G.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303−305.
(54) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311−2316.
(55) Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289−294.
(56) In the case of **9**, a catalytic amount of $Pd(PPh_3)_4$ was added, following the literature example.[55]
(57) **8** was transformed further at a later stage in this work; see Scheme 4.
(58) Jones, R. H.; Mann, M. J.; McLaughlin, K. C. *J. Org. Chem.* **1954**, *19*, 1428−1434.
(59) Sabaté-Alduy, C.; Bastide, J. *Bull. Soc. Chim. Fr.* **1972**, 2764−2769.
(60) Perron, A.; Mazet, M.; Piekarski, S. *Bull. Soc. Chim. Fr.* **1976**, 2006−2010.
(61) Meyer, F.; Kaifer, E.; Kircher, P.; Heinze, K.; Pritzkow, H. *Chem.−Eur. J.* **1999**, *5*, 1617−1630.
(62) Rubessa, F. *Farmaco, Ed. Sci.* **1967**, *22*, 692−697.
(63) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 4−4000.
(64) Begtrup, M.; Boyer, G.; Cabildo, P.; Cativiela, C.; Claramunt, R. M.; Elguero, J.; Garcia, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.* **1993**, *31*, 107−168.

SCHEME 4. Pd-Catalyzed Route



SCHEME 5. Ligands from Side Chain Functionalizations



yields (%)

a R = Me, L = PPh_2	**29a** 78	
b R = Ph, L = SCH_3	**29b** 82	
c R = *t*-Bu, L = PPh_2	**29c** 47	**30c** 88
d R = *t*-Bu, L = SCH_3	**29d** 75	**30d** 92
e R = *t*-Bu, L = SPh	**29e** 63	
f R = *t*-Bu, L = SCH_2CH_2OH	**29f** 60	
g R = *t*-Bu, L = S-*t*-Bu	**29g** 49	

literature precedents, all of the unsymmetrical pyrazole derivatives in this study would exist as two tautomers, only one of which is shown for clarity. However, in the ^{13}C NMR spectra of **29** and **30** (as well as those of **12**−**15**) the two downfield resonances for C3 and C5 were unusually broadened, a result ascribed to the dynamic equilibrium between the two tautomers and the especially large change in chemical shift for the two ring carbons (C3 and C5) closest to the shifting proton.[64]

Conclusions

Here we present flexible syntheses of pyrazoles with two different substituents at C3 and C5, which are expected to be of interest not only to coordination and organometallic chemists, but to anyone who wants to make pyrazoles with functionalized substituents in defined positions on the heterocycle. Although the focus of this paper is the synthesis of thioethers and phosphines, we note that 3-(chloromethyl)pyrazole itself and its 5-methyl derivative **20** have been converted to a number of amines and other products through nucleophilic substitutions.[61,63,65−67] Future reports from our laboratories will show ways in which the new, related chloroalkyl compounds **21**−**23** display similar reactivity and versatility.

Experimental Section

General Procedures. Compounds **5** and **6** were either purchased or readily made by reacting the appropriate alcohol with dihydropyran under catalysis of toluenesulfonic acid. Dry THF and ether were distilled from benzophenone and sodium. Other solvents for manipulations of phosphines were deoxygenated by bubbling nitrogen through them. Other reagents were purchased and used as received. Reactions were performed under nitrogen using a combination of Schlenk and inert-atmosphere glovebox techniques, and workups were done in air unless otherwise specified.

Unless otherwise specified, NMR spectra were recorded using a 200 or 500 MHz spectrometer at room temperature. ^1H and ^{13}C NMR chemical shifts are reported in parts per million downfield from tetramethylsilane and referenced to residual solvent resonances (^1H NMR, 7.27 ppm for $CHCl_3$ in $CDCl_3$, 2.05 ppm for CHD_2COCD_3 in acetone-d_6, 2.50 ppm for CHD_2SOCD_3 in DMSO-d_6, 3.31 ppm for CHD_2OD in CD_3OD; ^{13}C NMR, 77.23 ppm for $CDCl_3$, 29.92 ppm for CD_3COCD_3, 39.51 ppm for CD_3SOCD_3, 49.15 ppm for CD_3OD), where ^1H NMR signals are given followed by multiplicity, coupling constants J in hertz, and integration in parentheses. For complex coupling patterns, the first coupling constant listed corresponds to the first splitting listed, e.g., for "(dt, J = 3.2, 7.9 Hz, 1 H)" the doublet exhibits the 3.2 Hz coupling constant. $^{31}P\{^1H\}$ NMR chemical shifts were referenced to external 85% H_3PO_4(aq). Elemental analyses were performed at NuMega Resonance Labs (San Diego).

General Procedure for the Synthetic Route shown in Scheme 3. 5-*tert*-Butyl-3-(chloromethyl)pyrazole hydrochloride (22) and Intermediates 6-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2,2-dimethylpent-4-yn-3-one (10), 5-*tert*-Butyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]methylpyrazole (14), and 5-*tert*-Butylpyrazole-3-methanol Hydrochloride (18·HCl). A solution of **5** (30.0 g, 0.214 mol) in dry THF (250 mL) under a nitrogen atmosphere was cooled to −78 °C. A solution of *n*-BuLi in hexane (2.5 M, 85.0 mL, 0.214 mol) was added dropwise over 30 min to the cold reaction mixture. The mixture was stirred for 1 h at −78 °C and slowly warmed to room temperature. After being stirred for 2.5 h, the mixture was cooled to −40 °C. A solution of $ZnCl_2$ (29.17 g, 0.214 mol) in THF (100 mL) was slowly added over 15 min before the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C, and pivaloyl chloride (25.5 g, 0.214 mol) was added. The reaction was slowly warmed to room temperature and stirred overnight (14 h) before addition of saturated NH_4Cl solution, followed by NH_3 in water. The organic layer was extracted with diethyl ether (2 × 100 mL). The organic phases were combined, dried with $MgSO_4$, and filtered, and the filtrate was concentrated by

(65) Di Vaira, M.; Mani, F.; Stoppioni, P. *J. Chem. Soc., Dalton Trans.* **1994**, 3739−3743.
(66) Meyer, F.; Beyreuther, S.; Heinze, K.; Zsolnai, L. *Chem. Ber./Recl.* **1997**, *130*, 605−613.
(67) Yuan, Y.; Jiménez, M. V.; Sola, E.; Lahoz, F. J.; Oro, L. A. *J. Am. Chem. Soc.* **2002**, *124*, 752−753.

