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Modular Catalysts for Diene Cycloisomerization: Rapid and Enantioselective Variants for Bicyclopropane Synthesis

Jeremy A. Feducia, Alison N. Campbell, Michael Q. Doherty, and Michel R. Gagné*

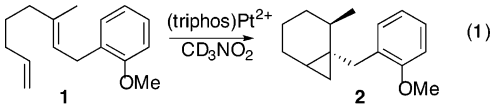
Contribution from the Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

Received June 20, 2006; E-mail: mgagne@unc.edu

Abstract: Deconstructing the tridentate (triphos)Pt(II) first-generation catalysts into mixed diphosphine/monophosphine combinations (P_2P) has led to new, more active catalysts for the cycloisomerization of 1,6-, and 1,7-dienes into bicyclo-[3.1.0] and -[4.1.0] products. When the diphosphine was the small bite angle dppm, reaction rates were ~20-fold faster than with triphos, although reaction rates and diastereoselectivities were also sensitive to the monophosphine (PMe_3 being optimal for rate, PPh_3 being optimal for selectivity). When the diphosphine was xyl-BINAP or SEGPHOS, the catalysts were enantioselective, and enantio-ratios up to 98:2 were observed. Both sets of catalysts showed enhanced functional group tolerance in comparison to the original (triphos)Pt^{2+} catalyst. X-ray structures for both precatalysts are also reported.

Introduction

The consumption of unsaturation as a means to drive the formation of new rings is a key feature of metal-catalyzed diene and enyne cycloisomerization reactions.[1] In the latter case, the alkyne's heightened kinetic and thermodynamic potential can lead to products wherein all of the unsaturation is consumed and complex multicyclic products ensue.[2,3] Despite utilizing a diverse set of mechanisms,[4] Pt, Pd, Ru, Rh, and Au enjoy special positions as catalysts combining high activity and controllable product selectivity,[1] although efforts to render them chiral for asymmetric catalysis have been slower to develop.[5,6] In contrast to enynes, incomplete consumption of the available unsaturation typifies diene cycloisomerization reactions, and the resulting products are considerably less structurally diverse (diene → cycloalkene is typical).[4] Cyclopropanes,[7] for example, are common products of enyne cycloisomerization;[2] however, the analogous conversion of a diene into a cyclopropane was, until recently, unknown.



Contrasting most diene cycloisomerization reactions are electrophilic (triphos)Pt^{2+} catalysts reported by our group for the intramolecular conversion of 1,6-, and 1,7-dienes into bicyclopropanes (e.g., eqs 1 and 2),[8] and by Vitagliano's group for the intermolecular coupling of two alkenes into a cyclopropane.[9] In both cases, two degrees of unsaturation are consumed to make bicyclic and monocyclic products, respectively.[10]

Experimental evidence from both groups implicate ionic mechanisms and the intermediacy of carbocations.[11,12] A typical mechanistic scheme for the reaction in eq 1 is outlined in Scheme 1, with the key features being the electrophilic activation of the terminal alkene, the generation of a 3° carbocation, and a 1,2-hydride shift to establish the α,γ-arrangement of metal

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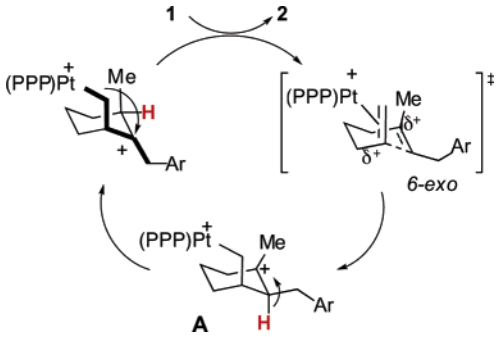
10.1021/ja064335d CCC: $33.50

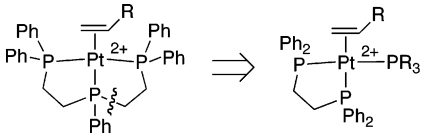
Scheme 1



and cation needed for ring-closing cyclopropanation.[13] Several points deserve comment: (1) Square planar Pt(II) complexes have a strong preference for coordinating/activating the less substituted alkene,[14] in contrast to soft Lewis acids like Hg(II) or Ag(I).[15] This reactivity pattern provides a predictable location for initiating electrophilic reactions in a poly ene and complements traditional strategies for initiating cation−olefin reactions, which rely on reagents like H^+,[16] Br^+, and RSe^+ to activate the more basic (more highly substituted) alkene.[17] (2) The 1,2-migration shown in red was confirmed by D-labeling experiments.[8a] (3) The cyclopropanation step proceeds via the addition of a comparatively nucleophilic Pt−C bond to the empty orbital of the γ-carbocation, we presume in direct analogy to the double inversion (W-conformation) processes that have been observed for Sn, Fe, and Ti. The latter three have been shown to be rigorously stereospecific and proceed via double inversion stereochemistries.[13]

Because the individual steps (obviously excluding the Pt) are so similar to the reactions involved in terpene biosynthesis (cation generation, cation−olefin cyclization, hydride shifts, etc.),[18] it is not surprising that terpene-like poly ene substrates

Scheme 2



generate terpene-like cycloisomerization products.[19,20] For example, the [3.1.0]-bicyclic core of **4** (α-thujane) constitutes the carbon skeleton of a large number of monoterpenoids,[18b] while the [4.1.0] fragment of **2** is found in thousands of steroid-like natural products.

The principle that guided the discovery of the (triphos)Pt^{2+} catalysts was the utilization of ligands that would block the sites cis to a putative intermediate alkyl (e.g., **A** in Scheme 1), and thereby inhibit β-H elimination as a competing decomposition pathway. This approach, demonstrated by Hahn and Vitagliano in numerous electrophilic activation systems,[21] ultimately led to the discovery of the catalysts described above. Efforts to improve the reactivity and selectivity of this first generation catalyst, however, were hampered by the difficulty of synthesizing derivatives of the tridentate ligands[22] (triphos itself is commercially available), especially chiral analogues for developing asymmetric versions of the reactions.

