Synthetic Methods

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Pd-PEPPSI-IPent: An Active, Sterically Demanding Cross-Coupling Catalyst and Its Application in the Synthesis of Tetra-*Ortho*-Substituted Biaryls**

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Transition-metal-catalyzed cross-coupling has become one of the most powerful carbon–carbon bond-forming processes.[1] Phosphine-based ligands have been investigated most intensively so as to improve catalytic proficiency in these transformations. Recently, a number of monoligated Pd–N-heterocyclic carbene (Pd–NHC) complexes have been prepared and show high levels of activity in a variety of Pd-catalyzed cross-coupling reactions as reported by Caddick, Cloke, and co-workers[2a] César, Bellemin-Laponnaz, and Gade,[2b] Nolan and co-workers,[2c–f] Beller and co-workers,[2g] Herrmann and co-workers,[2h] Organ and co-workers,[2i] and others (Figure 1). The activities of complexes **1**–**14** have been correlated with the steric environment around Pd, that is, the bulkier ligands lead to higher catalytic activity.[3a] For example, we have observed that yields obtained by using Pd-PEPPSI-IPr (**14**) were much greater than those obtained when using Pd-PEPPSI-IMes (**13**) in the Negishi, Suzuki–Miyaura,[2i] Kumada–Tamao–Corriu,[3b] and Buchwald–Hartwig–Yagupol'skii[3c] amination reactions. Since the σ-donor abilities of *i*Mes and *i*Pr carbenes are similar, sterics are likely to be involved in the improved performance of the latter.[3d]

We have been using calculations to study the origin of the increased catalytic activity brought on by the increased steric bulk on the NHC, and it appears that whereas oxidative addition is not altered significantly by the sterics, the metal–metal exchange and the reductive elimination are affected.[3d] On the basis of this analysis, we set out to compare the reactivities of sterically demanding analogues **15**, **16** (Figure 3), and **17**[4] with **14**, which is already considered to be bulky and has been demonstrated to be quite reactive.

Whereas *ortho*-substituted biaryls are important substructures of many biologically active compounds and organic materials,[5] the formation of tetra-*ortho*-substituted biaryls under mild conditions remains a challenge.[1] In 1997, Johnson and Foglesong reported a Suzuki–Miyaura coupling, using

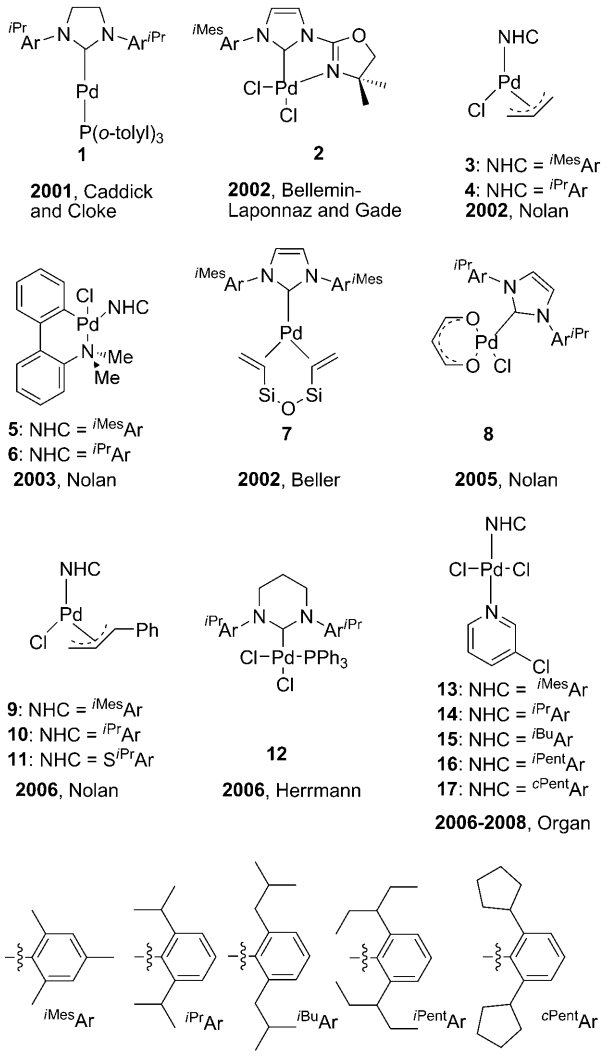

Figure 1. A selection of monoligated palladium–N-heterocyclic carbene (NHC) complexes used in palladium-catalyzed cross-coupling reactions.