rotary evaporation. The residue containing **10** was dissolved in methanol (100 mL) and the resulting solution cooled to 0 °C. Hydrazine monohydrate (10.7 g, 0.214 mol) was added to the cold reaction mixture. Within a minute, the reaction had warmed to reflux by itself but was allowed to cool to room temperature and stirred for 2 h. To deprotect the THP derivative **14**, the reaction solution was acidified with aqueous HCl until the pH of the mixture reached 2 and then stirred for 14 h. The reaction mixture was concentrated by rotary evaporation and the residue placed under vacuum for 14 h to give crude hydrochloride salt **18**·HCl. The solid residue was then stirred in thionyl chloride (100 mL) for 15 h. After hexane was added, precipitated solid was filtered, washed with hexane (100 mL), and placed under vacuum to give hydrochloride salt **22** (31.9 g, 0.152 mol, 71% from **5**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 14.8 (br s, 2 H), 6.42 (s, 1 H), 4.79 (s, 2 H), 1.46 (s, 9 H) ppm; $^{13}C\{^1H\}$ NMR and APT δ 158.6, 144.5, 103.7, 33.6 (CH_2), 32.1 [$-C(CH_3)_3$], 29.7 [$-C(CH_3)_3$] ppm. Anal. Calcd for $C_8H_{14}N_2Cl_2$ (209.12): C, 45.95; H, 6.75; N, 13.39. Found: C, 45.70; H, 6.97; N, 13.13.

Spectral data for a sample of **10** purified by chromatography (silica; hexanes/ethyl acetate, 4:1): ^{1}H ($CDCl_3$, 500 MHz) δ 4.74 (t, J = 5.5 Hz, 1 H), 4.36 (s, 2 H), 3.75 (m, 1 H), 3.47 (m, 1 H), 1.8−1.62 (2 H), 1.6−1.42 (4 H), 1.12 (s, 9 H) ppm; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 193.3, 97.1, 89.6, 82.9, 62.0, 53.8, 44.6, 30.2, 25.9, 25.3, 18.9 ppm. Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C, 69.61; H, 8.99. Found: C, 69.23; H, 9.02.

Spectral data for a sample of **14** purified by chromatography (silica; hexanes/ethyl acetate, 4:1): ^{1}H ($CDCl_3$, 500 MHz) δ 9.3−11.0 (br, 1 H), 6.09 (s, 1 H), 4.75 (d, J = 12.3 Hz, 1 H), 4.72 (narrow m, 1 H), 4.56 (d, J = 12.3 Hz, 1 H), 3.93 (ddd, J = 3, 8, 11 Hz, 1 H), 3.54−3.58 (m, 1 H), 1.82−1.90 (m, 1 H), 1.72−1.78 9m, 1 H), 1.50−1.68 (m, 4 H), 1.33 (s, 9 H) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 156.8 (br), 146.4 (br), 101.0, 98.3, 62.5, 62.3 (sl br), 30.7, 30.5, 25.6, 19.6 ppm. Anal. Calcd for $C_{13}H_{22}N_2O_2$ (238.33): C, 65.55; H, 9.30; N, 11.75. Found: C, 65.86; H, 8.91; N, 11.79.

^{1}H NMR data for hydrochloride salt **18**·HCl in $CDCl_3$ were as follows: δ 6.28 (s, 1 H), 4.85 (s, 2 H), 1.41 (s, 9 H) (resonances for OH and NH not assignable) ppm.

5-Methyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]methylpyrazole (12) and Intermediate 5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-3-yn-2-one (7). Following the first part of the general procedure above, to **5** (14.93 g, 107 mmol) and dry THF (60 mL) cooled to −78 °C was added dropwise *n*-butyllithium (50 mL, 120 mmol, 2.4 M in hexanes). After addition was completed a solution of $ZnCl_2$ (14.65 g, 107 mmol) in THF (80 mL) was added dropwise. The reaction slurry was slowly brought to 0 °C, and acetyl chloride (9.15 g, 117 mmol) was added at once. The solution was heated for 30 min at 40 °C and then cooled to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NH_4Cl (5 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. To a solution of the crude residue in methanol (100 mL) was added hydrazine hydrate (7.50 g, 150 mmol). The mixture warmed, then cooled to ambient temperature, and stirred for 12 h before the solvent was removed by rotary evaporation. The crude material was normally carried to the next step without further purification. For characterization purposes a small sample was chromatographed (SiO_2, 25% ethyl acetate/petroleum ether and then Et_2O) to give **12** as a thick colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.04 (br s, 1 H), 6.03 (s, 1 H), 4.73 (d, J = 12.3 Hz, 1 H), 4.72−4.68 (m, 1 H), 4.55 (d, J = 12.3 Hz, 1 H), 3.91−3.86 (m, 1 H), 3.54−3.50 (m, 1 H), 2.28 (s, 3 H), 2.00−1.40 (m, 6 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 146.6, 143.3, 104.2, 97.9, 62.3, 61.7, 30.6, 25.5, 19.4, 11.9 ppm; IR (neat, NaCl) 3200, 2948, 1580, 1441, 1385, 1343, 1262, 1200, 1120, 1023 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$ (196.25): C, 61.20; H, 8.22; N, 14.27. Found: C, 60.87; H, 8.12; N, 13.94.

From another reaction, a sample of **7** was purified using silica gel and exhibited the following data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (t, J = 3.3 Hz, 1 H), 4.44−4.37 (m, 2 H), 3.84−3.80 (m, 1 H), 3.56−3.52 (m, 1 H), 2.34 (s, 3 H), 1.85−1.71 (m, 2 H), 1.66−1.51 (m, 4 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 184.1, 97.4, 87.9, 85.4, 62.2, 54.0, 32.7, 30.3, 25.4, 19.0 ppm; IR ($CDCl_3$) 2214, 1677, 1442 cm^{-1}.

