A New Set of Structurally Related Enantiopure Polypyrazolyl Ligands of Varying Rotational Symmetry: Synthesis, Metal Complexation, and Comparison of Asymmetric Induction

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A new family of enantiomerically pure pyrazoles with a variety of substitutions on a key stereogenic center was synthesized from (*R*)-(+)-pulegone by a straightforward, large-scale route involving initial construction of the pyrazole ring via formylation/dehydration with hydrazine followed by ozonolysis to yield a readily functionalized ketone (**5**). Alkylation of **5** with a variety of Grignard reagents, dehydration, hydrogenation, and recrystallization afforded the set of new chiral pyrazoles (**7a**−**c**). Cis and/or trans diastereomers of one of these pyrazoles having a phenyl substituent (**7a**) were elaborated into enantiopure, multidentate C_1-symmetric bis(pyrazolyl)diphenylborate (Tl[*cis*-Ph_2Bp^{pm}]), C_2-symmetric bis(pyrazolyl)methane (*cis*- and *trans*-X^{pm}), and C_3-symmetric tris(pyrazolyl)phosphine oxide (*cis*- and *trans*-OP^{pm}) and tris(pyrazolyl)hydroborate (K[*trans*-Tp^{pm}]) ligands. Interestingly, epimerization of the benzylic stereogenic center occurred during the synthesis of K[*trans*-Tp^{pm}], as determined by comparison of 2D NMR spectral and X-ray crystal structural data for the starting *cis*-pyrazole (*cis*-**7a**) and the copper complex (*trans*-Tp^{pm})Cu(CH_3CN). Comparison of the abilities of copper complexes of the various $[Ph_2Bp^{pm}]^-$, X^{pm}, OP^{pm}, and Tp^{pm} ligands to catalyze the cyclopropanation of styrene by ethyldiazoacetate revealed significantly enhanced enantioselectivity for the Tp^{pm} case. This result represents the first example of a high degree of enantiocontrol in a catalytic reaction of any complex of a Tp ligand and provides experimental support for the possible efficacy of higher order rotational symmetry in metal-mediated stereoselective reactions.

The particular efficacy of C_2-symmetric ligands[1] in enantioselective metal-mediated organic reactions is well-known, recent exemplary successes being the use of N-donor chelates to control the course of group transfer reactions (e.g., olefin cyclopropanation,[2] aziridination,[3] epoxidation[4]).[5] Arguments also have been advanced in support of the potential for enhanced enantioselectivity with systems having higher rotational symmetry, such as C_3 and D_4, in which increased stereodifferentiating interactions and/or reduced numbers of diastereomeric transition states (particularly in octahedral complexes) are invoked.[6,7] Experimental demonstration of these notions has been difficult to achieve, however, and there has been relatively scant implementation of ligands with 3- or 4-fold rotational symmetry in asymmetric metal-mediated catalysis.[8]

In efforts to explore the effectiveness of C_3-symmetric ligand systems, we have targeted enantiopure tris(pyrazolyl)hydroborates (Tp's) of general type **1**, which, on the basis of extensive precedence,[9] would be expected to form a wide range of metal complexes. We have reported the synthesis and characterization of metal complexes of a relatively small class of such ligands

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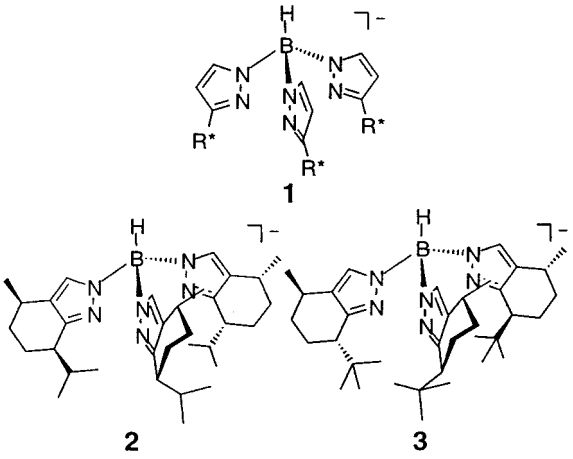


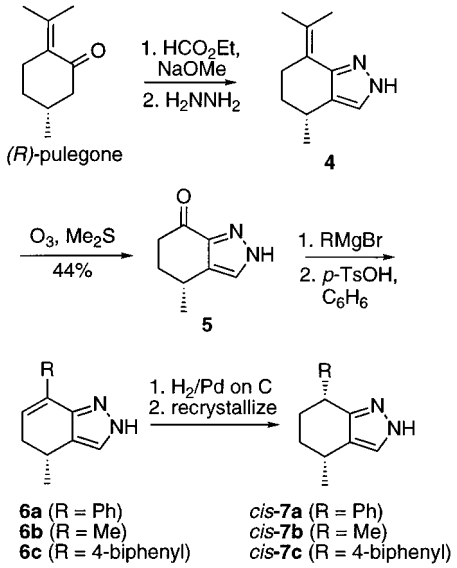
derived via standard synthetic methods from readily available (2*S*,5*R*)-(−)-menthone (Tp^{Menth}, **2**) or (*R*)-(+)-pulegone ($Tp^{Mementh}$, **3**).[10] Frustrated by a lack of success in attempts to use these complexes as enantioselective catalysts and by our inability to broadly vary the nature of the stereodifferentiating groups appended to the stereogenic centers surrounding the bound metal ion, we sought to develop a new, more versatile synthetic approach that would allow us to more thoroughly modulate the nature of the chiral cavity provided by the strongly binding Tp unit. Ligands related to **2** and **3** but with aryl instead of simple branched alkyl substituents proximal to the metal binding site were particularly attractive targets, in part because of indications in the literature of the possible importance of edge−face and/or face−face aromatic interactions in substrate recognition processes.[11]

Herein, we report general routes to several differently appended chiral pyrazoles, the elaboration of one diastereomeric pair having phenyl substituents into ligand systems of C_1, C_2, and C_3 symmetry (including a Tp), and the characterization of metal complexes of these ligands. In a preliminary test of the ability of these ligands to promote enantioselective reactions, we examined catalysis by their copper complexes of the cyclopropanation of styrene by ethyldiazoacetate. These studies revealed significantly enhanced enantioselectivity for the C_3-symmetric Tp case, thus illustrating for the first time a high degree of asymmetric induction using a Tp complex and providing experimental support for the notion that higher order symmetry may be effective in metal-mediated stereoselective reactions.[12]

Results and Discussion

Pyrazole Synthesis. The critical intermediate in our new, versatile synthetic route to optically active

Scheme 1



pyrazoles is the ketone **5** (Scheme 1), which we prepared on a 25 g scale from commercially available (*R*)-(+)-pulegone via a classical formylation/cyclization sequence (to give **4**)[13] followed by ozonolysis (44% overall yield). This ketone allows access to a wide range of pyrazoles with differing appendages, depending on the choice of reagent used to add to the carbonyl group. In our initial studies, we have found that addition of Grignard reagents works well, although extra equivalents of nucleophile must be used because of the presence of the acidic pyrazole N−H. For instance, treatment of **5** with PhMgBr (3 equiv) afforded a mixture of diastereomeric alcohols that were dehydrated under Dean−Stark conditions to give alkene **6a**. This alkene was identified by ^{1}H NMR spectral and GC/MS analysis but was used without further purification (**6c** was isolated and fully characterized). Subsequent hydrogenation of **6a** with 1 atm of H_2 over Pd/C gave a 4:1 mixture of diastereomeric pyrazoles *cis*- and *trans*-**7a** (69% yield based on **5**). The major isomer *cis*-**7a** was isolated from this mixture by a recrystallization from acetone (23% yield from **5**). We were unable to isolate the trans isomer in pure form from the mother liquor but did succeed in obtaining it via a ligand degradation procedure (vide infra). We determined the stereochemistries of the two isomers from COSY and NOESY NMR spectral data, under the assumption that the configuration at the methyl group of the starting (*R*)-(+)-pulegone was retained during the synthesis. These assignments were confirmed by an X-ray crystal structure of *cis*-**7a** (see Supporting Information). The predominance of the cis product from the hydrogenation of **6a** may be explained by the methyl group exerting steric control over the face to which H_2 is delivered by the catalyst surface.