To circumvent this impediment, we reasoned that the tridentate architecture could be deconstructed into a modular combination of bi- and monodentate phosphine ligands (Scheme 2). If successful, this approach would enable the effect of ligand bite angle, cone angle, basicity, etc., to be independently assessed under catalytic conditions. One potential pitfall of this approach, however, was the possibility that monophosphine dissociation at the stage of an intermediate alkyl (e.g., **A** in Scheme 1) could provide a pathway for β-H elimination and catalyst deactivation. The electrophilic nature of the P_3PtR^+ along with the near rigorous need for associative ligand substitution at a substitution inert Pt(II)[23] were each considered variables favoring a successful outcome.

With regards to the catalytic asymmetric cycloisomerization of dienes, several catalysts are known, in particular the chiral Ni-based catalysts of Leitner, which give up to 80% ee for the cycloisomerization of diethyl diallyl malonate (eq 3), and the L_2Pd^{2+} catalysts of Heumann, which give ee's up to 60% for L_2 = bisoxazoline and sparteine (eq 4).[24,25] Because no enantioselective catalysts for the conversion of dienes into bicyclopropanes have been reported, the design and synthesis of chiral metal catalysts for this transformation represent both an obvious and desirable direction of endeavor, the modular

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(22) For typical procedures, see: DuBois, D. L.; Miedaner, A.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1991**, *113*, 8753−8764.

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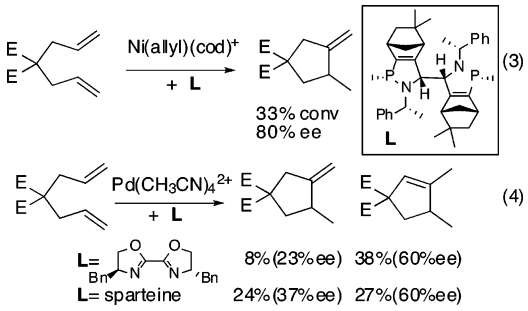
(25) For recent examples of chiral Pd(II), Pt(II), and Au(I) catalysts in related electrophilic activation processes, see ref 6.

catalyst design described herein being highly amenable to the search for selective catalysts.



We report herein two parallel lines of research that have led to new catalysts for the diastereo- and enantioselective cycloisomerization of 1,6-, and 1,7-dienes into [3.1.0]- and [4.1.0]-bicyclic products. One catalyst class utilizes a bidentate ligand with a small bite angle to achieve activities that are at least 20-fold higher than first-generation catalysts along with a higher functional group compatibility profile and a broader substrate scope, while the second class utilizes chiral bidentate ligands to achieve reactions with enantioselectivities reaching 98:2 er.

Results and Discussion

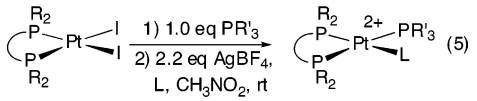
Catalyst Activation. In the first-generation catalysts, activation was most conveniently achieved by protonolysis of the [(triphos)Pt−Me][BF_4] precursor with $HNTf_2$ to give CH_4 and the desired [(triphos)Pt−L][NTf_2][BF_4] catalyst,[8a] where L could be either a weak placeholder ligand like acetone or the terminal alkene of the substrate itself. This methodology proved to be key to cleanly generating the active catalyst in a form that maximized activity while minimizing the production of compounds that tended to either consume the cyclopropane product or lead to Brønsted acid-derived byproducts. The analogous activation protocol with the modular [(P_2P)PtMe][BF_4] precursors was entirely unsuccessful, which ultimately led to a wholly different direction of research.[26] These studies showed that, for reasons attributable to torsional strain in the triphos coordination geometry, protonolysis was at least 50 000 times more rapid for [(triphos)Pt−Me][BF_4] than for a large number of [(P_2P)-PtMe][BF_4] precursors. Fortunately, however, conditions for achieving iodide abstraction from intermediate [(P_2P)Pt−I][I] compounds with Ag^+ salts could be employed. Iodides were significantly easier to activate than were the analogous chloride complexes.

Typical activation procedures for in situ screening of ligand variants began with isolated P_2PtI_2 complexes, to which was added 1 equiv of the monodentate ligand in nitromethane[27] (room temperature), followed by activation with 2.2 equiv of $AgBF_4$ in the presence of substrate (eq 5). Attempts to activate in the absence of substrate were typically unsuccessful as iodide associative displacement (or more likely Pt−I···Ag) required a ligand that was better than the nitromethane solvent. Although a number of solvents were investigated, nitromethane consistently provided the best results; nitroethane was usually an acceptable replacement (although it is a bit slower), while CH_2Cl_2 was considerably slower.

Table 1. The Effect of Bidentate Ligand on the Cycloisomerization of **1** (Eq 1) Using [P_2($PMePh_2$)Pt][BF_4]$_2$[a]

P_2 (∠)[b]	*t* (h)	dr	yield[c]
dppm (72°)	**1.5**	**26:1**	**79%**
dppbz (83°)	5	12:1	25%
dppe (85°)	6	19:1	56%
dppp (91°)	15	5:1	45%
dppb (98°)	7	7:1	16%

[a] Reaction conditions: 5% (P_2)PtI_2 (0.06 M in CD_3NO_2), 5% $PMePh_2$, 11% $AgBF_4$, 23 °C. [b] See ref 28b. [c] By GC.



Because bite angle is often an important determinant of bidentate ligand activity,[28] a systematic screen of this variable was carried out by varying the length of the carbon spacer. $PMePh_2$ was chosen as the monodentate phosphine for these experiments because of its close structural and electronic resemblance to the triphos deconstruction product (Scheme 2). As shown in Table 1 for the reaction in eq 1, both the dr and the rate were sensitive to changes in the bidentate ligand size and structure. The dppm ligand, with its single methylene bridge and small bite angle (72°), proved to be the most active, selective, and high-yielding of the diphosphines.