$[Pd(PPh_3)_4]$ in the presence of Na_2CO_3, to prepare an unsymmetrical biaryl in 12% overall yield from an aryl bromide.[6a] In 2001 and 2002, Fu and co-workers reported Negishi[6b] and Stille[6c] cross-coupling protocols employing $[Pd\{P(tBu)_3\}_2]$. In each article, the authors have provided an example for the preparation of a tetra-*ortho*-substituted biaryl from an aryl chloride at 100 °C. In a series of publications, Buchwald and co-workers also reported

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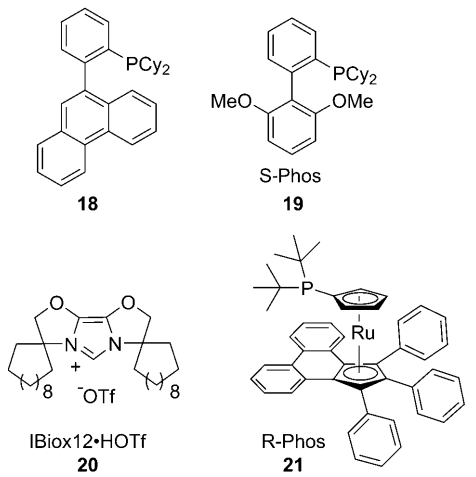


Figure 2. Ligands used in the palladium-catalyzed synthesis of tetra-substituted biaryls.

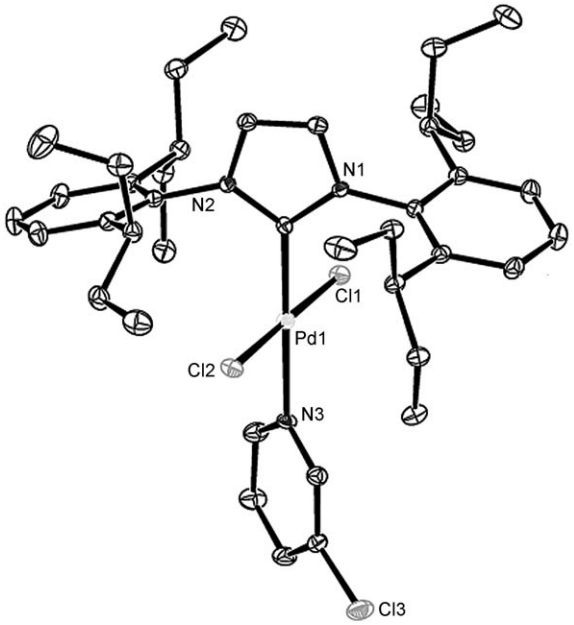
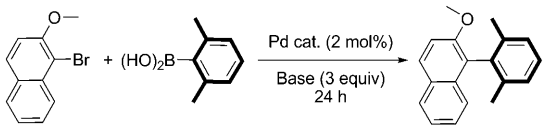


Figure 3. ORTEP representation of the crystal structure of Pd catalyst **16**.[14] Hydrogen atoms are omitted for clarity.

Suzuki–Miyaura reactions for the synthesis of tetra-*ortho*-substituted biaryls from aryl bromides using hindered biarylphosphine ligands (**18** and **19**, Figure 2) in conjunction with $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) at 110 °C.[6d–f] In 2004, similar biaryls were prepared by Glorius and coworkers, in which they coupled suitably substituted aryl chlorides and boronic acids using IBiox12·HOTf (**20**)/$Pd(OAc)_2$ at 110 °C.[6g] In 2008, Hoshi, Hagiwara, and coworkers reported Suzuki–Miyaura couplings employing ruthenocenylphosphine R-Phos (**21**)/$[Pd_2(dba)_3]$, which led to the formation of three tetra-*ortho*-substituted biaryls from aryl chlorides and boronic acids at 100 °C.[6h] The need for significantly elevated temperatures is a major drawback for these systems and the development of a catalyst that could affect such conversions at much lower temperatures would be a considerable advancement in the production of sterically congested biaryls.