In a further demonstration of the generality of the functionalization route, addition of MeMgBr or 4-biphenylmagnesium bromide to **5** proceeded analogously to yield the pyrazoles *cis*-**7b** or *cis*-**7c**, respectively, after recrystallization. The stereochemistry of these products was also determined using 2D NMR methods (see Supporting Information).[12]

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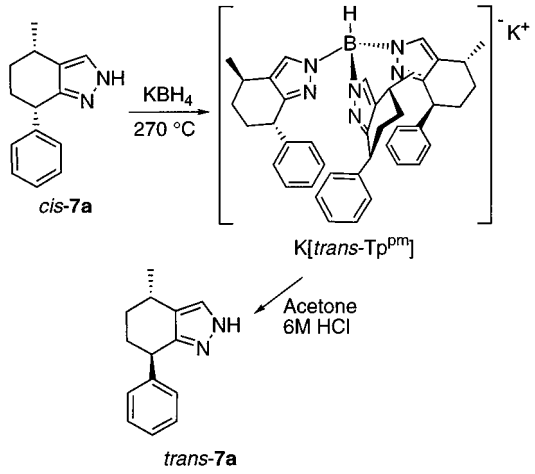
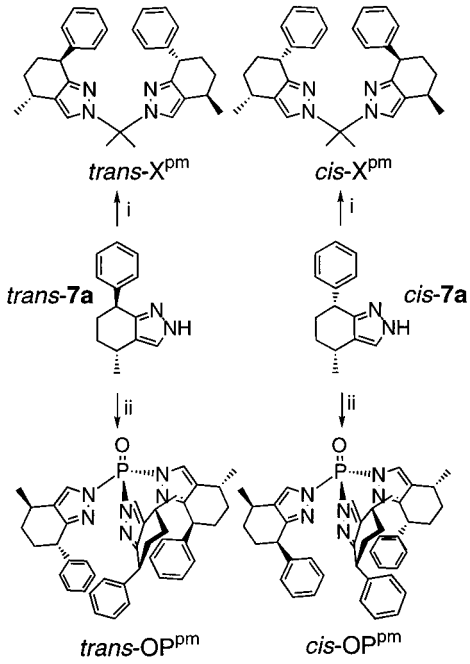
Scheme 2



Ligand Synthesis. Inspired by the potential for good asymmetric induction with ligands having aryl substituents that may participate in chiral recognition during catalysis,[11] we have focused our efforts so far on elaborating the pyrazoles *cis*- and *trans*-**7a** into multidentate chelates. Ligands of varying rotational symmetry were targeted, a key ultimate objective being to evaluate the role of this symmetry element in enantioselection.

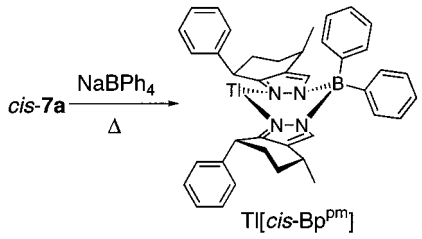
Using a well-precedented method,[9] K[*trans*-Tp^{pm}] was prepared by slow heating of *cis*-**7a** and KBH_4 to 270 °C, with concomitant evolution of 3 equiv of H_2 (Scheme 2). Mass spectral and chemical analysis data of the isolated product matched the expected formulation, and the IR spectrum exhibited a characteristic B−H stretch at 2409 cm^{-1}. Only one pyrazole environment was observed in the ^1H and ^{13}C NMR spectra, indicative of 3-fold rotational symmetry and complete N1/N2 regioselectivity. Although we collected three data sets from three different crystals, extreme twinning problems precluded the successful solution of an X-ray crystal structure of the molecule. Nonetheless, an X-ray structure of a Cu(I) complex of the ligand confirmed its topology (vide infra). Surprisingly, these data showed that it contained pyrazolyl groups with trans instead of cis stereochemistry, indicating that epimerization at the activated benzylic position occurred during the high-temperature reaction with KBH_4. Moreover, we were able to isolate *trans*-**7a** as a pure material in high yield by treating K[*trans*-Tp^{pm}] with 6 M HCl in acetone. Attempts to synthesize *trans*-**7a** from its cis isomer directly by reaction with strong base (NaH in refluxing THF) or strong acid (boiling concentrated HCl in acetone) failed, making the decomposition of K[*trans*-Tp^{pm}] the best route currently available toward this pyrazole diastereomer.[14]

Scheme 3[a]



[a] Key: (i) $(MeO)_2C(CH_3)_2$, *p*-TsOH. (ii) Cl_3PO, Et_3N.

Scheme 4



Whereas only one diastereomeric form of **7a** could be incorporated into a Tp ligand, both *cis*- and *trans*-**7a** were converted successfully using established procedures[10a,15] into neutral, tridentate phosphine oxides *cis*-OP^{pm} and *trans*-OP^{pm} and bidentate chelates *cis*-X^{pm} and *trans*-X^{pm} (Scheme 3). The ^1H and ^{13}C NMR spectra of all of these compounds were indicative of one pyrazole environment, consistent with complete N1/N2 regioselectivity and C_3 (OP^{pm}) or C_2 (X^{pm}) symmetry. Note that the X^{pm} ligands are topologically complementary to chiral bis(oxazoline) ligands that have proven to be successful in many stereocontrolled reactions of metal reagents.[2d,3a,16]

Finally, *cis*-**7a** has also been incorporated into a bis(pyrazolyl)diphenylborate ligand Tl[*cis*-Ph_2Bp^{pm}] via Trofimenko's procedure,[17] which involves heating to 200 °C with $NaBPh_4$ with elimination of benzene followed by metathesis with TlOAc (Scheme 4). In contrast to the analogously thermolytic K[*trans*-Tp^{pm}] synthesis, no pyrazole isomerization occurs during formation of Tl[*cis*-Ph_2Bp^{pm}], as indicated by isolation of only *cis*-**7a** upon hydrolysis. A single set of pyrazolyl resonances in its ^1H and ^{13}C NMR spectra suggest a C_2-symmetric

(14) Due to the production of significant amounts of *trans*-**7a** during the KBH_4 thermolysis reaction, recrystallization of the recovered pyrazole from the K[*trans*-Tp^{pm}] synthesis from acetone yielded a 1:1 mixture of *cis*- and *trans*-**7a**. Surprisingly, this mixture does not form K[*trans*-Tp^{pm}] when it is heated with KBH_4. In contrast to the synthesis run with pure *cis*-**7a**, H_2 does not begin to evolve until the reaction has been heated above 270 °C (with pure *cis*-**7a** the reaction is *complete* at this temperature). Three equivalents of H_2 was not evolved, even when the temperature was raised to 340 °C for 6 h. An intractable mixture resulted from this procedure. This strange behavior remains unexplained, but it implies that the cis/trans isomerization process which occurs during the Tp synthesis is somehow linked to Tp formation (or occurs afterwards).

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(17) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 6288.

structure. However, several achiral analogues have been structurally characterized, and all of them exhibit central six-membered chelate rings that are in a boat conformation.[18] We surmise that Tl[*cis*-Ph_2Bp^{pm}] adopts a similar geometry (here C_1 symmetric) but appears in NMR spectra to be of higher symmetry due to rapid fluxionality in solution (presumably a boat/boat interconversion).

A Copper(I) Complex of *trans*-Tp^{pm}. The topological features of *trans*-Tp^{pm}, in particular the absolute configuration and the N1/N2 regiochemistry, were revealed by an X-ray crystal structure analysis of the Cu(I) complex (*trans*-Tp^{pm})Cu(CH_3CN). The compound was prepared by reacting K[*trans*-Tp^{pm}] with CuCl in CH_2Cl_2 and recrystallizing the recovered white solid from CH_2Cl_2/CH_3CN/pentane.[19]

In the structure of (*trans*-Tp^{pm})Cu(CH_3CN) (Figure 1, bond lengths and angles in Table 1, crystallographic data in Table 2), tridentate binding of the ligand yields a Cu(I) geometry typical for TpCu(L) compounds,[20] here with an array of phenyl substituents that provide a chiral C_3-symmetric fence encapsulating the CH_3CN ligand in a deep cavity walled by the aromatic π faces. Similar encapsulation by aryl rings has been reported for complexes of various aryl-substituted tripodal[8f] and achiral Tp ligands,[9,21,22] a particularly pertinent example being the mesityl-substituted ligand TpMs (TpMs = tris(3-mesityl-1-pyrazolyl)hydroborate)[22a] in which the aryl rings are "locked" by steric interactions involving the *ortho*-methyl substituents into positions approximately orthogonal to their connected pyrazolyl units. Consideration of space-filling models of the structure of (*trans*-Tp^{pm})Cu(CH_3CN) (Figures 1b and 1c) reveals relatively close packing of the phenyl rings about the CH_3CN molecule that is buried within the ligand cavity, an arrangement that may have implications for understanding catalytic reactivity results (vide infra).

