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SO_2 conversion to sulfones: development and mechanistic insights of a sulfonylative Hiyama cross-coupling†

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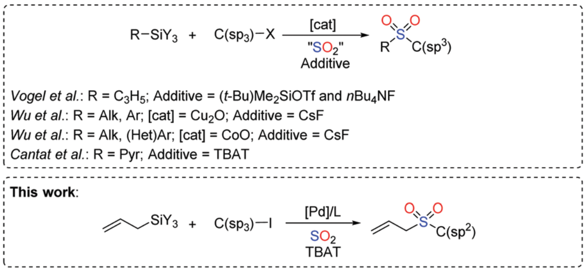
A Pd-catalyzed Hiyama cross-coupling reaction using SO_2 is described. The use of silicon-based nucleophiles leads to the formation of allyl sulfones under mild conditions with a broad functional group tolerance. Control experiments coupled with DFT calculations shed light on the key steps of the reaction mechanism, revealing the crucial role of a transient sulfinate anion.

Present in many contemporary pharmaceuticals, agrochemicals and materials (*e.g.* the antibiotic Thiamphenicol or the herbicide pyroxasulfone), sulfones are also used as key intermediates in organic synthesis[1,2] (*e.g.* the Julia olefination[3] or the Ramberg–Bäcklund reaction[4]). Given this combination of a prominent biological activity and an appealing synthetic utility, numerous methodologies have been developed for their preparation.[1] Because it has a high atom-efficiency, the insertion of a sulfur dioxide molecule upon coupling a nucleophile with an electrophile has recently emerged as a valuable route.[5] Organomagnesium,[6] organozinc[7] and organoboron[8] compounds were successively reported as nucleophiles; yet, they suffer from toxicity issues, functional group incompatibility, and/or air-sensitivity.[9]

Because they are readily available, air-stable and show an improved functional-group tolerance, organosilanes were recently considered to produce sulfones from SO_2 or SO_2 surrogates.[10] However, up-to-date methods are still limited to sp^3-hybridized electrophiles, which react through *S*-alkylation after the formation of an intermediate sulfinate anion (Scheme 1). Unlocking the utilization of sp^2-hybridized electrophiles would require a change of mechanism; and, to tackle this issue, we report herein the first sulfonylative Hiyama cross-coupling affording sulfones from organosilanes, sulfur dioxide and aryl iodides, in a single-step reaction (Scheme 1). Mechanistic control experiments, combined with DFT calculations performed on the key reaction steps, provide insight into the mechanism of the reaction.

Shortly after the discovery of the eponymous coupling, Hiyama *et al.* reported the carbonylative coupling of aryl iodides with organosilanes in the presence of a palladium catalyst (Fig. 1a).[11] SO_2 is both more electrophilic and nucleophilic than CO,[12] and its frontier orbitals are centered on the sulfur atom as they are on the carbon atom of carbon monoxide (Fig. 1c). Besides, the migratory insertion of SO_2 in a Pd–C bond has already been reported by Goddard and co-workers (Fig. 1b).[13] We hence hypothesized the feasibility of a sulfonylative Hiyama cross-coupling.

We began our investigation by exploring the coupling of triethoxy(allyl)silane (**1a**), 4-iodotoluene (**2**), and gaseous sulfur dioxide, generated by thermal decomposition of $K_2S_2O_5$ in a two-chamber apparatus (see ESI†). In the presence of $Pd(acac)_2$ as a catalyst and $TBAF{\cdot}3H_2O$ as a fluoride source to activate the weakly polar C–Si bond, the desired sulfone **3a** was obtained in 12% yield (Table 1, entry 1). By contrast, the bench stable surrogate of SO_2, DABSO, popularized by Willis *et al.*,[14] gave no desired product (Table 1, entry 2), presumably due to the coordination of the DABCO by-product to palladium. Changing the fluoride source to the anhydrous tetrabutylammonium difluorophenyl-silicate (TBAT) improved the reaction efficiency (17% yield, Table 1, entry 3). While two equivalents of SO_2 increased the yield up to 26% (Table 1, entry 4), an excess of SO_2 was detrimental to the reaction (Table 1, entry 5), possibly because of a poisoning of the catalyst. After screening a variety



Scheme 1 Representative state-of-the-art of sulfone synthesis from SO_2 and organometallic compounds.