In addition to the significant observation that cyclopropane **2** was indeed obtained with these modified catalysts, no dehydrogenated products were detected by GC/MS, indicating that the feared possibility of PR_3 loss and β-H elimination from an intermediate Pt−R^+ was not competitive. In comparison to the original triphos catalyst, which required elevated temperatures (40 °C) and longer reaction times (10+ h), this catalyst is much improved, and the yields reflect this.[8a]

An additional optimization cycle was achieved by testing the monophosphine's effect on rate and selectivity with (dppm)-PtI_2. Although there was considerable scatter in the data, Table 2 clearly showed the reaction to be incompatible with monodentate phosphines that were either too large or too electron deficient. $PMePh_2$ provided the best combination of rate (time to 100% conversion) and diastereoselectivity (1.5 h, 26:1 dr, 79%), PMe_3 (3 h, 12:1 dr, 94%) proved optimal with respect to yield, and PPh_3 (0.8 h, 38:1 dr, 64%) was the most diastereoselective. The catalysts with the more bulky monodentate ligands, however, proved to be a bit capricious and not as general as those generated from the smaller, more electron-rich catalysts (PMe_3 and PMe_2Ph). Because the yield of cyclopropane was significantly higher for the PMe_3 catalyst,[29] this catalyst was chosen for an evaluation of substrate scope (Table 3).

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(27) For exploratory reactions, CD_3NO_2 was utilized because traces of propionitrile present in reagent grade CH_3NO_2 poison the catalyst. For preparative work, nitromethane that had been twice precipitated from a 50:50 solution with Et_2O at −78 °C was sufficiently pure for use, see: Parrett, F. W.; Sun, M. S. *J. Chem. Educ.* **1977**, *54*, 448−449.

(28) (a) Freixa, Z.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **2003**, 1890. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (c) Raebiger, J. W.; Miedaner, A.; Curtis, C. J.; Miller, S. M.; Anderson, O. P.; DuBois, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 5502.

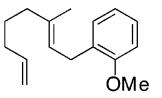
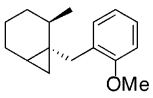
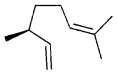
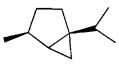
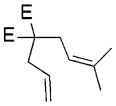
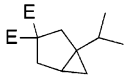
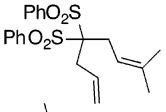
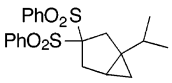
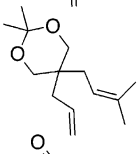
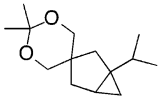
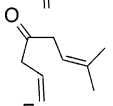
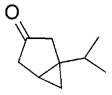
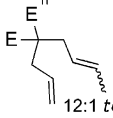
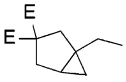
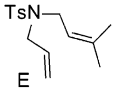
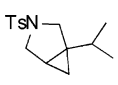
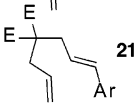
(29) The balance of material in these runs is usually a mixture of many isomerized (presumably cycloisomerized), alkene-containing products that have proven difficult to separate and identify. The cyclopropanes were most conveniently separated from the remaining, more highly retained material using Ag^+-impregnated silica gel.

Table 2. Conversion of **1** to **2** (Eq 1) for Various (dppm)Pt(PR_3)-Dications (5 mol %)[a]

PR_3	*t* (h)	dr	GC yield[b]
$P(OMe)_3$	1	5:1	74%
PMe_3	**3**	**12:1**	**94%**
PMe_2Ph	1	17:1	83%
PEt_3	3	20:1	87%
P(2-furyl)$_3$	3.5	23:1	43%
$PMePh_2$	1.5	26:1	79%
PPh_3	0.8	38:1	64%
P(4-OMePh)$_3$	0.5	15:1	81%
$P(C_6F_5)_3$	3	24:1	53%
$P(NMe_2)_3$	48	78:1	10%

[a] Reaction conditions: 5% (dppm)PtI_2, 5% PR_3, 11% $AgBF_4$, in CD_3NO_2 (0.06 M in catalyst), 23 °C. [b] Yield obtained by calibrated GC analysis at 100% conversion.

Table 3. Cycloisomerization of Dienes with 5 mol % [(dppm)Pt(PMe_3)][BF_4]$_2$[a]

entry	diene	product	time, yield[b]
1			3 h, 86(94) 12:1 dr[c]
2			1.5 h, 72(81) 57:1 dr[c]
3			3 h, 70(80)
4			19 h, 62(74)
5	 E= CO_2Me		3 h, 71 4.5:1[c] (**10:23**)
6			1 h, 78 5.8:1[c] (**12:24**)
7			3 h, 73
8			45 h,[d] 64(82)
9	 12:1 *tc*		94 h,[d] 18
10			10 min, --
11		—	NR

a, Ar= Ph
b, Ar= 3,4,5-$(OMe)_3C_6H_2$

[a] Reaction conditions: 5% (dppm)PtI_2, 5% PMe_3, 11% $AgBF_4$, in $MeNO_2$ (0.06 M in catalyst), 23 °C. [b] Isolated yield; in parentheses is the GC yield prior to isolation. [c] By GC. [d] 10% catalyst loading, 40 °C.