Catalytic Cyclopropanations. We tested (*trans*-Tp^{pm})Cu(CH_3CN) and copper complexes generated in situ from both cis and trans forms of X^{pm} and OP^{pm} (1−10 equiv) and [Cu(CH_3CN)$_4$]BF_4 as catalysts for the production of chiral cyclopropane **8** from styrene and ethyldiazoacetate (Scheme 5). The complexes of the neutral X^{pm} and OP^{pm} were not isolated or structurally characterized, but binding of the ligands to Cu(I) was confirmed by ^{1}H NMR spectral data that revealed significant shifting of ligand resonances. For the X^{pm} cases, the peaks were sharp, but the Cu(I)/OP^{pm} solutions exhibited broad peaks indicative of a fluxional process(es) that interchanges pyrazolyl ring environments, perhaps involving dissociation of one pyrazolyl arm.[23] An additional catalyst was generated by reaction of equimolar amounts of Tl[*cis*-Ph_2Bp^{pm}] and CuCl in CH_3CN. After removal of precipitated TlCl, an air-

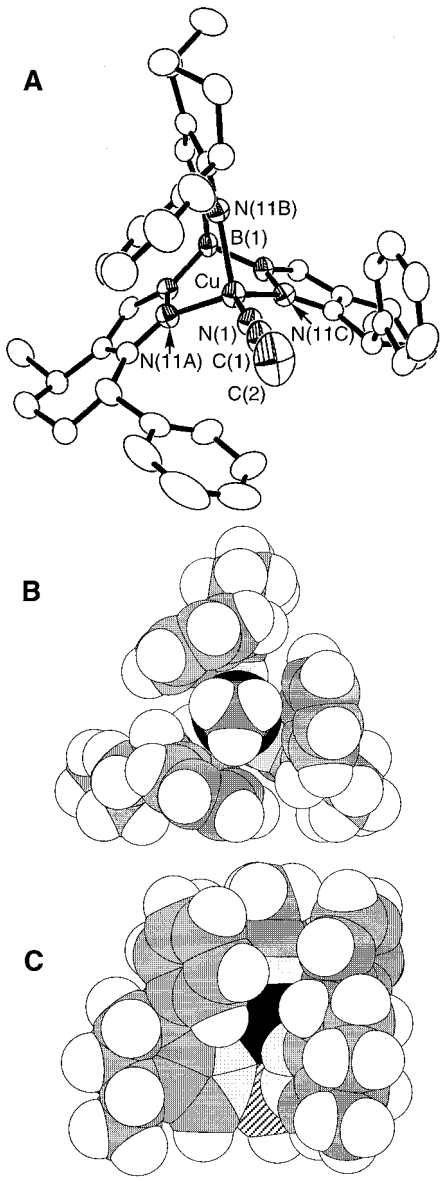

Figure 1. Representation of the X-ray crystal structure of (*trans*-Tp^{pm})Cu(CH_3CN)·CH_2Cl_2 showing non-hydrogen atoms as 50% thermal ellipsoids and selected atom labels (A) and space-filling Chem3D drawings of the same molecule down the Cu···B vector (B) and from the side (C) (the CH_2Cl_2 solvate has been eliminated for clarity).

(18) (a) Bortolin, M.; Bucher, U. E.; Ruegger, H.; Venanzi, L. M. *Organometallics* **1992**, *11*, 2514−2521. (b) Trofimenko, S.; Calabrese, J. C.; Thompson, J. S. *Inorg. Chem.* **1992**, *31*, 974−979.

(19) Recrystallization in the absence of CH_3CN yielded [(*trans*-Tp^{pm})-Cu]$_2$, which was found in a preliminary X-ray crystal structure (marred by disorder problems) to be analogous to several other published dimers of achiral Tp and bis(pyrazolyl)dihydroborate ligands that have two-coordinate Cu(I) ions in a linear geometry bridged by two bidentate chelates. See ref 12 and (a) Carrier, S. M.; Ruggiero, C. E.; Houser, R. P.; Tolman, W. B. *Inorg. Chem.* **1993**, *32*, 4889−4899. (b) Houser, R. P. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, 1996. (c) Yoon, K.; Parkin, G. *Polyhedron* **1995**, *14*, 811−821. (d) Kiani, S.; Long, J. R.; Stavropoulos, P. *Inorg. Chim. Acta* **1997**, *263*, 357−366.

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(21) (a) Ghosh, P.; Parkin, G. *Polyhedron* **1997**, *16*, 1255−1257. (b) Ghosh, P.; Parkin, G. *Inorg. Chem.* **1996**, *35*, 1429−1430.

(22) (a) Rheingold, A. L.; White, C. B.; Trofimenko, S. *Inorg. Chem.* **1993**, *32*, 3471−3477. (b) Han, R.; Parkin, G.; Trofimenko, S. *Polyhedron* **1995**, *14*, 387−391.

(23) There is structural precedent for η^2 binding of analogous tris(pyrazolyl)phosphine oxide ligands, including our finding that treatment of an η^3-bound complex [(OP^{camph})Cu(CH_3CN)]$^+$ (OP^{camp} = tris[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-phosphine oxide)[23b] with PPh_3 does not cause displacemnt of CH_3CN but instead yields the crystallographically characterized [(η^2-OP^{camph})Cu(CH_3CN)(PPh_3)]$^+$ in which a pyrazolyl arm dangles free. (a) Kettler, P. B.; Tokar, C. J.; Tolman, W. B. Unpublished results. (b) Tokar, C. J.; Kettler, P. B.; Tolman, W. B. *Organometallics* **1992**, *11*, 2738−2739.

Table 1. Selected Bond Lengths (Å) and Angles (deg) for (*trans*-Tp^{pm})Cu(CH$_3$CN)·CH$_2$Cl$_2$[a]

Cu(1)−N(1)	1.862(4)	N(1)−Cu(1)−N(11C)	127.2(2)
Cu(1)−N(11B)	2.077(4)	N(11C)−Cu(1)−N(11B)	89.8(2)
N(1)−C(1)	1.129 (7)	N(11C)−Cu(1)−N(11A)	91.5(2)
B(1)−N(12B)	1.544(7)	C(1)−N(1)−Cu(1)	177.4(5)
B(1)−N(12A)	1.559(7)	N(12B)−B(1)−N(12C)	109.9(4)
N(11A)−N(12A)	1.368(5)	N(12C)−B(1)−N(12A)	108.3(4)
N(11B)−N(12B)	1.371(5)	C(15A)−N(11A)−Cu(1)	139.8(3)
N(11C)−N(12C)	1.365(5)	C(15B)−N(11B)−N(12B)	106.6(4)
N(12B)−C(13B)	1.358(6)	N(12B)−N(11B)−Cu(1)	114.5(3)
C(13A)−C(14A)	1.379(7)	C(15C)−N(11C)−Cu(1)	139.8(3)
C(13B)−C(14B)	1.378(7)	C(13A)−N(12A)−N(11A)	109.9(4)
C(14A)−C(19A)	1.503(7)	N(11A)−N(12A)−B(1)	120.4(4)
C(14B)−C(19B)	1.523(7)	C(13B)−N(12B)−B(1)	131.2(4)
Cu(1)−N(11C)	2.057(4)	C(13C)−N(12C)−N(11C)	109.8(4)
Cu(1)−N(11A)	2.090(4)	N(11C)−N(12C)−B(1)	121.1(4)
C(1)−C(2)	1.476(8)	N(1)−Cu(1)−N(11B)	120.1(2)
B(1)−N(12C)	1.549(7)	N(1)−Cu(1)−N(11A)	126.6(2)
N(11A)−C(15A)	1.341(6)	N(11B)−Cu(1)−N(11A)	91.0(2)

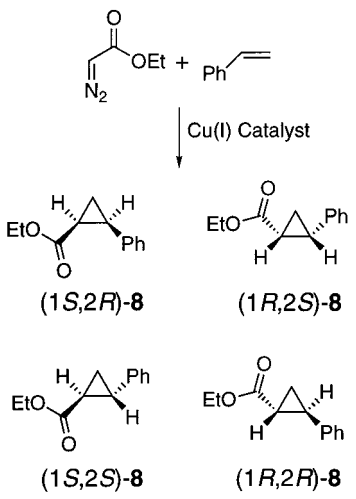
[a] Estimated standard deviations are in parentheses.