5-Phenyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]methylpyrazole (13) and Intermediate 4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-phenylbut-2-yn-1-one (9). In a manner similar to that used to make **12**, **5** (1.4898 g, 10.6 mmol) in THF (10 mL) was cooled to −78 °C, and *n*-butyllithium (4.3 mL, 10.7 mmol, 2.5 M in hexanes) was added dropwise. After addition was completed, the cooling (dry ice) bath was removed for 10 min before being returned. To the cold flask was added dropwise a solution of $ZnCl_2$ (1.448 g, 10.6 mmol) in THF (10 mL). After 0.5 h, a water/ice bath was put around the flask. After an additional 1 h at 0 °C, $Pd(PPh_3)_4$ (0.22 g, 0.19 mmol) was added as a suspension in THF, followed 20 min later by benzoyl chloride (1.49 g, 10.6 mmol). The solution was heated for 30 min at 40 °C and then cooled to room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The crude material from further workup was chromatographed over a silica column (15 cm long × 2.2 cm diameter) using ethyl acetate/petroleum ether (1:10) to afford alkynyl ketone **9** as a pale yellow oil (1.266 g, 49%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08−8.06 (m, 2 H), 7.55−7.52 (m, 1 H), 7.42−7.41 (m, 2 H), 4.80 (s, 1 H), 4.48 (s, 2 H), 3.82−3.78 (m, 1 H), 3.52−3.48 (m, 1 H), 1.79−1.68 (m, 2 H), 1.63−1.48 (m, 4 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 177.3, 136.4, 134.2, 129.5, 128.5, 97.4, 90.5, 83.5, 62.0, 54.0, 30.1, 25.2, 18.9 ppm; IR ($CDCl_3$) 2233, 1646, 1450 cm^{-1}. To a solution of the ketone (0.987 g, 4.04 mmol) in methanol (10 mL) at room temperature was added hydrazine hydrate (0.202 g, 4.04 mmol). Immediate warming of the mixture was noted. After 1 h, TLC using ethyl acetate/diethyl ether (1:10) and anisaldehyde showed a single major spot with R_f = 0.9 as well as a trace of impurity with R_f = 0.5. The mixture was concentrated by rotary evaporation and the residue stored overnight under vacuum. Only the major TLC spot (R_f = 0.9) remained. Compound **13** was obtained as a pale yellow, thick oil (1.03 g, 98% from **9**, 48% overall from **5**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (t, J = 7 Hz, 2 H), 7.36 (dd, J = 7.0 Hz, 7.3 Hz, 2 H), 7.29 (t, J = 7.3 Hz, 1 H), 6.58 (s, 1 H), 4.80 (d, J = 12.5 Hz, 1 H), 4.72 (t, J = 3.8 Hz, 1 H), 4.64 (d, J = 12.5 Hz, 1 H), 3.93−3.88 (m, 1 H), 3.57−3.52 (m, 1 H), 1.85−1.82 (m, 1 H), 1.75−1.70 (m, 1 H), 1.64−1.50 (m, 4 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 148.9, 145.3, 132.0, 128.8, 128.1, 125.8, 102.2, 98.2, 62.5, 61.3, 30.6, 25.5, 19.5 ppm; IR (neat, NaCl) 3268 (ν_{NH}), 2943, 1746, 1461, 1438, 1113 cm^{-1}.

5-Methylpyrazole-3-methanol (16). Crude THP-protected (hydroxymethyl)pyrazole **12** (21.00 g, 107 mmol) was dissolved in methanol (100 mL) along with *p*-TsOH·H_2O (0.250 g, 1.0 mmol). The reaction solution was brought to reflux for 8 h, then cooled to room temperature, and quenched with solid K_2CO_3. The reaction slurry was concentrated on a rotary evaporator, and the crude residue was chromatographed (SiO_2; ethyl acetate/petroleum ether, 1:1) to yield **16** (3.89 g, 35.7 mmol, 32%, two steps from **5**) as an off-white powder: mp 78−80 °C (lit. mp 86−87 °C,[58] 80 °C,[59] 86 °C[60]); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.94 (br s, 1 H), 5.98 (s, 1 H), 4.58 (s, 2 H), 2.23 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR (acetone-d_6, 125.7 MHz) δ 151.1, 143.3, 103.4, 57.9, 11.8 ppm; IR (neat, NaCl) 3226, 2876, 1579, 1437, 1303, 1143, 1023, 1002 cm^{-1}. Anal. Calcd for $C_5H_8N_2O$ (112.13): C, 53.56; H, 7.19; N, 24.98. Found: C, 53.52; H, 7.12; N, 24.37.

5-Phenylpyrazole-3-methanol Hydrochloride (17·HCl). The THP ether **13** (1.02 g, 3.98 mmol) was dissolved in methanol (12 mL), and at room temperature a solution of concentrated aqueous hydrochloric acid and methanol (1:1) was

added slowly until the pH of the reaction mixture was 2. After the mixture was stirred for 3 h, TLC showed conversion to a new product (R_f = 0.8; ethyl acetate/petroleum ether, 1:10; anisaldehyde]. The solution was concentrated under vacuum and the white crystalline residue recrystallized from CH_2Cl_2, affording **17**·HCl (0.616 g, 74%) as white crystals: ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.82 (d, J = 6.8 Hz, 2 H), 7.38−7.42 (m, 3 H), 6.73 (s, 1 H), 4.54 (s, 2 H) ppm; ^{13}C{^{1}H} NMR (50.3 MHz, DMSO-d_6) δ 148.9, 147.2, 130.9, 129.0, 128.4, 125.6, 101.1, 55.3 ppm. Anal. Calcd for $C_{10}H_{11}ClN_2O$ (210.66): C, 57.00; H, 5.26; N, 13.29. Found: C, 56.97; H, 5.07; N, 13.26.

General Procedure for the Palladium-Catalyzed Route Shown in Scheme 4. 5-Phenylpyrazole-3-methanol (17). To a solution of **5** (5.00 g, 35.7 mmol) in triethylamine (100 mL) at room temperature under a nitrogen atmosphere was added PhCOCl (5.01 g, 35.7 mmol). Catalytic amounts of CuI (0.339 g, 1.78 mmol) and $(PPh_3)_2PdCl_2$ (0.25 g, 0.36 mmol) were added to the mixture, which was stirred for 15 h, at which time analysis of an aliquot by NMR spectroscopy showed that the reaction was complete. The mixture was filtered and the filtrate concentrated by rotary evaporation. The residue was passed through a short silica gel column, eluted with diethyl ether. The eluant was concentrated by rotary evaporation. The concentrate was dissolved in methanol (30 mL), and hydrazine monohydrate (1.790 g, 35.7 mmol) was added. After 5 s, the reaction warmed by itself but was stirred for 2 h. The solution was acidified until pH 2 using concentrated aqueous HCl and heated under reflux for 15 h. After cooling, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$, and water (100 mL) was added. Extraction with diethyl ether (50 mL) resulted in some precipitation (which turned out to be product), which was removed by filtration and washed with ether. The aqueous phase was further extracted with CH_2Cl_2 (3 × 50 mL). Combined organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated. The residue was purified over a short column of silica. The combined yield of product **17** as a solid was 3.41 g, 19.6 mmol, 55%. In another run on a smaller scale, the crude product was recrystallized from acetone and petroleum ether to give **17** (61%): mp 149.0−149.4 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.71 (d, J = 7.2 Hz, 2 H), 7.41−7.24 (m, 3 H), 6.59 (s, 1 H), 4.66 (s, 2 H) ppm; ^{13}C{^{1}H} (CD_3OD, 125.7 MHz) δ 154.8, 145.1, 132.9, 129.9, 129.2, 126.7, 102.2, 57.7 ppm; IR (acetone-d_6) 3518, 3302, 3064, 2940, 2876, 1607, 1463, 1267, 1259, 1200, 956, 918, 771, 698 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O$ (174.20): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.67; H, 5.86; N, 16.12.