We chose the Suzuki–Miyaura coupling to explore the effect of catalyst bulk on biaryl formation, and used the reaction between 2-methoxynapthalene bromide (**22**) and 2,6-dimethylphenyl boronic acid (**23**) to optimize the reaction conditions (Table 1). Since the choice in the base can be critical,[7] we screened several base/solvent systems . Interestingly, the most widely utilized base, K_3PO_4, for the synthesis of tetra-*ortho*-substituted biaryls led to poor results when **16** was used, even at high temperatures (Table 1, entries 1, 2, and 9). Pushing forward, we identified two promising base/solvent systems: KOH in dioxane and KO*t*Bu in *t*BuOH. By using the former system at 65 °C with a slight excess of aryl boronic acid (1.2 equiv) and **14**, the desired product was produced in 41 % yield (Table 1, entry 17); under the same reaction conditions, **16** led to 91 % yield of the product (Table 1, entry 13). The KO*t*Bu/*t*BuOH conditions (in the presence of the 4 Å molecular sieves)[8] resulted in excellent conversion with both catalysts **14** and **16** (Table 1, entries 16 and 14, respectively). When $PdCl_2$ was used under the same reaction conditions, no product formation was detected (Table 1, entries 20 and 21). These results confirm that if there is any palladium black formed from the Pd–NHC catalysts, then the resulting colloidal Pd is not catalytically active in this

Table 1: Base and solvent screening for biaryl synthesis using Pd–NHC complexes.



22 (1 equiv) **23** (1.2 equiv) **24**

Entry	Cat.	Reaction conditions	Conversion [%][a]
1	**16**	$K_3PO_4H_2O$, 70 °C, toluene	0
2	**16**	K_3PO_4, 100 °C, toluene	46
3	**16**	CsF, 70 °C, toluene	0
4	**16**	K_2CO_3, 70 °C, toluene	0
5	**16**	K_2CO_3, 70 °C, dioxane	0
6	**16**	KOAc, 60 °C, toluene	0
7	**16**	KO*t*Bu, 70 °C, toluene	< 2
8	**16**	KOH, 70 °C, toluene	16
9	**16**	$K_3PO_4H_2O$, 40 °C, dioxane	0
10	**16**	Cs_2CO_3, 40 °C, dioxane	3
11	**16**	CsF, 40 °C, dioxane	15
12	**16**	KOH, 40 °C, dioxane	80
13	**16**	KOH, 65 °C, dioxane	91
14	**16**	KO*t*Bu, 65 °C, *t*BuOH, 4 Å M.S.	90
15	**14**	KOH, 40 °C, dioxane	25
16	**14**	KO*t*Bu, 65 °C, *t*BuOH, 4 Å M.S.	95
17	**14**	KOH, 65 °C, dioxane	41
18	**15**	KOH, 65 °C, dioxane	4
19	**17**	KOH, 65 °C, dioxane	9
20	$PdCl_2$	KOH, 70 °C, dioxane	0
21	$PdCl_2$	KO*t*Bu, 65 °C, *t*BuOH, 4 Å M.S.	0
22	–	KO*t*Bu, 65 °C, *t*BuOH, 4 Å M.S	0

[a] Conversion was determined by GC/MS/MS methods using a calibrated internal standard (undecane); reactions were performed in duplicate. M.S. = molecular sieves.

coupling. Additionally, in the absence of any catalyst product formation was not observed under the standard reaction conditions (Table 1, entry 22).

To additionally investigate the intricacies of the model reaction employing KOH/dioxane, coupling reactions employing **14** and **16** were monitored at 40 and 70 °C (Figure 4). At lower temperature, the activation for both catalysts appeared to be slow; no product was observed within the first two hours of the reaction. However, at 70 °C both catalysts turned over immediately and the reaction employing **16** was complete within two hours, whereas **14** stalled at approximately 40 % conversion. In both reactions involving **14**, unreacted 2-methoxynaphthalene bromide was recovered. To shed some light onto the poorer performance of **14**, we conducted some control experiments. At 70 °C, the addition of an additional 2 mol % of **14** after two hours did not improve the yield. However, the addition of an extra 1.2 equivalents of 2,6-dimethylphenyl boronic acid (with or without an extra 2 mol % **14**) after two hours led to a 10 % improvement in the overall yield (51 %). It can be inferred from these results that at 70 °C **14** remained active after two hours, but the boronic acid was completely consumed to give the corresponding undesired phenol, which was observed in the GC analysis.

