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# Rapid Sonogashira cross-coupling of iodoferrocenes and the unexpected cyclo-oligomerization of 4-ethynylphenylthioacetate†

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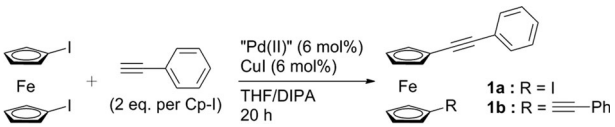
**A systematic study into the Sonogashira cross-coupling of 1,1′-diiodoferrocene ($fcI_2$) confirms that the Pd(0)–$P(^tBu)_3$ system provides a remarkable rate increase over Pd(0)–$(PPh_3)_2$. Attempts to couple 4-ethynylphenylthioacetate (2) with $fcI_2$ instead produced a novel cyclic trimer of the former, from *syn* addition of S–Ac across C≡C.**

Whilst large quantities of pure iodo-[1] and 1,1′-diiodoferrocene[2] can now easily be obtained, the full synthetic exploitation of these useful starting materials may only be realized through optimizing onward reaction conditions (enabling high product yields). Towards this end, increasing the typically low/moderate reactivity of iodoferrocenes[3] (*versus* aryliodides/bromides) under Sonogashira cross-coupling conditions was considered a primary target. Convenient and widely applicable, this reaction (from Fc–I containing materials) has been used to construct compounds for molecular[4] and organic[5] electronics, the study of intramolecular electron transfer,[6] photo-[7] and electro-chemical sensing,[8] catalysis (pincer complexes),[9] and artificial bio-receptors.[10] It is worth noting that just two years after the seminal 1975 papers concerning aryl iodides by Heck,[11] Cassar[12] and Sonogashira *et al.*,[13] cross-coupling of iodoferrocenes was under investigation.[14]

In the reports referenced above, syntheses have usually employed the convenient $PdCl_2(PPh_3)_2$ precatalyst in DIPA/THF. However, variances in substrate structure and reagent stoichiometry make it difficult to ratify the superiority of any particular set of conditions. Of particular significance, one paper[15] describes unsuccessful attempts with Buchwald and Fu's $Pd(PhCN)_2Cl_2$–$P(^tBu)_3$ combination – utilized to rapidly cross-couple electron-rich aryl-bromides at room temperature.[16]




**Scheme 1** Model reaction used to study the Sonogashira cross-coupling of iodoferrocenes and terminal alkynes.

It appeared that normally outstanding catalytic systems might offer little or no benefit over the use of $PPh_3$-ligated complexes in Sonogashira reactions with iodoferrocenes.

We were accordingly motivated to explore the reaction between $fcI_2$ and phenylacetylene as a model in an attempt to optimise the Sonogashira cross coupling of iodoferrocenes and terminal alkynes in general (Scheme 1). Concentration, temperature, phosphine (14 examples), solvent (3 examples), time and the phenylacetylene/$fcI_2$ ratio were systematically varied to examine their individual effects. Product yields were determined *via* $^1H$ NMR spectroscopy of crude reaction mixtures.

As shown in Fig. S2 (ESI†), overall reaction yields were found to increase substantially with substrate concentration (using $PdCl_2(PPh_3)_2$ at 80 °C). The effect of phosphine ligand on reaction yields was subsequently explored by employing $PdCl_2(MeCN)_2$ *at room temperature* – $PR_3$ was added separately to form $PdCl_2(PR_3)_2$ *in situ*. Though $PPh_3$ was found to be the best ligand within its local steric/electronic landscape (10% yield **1b**, Fig. 1), the $PdCl_2(MeCN)_2$–$P(^tBu)_3$ combination provided an exceptional rate improvement (93% yield **1b**). Furthermore, whilst all reactions were run for 20 h, with $P(^tBu)_3$ a large exotherm, and rapid and complete precipitate formation was observed after ~15 min. Such observations eliminate any previous doubt[15] as to the superior reactivity of bulky, electron-rich phosphines[16,17] in this context.

In comparison, other variables provided only small changes in yields. It was additionally noted that hydrodehalogenation reactions (Fc–I → Fc–H) occur under these conditions (limiting yields in some cases), attributed to adventitious water. Full experimental details may be found in the ESI.†

Intrigued as to why previous reactions using $PdCl_2(PhCN)_2$–$P(^tBu)_3$ had proven unsuccessful, we noted that in these attempts

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, tables of data for all catalytic runs, discussion of hydrodehalogenation reactions, $^1H/^{13}C\{^1H\}$ NMR spectra, crystallographic information. CCDC 927952. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43116a

