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Platinum(II) Catalysts for Highly Enantioselective 1,6-Enyne Cycloisomerizations. Synthetic, Structural, and Catalytic Studies

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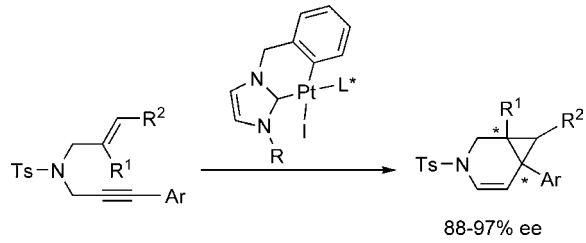
ABSTRACT



A new family of cyclometalated (*N*-heterocyclic carbene)-Pt^{II} complexes bearing monodentate phosphines as ancillary ligands has been designed for use as precatalysts in 1,6-enyne cycloisomerization reactions. Highly enantioselective skeletal rearrangements of allylpropargyl-tosylamide derivatives have been developed by using (*S*)-Ph-Binepine as the chiral auxiliary. Enantiomeric excesses up to 97% have been obtained.

Transition-metal-promoted enyne cycloisomerizations have emerged as highly useful tools for the synthesis of functionalized cyclic and heterocyclic compounds. Among them, a well-known class of reactions involves activation of the acetylenic moiety of the substrates by highly electrophilic metal derivatives, intramolecular addition of the olefin, and subsequent skeletal rearrangements to cyclic products, with no loss or gain of any atoms.[1] Owing to the outstanding synthetic potential of these transformations, the development of enantioselective protocols is a valuable challenge[2] that has met so far with limited success, at least as far as platinum catalysts are concerned.[3] With the aim of setting enantioselective variants of these enyne cycloisomerization reactions, we first envisioned the use as precatalysts of ligand-modified, square planar platinum(II) complexes bearing a single coordination site potentially available for substrate coordination.[4] These first-generation chiral catalysts were cationic platinum(II) complexes ((NHC)Pt(diphosphine)I$^+$I$^-$) com-

(1) (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215–236. (c) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916–5923. (d) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449. (e) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. (f) Jiménez-Núñez, E.; Echavarren, A. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371–384.

(2) Review: (a) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048–1052. For additional examples, see: (b) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104–4106. (c) Mikami, K.; Yusa, Y.; Hatano, M.; Wakabayashi, K.; Aikawa, K. *Chem. Commun.* **2004**, 98. (d) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018–9024. (e) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764–2765, and references therein.

(3) Chiral platinum catalysts have been applied so far only to cyclization reactions involving addition of nucleophiles to the enyne substrates: (a) Paz-Muñoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300. (b) Toullec, P. Y.; Chao, C. M.; Chen, Q.; Gladiali, S.; Genêt, J.-P.; Michelet, V. *Adv. Synth. Catal.* **2008**, *350*, 2401–2408, and references therein.

(4) The use of tri-coordinated platinum complexes in the related enantioselective diene cycloisomerization reactions has been introduced by Gagné *et al.*: Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290–13297.

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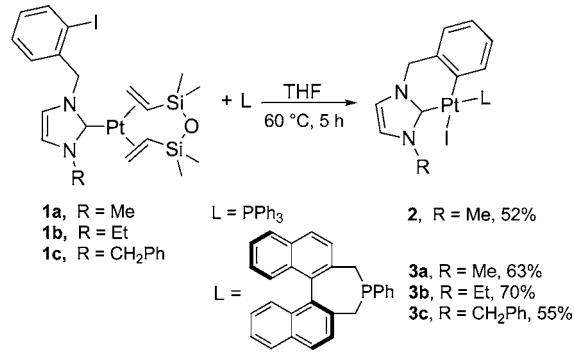
bining a monodentate imidazolylidene (NHC) and a chiral bidentate phosphine ligand.[5] Based on an analogous strategy, we disclose here the newly designed Pt^{II} complexes **3** as the first highly enantioselective platinum catalysts for 1,6-enyne cycloisomerization processes.

The new Pt^{II} complexes, **2** and **3** in Scheme 1, display a six-membered metallacyclic structure made of both a *N*-heterocyclic carbene-Pt and a σ-aryl-Pt bond. A monodentate phosphane occupies the third coordination site, while an arguably labile halide ion is the fourth platinum ligand. For the synthesis of the metallacyclic moieties we have envisioned intramolecular oxidative addition reactions on the *N*-(*o*-iodobenzyl)-imidazolylidene-$Pt^{(0)}$(dvtms) complexes **1**, which are easily available by adapting known methods.[6] Heating of **1a**−**c** in the presence of either PPh_3 or (*S*)-Ph-Binepine[7] in THF led to the desired complexes **2** and **3**, respectively, in good yields.

Scheme 1. Synthesis of Cyclometalated NHC-Phosphine-Pt^{II} Complexes



Complexes **3** were obtained as nonseparable mixtures of two isomers in approximate 8:2 ratios. An X-ray diffraction study on complex **3a** allowed unambiguous assignment of a *trans* relative arrangement of the phosphine and carbene ligands (Figure 1).

