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Catalysis of aldehyde and imine silylcyanation by platinum and palladium NCN-pincer complexes

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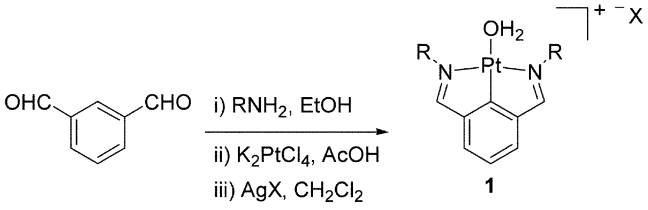
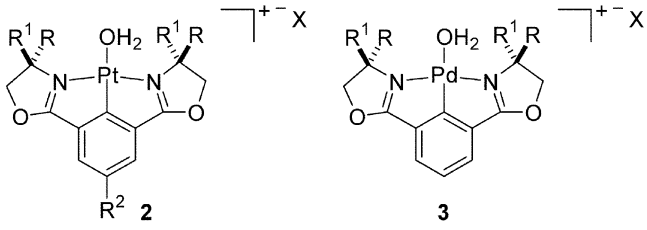
Abstract—The room temperature addition of trimethylsilylcyanide to aromatic and aliphatic aldehydes to give the corresponding cyanohydrins is efficiently catalysed by 1 mol% of ((2,6-bis(*N*-cyclohexyl)imino)phenyl)aquoplatinum(II) trifluoromethanesulfonate **1a**. This methodology is also applicable to the addition of trimethylsilylcyanide to Schiff bases resulting in the formation of α-amino nitriles.

Organometallic NCN-pincer complexes are air-stable and versatile compounds that are finding extensive application in catalysis and material science.[1] As part of a programme investigating group 10 metal containing pincer complexes, we recently reported the facile three-step synthesis of platinum species **1** starting from isophthaldehyde (Scheme 1).[2] These cationic complexes act as Lewis acid catalysts for the Michael reaction between ethyl α-cyanoacetate and methyl vinyl ketone, and the Diels–Alder reaction between acrylonitrile and cyclopentadiene.

We,[3] and others,[4] have also reported the synthesis of related platinum **2** and palladium **3** bisoxazoline containing NCN-pincer complexes, and these are also active as catalysts for the Michael reaction of activated nitriles.[3] Complexes **2** and **3** also catalyse the aldol reaction between isonitriles and aldehydes,[4a] and in all of this chemistry evidence points to the pincer complexes activating the nitrile or isonitrile substrate through coordination to the group 10 metal.

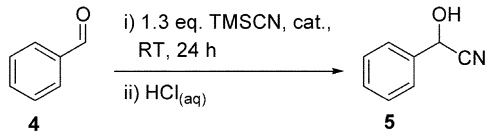


Scheme 1.



In seeking further applications of these complexes in synthesis we chose to investigate their potential as catalysts for the silylcyanation of aldehydes. This reaction is catalysed by a wide array of Lewis acids including ZnI_2,[5] $AlCl_3$,[6] TMSOTf[7] and $LnCl_3$ (Ln = La, Ce, Sm).[8] Asymmetric variants of this reaction have been successfully developed using titanium based chiral Lewis acids which both activate and control the facial selectivity of a metal coordinated aldehyde.[9]

We initially chose to study the addition of trimethylsilylcyanide to benzaldehyde **4** catalysed by complexes **1**–**3** (Scheme 2, Table 1).



Scheme 2.