3-(Chloromethyl)-5-methylpyrazole Hydrochloride (20). To thionyl chloride (20 mL) was added slowly the free base of hydroxymethyl compound **16** (1.566 g, 14.0 mmol). After the addition the reaction solution was heated to 80 °C for 1 h. The reaction was cooled to room temperature, and hexanes (50 mL) was added. The resulting precipitate was filtered and washed with hexanes (2 × 10 mL). The solid was placed under vacuum to give **20** (2.11 g, 12.7 mmol, 91%) as a light brown powder: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 14.24 (s, 2 H), 6.31 (s, 1 H), 4.71 (s, 2 H), 2.25 (s, 3 H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 50.3 MHz) δ 145.6, 143.0, 105.3, 36.6, 10.7 ppm; IR (KBr) 3400, 2745, 1596, 1292, 1240, 1161 cm^{-1}. Anal. Calcd for $C_5H_8Cl_2N_2$ (166.01): C, 35.95; H, 4.83; N, 16.77. Found: C, 35.92; H, 4.78; N, 16.62. This compound was made previously without NMR or analytical data.[58,61]

3-(Chloromethyl)-5-phenylpyrazole Hydrochloride (21). Hydroxymethyl compound **17**·HCl (0.59 g, 2.79 mmol) was dissolved in thionyl chloride (5.8 mL, 80 mmol), and the resulting mixture was heated at 40 °C for 2 h, followed by heating at 65 °C for 10 min. The mixture was allowed to cool to room temperature, and hexanes (12 mL) was added. The resulting white solid was filtered off and dried under vacuum, affording 0.608 g (95%) of the product **21**: mp 171.8−172.4 °C dec; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.42 (s, 2 H), 7.80 (d, J = 8 Hz, 2 H), 7.28−7.60 (m, 3 H), 6.78 (s, 1 H), 4.75 (s, 2 H) ppm; ^{13}C{^{1}H} NMR (50.3 MHz, DMSO-d_6) δ 146.3, 145.8, 130.2, 129.1, 128.4, 125.5, 102.6, 37.9 ppm; IR (KBr) 3152, 3000−2200, 1605, 1595, 1458, 1266 cm^{-1}. Anal. Calcd for $C_{10}H_{10}Cl_2N_2$ (229.11): C, 52.42; H, 4.39; N, 12.23. Found: C, 52.46; H, 4.23; N, 12.26. This compound was made previously with only elemental analysis for N reported.[58]

Palladium-Catalyzed Route to 5-*tert*-butylpyrazole-3-methanol (18). To a solution of **5** (5.00 g, 35.7 mmol) in triethylamine (50 mL) was added 2,2-dimethylpropionyl chloride (4.70 g, 39.0 mmol), followed by CuI (0.0312 g, 0.0164 mmol, 0.5%) and $(PPh_3)_2PdCl_2$ (0.0342 g, 0.00489 mmol, 0.1%). The mixture was stirred for 4 days, after which time the reaction was complete on the basis of the disappearance of the alkyne (R_f = 0.70; petroleum ether/dichloromethane, 8:1). This reaction time can be shortened to a day by using 5−10 times more of the two catalysts. The mixture was diluted with water (100 mL), and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The organic phases were combined and washed with 2 N HCl (50 mL), followed by saturated $NaHCO_3$ (50 mL) and then H_2O (50 mL). The organic phase was dried with $MgSO_4$ and filtered. The organic solution was concentrated by rotary evaporation, leaving crude alkynyl ketone (7.00 g). The crude ketone was dissolved in methanol (30 mL), and hydrazine monohydrate (1.57 g, 31.4 mol) was added to the mixture. After 5 s, the reaction warmed to reflux temperature. After being stirred for another 2 h, the reaction mixture was acidified until pH 2 with concentrated HCl and allowed to stir for 15 h. The reaction mixture was neutralized with solid $NaHCO_3$ and concentrated by rotary evaporation. To the residue was added diethyl ether (100 mL), and insoluble solids were filtered off. The filtrate was concentrated by rotary evaporation, and the residue was purified by Kugelrohr distillation at 120 °C and ca. 1.5 Torr to give **18** (4.13 g, 26.8 mmol, 75%) as a thick oil of sufficient purity for subsequent use (^{1}H NMR): mp 108.0−108.8 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 6.10 (s, 1 H), 4.56 (s, 2 H), 1.30 (s, 9 H) ppm; ^{13}C {^{1}H} (CD_3OD, 50.3 MHz) δ 158.0, 151.3, 101.1, 58.4, 32.3, 30.9 ppm; IR (neat oil, NaCl plates) 3248 (br), 3138, 2952, 2919, 2865, 1560, 1458, 1357, 1294, 1232, 1143, 997, 802 cm^{-1}. For elemental analysis, the oil was crystallized from a minimum of acetone and petroleum ether to give a crystalline solid. Anal. Calcd for $C_8H_{14}N_2O$ (154.21): C, 62.31; H, 9.15; N, 18.17. Found: C, 62.12; H, 8.91; N, 18.18.

5-*tert*-Butyl-3-(chloroethyl)pyrazole Hydrochloride (23) and Intermediates 7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2,2-dimethylhept-4-yn-3-one (11), 5-*tert*-Butyl-3-{2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl}pyrazole (15), and 5-*tert*-Butylpyrazole-3-ethanol Hydrochloride (19·HCl). Following the general procedure, to THP-protected butynol **6** (5.30 g, 34.4 mmol) in dry THF (60 mL) cooled to −78 °C over 10 min was added a solution of *n*-BuLi in hexane (1.6 M, 22.0 mL, 34.4 mmol). The mixture was slowly warmed to −30 °C and stirred for 0.5 h. The reaction mixture was stirred for 2.5 h and then cooled to −40 °C. A solution of $ZnCl_2$ (4.68 g, 34.4 mmol) in THF (30 mL) was slowly added to the reaction mixture over 5 min. The reaction mixture was warmed to room temperature and stirred for 15 min before pivaloyl chloride (4.14 g, 34.4 mmol) was added. The reaction was slowly warmed to room temperature and stirred overnight (14 h), after which the reaction mixture was quenched with saturated NH_4Cl solution, followed by NH_3 in water. The organic layer was extracted with diethyl ether (2 × 50 mL). The organic phases were combined, dried with $MgSO_4$, and filtered. The solution was concentrated by rotary evaporation. The residue was dissolved in methanol (50 mL) and cooled to 0 °C. Hydrazine monohydrate (1.72 g, 34.4 mmol) was added to the cold reaction mixture. After a few seconds, the reaction had warmed to reflux, but cooled quickly. Stirring was continued for 2 h. (In another run, volatile materials were removed, leaving a gummy residue. Trituration of the residue with ether and filtration led to isolation of pure THP derivative **15** as a solid. See the spectral data below.) The reaction solution was