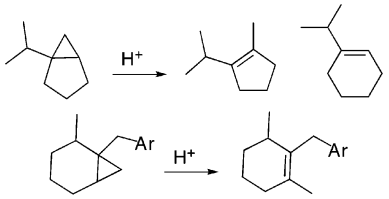
In all cases, the reactions were found to be 10−20 times faster than the original (triphos)Pt^{2+} catalyst, they could be carried out at room temperature instead of 40 °C, and, where different cycloisomerization pathways existed (entries 5 and 6, vide infra), they showed an enhanced propensity to generate the cyclopropane product. As demonstrated by entries 1 and 4, the bicyclo-[4.1.0] structures can be accessed from both 1,6- and 1,7-dienes, although in the latter case the rates are slightly diminished. Some enhancements in the functional group compatibility were also observed (entries 5−9); the original triphos catalyst was unable to cyclize sulfone **11** and gave poor yields of acetal product **14**. The bicyclo-[3.1.0] ketone **16**, which is applicable to the synthesis of a number of thujone and thujanol derivatives,[19] is much slower than the other substrates, a phenomenon that can likely be traced to the catalyst resting as a nonproductive ketone adduct instead of an alkene adduct (^{31}P NMR).[30] The limit of activity with the PMe_3 catalyst appears to be represented by **17** (entry 9), which formally requires the intermediacy of a secondary carbocation in the proposed mechanism (vide infra).

The sulfonamide **19**, however, was not compatible with the catalyst, and immediate decomposition to a myriad of products occurs, in contrast to chiral catalysts, which efficiently process this reactant (vide infra). A class of substrates that surprisingly did not react were the cinnamyl malonates (entry 11). Based on cation stabilities,[31] we expected that the cinnamyl case (**21a**) would provide a benzyl cation of stability similar to that of a tertiary cation, and the trimethoxy cinnamyl (**21b**) to an even more stabilized cation. Nevertheless, no reaction was observed for either substrate, despite seemingly generating cations that would be more stable than the 2° cation proposed for **9**.

It is worth noting that, although Pt(II)-salts (e.g., $PtCl_2$) are known to react with cyclopropanes,[32] we find that the present electron-deficient complexes are rather inert to cyclopropanes. If traces of acid are present in the catalyst, however, cyclopropane consumption can be a significant side reaction.[33] The activation protocol utilized herein minimizes the generation of trace acids and combined with the high cyclopropanation tendencies of the PMe_3-based catalyst provides good yields of product.

Although a direct relationship between the structure of the (dppm)(PMe_3)Pt^{2+} catalyst and its superior cyclopropanation tendencies is not obvious, what is clear from the X-ray structure of the catalyst precursor [(dppm)(PMe_3)PtI][I] (**22**) is the reduced bite angle of the dppm ligand (Figure 1).[34] The P3−Pt−P2 bond angle of 72° results in an obvious distortion of the square plane such that the bond angles around the I (where alkene coordination occurs) are expanded, which reduces the

(30) Because of extensive splitting and the number of species in solution, in situ monitoring is uninformative (^{31}P NMR); however, in the triphos catalysts a resonance for the trans phosphorus is observed at a position similar to the previously described acetone adduct (δ 79.6 ppm, J_{Pt-P} = 3420 Hz). No evidence for an η^2-alkene adduct is observed (see ref 9).
(31) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.
(32) Puddephatt, R. J. *Coord. Chem. Rev.* **1980**, *33*, 149−194.
(33) In several instances, we have identified the isomerization products, and found them to include the following:



(34) A suitable crystal was obtained from a solution of CH_2Cl_2 and pentane at −26 °C.

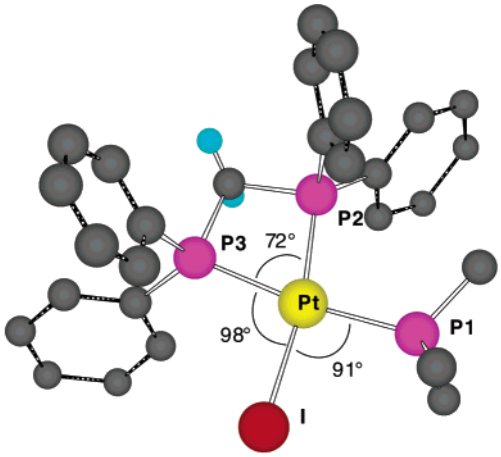
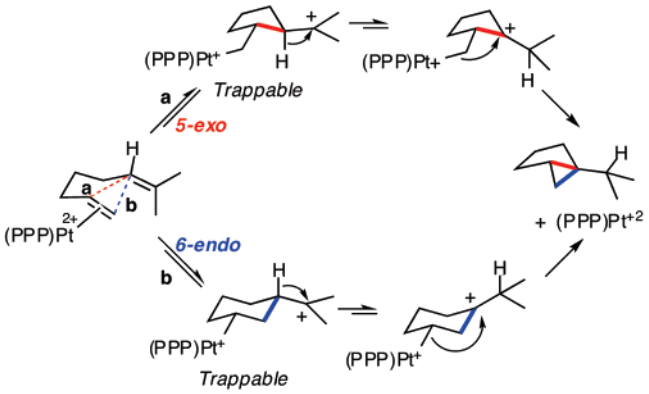


Figure 1. Chem3D representation of the X-ray structure of the cation of **22**. Selected bond lengths (Å): Pt−P_1 = 2.3172(13), Pt−P_2 = 2.2410(13), Pt−P_3 = 2.3242(12), Pt−I = 2.6329(4). Selected bond angles (deg): P_1−Pt−P_2 = 99.16(5), P_2−Pt−P_3 = 72.13(5), P_1−Pt−I = 90.98(4), P_3−Pt−I = 97.73(3).

Scheme 3. Possible Cyclization Pathways to the Thujane Ring Skeleton



steric congestion around the site of activation. The structural parameters are otherwise similar to previously reported structures.[28b]

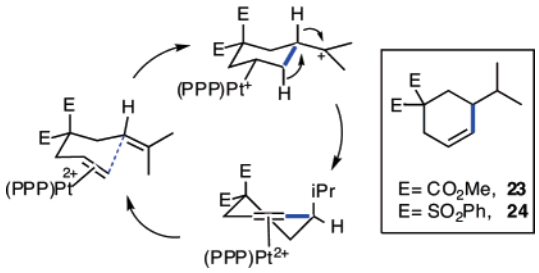
Previous mechanistic studies on the triphos-based catalyst have demonstrated that alkene activation and cation generation are rapid and reversible on the time scale of cyclopropanation.[8a] For example, studies have shown that several trappable cations are in equilibrium prior to hydride transfer (Scheme 3). Although the choice of pathway(s) (initial 6-*endo* or 5-*exo* cyclization) to the products is not known,[35,36] it seems likely that the dppm ligand plays a subtle role in enhancing the rate of the reaction, perhaps by somehow facilitating a rate-determining hydride shift followed by a fast cyclopropanation step or via a scenario where the hydride shift is rapid and it is the C−C bond forming cyclopropanation step that is somehow facilitated.

