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Combinatorial Chemistry

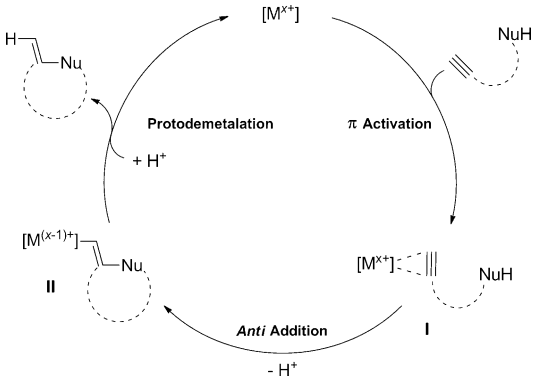
Combinatorial Approach to Chiral Tris-ligated Carbophilic Platinum Complexes: Application to Asymmetric Catalysis

Alexandre Pradal,[a] Serafino Gladiali,[b] Veronique Michelet,*[a] and Patrick Y. Toullec*[a]

Abstract: A straightforward methodology for the synthesis of libraries of chiral tris-ligated cationic platinum complexes and their in situ evaluation as asymmetric carbophilic catalysts in a model domino hydroarylation/cyclization reaction of a 1,6-enyne was developed. A catalyst-generation process based on a combination of a monodentate and a bidentate phosphorus ligand allowed the formation of 108 chiral complexes. One-pot screening of the stereoinduction obtained with this library in a test domino addition/cyclization reaction validated this approach and stressed the key role played by the monodentate ligand partner in obtaining high enantioselectivities. In the case of two challenging substrate/nucleophile combinations, the combinatorial approach resulted in a significant gain in enantioselectivity.

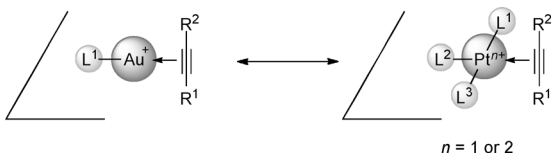
Introduction

The development of synthetic methodologies involving the use of π Lewis acid catalysts has received considerable attention in the last decade. The late heavy transition metals, especially the triad constituted by platinum, gold, and mercury, indeed have excellent affinity towards carbon–carbon multiple bonds.[1] On coordination to these carbophilic metal centers, the multiple bond is activated towards *anti* attack of a wide array of nucleophiles, which proceeds by an outer-sphere mechanism (intermediate **I**, Scheme 1). On nucleophilic attack, slippage of the metal fragment along the multiple-bond axis generates a σ-bound metal complex (intermediate **II**). Since the protodemetalation step mandatory for completing the catalytic cycle is considerably more difficult for metal–C_{sp^3} than for metal–C_{sp^2} intermediates, processes involving nucleophilic additions to alkynes (or alternatively allenes) have been considerably more successful than additions to alkenes. The late transition metals exhibiting this reactivity have been therefore termed "alkynophilic". Although gold catalysts, especially cationic gold(I) complexes, display the highest activity in many transformations, allowing these processes to occur under very mild reaction conditions, a parallel in reactivity has often been observed with platinum(II) species, and a wide range of synthetic applications exploiting the carbophilic character of platinum complexes has also appeared.[2]



Scheme 1. General catalytic cycle of cycloisomerization reactions of alkyne-containing substrates in the presence of carbophilic Lewis acids.

Reports of enantioselective variants of reactions involving π Lewis acid catalysis have so far been scarce. Limiting our discussion to transformations in which the initial step involves the carbophilic activation of an alkyne and the stereodetermining event is the consecutive nucleophilic attack, this situation is a direct consequence of the respective mode of coordination associated with Au^{I} and Pt^{II} complexes (Scheme 2). Cationic Au^{I} complexes have a linear structure in which the coordinated C–C π system occupies the position *trans* to the neutral two-electron donor ligand stabilizing the metal center. Furthermore,



Scheme 2. Schematic representations of the geometries of linear Au^{I} alkyne and square-planar Pt^{II} alkyne complexes.

[a] *Dr. A. Pradal, Dr. V. Michelet, Dr. P. Y. Toullec*
Institut de Recherche de Chimie Paris, UMR 8247
Chimie ParisTech, ENSCP
11, rue Pierre et Marie Curie
75231 Paris CEDEX 05 (France)
Fax: (+33) 144071062
E-mail: veronique.michelet@chimie-paristech.fr
patrick.toullec@chimie-paristech.fr

[b] *Prof. S. Gladiali*
Dipartimento di Chimica e Farmacia, Universita di Sassari
Via Vienna 2, 07100 Sassari (Italy)