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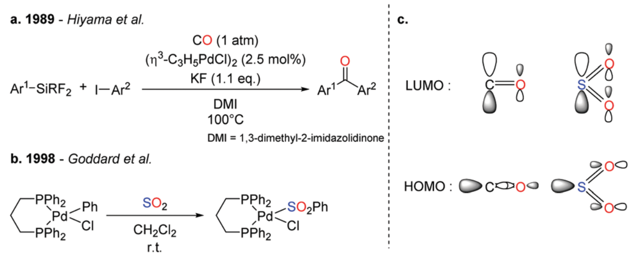
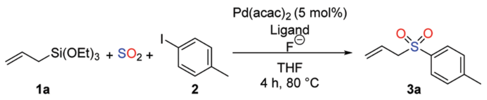


Fig. 1 (a) First example of a carbonylative Hiyama cross-coupling; (b) insertion of SO_2 in a Pd–C bond; (c) frontier orbitals of CO and SO_2.

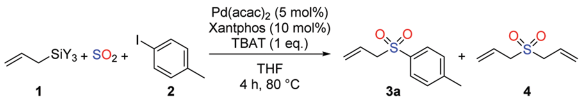
Table 1 Influence of the reaction conditions on the sulfonylative Hiyama cross-coupling of triethoxy(allyl)silane (**1a**) with 4-iodotoluene (**2**) (see Table S1 for a more exhaustive table, ESI)[a]



Entry	Fluoride source (eq.)	SO_2 source (eq.)	Ligand (%)	Yield in 3a (%)
1	TBAF·3H_2O (1)	SO_2[b] (1)	—	12
2	TBAF·3H_2O (1)	DABSO (0.5)	—	0
3	TBAT (1)	SO_2[b] (1)	—	17
4	TBAT (1)	SO_2[b] (2)	—	26
5	TBAT (1)	SO_2[b] (4)	—	0
6	TBAT (1)	SO_2[b] (2)	XPhos (10)	41
7	TBAT (1)	SO_2[b] (2)	Xantphos (10)	78
8	TBAT (1)	SO_2[b] (2)	Xantphos (5)	65
9	TBAF (1 M in THF) (1)	SO_2[b] (2)	Xantphos (10)	71

[a] Results obtained in THF at 80 °C during 4 h on a 0.1 mmol scale. [b] SO_2 was generated by thermal decomposition of $K_2S_2O_5$, see ESI. TBAF = tetrabutyl ammonium fluoride; TBAT = tetrabutylammonium difluorophenyl-silicate. Yields measured by ^1H NMR (internal standard: mesitylene).

Table 2 Formation of the diallyl sulfone (**4**) as a side-product



Y_3	Yield 3a (%)	Yield 4 (%)	4/3a ratio	ΔG^a (kcal mol^{-1})
$(OMe)_3$ (**1b**)	51	23	0.45	2.98
$(OEt)_3$ (**1a**)	78	10	0.13	3.60
$Me_2(OMe)$ (**1c**)	74	7	0.09	11.94
Me_3 (**1d**)	54	0	0	15.60

[a] Gibbs free energy variation for the fluoride transfer from $Me_3SiF_2^-$ to allylsilanes **1** (see ESI for computational details). Yields measured by ^1H NMR (internal standard: mesitylene).

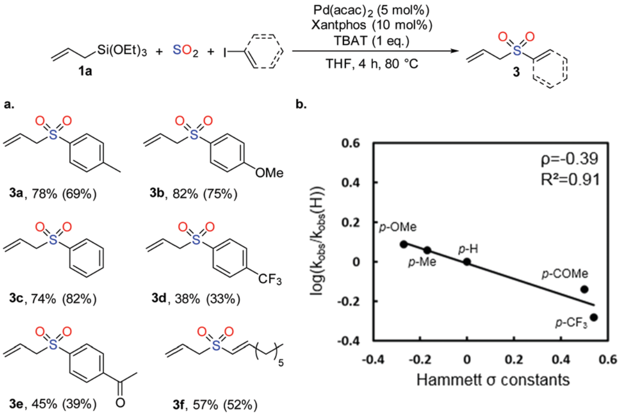
of palladium sources and phosphine ligands (Table 1, entries 5–7 and Table S1, ESI†), a set of conditions (Pd(acac)$_2$ 5 mol%, Xantphos 10 mol%, TBAT 1 eq.) gave the best results in our hands, yielding the desired sulfone **3a** in 78% yield (Table 1, entry 7). No reaction took place without the catalyst, even after 24 h (Table S1, ESI†).