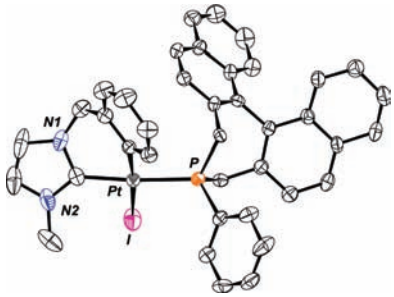


Figure 1. ORTEP view of the platinum(II) complex **3a**.

The same geometry can be tentatively assigned to complex **2**, as well as to both isomers of complexes **3b**,**c** since they all display $^2J_{P-C(carbene)}$ and/or $^1J_{P-Pt}$ coupling constants in the same range as that of **3a** ($^2J_{C-P} \approx 147$ Hz and $^1J_{P-Pt} \approx 2750$ Hz). The solid-state structure of complex **3a** displays a dihedral angle of 49° between the imidazolylidene moiety and the coordination plane with a δ-conformation of the six-membered platinacycle. Owing to this peculiar coordination mode of the unsymmetrical NHC moiety, the square planar complex **3a** displays axial chirality,[8] which combined with the presence of the enantiomerically pure phosphepine ligand is expected to generate diastereomeric pairs. Thus, the observed isomers of complexes **3a**−**c** can be tentatively assigned as epimeric complexes with opposite axial configurations.

The suitability of the new NHC/phosphine-ligated complexes as precatalysts for cycloisomerization reactions has been demonstrated at first by using the triphenylphosphine complex **2** as promoter for the 6-*endo-dig* skeletal rearrangement of *N*-tosyl allyl(3-phenylpropynyl)amine **4a** leading to the 3-azabicyclo[4.1.0]hept-4-ene **5a**[9] (Scheme 2 and Table 1, entry 1). At a 4 mol % catalyst loading, in the presence of $AgBF_4$ as the halide scavenger, quantitative conversion was observed after 20 h at 90 °C, with **5a** being the only product.

Scheme 2. Cycloisomerization Reactions Promoted by the Pt^{II} Complexes **2** and **3**

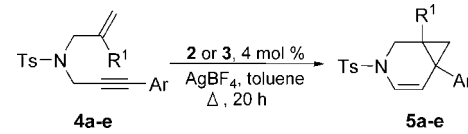


Table 1. Enantioselective Platinum-Catalyzed Cycloisomerizations of Allylpropargylamines

	substrate			catalyst	product	yield (%)[a]	ee (%)[b]
		R^1	Ar				
1	**4a**	H	Ph	**2**	**5a**	90	
2	**4a**	H	Ph	**3a**	**5a**	88	93
3	**4a**	H	Ph	**3b**	**5a**	81	94
4	**4a**	H	Ph	**3c**	**5a**	90	96
5	**4b**	H	3,5-$(Me_2)C_6H_3$	**3a**	**5b**	95	90
6	**4b**	H	3,5-$(Me_2)C_6H_3$	**3c**	**5b**	78	93
7	**4c**	H	4-MeO-C_6H_4	**3b**	**5c**	77	91
8	**4d**	H	4-NO_2-C_6H_4	**3c**	5d	51	97
9	**4e**	Me	Ph	**3b**	5e	93	81
10	**4e**	Me	Ph	**3c**	5e	98	88

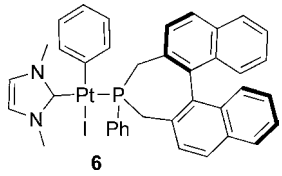
[a] Reaction performed at 60 °C, except for entry 1 to which a reaction temperature of 90 °C was applied. [b] By HPLC.

Based on this encouraging result, we next considered using chiral Pt^{II} complexes in the same reaction. Following a preliminary screening of a few monodentate phosphorus derivatives,[10] (*S*)-Ph-Binepine has been selected as the preferred chiral ligand. The Pt-phosphepine complexes **3a**−**c** displayed high catalytic activity and allowed the cycloisomerization of **4a** to be performed in rather mild conditions (60 °C). They afforded

the expected bicyclic compound **5a** in good yields, with total product selectivity and, most significantly, in very high enantiomeric excesses (entries 2−4 in Table 1).

The efficiency of the cyclometalated catalysts **3** was further assessed by cyclization experiments on the *N*-Ts propynylamines **4b**−**e**, which display either substituted aryl groups on the alkyne unit (entries 5−8) or a methyl substituent on the allyl moiety (entries 9 and 10). Yields for the isolated products **5b**−**e** were typically high, and good enantiomeric excesses (88−97%) were attained in all cases.

A few key structural features of complexes **3**, relevant to chiral induction, have been identified so far. So, the high enantioselectivity levels can be ascribed, at least in part, to the metallacyclic structure of the catalyst and its subsequent restricted conformational freedom, since the analogous acyclic complex **6** (Figure 2) afforded a racemic sample of **5a** under the reaction conditions of entry 2.



