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A “Hard/Soft” Mismatch Enables Catalytic Friedel–Crafts Acylations

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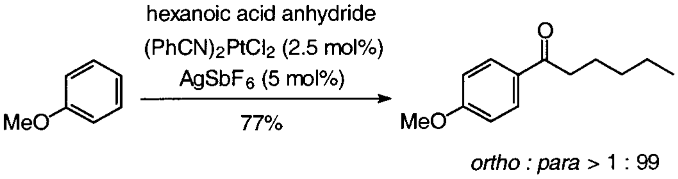
ABSTRACT



Cationic complexes of Pt(II) and other late transition metals efficiently catalyze Friedel–Crafts acylations of moderately activated arenes by carboxylic acid anhydrides. The nature of the catalytically relevant species formed from $(PhCN)_2PtCl_2$ and $AgSbF_6$ and their interactions with the substrates are studied by NMR and ESI-MS.

The Friedel−Crafts acylation (FC-acylation) of arenes leading to aromatic ketones is a transformation of significant industrial importance.[1] The fact that (over) stoichiometric amounts of Lewis acids such as $AlCl_3$, BF_3, $TiCl_4$, or $SnCl_4$ are required, however, constitutes a serious drawback since these oxophilic promoters are a significant cost factor and cause environmental problems due to strongly acidic waste streams. The development of truly catalytic alternatives is therefore highly desirable and constitutes a field of current interest.

Considerable progress in this direction has been made in recent years. Most notable are the introduction of lanthanide triflates[2] and related complexes[3] as well as the use of catalytically competent binary Lewis acid mixtures.[4,5] Although these reagents exhibit an excellent application profile in many acylation reactions, catalyst loadings of ≥ 10% are frequently required. Moreover, some recipies are based on very moisture sensitive reagents such as $SiCl_4$, $SbCl_5$, $B(OTf)_3$, and $TiCl(OTf)_3$ that are difficult to handle and require rigorously anhydrous reaction media.

Herein we report an alternative approach toward catalytic FC-acylations. The new protocol employs only air stable

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(1) (a) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: London, 1973. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 773. (c) For a timely and comprehensive treatise, see: *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000.

(2) See the following for leading references: (a) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun*. **1993**, 1157. (b) Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun*. **1996**, 183. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1998**, *120*, 2985. (d) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545. (e) Kobayashi, S.; Komoto, I. *Tetrahedron* **2000**, *56*, 6463. (f) Reetz, M. T.; Giebel, D. *Angew. Chem*. **2000**, 112, 2614; *Angew. Chem., Int. Ed.* **2000**, *39*, 2498.

(3) (a) Matsuo, J.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403. (b) Kobayashi, S.; Iwamoto, S. *Tetrahedron Lett*. **1998**, *39*, 4697. (c) Desmurs, J. R.; Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett*. **1997**, *38*, 8871. (d) Barrett, A. G. M.; Braddock, D. C.; Chadwick, D.; Catterick, D.; Henschke, J. P.; McKinnell, R. M. *Synlett* **2000**, 847. (e) Nishikido, J.; Nakajima, H.; Saeki, T.; Ishii, A.; Mikami, K. *Synlett* **1998**, 1347. (f) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H.; Maruta, M. *Synlett* **1996**, 171. (g) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc*. **1988**, *110*, 2560.

(4) (a) Izumi, J.; Mukaiyama, T. *Chem. Lett*. **1996**, 739. (b) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 2053. (c) Suzuki, K.; Kitagawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3729. (d) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Suda, S.; Kobayashi, S. *Chem. Lett*. **1991**, 1059. (e) Mukaiyama, T.; Suzuki, K.; Han, J. S.; Kobayashi, S. *Chem. Lett*. **1992**, 435. (f) Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *Chem. Lett*. **1986**, 165.

(5) For further methods, see: (a) Kusama, H.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 2379. (b) Effenberger, F.; Epple, G. *Angew. Chem*. **1972**, *84*, 295. (c) Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber*. **1983**, *116*, 1195. (d) Effenberger, F.; Steegmüller, D. *Chem. Ber*. **1988**, *121*, 117. (e) Pivsa-Art, S.; Okuro, K.; Miura, M.; Murata, S.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1703. (f) Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533. (g) Hino, M.; Arata, K. *Chem. Lett*. **1978**, 325. (h) Nomiya, K.; Sugaya, Y.; Sasa, S.; Miwa, M. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 2089. (i) Yamaguchi, T.; Mitoh, A.; Tanabe, K. *Chem. Lett*. **1982**, 1229. (j) Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P.; Graille, J.; Pioch, D. *J. Org. Chem*. **1986**, *51*, 2128.

