Platinum Catalysis

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A Highly Strained Planar-Chiral Platinacycle for Catalytic Activation of Internal Olefins in the Friedel–Crafts Alkylation of Indoles**

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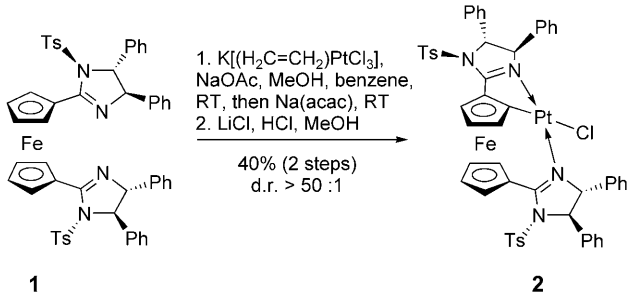
Platinum(II)[1] and gold(I)[1a,2] catalysis have experienced significant growth over the past five years, as these late transition metals have the ability to catalyze atom economical reactions of unactivated alkynes, olefins, or allenes, creating a significant increase in the molecular complexity of a single synthetic step by using simple starting materials. The catalysts are compatible with most functional groups because of their low oxophilicity, and they are usually robust towards moisture or air. Platinum(II)–olefin complexes are reported to be highly reactive toward outer-sphere attack by nucleophiles, and the resulting platinum(II)–alkyl complexes undergo rapid protonolysis[3] with Brønsted acids rather than β-hydride elimination, which is the preferred pathway for palladium(II)–alkyl complexes. In contrast, π-ligand exchange is relatively slow for platinum(II) complexes.[1] Catalysts allowing a more rapid ligand exchange could lead to enhanced activity of this expensive metal and potentially expand the scope of the reaction to additional applications. Due to the reactivity issue and despite considerable progress made in this field, the asymmetric activation of π ligands by gold or platinum complexes is still an area with the potential for development.[1]

Recently we found that ferrocene imidazoline mono- and bispalladacycle complexes have the ability to efficiently differentiate enantiotopic olefin faces.[4] The homologous platinacycles could have similar properties. We hypothesized that a ligand exchange acceleration might be achieved by structural distortion of the square planar geometry around platinum(II) (ground-state destabilization). To develop a platinum(II) complex with increased activity, we designed the monoplatinacycle complex **2** in which the Pt^{II} center binds to two imidazoline units (Scheme 1): one connected to the same Cp plane as the metal, and the second one connected to the Cp′ ligand, potentially resulting in severe structural distortion by coordination.



Scheme 1. Formation of the strained complex **2** by diastereoselective cycloplatination.

When $[(dmso)_2PtCl_2]$ was used it resulted in negligible product formation, cycloplatination[5] of bisimidazoline **1**[6] occurred—accompanied by partial ferrocene oxidation—upon treatment with $K[(H_2C{=}CH_2)PtCl_3]$, initially forming an inseparable mixture of monomer **2** and a major product, which is likely to be represented by a Cl-bridged dimer (*cis*/*trans* isomers around the Pt square plane). Treatment of the reaction mixture with Na(acac) (acac = acetylacetonate) completely converts both the monomer and the dimer into the same monomeric acac complex, which provides the diastereomerically pure **2** after treatment with LiCl and HCl. To our knowledge, this is the first example of a highly diastereoselective, direct cycloplatination of an enantiopure ferrocene derivative.[7] The constitution and configuration of **2** were confirmed by X-ray crystallographic analysis (Figure 1).[8] Both imidazoline units coordinate to the same Pt center in a *trans* fashion, resulting in a unique geometry in which the C atom connected to the metal center is strongly pyramidalized (angle between the upper Cp plane in Scheme 1 and the Cp–Pt bond: 159°, deviation of the Pt atom from the upper Cp plane in Scheme 1: 0.74 Å). The central metal adopts a distorted square planar geometry having a close contact distance between Pt and Fe of 3.19 Å. This complex can be described as a planar-chiral pincer complex as it has a terdentate monoanionic ligand.

To establish proof of principle for the enhanced reactivity of such a distorted catalyst system, the intramolecular Friedel–Crafts alkylation using unactivated olefins was selected. Atom economical hydroarylation reactions of olefins provide an attractive platform to prepare partially saturated poly(hetero)cyclic aromatic compounds. Asymmetric transition-metal-catalyzed methodologies are rare. Ellman et al. described efficient rhodium(I)-catalyzed intramolecular hydroarylations by using an imine directing group on the aromatic substrates for C–H activation.[9] Widenhoefer et al.

