

Asymmetric Oxidative Cation/Olefin Cyclization of Polyenes: Evidence for Reversible Cascade Cyclization**

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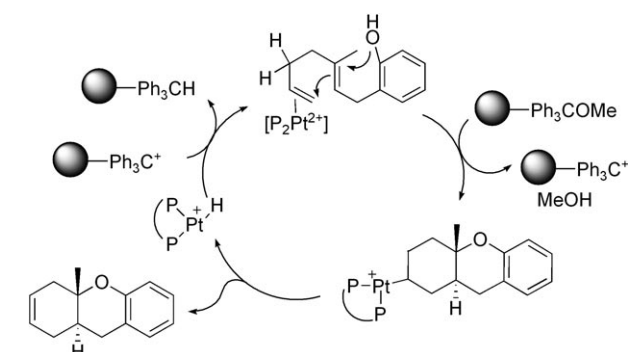
The biosynthesis of cyclic terpenes from polyene precursors by cyclase enzymes is one of nature's most elegant chemical transformations.^[1] The ease with which nature creates complex molecular architectures from achiral precursors has motivated efforts to develop similarly powerful synthetic methodologies.^[2] A limited number of asymmetric methods have been developed,^[3] including the notable Brønsted/Lewis acid (BLA) cascade reactions developed by Yamamoto and co-workers,^[4] and the recent halocyclization of polyprenoids reported by Ishihara and co-workers.^[5] We recently reported a regio- and diastereoselective oxidative polycyclization of di- and trienols catalyzed by achiral [(dppe)Pt] dication, wherein turnover was achieved by the trityl cation abstracting a hydride from a putative [(dppe)Pt-H]⁺ intermediate (Scheme 1).^[6,7] Since there are so few asymmetric methods

A wide variety of readily available chiral diphosphine ligands for the conversion of **1** into **2** were screened to find the optimal combination of catalyst and conditions for the transformation (Table 1). In general the results with the standard array of chiral diphosphine ligands (binap, MeO-biphep, etc.) were disappointing. Additional substitution on the aryl ring of the P atom, however, gave noticeable

Table 1: Representative screen of diphosphine ligands for [Pt²⁺]-catalyzed polycyclization.^[a]

Entry	Ligand	ee [%] for 2 ^[b]
1	(S)-binap	7
2	(S)-tol-binap	12
3	(S)-xylyl-binap	48
4	(R)-MeO-biphep	12
5	(R)-xylyl-MeO-biphep	46
6	(R)-dtbm-MeO-biphep	n.r.
7	(R)-segphos	20
8	(R)-dtbm-segphos	n.r.
9	(R)-bicip	52
10	(R)-bdpp	41
11	(S,S)-chiraphos	20
12	(S)-xylyl-phanephos (3)	75

[a] Conditions: 10 mol% [PtX₂] (X = Cl or I), 22 mol% AgBF₄, 2.1 equiv Ph₃COMe, and EtNO₂. [b] Determined by GC analysis. binap = (1,1'-binaphthalene)-2,2'-diylbis(diphenylphosphine); biphep = 2,2'-bis(diphenylphosphanyl)biphenyl; segphos = 4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphine); bicip = 2,2'-bis(diphenylphosphanyl)dicyclopentane; bdpp = 2,4-bis(diphenylphosphino)pentane; chiraphos = 2,3-bis(diphenylphosphano)butane; phanephos = 4,12-bis(diphenylphosphanyl)-[2,2]paracyclophane; n.r. = no reaction.

