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Enantioselective Cascade Cyclization/Protodemetalation of Polyenes with N_3Pt^{2+} Catalysts

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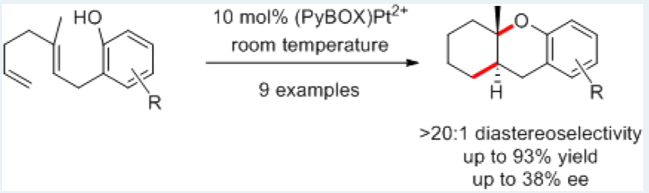
Supporting Information

ABSTRACT: The combination of the N-based pincer ligand PyBOX with Pt^{2+} leads to new catalysts for the enantioselective cycloisomerization of dienyl- and trienyl-ols. The mechanistic combination of electrophilic cyclization followed by rapid protodemetalation is surprising and leads to a powerful construct for developing new reactions.



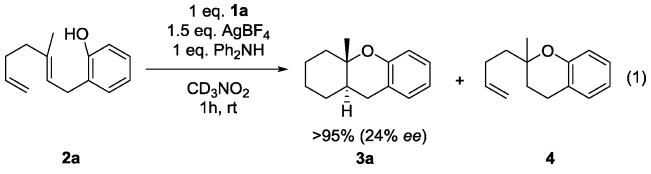
KEYWORDS: *electrophilic catalysis, cycloisomerization, platinum, protodemetalation*

The steroid skeleton is biosynthesized by a fascinating cationic cascade cyclization of polyenes like squalene or squalene oxide. The commercial import of bioactive steroids is, however, not matched by synthetic methods for their de novo synthesis. In fact, nearly all steroidal active ingredients are accessed through semisynthetic means (i.e., derived from the natural pool). It is, therefore, not surprising that biomimicking stereoselective cascade syntheses of steroid-like compounds is of significant interest.[1] The available methods include nonmetal electrophiles such as Brønsted−Lewis acids,[2] haloniums,[3] organocatalysts,[4] and metal electrophiles such as Hg(II),[5] Pd(II),[6] Pt(II),[6c,7] Ir(I),[8] and Au(I).[9] Our group has focused on Pt(II)-based catalysts and previously reported that the powerful electrophile $[(triphos)Pt][BF_4]_2$ can stoichiometrically convert various polyenes to form polycyclic Pt-alkyl$^+$ structures with high diastereoselectivity.[6l,o,p]

Despite the successful development of catalytic tandem cyclization/β-H elimination,[7a,b,h] cyclization/fluorination,[7f] and cyclization/oxygenation[7g] reactions, the parent cyclization/protonation reaction (a catalytic cycloisomerization) putatively obtained via protodemetalation of a cyclization-derived Pt-alkyl has not been achieved, because protonolysis of the resulting bulky (triphos)Pt-alkyl$^+$ complexes requires strong acids like TfOH, which are not compatible with polyene substrates.[10] This reactivity exemplifies the underlying problem that the properties of electrophilic alkene activation and protodemetalation have opposite ligand preferences, the former favoring electron-deficient ligands and the latter electron-rich ligands.[11,12] Our own investigations on the (triphos)Pt-R$^+$ system have shown that protodemetalation of Pt−C bonds with acids milder than HOTf is feasible when more electron-rich tridentate phosphine ligands are employed; however, electron-rich ligands also decrease the electrophilicity of Pt(II) catalysts and hinder the cascade cyclization portion of the tandem process.[7c] Herein, we report the development of a new generation of chiral platinum catalysts that carry out the cyclization/protodemetalation of polyenes under exceedingly mild conditions.

The PyBOX (pyridine-2,6-bisoxazolines) ligands form pincer complexes with a variety of metals, and they have proven to be highly effective in asymmetric catalysis.[13] However, to the best of our knowledge, there are no reported uses of platinum(II)−PyBOX complexes in catalysis.[14] This rarity could be due to the difficulties in synthesizing such complexes, because "hard" nitrogen ligands tend to be poor ligands for "soft" complexes of Pt(II).[15] We report herein that this mismatch has significant catalytic advantages. Consistent with its poor ligand quality, an especially labile Pt source, $Pt(DMSO)_2I_2$, was required to successfully obtain the cationic (PyBOX)Pt−I$^+$ catalyst precursor; the NNN ligand does not displace the typical alkene-based precursor.