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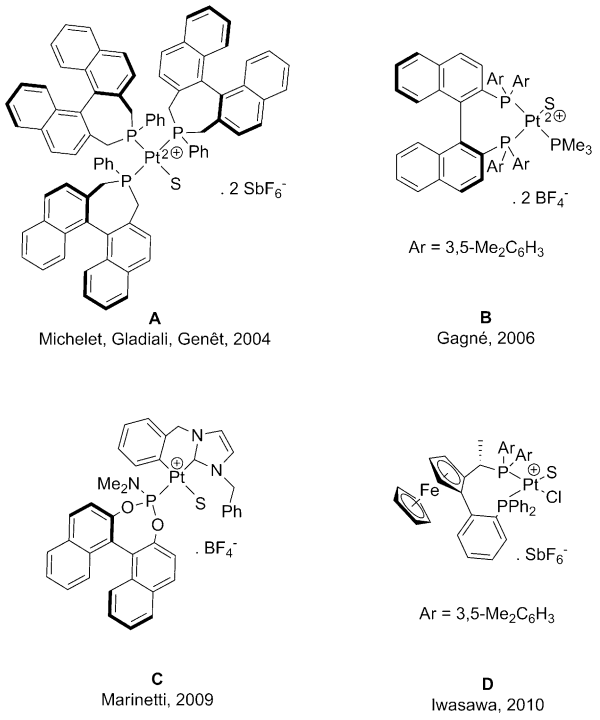
theoretical investigations and spectroscopic data indicate a low barrier of rotation of the alkyne around the metal-to-ligand centroid axis. Thus, efficient transfer of chiral information between the coordinated ligand L^1 and the unsaturated substrate in the opposite position relative to the metal center is extremely difficult to achieve. Indeed, the few highly enantioselective gold-catalyzed transformations[3] proceeding via alkyne activation that appeared in the literature since 2005 are based on a combination of a monocationic metal fragment and an extremely bulky chiral ligand, which can be derived from a bidentate atropisomeric phosphane,[4] a phosphoramidite or phosphite,[5] or an *N*-heterocyclic carbene.[6] Furthermore, in many instances, chiral induction is also extremely dependent on the steric hindrance of the substrate engaged in the transformation and thus has a limited scope.

Platinum(II) d^8 complexes are characterized by a coordination number of four and a square-planar geometry. As only one coordination site is required for π activation of the substrate and the subsequent steps of the general catalytic cycle presented in Scheme 1, the chiral environment around the metal center can be designed by careful choice of the ligands occupying the three remaining sites. This structural arrangement places two ligands, potentially chiral, on coordination sites *cis* to the activated carbon–carbon multiple bond and thus induces a much more pronounced steric interaction between the coordinated substrate and the chiral pocket surrounding the metal center and, expectedly, stronger chiral induction in the chemical transformation. Such a strategy has already received much attention and resulted in the development of a range of platinum-catalyzed asymmetric transformations involving carbophilic activation of carbon–carbon multiple bonds.[7] In a first approach, combinations of three neutral monodentate ligands (L^1) or a mono- and a bidentate ligand (L^2) on a dicationic platinum center were investigated. A system consisting of three chiral monodentate phosphines ligated to a dicationic platinum center generated in situ was used as catalyst for the asymmetric hydroxy- and alkoxycyclization of 1,6-enynes[8] (Scheme 3, complex **A**). The participation of complexes formed from combinations of chiral bidentate phosphine ligands and achiral monodentate ligands (a phosphine or an *N*-heterocyclic carbene) in the enantioselective Pt-catalyzed cycloisomerization of 1,5-dienes,[9] 1,5-enynes,[10] and 1,6-enynes[11] has also been reported (Scheme 3, complex **B**). A second class of platinum catalysts resulting from the association of an achiral metallacyclic *N*-heterocyclic carbene ligand and a chiral monophosphine ligand has been applied in the cycloisomerization of 1,6-enynes[12] and 1,5-enynes.[13] (Scheme 3, complex **C**). A third option consisting of the combination of a chiral neutral bidentate ligand and an anionic monodentate ligand leads to the formation of monocationic platinum complexes that have found application in the cycloaddition of alkynones with alkenes[14] (Scheme 3, complex **D**).

During the last decades, combinatorial methods have become popular and are routinely used in a number of areas of chemistry, including therapeutic-drug discovery, peptide synthesis, and materials science.[15] More recently, combinatorial homogeneous catalysis,[16] that is, the synthesis and application in catalytic reactions of a large number of soluble catalysts under a variety of conditions including temperature, solvent, pressure, and additives, has become a tool of increasing interest for catalyst optimization. The automated formation of the catalysts and performance of the catalytic tests, which were made possible by the development of robotics,[17] coupled with high-throughput analytical techniques,[18] allow the screening of a previously inaccessible number of catalyst systems.[19] As mechanistic knowledge is often insufficient to design the optimum catalyst combination, asymmetric homogeneous catalysis remains a field of research driven by empiricism, leaving room for intuition and serendipity. The development of libraries of new chiral transition-metal complexes from combinations of known chiral and achiral ligands is expected to introduce a large diversity of catalytic properties for tackling issues of activity and selectivity raised by modern homogeneous catalysis. Considering the prominent role played by bidentate chiral phosphine ligands in late transition-metal asymmetric catalysis, most combinatorial approaches to the design of ligating architectures have dealt with associations of two monodentate ligands (a phosphine or an *N*-heterocyclic carbene), the spatial arrangement of which around the metal center is dictated by steric repulsion[20] or supramolecular interactions,[21] including metal coordination,[22] hydrogen bonding,[23] and charge-transfer complexation.[24]