During the screening process, the diallyl sulfone (**4**) was identified as a side-product. The relative proportion of **4** was found to depend directly on the nature of the substituents at the silicon atom (Table 2): the quantity of diallyl sulfone (**4**) increases with the fluoride-affinity of the organosilane (computed by the Gibbs free energy variation for the fluoride transfer from $Me_3SiF_2^-$ to the allylsilane). As a result, tri(ethoxy)allyl silanes were selected to explore this new reaction, as it provides the best balance between selectivity and productivity (see ESI†).

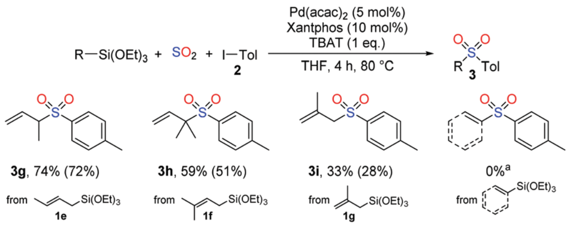
The chosen reaction conditions enabled the synthesis of allyl arylsulfones **3a–3e** from aryl iodides bearing electron-donating substituents as well as electron-withdrawing in 38–82% yield. The reaction tolerates well the presence of a ketone group and **3e** was formed in 45% yield. Interestingly, sulfones bearing electron-donating substituents **3a–3b** were obtained in better yields (78–82%) than the ones bearing electron-withdrawing substituents (**3d–3e**, 38–45%, Scheme 2a), as reflected by a Hammett correlation with a slope of $\rho = -0.39$ (Scheme 2b). Alkenyl sulfone **3f** was also prepared in 57% yield (Scheme 2a). Using aryl bromides, diallyl sulfone (**4**) was exclusively formed, presumably due to the more difficult activation of the C–Br bond by oxidative addition.

As regards the nucleophile, methyl-substituted allylsilanes **1e–1g** successfully provided the desired sulfones in 33–74% yields, with the selective formation of the α-substituted sulfones from the corresponding γ-substituted allylsilanes, while the classical Hiyama cross-coupling reaction using substituted allylsilanes usually faces regioselectivity issues.[15] Disappointingly, triethoxy(phenyl)silane and triethoxy(vinyl)silane exhibited no reactivity (Scheme 3).

These surprising results prompted us to conduct mechanistic control experiments. The catalytic system is an efficient catalyst in Hiyama couplings and, in the absence of SO_2, 1-allyl-4-methylbenzene (**6a**) and biphenyl (**6b**) were formed from triethoxy(allyl)silane (**1a**) and triethoxy(phenyl)silane (**5**), respectively (Scheme 4a). Nevertheless, in the presence of SO_2, sulfone **3a** was obtained in 78% yield, while the corresponding diarylsulfone **7**



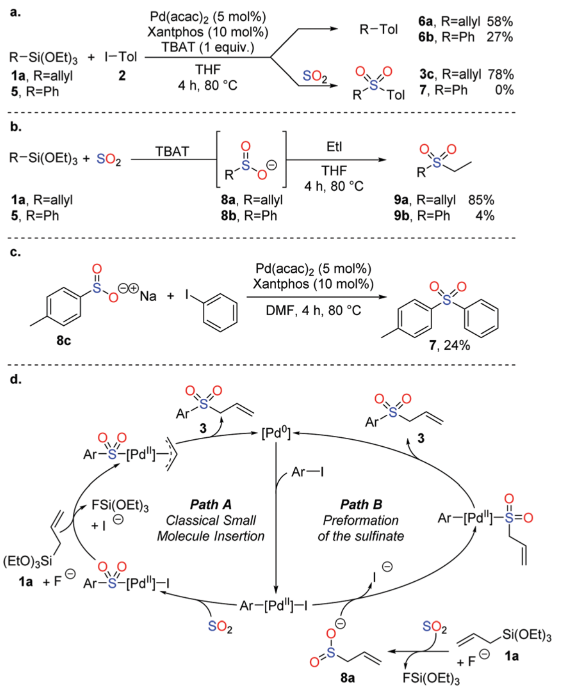
Scheme 2 (a) Substrate scope in organoiodides; (b) Hammett plot of the reaction. Reaction conditions: electrophile (1 eq.), allylSi(OEt)$_3$ (**1a**, 1.1 eq.), electrophile (1 eq.), SO_2 (2 eq., generated by thermal decomposition of $K_2S_2O_5$, see ESI†), TBAT (1 eq.), Pd(acac)$_2$ (5 mol%), Xantphos (10 mol%), THF, 80 °C, 4 h. Yields measured by ^1H NMR (internal standard: mesitylene). Yields of isolated products from scaled-up experiments (1 mmol scale) are given within parentheses.‡