Keywords: silylcyanation; catalysis; pincer complexes.
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Table 1. Addition of TMSCN to benzaldehyde **4**

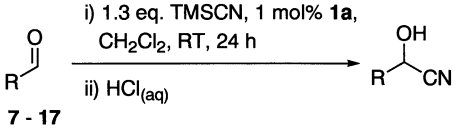
Entry	Catalyst (mol%)	Solvent	Conversion to **5** (%)[a]
1	None	CH_2Cl_2	<1
2	None	Toluene	<1
3	**1a** (1)	CH_2Cl_2	81[b]
4	**1a** (0.1)	CH_2Cl_2	79
5	**1a** (0.01)	CH_2Cl_2	23
6	**1a** (1)	Toluene	68
7	**1a** (0.5)	Toluene	49
8	**1b** (1)	CH_2Cl_2	61
9	**2a** (1)	CH_2Cl_2	89
10	**2b** (1)	CH_2Cl_2	91
11	**3a** (1)	CH_2Cl_2	83
12	**6** (1.7)	CH_2Cl_2	<1
13	NaOTf (3.4)	CH_2Cl_2	<1
14	AgOTf (1)	CH_2Cl_2	88
15	AgOTf (0.1)	CH_2Cl_2	<1

[a] Conversion determined by ^{1}H NMR [**4**: 10.0 (1 H, s, PhC*H*O), **5**: 5.50 (1 H, s, PhC*H*(CN)OH)].

[b] 84% isolated yield after 24 h with 3× the concentration of reactants.[10]

In the absence of a catalyst, combining benzaldehyde with 1.25 equivalents of TMSCN did not result in the formation of cyanohydrin **5** (entries 1 and 2). Under the same conditions in CH_2Cl_2, addition of 1 mol% of **1a** (R = C_6H_{11}, X = OTf) resulted in the clean formation of **5** following addition of 3N HCl to hydrolyse the TMS ether initially formed in the reaction (entry 3). Reducing the catalyst loading to 0.1 mol% gave an essentially identical result (entry 4), although a further ten-fold reduction in loading resulted in a significantly reduced conversion (entry 5). Toluene proved inferior as a solvent (entries 6 and 7) and the tetrafluoroborate complex **1b** (R = ^{t}Bu, X = BF_4, entry 8) is a less effective catalyst. Platinum bisoxazoline complexes **2a** (R = R^1 = Me, R^2 = H, X = OTf) and **2b** (R = R^1 = Me, R^2 = NO_2, X = OTf), and palladium bisoxazoline **3a** (R = R^1 = Me, X = OTf), also resulted in good conversion to **5** under the standard conditions used (entries 9–11). The similar results obtained with **2a** and the more Lewis acidic complex **2b**, and the marginal superiority of these over **3a** and **1a**, mirrors our previous findings applying these complexes as catalysts to the Michael and Diels–Alder reactions of nitriles.[3c] Use of 2,6-bis(*N*-cyclohexyl)-imino)phenyl)platinumchloride **6**[2] (from which **1a** is obtained by treatment with AgOTf) and NaOTf as a catalysts did not result in any product formation (entries 12 and 13), confirming that cationic transition metal complexes are responsible for the observed catalysis. Silver triflate is also active (entries 14 and 15). The absence of silver salts in complexes **1**–**3** was ensured by either recrystallisation or repeated precipitation of these complexes, and confirmation of purity by microanalysis. Combination of **4**, NaCN (1.3 equiv.) and **1a** (1 mol%) in CH_2Cl_2 resulted in only an 8% conversion to **5** after 24 h.

We next investigated the range of this methodology with aldehydes **7**–**17** (Scheme 3, Table 2) and catalyst **1a**. Although platinum bisoxazoline complexes **2a**/**b**

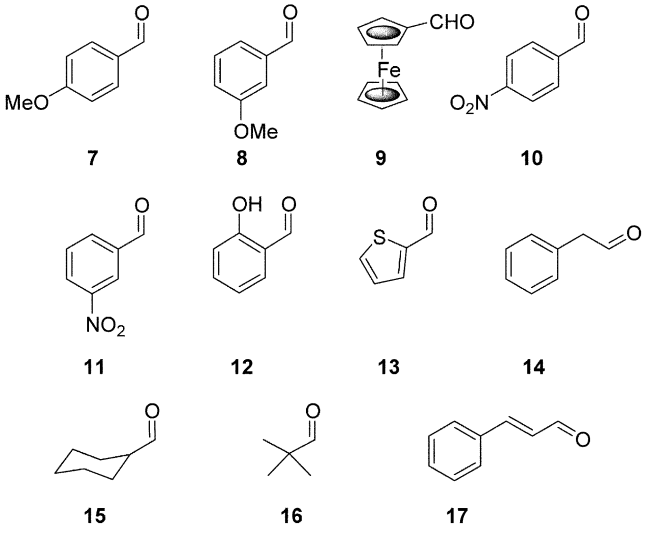


Scheme 3.