After obtaining these promising early results, **14** and **16** were evaluated in the coupling of a variety of hindered aryl bromides (Table 2). A tetrasubstituted heterobiaryl was successfully synthesized using KOH/dioxane (Procedure A) with **14** (Table 2, entry 1), although with other substrates this base/solvent system resulted in significant phenol formation.[9] This side reaction was avoided by using K*t*OBu/*t*BuOH in the presence of 4 Å molecular sieves (Procedure B), which effectively produced a variety of biaryls. Whereas these conditions were good for **16**, they were less so for **14**. That phenol formation is base dependent suggests that transmetalation is rate limiting. Additional investigation of hindered aryl chlorides was particularly productive (Table 3). Chlorides, which are sluggish toward oxidative addition, coupled not only with higher yields than the corresponding bromides, but the product mixtures were also generally much cleaner. By using **16** at 65 °C (except in the case of entries 5 and 9 in Table 3) and the KO*t*Bu/*t*BuOH system, we were able to synthesize a striking array of hindered biaryls from aryl chlorides under very mild reaction conditions. The examples in Table 4 illustrate that the conditions are quite tolerant of sensitive functional groups. Two final experimental observations are of note: a) the use of the S-Phos (**19**)/Pd catalyst system to couple chlorides under

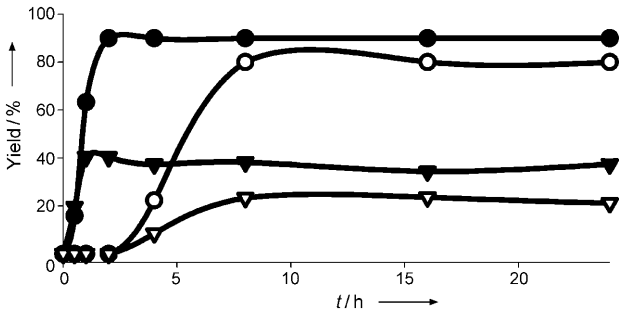
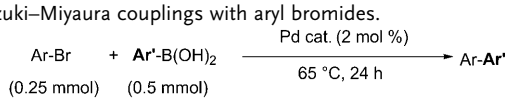
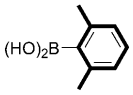
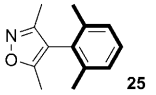
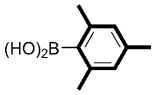
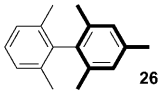
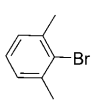
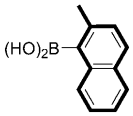
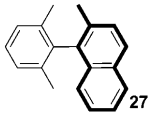
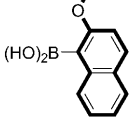
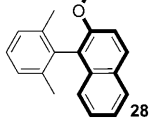
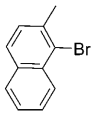
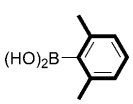
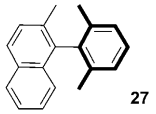
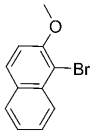
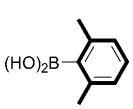
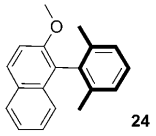
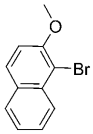
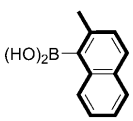
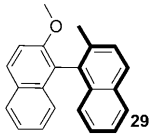


Figure 4. Effect of the temperature and reaction time on the model Suzuki–Miyaura reaction utilizing Pd-PEPPSI complexes. ●: **16** at 70 °C, ○: **16** at 40 °C, ▼: **14** at 70 °C, ▽: **14** at 40 °C.