Scheme 3 Substrate scope in organosilanes. [a]In the case of aryl- and vinylsilane, the nucleophile were fully recovered. Reaction conditions: organosilane (1.1 eq.), 4-iodotoluene (**2**, 1 eq.), SO_2 (2 eq., generated by thermal decomposition of $K_2S_2O_5$, see ESI†), TBAT (1 eq.), $Pd(acac)_2$ (5 mol%), Xantphos (10 mol%), THF, 80 °C, 4 h. Yields measured by ^{1}H NMR (internal standard: mesitylene). Yields of isolated products from scaled-up experiments (1 mmol scale) are given within parentheses.‡

was not observed starting from phenylsilane **5**. These observations demonstrate that the successful formation of sulfones **3a–3i** cannot be explained by a direct transposition of the mechanism reported for carbonylative cross-couplings,[16] where the insertion of the small molecule occurs after the oxidative addition (path A, Scheme 4d).

Careful ^{1}H NMR monitoring of the reaction revealed the formation of the allylsulfinate anion **8a** as an intermediate (Fig. S3, ESI†). Another pathway was hence devised, where **8a** is involved in a ligand exchange after an oxidative addition step (path B in Scheme 4d). The desired sulfone **3** would then be obtained through a reductive elimination step.



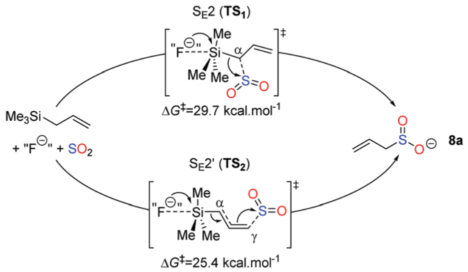
Scheme 4 Mechanistic control experiments: (a) comparison between Hiyama cross-coupling and the sulfonylative version; (b) *in situ* sulfinate formation; (c) direct cross-coupling of aryl sulfinate **7c** with phenyl iodide (DMF was used for solubility of **8c**, see ESI† for more details); (d) proposed pathways for the mechanism of the reaction. Yields measured by ^{1}H NMR (internal standard: mesitylene).

To probe the role of transient sulfinate anions, the organosilane nucleophiles **1a** and **5** were reacted with SO_2 and ethyliodide, in the absence of the palladium catalyst. While sulfone **9a** was formed in 85% yield from the allylsilane, only 4% of the ethylphenylsulfone **9b** were observed, suggesting that the formation of phenylsulfinate from triethoxy(phenyl)silane (**5**) is blocked (Scheme 4b). This finding was confirmed when diarylsulfone **7** was obtained in 24% yield from the preformed arylsulfinate **8c** exposed to phenyl iodide, in the presence of the palladium catalyst (Scheme 4c). All together, these data support path B in Scheme 4d, with the metal catalyst enabling the coupling between a transient sulfinate anion and the arylhalide electrophile.