Table 2. Crystallographic Data for (*trans*-Tp^{pm})Cu(CH$_3$CN)·CH$_2$Cl$_2$

empirical formula	$C_{45}H_{51}N_7BCl_2Cl$
fw	835.18
space group	$P2_12_12_1$ (No. 19)
a (Å)	12.3557(1)
b (Å)	17.6388(1)
c (Å)	19.4443(2)
V (Å^3)	4237.69(6)
Z	4
ρ_{calcd} (Mg/m^3)	1.309
abs coeff (mm^{-1})	0.682
radiation, λ (Å)	Mo Kα, 0.710 73
$2\theta_{max}$ (deg)	50.04
no. of reflns collected	7413
no. of indep reflns with $I > 2\sigma(I)$	5872
final R1[a] [$I > 2\sigma(I)$]	0.0588
wR2[a] [$I > 2\sigma(I)$]	0.1295
largest diff. peak and hole e Å^{-3})	0.292 and −0.709

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2/\Sigma[w(F_o^2)^2]]^{1/2}$, where $w = q/\sigma^2(F_o^2) + (aP)^2 + bP$.

Scheme 5



sensitive solid was isolated, which was used without further purification. ^{1}H NMR analysis of this solid in CD$_3$CN or CD$_2$Cl$_2$ revealed a species with two different sets of pyrazole peaks of approximately equal intensity.[24] This finding is consistent with either a nonfluxional dimeric structure similar to that observed for [(Bp^{tBu})Cu]$_2$ (Bp^{tBu} = bis(3-*tert*-butyl-1-pyrazolyl)-dihydroborate)[19b,25] or a nonfluxional monomeric species in which the pyrazoles are rendered inequivalent due to the lack of a mirror plane or C_2 axis in the boat conformer. Attempts to further characterize this species are ongoing.

The cyclopropanations were carried out in CH$_2$Cl$_2$ at room temperature with 1 mol % of catalyst and 10 equiv of styrene relative to ethyldiazoacetate (added slowly via syringe pump). The results are presented in Table 3. The best % ee's were obtained for the C_3-symmetric *trans*-Tp^{pm} system, which catalyzed the reaction with high enantioselectivity (81% ee trans, 85% ee cis). Indeed, this is the first example of a Tp system inducing a high level of asymmetric induction in any type of catalytic reaction.[26] Although the % ee's achieved by (*trans*-Tp^{pm})Cu(CH$_3$CN) are less than the highest values reported for this reaction using C_2-symmetric bis(oxazoline) ligands (99% ee trans, 97% ee cis),[2d] they are much greater than those obtained by the other ligands constructed from the same (or diastereomeric) pyrazoles *cis*- and *trans*-**7a**. In particular, the enantioselectivities of the reactions catalyzed by C_2-symmetric *cis*- and *trans*-X^{pm} are poor, which is somewhat surprising given the similarity of these ligands to the bis(oxazoline) ligand system. Given that the highest enantioselectivities were obtained with strongly binding, anionic *trans*-Tp^{pm} and *cis*-Ph$_2$Bp^{pm}, it would appear that the strongest determinant of enantioselectivity is binding ability, although the divergent results for these two ligands indicate that other structural factors (including their differing rotational symmetry) may be important as well. Slight increases in asymmetric induction were observed when the X^{pm}/Cu(I) ratios were increased, but % ee's reached a maximum level at a ratio of 6:1, suggesting that ligand dissociation/association equilibria and catalysis by unligated Cu(I) species are only partially responsible for the poor behavior of these systems. For the OP^{pm} cases, a binding ability between that of X^{pm} and the anionic *trans*-Tp^{pm} and *cis*-Ph$_2$Bp^{pm} ligands coupled with the tendency for OP^{pm} to coordinate in an η^2 fashion (i.e., like the X^{pm} ligands) may explain the observed intermediate level of enantioselection.

It is difficult to rationalize the observed absolute stereochemistry of the favored products for the Tp^{pm} case using the often applied Pfaltz model,[2a,b] wherein a metal carbene is attacked by an olefin so as to minimize steric interactions between ligand substituents and the carbenoid ester group. Indeed, examination of space-filling models derived from the X-ray structure coordinates of Tp^{pm}Cu(CH$_3$CN) reveals that a copper−carbene intermediate would be completely enclosed by the array of phenyl groups and, thus, would be inaccessible to attack by the olefin substrate, suggesting that alternate cyclopropanating species and pathways should be considered (e.g., a diazoalkane complex as the reac-

(24) For instance, there are two methyl group doublets at δ 1.14 (d, J = 7 Hz, 3H) and 1.24 (d, J = 7 Hz, 3H) ppm and two benzylic hydrogen features at δ 3.9−4.0 (m, 1H) and 4.0−4.2 (br, 1H) ppm (300 MHz, CD$_3$CN).

(25) Houser, R. P.; Tolman, W. B. *Inorg. Chem.* **1995**, *34*, 1632−1633.

(26) Complete enantiocontrol at the metal was observed in intramolecular C−H bond activation reactions of rhodium complexes of **2** and **3**, see: Keyes, M. C.; Young, V. G., Jr.; Tolman, W. B. *Organometallics* **1996**, *15*, 4133−4140.

Table 3. Results for the Cyclopropanation of Styrene by Ethyldiazoacetate To Yield 10

catalyst	*cis*:*trans*[a]	*cis* % ee[b]	*trans* % ee[b]	yield[c]
(*trans*-Tp^{pm})Cu(CH_3CN)	60:40	85% (1*R*,2*S*)	81% (1*R*,2*R*)	46%
cis-Ph_2Bp^{pm}/Cu(I)[d]	40:60	56% (1*S*,2*R*)	10% (1*S*,2*S*)	25%
trans-OP^{pm} (10 equiv)/Cu(I)[e]	35:65	24% (1*R*,2*S*)	36% (1*R*,2*R*)	51%
trans-OP^{pm} (3 equiv)/Cu(I)[e]	31:69	18% (1*R*,2*S*)	25% (1*R*,2*R*)	49%
cis-OP^{pm} (3 equiv) /Cu(I)[e]	38:62	4% (1*S*,2*R*)	9% (1*R*,2*R*)	49%
trans-X^{pm} (10 equiv) /Cu(I)[e]	50:50	18% (1*R*,2*S*)	12% (1*S*,2*S*)	20%
trans-X^{pm} (6 equiv)/Cu(I)[e]	50:50	20% (1*R*,2*S*)	20% (1*S*,2*S*)	57%
trans-X^{pm} (3 equiv)/Cu(I)[e]	49:51	10% (1*R*,2*S*)	12% (1*S*,2*S*)	40%
trans-X^{pm} (1 equiv)/Cu(I)[e]	65:35	10% (1*R*,2*S*)	4% (1*S*,2*S*)	55%
cis-X^{pm} (3 equiv)/Cu(I)[e]	56:44	14% (1*S*,2*R*)	6% (1*R*,2*R*)	42%

[a] Determined by GC/MS. [b] Determined by GC/MS analysis of chiral amide derivatives (ref 2d). The absolute configuration of the major enanantiomer is given in parentheses. [c] Isolated overall yield of **10** after Kügelrohr distillation. [d] The solid resulting from treatment of *cis*-Ph_2Bp^{pm} with CuCl in CH_3CN was used, as described in the text. [e] Cu(I) refers to $[Cu(CH_3CN)_4]BF_4$.

tive intermediate).[27] The Pfaltz model also cannot be applied successfully to explain the observed configurations for the products of the OP^{pm}/Cu(I)-catalyzed reactions, but it does work well for the C_2-symmetric X^{pm} ligands. Differences in the mechanisms traversed by the different systems are, thus, possible causes of the divergent stereoselectivities we have observed.

Conclusion

Despite the uncertainties regarding the mechanism(s) of the cyclopropanation reactions and the nature of the catalytic species, the good results obtained with C_3-symmetric *trans*-Tp^{pm} relative to those found with the C_2-symmetric X^{pm} ligands comprised of identical (or diastereomeric) pyrazolyl components suggest that the theoretical advantages of C_3 symmetry proposed by Burk and Harlow[6a,b] may indeed have practical merit, although other differences between these two ligand systems make this a less than perfect comparison.[28] Additional complications also hinder direct assessment of rotational symmetry element influences in the OP^{pm} and *cis*-Ph_2Bp^{pm} instances (e.g., fluxionality, interconversion of η^2 and η^3 forms, lack of detailed structural information).