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ingredients and is therefore distinguished by its practicality, by good turn-over numbers, and by a reasonably wide scope.[6]

Conventional promoters for FC-acylations are highly oxophilic Lewis acids that remain coordinated to the aryl ketones formed. We reasoned that it might be possible to overcome this product inhibition by using *late* transition metals salts as the catalysts: a mismatch between their “soft” metal center and the “hard” carbonyl oxygen atoms of the products should avoid the formation of kinetically inert complexes and thus result in catalytic turn-overs. Although late transition metal salts exhibit, a priori, rather poor Lewis acidity, sufficient reactivity can be gained by rendering them cationic.[7]

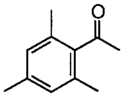
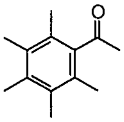
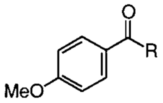
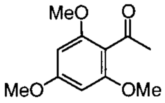
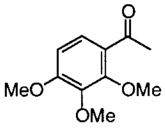
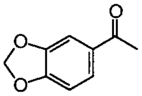
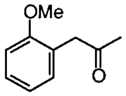
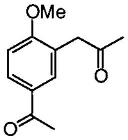
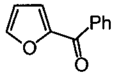
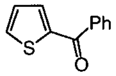
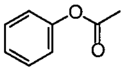
Encouraged by our excellent experiences with $PtCl_n$ (n = 2, 4) as catalyst for various C−C bond forming reactions,[8,9] we screened different platinum salts for their ability to promote the acylation of anisole by acetic acid anhydride. While $PtCl_2$, $PtCl_4$, and neutral L_2PtCl_n complexes (L = PhCN, PPh_3, $P(C_6F_5)_3$, PEt_3, COD) showed no appreciable activity (entries 1, 3, 13, 15), excellent results were obtained after treatment with AgX (Table 1).[10] Thereby, a pronounced influence of the counterion X was observed, with SbF_6 > ClO_4 > OTf ≫ PF_6, BF_4, OAc (entries 4−9). Similarly, the reaction medium plays an important role in ensuring catalytic turn-over, with CH_2Cl_2 being the solvent of choice.[11] Under these optimized conditions, as little as 1 mol % of $(PhCN)_2PtCl_2$ and 2 mol % of $AgSbF_6$ are necessary to obtain 4-methoxyacetophenone in 75% isolated yield (entry 4, footnote c).

Table 1. Comparison of the Catalytic Activity of Neutral and Cationic Pt Reagents in the Acylation of Anisole by Ac_2O. All Reactions Were Carried Out in Refluxing CH_2Cl_2 for 20 h[a]

entry	Pt compound (2.5 mol %)	additive (5 mol %)	yield (%)
1	$PtCl_2$		0
2		$AgSbF_6$	47
3	$(PhCN)_2PtCl_2$		0
4		$AgSbF_6$	75[b,c]
5		$AgClO_4$	56
6		AgOTf	33
7		$AgPF_6$	19
8		$AgBF_4$	5
9		AgOAc	4
10	$(PPh_3)_2PtCl_2$	$AgSbF_6$	65
11	$(COD)PtCl_2$	$AgSbF_6$	80
12	$[P(C_6F_5)_3]_2PtCl_2$	$AgSbF_6$	68
13	$PtCl_4$		23
14		$AgSbF_6$	80
15	$(PEt_3)_4PtCl_4$		0
16		$AgSbF_6$	72

[a] The ratio of *para*:*ortho* substitution is ≥99:1 in all cases (GC). [b] If only 2.5 mol % of $AgSbF_6$ is used, the FC-acylation proceeds similarly well (67% isolated yield). [c] The same result (75% yield) is obtained with only 1 mol % of $(PhCN)_2PtCl_2$ in combination with 2 mol % of $AgSbF_6$ after a prolonged reaction time (72 h).

Table 2. Acylations of Arenes by Different Carboxylic Acid Anhydrides Catalyzed by $(PhCN)_2PtCl_2$ (2.5 mol %) and $AgSbF_6$ (5 mol %)[a]

entry	arene	product	yield (%)
1	mesitylene		76
2	pentamethylbenzene		70
3 4 5	anisole		75 (R = Me) 77 (R = Ph) 77 (R = C_5H_{11})
6	1,3,5-trimethoxybenzene		70
7	1,2,3-trimethoxybenzene		62
8	methylenedioxybenzene		61
9			61
10	furan		80
11	thiophene		92
12	phenol		76

[a] All reactions were carried out in refluxing CH_2Cl_2 as the reaction medium until complete conversion of the substrate was observed by TLC (<24 h).