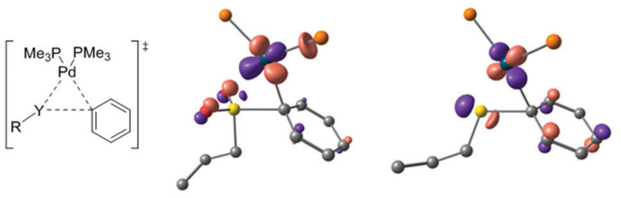
The regioselectivity observed with substituted allylsilanes (Scheme 3) readily derives from this mechanism. With an allylic nucleophile, the sulfinate formation can proceed through two different mechanisms: either a bimolecular electrophilic substitution at the α position of the silane (**TS_1**, Scheme 5), or the corresponding S_E2' mechanism with formation of the C–S bond at the γ position (**TS_2**, Scheme 5).§ DFT calculations revealed that the S_E2' path ($\Delta G^‡$(**TS_2**) = 25.4 kcal mol^{-1}) is favored over the corresponding *ipso* reaction ($\Delta G^‡$(**TS_1**) = 29.7 kcal mol^{-1}). Besides in the case of trimethyl(aryl)silane, for which only **TS_1** can be considered, the transition state lies 34.0 kcal mol^{-1} higher than the starting materials, which explains its lack of reactivity.

In classical Hiyama cross-coupling reactions, the rate-determining step (RDS) is usually the transmetallation.[17] Here, the pre-formation of a sulfinate anion circumvents such a transmetallation and the Pd-catalyst instead mediates the formation of the second C–S bond, connecting the electrophile and the SO_2 fragment. According to the Hammett plot (Scheme 2b), the rate-determining step of the catalytic reaction is facilitated with electron-rich electrophiles ($\rho < 0$), suggesting that the rate-determining step is the reductive elimination,[18] rather than the oxidative addition.[19]

In fact, the energy barrier computed for the reductive elimination of an allylsulfone from $(allylSO_2)$-$Pd(PMe_3)_2$-Ph is high, at 37.1 kcal mol^{-1} (compared to 23.2 kcal mol^{-1} for allyl-$Pd(PMe_3)_2$-Ph). Importantly, the DFT calculations also point to the positive influence of electron-donating groups on the kinetics of this step, in agreement with the slope of the experimental



Scheme 5 Computed reaction pathways for the formation of the sulfinate *via* S_E2 or S_E2'. Level of theory: B3LYP/G-D3/6-311+G(d) (C, H, O) and 6-311++G(d,p) (F, S, Si), PCM was used for THF solvation. Values given correspond to Gibbs free energies with respect to the starting materials (G = 0.0 kcal mol^{-1}). "F^-" stands in fact for the anion FSO_2^-.¶



		Y=SO$_2$	Y=S
R=CF$_3$	↑ σ	37.5 ↓	24.4 ↑ *k*
R=H		37.1	26.4
R=NMe$_2$		34.2 ↓ *k*	27.9

Fig. 2 Representations of the HOMO in the transition states for the reductive elimination from (allylY)-Pd(PMe$_3$)$_2$-Ph (with Y = SO$_2$ or S, hydrogens and methyl groups from PMe$_3$ were omitted for clarity) and Gibbs free energy of the transition states ($\Delta G^{\ddagger}$(TS)) with respect to the starting material (G = 0.0 kcal mol^{-1}). Level of theory: B3LYP/G-D3/6-311+G(d) (C, H, O, N, F), 6-311++G(d,p) (P, S) and SDD (Pd), PCM was used for THF solvation.

Hammett plot (Fig. 2). Hartwig *et al.* have shown that the formation of C–S bonds by reductive elimination from Pd(II) thiolate complexes are, on the contrary, facilitated with electron-deficient aryl partners.[20] The inverse trends may be attributed to the lower nucleophilicity of the sulfinate anion compared to the thiolate anion, the lone pair of the sulfur atom being partly delocalized on the two oxygen atoms (Fig. 2).

In conclusion, we have developed a practical palladium-catalyzed synthesis of allyl aryl sulfones from readily available organosilanes, aryl halides, and sulfur dioxide. This process represents the first approach that introduces a sp^2-hybridized electrophile with an organosilane in a sulfonylative cross-coupling. Experimental and theoretical investigations have demonstrated the key role of transient sulfinate anions and their coupling with the aryl halides, mediated by palladium, and they highlight the challenges facing the synthesis of diaryl sulfones from organosilanes.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ As shown in entry 9 of Table 1, TBAF (1 M in THF) is a competent fluoride source and it was used for scaled-up experiments to avoid the formation of the allyl phenyl sulfone **3c** from TBAT.