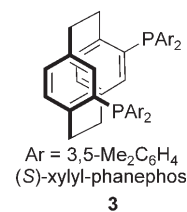


Scheme 1. Proposed catalytic cycle for [Pt²⁺]-catalyzed polycyclization.

for such cascade cyclizations,^[8] we initiated efforts to render this initial discovery into an oxidative method that was regio-,^[9] stereo-, and enantioselective.^[10,11] In the course of discovering and then subsequently mechanistically examining such an enantioselective variant, we have also made the surprising observation that the initial cascade cyclization is not necessarily the stereochemistry-determining step.

improvements in the selectivities (Table 1, entry 3 versus 1 and entry 5 versus 4). Ligands that had larger groups at the 3,5-positions of the ring did not turnover (Table 1, entries 6 and 8; dtbm = 3,5-di-*t*-butyl-4-methoxy). Moderate enantioselectivities were also observed with the bicip and bdpp chiral bisphosphine ligands, and the best ligand was xylyl-phanephos (**3**); the catalyst derived from halide abstraction from [(xylyl-phanephos)PtCl₂] ((**3**)PtCl₂) yielded **2** in 75% ee.

Solvents and counterions were examined to additionally improve the system. Of the series of counterions, BF₄⁻, SbF₆⁻, NTf₂⁻, OTf⁻, and F₃CCO₂⁻, BF₄⁻ gave



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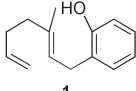
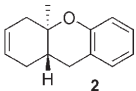
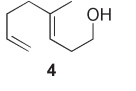
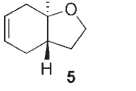
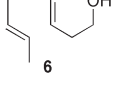
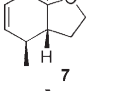
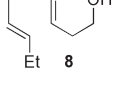
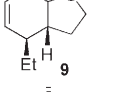
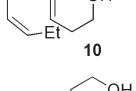
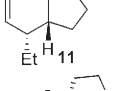
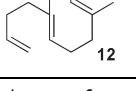
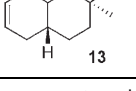
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the highest enantioselectivity without affecting the product yield. The OTf[−] counterion exhibited a slight increase in the enantioselectivity of the reaction, but acid-catalyzed products dominated the reaction mixture. With regard to solvent choice, it had been previously shown that highly polar nitro-containing solvents (i.e. nitromethane) were crucial for achieving good yields and high reaction rates in the [Pt²⁺]-mediated olefin cyclizations.^[12] For this reason, nitromethane (70% *ee*), nitroethane (75% *ee*), 1-nitropropane (74% *ee*), and 2-nitropropane (71% *ee*) were screened as possible solvents for the enantioselective synthesis of **2** with [(**3**)Pt²⁺]. All solvents led to comparable rates, but nitroethane was optimal with respect to the enantioselectivity. In the case of volatile products, nitromethane was preferable because the product could be extracted into pentane.

The optimum catalyst was applied to a collection of diene and triene substrates (Table 2). The reaction was compatible with monosubstitution and 1,2-disubstitution at the terminal alkene, however, *Z* alkenes were better behaved than the *E* alkenes. This sensitivity to alkene stereochemistry was not previously observed in the achiral dppe catalysts, and like the chiral catalyst, a trisubstituted terminal alkene was not tolerated (not shown). In each case a single stereo- and regioisomer of the product was obtained. Although perfect stereospecificity was observed in the *E* and *Z* substrates (Table 2, entries 4 versus 5), they markedly differed in their enantioselectivities; the terminal *Z* alkene (Table 2, entry 5)

Table 2: Asymmetric polycyclizations catalyzed by [(*S*)-xylyl-phanephos]Pt(BF₄)₂.^[a,b]

Entry	Substrate	Product	Yield [%] ^[c]	% <i>ee</i>
1			73	75
2 ^[d]			75	79
3			n.d.	12
4			n.d.	10
5			61	87
6			76	64 ^[e]

[a] All absolute configurations were assigned by analogy to the known hydrogenated product of **13**. For poorly selective reactions this assignment should be interpreted cautiously. [b] Conditions: 10 mol% **3**, 22 mol% AgBF₄, 2.1 equiv Ph₃COMe (resin), EtNO₂, RT. [c] Yield of isolated product. [d] Solvent was MeNO₂. [e] Determined after hydrogenation of product. n.d. = not determined.

cyclized with the highest selectivities (up to 87% *ee*), non-substituted terminal alkenes provided moderate to good selectivities (Table 2, entries 1, 2, and 6), and terminal *E* alkenes had poor selectivities (Table 2, entries 3 and 4). The absolute stereochemistry of **13** was determined by using hydrogenation to give known **13-H₂**, the optical rotation of which was compared to reported values.^[13] The stereochemistry of the remaining compounds in Table 2 were assigned by analogy.

