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Enabling Ligand Screening for Palladium-Catalysed Enantioselective Aza-Michael Addition Reactions

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Abstract: The bis(trifluoromethanesulfonate)palladium(II) dihydrate complex, $Pd(OTf)_2 \cdot 2\,H_2O$ (**1**), is an active palladium(II) precursor for the generation of dicationic palladium(II) catalysts. Parallel ligand screening is enabled for the first time, and twenty-four chiral ligands were evaluated for the asymmetric aza-Michael addition of aromatic amines to α,β-unsaturated *N*-alkenoylimides and carbamates. Enantioselectivities of >99% can be obtained. Catalytic precursors generated from **1** using the new protocol have been identified.

Keywords: asymmetric catalysis; conjugate addition; hydroamination; ligand effects; palladium

Introduction

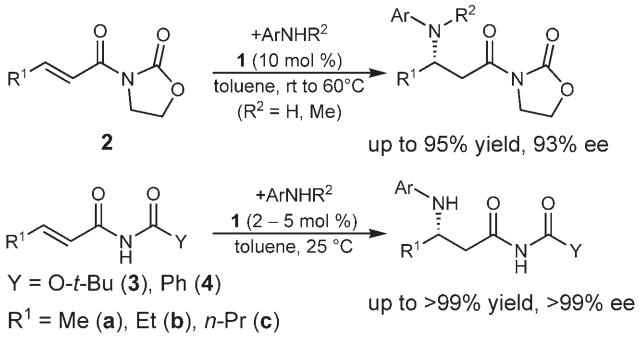
Enantioselectivity of a catalytic process is dependent on the attainment of a kinetically favourable transition state, which is often highly sensitive to stereoelectronic effects exerted by the ligand and substrate(s). Invariably, judicious modification of a ligand's structure is necessary to accommodate substrate changes. The problem is alleviated to a certain extent by the increasing commercial availability of chiral ligands, as well as the advent of easy-to-synthesise modular ligands, driven and complemented by advances in high-throughput experimentation techniques and laboratory automation.[1] Ideally, a catalyst is prepared *in situ* by mixing a metal precursor with the requisite ligand prior to the introduction of substrates. However, this is only feasible if the system does not generate competing catalytic species that can interfere with the intended reaction pathway.

Previously, we demonstrated that [*R*-(BINAP)Pd-(solvate)$_2$]$^{2+}$[TfO$^-$]$_2$ (**1**) catalyses the addition of aromatic amines to α,β-unsaturated *N*-oxazolidinones (**2**),[2,3] carbamates (**3**)[4] and imides (**4**)[5] with excellent yields and enantioselectivities (Scheme 1).

Dicationic palladium complexes are generally prepared by halide abstraction from the corresponding ligated palladium(II) dihalides using silver salts.[6] Occasionally, the halide abstraction is performed *in situ*,[7] but this still requires the preparation of (diphosphine)PdX_2, and the presence of silver cation in the reaction mixture is not always desirable. Most importantly, the introduction of different ligands is an expensive and time-consuming process. As the aza-Michael reactions are highly sensitive to the steric and electronic structures of the substrates, we wanted to develop a method for ligand screening that will facilitate the identification of more active and/or selective catalysts. Herein, we describe a method of generating these catalysts *in situ*, and subsequent ligand screening in these aza-Michael addition reactions.

Results and Discussion

Preliminary examination of Pd precursors for the addition of aniline to butenoyl-*N*-imide **4a** was conducted us-



Scheme 1. Asymmetric aza-Michael reactions catalysed by palladium complex **1**.