gave the highest conversion to cyanohydrin **5**, **1a** was employed due to its straightforward synthesis from isophthaldehyde (54% for 3 steps). An X-ray crystal structure analysis of catalyst **1a** (Fig. 1)[11] reveals the distorted square-planar environment about platinum, and the presence of a metal coordinated water, hydrogen-bonded to the triflate counter ion (O(1)–O(4) distance = 2.697 Å).

This study revealed a significant difference in the conversion of aldehydes containing electron donating substituents (entries 1–3) versus aldehydes substituted with an electron withdrawing nitro group (entries 4–5), the latter proving to be unsuitable for this procedure. Salicylaldehyde, containing an intramolecular hydrogen-bonded carbonyl, also gave a very low conversion (entry 6). However, 2-thiophenecarboxaldehyde gave a moderate yield of the corresponding cyanohydrin (entry 7), and aliphatic aldehydes containing adjacent pri-

Table 2. Addition of TMSCN to aldehydes **7**–**17**



Entry	Substrate	Conversion to cyanohydrin (%)[a]
1	**7**	92
2	**8**	68
3	**9**	93
4	**10**	3
5	**11**	8
6	**12**	4
7	**13**	43
8	**14**	67
9	**15**	94
10	**16**	81
11	**17**	95

[a] Conversion determined by ^{1}H NMR [**7**–**17**: 9.60–10.15 (1 H, s, RC*H*O), product cyanohydrins: 4.30–5.79 (1 H, s, RC*H*(CN)OH)].

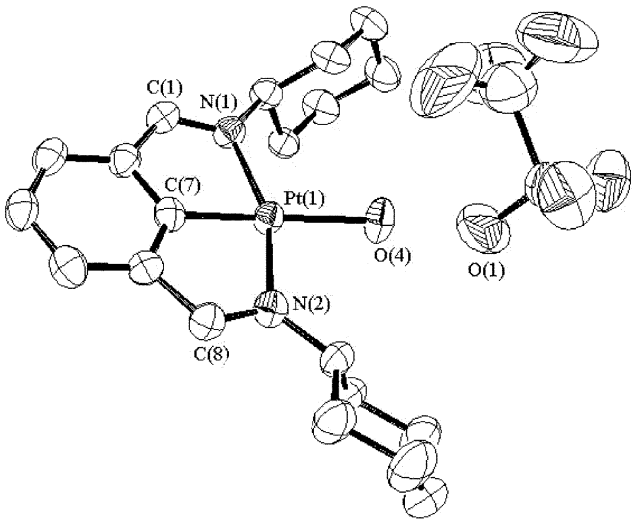


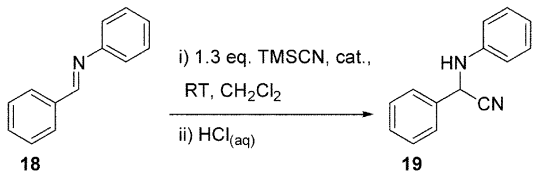
Figure 1. Representation of the crystal structure of **1a**. Selected bond distances (Å) and angles (deg): C(7)–Pt(1) = 1.903(5), N(1)–Pt(1) = 2.056(5), N(2)–Pt(1) = 2.052(5), O(4)–Pt(1) = 2.183(5), C(1)–N(1) = 1.294(7), C(8)–N(2) = 1.293(7), N(1)–Pt(1)–N(2) = 159.20(18), C(7)–Pt(1)–O(4) = 176.92(18).

mary, secondary and tertiary centres worked well (entries 8–10). Cinamaldehyde gave exclusively the 1,2-addition product, also in good conversion (entry 11). The ketones acetophenone and acetylferrocene did not react with TMSCN in the presence of **1a**.