acidified to pH 2 using concentrated aq HCl (as monitored using pH paper) and stirred for 14 h. The reaction mixture was concentrated by rotary evaporation and the residue containing **19**·HCl placed under vacuum for 14 h. The solid residue was then dissolved in thionyl chloride (12 mL) and dichloromethane (150 mL) and the resulting solution stirred for 72 h. The precipitate occurred when petroleum ether (200 mL) was added to the reaction mixture. After concentration under vacuum, the residual solid was washed with petroleum ether (50 mL) and placed under vacuum to give hydrochloride salt **23** (6.40 g, 28.7 mmol, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 15.6 (br s, 2 H), 6.24 (s, 1 H), 3.86 (t, J = 6.5 Hz, 2 H), 3.33 (t, J = 6.5 Hz, 2 H), 1.43 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 158.2, 145.3, 103.8, 42.1, 32.2, 30.0, 29.0 ppm. Anal. Calcd for $C_9H_{16}Cl_2N_2$ (223.14): C, 48.44; H, 7.23; N, 12.55. Found: C, 48.83; H, 6.91; N, 12.36.

Data for alkynyl ketone **11**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.67 (t, J = 3.5 Hz, 1 H), 3.92−3.86 (m, 2 H), 3.64−3.60 (m, 1 H), 3.56−3.51 (m, 1 H), 2.70 (t, J = 6.8 Hz, 2 H), 1.86−1.80 (m, 1 H), 1.75−1.70 (m, 1 H), 1.64−1.52 (m, 4 H), 1.20 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 194.1, 98.9, 92.5, 79.5, 64.8, 62.2, 44.7, 30.6, 26.1, 25.5, 20.7, 19.3 ppm; IR ($CDCl_3$) 2213, 1668, 1477 cm^{-1}.

Data for THP-protected intermediate pyrazole **15**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (br, 1 H), 5.94 (s, 1 H), 4.63 (t, J = 3.5 Hz, 1 H), 4.02−3.98 (m, 1 H), 3.83−3.79 (m, 1 H), 3.69−3.65 (m, 1 H), 3.49−3.47 (m, 1 H), 2.93 (t, J = 6.5 Hz, 2 H), 1.85−1.80 (m, 1 H), 1.75−1.69 (m, 1 H), 1.61−1.51 (m, 4 H), 1.31 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 157.8, 145.5, 100.4, 98.8, 66.6, 62.2, 31.4, 30.7, 30.4, 27.7, 25.4, 19.5 ppm.

Data for intermediate hydrochloride salt **19**·HCl: mp 188.9−189.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 15.3 (br, 2 H), 6.21 (s, 1 H), 3.98 (s, 2 H), 3.10 (s, 2 H), 1.44 (br s, 1 H), 1.43 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 158.2, 146.8, 103.5, 60.3, 32.1, 30.0, 29.3 ppm; IR ($CDCl_3$) 3406, 3387 (br), 1598, 1481 cm^{-1}.

Palladium-Catalyzed Route to 5-Isopropylpyrazole-3-methanol (27) via Intermediates 1-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-5-methylhex-2-yn-3-one (8) and 5-Isopropyl-3-(tetrahydro-2*H*-pyran-2-yl)oxymethylpyrazole (25). To a solution of **5** (5.00 g, 35.7 mmol) in triethylamine (50 mL) at room temperature under a nitrogen atmosphere was added isobutyryl chloride (4.18 g, 39.2 mol), followed by CuI (0.0312 g, 0.0164 mmol, 0.5%) and $(PPh_3)_2PdCl_2$ (0.0342 g, 0.00489 mmol, 0.1%). After 2 h, the mixture had become so thick with precipitate that more Et_3N (5 mL) was added to aid stirring. The reaction was complete on the basis of the disappearance of the alkyne, but as a precaution the reaction was stirred for an additional 14 h. The mixture was diluted with water (100 mL) and extracted with diethyl ether (2 × 100 mL). The organic phases were combined and washed with 2 N HCl (50 mL), followed by saturated $NaHCO_3$ (50 mL). The organic phase was dried with $MgSO_4$ and filtered and the filtrate concentrated by rotary evaporation, leaving crude alkynyl ketone **8** (6.88 g). The crude ketone was dissolved in methanol (30 mL). Hydrazine monohydrate (1.64 g, 32.7 mol) was added, after 5 s leading to reflux. After an additional 2 h, the reaction was acidified to pH 2 with concentrated HCl and stirred for 15 h to deprotect **25**. The reaction mixture was neutralized with solid $NaHCO_3$ and concentrated by rotary evaporation, and to the residue was added diethyl ether (100 mL). Insoluble solids were filtered off, and the filtrate was concentrated by rotary evaporation. The crude residue was purified by Kugelrohr distillation at 120 °C and ca. 1.5 Torr to give **27** (3.14 g, 22.4 mmol, 63%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (br s, 2 H), 5.99 (s, 1 H), 4.63 (s, 2 H), 2.93 (sept, J = 7.0 Hz, 1 H), 1.23 (d, J = 7.0 Hz, 6 H) ppm; ^{13}C{^{1}H} ($CDCl_3$, 50.3 MHz) δ 154.4, 149.8, 100.4, 57.8, 26.6, 22.6 ppm; IR (neat, NaCl plates) 3220 (br), 3141, 2962, 2926, 2869, 1567, 1459, 1358, 1165, 994, 800 cm^{-1}. Anal. Calcd for $C_7H_{12}N_2O$ (140.18): C, 59.98; H, 8.63; N, 19.98. Found: C, 58.93; H, 8.42; N, 18.90.