Regardless of the source of the selectivity for cyclopropanes over other cycloisomerization products, the (dppm)(PMe_3)Pt^{2+} catalyst is the most efficient, most functional group tolerant catalyst yet discovered for the cycloisomerization of 1,6- and 1,7-dienes into bicyclopropanes.

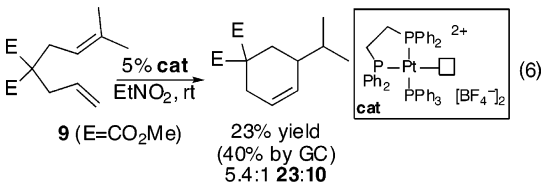
The only substrates that generated significant quantities of a second cycloisomerization product were the malonate- and

(35) The pathways differ only in the timing of ring construction, cyclohexyl followed by pinching to the 5-3 in the 6-*endo* pathway, or beginning with the cyclopentane (5-*exo* path) and annulating the cyclopropane in step 2.
(36) The biosynthetic pathway to the thujanes goes via a conceptually related 6-*endo* pathway; see ref 19b.

Scheme 4. Possible Mechanism for Cyclohexene Formation with 4,4-Disubstituted Substrates



bissulfone-derived dienes, **9** and **11**, respectively (Scheme 4). In both cases, a cyclohexene product was obtained in a ratio that depended on the catalyst, although the selectivity for cyclopropane using [dppm(PMe_3)Pt][BF_4]$_2$ was higher than that obtained with the triphos catalyst (4−5:1 vs ∼3:1). The mechanism that we presume to be operative follows the sequence previously proposed by Vitagliano for intermolecular coupling of ethylene with tri- and tetrasubstituted alkenes.[10g] In this case, a sequence of 1,2-hydride shifts migrate the cation to the position β to the Pt, which can be considered a slipped form of an η^2-alkene complex. Attempts to reoptimize the catalyst by independently varying the mono- and bidentate ligands to favor this cycloisomerization pathway were partially successful, with [(dppe)Pt(PPh_3)][BF_4]$_2$ being able to invert the major product of catalysis to the cyclohexene in a 5.4:1 ratio (eq 6); yields remained low. Unfortunately, attempts to promote cyclohexene formation with this catalyst on several representative substrates were unsuccessful, and only traces (<5%) of cyclohexene products were present, if at all. The role of the ester and sulfone functional groups in shifting the reaction pathway is not known, although we note that in situ monitoring of the catalytic reactions shows that at least some of the catalyst rests at a coordinated ester/sulfone stage in addition to coordinated alkene.



Chiral Catalysts. The test reaction for our search for enantioselective variants of the (P_2P)Pt^{2+} catalysts was the conversion of **1** to the [4.1.0] bicycloheptane **2**, proceeding via the putative mechanism in Scheme 1. As before, the catalysts were generated by first adding the monodentate phosphine to the chiral P_2PtI_2 to generate the (P_2P)Pt−I^+ precatalyst (30 min), followed by activation with 2.5 equiv of $AgBF_4$ in the presence of substrate. This protocol enabled an efficient screening of various combinations of chiral bi- and achiral monodentate ligands.

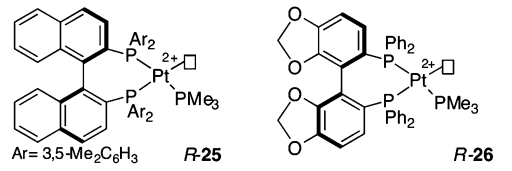
Early in the study, it was noted that most chiral bidentate ligands (e.g., BINAP) required a small monodentate ligand (i.e., PMe_3) to efficiently generate the requisite P_2P−Pt^{2+} catalyst structure. As shown in Table 4, yields of **2** were good to excellent, although the diastereoselectivities were modest. The enantioselectivities varied considerably with diphosphine structure, and optimal selectivities were observed with 3,5-xyl-

Table 4. The Effect of Diphosphine on the Cycloisomerization of **1** (Eq 1) for in situ Generated $[(P_2)(PMe_3)Pt^{2+}][BF_4]_2$[a]

P_2	% **2**[b]	dr[b]	% ee
3,5-xyl-BINAP	**92%**	**3.5:1**	**91%**
Tol-BINAP	60%	3.3:1	63%
BINAP	86%	3.5:1	62%
SEGPHOS	84%	2.7:1	75%
C1-TUNEPHOS	77%	5:1	57%
C2-TUNEPHOS	83%	3.6:1	53%
C3-TUNEPHOS	69%	3.8:1	55%
CHIRAPHOS	36%	6.4:1	11%
QUINAP	77%	16:1	72%
BINAP(S)	34%	9.7:1	0%

[a] Reaction conditions: 10% $(P_2)PtI_2$ (0.02 M in CD_3NO_2), 10% PMe_3, 25% $AgBF_4$, 23 °C. [b] By calibrated GC analysis.