Our studies began with an attempt to synthesize an (NNN)Pt variant of the readily isolable (PPP)Pt−alkyl$^+$ complexes,[6c,7d,e] with initial experiments employing the commercially available isopropyl PyBOX ligand **1a** (see Chart 1). (*R*)-**1a** was preactivated by $AgBF_4$ to generate the dication and then reacted with **2a** along with a stoichiometric quantity of Ph_2NH. As shown in eq 1, ^{1}H NMR spectroscopy revealed that after 1



h, **2a** was completely consumed, but the (NNN)Pt-alkyl$^+$ complex was not observed; the only observable organic product was **3a**. We presumed that **3a** was formed by the rapid protodemetalation of an unobserved (NNN)Pt-R$^+$ complex with $Ph_2NH_2^+$. The lack of **4**, a reporter for the build-up of even trace Brønsted acid,[16] indicated that protodemetalation was

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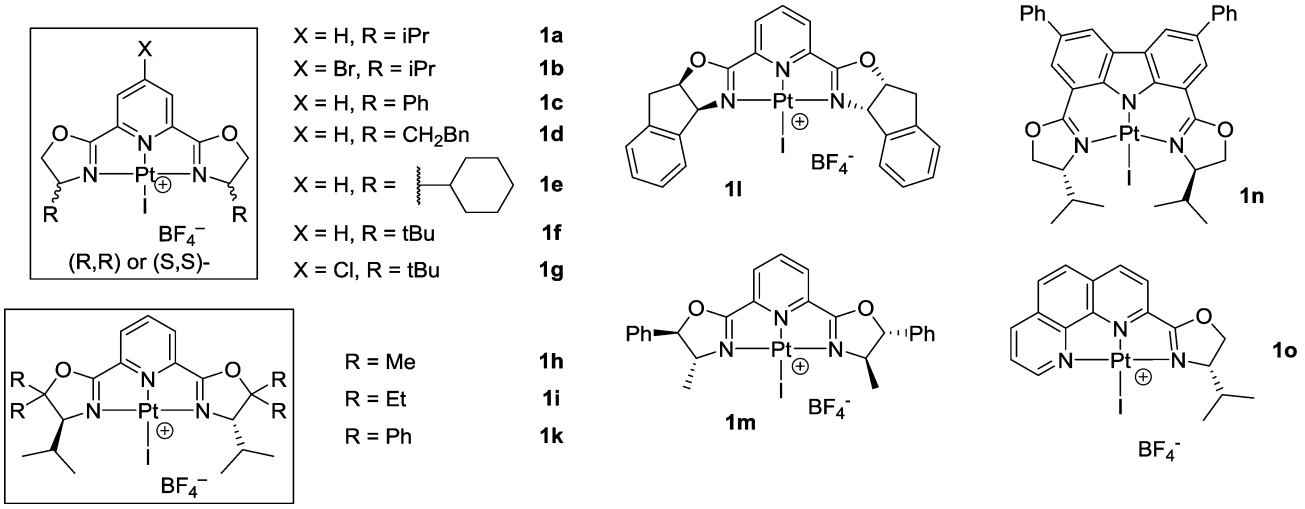
Chart 1. Pre-Catalysts Employed in This Study

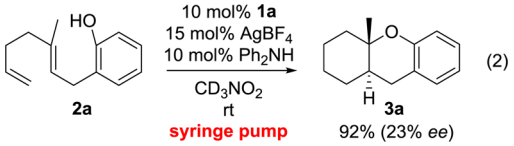


much more rapid than for (PPP)Pt-R$^+$ analogues and thus suggested the feasibility of a general catalytic cyclization/protonation pathway.

When this reaction was repeated with 10 mol % (PyBOX)-Pt^{2+}, no desired product was formed after even a prolonged period of time. In fact, the only organic product observed in GC was the β-hydride elimination product **5**, which was not even observed under stoichiometric conditions. Intrigued by this observation, we began a study to test the effect of additives on the outcome of the reaction, surmising that the principal difference between stoichiometric and catalytic conditions was the presence of excess substrate.