In another run, alkynyl ketone **8** was purified by chromatography over silica and exhibited the following data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (t, J = 3.3 Hz, 1 H), 4.40 (s, 2 H), 3.83−3.78 (m, 1 H), 3.55−3.50 (m, 1 H), 2.62 (q, J = 7 Hz, 1 H), 1.82−1.69 (m, 2 H), 1.68−1.49 (m, 4 H), 1.16 (d, J = 7 Hz, 6 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 191.5, 97.3, 89.0, 84.0, 62.2, 54.0, 43.0, 30.3, 25.4, 19.0, 17.9 ppm; IR ($CDCl_3$) 2213, 1677, 1468 cm^{-1}.

Similarly, data for THP-protected pyrazolemethanol derivative **25** were obtained: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.6 (br s, 1 H), 6.05 (s, 1 H), 4.74−4.70 (m, 2 H), 4.53 (d, J = 12 Hz, 1 H), 3.91−3.87 (m, 1 H), 3.55−3.51 (m, 1 H), 2.99 (q, J = 7 Hz, 1 H), 1.83−1.79 (m, 1 H), 1.72−1.67 (m, 1 H), 1.61−1.49 (m, 4 H), 1.24 (d, J = 7 Hz, 6 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 154.3, 146.4, 101.3, 98.1, 62.3, 62.0, 30.6, 26.7, 25.5, 22.6, 19.5 ppm.

Palladium-Catalyzed Route to 5-(Adamantan-1-yl)-pyrazole-3-methanol (28) via Intermediates 4-(Tetrahydro-2*H*-pyran-2-yl)oxy-1-(adamantan-1-yl)but-2-yn-1-one (24) and 3-(Tetrahydro-2*H*-pyran-2-yl)oxymethyl-5-(adamantan-1-yl)pyrazole (26). To a solution of **5** (2.50 g, 17.8 mmol) in triethylamine (40 mL) at room temperature under a nitrogen atmosphere was added 1-adamantanecarbonyl chloride (3.90 g, 19.6 mmol), followed by CuI (0.0312 g, 0.0164 mmol, 0.9%) and $(PPh_3)_2PdCl_2$ (0.0342 g, 0.00489 mmol, 0.3%). After 5 days of stirring, the reaction was complete on the basis of the disappearance of the alkyne. This reaction time can be shortened to a day by using 5−10 times more of the catalysts. The mixture was diluted with water (100 mL) and extracted with diethyl ether (100 mL). The combined organic phases were washed with 2 N HCl (50 mL), followed by saturated $NaHCO_3$ (50 mL) and then H_2O (50 mL). The organic phase was dried with $MgSO_4$ and filtered and the filtrate concentrated by rotary evaporation, leaving crude alkynyl ketone **24** (4.64 g). The crude ketone was dissolved in methanol (30 mL). Hydrazine monohydrate (0.783 g, 15.6 mol) was added, and within 5 s, the reaction had warmed to reflux. The cooling mixture was stirred for 2 h, acidified to pH 2 with concentrated HCl, and stirred for an additional 15 h to deprotect **26**. The reaction mixture was neutralized with solid $NaHCO_3$, diluted with water (50 mL), and extracted with ethyl acetate (2 × 100 mL). The organic phases were combined, dried with $MgSO_4$, and filtered, and the filtrate was concentrated by rotary evaporation. The crude residue was recrystallized from a minimal amount of acetone and hexane, affording **28** (3.20 g, 13.7 mmol, 77%) as a solid: mp 171.2−172.0 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 6.08 (s, 1 H, H4), 4.55 (s, 2 H), 2.03 (s, 3 H), 1.95 (s, 6 H), 1.80 (s, 6 H) ppm; ^{13}C{^{1}H} (CD_3OD, 50.3 MHz) δ 158.1, 151.5, 100.4, 58.5, 43.6, 37.9, 34.4, 30.1 ppm; IR (KBr) 3213 (br), 3155, 2919, 2855, 1566, 1445, 1359, 1159, 1051, 987, 808 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32): C, 72.38; H, 8.68; N, 12.06. Found: C, 71.98; H, 8.34; N, 11.90.

From another run, alkynyl ketone **24** was purified on silica using hexanes/ethyl acetate solution (4:1) and exhibited the following data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (t, J = 3 Hz, 1 H), 4.39 (s, 2 H), 3.79 (m, 1 H), 3.49 (m, 1H), 2.0−1.4 (m, 21 H) ppm; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 193.1, 173.3, 97.1, 89.5, 83.0, 62.1, 53.9, 44.7, 42.2, 38.3, 37.9, 36.5, 36.3, 30.2, 27.9, 27.4, 25.3, 19.0 ppm; IR (neat, NaCl plates) 2216, 1668 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_3$ (302.41): C, 75.46; H, 8.66. Found: C, 75.19; H, 8.36.

Similarly, purified THP-protected pyrazolemethanol derivative **26** exhibited the following data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.08 (s, 1 H), 5.3−6.1 (br s, 2 H), 4.74 (d, J = 12 Hz, 1 H), 4.73 (narrow m, 1 H), 4.55 (d, J = 12 Hz, 1 H), 3.92 (dt, J = 2.5, 9.5 Hz, 1 H), 3.54−3.57 (m, 1 H), 1.5−2.1 (m, 21 H) ppm; ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 157.2 (br), 146.9 (br), 100.5 (br), 98.4, 62.5, 62.4, 42.7, 39.2, 36.9, 36.7, 30.7, 28.7,

28.2, 25.6, 19.6 ppm; IR (neat, NaCl plates) 2216, 1668 cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_2$ (316.44): C, 72.12; H, 8.92. Found: C, 72.10; H, 9.18.

3-(Diphenylphosphinomethyl)-5-methylpyrazole (29a). To a flask purged with argon were added dry THF (20 mL) and diphenylphosphine (3.191 g, 17.1 mmol). The solution was cooled to −78 °C in an acetone/dry ice bath, and *n*-BuLi was added dropwise (7.5 mL, 2.50 M in hexanes, 18.8 mmol). The resulting red solution was stirred for 2 h at −78 °C before hydrochloride salt **20** (0.576 g, 3.45 mmol) was added as a solid. The cold bath was removed, and the reaction was stirred at room temperature for 19 h. Degassed water (25 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by radial chromatography using SiO_2 and ethyl acetate/petroleum ether (1:9) to give pure **29a** (0.7521 g, 2.68 mmol, 78%) as a thick colorless air-sensitive oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.14 (br s, 1 H), 7.45−7.40 (m, 4 H), 7.36−7.30 (m, 6 H), 5.77 (s, 1 H), 3.41 (s, 2 H), 2.21 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 145.5 (br s), 143.8 (br s), 138.4 (d, J = 14.2 Hz), 132.9 (d, J = 18.9 Hz), 129.0, 128.6 (d, J = 6.5 Hz), 104.6 (d, J = 5.0 Hz), 27.3 (d, J = 15.2 Hz), 12.3 ppm; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 81.0 MHz) δ −14.56 ppm; IR (neat, NaCl) 3192, 3134, 3027, 2926, 1582, 1480, 1433, 1306, 1096, 1026 cm^{-1}.