§ As shown in the ESI,† the unimolecular pathway has to be discarded, the fluoride transfer from the fluoride source to the organosilane and subsequent C–Si bond scission of the hypervalent species being too energetically demanding.

¶ As already reported,[10d] and experimentally evidenced (see ESI†), the fluoride anion is actually transferred to SO$_2$ to yield the stable anion FSO$_2^-$ which acts as the fluoride source.

1 G. Manolikakes, N.-W. Liu and S. Liang, *Synthesis*, 2016, 1939.
2 B. M. Trost and C. A. Kalnmals, *Chem. – Eur. J.*, 2019, **25**, 11193.
3 M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 1973, **14**, 4833.
4 L. Ramberg and B. Bäcklund, *Ark. Kemi, Mineral. Geol.*, 1940, **13**, 50.
5 D. Zheng and J. Wu, *Sulfur Dioxide Insertion Reactions for Organic Synthesis*, Springer, Singapore, 2017, ch. 3.
6 A. S. Deeming, C. J. Russel, A. J. Hennessy and M. C. Willis, *Org. Lett.*, 2014, **16**, 150.
7 B. N. Rocke, K. B. Bahnck, M. Herr, S. Lavergne, V. Mascitti, C. Perreault, J. Polivkova and A. Shavnya, *Org. Lett.*, 2014, **16**, 154.
8 Y. Chen and M. C. Willis, *Chem. Sci.*, 2017, **8**, 3249.
9 Y. Nakao and T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893.
10 (*a*) L. Bouchez and P. Vogel, *Synthesis*, 2002, 225; (*b*) D. Zheng, M. Chen, L. Yao and J. Wu, *Org. Chem. Front.*, 2016, **3**, 985; (*c*) D. Zheng, R. Mao, Z. Li and J. Wu, *Org. Chem. Front.*, 2016, **3**, 359; (*d*) N. von Wolff, J. Char, X. Frogneux and T. Cantat, *Angew. Chem., Int. Ed.*, 2017, **56**, 5616.
11 Y. Hatanaka and T. Hiyama, *Chem. Lett.*, 1989, 2049.
12 M. Tiwari, Vinit and C. M. Ramachandran, *Chem. Phys. Lett.*, 2019, **726**, 111.
13 G. Pelzer, J. Herwig, W. Keim and R. Goddard, *Russ. Chem. Bull.*, 1998, **47**, 904.
14 H. Woolven, C. Gonzalez-Rodriguez, I. Marco, A. L. Thompson and M. C. Willis, *Org. Lett.*, 2011, **13**, 4876.
15 Y. Hatanaka, K.-i. Goda and T. Hiyama, *Tetrahedron Lett.*, 1994, **35**, 6511.
16 Y. Hatanaka, S. Fukushima and T. Hiyama, *Tetrahedron*, 1992, **48**, 2113.
17 C. Amatore, L. Grimaud, G. Le Duc and A. Jutand, *Angew. Chem.*, 2014, **126**, 7102.
18 A rate-determining reductive elimination is in addition compliant with the higher efficiency of Xantphos as a ligand (Table 1 and Table S1, ESI†). Indeed, because of the steric pressure induced by its wide bite angle (111°), Xantphos is known to promote difficult reductive eliminations, notably with weakly nucleophilic partners. See: (*a*) P. J. C. Kamer, P. W. N. M. Van Leeuwen and J. N. H. Reek, *Acc. Chem. Res.*, 2001, **34**, 895; (*b*) V. V. Grushin and W. J. Marshall, *J. Am. Chem. Soc.*, 2006, **128**, 12644; (*c*) K. Fujita, M. Yamashita, F. Puschmann, M. M. Alvarez-Falcon, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 9044.
19 Troupel *et al.* showed that oxidative addition is facilitated with electron-poor electrophiles ($\rho > 0$): J.-F. Fauvarque, F. Pflüger and M. Troupel, *J. Org. Chem.*, 1981, **208**, 419.
20 G. Maan, D. Baranano, J. F. Hartwig, A. L. Rheingold and I. A. Guzei, *J. Am. Chem. Soc.*, 1998, **120**, 9205.