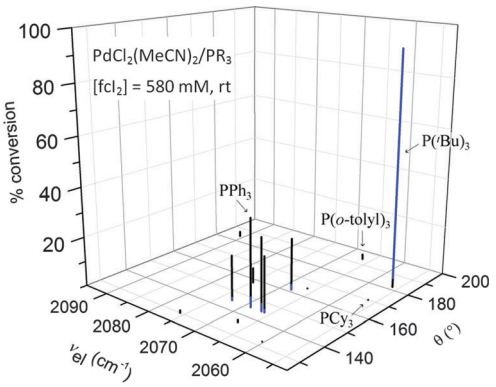
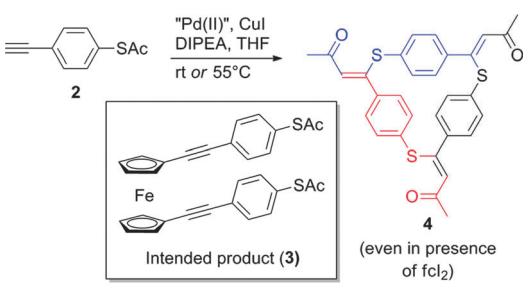



**Fig. 1** A 3D map of the effect of phosphine ligand on reaction conversion – plotted on the *z*-axis where the height of black bars = % **1a**, blue bars = % **1b** ($\nu_{el}$ = Tolman electronic parameter, $\theta$ = Tolman cone angle).

substrates had featured thioacetyl and pyridyl functionalities.[15] This prompted investigation into the apparently straightforward, though as yet unreported, Sonogashira cross-coupling reaction between 4-ethynylphenylthioacetate (**2**) and $fcI_2$. The intended product, 1,1′-bis[(4-thioacetylbenzene)ethynyl]ferrocene (**3**), has previously been prepared *via* Stille coupling.[18]

Remarkably, all attempts to synthesise **3** *via* Sonogashira coupling failed – $^1$H NMR spectroscopy of the crude product mixture indicated that the $fcI_2$ had not appreciably reacted even after 24 h ($PdCl_2(PPh_3)_2$, 55 °C). However, upon closer inspection it became apparent that resonances attributable to **2** had disappeared, and new peaks were observed at approximately $\delta$ 2.3, 6.4 and 7.0 ppm (intensities 3 : 1 : 4). Column chromatography led to the isolation of a bright yellow solid, the identity of which was unambiguously confirmed by X-ray crystallography‡ as that of the novel cyclic trimer (**4**, 24%; Scheme 2 and Fig. 2). A material with matching spectral features was produced using $PdCl_2(MeCN)_2$–$P(^tBu)_3$ in an analogous procedure at room temperature.

Overall this reaction may be described as cyclo-oligomerization of **2**, generating **4** *via* the intermolecular *syn* addition of acetyl and thiolate moieties to C≡C (accompanied by cleavage of the S–Ac bond, and reduction to C=C). Whereas **4** comprises all-*Z* linkages, reaction between monofunctional analogues of **2** (*S*-phenylthioacetate and phenylacetylene) yielded the known compound **5**[19] in 80% yield as a mixture of *Z* (81%) and *E* (19%) isomers (Scheme 3). Sequential elimination of components showed that $PdCl_2(PPh_3)_2$, CuI and DIPEA were all necessary for the reaction to occur in THF at a reasonable rate (proceeding sluggishly in the absence of CuI,




**Scheme 2** An unexpected product (**4**) is formed *via* cyclo-oligomerization of 4-ethynylphenylthioacetate (**2**) under Sonogashira conditions.

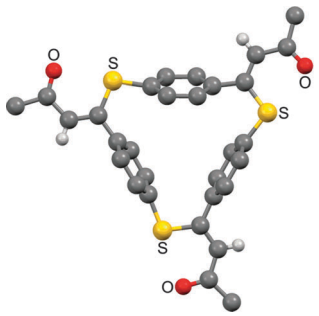
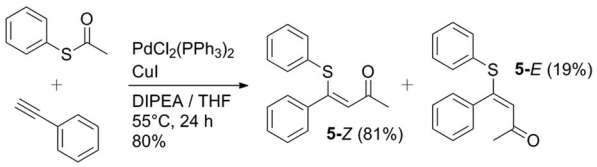


**Fig. 2** The crystal structure of one (**4-A**) of the three independent molecules present in the crystals of **4**.




**Scheme 3** Monofunctional analogues of 4-ethynylphenylthioacetate react under Sonogashira conditions to form the addition product **5**.