Table 1. Pd precursors for the addition of $PhNH_2$ to **4a**.[a]

Entry	[Pd] precursor	Time [h]	Yield [%][b]	ee [%][c]
1	$Pd_2(dba)_3 \cdot CHCl_3$	18	–	–
2	$PdCl_2$	18	–	–
3	$Pd(NO_3)_2$	18	–	–
4	$PdCl_2(NCCH_3)_2$	18	–	–
5	$Pd(acac)_2$	18	–	–
6	$Pd(OAc)_2$	18	37	2
7	$Pd(TFA)_2$	18	–	–
8	$Pd(OTf)_2 \cdot 2\,H_2O$	18	86 (84)[d]	91 (89)[d]
9[e]	$Pd(OTf)_2 \cdot 2\,H_2O$	18	89	89
10[f]	$Pd(OTf)_2 \cdot 2H_2O$	18	83	92

[a] $PhNH_2$/**4a**/$Pd(OTf)_2$/(*R*)-BINAP ratio of 1/1.1/0.05/0.055 at 25 °C in toluene.
[b] Calculated by ^1H integration.
[c] Determined by chiral HPLC.
[d] Value in parenthesis corresponds to result afforded by complex **1** (ref.[5]).
[e] M:L ratio of 1:2.
[f] M:L ratio of 1 : 0.5.

ing the ligand (*R*)-BINAP (Table 1). Unsurprisingly, none of the common palladium(0) or palladium(II) complexes containing strongly coordinating anionic ligands was found to be active under these conditions (entries 1–5). Interestingly, while palladium(II) acetate initiated some product formation, palladium(II) trifluoroacetate was completely inactive (entries 6 and 7). Ultimately, bis(trifluoromethanesulfonato)palladium(II) provided a result comparable to that obtained with complex **1**, and the system appeared to be insensitive to the M:L ratio (entries 8–10).[8]

The additions of the aromatic amines to substrates **3** and **4** were subsequently re-examined and the results were compared to that obtained previously with the isolated complex (Table 2).[4,5] Indeed, the reaction outcomes proved to be largely similar.[9] In most cases, ee enhancement was obtained with the new catalyst system; in two cases, optically pure products can be attained (entries 2 and 5).

These results demonstrate that $Pd(OTf)_2 \cdot 2\,H_2O$ can be used to generate catalytically active dicationic palladium(II) triflate complexes *in situ* without involving extraneous reagents, thus enabling parallel ligand screening. Subsequently, twenty-four commercially available chiral ligands were evaluated in parallel, for the addition of aniline to the Michael acceptor **4a** (Figure 1). The results show that the highest product yields are generally afforded by diphosphine ligands. Also, those with biaryl-derived chirality are by far the most selective: Among these, five ligands gave enantioselectivity of $\geqslant 90\%$ (BINAP, Tol-BINAP, C3-Tunephos, Difluorphos and CTH-P-Phos). Remarkably, the reaction is fairly insensitive to electronic effects of these biaryl ligands.

Other C_2-symmetric diphosphine ligands are less selective (DIOP, Phanephos). The Solvias family of diphosphines also offered low enantioselectivities: Josi-

Table 2. Comparison of isolated complex and that generated *in situ*.[a]

Entry	Substrate	R^1	Ar	Time [h]	Yield [%][b]	Ee [%][c]
1	**3a**	Me	Ph	18	89 (>99)	97 (97)
2	**3a**	Me	4-Cl-C_6H_4	18	82 (>99)	>99 (>99)
3	**3a**	Me	4-MeO-C_6H_4	40	38 (99)	76 (73)
4	**3b**	Et	Ph	72	54 (98)	88 (90)
5	**3b**	Et	4-Cl-C_6H_4	72	61 (92)	>99 (85)
6	**3b**	Et	4-MeO-C_6H_4	72	31 (>99)	19 (16)
7	**3c**	Pr	Ph	120	50 (98)	89 (89)
8	**3c**	Pr	4-Cl-C_6H_4	120	45 (90)	92 (89)
9	**3c**	Pr	4-MeO-C_6H_4	120	30 (82)	9 (17)
10	**4a**	Me	Ph	18	86 (84)	91 (89)
11	**4a**	Me	4-Cl-C_6H_4	18	81 (88)	81 (73)
12	**4a**	Me	4-Me-C_6H_4	18	86 (81)	85 (83)
13	**4a**	Me	4-MeO-C_6H_4	18	81 (70)	78 (80)
14	**4b**	Et	Ph	72	86 (75)	80 (63)
15	**4b**	Et	4-Cl-C_6H_4	72	75 (70)	60 (54)
16	**4b**	Et	4-Me-C_6H_4	72	22 (70)	79 (59)
17	**4b**	Et	4-MeO-C_6H_4	72	67 (76)	52 (51)
18	**4c**	Pr	Ph	72	79 (69)	68 (67)
19	**4c**	Pr	4-Cl-C_6H_4	72	73 (78)	54 (58)
20	**4c**	Pr	4-Me-C_6H_4	72	70 (71)	68 (70)
21	**4c**	Pr	4-MeO-C_6H_4	72	60 (69)	57 (55)