5-(Methylthiomethyl)-3-phenylpyrazole (29b). To the chloride **21** (0.286 g, 1.25 mmol) suspended in dry THF (5 mL) under nitogen was added lithium thiomethoxide (0.135 g, 2.5 mmol) as a slurry in THF (5 mL). After the mixture was stirred for 4 h, a clear solution resulted. TLC (ethyl acetate/petroleum ether, 1:1) showed a new compound, R_f = 0.7. The reaction solution was diluted with water (10 mL) and extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, and filtered, and the filtrate was concentrated, leaving **29b** (0.211 g, 82%) as a pale brown oil. From another run starting with **21** (0.500 g), product was purified by Kugelrohr distillation (170 °C, 0.8 mmHg) to give analytically pure product in 48% yield: ^1H NMR ($CDCl_3$, 200 MHz) δ 12.0 (s, 1 H), 7.50−7.80 (m, 2 H), 7.10−7.30 (m, 3 H), 6.43 (s, 1 H), 3.60 (s, 2 H), 1.98 (s, 3 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50.3 MHz) δ 148.2, 146.6, 131.2, 128.9, 128.3, 125.8, 102.3, 29.5, 15.3 ppm. Anal. Calcd for $C_{11}H_{12}N_2S$ (204.29): C, 64.67; H, 5.92; N, 13.71. Found: C, 64.45; H, 5.72; N, 13.50.

5-*tert*-Butyl-3-(diphenylphosphinomethyl)pyrazole (29c). A dry argon-filled Schlenk flask was charged with a stir bar and triphenylphosphine (1.0356 g, 3.948 mmol), followed by dry THF (10 mL). The resulting solution was cooled to 0 °C, and lithium ribbon (0.0558 g, 8.039 mmol) was added. After 15 min the mixture was allowed to warm to room temperature and stirred until lithium metal was gone (4 h). The resulting dark red solution was cooled in a dry ice/acetone bath, and solid **22** (0.2792 g, 1.335 mmol) was added all at once before the reaction mixture was slowly allowed to warm to room temperature. After 16 h, water (1 mL) was added. The organic layer was separated, dried over $MgSO_4$, and filtered and the filtrate concentrated. The residue was purified by radial chromatography using petroleum ether, followed by diethyl ether to elute product **29c** (0.279 g, 47%) as a thick air-sensitive oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.73 (br s, 1 H), 7.42−7.46 (m, 4 H), 7.33−7.35 (m, 6 H), 5.75 (s, 1 H, H4), 3.41 (s, 2 H), 1.26 (s, 9 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 157.3 (br s), 145.4 (br s), 138.5 (d, J = 14.7 Hz), 133.0 (d, J = 18.9 Hz), 129.0 (s), 128.6 (d, J = 6.4 Hz), 101.6 (d, J = 4.7 Hz), 31.5 (s), 30.5 (s), 27.5 (d, J = 15.1 Hz), 15.5 (s) ppm; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 80.95 MHz) δ −14.31 ppm; IR (NaCl) 3186, 3071, 2963, 1567, 1481, 1462, 1434, 1366, 1299, 1237, 1184, 1097, 1027, 999, 910, 736, 695 cm^{-1}.

5-(*tert*-Butyl)-3-(methylthiomethyl)pyrazole (29d). Chloromethyl compound **22** (1.00 g, 4.78 mmol) was partially dissolved in dry THF (25 mL) under a nitrogen atmosphere. At room temperature, lithium thiomethoxide (0.52 g, 9.60 mmol) was added to the mixture. The reaction mixture became slightly brown. While the reaction was stirring, it was monitored with TLC. It was complete after 5 h on the basis of TLC (R_f = 0.52; THF/hexanes, 2:1). The reaction was quenched with water (3 mL), and the organic phase was extracted with diethyl ether (3 × 25 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by Kugelrohr distillation at 135−150 °C under oil pump vacuum (1.4 Torr) to give **29d** (0.66 g, 3.59 mmol, 75%) as a solid: mp 62.9−63.5 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (br s, 1 H), 6.09 (s, 1 H), 3.72 (s, 2 H), 2.11 (s, 3 H), 1.35 (s, 9 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 156.6, 147.7, 101.0, 31.4, 30.6, 30.5, 15.6 ppm; IR (KBr) 3167, 3082, 2974, 2914, 2870, 1663, 1567, 1464, 1366, 1301, 1236, 1143, 1015, 834 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2S$ (184.31): C, 58.65; H, 8.75; N, 15.20. Found: C, 58.32; H, 8.87; N, 14.94.

5-(*tert*-Butyl)-3-(phenylthiomethyl)pyrazole (29e). To a solution of benzenethiol (526.7 mg, 4.78 mmol) in dry DMF (5 mL) was added NaH (191.1 mg of a 60% suspension in oil, 4.78 mmol). The mixture was allowed to stir for 0.5 h before the chloride **22** (0.500 g, 2.39 mmol) was added in one portion. After 21 h, the mixture was worked up with ether and water, followed by radial chromatography over silica using ethyl acetate/petroleum ether, affording **29e** as a thick oil (479.7 mg, 63%): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37 (∼d, $J \approx$ 8 Hz, 2 H), 7.27 (∼t, $J \approx$ 8 Hz, 2 H), 7.19 (tt, J = 1.5, 7.5 Hz, 1 H), 6.01 (s, 1 H), 4.16 (s, 2 H), 1.31 (s, 9 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 156.1, 147.1, 136.6, 129.7, 129.0, 126.4, 101.1, 31.4, 31.4, 30.4 ppm; IR (KBr) 3179, 3089, 2968, 2879, 1573, 1478, 1362, 1301, 1234, 1139, 1017, 839, 734, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2S$ (246.37): C, 68.25; H, 7.36; N, 11.37. Found: C, 67.86; H, 7.70; N, 11.35.