Intrigued by the markedly different results for the xylyl-phanephos ligand, we obtained an X-ray crystallographic structure of the catalyst precursor (Figure 1).^[14,15] Except for a particularly broad bite angle (103.75°), there is surprisingly little quadrant differentiation, which is normally observed in highly selective ligands like binap.

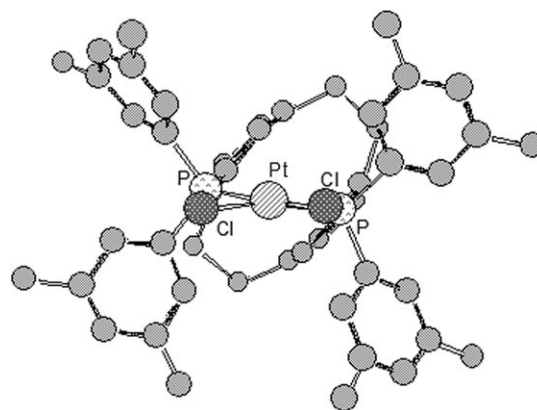
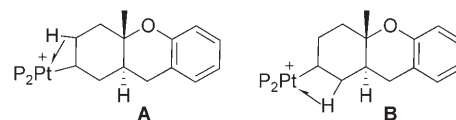
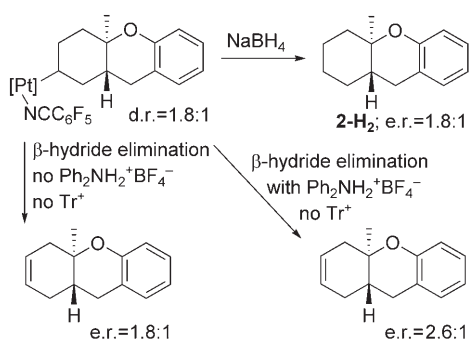


Figure 1. X-ray crystallographic structure of [(**3**)PtCl₂]. Bond angles include P–Pt–P (103.75°), average P–Pt–Cl (85.00°), and Cl–Pt–Cl (87.58°).

In situ monitoring of [(binap)Pt²⁺]- and [(xylyl-binap)Pt²⁺]-catalyzed reactions indicated, from *J*_{Pt–P} coupling constants^[16] and ¹⁹F NMR data, that the catalyst rested as an alkyl–nitrile species. Unfortunately the reactions run with xylyl-phanephos resulted in a complex multicomponent mixture (³¹P NMR spectra). The alkyl–nitrile species, for both xylyl-MeO-biphep and xylyl-binap, were observed as a mixture of two isomers in a ratio of 1.8:1 (³¹P NMR methods)—solutions of these species could be generated at 0°C, where they were stable to β-hydride elimination.



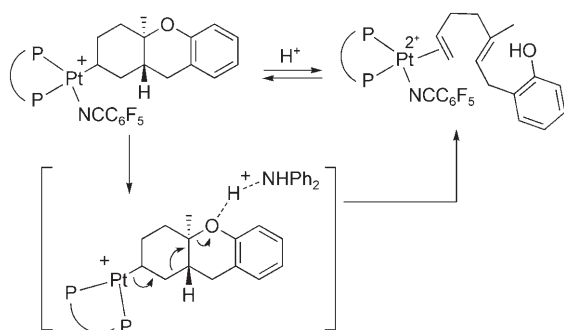
For one of these solutions, the benzopyran complex was cleaved from the Pt with NaBH₄ to yield reduced compound **2-H₂** with an enantiomeric ratio (e.r.) that was identical to the d.r. of the alkyl–nitrile species (Scheme 2); thus the two isomers appeared to be a matched and mismatched combination of the *trans* ring junction and the ligand chirality.