Following the first report on ZnI_2 catalysed addition of TMSCN to imines,[12] several publications have recently appeared employing lanthanide triflates as active and selective Lewis acid catalysts for this transformation.[13]

To test if **1a** was suitable for this reaction, *N*-benzylideneaniline **18** was combined with TMSCN with and without platinum complex **1a** (Scheme 4, Table 3). No reaction took place in the absence of the catalyst (entry 1), even after 9 days (entry 2). In contrast, addition of 1 mol% of **1a** resulted in a 77% conversion to **19** (entry 3), though a longer reaction time did not lead to further product formation. Similarly, imines **20**–**24** were examined as substrates for this C–C bond forming reaction (Scheme 5, Table 4).

As found with the aldehyde substrates, imines containing electron-donating substituents (entry 1) are superior to those containing electron-withdrawing substituents, either *para* to the imine (entry 2) or attached directly to the nitrogen (entry 3). *N*-Benzylidenebenzylamine **23**

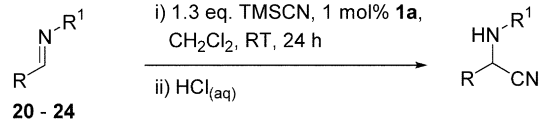


Scheme 4.

Table 3. Addition of TMSCN to imine **18**

Entry	Catalyst (mol%)	Time (h)	Conversion to **19** (%)[a]
1	None	24	<1
2	None	216	3
3	**1a** (1)	24	77
4	**1a** (1)	216	75

[a] Conversion determined by ^{1}H NMR [**18**: 8.47 (1 H, s, PhC*H*NPh), **19**: 5.43 (1 H, s, PhC*H*(CN)NHPh)].

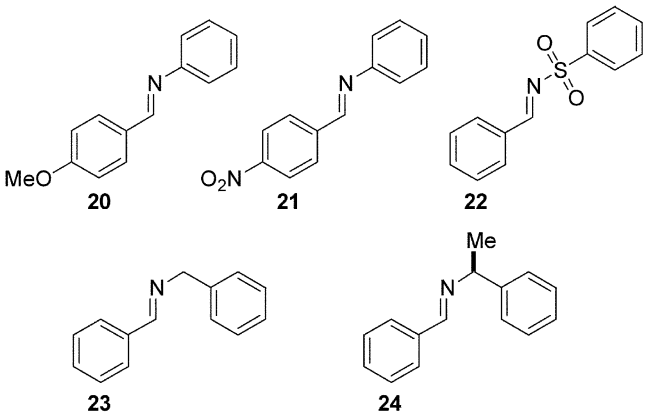


Scheme 5.

gave a moderate yield of the corresponding α-amino nitrile (entry 4) and use of the related (*S*)-α-methylbenzylamine derived imine **24** resulted in a moderate 3.7:1 selectivity for the (*S*,*S*)-diastereoisomer (entry 5).[14]

In the course of our previous work on the synthesis and application of palladium bisoxazoline complexes **3**, we generated enantiopure C_2-symmetric derivatives and applied these to the asymmetric Michael reaction of α-nitrile esters (up to 34% e.e.).[3a,b,15] Application of complex **3b** (R = CH_2Cy, R^1 = H, X = OTf) to the reaction depicted in Scheme 2, in both CH_2Cl_2 and toluene, resulted in conversion to **5** in >98% and 19% respectively. In both cases product **5** was determined to be

Table 4. Addition of TMSCN to imines **20**–**24**



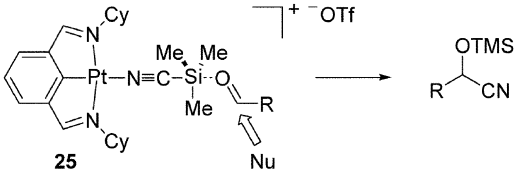
Entry	Substrate	Conversion to α-amino nitriles (%)[a]
1	**20**	70
2	**21**	53
3	**22**	27
4	**23**	46
5	**24**	80[b,c]

[a] Conversion determined by ^{1}H NMR [**20**–**24**: 8.38–9.10 (1 H, s, ArC*H*NR), product α-amino nitriles: 4.40–5.58 (1 H, s, ArC*H*(CN)NHR)].