In any case, with the development reported herein of a general pyrazole synthesis that allows variation of the nature of the groups attached to the stereogenic center in derived ligands of variable charge, denticity, and symmetry, we are now poised to significantly broaden the scope of our reactivity studies and to more definitively establish the importance of rotational symmetry elements in asymmetric induction. The discovery of high enantioselectivity in a catalytic intermolecular reaction of a Tp−metal system is particularly exciting in view of the wide range of metal complexes and reaction types that may be accessed with this strongly binding ligand.

Experimental Section

General Procedures. All reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents were purchased from commercial sources and dried under N_2 by standard methods immediately before use.[29] All air-sensitive reactions were performed either in a Vacuum Atmospheres glovebox under an N_2 atmosphere or by using standard Schlenk and vacuum-line techniques. NMR experiments were carried out on a Varian VXR-500, VXR-300, VAC-200, or VAC-300 spectrometer using standard parameters. ^1H and ^{13}C NMR chemical shifts are reported versus tetramethylsilane and referenced to the residual solvent peaks. IR spectra were collected on a Mattson Polaris spectrophotometer. Electron ionization (EI) and chemical ionization (CI) mass spectra were determined on a Finnigan MAT 95 mass spectrometer. EI mass spectra were obtained at 70 eV; isobutane was used as the ionizing agent when CI mass spectra were obtained. Fast atom bombardment (FAB) mass spectra were obtained on a VG-7070E-HF mass spectrometer using xenon gas for ionization. GC/MS data were obtained on a HPG1800A GCD system equipped with a HP-5 column (30 m, 15 psi, 2.00 min at 50 °C, 50−250 °C (20 deg min^{-1})). Elemental analyses were determined by Atlantic Microlabs, Norcross GA. Optical rotations were determined on a Jasco DIP-370 digital polarimeter, and they are reported according to the method suggested by Dewey and Gladysz.[30] Ozone was generated using a Welsbach ozone generator. The output of the ozone generator was calibrated by passing ozone through a known amount of 1-hexene in CH_2Cl_2/MeOH until the solution turned blue.

(*R*)-7-Isopropylidene-4-methyl-4,5,6,7-tetrahydro-2*H*-indazole (4). Ethyl formate (266 mL, 3.28 mol) in toluene (250 mL) was added to a suspension of NaOMe (177 g, 3.28 mol) in toluene (2 L) over 20 min. After the solution was stirred for 0.5 h, (*R*)-(+)-pulegone (266 mL, 1.64 mol) in toluene (250 mL) was added over 15 min. After for 7−8 h of stirring, the solution was quenched with H_2O (400 mL), the layers were separated, and the organic layer was extracted with 2 M NaOH (3 × 150 mL). The combined aqueous layers were washed once with pentane (100 mL) and then acidified to pH 1 with concentrated HCl. Upon acidification, the solution became hot and cloudy. After the mixture was cooled to room temperature, the aqueous layer was extracted with Et_2O (4 × 100 mL), the combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. Vacuum distillation (70−80 °C, 0.1 Torr) of the dark oil yielded a light yellow oil, which was identified by GC/MS as 3-isopropylidene-6-methyl-2-oxo-cyclohexanecarbaldehyde (254 g, 1.41 mol, 86% yield). This compound was dissolved in MeOH (1 L), hydrazine monohydrate (75.3 mL, 1.55 mol, 1.1 equiv) in MeOH (200 mL) was added, and the solution was stirred for 3 h. The solvent was then removed in vacuo, and the residue was dissolved in CH_2Cl_2 (500 mL). This solution was washed with water (2 × 100 mL) and dried over $MgSO_4$. Removal of the CH_2Cl_2 in vacuo yielded a thick brown oil. Bulb-to-bulb distillation of this oil (140 °C, 0.1 Torr) afforded the title compound as a thick pale

(27) Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 8737−8738 and references therein.

(28) Another comparison of the reactivity C_2- and C_3-symmetric transition-metal complexes derived from the same building block has been published, but the evidence suggests that one arm of the C_3-symmetric ligand disassociates during the reaction (ref 6b).

(29) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(30) Dewey, M. A.; Gladysz, J. A. *Organometallics* **1993**, *12*, 2390−2397.

yellow oil, which slowly crystallized upon the addition of seed crystals (167 g, 0.95 mol, 58% yield from (*R*)-(+)-pulegone). Mp 40−45 °C; $[\alpha]_D^{26} = -26.6 \pm 0.1$ ($c = 5.3 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 3200 (br), 2920, 1454, 1372, 1106, 951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, $J = 6.9$ Hz), 1.34−1.44 (m, 1H), 1.88 (s, 3H), 1.9−2.0 (m, 1H), 2.17 (s, 3H), 2.2−2.3 (m, 1H), 2.6−2.9 (m, 2H), 7.42 (s, 1H), 9.5−9.8 (br, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.3, 22.0, 22.8, 27.6, 33.1, 113.0, 121.2, 123.1, 126.6, 133.5 (10 of 11 expected peaks) ppm; EI-MS (*m*/*z*, rel intensity) 176 (M^+, 22), 161 ([M − CH_3^+], 100). Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.44; H, 9.12; N, 16.13.

(4*R*)-4-Methyl-2,4,5,6-tetrahydro-2*H*-indazole-7-one (5). Freshly distilled **4** (40 g, 0.22 mol) was dissolved in CH_2Cl_2/MeOH (1:1 v/v, 500 mL) and cooled to −78 °C. One equivalent of ozone[31] was bubbled through the solution, while the temperature was maintained at −78 °C. After 1 equiv of ozone was added, the solution turned a faint blue-green color which grew stronger as more excess ozone was added. The excess ozone was eliminated by sparging with N_2 for 5 min, dimethyl sulfide (16.2 mL, 0.22 mol) was added to the resulting suspension, and the mixture was warmed to room temperature overnight. The volatiles were removed in vacuo, and the resulting slurry was washed with Et_2O (100 mL). Microcrystalline, white **5** (21.4 g) was collected by filtration, and the solvent was removed from the filtrate in vacuo. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and washed with 50 mL H_2O, the organic layer was dried over $MgSO_4$, and the solvent was removed. Et_2O (20 mL) was added to the residue to precipitate additional product (3.6 g), which was collected by filtration. The combined yield of **5** was 25 g (0.166 mol, 76% yield). Mp 195−200 °C (dec); $[\alpha]_D^{26}$ 12.4 ± 0.1 ($c = 5.2 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 3246, 2966, 1666, 1361, 1061, 637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, 3H, $J = 6.8$ Hz), 1.7−1.9 (m, 1H), 2.1−2.3 (m, 1H), 2.4−2.7 (m, 2H), 2.9−3.1 (m, 1H), 7.55 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 131.5, 130.7, 37.1, 32.2, 26.1, 18.8 ppm; EI-MS (*m*/*z*, rel intensity) 150 (M^+, 50), 135 ([M − CH_3^+], 100). Anal. Calcd for $C_8H_{10}N_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.83; H, 6.75; N, 18.63.