5-(*tert*-Butyl)-3-[(2-hydroxyethyl)thiomethyl]pyrazole (29f). Chloromethyl compound **22** (0.204 g, 0.976 mmol) was dissolved in dry DMF (5 mL) under a nitrogen atmosphere. At room temperature, a mixture of 2-mercaptoethanol and lithium hydroxide monohydrate (0.153 g, 1.95 mmol, and 0.0819 g, 1.95 mmol, respectively) in dry DMF (5 mL) was added to the solution. After the reaction was stirred overnight (15 h), it was complete (TLC R_f = 0.2, ether). The reaction mixture was poured into diethyl ether (25 mL) and the solution washed with water (5 × 50 mL). The organic phases were dried over $MgSO_4$ and filtered, and the filtrate was concentrated. The residual oil was placed under oil pump vacuum (1.4 Torr) to give **29f** (0.126 g, 0.586 mmol, 60%) as a solid: mp 85.7−86.9 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.02 (s, 1 H), 5.70 (v br s, 2 H), 3.74−3.76 (m, 4 H), 2.73−2.76 (m, 2 H), 1.32 (s, 9 H) ppm; $^{13}C\{^1H\}$ and DEPT NMR ($CDCl_3$, 125.7 MHz) δ 156.3 (br, C), 148.5 (br, C), 100.8 (CH), 61.2 (CH_2), 35.0 (CH_2), 31.4 (C), 30.4 (CH_3), 28.4 (CH_2) ppm; IR (NaCl, $CDCl_3$) 3467 (sharp), 3244 (br), 2966, 2867, 1556, 1461, 1283, 1139, 1056, 1000, 800, 755, 650 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2OS$ (214.32): C, 56.04; H, 8.49; N, 13.07. Found: C, 56.19; H, 8.79; N, 13.06.

5-(*tert*-Butyl)-3-(tert-butylthiomethyl)pyrazole (29g). *Tert*-Butyl disulfide (0.74 mL, 3.85 mmol) was dissolved in dry THF (4 mL) under a nitrogen atmosphere. At −78 °C, *n*-BuLi (2.40 mL, 3.85 mmol) was added to the mixture. After 2 h and at room temperature, the chloromethyl compound **22** (0.2689 g, 1.28 mmol) was added to the mixture. As monitored by TLC, the reaction was complete after 31 h (diethyl ether/petroleum ether, 1:1; plate stained with iodine). The reaction was quenched with water (150 mL), and the organic phase was extracted with diethyl ether (3 × 25 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by Kugelrohr distillation at 120−190 °C under oil pump vacuum (1.4 Torr) to give **29g** (0.1421 g, 0.628 mmol, 49%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.04 (br s, 1 H), 6.05 (s, 1 H), 3.79 (s, 2 H), 1.34 (s, 9 H), 1.31 (s, 9 H, $C(CH_3)_3$) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz) δ 156.7, 147.5, 100.9, 42.9, 31.5, 31.0, 30.5, 25.6 ppm; IR (neat, NaCl) 3200, 3103, 3047, 2956, 2900, 2865, 1567, 1461, 1367, 1267, 1161, 1006, 800, 739 cm^{-1}. Anal. Calcd

for $C_{12}H_{22}N_2S$ (226.39): C, 63.66; H, 9.80; N, 12.38. Found: C, 63.53; H, 9.89; N, 12.01.

5-*tert*-Butyl-3-(2-diphenylphosphinoethyl)pyrazole (30c). Triphenylphosphine (1.15 g, 4.38 mmol), lithium ribbon (61 mg, 8.77 mmol), and naphthalene (10 mg, 0.078 mmol) were dissolved in dry THF (25 mL) and stirred for 2 days, until all of the lithium had dissolved. The reaction was cooled in a water/ice bath to 0 °C, and solid hydrochloride **23** (195 mg, 0.88 mmol) was added. The reaction was warmed to room temperature and stirred for 5 h, at which point degassed ethanol (5 mL) was added. Removal of the solvent on a high vacuum line yielded a brown oil, which was purified by radial chromatography (ethyl acetate/petroleum ether, 1:1) under a N_2 atmosphere to give phosphine **30c** (258 mg, 0.78 mmol, 88%) as a clear oil which solidified to a white solid: mp 90.9−91.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.06 (br s, 1 H, NH), 7.46 (td, $^3J_{HH}$ = 7.5 Hz, J_{PH} = 1.5 Hz, 4 H), 7.32−7.36 (m, 6 H), 5.91 (s, 1 H), 2.62−2.75 (m, 2 H), 2.35−2.45 (m, 2 H), 1.30 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 138.5 (d, J_{PC} = 12.6 Hz), 134.0, 133.9, 132.9 (d, J_{PC} = 19 Hz), 128.8, 128.7 (d, J_{PC} = 6.6 Hz), 100.1, 31.8, 30.6, 28.0 (d, $^2J_{PC}$ = 12 Hz), 22.9, 14.3 ppm; ^{31}P{^{1}H} NMR ($CDCl_3$, 80.95 MHz) δ ∠17.3 ppm; IR (CH_2Cl_2 solution evaporated on NaCl plate) 3192, 2963, 1570, 1480, 1434, 1364, 999, 796, 740, 650 cm^{-1}. Anal. Calcd for $C_{21}H_{25}N_2P$ (336.41) C, 74.98; H, 7.49; N, 8.33. Found: C, 74.85; H, 7.54; N, 7.97.

5-*tert*-Butyl-3-(2-methylthioethyl)pyrazole (30d). Methyl disulfide (890 mg, 9.45 mmol) was dissolved in dry THF (20 mL) and the solution cooled to −78 °C. A solution of *n*-BuLi (6.00 mL, 1.6 M in hexane, 9.60 mmol) was added over 5 min from an addition funnel. The reaction was warmed to room temperature over 2 h, and a white precipitate formed. Hydrochloride **23** (1.05 g, 4.69 mmol) was added as a solid, and the solution was allowed to stir overnight. The reaction was quenched with water (5 mL) and concentrated on a rotary evaporator. The residual brown oil was purified by Kugelrohr distillation at 145−150 °C under oil pump vacuum to give **30d** (854 mg, 4.30 mmol, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.2 (br s, 1 H), 5.92 (s, 1 H), 2.92 (t, 2 H, J = 8 Hz), 2.79 (t, 2 H, J = 8 Hz), 2.12 (s, 3 H), 1.31 (s, 9 H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125.7 MHz) δ 156.8, 148.8, 100.3, 34.0, 31.4, 30.5, 28.0, 15.8 ppm; IR (neat, NaCl) 3188, 3132, 3101, 2961, 2868, 1573, 1463, 1438, 1365, 1302, 1274, 1237, 1207, 1138, 1109, 1010, 957, 927, 796 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2S$ (198.12): C, 60.56; H, 9.15; N, 14.12. Found: C, 60.21; H, 9.49; N, 13.82.

Acknowledgment. San Diego State University is thanked for support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **7**−**11**, **13**−**15**, **19**·HCl, **24**, **25**, **29a**, and **29c** and the ^{1}H NMR spectrum of **26**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

JO026083E