[b] As a 3.7:1 ratio of *S*,*S*/*S*,*R* diastereoisomers.

[c] Toluene as solvent (61% yield, 3:1 diastereomeric ratio in CH_2Cl_2).

racemic.[16] To further study the mode of catalysis by the NCN-pincer complexes, we combined **1a** and benzaldehyde in a 1:0.9 ratio in CD_2Cl_2, and observed no change in chemical shift of the carbonyl hydrogen (PhC*H*O) in the ^1H NMR spectrum. In contrast, we have previously noted the downfield chemical shift in the ^1H NMR of acetonitrile when combined with approximately one equivalent of group 10 NCN pincer complexes in CD_2Cl_2 (e.g. 2.66 ppm with **2a** versus 1.93 ppm).[3c] This points to catalysis proceeding via activation of TMSCN rather than the aldehyde. The $^1H/^{13}C$ NMR spectra of 1:1 TMSCN/**1a** in CD_2Cl_2 were complex and inconclusive. Significantly, the suitability of both aldehyde and imine substrates to catalysis by **1a** correlate to the basicities of the carbonyl oxygens and imine nitrogens respectively, and are opposite to their intrinsic reactivity towards nucleophiles. This points to a requirement for Lewis acid activation in the catalytic cycle, and we tentatively suggest the involvement of intermediate **25** in the silylcyanation of aldehydes catalysed by **1a**. The lack of enantioselectivity with **3b** suggests silylcyanation cannot be an intramolecular process, and in the corresponding intermediate to **25** arising from **3b**, the five bond distance between the metal and the carbonyl carbon is too great for the oxazoline substituents to control facial selectivity.



Imines are known to coordinate to platinum complexes **2**, but organolithium addition to these requires a stoichiometric quantity of pincer complex.[4c] Attempts to use **1a** as a catalyst for the reaction between **18** and 2-trimethylsilyloxycyclohexene proved unsuccessful, suggesting that catalysis of imine silylcyanation is mechanistically similar to aldehyde silylcyanation.

In conclusion, we have demonstrated that platinum and palladium NCN-pincer complexes are efficient catalysts for the synthesis of many (racemic) cyanohydrins and α-amino nitriles. This is a further example of the growing use of these stable complexes in catalysis, which are ideal for immobilisation on a solid or dendrimer support.[1b]

Acknowledgements

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10. To a solution of **4** (3.6 mmol) and 0.024 g (0.036 mmol) of **1a** in CH_2Cl_2 (10 mL not specifically dried) was added TMSCN (0.6 mL, 4.5 mmol) and the resulting solution stirred at room temperature for 24 h. Following cautious addition of 3N hydrochloric acid solution (10 mL) utilising a sodium hypochlorite trap, and subsequent vigorous stirring for 12 h, the organic fraction was separated, dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography (gradient elution, 10% EtOAc/petroleum ether to 100% EtOAc) gave **5** (0.40 g, 84%) with $^1H/^{13}C$ NMR data consistent with that previously reported: Gerrits, P. J.; Zumbrägel, F.; Marcus, J. *Tetrahedron* **2001**, *57*, 8691.
11. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 217546. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.com.ac.uk).
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16. Sample filtered through a short plug of silica to remove catalyst eluting with CH_2Cl_2. Column = CP-Chirasil-Dex CB: Initial temperature 75°C, initial time 1 min, ramp 1.5 deg./min to 195°C. 38.5 and 39.0 min corresponding to enantiomers of silylated **5** and 66.3 and 67.5 min corresponding to **5**.