Following our ongoing study on domino nucleophilic addition/enyne cyclization reactions catalyzed by carbophilic Lewis acids[4d,f,h,25] and our report on Pt-catalyzed enantioselective hydroarylation/cyclization of 1,6-enynes,[26] we envisioned the synthesis of libraries of complexes with a chiral tris-ligated en-

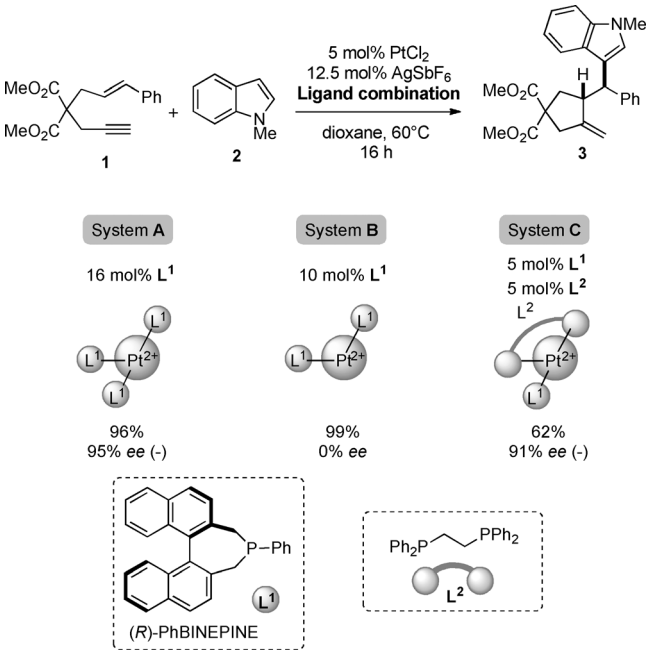


Scheme 3. Representative tris-ligated chiral platinum complexes having a single coordination site, complexes used as alkynophilic Lewis acid catalysts.

vironment around a square-planar late transition-metal center, that is, platinum, by using combination of a mono- and a bidentate ligand, at least one of which is chiral. Herein, we report on the synthesis of libraries of chiral tris-ligated platinum complexes by synergetic use of libraries of mono- and bidentate phosphorus ligands and their in situ evaluation as carbophilic Lewis acid catalysts for the asymmetric domino hydroarylation/cyclization reaction of 1,6-enynes. Three routes to the introduction of the chiral information in the library of complexes were sequentially investigated: 1) the use of a library of chiral bidentate ligands $\mathbf{L^2}$; 2) the use of a library of a chiral monodentate ligands $\mathbf{L^1}$; and 3) the use of libraries of both chiral bidentate ligands $\mathbf{L^2}$ and chiral monodentate ligands $\mathbf{L^1}$.

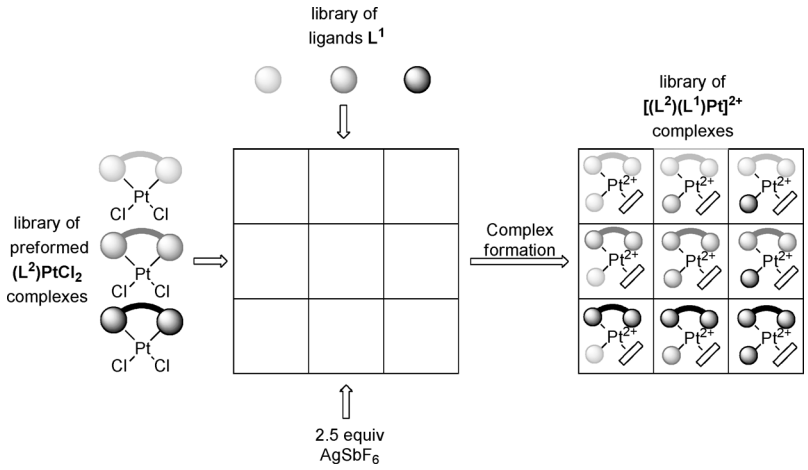
Results and Discussion

Preliminary experiments showed that in the presence of an catalytically active species $[L_3Pt^{2+}]$ of type **A** (L = (*R*)-BINEPINE[27]) formed in situ, good yields and high enantioselectivities were obtained for the domino 5-*exo* cyclization/nucleophilic addition of 1,6-enyne **1** with a variety of electron-rich aromatic and heteroaromatic nucleophiles such as **2** (Scheme 4, system A). Control experiments ruled out the hypothesized involvement of the $[L_2Pt^{2+}]$ complex (Scheme 4, system B) and demonstrated the possibility to mimic the optimal chiral environment around the Pt center by association between a chiral monodentate phosphane and an achiral bidentate bis-phosphine (Scheme 4, system C).