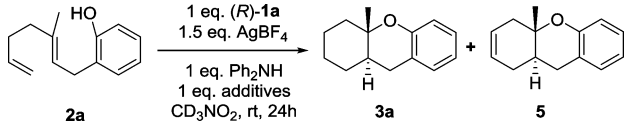
In this set of experiments, 1 equiv of **2a** was combined with 1 equiv of the activated catalyst and 1 equiv of a terminal alkene; the distribution of products was monitored by GC-MS. When 1 additional equiv of **2a** was added to the mixture, the yield of **3a** was drastically reduced, and the major product was **5** (entry 1, Table 1). A significant drop in reaction rate was also noted (12 h for 2 equiv of **2a** vs 1 h for 1 equiv). Styrene was particularly adept at shifting the product distribution to **5**, though electron-withdrawing groups partially reversed this trend. Notably, in all of these cases, the enantioselectiviy of **3a** and **5** were similar, suggesting that both products likely formed from the same intermediate (the alkyl).

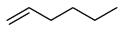
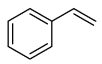
The mechanistic source for this additive effect remains unclear, but this issue can awkwardly be circumvented by the sequential addition of 1 equiv of **2a** after the previous equivalent was fully consumed. Better yet is the slow addition of **2a** to the catalyst by syringe pump, which enables the substrate concentration to be kept suitably low that rapid consumption occurs and protodemetalation dominates. Thus, adding 10 equiv of **2a** over 12 h via syringe pump to the activated catalyst with 1 equiv of Ph_2NH at room temperature resulted in an excellent isolated yield of **3a,** with an enantioselectivity that is only slightly reduced from stoichiometric conditions (eq 2).



(2)

Table 1. Effects of Terminal Alkenes on the Reaction Outcome



Entry	Additives	% yield of 3a[a] (% ee[b])	% yield of 5[a] (% ee[b])
1	**2a**	5 (23)	89 (25)
2		8 (19)	36 (18)
3		43 (18)	10 (12)
4		12 (22)	85 (24)
5		56 (34)	17 (35)

[a]GC yield, with hexamethylbenzene as internal standard. [b]ee determined by chiral GC.

Because stoichiometric mixtures of catalyst and **2a** effectively mimicked the efficiency and enantioselectivity of the syringe pump addition method, the reaction conditions were conveniently optimized in this fashion. Controls supported the viability of this approach and confirmed that no cyclization/protodemetalation occurred without the platinum complex (entry 2, Table 2).

In a previous computational study, bases that hydrogen bond to the protic terminus were found to greatly facilitate the cyclization,[17] hence its inclusion (Ph_2NH) in the originally tested condition (entry 1, Table 2, 24% ee). Weaker (Ph_3N) and stronger (Ph_2NMe and $PhNH_2$) bases were also explored,[18] but the highest enantioselectivity was achieved when no base was employed while still maintaining high conversion to **2a** (entry 3). Again, the lack of **4** indicates that alkyl protonolysis is considerably faster than Brønsted cyclization of **2a**.

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Table 2. Selected Optimization Studies[a]

entry	catalyst	solvent	base	temp	yield (%)[b]	ee (%)[c]
1	**1a**	CD_3N0_2	Ph_2NH	rt	>95	24
2	none	CD_3NO_2	Ph_2NH	rt	0	N/A
3	**1a**	CD_3NO_2	none	rt	>95	42
4	**1a**	$EtN0_2$	none	rt	>95	37
5	**1a**	CH_2Cl_2	none	rt	trace	N/A
6	**1a**	CH_3CN	none	rt	0	N/A
7	**1a**	CD_3NO_2	none	0 °C	95	40
8	**1f**	CD_3NO_2	none	rt	0	N/A
9	**1h**	CD_3NO_2	none	rt	>95	45
10	**1i**	CD_3NO_2	none	rt	79	48
11	**1k**	CD_3NO_2	none	rt	0	N/A
12	**1n**	CD_3NO_2	none	rt	0	N/A

[a]AII reactions performed with 1 equiv of [(NNN)Ptl][BF_4], activated with 1.5 equiv of silver salts (see Supporting Information). [b]GC yield with hexamethylbenzene as internal standard. [c]ee determined by chiral GC.