[a] $ArNH_2$/alkene/$Pd(OTf)_2 \cdot 2\,H_2O$/(*R*)-BINAP ratio of 1/1.1/0.05/0.055 at 25 °C in toluene. Values in parenthesis correspond to results obtained with complex **1**.
[b] Calculated by ^1H integration.
[c] Determined by chiral HPLC.

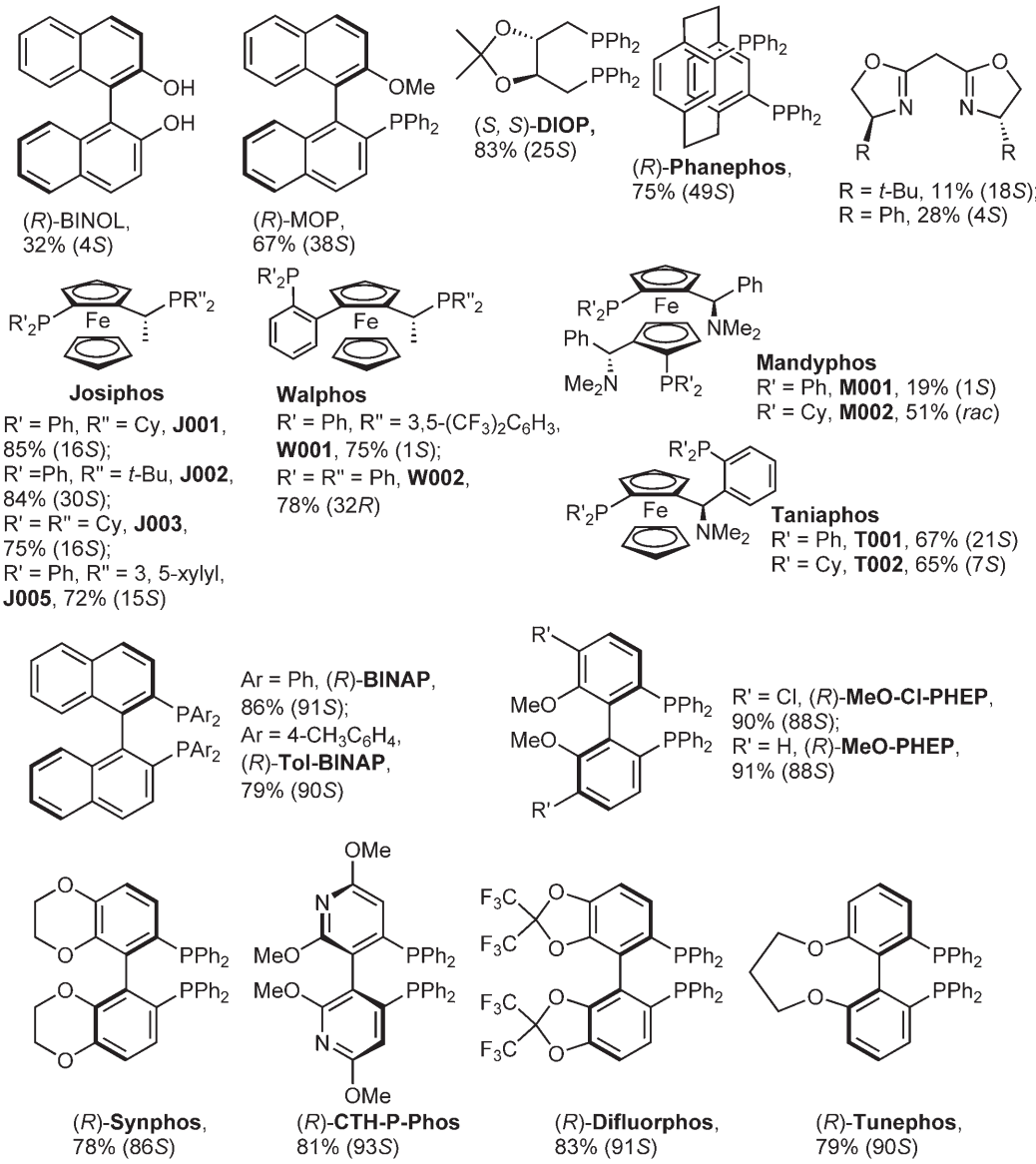


Figure 1. Evaluation of twenty-four commercially available ligands in the addition of aniline to **4a**.