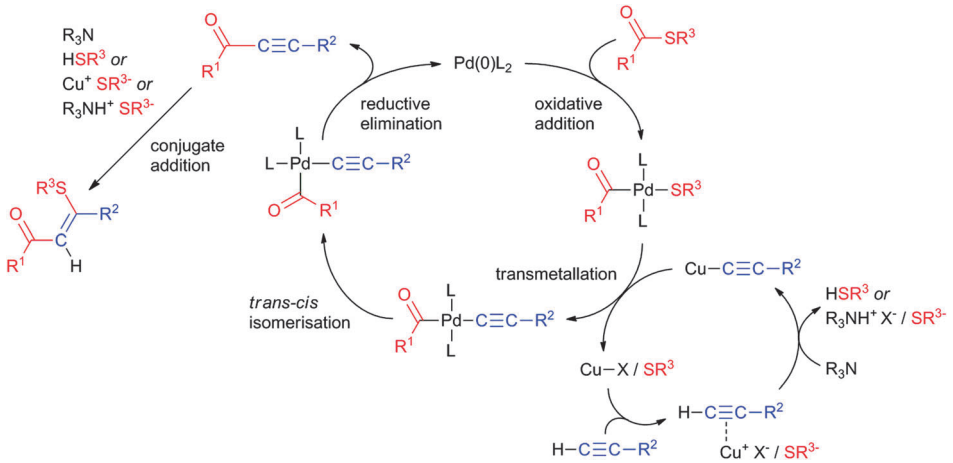
and not at all without $PdCl_2(PPh_3)_2$); $fcI_2$ is not required in any case. Based on studies by other groups,[20] we propose a reaction mechanism such as that shown in Scheme 4. (Tokuyama *et al.* previously isolated a series of 1-alkynyl ketones *via* an analogous process, using an excess of CuI to trap the thiolate anion.[20a] Under more forcing conditions, Minami *et al.* used a similar Pd/Cu catalysed reaction to prepare 2,3-dihydrothiopyran-4-one derivatives, isolating and reacting key intermediates to demonstrate the reaction pathway.[20b]) In the absence of Cu(I), it is speculated that an alkyne insertion step may occur in place of transmetallation.[21]

It was of additional interest to identify where Fc–I sits within the well-established aryl halides/triflate rate series,[22] and the observation that **4** forms even in the presence of $fcI_2$ is particularly revealing. From the above discussion it is certainly evident that $k_{(Ar–I)} \gg k_{(Fc–I)}$, as aryl iodides will rapidly cross-couple with terminal alkynes under most circumstances (resulting in high to quantitative yields, even at room temperature).[13] Noting also that aryl bromides are readily cross-coupled in the presence of thioacetate moieties,[23] it is inferred that rates of oxidative addition to Pd(0) follow the series: $k_{(Ar–I)} > k_{(Ar–OTf)} > k_{(Ar–Br)} > k_{(S–Ac)} > k_{(Fc–I)}$ (assuming oxidative addition to Pd(0) is always the rate-limiting step).

In conclusion, a systematic study into the Sonogashira cross-coupling of iodoferrocenes indicates that yields are maximised by employing high reagent concentrations and reaction temperatures. Though not immediately apparent given prior reports utilising iodoferrocenes,[15] we have shown that superior reactivity *can* be obtained in this context using the $PdCl_2(MeCN)_2$–$P(^tBu)_3$ combination. Utilisation of such conditions may prove invaluable when attempting cross-couplings of iodoferrocenes at room temperature or lower concentrations (Fig. S2, ESI†), for example when working with temperature-sensitive substrates or small quantities of advanced intermediates (following multi-step syntheses).

It was further demonstrated that the cross-coupling of terminal alkynes and iodoferrocenes is impracticable in the




**Scheme 4** A proposed reaction mechanism: producing cross-coupled acetyl-alkyne and thiolate products that subsequently react under basic conditions to produce $R^1C(O)CH{=}C(R^2)S(R^3)$-type compounds (interpreted from work by Tokuyama and Minami *et al.*[20]).



presence of thioacetate moieties. This is presumably due to a competing Pd-catalysed reaction between the thioacetate group and terminal alkyne(s), effectively blocking oxidative addition of Fc–I to Pd(0). Whilst the bifunctional ligand **2** yielded an isolable cyclic trimer (**4**), it is considered that systems of higher complexity have previously formed unexpected, potentially polymeric, product mixtures under Sonogashira conditions. Future work in our laboratories will explore these Fc–I and S–Ac based catalytic processes in more detail, the latter being important for biological applications (*e.g.* functionalization of SAc-terminated bioconjugates,[24] modification of biologically-relevant small molecules[25]) and the syntheses of novel chelates, redox-active materials and conducting polymers with β-thioketone linkages.

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## Notes and references

‡ Crystal data for **4**: $C_{30}H_{24}O_3S_3{\cdot}CH_2Cl_2$, $M$ = 613.60, monoclinic, *Cc* (no. 9), $a$ = 24.8640(4), $b$ = 24.0808(3), $c$ = 15.1854(3) Å, $\beta$ = 96.5311(18)°, $V$ = 9033.2(3) Å$^3$, $Z$ = 12 [3 independent molecules], $D_c$ = 1.354 g cm$^{-3}$, $\mu$(Mo-Kα) = 0.455 mm$^{-1}$, $T$ = 173 K, yellow blocks, Oxford Diffraction Xcalibur 3 diffractometer; 22 101 independent measured reflections ($R_{int}$ = 0.0304), $F^2$ refinement,[26] $R_1$(obs) = 0.0489, w$R_2$(all) = 0.1470, 18 011 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], $2\theta_{max}$ = 65°], 1099 parameters. The absolute structure of **4** was determined by a combination of *R*-factor tests [$R_1^+$ = 0.0489, $R_1^-$ = 0.0498] and by use of the Flack parameter [$x^+$ = 0.00(4), $x^-$ = 1.01(4)]. CCDC 927952.

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