(4*R*,7*R*)-4-Methyl-7-phenyl-4,5,6,7-tetrahydro-2*H*-indazole (*cis*-7a). Phenylmagnesium bromide (0.067 mol) was generated in THF (150 mL) by a standard method.[32] A solution of **5** (4 g, 0.026 mol) in THF (150 mL) was added via cannula, and the reaction was stirred at room temperature overnight. The mixture then was quenched with H_2O (50 mL) followed by 6 M HCl (50 mL), and the THF was removed in vacuo. The remaining solution was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 70 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford 5.9 g of a white semisolid. ^1H NMR and GC/MS showed the product to consist of a mixture of three products (the cis addition product, the trans addition product, and the product of dehydration (**6a**)); this mixture was used without further purification. A catalytic amount of *p*-toluenesulfonic acid (10−20 mg) was added to a solution of the mixture in benzene (50 mL), and it was refluxed in a Dean−Stark apparatus for 2 h. The solution was cooled, 5 drops of saturated $NaHCO_3$ were added, and the solution was stirred for 5 min. The solution then was dried over $MgSO_4$ and filtered, and the solvent was removed to yield an off-white semisolid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 3H, $J = 6.6$ Hz), 2.12−2.23 (m, 1H), 2.52−2.69 (m, 1H), 2.96−3.05 (m, 1H), 6.12−6.16 (m, 1H), 7.35−7.6 (m, 6H) ppm; GC/MS M^+ 210, t_R = 12.53 min. This material was dissolved in absolute ethanol (50 mL) and stirred over 10% Pd on C (100 mg) under 1 atm of H_2. After 18 h of stirring, the catalyst was filtered off and replaced and the reaction was stirred for another day under 1 atm of H_2. The catalyst was filtered off, and the solvent was removed *in vacuo* to afford an off-white solid, which was shown by GC/MS and ^1H NMR to be an 80:20 mixture of the cis and trans isomers of the title compound (3.8 g, 0.018 mol, 69% yield from **5**). Recrystallization from hot acetone afforded pure *cis*-**7** (1.3 g, 0.006 mol, 23% yield from **5**). Mp 120−123 °C; $[\alpha]_D^{26} = -2.5 \pm 0.2$ ($c = 5.4 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 3204, 2930, 1947 (w), 1661 (w), 1607 (w), 1447, 757, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3H, $J = 6.9$ Hz), 1.3−1.5 (m, 1H), 1.7−1.8 (m, 1H), 1.8−2.0 (m, 1H), 2.0−2.2 (m, 1H), 2.7−2.9 (m, 1H), 4.05−4.1 (m, 1H), 7.0−7.4 (m, 6H) ppm; ^{13}C NMR (75 Hz, $CDCl_3$) δ 22.4, 26.7, 28.9, 31.5, 39.1, 122.5, 126.6, 128.3, 128.6, 133.0, 144.8 ppm (11 of 12 expected peaks); EI-MS (*m*/*z*, rel intensity) 212 (M^+, 73), 197 ([M − CH_3^+], 100). Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.11; H, 7.62; N, 13.21.

(4*R*,7*R*)-4-Methyl-7-methyl-4,5,6,7-tetrahydro-2*H*-indazole·HCl (*cis*-7b·HCl). This compound was synthesized by the above procedure starting with **5** (15 g, 0.1 mol) and a commercial solution of methylmagnesium bromide in THF/toluene (Aldrich, 1.4 M, 214 mL, 0.3 mol), which yielded the title compound in an approximately 80:20 ratio of cis to trans forms after the reduction step. The HCl salt of the title compound was generated by bubbling HCl gas through a CH_2Cl_2 solution of the final pyrazole, and this product was recrystallized from a hot mixture of $CHCl_3$/*tert*-butyl methyl ether to yield pure *cis*-**7b**·HCl (4.5 g, 0.03 mol, 30% yield from **5**). Mp 194−194 °C; $[\alpha]_D^{26} = 35.6 \pm 0.3$ ($c = 6.04 \times 10^{-3}$ g/mL, $CHCl_3$) IR (KBr) 2661, 1571, 1466, 1363, 1092, 606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, 7.0 Hz, 3H), 1.37 (d, 7.2 Hz, 3H), 1.40−1.43 (m, 1H), 1.60−1.75 (m, 1H), 1.80−1.95 (m, 2H), 2.70−2.72 (m, 1H), 3.00−3.05 (m, 1H), 7.56 (s, 1H), ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 20.3, 21.4, 25.9, 26.5, 26.8, 28.0, 122.7, 128.9, 148.4 ppm; EI-MS (*m*/*z*, rel intensity) 150.1 ([M − HCl]$^+$, 60), 135.1 ([M − HCl − CH_3]$^+$, 100). Anal. Calcd for $C_9H_{15}N_2Cl$: C, 57.90; H, 8.10; N, 14.79. Found: C, 57.16; H, 7.79; N, 14.79.

(4*R*)-7-Biphenyl-4-yl-4-methyl-4,5-dihydro-2*H*-indazole (6c, R = 4-Biphenyl). 4-Biphenylmagnesium bromide (0.200 mol) was generated in THF (300 mL) by a standard method.[32] A solution of **5** (10 g, 0.066 mol) in THF (300 mL) was added via cannula, and the reaction was stirred at room temperature for 18 h. The reaction was quenched with water (300 mL), and the THF was removed in vacuo. The remaining solution was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford a pale yellow semisolid. ^1H NMR and GC-MS analysis showed the product to consist of biphenyl, the cis and trans addition products, and **6c**. This mixture was dissolved in ether (500 mL), and HCl gas was bubbled through the solution for several minutes. The resulting white precipitate was collected by filtration, dissolved in CH_2Cl_2 (100 mL), and neutralized with saturated aqueous $NaHCO_3$ (100 mL). The organic layer was separated and dried over $MgSO_4$, and the solvent was removed in vacuo to afford a pale yellow semisolid. A catalytic amount of *p*-toluenesulfonic acid (10−20 mg) was added to a solution of this mixture in xylenes (300 mL), and it was refluxed in a Dean−Stark apparatus for 18 h. The solution was cooled, 5 drops of saturated aqueous $NaHCO_3$ was added, and the solution was stirred for 5 min. The solution was then dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford **6c** as a pale yellow solid (12.9 g, 0.045 mol, 68% yield from **5**). Mp 114−116 °C; $[\alpha]_D^{26} = -66.0 \pm 0.5$ ($c = 6.5 \times 10^{-3}$ g/mL, $CHCl_3$); FTIR (KBr) 3156, 3114, 2924, 1603, 1567, 1483, 1455, 1401, 1378, 1188, 1061, 998, 941, 892, 845, 811, 766, 744, 690 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.02 (d, $J = 6.6$ Hz, 3H), 1.86−1.97 (m, 1H), 2.14−2.25 (m, 1H), 2.72−2.85 (m, 1H), 6.00 (dd, $J = 3.3$, 5.7 Hz, 1H), 6.27 (s, 1H), 7.24 (m, 3H), 7.49−7.54 (m, 4H), 7.82 (d, $J = 8.4$ Hz, 2H) ppm; ^{13}C NMR (75 Hz, C_6D_6)

(31) Vogel, I. A. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; John Wiley and Sons: New York, 1989, p 592.
(32) Reference 31, p 534.

δ 20.3, 26.4, 34.4, 121.8, 125.1, 127.3, 127.7, 127.8, 129.38, 129.42, 134.4, 138.9, 141.0, 141.6, 147.4 ppm (15 of 16 peaks observed); EI-MS (*m*/*z*, rel intensity) 286.1 (90.4, M^+), 271.1 (100, $M^+ - CH_3$). Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.72; H, 6.62; N, 9.14.

(4*R*,7*R*)-7-Biphenyl-4-yl-4-methyl-4,5,6,7-tetrahydro-2*H*-indazole·HCl (7c·HCl). Pyrazole **6c** (12.9 g, 0.045 mol) was dissolved in absolute ethanol (400 mL) and stirred over 10% Pd on C (400 mg) under 1 atm of H_2 for 18 h. If the hydrogenation was not complete after 18 h, the catalyst was filtered off and replaced and the reaction was stirred for another 18 h under 1 atm of H_2. After the hydrogenation was complete, the catalyst was removed by filtration and the solvent removed in vacuo to afford a white semisolid, which was shown by ^{1}H NMR to be an 80:20 mixture of *cis*- and *trans*-**7c**. This mixture was dissolved in CH_2Cl_2 (100 mL), and HCl gas was bubbled through the solution until it reached pH 1. The solvent was removed in vacuo, and the resulting solid was then recrystallized from hot $CHCl_3$/Et_2O to afford pure *cis*-**7c** as a microcrystalline white solid (6.9 g, 0.021 mol, 47% yield from **6c**). Mp 170−172 °C; $[\alpha]_D^{26} = 54.7 \pm 0.5$ ($c = 5.6 \times 10^{-3}$ g/mL, $CHCl_3$); FTIR (KBr) 2959, 2924, 2861, 2741, 2362, 2348, 1572, 1561, 1489, 1090, 836, 759, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.9$ Hz, 3H), 1.39−1.51 (m, 1H), 1.75−1.85 (m, 1H), 1.99−2.16 (m, 2H), 2.76−2.85 (m, 1H), 4.36−4.39 (m, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 7.28−7.32 (m, 1H), 7.37−7.42 (m, 2H), 7.47−7.55 (m, 4H), 7.69 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 26.6, 27.3, 30.6, 36.9, 124.4, 127.3, 127.5, 127.6, 128.3, 128.9, 129.3, 140.1, 140.8, 145.2 ppm; EI-MS (*m*/*z*, rel intensity) 288.2 ([M − HCl]$^+$, 100), 273.1 ([M − HCl − CH_3]$^+$, 38). Anal. Calcd for $C_{20}H_{21}N_2Cl$: C, 74.04; H, 6.53; N, 8.64. Found: C, 72.17; H, 6.64; N, 8.44.