Representative FC-acylation reactions catalyzed by $(PhCN)_2$-$PtCl_2/AgSbF_6$ are summarized in Table 2. Although toluene is acylated only slightly under these conditions, the reaction works well with moderately or strongly activated arenes. Even the sterically hindered position in pentamethylbenzene is smoothly acylated. Heterocycles such as furan or thiophene are equally well suited. *N*,*N*-Dimethylaniline or indole, however, do not react, most likely because the catalytically

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[6] For previous studies from this laboratory on the evolution of transition metal promoted transformations into catalytic processes, see: (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (d) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567.

relevant cationic Pt(II) species are inhibited by coordination with the N atoms of these substrates. Carboxylic acid anhydrides other than Ac_2O can be used with similar efficiency (entries 4, 5, 10, 11). It is also worth mentioning that phenol is *O*- rather than *C*-acylated under these conditions (entry 12).

To study the scope of the proposed "hard/soft-mismatch" principle, a variety of other transition metal salts have also been screened (Table 3). Among them, the combination of $(MeCN)_2PdCl_2$ and $AgSbF_6$ shows appreciable activity, although the reaction rate is significantly lower than with the corresponding platinum system. Good results are obtained with $[RuCl_2(CO)_3]_2$ or $CuCl_2{\cdot}2[P(C_6F_5)_3]$ in combintion with $AgSbF_6$. Even better is a mixture of $RuCl_3$ and AgX, affording the desired product in up to 81% yield. Since the commercial hydrate of $RuCl_3$ is used for solubility reasons, however, it cannot be excluded that traces of HX (X = OTf, SbF_6) are formed under these conditions which may themselves be catalytically relevant.[12] Despite this ambiguity, $RuCl_3{\cdot}(H_2O)_n$ is an attractive pre-catalyst due to its comparatively low cost and because the solvents need not be rigorously dried.

Table 3. Acylation of Anisole by Ac_2O: Screening of the Catalytic Activity of Various Transition Metal Salts (2.5 mol %) in the Presence of AgX (5 mol %). All Reactions Were Carried out in Refluxing CH_2Cl_2 unless Stated Otherwise

no.	metal salt	AgX	*t* (h)	yield (%)
1	(COD)CuCl	$AgSbF_6$	20	58
2	$CuCl_2{\cdot}2[P(C_6F_5)_3]$	$AgSbF_6$	20	78
3	$(MeCN)_2PdCl_2$	$AgSbF_6$	72	75
4	$RhCl(CO)(PPh_3)_2$	$AgSbF_6$	20	2
5	$[RuCl_2(CO)_3]_2$ [a]	$AgSbF_6$	72	79
6	$RuCl_3{\cdot}(H_2O)_n$ [b]		21	31
7	$RuCl_3{\cdot}(H_2O)_n$ [c]	$AgBF_4$ [c]	21	80
8	$RuCl_3{\cdot}(H_2O)_n$ [d]	AgOTf	48	45
9	$RuCl_3{\cdot}(H_2O)_n$	$AgSbF_6$	20	81
10	$RhCl_3{\cdot}(H_2O)_n$ [e]	$AgBF_4$ [e]	21	70
11	$Hg(ClO_4)_2{\cdot}(H_2O)_n$ [f]		21	73

[a] Using only 1.25% of the dimeric complex. [b] 8 mol % in CH_3NO_2 at 50 °C. [c] 8 mol % (each metal) in CH_3NO_2 at 50 °C. [d] 5 mol %. [e] 10 mol % (each metal) in CH_3NO_2 at 50 °C. [f] 5 mol % in CH_3NO_2 at 50 °C.