Scheme 4. Asymmetric Pt-catalyzed domino cyclization/hydroarylation of 1,6-enynes.

To obtain the simplest and most reliable protocol for accessing libraries of chiral environments featuring a tris-ligated platinum center, we focused on a two-step methodology. In the first step, $PtCl_2$ was mixed with a set of bidentate chelating bis-phosphines $\mathbf{L^2}$ to form the corresponding library of square-planar complexes of general formula $[(\mathbf{L^2})PtCl_2]$, which can be purified and characterized by ^1H and ^{31}P NMR spectroscopy. In the second step, addition of 2.5 equivalents of a silver salt followed by addition of one equivalent of a monodentate phosphine ligand $\mathbf{L^1}$ led to in situ formation of a library of tris-ligated complexes $[(\mathbf{L^2})(\mathbf{L^1})Pt]^{2+}$ having a single empty coordination site (Scheme 5). Considering the low stability of these intermediates, neither purification nor characterization was performed at this stage. Consequently, the asymmetric induction of these libraries was evaluated in situ by adding substrate and nucleophile (1,6-enyne and electron-rich aromatic or heteroaromatic compounds, respectively; see Scheme 4) and analyzing the enantioselectivity by chiral HPLC techniques after filtration of the crude reaction mixture through a pad of silica gel.