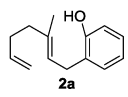
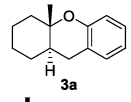
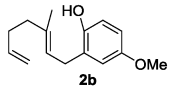
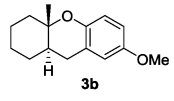
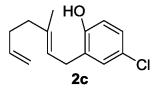
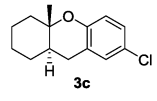
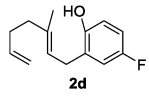
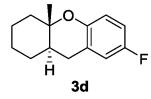
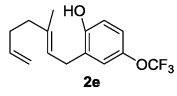
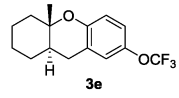
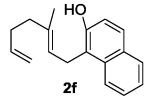
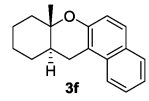
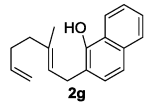
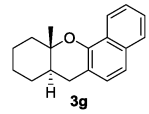
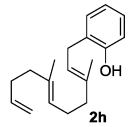
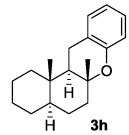
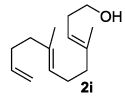
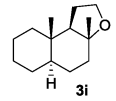
The reaction outcome depends strongly on the choice of solvent, with nonpolar solvents being hampered by poor catalyst solubility.[18] Polar, noncoordinating solvents like nitromethane and nitroethane provided the highest conversion to **3a** (entries 3 and 4, Table 2), whereas CH_2Cl_2 provided only traces of **3a** (entry 5) due to the formation of inactive (PyBOX)Pt−Cl^+ by chloride abstraction from the solvent. A polar, coordinating solvent such as acetonitrile (entry 6) competitively coordinates to the dicationic platinum catalyst and hinders access to the free coordination site on platinum. The identity of the counterion in the silver salt was unimportant, and lower temperatures did not improve the ee (0 °C, 40% ee).

Using the optimum conditions, a series of PyBOX ligand variants were examined (Chart 1). Across the series steric effects were found to principally impact catalyst reactivity. Illustrative was **1a** and **1f** with oxazoline *iso*-Pr and *tert*-Bu groups at C2. The former gave high conversion, although the latter was unreactive even at elevated temperature (entries 3 and 8, Table 2). Some sensitivity to the C3-geminal alkyl group was also noted for **1a**, **1h** (R = Me, entry 9), **1i** (R = Et, entry 10), and **1k** (R = Ph, entry 11). As the bulkiness of the C3 substituents increased, sharp drops in reactivity were noted, with side products (e.g., **4**) forming for the slower reactions. Consistent with unpublished studies showing the necessity of a dicationic platinum cyclization initiator, the anionic ligand **1n** did not consume substrate (entry 12). Among all screened ligands, only **1h** was comparable to **1a**, but the latter's commercial availability made it the preferred choice.

The optimized condition was subsequently applied to a variety of dienyl and trienyl phenols and alcohols using the syringe pump method (Table 3). In all cases, the reaction went to completion with 10 mol % (*R*)-**1a**, and the products were obtained in a highly diastereoselective manner. Electron-withdrawing groups or electron-donating groups on the aryl gave products in good yield but lower enantioselectivity than **2a**. Both **3d** and **3e** were isolated in low yield due to their high volatility (entries 4 and 5, 86% and 83% GC yield, respectively). Triene alcohol and triene phenol substrates gave lower isolated yields than did **3a**.

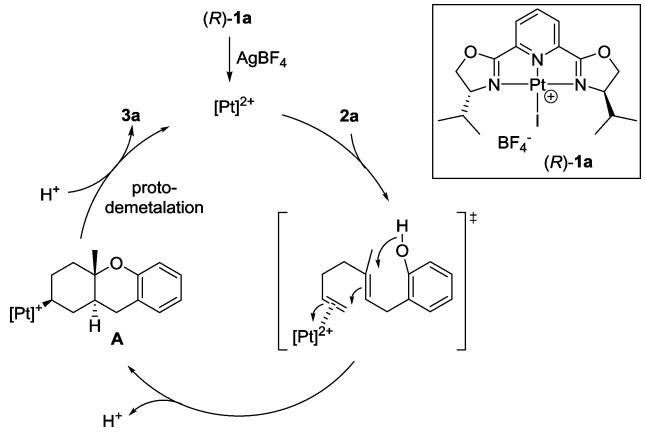
A proposed catalytic cycle is shown in Scheme 1. It includes the coordination of the (PyBOX)Pt^{2+} catalyst to the least-substituted C═C bond in the substrate, initiation of the

