Intramolecular Facilitation of Aryl-transfer from Tin in Palladium-catalysed Cross-coupling

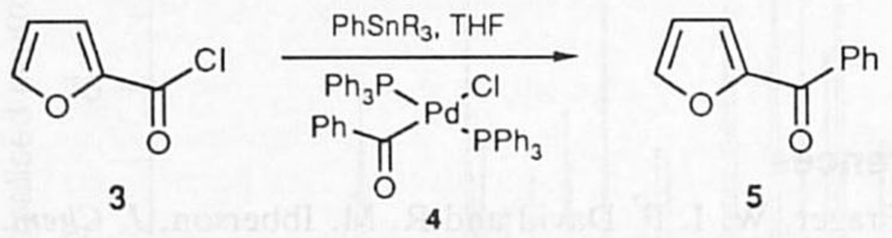
John M. Brown,[a] Mark Pearson,[a] Johann T. B. H. Jastrzebski[b] and Gerard van Koten[b]

[a] *Dyson Perrins Laboratory, South Parks Rd., Oxford, OX1 3QY, UK*
[b] *Department of Metal-mediated Synthesis, University of Utrecht, 3584 CH Utrecht, The Netherlands*

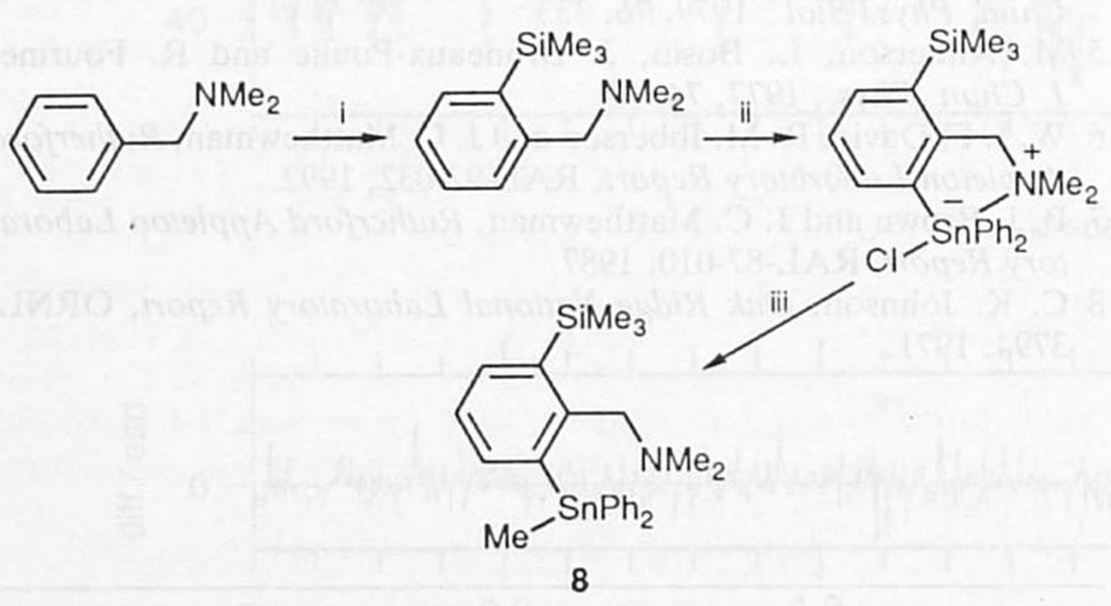
A neighbouring tertiary amino-group in the organotin reagent accelerates the palladium-catalysed arylation of furoyl chloride by a hundredfold.