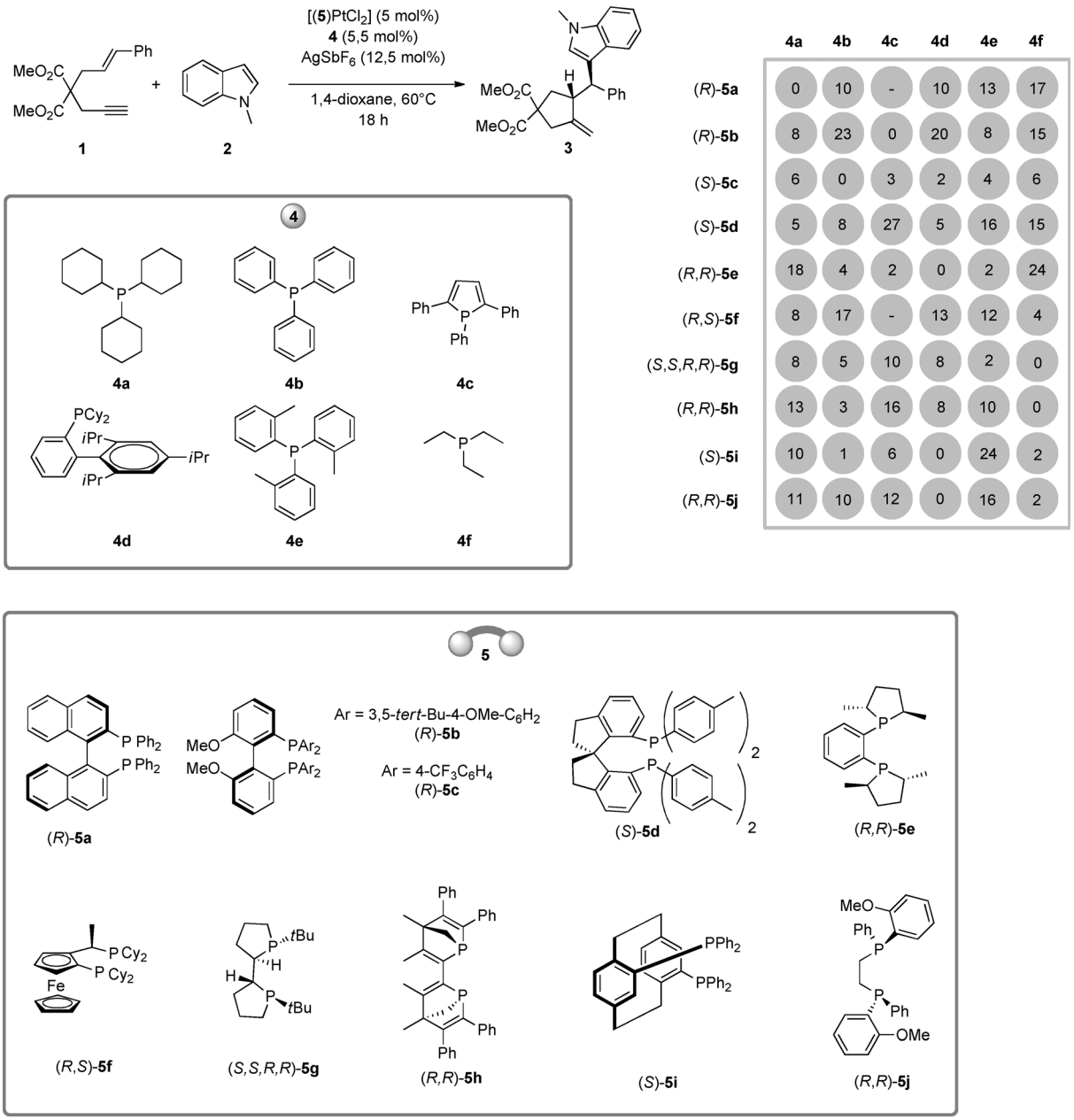


Scheme 5. Library of tris-ligated $[(\mathbf{L^2})(\mathbf{L^1})Pt]^{2+}$ complexes.

In a first test, we focused on the combination of enyne **1** as substrate and *N*-methylindole (**2**) as nucleophile to validate the combinatorial approach proposed in this study. In accordance with the optimized conditions obtained with catalyst **A** for the domino hydroarylation/cyclization reaction,[26] the catalytic tests were performed in 1,4-dioxane for 18 h at 60 °C.[28]

Library of chiral Pt complexes with chiral ligands L^2

A first library formed from the combination of an achiral monodentate phosphorus ligand (**4a–f**) and a chiral chelating bis-phosphine (**5a–j**) was synthesized and evaluated in asymmetric catalysis (Scheme 6). These ligands sets were chosen to screen a large scope of stereoelectronic parameters for phos-

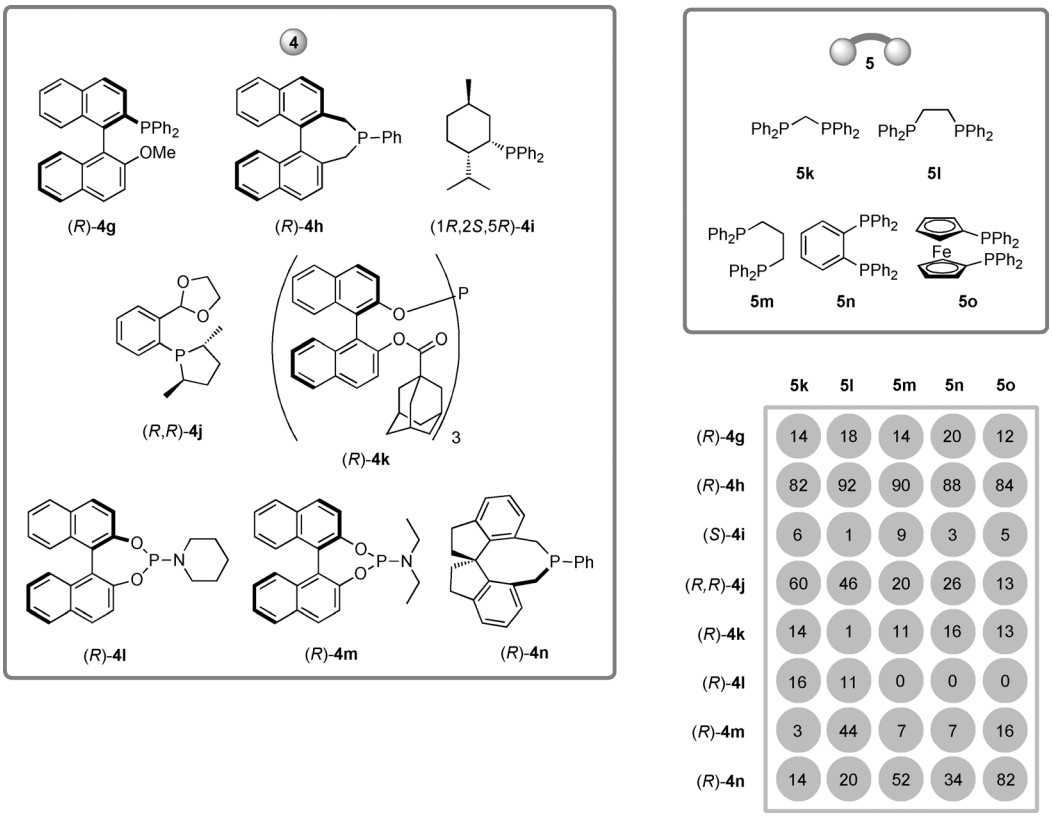


Scheme 6. Combinatorial screening in a domino cyclization/hydroarylation reaction of Pt complexes combining an achiral monodentate ligand **4** and a chiral bidentate ligand **5**.