K[*trans*-Tp^{pm}]. Pure *cis*-**7a** (5.0 g, 23 mmol) and KBH_4 (0.42 g, 7.9 mmol) were slowly heated to 270 °C. Hydrogen evolution was monitored using a wet-test meter. When the temperature reached 270 °C, 1 equiv of hydrogen per pyrazole had been evolved and the reaction mixture had solidified. After the mixture was cooled to room temperature under N_2, the solid was triturated with Et_2O (1 × 5 mL). The remaining solid was dissolved in CH_2Cl_2 and filtered. The volume of the resulting solution was reduced, and Et_2O was allowed to slowly diffuse into the solution, which resulted in the formation of colorless crystals of K[*trans*-Tp^{pm}] (1.31 g, 1.9 mmol, 24% yield). Mp > 270 °C; $[\alpha]_D^{26} = -80 \pm 1$ ($c = 3.1 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 2948, 2848, 2409 (B−H), 1451, 1384, 1140, 758, 703 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.16 (d, 9H, $J =$ 6.6 Hz) 1.1−1.3 (m, 3H), 1.6−1.7 (m, 3H), 1.7−1.9 (m, 3H), 1.9−2.1 (m, 3H), 2.7−2.9 (m, 3H), 3.6−3.7 (m, 3H), 6.7−6.9 (m, 15H), 7.62 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 21.8, 28.1, 33.7, 34.2, 43.1, 120.3, 126.2, 128.3 (overlapping, unresolved peaks apparent), 128.5, 131.4, 147.5, 152.3 ppm (11 of 12 expected peaks); FAB-MS (MNBA matrix) (*m*/*z*, rel intensity) 685 ([M + H]$^+$, 1), 435 (100). Anal. Calcd for $C_{42}H_{46}N_6BK$: C, 73.67; H, 6.77; N, 12.27. Found: C, 73.01; H, 6.75; N, 12.43.

***trans*-(4*R*,7*S*)-4-Methyl-7-phenyl-4,5,6,7-tetrahydro-2*H*-indazole (*trans*-7a).** K[*trans*-Tp^{pm}] (1.31 g, 1.9 mmol) was stirred in a mixture of H_2O (8 mL), 6 M HCl (2 mL), and acetone (10 mL) for 1 h. The acetone was removed in vacuo, and the remaining suspension was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed once with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo yielded pure *trans*-**7a** as a white solid (1.15 g, 95%). Mp 117−118 °C; $[\alpha]_D^{26} = -51.1 \pm 0.6$ ($c = 6.7 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 3214, 2935, 1946 (w), 1661 (w), 1604 (w), 1449, 753, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, 3H, $J = 6.6$ Hz) 1.1−1.4 (m, 1H), 1.6−1.8 (m, 1H), 1.9−2.0 (m, 1H), 2.1−2.2 (m, 1H), 2.7−2.9 (m, 1H), 3.8−3.9 (m, 1H), 6.5 (s, 1H), 7.0−7.4 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 27.4, 32.5, 34.4, 41.1, 126.7, 128.2, 128.4, 128.6, 144.3 ppm; EI-MS (*m*/*z*, rel intensity) 212 (M^+, 74), 197 ($M - CH_3^+$, 100).

Tl[*cis*-Ph$_2$Bp^{pm}].[17] In a small flask fitted with a stir bar and a short path distillation head, *cis*-**7a** (1.0 g, 0.0047 mol) and $NaBPh_4$ (0.8 g, 0.0023 mol) were slowly heated to 200 °C in a salt bath. After 4 h, the reaction mixture stopped evolving benzene and the apparatus was cooled to room temperature under N_2. After cooling, the tan glass was dissolved in CH_2Cl_2 (5 mL) and TlOAc (0.61 g, 0.0023 mol) was added to the cloudy solution. After 3 h of stirring, this solution was filtered and the solvent was removed from the filtrate to give an off-white powder. This powder was placed on a glass frit and rinsed with cold methanol (3 × 5 mL). The remaining white powder was thoroughly dried under vacuum and precipitated from pentane at −80 °C to yield the title compound as a white powder (0.33 g, 18% yield). Mp 180−185 °C; $[\alpha]_D^{25} = -22.5 \pm 0.2$ ($c = 5.5 \times 10^{-3}$ g/mL, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.27 (d, $J = 6.6$ Hz, 6H), 1.5−1.7 (m, 2H), 1.8−2.0 (m, 4H), 2.0−2.2 (m, 2H), 2.8−3.0 (m, 2H), 3.8−4.0 (m, 2H), 6.9−7.4 (m, 20H), 7.44 (s, 2H) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 135.2, 133.7, 129.5, 129.1, 128.6, 127.4, 126.4, 41.5, 30.8, 30.2, 26.1, 23.1, 13.9 ppm (13 of 16 expected peaks observed); FAB-MS (*m*/*z*, rel intensity) 587.3 (M^- − Tl, 40). Anal. Calcd for $C_{40}H_{40}N_4BTl$: C, 60.66; H, 5.09; N, 7.07. Found: C, 61.84; H, 5.57; N, 7.03.

***trans*-X^{pm}.** This preparation is a modification of a procedure recently published by Jameson.[15] A catalytic amount of *p*-toluenesulfonic acid (10 mg) was dissolved in toluene (50 mL) and cyclohexane (25 mL) and refluxed in a Dean−Stark apparatus for 30 min. *trans*-**7a** (0.55 g, 2.6 mmol) and 2,2-dimethoxypropane (0.16 mL, 0.0013 mol) were added, and the mixture was refluxed overnight. The reaction was cooled to room temperature, 5 drops of saturated $NaHCO_3$ were added, and the solution was stirred for 5 min. The reaction was dried over $MgSO_4$ and filtered, and the solvent was removed to reveal an off-white semisolid. The product was recrystallized from hexane to yield a white solid (0.46 g, 0.99 mmol, 76% yield). Mp 128 °C; $[\alpha]_D^{22} = -78.7 \pm 0.8$ ($c = 1.31 \times 10^{-2}$ g/mL, $CHCl_3$); IR (KBr) 2924, 2863, 1451, 1364, 1280, 1187, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, 6H, $J = 6.6$ Hz), 1.3−1.5 (m, 2H), 1.6−1.8 (m, 2H), 1.9−2.0 (m, 2H), 2.13 (s, 6H), 2.2−2.3 (m, 3H), 2.7−2.9 (m, 2H), 4.0−4.1 (m, 2H), 7.1−7.3 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 27.5, 27.6, 31.8, 33.9, 41.3, 76.8, 123.8, 125.9, 128.0, 128.1, 145.6, 149.3 ppm (13 of 14 expected peaks observed); EI-MS (*m*/*z*, rel intensity) 464 (M^+, 1) 252 (100). Anal. Calcd for $C_{31}H_{36}N_4$: C, 80.13; H, 7.81; N, 12.06. Found: C, 80.07; H, 7.90; N, 11.96.

***cis*-X^{pm}.** The product was synthesized using the above procedure with *cis*-**7a** (1 g, 0.0047 mol) and 2,2-dimethoxypropane (0.29 mL, 0.0023 mol). The crude product was dissolved in Et_2O (3 mL), and the pure product immediately crystallized (0.47 g, 0.001 mol, 43% yield). Mp 134−136 °C; $[\alpha]_D^{22} = 30 \pm 1$ ($c = 2.9$ ' 10^{-2} g/mL, $CHCl_3$); IR (KBr) 2921, 2863, 1469, 1449, 1373, 1166, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 6H, $J = 6.8$ Hz), 1.2−1.4 (m, 2H), 1.6−1.8 (m, 2H), 1.9−2.2 (m, 4H), 2.23 (s, 6H), 2.6−2.8 (m, 2H), 4.2−4.3 (m, 2H), 6.9−7.3 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 27.5, 27.7, 27.8, 32.1, 38.9, 76.4, 123.8, 123.9, 125.7, 127.9, 128.3, 145.9, 149.6 ppm; EI-MS (*m*/*z*, rel intensity) 464 (M^+, 1) 252 (100). Anal. Calcd for $C_{31}H_{36}N_4$: C, 80.13; H, 7.81; N, 12.06. Found: C, 79.84; H, 7.86; N, 11.98.