Chart 1. Optimum Catalysts for Diene Cycloisomerization



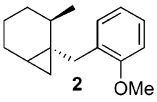
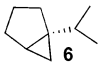
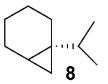
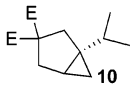
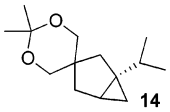
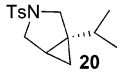
[*R*-xyl-BINAP(PMe_3)Pt][BF_4]$_2$ [*R*-SEGPHOS(PMe_3)Pt][BF_4]$_2$

BINAP (xyl-BINAP). Interestingly, the series of C1-, C2-, and C3-TUNEPHOS ligands indicated that the bite angle[37] was not a significant factor, in contrast to our expectations based on the achiral work (vide supra). A moderately enantio- but highly diastereoselective catalyst was found with the P,N ligand QUINAP;[38] however, the P,S ligand BINAP(S)[39] was poorly behaved.[40,41]

The catalysts in Chart 1 proved to be the most useful of the tested combinations generating **2** with ee's of 91% and 75%, and with GC yields of 92% and 84%, respectively. The reactions were found to be sensitive to solvent (yield and % ee for the major isomer increased from CH_2Cl_2 (38%, 91% ee), to $EtNO_2$ (77%, 91% ee), to $MeNO_2$ (85%, 88% ee)) and concentration.[42] Under the optimized conditions, these catalysts were highly chemoselective and could be run with catalyst loadings as low as 2 mol %, although our general protocol utilized 5 mol % loadings.

With a competent and robust catalyst in hand, we turned our attention to an evaluation of scope. As shown in Table 5, a number of 1,6- and 1,7-dienes could be converted to the expected [3.1.0] and [4.1.0] products while maintaining a high level of enantioselectivity. In most cases, *R*-**25** was best, although *R*-**26** did reproducibly surpass it for the aza-bicycle in entry 6. This latter entry is noteworthy as the dppm/PMe_3 catalyst completely destroyed this substrate within 10 min. Yields for the isolated products are typically fair to good, as higher levels of alkene byproducts are obtained relative to the dppm/PMe_3 catalyst. For the reaction of **1**, several of these

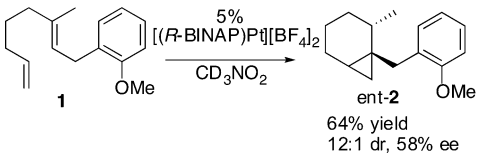
Table 5. Cycloisomerization Reactions with *R*-**25** and *R*-**26** (5 mol %)[a]

entry	diene	product[b]	cat	t(h)	yield[c](GC yield)	%ee[d]
1	**1**	 **2**	**25**	0.75[e]	70% (83%) 3.9:1 dr[f]	95%/67%
			26	3	(77%) 3:1 dr[f]	79%/70%
2	**5**	 **6**	**25**	1.5	55% (72%)	92%
			26	2	(64%)	84%
3	**7**	 **8**	**25**	14[g]	43% (56%)	69%
			26	23[g]	(36%)	35%
4	**9**	 **10**	**25**	8.5	47% (58%)	87%
			26	21	(60%)	91%
5	**13**	 **14**	**25**	3	70% (91%)	93%
			26	3	(69%)	87%
6	**19**	 **20**	**25**	8.5[h]	(50%)	88%
			26	4.5[h]	44% (58%)	96%

[a] Reaction conditions: 5% $(P_2)PtI_2$, 5% PMe_3, 12.5% $AgBF_4$, in $MeNO_2$ (0.05 M in catalyst), 23 °C. [b] The absolute stereochemistries of entries 1−5 are in analogy to entry 6 (vide infra). [c] Isolated yields of analytically pure product; yields in parentheses are calibrated GC yields. [d] Enantioselectivities were obtained by chiral GC (β-cyclosil column). [e] 0.02 M in catalyst. [f] By GC. [g] 10% catalyst loading. [h] 40 °C.

byproducts were identified and shown to result from further reactions on **2**,[33] but in the other entries they were present in trace quantities, and not identified. The susceptibility of **2** to additional reactions could be partially compensated for by concentration and catalyst loading variations; lower concentrations (0.02 M) provided improved yields (82%) and selectivities (95% ee for the major), as did higher catalyst loadings (10 mol %, 0.02 M, 92%).

In general, the reaction rates are slightly slower than those with the dppm/PMe_3 catalyst, although they are still quicker than those with the triphos-based catalyst. As reflected in the yields, these chiral catalysts are also more prone to generating non-cyclopropane byproducts than is the dppm/PMe_3 catalyst.



As part of a sequence of experiments to identify the role of possible catalyst impurities, a cycloisomerization reaction on **1** was carried out in the absence of PMe_3. Activating $(P_2)PtI_2$ with 2.5 equiv of $AgBF_4$ in the presence of 10 equiv of **1** led to a catalyst that provided enantiomeric **2** (*ent*-**2**)[43] in moderate yields and enantioselectivity. The absence of PMe_3 thus inverts the sense of selectivity, leading to a situation where both enantiomers of product can be obtained from a single enantiomer of BINAP. This same trend was observed when the chiral diphosphine was modified (Table 6), although none of these catalysts proved as enantioselective or high yielding as the P_2P

(37) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223−6226.
(38) In situ analysis (^{31}P NMR) suggests that the major species has the PMe_3 coordinated cis to the P-ligand of QUINAP (J_{P-P} is 20 Hz, cf. ~200 Hz for a trans coupling), that is, a PPN ligand array.
(39) Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett.* **2004**, *6*, 1301−1304.
(40) The PHOX ligands give a stable $(PN)PtI_2$ complex; however, PR_3 addition displaces the nitrogen from the metal. Catalysts derived from this ligand do not form cyclopropane products.
(41) The Josiphos and Walphos ligands in the Solvias ligand kit were also screened and found to not provide any cyclopropane products.
(42) Yields at higher concentrations were compromised by the formation of tetrasubstituted alkene (see ref 33). This was especially problematic for **2**.
(43) Because the absolute stereochemistry of **2** was assigned by analogy to **20**, we caution against any overinterpretation of the absolute assignment.