phine ligands. The set of chiral bidentate ligands included 1) atropisomeric phosphanes including BINAP[29] ((*R*)-**5a**) and MeO-BIPHEP derivatives[30] with either electron-donating and hindered ((*R*)-**5b**) or electron-withdrawing ((*R*)-**5c**) aryl substituents; 2) C_2-symmetric spiroindanyldiphosphane Tol-SDP[31] ((*S*)-**5d**); 3) C-stereogenic cyclic dialkyl- and trialkylphosphanes Me-DUPHOS[32] ((*R*,*R*)-**5e**) and TANGPHOS[33] ((*S*,*S*,*R*,*R*)-**5g**); 4) C_1- and C_2-symmetric planar chiral diphosphanes tetrakis-cyclohexyl-Josiphos derivative[34] (*R*,*S*)-**5f** and [2.2]PHANEPHOS[35] ((*S*)-**5i**); 5) P-stereogenic bidentate phosphanes BIPNOR[36] ((*R*,*R*)-**5h**) and DIPAMP[37] ((*R*,*R*)-**5j**). Enantioselectivities were low for all ligand combinations tested (< 30% *ee*, see Scheme 6), that is, introduction of chiral information on the bidentate ligand has little or no effect on the stereoinduction in comparison with the corresponding chiral tris-coordinated Pt complexes.

Library of chiral Pt complexes with chiral ligands L[1]

Alternatively, a second approach based on the combination of chiral monodentate phosphine ligands **4g**–**n** and achiral bidentate phosphine ligands **5k**–**o** was studied. The chiral monodentate ligand set was designed to include 1) the atropisomeric triarylphosphane MOP[38] ((*R*)-**4g**); 2) the C_2-symmetric electron-rich dialkylphosphine (*R*)-BINEPINE ((*R*)-**4h**)[27] and spirophospholane (*R*)-SITCP ((*R*)-**4n**);[39] 3) the C-stereogenic phosphines (1*R*,2*S*,5*R*)-**4i**[40] and (*R*,*R*)-**4j**;[41] 4) the sterically congest-



	5k	5l	5m	5n	5o
(*R*)-**4g**	14	18	14	20	12
(*R*)-**4h**	82	92	90	88	84
(*S*)-**4i**	6	1	9	3	5
(*R*,*R*)-**4j**	60	46	20	26	13
(*R*)-**4k**	14	1	11	16	13
(*R*)-**4l**	16	11	0	0	0
(*R*)-**4m**	3	44	7	7	16
(*R*)-**4n**	14	20	52	34	82

Scheme 7. Combinatorial screening in a domino cyclization/hydroarylation reaction of Pt complexes combining a chiral monodentate ligand **4** and an achiral bidentate ligand **5**.

ed triaryl phosphite (*R*)-**4k**[42] and the C_2-symmetric electron-poor binaphthol-based phosphoramidites (*R*)-**4l** and (*R*)-**4m**[43] (Scheme 7).

Only marginal enantioselectivities were observed for the combinations of ligands involving the monodentate phosphite (*R*)-**4k** or the phosphoramidite ligands (*R*)-**4l** and (*R*)-**4m** as well as for the phosphane ligands (*R*)-**4g** and (1*R*,2*S*,5*R*)-**4i** (Scheme 7). In contrast, moderate to excellent enantioselectivities were obtained with combinations involving the aryldialkylphosphanes (*R*)-**4h**, (*R*,*R*)-**4j** and (*R*)-**4n**. The optimal combination was reached in all cases with a different bidentate partner, **5l**, **5k**, and **5o** to give 95, 60, and 82% *ee*, respectively. In the case of (*R*)-**4h**, a clear relationship could be established between the bite angle[44] of the achiral bidentate ligand and the enantioselectivity (Figure 1), with the optimum enantiomeric excess observed for **5l** (bite angle of 85°). In the case of monodentate ligand (*R*)-**4n**, a relationship between the bite angle of **5** and the enantioselectivity also seems to exist but with a different optimum: the complex formed from ligand **5o** (bite angle of 99°) led to the highest enantiomeric excess, whereas that involving ligand **5l** afforded only a very moderate enantioselectivity (20% *ee* for a bite angle of 85°). For the chiral monodentate ligands (*R*)-**4h** and (*R*)-**4n**, the active species $[(\mathbf{L^1})_3Pt^{2+}]$ furnished a highly enantioselective catalyst for the 1,6-enyne **1**/heteroaromatic nucleophile **2** test combination (Scheme 4, system A), with enantioselectivities of 95 and 88% respectively. Overall, these results reveal the key factors influencing the enantioselectivity of this asymmetric transformation: 1) The need for a chiral electron-rich ligand of moderate steric hindrance as the monodentate partner $\mathbf{L^1}$; 2) The need for a complementary achiral bidentate partner of carefully optimized bite angle $\mathbf{L^2}$.