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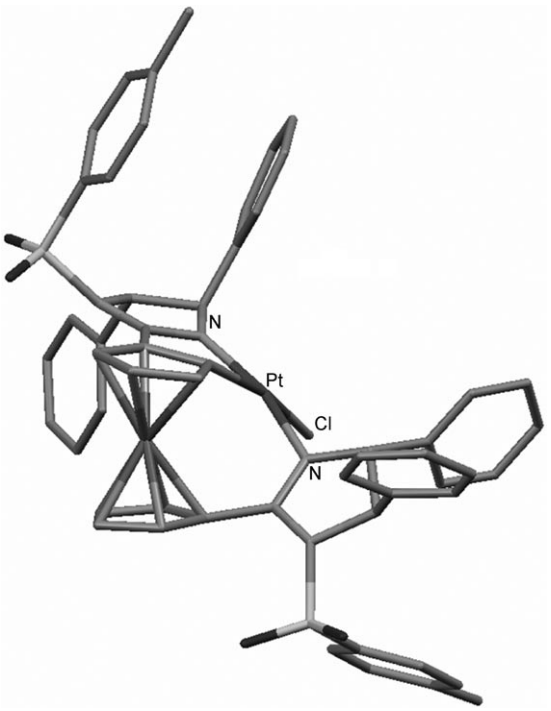
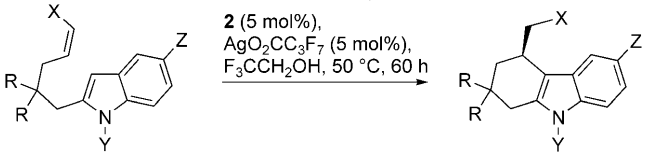


Figure 1. X-ray crystal structure of the strained platinacycle **2**.

Table 1: Intramolecular Friedel–Crafts alkylation of indoles.



3 **4**

#	**4**	R	X	Y	Z	Yield [%][a]	*ee* [%][b]
1	**a**	CO_2Me	Et	Me	H	95	82
2	**b**	CO_2Bn	Et	Me	H	90	86
3	**c**	CO_2tBu	Et	Me	H	85	90
4	**d**	$CH_2OC(O)t$Bu	Et	Me	H	68	78
5[c]	**e**	CO_2tBu	Me	Me	H	92	88
6	**f**	CO_2tBu	*n*Pr	Me	H	90	89
7	**g**	CO_2tBu	*i*Bu	Me	H	45	89
8	**h**	CO_2tBu	Ph	Me	H	70	84
9	**i**	CO_2tBu	Et	Et	H	92	92
10	**j**	CO_2tBu	Et	*i*Pent	H	90	85
11	**k**	CO_2Me	Et	allyl	H	50	83
12	**l**	CO_2tBu	Et	Me	F	85	92
13[d]	**m**	CO_2tBu	Et	Me	Cl	70	85
14	**n**	CO_2tBu	Et	Me	Me	85	80
15	**o**	CO_2tBu	Et	Me	OMe	92	80

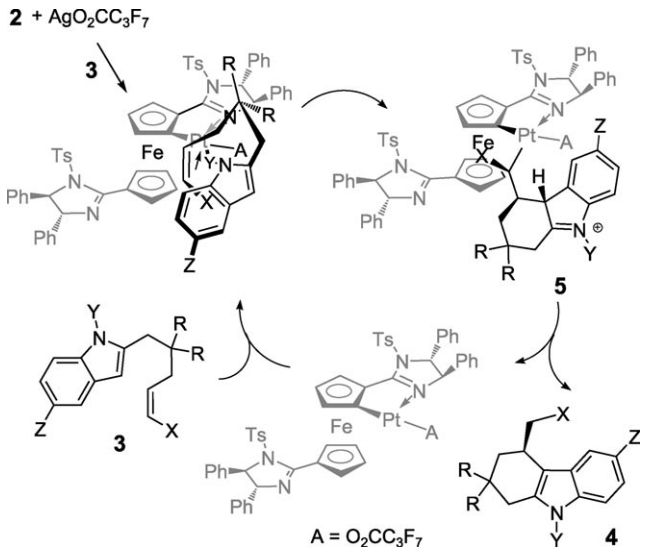
[a] Yield of isolated products. 30 mg scale (entries 2–15) and 200 mg scale (entry 1). [b] Determined by HPLC methods. [c] 3:1 mixture of *Z*/*E*-**3e**. [d] Reaction temperature of 60 °C.

developed a conceptually different approach,[10] in which a cationic platinum(II)–bisphosphine complex activated a terminal olefin for the nucleophilic outer-sphere attack by an indole moiety to provide biologically interesting, partially saturated carbazole derivatives.[11] Previously, internally disubstituted alkenes failed to undergo platinum-catalyzed enantioselective hydroarylations of indoles,[12] therefore, these challenging substrates were investigated herein.