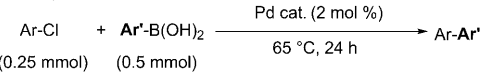
Table 2: Hindered Suzuki–Miyaura couplings with aryl bromides.

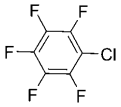
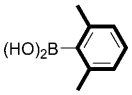
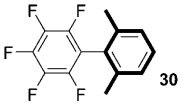
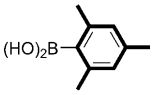
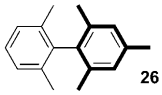
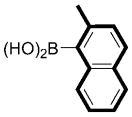
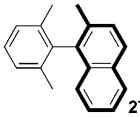
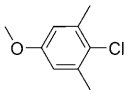
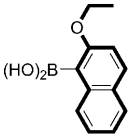
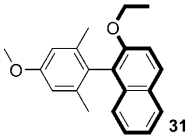
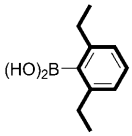
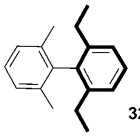
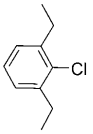
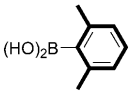
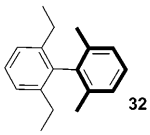
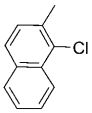
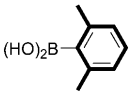
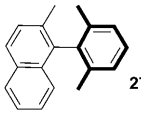
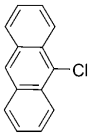
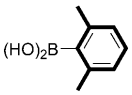
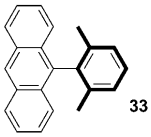
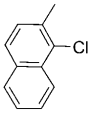
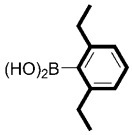
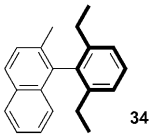
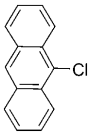
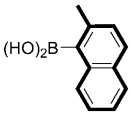
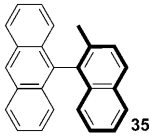


Entry	ArBr	$(OH)_2BAr'$	Product	**14** Yield [%][a]	**16** Yield [%][a]
1			 **25**	87[b]	69[b]
2			 **26**	44[c]	88[c]
3				–	(45 % with **15**)
4				–	(45 % with **17**)
5			 **27**	30[c]	75[c]
6			 **28**	< 2[c]	80[c]
7			 **27**	42[e]	82[e]
8			 **24**	41[b]	90[b]
9				95[c]	91[c] (80)[d]
10				–	50[f]
11			 **29**	64[c]	90[c]

[a] Yields of isolated products are the average of two runs. [b] Procedure A: KOH (0.75 mmol), dioxane (1 mL). [c] Procedure B: KO*t*Bu (0.75 mmol), *t*BuOH (1 mL), 4 Å M.S. [d] 2.1 mmol scale and **16** (1.2 mol %) [e] Procedure C: KO*t*Bu (0.75 mmol), *t*BuOH (0.7 mL), dioxane (0.3 mL), 4 Å M.S. [f] KOH (0.75 mmol), dioxane (1 mL), **16** (10 mol %), RT.

Table 3: Hindered Suzuki–Miyaura couplings with aryl chlorides.



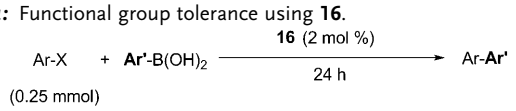
Entry	ArCl	$(OH)_2BAr'$	Product	**14** Yield [%][a]	**16** Yield [%][a]
1			 **30**	8[b]	59[b]
2			 **26**	< 2[c]	70[c] (74)[d]
3			 **27**	32[c]	78[c]
4			 **31**	34[c]	49[c]
5			 **32**	0[c,e]	65[c,e]
6			 **32**	0[c]	61[c]
7			 **27**	47[c] –	95[c] (32% using **19**/$[Pd_2(dba)_3]$)[c]
8			 **33**	0[c]	95[c]
9			 **34**	0[c,e]	80[c,e]
10			 **35**	0[c]	88[c]