Table 6. The Effect of Diphosphine on the Cycloisomerization of **1** (Eq 7) for in situ Generated $[(P_2)Pt^{2+}][BF_4]_2$[a]

P_2	% **2**[b]	dr[b]	ee[c]
xyl-BINAP	50%	12:1	25%
BINAP	64%	15:1	58%
SEGPHOS	54%	21:1	65%
C1-TUNEPHOS	55%	15:1	56%
CHIRAPHOS	79%	27:1	39%
QUINAP	47%	17:1	59%[d]
BINAP(S)	52%	15:1	0%

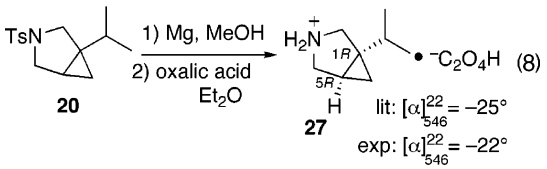
[a] Reaction conditions: 10 mol % $(P_2)PtI_2$ (0.02 M in CD_3NO_2), 25% $AgBF_4$, 23 °C. [b] By calibrated GC analysis. [c] Opposite absolute stereochemistry than $(P_2P)Pt^{2+}$ catalysts. [d] Same absolute stereochemistry as $(P_2P)Pt^{2+}$ catalyst.

analogues (yet they were significantly more diastereoselective). Interestingly enough, the QUINAP catalyst did not change its sense of enantioselectivity.

Attempts to improve the $(P_2)Pt^{+2}$ catalyst through counterion modifications (SbF_6^- or OTf^-) led to species that rapidly decomposed the transiently observed cyclopropanes. When applied to a different diene arrangement, the reactivity of these catalysts also did not translate and multiple isomeric products were obtained in the cycloisomerization of **3** (GC/MS). In the end, the chiral P_2Pt^{2+} catalysts do enantioselectively provide *ent*-**2**, but only with **1** and only as the BF_4^- salt. We suspect that this is a consequence of their overly electrophilic nature.

Perhaps the most surprising aspect of these results was that no products corresponding to loss of H_2 from a putative β-H elimination pathway were observed in the GC/MS of the reactions. The original guiding notion that the cis coordination sites need to be rigorously blocked to prevent β-H elimination may need to be revisited, especially for Pt(II) where the data indicate that β-H elimination does not compete with cycloisomerization.

The absolute stereochemistry of the bicyclopropane products was ascertained directly for the aza-bicycle in entry 6 of Table 5. As shown in eq 8, the product was detosylated with Mg in MeOH[44] to yield the volatile free base, which was directly converted to the mono-oxalate salt and analyzed by optical rotation. The sign of the rotation matched that of the previously reported compound,[45] and established that (*R*)-xyl-BINAP and (*R*)-SEGPHOS generated the 1*R*,5*R*-azabicyclohexane (**20**). The remainder of the [3.1.0] bicyclic structures in Table 5 were assigned by analogy, as was the [4.1.0] in entry 3. Compounds **2** and **8** we assign for the sake of convenience by analogy, although the consequences of a change in diene arrangement are unknown (compare Schemes 1 and 3).[46]



Consistent with this stereochemical analysis were double stereodifferentiating reactions carried out with enantiomeric pairs of catalyst and (3*S*)-β-citronellene (**3**). In separate experiments,

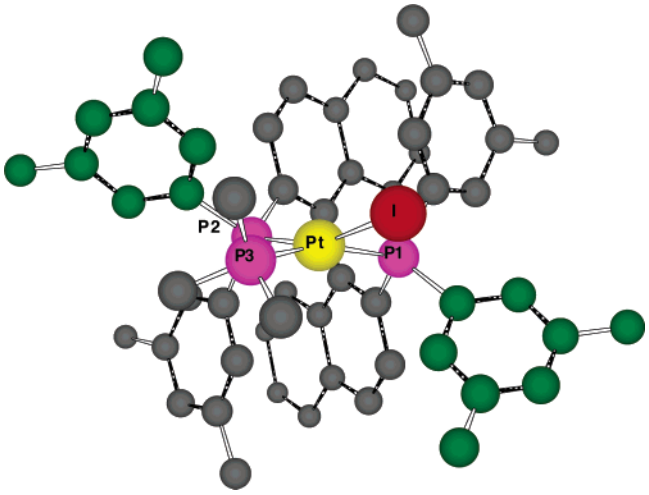
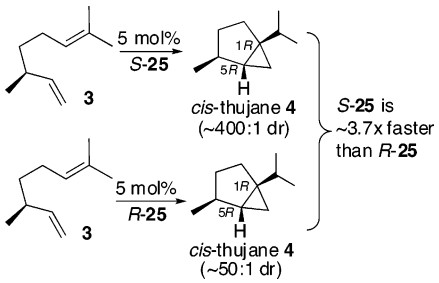


Figure 2. Chem3D representation of the X-ray structure of the *R*-**28** cation. Selected bond lengths (Å): Pt−P_1 = 2.3321(12), Pt−P_2 = 2.2653(12), Pt−P_3 = 2.3450(12), Pt−I = 2.6469(4). Selected bond angles (deg): P_1−Pt−P_2 = 91.66(4), P_2−Pt−P_3 = 98.04(5), I−Pt−P_1 = 88.74(3), I−Pt−P_3 = 86.91(3).

Scheme 5. Double Stereodifferentiating Reactions on β-Citronellene (**3**)

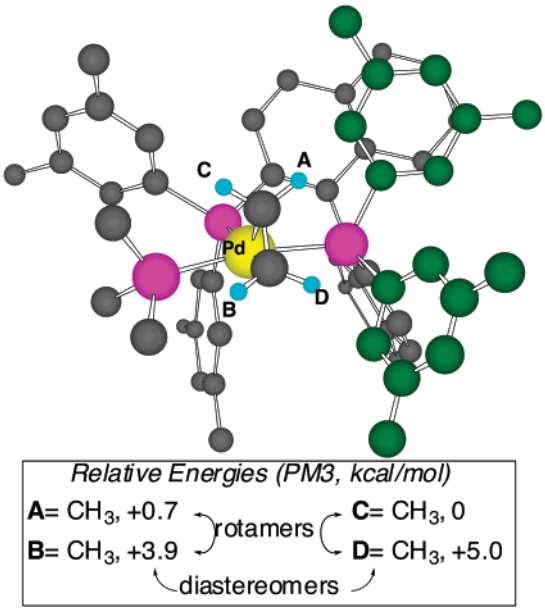


the initial cyclization rate of **3** to the natural product *cis*-thujane (**4**) was determined (Scheme 5). In the event, *S*-**25** cyclizes **3** ~3.7 times faster than does *R*-**25**, suggesting that the (*S*)-catalyst is matched to the 1*R*,5*R* stereochemistry of **4**. Conversely, the (*R*)-catalyst is better matched to the 2*S*,5*S* enantiomer of **4** and by analogy to the 2*R*,5*R* stereochemistry of **20** (eq 8).[47] For *cis*-thujane **4**, the matched catalyst is also more diastereoselective, although the existing stereogenic center is clearly stereodominant.[48]