phos and Walphos induced the highest conversions. One of the Walphos ligands (**W002**) offered opposite stereocontrol (*R*), suggesting a possible synergistic effect between the elements of chirality. Use of the aminodiphosphines was less successful; Taniaphos led to lower product yield, while Mandyphos ligands gave the lowest yields with a complete loss of selectivity. BOX and BINOL ligands, previously shown to be effective in Lewis acid-catalysed processes, are incompatible with cationic palladium in this instance, showing low turnover with little/no selectivity.

A solution of $Pd(OTf)_2 \cdot 2\,H_2O$ and BINAP in dichloromethane was found to contain two catalytic precursors [Eq. (1)], the expected mono-ligated bis-aqua complex **5** ($\delta_P = +34$ ppm) with an associated observed molecular ion at $m/z = 877$ {corresponding to a molecular composition of $[Pd(BINAP)(OTf)]^+$}, and a novel bis-ligated complex **6** ($\delta_P = +18$ ppm), identifiable by a characteristic mass ion at $m/z = 1499$ $\{[Pd(BINAP)_2(OTf)]^+\}$.

$$Pd(OTf)_2{\cdot}2\,H_2O + BINAP \xrightarrow{CH_2Cl_2} [(BINAP)Pd(OH_2)_2]^{2+}[TfO^-]_2 + [(BINAP)_2Pd]^{2+}[TfO^-]_2 \quad (1)$$

5 **6**

The formation of the complexes is dependent on the reaction conditions – complex **5** can be isolated by performing the reaction in the presence of a small amount of acetonitrile. Conversely, complex **6** may be obtained

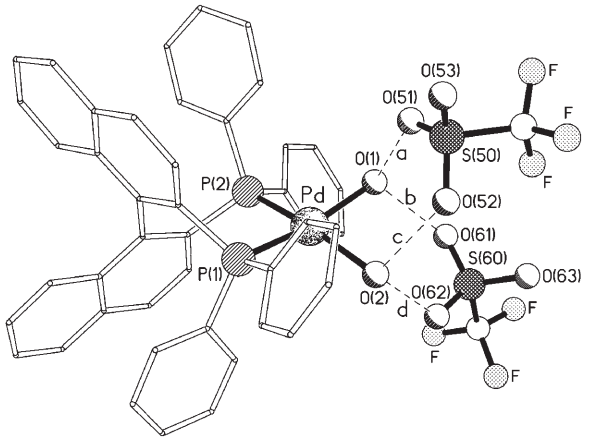


Figure 2. The molecular structure of **5**. The aqua···triflate hydrogen bonds have O···O separations (Å) of **a**) 2.716(6), **b**) 2.612(14), **c**) 2.716(6) and **d**) 2.994(10) Å.

Table 3. Selected bond lengths (Å) and angles (°) for **5**.

Pd–O(1)	2.141(3)	Pd–O(2)	2.138(3)
Pd–P(1)	2.2376(11)	Pd–P(2)	2.2367(11)
O(1)–Pd–O(2)	88.89(13)	O(1)–Pd–P(1)	167.98(11)
O(1)–Pd–P(2)	90.06(10)	O(2)–Pd–P(1)	91.93(10)
O(2)–Pd–P(2)	168.91(11)	P(1)–Pd–P(2)	91.39(4)

Table 4. Selected bond lengths (Å) and angles (°) for **6**.