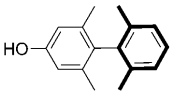
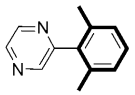
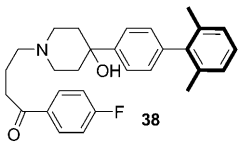
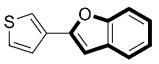
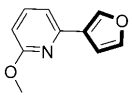
[a] Yields of isolated products are the average of two runs. [b] Procedure A: KOH (0.75 mmol), dioxane (1 mL) . [c] Procedure B: KO*t*Bu (0.75 mmol), *t*BuOH (1 mL), 4 Å M.S. [d] 0.5 mmol scale. [e] Reaction was performed at 80 °C.

identical reaction conditions to those used for **16** led to significantly lower yields (e.g., Table 3, entry 7),[10] and b) **16** is active enough to produce a highly hindered tetra-*ortho*-substituted biaryl by using the Suzuki–Miyaura reaction at room temperature (e.g., Table 2, entry 10).[11]

We have demonstrated previously that a dramatic reduction in catalyst performance can simply result from removing a methyl group from both isopropyl units on one side of the *i*Pr catalyst **14**.[12] Examining entries 13, 17, 18, and 19 in Table 1, and entries 2–4 in Table 2, shows a similar sensitivity to changing not only the bulk, but the nature of the bulk that surrounds Pd. From the analysis of these data relating to the structures of catalysts **14**, **15**, **16**, and **17**, several things are essential for high catalytic activity with Pd–NHC complexes: 1) branching at the first carbon atom of the *ortho*-alkyl substituent on the aryl ring (e.g., **15** versus **16**) is necessary, 2) increasing the bulk (provided point 1 above is satisfied) improves catalyst performance (e.g., **14** versus **16**), and

Table 4: Functional group tolerance using **16**.



Entry	X	Product	Yield [%][a]
1	Br	 **36**	51[b]
2	Cl	 **37**	quant.[c]
3	Cl	 **38**	90[b] (89)[c]
4	Br	 **39**	85[d]
5	Cl	 **40**	70[e]

[a] Yields of isolated products are the average of two runs. [b] Procedure A: $Ar'B(OH)_2$ (0.5 mmol), KOH (0.75 mmol), dioxane (1 mL), 65 °C. [c] Procedure B: $Ar'B(OH)_2$ (0.5 mmol), KO*t*Bu (0.75 mmol), *t*BuOH (1 mL), 4 Å M.S., 65 °C. [d] $Ar'B(OH)_2$ (0.3 mmol), KO*t*Bu (0.375 mmol), *i*PrOH (1 mL), 4 Å M.S., 30 °C. [e] $Ar'B(OH)_2$ (0.3 mmol), KO*t*Bu (0.375 mmol), *t*BuOH (1 mL), 4 Å M.S., 30 °C.

3) conformational flexibility in the alkyl substituent is essential (**16** versus **17**).

Pd-PEPPSI-IPent (**16**) proved to be an excellent catalyst for the Suzuki–Miyaura cross-coupling of sterically hindered aryl bromides/chlorides with aryl boronic acids to form bulky tetra-*ortho*-substituted biaryls in good yields under mild reaction conditions. *Ortho* substituents, such as methyl, primary alkyl, phenyl, fluorine, and alkoxy groups are accommodated. These results, in addition to our earlier reports, suggest that for effective cross-coupling reactions, a sterically demanding yet conformationally flexible environment, also referred to as the "flexible steric bulk",[6g,13] in the vicinity of the metal center is essential. Additional investigation of the use of Pd-PEPPSI-IPent (**16**) in various challenging cross-coupling reactions is currently underway.

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[10] When the identical conditions were used to couple analogous bromide substrates, identical yields (ca. 90%) were obtained using S-Phos (**19**)/Pd and **16**.

[11] To the best of our knowledge, there exists only one example of a Suzuki–Miyaura tetra-*ortho*-substituted biaryl produced at room temperature. However, this coupling employed an activated dimethoxyphenyl boronic acid derivative. See: C. Song, Y. Ma, Q. Chai, C. Ma, W. Jiang, M. B. Andrus, *Tetrahedron* **2005**, *61*, 7438–7446.

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[14] CCDC 718904 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