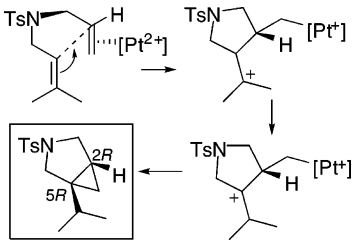
To help generate a model for the sense of asymmetric induction in the cyclopropanation reactions, an X-ray structure of the iodide precursor to *R*-**25** was obtained, *R*-**28**. As shown in Figure 2, the structure shows the expected distortion that rotates the P3−Pt−I plane 25° counter clockwise from the P2−Pt−P1 plane. As indicated by the forward projecting green 3,5-xylyl substituents, the coordination site for alkene activation (after I^- removal) is highly asymmetric and should efficiently promote diastereoselective alkene binding/activation (vide infra). Because small bite angles were of importance in the dppm catalysts, it is worth noting that the two I−Pt−P bond angles are significantly smaller, 87° and 89°, than those observed in the dppm/PMe_3 structure (98° and 91°, respectively), consistent

(44) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455−9461.
(45) Poloñski, T.; Milewska, M. J.; Katrusiak, A. *J. Am. Chem. Soc.* **1993**, *115*, 11410−11417.
(46) We note that each of the substrates in Table 5 gives −ve rotations (MeOH, 546 nm), except for **2** which gives a +ve rotation.
(47) A change in priority due to N and branching inverts the Cahn-Ingold-Prelog designators.
(48) In a traditional kinetic resolution mode using racemic **3** and *R*-**25** (5 mol%), an *S*-factor of 3.5 ± 0.3 was obtained. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240.

Scheme 6. Diastereofacial Binding Energetics from PM3 Calculations on a Pd Analogue



Scheme 7. Model for Stereochemical Transfer Invoking a Stereochemistry-Defining Alkene Activation Step



with the need for a small ligand at the P1 site for these catalysts; the dppm catalyst, on the other hand, could tolerate monodentate ligands as large as PPh_3.

To address the question of diastereofacial preference in this coordination environment, the coordinates from the X-ray structure were imported in MacSpartan and the iodide ligand was replaced with propylene and the metal changed to Pd. Because there are two diastereofaces to the alkene and two rotamers for each diastereomer, four possible η^2-alkene starting structures were generated. Each structure was geometry optimized at the PM3 level, and the energies were compared (Scheme 6). For both diastereomers, the lowest energy rotamers project the methyl substituent into the top quadrants of the chiral environment (**A** and **C**), with the lowest energy structure being that which points it toward the PMe_3, **C**.

Given the significant proviso that alkene activation/C−C bond formation is not likely turnover limiting, and that this process is quite likely reversible (it is with triphos), this model for alkene activation does correctly predict that antara-facial attack of the trisubstituted alkene onto the activated alkene of the lowest energy isomer will afford the observed 2*R*,5*R* isomer of **20** (Scheme 7). The model also holds for the 6-*endo* pathway (Scheme 3), which first creates a stereogenic platinated carbon center and then transfers this information into the cyclopropane by an invertive cyclopropanation.[13]

Summary

We describe herein how deconstructing the tridentate architecture of the triphos ligand into a modular combination of bidentate and monodentate ligands provides an efficient approach for catalyst discovery and optimization. Two significant catalyst types were successfully discovered and optimized. The first class utilized the small bite angle diphosphine dppm in combination with PMe_3 to generate the most efficient catalyst yet discovered for the cycloisomerization of 1,6- and 1,7-dienes into bicyclopropanes. These catalysts efficiently operate at the 5 mol % level, at ambient temperatures, and show tolerance to functional groups that include sulfonamides, acetals, esters, sulfones, and ketones (somewhat).

A class of catalysts for the enantioselective cycloisomerization of dienes was also discovered and optimized. The optimum catalyst was based on the xyl-BINAP ligand in combination with PMe_3, although in one case the SEGPHOS ligand was preferable. Although more limited in reaction scope, these chiral catalysts provided bicyclopropane products with enantioselectivities into the mid-90s; they represent the most enantioselective catalysts for diene cycloisomerization yet discovered (cf., eqs 3 and 4).

During the course of catalyst discovery, several unexpected leads presented themselves. For example, in the case of allyl prenyl malonate substrate, a minor cyclohexene byproduct was isolated. Subsequent experiments to optimize the formation of this alternative cycloisomerization product were undertaken, and conditions (alternative diphosphine and monophosphine) for generating the cyclohexene as the major product were discovered. Unfortunately, this new catalyst was not similarly successful on other substrate classes, and so the endeavor was only partially successful. A similarly surprising result was observed in the asymmetric cycloisomerization chemistry, where leaving the PMe_3 out of the catalyst formulation actually inverts the absolute sense of the stereoselection. Efforts to optimize this lead were only partially successful, but again showed that breaking the original tridentate architecture into a modular combination of ligands is not only efficient with respect to catalyst discovery and optimization, but ultimately also leads to catalysts that can be easily constructed from commercially available components.

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Supporting Information Available: Full experimental procedures, X-ray data tables, and sample NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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