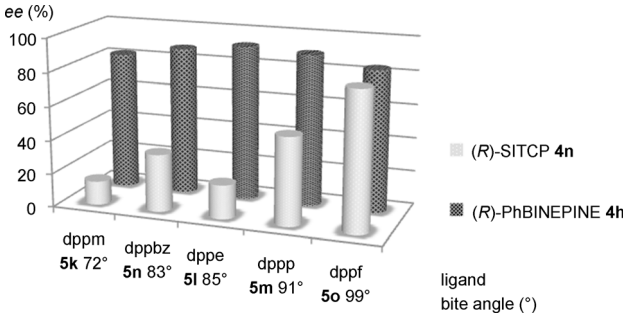
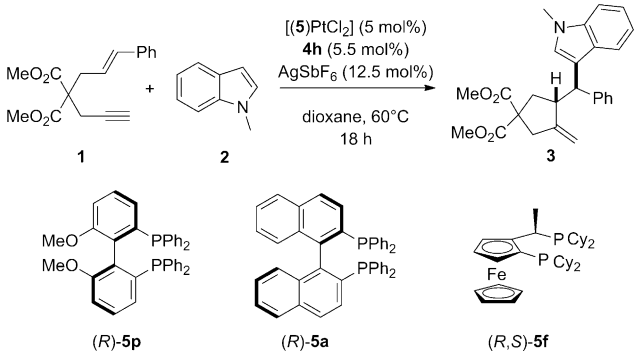


Figure 1. Effect of the bite angle of the achiral $\mathbf{L^2}$ ligand on the enantioselectivity of the domino hydroarylation/cyclization reaction of **1** with **2** involving monodentate ligands **4h** and **4n**.

Library of chiral Pt complexes with a combination of chiral L^1 and L^2 ligands

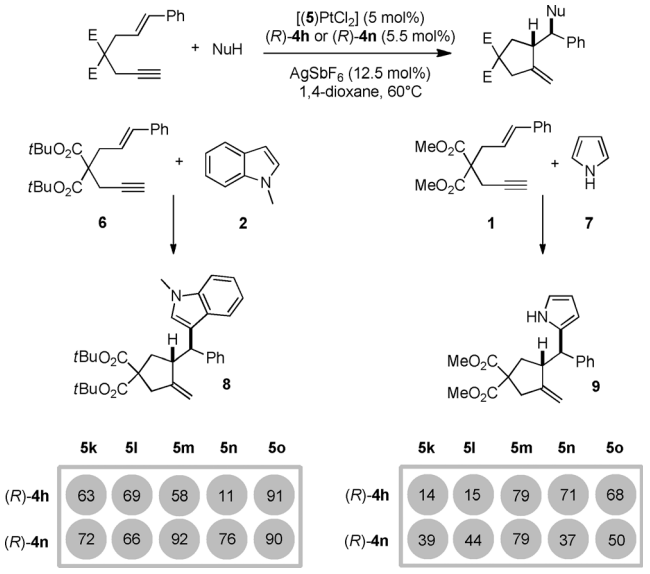
To further highlight the relative roles played by the bidentate and monodentate ligands in the stereoinduction observed in the presence of the complex formed by their association, combinations of both chiral monodentate and bidentate ligands

Table 1. Combinatorial screening in a domino cyclization/hydroarylation reaction of Pt complexes combining a chiral monodentate ligand **4** and a chiral bidentate ligand **5**.



Entry	L^1	L^2	Enantiomeric ratio [%][a]
1	(*R*)-**4h**	(*R*)-**5p**	92.5/7.5 (−)
2	(*R*)-**4h**	(*S*)-**5p**	90.5/9.5 (−)
3	(*S*)-**4h**	(*R*)-**5p**	7/94 (+)
4	(*S*)-**4h**	(*S*)-**5p**	8/92 (+)
5	(*S*)-**4h**	(*R*)-**5a**	7/94 (+)
6	(*S*)-**4h**	(*S*)-**5a**	8/92 (+)
7	(*R*)-**4h**	(*R,S*)-**5f**	75/25 (−)
8	(*S*)-**4h**	(*R,S*)-**5f**	8.5/91.5 (+)

[a] Determined by chiral HPLC.



Scheme 8. Combinatorial evaluation in domino cyclization/hydroarylation reactions of **6**/**2** and **1**/**7** of Pt complexes involving chiral monodentate ligands (*R*)-**4h**, (*R*)-**4n** and achiral bidentate ligands **5k–o**.

were also been investigated. All tests were done with the monodentate ligand (*R*)- or (*S*)-**4h**. In combination with the C_2-symmetric chiral bidentate ligand MeOBIPHEP (**5p**), catalytic experiments gave enantiomeric excesses between 81 and 86%, and no match/mismatch effect was observed (Table 1, entries 1, 4 versus 2, 3). The sense of the stereoinduction is only governed by the stereochemistry of the chiral monodentate partner. A similar situation was also monitored for a second atropisomeric ligand, namely, BINAP (**5a**), which led to enantioselectivities in the same range (Table 1, entries 5, 6). In contrast, with the C_1-symmetric bidentate ligand (*R,S*)-**5f**, a significant match/mismatch effect was observed, whereas the sense of stereoinduction remained dictated by the stereochemistry of the monodentate partner **4h**, which led to enantiomeric ratios of 8.5/91.5 and 75/25, respectively (Table 1, entries 7 and 8).