Spectroscopic investigations provide some insights into the nature of the catalytically relevant species as well as into their interactions with the substrates. Whereas addition of $(PhCN)_2PtCl_2$ (1 equiv) to either Ac_2O or anisole causes only marginal changes in the IR and ^{13}C NMR spectra of these reagents, exposure to the cationic species generated from $(PhCN)_2PtCl_2/2AgSbF_6$ leads to strong effects.[13] The observed shifts for Ac_2O (Table 4) are in accordance with the expected complexation of its carbonyl function onto a Lewis acidic agent ($\Delta\delta = +2.4$ ppm; $\Delta\nu = -31/-50$ cm^{-1}), whereas a *significant upfield* shift is noticed for C(*para*) of anisole ($\Delta\delta = -5.9$ ppm), indicating a *higher electron density* at the position undergoing FC-acylation (Table 5). The signal of H-4 is fully preserved in the ^1H NMR spectrum. These results are best interpreted in terms of a preferred coordination of anisole via the π-system rather than the ether oxygen although the precise hapticity of binding cannot yet be unambiguously deduced. It is conceivable that such an intermediate undergoes reversible electrophilic substitution with formation of a *para*-substituted Pt−arene complex.[14−16]

Table 4. Characteristic Changes in the IR ($\Delta\nu$, cm^{-1}) and ^{13}C NMR Spectra ($\Delta\delta$, ppm) of Acetic Anhydride upon Addition of a Neutral or a Cationic Pt(II) Complex (1 equiv of each) to a Solution in CD_2Cl_2

	$(MeCN)_2PtCl_2$	$(MeCN)_2PtCl_2/2AgSbF_6$
$\Delta\delta$(C=O)	−0.03	+2.4
$\Delta\nu$(C=O)	±0	−31/−50

Table 5. Changes ($\Delta\delta$, ppm) in the ^{13}C Chemical Shifts of Anisole upon Addition of a Neutral or a Cationic Pt(II) Complex (1 equiv. each) to a Solution in CD_2Cl_2

	$(MeCN)_2PtCl_2$	$(MeCN)_2PtCl_2/2AgSbF_6$
C(quart.)	−0.06	+1.7
C(*ortho*)	−0.05	+0.4
C(*meta*)	+0.08	−1.2
C(*para*)	−0.04	−5.9
OMe	−0.02	+0.5

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(7) For previous applications of cationic Pd(II) or Pt(II) complexes in synthesis, see: (a) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463. (b) Kataoka, Y.; Matsumoto, O.; Ohashi, M.; Yamagata, T.; Tani, K. *Chem. Lett.* **1994**, 1283. (c) Ghosh, A. K.; Matsuda, H. *Org. Lett*. **1999**, *1*, 2157. (d) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem*. **1999**, *64*, 8660. (e) Nieddu, E.; Cataldo, M.; Pinna, F.; Strukul, G. *Tetrahedron Lett*. **1999**, *40*, 6987. (f) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett*. **1998**, *39*, 6253. (g) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc*. **1998**, *120*, 2474. (h) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc*. **1998**, *120*, 4548. (i) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 2648. (j) Cataldo, M.; Nieddu, E.; Gavagnin, R.; Pinna, F.; Strukul, G. *J. Mol. Catal. A: Chem*. **1999**, *142*, 305. (k) Gorla, F.; Venanzi, L. M. *Helv. Chim. Acta* **1990**, *73*, 690. (l) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem*. **1999**, *64*, 5017. (m) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

(8) (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc*. **1998**, *120*, 8305. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc*. **2000**, *122*, 6785.

(9) Fürstner, A.; Voigtländer, D. *Synthesis* **2000**, 959.

(10) Several control experiments have shown that AgX (X = SbF_6, OTf, ClO_4, BF_4, PF_6) itself is not responsible for the observed catalytic activity in any of these cases.

(11) A screening of different solvents in the acylation of anisole by Ac_2O catalyzed by $PtCl_2(PhCN)_2$ (2.5 mol %) and $AgSbF_6$ (5 mol %) gave the following results: CH_2Cl_2 (75%), $CHCl_3$ (56%), CH_3NO_2 (63%), MeCN (3%), THF (0%).

(12) Triflic acid is known to catalyze various FC acylations, cf. refs 5b, 5c, 5d, and literature cited therein.

(13) Precipitated AgCl was filtered off under Ar prior to these spectroscopic investigations.

(14) Note, however, that neutral Pt(II) triflate (trifluoroacetate) salts complexed by phosphines do *not* undergo electrophilic substitution of arenes, cf: (a) Brainard, R. L.; Nutt, W. R.; Lee, T. R.; Whitesides, G. M. *Organometallics* **1988**, *7*, 2379. (b) Peters, R. G.; White, S.; Roddick, D. M. *Organometallics* **1998**, *17*, 4493.

Such a species, although not present in detectable amounts, could be so reactive toward the acylating agent that *ipso*-substitution may well proceed rapidly. However, this is only one of several mechanistic possibilities, and further studies are necessary before final conclusions can be made.