Table 3. Asymmetric Cycloisomerizations Catalyzed by (*R*)-(*i*-Pr-PyBOX)Pt^{2+}[a]

Entry	Substrate	Product[b]	Yield (%)[c]	ee (%)
1	 **2a**	 **3a**	93 (89[g])	37 (37[g])[d]
2	 **2b**	 **3b**	78	30[d]
3	 **2c**	 **3c**	85	26[d]
4	 **2d**	 **3d**	53 (86[f])	25[e]
5	 **2e**	 **3e**	49 (83[f])	27[e]
6	 **2f**	 **3f**	78	33[e]
7	 **2g**	 **3g**	84	31[d]
8	 **2h**	 **3h**	60	38[d]
9	 **2i**	 **3i**	65	32[d]

[a]Reaction conditions: catalyst (10 mol %), $AgBF_4$ (15 mol %), CD_3NO_2, rt, substrate added by syringe pump (see Supporting Information). [b]The absolute configuration of **3a** was assigned by comparing to an authentic sample of known configuration prepared from the hydrogenation of stereodefined *β*-hydride eliminated products.[7b] The remainder were assigned by analogy. [c]Isolated yield. [d]ee determined by chiral GC. [e]ee determined by chiral supercritical fluid chromatography. [f]GC yield. [g]1 mmol scale.

Scheme 1. Proposed Catalytic Cycle



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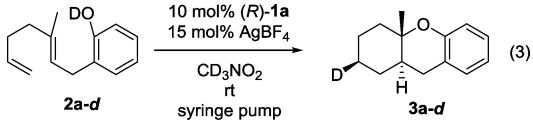
cascade to release a proton which rapidly protodemetalates the putative N_3Pt-alkyl$^+$ complex **A**, to generate the polycyclic product and turn over the catalytic cycle. Consistent with this scenario was the cyclization of **2a-*d***, which generates **3a-*d*** as a single diastereomer with deuterium residing at the C3 position of the **A** ring (sterol numbering) (eq 3). Attempts to isolate the



(3)

cationic complex **A** by quenching the reaction with a strong base such as styrene-bound piperidine, 2,4,6-*tert*-butylpyridine or proton sponge were not successful.

In summary, we have developed a new chiral platinum−PyBOX complex that is capable of the cyclization/protonation of polyenes to polycyclic structures with good yield, high diastereo-selectivity, and moderate enantioselectivity. These studies also demonstrate that changes in the hard/soft character of the ligands can significantly increase the tendency for (oxidatively-induced) protodemetalative reactions at a cationic Pt(II) center.[19] Studies to further understand this observation and to apply this finding to explore other turnover pathways are underway.

GENERAL PROCEDURE FOR PT(II)-CATALYZED CYCLOISOMERIZATION OF POLYENES

To a 3.5 mL vial with a septum cap was added (*R*)-[(*i*-Pr-PyBOX)PtI][BF_4] (71.0 mg, 0.1 mmol, 0.1 equiv) and $AgBF_4$ (29.2 mg, 0.15 mmol, 0.15 equiv) in CD_3NO_2 (0.5 mL). The resulting mixture was stirred in the dark for 1 h at room temperature. Substrate (1.0 mmol, 1.0 equiv) in CD_3NO_2 (1.0 mL) was loaded into a 1.0 mL Norm-Ject Plastic syringe. The syringe was then mounted to a Fisher Scientific Single Syringe Pump (model no. 14-831-200). The parameters of the syringe pump were set as the following: rate of 0.05 mL/h, volume of 1.0 mL, and diameter of 5.0 mm. The needle of the syringe was pierced through the septum cap of the vial containing the reaction mixture. The syringe pump was started with the above parameters. After the reaction was complete, the product was isolated from the reaction mixture by preparative thin-layer chromatography.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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