To validate the combinatorial approach to catalyst design through mixing of mono- and bidentate ligands developed here, this strategy was tested for two challenging combinations of substrates and nucleophiles. The domino hydroarylation/cyclization reactions of 1) sterically congested *tert*-butyl malonate-derived enyne **6** with *N*-methylindole (**2**) and 2) 1,6-enyne **1** with pyrrole (**7**) were investigated. Catalyst combinations involving the σ-donating chiral monodentate ligands (*R*)-**4h** and (*R*)-**4n** and the achiral bidentate ligand set **5k–o**, which showed the most promising stereoinductions in the case of our test combination (see Scheme 7), were evaluated (Scheme 8).

For the reaction involving substrate **6** and nucleophile **2**, the best ligand combination (*R*)-**4n**/**5m** afforded an enantiomeric excess of 92%. For the reaction involving substrate **1** and nucleophile **7**, two combinations, (*R*)-**4h**/**5m** and (*R*)-**4n**/**5m**, led to an *ee* of 79%. These results compared favorably to those obtained in the presence of the original catalyst system **A** with ligand (*R*)-**4h**, which furnished 80 and 70% *ee*, respectively, for the corresponding substrate/nucleophile combinations.[26]

Conclusion

We have reported a new combinatorial approach to the synthesis of square-planar platinum complexes with tris-ligated chiral environments and their in situ evaluation in the asymmetric homogeneous catalysis of hydroarylation/cyclization reactions of 1,6-enynes. The combinatorial strategy relies on a simple, reproducible procedure and involves the combination of commercially available mono- and bidentate phosphorus ligands. Nonbonded interactions between the two complexing entities allow the formation of a chiral environment around the metal center that can mimic either tridentate ligands or the association of three monodentate ligands. In this study, a library of more than 100 tris-ligated cationic platinum complexes $[Pt(L^1)(L^2)]^{2+}$ having a single active coordination site was prepared and evaluated in a catalytic test reaction of domino hydroarylation/cyclization of a 1,6-enyne involving activation by a carbophilic Lewis acid. Our investigations revealed negligible influence of the chirality present on the bidentate ligand L^2, and high enantioselectivities were observed exclusively in the case of ligand combinations in which monodentate ligand L^1 was chiral. The best results were obtained with monodentate ligands **4h** and **4n**, which have similar stereoelectronic properties: C_2-symmetric dialkyl aryl phosphanes with medium cone angle (e.g., 151° estimated for **4h**)[27] and strong σ-donating character. No clear trend could be established with respect to the bite angle of the bidentate partner L^2, so that combinatorial assays are needed in the search for the optimum ligand combination for a substrate-sensitive or

reagent-sensitive transformation. A significant improvement was indeed found in the case of two challenging hydroarylation/cyclization reactions. Our investigations therefore highlighted the potential of such a strategy for the optimization of the selectivity of transformations catalyzed by transition-metal complexes having three sites of coordination occupied by ligands throughout the catalytic cycle.[45,46] This concept for optimization of the activity and/or the selectivity of a variety of existing catalyst systems thus has promising applications in asymmetric homogeneous catalysis.

Experimental Section

Typical procedure for the synthesis of chiral tris-ligated platinum complexes and their in situ evaluation in an asymmetric hydroarylation/cyclization reaction

Degassed dioxane (0.2 mL) was added to a 3 mL vial containing [(**5**)$PtCl_2$] (0.00875 mmol, 0.05 equiv) and $AgSbF_6$ (0.0219 mmol, 0.125 equiv) under argon, and the solution was stirred at room temperature for 15 min. The chiral monodentate ligand **4** (0.01 mmol, 0.055 equiv) was then added and the solution heated to 60 °C for 30 min. After cooling to room temperature, the nucleophile (0.525 mmol, 3 equiv) and 100 μL of a solution of the 1,6-enyne (1.75 M in dioxane, 0.175 mmol, 1 equiv) were sequentially added and the reaction mixture was heated to 60 °C for 18 h. Purification was accomplished by filtration through a Grace Extract-Clean 8 mL filter filled with a pad of silica. Elution with spectroscopic grade *n*-hexane/*i*PrOH (90/10) gave first a fraction containing the excess of the aromatic nucleophile then a second fraction containing the product, which can be injected into a high-pressure liquid chromatograph without further manipulation.

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Keywords: asymmetric catalysis · combinatorial chemistry · cyclization · platinum · P ligands

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