6

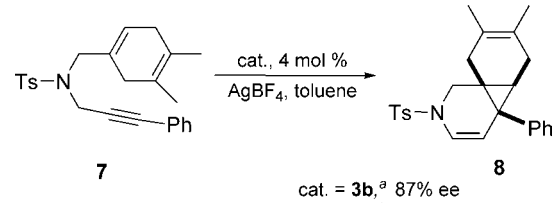
Figure 2. Molecular structure of complex **6**.

Moreover, based on the X-ray structure of **3a**, it could be anticipated that the R substituent of the imidazolylidene unit would play a role on the stereochemical course of the cyclization, because of its close proximity to the catalyst reaction site.[11] Only a small modulation of the enantioselectivity levels (93−96% ee) was observed when **3a** (R = Me), **3b** (R = Et), or **3c** (R = CH_2Ph) were used as catalysts in the cycloisomerization of **4a** (entries 2−4). A more pronounced effect was noticed, however, in the cycloisomerization of **4e**, where ee's of 81% and 88% were afforded by **3b** and **3c**, respectively (entries 9 and 10). Thus, modulation of the N substituent is likely to be a key parameter for future optimizations of analogous catalytic processes.

The substrate scope of this enantioselective cycloisomerization reaction seems to be restricted to aryl-substituted alkynes, since 2-butynamine derived enynes led to the corresponding cyclized products in ee's of <20%.

As an extension of the enantioselective approach to Pt-promoted cycloisomerizations developed here, the cycloisomerization of enyne **7**[12] bearing a cyclic olefinic moiety has been considered (Scheme 3).

Scheme 3. Enantioselective Cycloisomerization of Enyne **7**



7 **8**

cat. = **3b**,[a] 87% ee
3c,[b] 92% ee

Conditions: [a] T = 60 °C, 26% yield; [b] T = 90 °C, 40% yield

Catalysts **3** trigger the expected conversion of **7** into the tricyclic derivative **8** with high stereoselectivity levels (ee up to 92%). This result shows that substantial structural variations of the olefin function are accommodated by this new enantioselective process.

In conclusion, this work highlights the first known class of well-defined Pt^{II} complexes leading to highly enantioselective cycloisomerizations of representative enyne substrates. Further studies will explore the applications of these and analogous catalysts in stereoselective enyne skeletal rearrangements leading to different structural motifs.

Acknowledgment. We are very grateful to Dr. Thomas Riermeier and Dr. Renat Kadyrov (Evonik Degussa GmbH, Hanau, Germany) for a generous gift of (*S*)-Ph-Binepine.

Note Added after ASAP Publication. There was an error in Scheme 1 in the version published April 17, 2009; the corrected version was published April 23, 2009.

Supporting Information Available: Complete experimental procedures, characterization data, ee determinations, and crystallographic data for **3a** (CCDC 713409). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The use of (*S*,*S*)-Chiraphos as the ligand allowed enantiomeric excesses up to 74% to be attained in the model allylpropargylamine cycloisomerization reaction of Scheme 2 for R^1 = H and Ar = Ph. (a) Brissy, D.; Skander, M.; Retailleau, P.; Marinetti, A. *Organometallics* **2007**, *26*, 5782–5785. (b) Brissy, D.; Skander, M.; Retailleau, P.; Frison, G.; Marinetti, A. *Organometallics* **2009**, *28*, 140–151.

(6) Berthon-Gelloz, G.; Buisine, O.; Brière, J.-F.; Michaud, G.; Stérin, S.; Mignani, G.; Tinant, B.; Declercq, J.-P.; Chapon, D.; Markó, I. E. *J. Organomet. Chem.* **2005**, *690*, 6156–6168.

(7) (a) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron:Asymmetry* **1994**, *5*, 511–514. (b) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*, 4977–4980.

(8) For discussions on the axial chirality in square-planar carbene metal complexes, see: Enders, D.; Gielen, H. *J. Organomet. Chem.* **2001**, *617*−*618*, 70–80.

(9) For analogous reactions promoted by $PtCl_2$ or platinum complexes, see: (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316. Asymmetric Ir-promoted cyclisations of analogous enyne substrates have been described in ref 2d.

(10) Analogous Pt^{II} complexes with (*S*)-Monophos as the ligand also provide promising catalysts for the cycloisomerization reactions of Scheme 2. Compared to the phosphepine complexes **3**, the Monophos complexes display improved catalytic activities but slightly lower enantiomeric excesses. Quantitative conversion rates (92% and 88% isolated yields) and enantiomeric excesses of 75% and 84% have been obtained in the reactions of entries 2 and 5 in Table 1, respectively. The enantioselectivity levels were found to be largely temperature independent in a 40−90 °C range.

(11) With the assumption that the initial geometry is retained in the tricoordinated intermediate formed by halide abstraction.

(12) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, *71*, 9366–9372.