***trans*-OP^{pm}.**[10a] Phosphorus oxychloride (71 μL, 0.7 mmol) was slowly added to a stirred solution of *trans*-**7a** (0.4 g, 1.8 mmol), and triethylamine (0.32 mL, 2.3 mmol) in dry benzene (10 mL). The reaction was refluxed overnight. The resulting solution was filtered, and the solvent was removed in vacuo to afford a white powder. Recrystallization from toluene/pentane yielded the pure product (0.27 g, 0.4 mmol, 68% yield). Mp 112−118 °C; $[\alpha]_D^{22} = -148 \pm 1$ ($c = 4.6 \times 10^{-3}$ g/mL, $CHCl_3$); IR (KBr) 2983, 2851, 1450, 1296, 1086, 697 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.22 (d, 9H, $J = 6.9$ Hz), 1.3−1.5

(m, 3H), 1.7−1.9 (m, 3H), 1.9−2.1 (m, 3H), 2.1−2.4 (m, 3H), 2.8−2.9 (m, 3H), 3.9−4.1 (m, 3H), 7.0−7.4 (m, 15H), 7.50 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 19.9, 26.5, 30.4, 32.3, 40.9, 124.9, 126.6, 126.8, 130.7 (d, J = 12.1 Hz), 142.7, 158.6 (d, J = 14.7 Hz) ppm (11 of 12 expected peaks observed); FAB-MS (MNBA matrix) (*m*/*z*, rel intensity) 681 ([M + H]$^+$, 100). Anal. Calcd for $C_{42}H_{45}N_6PO$: C, 74.09; H, 6.66; N, 12.34. Found: C, 74.71; H, 6.93; N, 11.97.

***cis*-OP^{pm}.** Phosphorus oxychloride (71 μL, 0.7 mmol), *cis*-**7a** (0.5 g, 2.3 mmol), and triethylamine (0.41 mL, 2.9 mmol) in 10 mL of dry benzene were used in the above procedure. Recrystallization from Et_2O/pentane yielded the pure compound (0.28 g, 0.42 mmol, 60% yield). Mp 159−163 °C; $[\alpha]_D^{22}$ = 109 ± 1 (c = 4.2 × 10^{-3} g/mL, $CHCl_3$); IR (KBr) 2986, 2856, 1449, 1296, 1091, 700 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.22 (d, 9H, J = 6.9 Hz), 1.3−1.5 (m, 3H), 1.7−1.9 (m, 3H), 2.0−2.3 (m, 6H), 2.8−2.9 (m, 3H), 4.2−4.3 (m, 3H), 7.0−7.4 (m, 15H), 7.64 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 20.1, 25.7, 26.2, 29.5, 38.2, 124.7, 126.6, 130.9 (d, J = 12.1 Hz), 143.2, 157.8 (d, J = 14.7 Hz) ppm (10 of 12 expected peaks observed); FAB-MS (MNBA matrix) (*m*/*z*, rel intensity) 681 ([M + H]$^+$, 100). Anal. Calcd for $C_{42}H_{45}N_6PO$: C,74.09; H, 6.66; N, 12.34. Found: C, 73.47; H, 6.84; N,12.17.

(*trans*-Tp^{pm})Cu(CH$_3$CN). K[*trans*-Tp^{pm}] (0.25 g, 0.36 mmol) and CuCl (0.036, 0.36 mmol) were stirred in CH_2Cl_2 for 7 h. The cloudy solution was filtered through Celite, and the solvent was removed in vacuo. Recrystallization from CH_2Cl_2/CH_3CN/pentane yielded Tp^{pm}Cu(CH_3CN) as X-ray-quality crystals (0.157 g, 0.22 mmol, 60% yield). Mp 220 °C (dec); $[\alpha]_D^{26}$ = −140 ± 2 (c = 2.1 × 10^{-3} g/mL, CH_2Cl_2); IR (KBr) 2916, 2422 (B−H), 1446, 1369, 1303, 1129, 697 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6/CD_3CN) δ 1.06 (d, J = 7.5, 9H), 1.5−1.3 (m, 3H), 1.7−1.5 (m, 3H), 1.9−1.7 (m, 3H), 2.1−1.9 (m, 3H), 2.7−2.5 (m, 3H), 3.9−3.7 (m, 3H), 7.5−6.8 (m, 18H) ppm; Anal. Calcd for $C_{44}H_{49}N_7 \cdot 0.5CH_2Cl_2$: C, 67.42; H, 6.36; N, 12.37. Found: C, 67.57; H, 6.43; N, 12.42 (CH_2Cl_2 was observed in the ^{1}H NMR spectrum and in the crystal structure of this complex; samples consistently analyzed for the presence of 0.5 equiv of CH_2Cl_2, even after extended drying under vacuum).

Cyclopropanation Reactions. Neutral ligand (0.028 mmol, 3 equiv) and [Cu(CH_3CN)$_4$]BF_4 (3 mg, 0.0095 mmol) were stirred in CH_2Cl_2 (1 mL) for 1 h. Alternatively, (*trans*-Tp^{pm})Cu(CH_3CN) (6 mg, 0.0095 mmol) or the product of the reaction of Tl[*cis*-Ph_2Bp^{pm}] with CuCl (7 mg) was dissolved in CH_2Cl_2 (1 mL). Styrene (0.8 mL, 7.7 mmol) was added to the catalyst, and the solution was stirred for 0.5 h. Ethyl diazoacetate (90 μL, 0.8 mmol) in CH_2Cl_2 (2 mL) was added to this solution over 12 h using a syringe pump. The solution was then passed through a plug of silica, and the solvent was removed in vacuo. The resulting oil was purified by Kügelrohr distillation (85 °C/0.1 Torr) and characterized by GC/MS: cis (M$^+$ 190, t_R = 8.97 min), trans (M$^+$ 190, t_R = 9.27 min).[2d]

(*S*)-α-methylbenzylamine (50 μL, 0.38 mmol, 99% ee) was dissolved in 1,2-dichloroethane (1 mL), and the solution was cooled to 0 °C. Trimethylaluminum (0.2 mL of a 2.0 M solution in toluene, 0.4 mmol) was added, and the solution was warmed to room temperature and stirred for 1 h. Distilled cyclopropane (20 μL, 0.11 mmol) was added, and the solution was heated to reflux overnight. After the reaction was cooled to room temperature, it was quenched with water and 6 M HCl. The organic layer was separated, washed once with 6 M HCl, dried, and analyzed by GC/MS. The enantioselectivity values were determined by correlating the retention times of the products (M$^+$ 265) to those reported by Evans[2d] (Table 3); a representative GC trace is provided as Supporting Information.

X-ray Crystal Structure of Tp^{pm}Cu(CH$_3$CN)·CH$_2$Cl$_2$. A colorless crystal of Tp^{pm}Cu(CH_3CN)·CH_2Cl_2 (0.30 × 0.15 × 0.08 mm) was attached to a glass fiber and mounted on a Siemens SMART diffractometer for a data collection at 173(2) K. An initial set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced orientation matrixes determined from 177 reflections. Final cell constants were calculated from 8192 strong reflections from the actual data collection. The space group $P2_12_12_1$ was determined based on systematic absences and intensity statistics. A successful direct-methods solution[33] was calculated, which provided most non-hydrogen atoms from the *E*-map. Several full-matrix least-squares/difference-Fourier cycles were performed, which located the remainder of the non-hydrogen atoms, all of which were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with individual isotropic displacement parameters.

Selected bond lengths and angles, crystallographic data, and a fully labeled drawing are shown in Tables 1 and 2 and Figure 1, respectively. Full details, including positional and thermal parameters, can be found in the Supporting Information. All calculations were performed using SGI INDY R4400−SC or Pentium computers with the SHEXTTL-Plus V5.0 program suite.[34]

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Supporting Information Available: Two-dimensional NMR spectra (COSY, NOESY) of *cis*- and *trans*-**7a**, *cis*-**7b**, and *cis*-**7c**, a represenative GC trace of amide derivatives of catalytic cyclopropanation products, and full descriptions of the X-ray crystal structures of *cis*-**7a** and (*trans*-Tp^{pm})Cu(CH_3CN) (33 pages). Ordering information is given on any current masthead page.

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