Platinacycle **2** is in fact sufficiently active to catalyze this hydroarylation process (Table 1). The optimization of the reaction conditions for *Z*-configured internal olefin substrate **3a**, bearing an ethyl group (X) on the olefin, revealed a strong solvent influence (see the Supporting Information). The highest reactivity was obtained in 2,2,2-trifluoroethanol whereas either no or poor conversion was obtained in common solvents such as MeOH, CH_2Cl_2, 1,4-dioxane, acetone, or nitromethane. Catalyst activation by a silver salt increased the activity but had almost no impact on the enantioselectivity of the reaction. The highest reactivity was obtained by activating **2** in situ using $AgO_2CC_3F_7$, which delivered the target product, after 60 h at 50 °C, in 95 % yield and with 82 % *ee* (Table 1, entry 1). In contrast, *E*-**3a** did not react at all under the same conditions, implying that geometrically pure substrates are not necessary to obtain high enantioselectivities. The corresponding platinacycle with only one imidazoline unit provided **4a** in poor yield, albeit with 74 % *ee* under identical reaction conditions.

To facilitate the substrate formation, the indoles **3** were prepared by sequential malonate alkylation (see the Supporting Information). By using **3c**, derived from di-*tert*-butyl malonate, the product was formed with a slightly higher *ee* value of 90 % and in a yield of 85 % (Table 1, entry 3). Variation in the alkene substituent X had almost no influence on the enantioselectivity: Me (*Z*/*E* 3:1),[13] Et, *n*Pr, and *iso*-butyl gave nearly identical *ee* values (88–90 %, Table 1, entries 3, 5–7), whereas a Ph group resulted in a slight decrease (Table 1, entry 8). Similarly, variation of the indole N-alkyl substituent was tolerated (Table 1, entries 9–10) with the exception of an allyl group (Table 1, entry 11) which led to significantly lower activity presumably as a result of catalyst inhibition by competing olefin coordination. Both electron-withdrawing and electron-donating substituents Z on the aromatic core afforded smooth conversions and similar enantioselectivity (Table 1, entries 12–15) despite the projected difference in the indole nucleophilicity, which might indicate that C–C bond formation is not the rate-determining step.

The generally observed high enantioselectivity can be rationalized by the mechanistic proposal depicted in Scheme 2. The stereoselectivity depends at least in part on the enantiofacial selectivity of the alkene coordination. In analogy to our palladacycle catalysts, the olefin moiety is expected to bind *trans* to the upper imidazoline moiety (*trans* effect)[4,6] thereby releasing the catalyst strain.[14] Coordination at this position may, in principal, afford four different isomers, assuming the stereoelectronically preferred perpendicular orientation of the alkene to the platinum(II) square plane. In the coordination mode shown, steric repulsion between both olefin substituents and the ferrocene moiety is minimized. Outer-sphere attack by the indole core results in the formation of Pt–alkyl complex **5**. It is not yet clear if the imidazoline moiety liberated by the olefin coordination is involved in the subsequent proton transfer, possibly acting as a shuttle by abstracting the acidic proton on the C atom adjacent to the C=N double bond and transferring it to the



Scheme 2. Proposed mechanism for the intramolecular Friedel–Crafts alkylation of indoles.

Pt–C bond. The suggested mechanism is in line with the absolute configuration of a sulfonate derivative prepared from **4a** as determined by X-ray crystal structure analysis (see the Supporting Information).[8]

In summary, we have developed a platinum(II) catalyst which enables the enantioselective intramolecular Friedel–Crafts alkylation of indoles having disubstituted internal olefins. Adequate reactivity was accomplished through the design of a highly strained planar-chiral platinacycle, presumably providing an accelerated olefin coordination step. The catalyst was prepared by the first highly diastereoselective cycloplatination of an enantiopure ferrocene affording the first highly enantioselective application of a platinacycle in catalysis, in particular for olefin activation.[14] Application of this new catalyst to other reactions involving olefin and alkyne π-bond activation is currently being investigated.

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