Pd–P(1)	2.4271(13)	Pd–P(2)	2.4352(14)
Pd–P(3)	2.4678(13)	Pd–P(4)	2.4043(14)
P(1)–Pd–P(2)	86.43(5)	P(1)–Pd–P(3)	94.80(4)
P(1)–Pd–P(4)	172.21(5)	P(2)–Pd–P(3)	170.31(4)
P(2)–Pd–P(4)	94.10(5)	P(3)–Pd–P(4)	85.99(4)

by employing two equivalents of the diphosphine ligand. The structures of both these dicationic palladium complexes were subsequently determined by X-ray crystallography.

The racemic diaquo complex **5** adopts a solid state structure where both of the non-coordinated triflate counterions hydrogen bond to both of the aqua ligands (Figure 2).[10] The structure of this dication has been determined previously as the optically pure BF_4 salt (NATTEH).[11] In this literature structure, there were two independent dications and so four independent tetrafluoroborate anions, all four of which were disordered. However, it was still evident that these anions were hydrogen bonding to the aqua ligands, the shortest of the O···F contacts being *ca.* 2.67 Å. Here in **5** the dication has approximate C_2 symmetry about an axis that passes through the metal centre and bisects the naphthalene-naphthalene bond of the BINAP ligand, although the hydrogen-bonded triflate anions break this symmetry. The geometry at the palladium centre is distorted square planar with a marked tetrahedral twist, {Pd,P(1),P(2)} and {Pd,O(1),O(2)} being inclined by *ca.* 16° (the twists for the two independent dications in NATTEH are *ca.* 8 and 18°). With the two *trans* ligands being identical [i.e., both water, Pd–O(1) 2.141(3) and Pd–O(2) 2.138(3) Å], the Pd–P binding of the binap ligand is symmetric [Pd–P(1) 2.2376(11), Pd–P(2) 2.2367(11) Å]; the bite angle is 91.39(4)°. By contrast, in each of the two independent dications in NATTEH the bonding is more asymmetric with Pd–P distances of 2.183(3) and 2.236(3) Å and Pd–O bond lengths of 2.18(1) and 2.26(1) Å for dication **A**, whilst for dication **B** the Pd–P distances are 2.177(3) and 2.241(3) Å with Pd–O bond lengths of 2.18(1) and 2.24(1) Å.

The single crystal X-ray analysis of **6** revealed a chiral structure (the absolute structure was determined unambiguously from the X-ray data; see Experimental Section) with two *R*-BINAP ligands coordinated to a distorted square planar palladium centre (Figure 3), the two triflate counterions being non-coordinating. The dication has molecular C_2 symmetry about an axis that passes through the metal centre and bisects the naphthalene-naphthalene bond in each of the diphosphine ligands. Interestingly, the Pd–P coordination distances for the two BINAP ligands are noticeably different (Table 2); whereas the P(1)/P(2) ligand coordinates symmetrically [Pd–P(1) 2.4271(13), Pd–P(2) 2.4352(14) Å], the coordination of the P(3)/P(4) ligand is distinctly asymmetric with one bond shorter and one longer than those seen for the P(1)/P(2) ligand [Pd–P(3) 2.4043(14), Pd–P(4) 2.4678(13) Å]. It is not immediately apparent why this should be the case. [The associated P–Pd–P bite angles for the two chelating BINAP ligands are 86.43(5) and 85.99(4)° for the P(1)/P(2) and P(3)/P(4) ligands, respectively.] There is a noticeable tetrahedral twist in the metal coordination plane, the {Pd,P(1),P(2)} and {Pd,P(3),P(4)} planes being inclined by *ca.* 13°.

Finally, in the last part of the present study, the catalytic activity of complexes **5** and **6** were assessed for the ad-

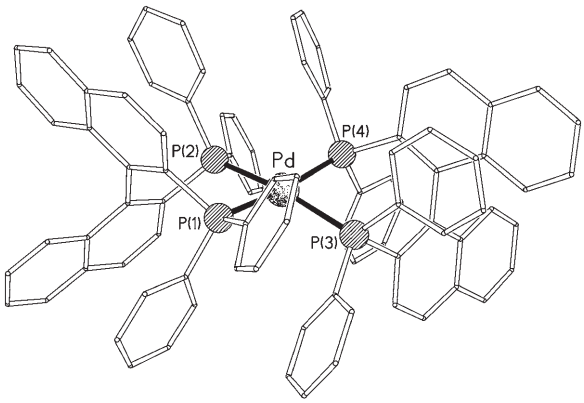


Figure 3. The molecular structure of the dication in **6** (the triflate counterions are not shown).