Scheme 2. Stoichiometric reactivity of the alkyl–nitrile resting state.

Surprisingly, the d.r. value of the alkyl–nitrile species (or the e.r. value of **2-H₂**) was lower than the e.r. value for the catalytic reaction (2.85:1).

The alkyl–nitrile intermediate (d.r.=1.8:1) was next generated *in situ* (0°C) under single turnover conditions (only the trityl cation was missing). When this reaction mixture was warmed to room temperature and allowed to undergo elimination to give products, the alkene products were obtained with an e.r. value (2.6:1) that nearly matched the value obtained under normal catalysis conditions (e.r.=2.85:1), and contrasted with value determined in the NaBH₄ cleavage studies (e.r.=1.8:1) (Scheme 2). When the alkyl–nitrile intermediate was prepared as described above (0°C) and separated from acidic species Ph₂NH₂⁺, which results from phenol trapping, the alkene was not formed with the e.r. value found under catalytic conditions (2.85:1), but rather with an e.r. value that matched the d.r. value of the alkyl–nitrile intermediate (1.8:1). These observations are inconsistent with an irreversible, stereochemistry-determining cascade cyclization, and suggested that Ph₂NH₂⁺ mediates a proton-coupled retrocyclization (Scheme 3).^[17,18]



Scheme 3. Proton-coupled retrocyclization.

Although there are several candidate steps for the stereochemistry-determining event^[19] the counterintuitive notion of an electrophilic cascade not being stereochemistry-determining is intriguing and will have important consequences in future efforts to improve such catalysts.

To summarize, we report herein an addition to the short list of catalysts that mediate an enantioselective cation/olefin

cascade cyclization of polyprenoids. Unlike the chiral acids (Yamamoto's BLA's) and the chiral iodonium salts' (Ishihara's R₃P-I⁺), this platinum catalyst mediates a stereospecific oxidative transformation, which works optimally on mono-substituted or terminal Z-disubstituted alkenes, and enables enantio- and regioselective access to structures that are not otherwise available.

Experimental Section

Typical polycyclization procedure: 2.2 equiv AgBF₄ was added to a 13.3 mM solution of [(3)PtCl₂] (typically 0.02 mmol) in EtNO₂. The reaction mixture was stirred for 1 h in the dark and then 21.0 equiv Ph₃COMe on polystyrene resin and 10 equiv substrate were added. The reaction mixture was stirred at room temperature in the dark until the reaction was complete by GC analysis (typically 6–14 h). The reaction mixture was then quenched by passage through a plug of silica gel and eluted with ether. The solvent was then removed *in vacuo* and the residue was purified by column chromatography. The enantiomeric excess was determined by chiral stationary phase gas chromatographic analysis using an Agilent Cyclosil column. In the case of volatile substrate **4**, nitromethane was used and **5** was isolated by first extracting into pentane under biphasic conditions.

Preparation of alkyl–nitrile intermediate: In a nitrogen filled glove box either [(xylyl-binap)PtI₂] or [(xylyl-MeO-biphep)PtI₂] (0.035 mmol), AgBF₄ (0.087 mmol), and NCC₆F₅ (0.105 mmol) were stirred in CD₃NO₂ for 1 h. AgI was removed by filtration through a PTFE filter. The solution was then cooled to –78°C and **1** (0.070 mmol) and Ph₂NH (0.070 mmol) were added to the reaction mixture. The reaction mixture was warmed to 0°C overnight after which the alkyl–nitrile intermediate was observed by ³¹P NMR spectroscopy.

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