ESI-MS investigations were carried out to characterize the dominant Pt(II) species in solution.[17] Careful analyses of a mixture of $PtCl_2(PhCN)_2$ and $2AgSbF_6$ in CH_2Cl_2 allowed us to identify the following cationic Pt(II) complexes: $[(PhCN)_2PtCl]^+$ (**I**), $[(PhCN)_3PtCl]^+$ (**II**), and $[(PhCN)_2PtCl(AgCl)]^+$ (**III**). Upon addition of anisole to the reaction mixture, the chloride-free Pt(II) complex $[(PhCN)_2Pt(C_6H_5OMe\text{-}H)]^+$ (**IV**) (Figure 1) is observed which derives from complex **I** and C_6H_5OMe via loss of HCl.[18,19] If the same experiment is carried out with an anisole sample that is selectively mono-deuterated at the *para*-position (deuterium incorporation > 98%),[20] the same complex **IV** *devoid of any deuterium label* is observed. This result shows that it is H-4, i.e., the proton resident at the position being acylated in the presence of an acid anhydride, that is rendered kinetically labile by interaction with the Lewis acidic platinum center.

Although a more detailed understanding of the present catalytic system must await further in-depth studies, the NMR and ESI-MS data summarized above prove that cationic Pt(II) entites reversibly activate the anhydride as well as the arene. The question as to which extent both effects must be operative to ensure efficient FC-acylations is subject to further investigations in this laboratory.

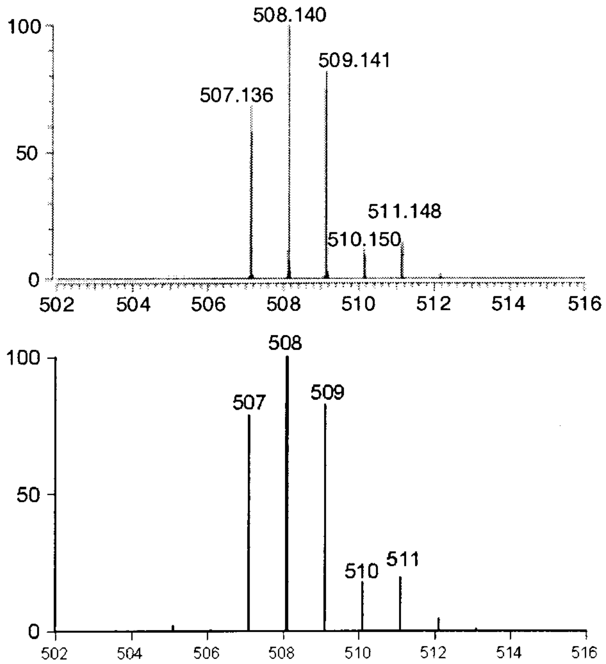

Figure 1. Comparison of the experimentally observed (top) and the calculated (bottom) isotope distribution patterns of the ESI-MS peak assigned to complex $[(PhCN)_2Pt(C_6H_5OMe)\text{-}H]^+$ (**IV**).

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[15] $Sc(OTf)_3$ has been shown to undergo reversible electrophilic substitution of arenes: Bisi Castellani, C.; Perotti, A.; Scrivanti, M.; Vidari, G. *Tetrahedron* **2000**, *56*, 8161.

[16] HgX_2 salts are known to induce electrophilic mercuration of arenes, cf.: (a) Olah, G. A.; Yu, S. H.; Parker, D. G. *J. Org. Chem.* **1976**, *41*, 1983. (b) Borovik, A. S.; Bott, S. G.; Barron, A. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 4117.

[17] The ESI MS spectra were recorded on an Ionspec Ultima high-resolution FT-MS spectrometer.

[18] In addition to **IV**, the methanol adducts $[(PhCN)_nPt(C_6H_5OMe\text{-}H)(MeOH)]^+$ ($n = 1, 2$) derived thereof as well as $[(PhCN)_2Pt(MeOH)\text{-}H]^+$ are detected. MeOH used as the solvent for the ESI-MS experiments is the source of this additional ligand.

[19] The assignments are unambiguous by (i) comparison of the experimentally observed isotope distribution patterns with the calculated ones and (ii) accurate mass determinations for the peaks of all individual platinum isotopes, cf. Figure 1.

[20] Prepared by metal halogen exchange between 1-bromo-4-methoxybenzene and t-BuLi in Et_2O at −78 °C, followed by quenching the aryllithium compound formed with D_2O.