dition of aniline to **4a**. Rather surprisingly, identical results were obtained – complex **5** gave 88% yield, 89% ee, whilst complex **6** afforded the product in 87% yield and 88% ee. Given that these results are similar to that obtained with complex **1**, this observation suggests that complex **6** undergoes dissociation of one of the BINAP ligands, to generate the catalytically active monoligated complex **5**. This is supported by the X-ray crystal data, which suggest weaker binding of one of the BINAP ligands in complex **6**.

Conclusion

In summary, we have demonstrated that $Pd(OTf)_2 \cdot 2\ H_2O$ can be used as a precursor in the rapid constitution of asymmetric hydroamination catalysts. Hence, identification of enantioselective ligands may be accomplished by parallel screening. In this work, important structural aspects for high enantioselectivity were elucidated for the aza-Michael addition of aromatic amines to *N*-imide, and different catalytic precursors were isolated and identified.

Experimental Section

Typical Catalytic Reaction

In a glove box, Radley's reaction tubes were charged with $Pd(OTf)_2 \cdot 2\ H_2O$[12] (6 mg), an appropriate amount of the corresponding ligand and a magnetic stirrer. Each tube was then fitted with a PTFE screw cap with integrated gas inlet valve and fitted rubber septum, placed in the carousel, and purged and filled successively with dry N_2. Dry toluene (0.5 mL) was introduced, and the solution of the catalytic precursor was stirred for 30 min. The temperature of the reaction block was maintained at 25 °C by means of a thermostat, before the addition of the Michael acceptor, amine and additional amount of toluene (0.5 mL). Periodically, small amounts of reaction aliquots were extracted and analysed by ^{1}H NMR spectroscopy. At the end of the reaction, the solvent was evaporated, and the residue was subjected to column chromatography. Characterisation data of the products are contained in previous reports.

X-Ray Crystallographic Study

***Crystal data for* 5:** $[C_{44}H_{36}O_2P_2Pd](CF_3SO_3)_2 \cdot 0.5\ CH_2Cl_2$, $M = 1105.67$, triclinic, $P\bar{1}$ (no. 2), $a = 11.2008(8)$, $b = 13.4496(12)$, $c = 16.6057(12)$ Å, $\alpha = 98.787(7)$, $\beta = 105.486(6)$, $\gamma = 98.946(7)°$, $V = 2331.3(3)$ Å^3, $Z = 2$, $D_c = 1.575\ g \cdot cm^{-3}$, μ(Mo-Kα) = $0.690\ mm^{-1}$, $T = 173$ K, yellow plate-like needles, Oxford Diffraction Xcalibur 3 diffractometer; 15356 independent measured reflections, F^2 refinement, $R_1 = 0.101$, $wR_2 = 0.266$, 13562 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 66°$], 625 parameters. CCDC 266252.

***Crystal data for* 6:** $[C_{88}H_{64}P_4Pd](CF_3SO_3)_2 \cdot 0.5\ CH_2Cl_2 \cdot 0.5\ Et_2O$, $M = 1729.34$, orthorhombic, $P2_12_12$ (no. 18), $a = 19.7973(5)$, $b = 30.2266(8)$, $c = 13.3181(3)$ Å, $V = 7969.6(3)$ Å^3, $Z = 4$, $D_c = 1.441\ g \cdot cm^{-3}$, μ(Mo-Kα) = $0.470\ mm^{-1}$, $T = 173$ K, yellow block-like needles, Oxford Diffraction Xcalibur 3 diffractometer; 27409 independent measured reflections, F^2 refinement, $R_1 = 0.079$, $wR_2 = 0.134$, 15615 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 66°$], 1061 parameters. The absolute structure of 6 was determined by a combination of *R*-factor tests [$R_1^+ = 0.0785$, $R_1^- = 0.0811$] and by use of the Flack parameter [$x^+ = +0.02(2)$, $x^- = +0.98(2)$]. CCDC 286581.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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