The palladium- or nickel-catalysed cross-coupling of unsaturated centres is one of the most important current methods of C–C bond formation, and there are two distinct operational approaches. In the first, a vinyl halide, trifluoromethanesulfonate (triflate) or related electrophile is treated with an organomagnesium or organozinc moiety in the presence of the catalyst,[1] whereas the second uses a weaker nucleophile, which is typically an organoborane[2] or organostannane.[3] Although forcing conditions are often required for cross-coupling of organostannanes (*e.g.* elevated temperatures, HMPA or other dipolar aprotic solvents[4]), the methodology instituted by Stille finds increasing favour in synthesis because of the internal compatibility of the C–Sn bond with many functional groups and the access to carbonyl compounds through acylation and carbonylation variants. This effectively limits the synthetic utility to sp^2- and sp-substituted tin compounds, in which transmetallation to Pd is easier than for their sp^3-analogues.[5] The mechanism of transmetallation is not known, but may require nucleophilic attack at tin (*e.g.* by Cl^-) prior to the onset of C–Pd bonding, since reactions involving triflates require added LiCl in order to proceed. Indeed, Beletskaya and coworkers have demonstrated that Cu and Hg cross-couplings are catalysed by iodide ion.[6] For this reason, we have examined the reactivity of arylstannanes carrying a suitably placed tertiary amine capable of functioning as an internal nucleophile.

8-Lithio-1-dimethylaminonaphthalene has proved to be a useful intermediate for organometallic chemistry,[7] and is a precursor to the corresponding stannanes.[8] Interestingly, the simple alkyl and aryl derivatives such as **1a** possess latent C–Sn bonding with an interatomic distance of 2.88 Å, but halo-derivatives such as **2a** are five coordinate with a formal N–Sn bond (r = 2.49 Å) *trans* to the halogen atom. The C–Sn of the phenyl group *trans* to nitrogen is appreciably longer than the *cis* C–Sn bonds, and easy transfer of one Ph group to platinum has been noted.[8] The cross-coupling of related complexes with furoyl chloride **3** catalysed by 4 mol% of [*trans*-$PhCO(Cl)Pd(PPh_3)_2$] **4** in THF was attempted according to scheme 1. It was established first through control experiments that the reaction of $MeSnPh_3$ with compound **3** did not occur appreciably at 40 °C but required extensive heating at 65 °C, and that compound **5** was the sole coupling product. The stannane **1b** prepared by the published route[8] was subjected to the same cross-coupling conditions. The reaction could conveniently be followed by ^{119}Sn NMR spectroscopy and under conditions where $MeSnPh_3$ was essentially unreactive a smooth reaction occurred at 40 °C. The formation of the internally complexed halide **2b** as the sole tin-containing product supports a role for the nitrogen lone pair in the palladation step. Carrying out the same reaction with the 1-naphthyl analogue **6** required much more forcing conditions, similar to those operating with $MeSnPh_3$ and led essentially to phenyl rather than 1-naphthyl transfer.



Scheme 1 For the reactions of the aminostannanes **1b**, **7** and **8**, Ph transfer was complete and chemospecific from the ^{119}Sn NMR. Preparative experiments on a 0.1–0.2 mmol scale led to the isolation of up to 80% of furophenone **5**.

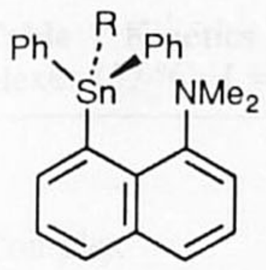


Scheme 2 *Reagents and conditions*: i, Bu^tLi, 30–40 petroleum ether; Me_3SiCl, THF, 53%; ii, Bu^tLi, 30–40 petroleum ether; Ph_2SnCl_2, Et_2O, 33%; iii, MeMgCl, THF, 25%

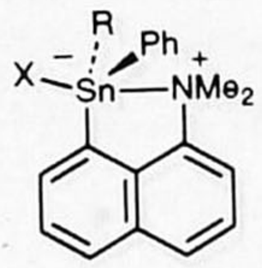
These results encouraged the preparation of the simple dimethylbenzylaminotin compound **7** by a directed lithiation–stannylation sequence and the analogue **8**, where the effect of steric buttressing[9] on reactivity can be gauged, *via* sequential double lithiation (Scheme 2). Both of these proved to be efficient reagents in the cross-coupling sequence of Scheme 1, comparable in reactivity to **1b** and giving rise to tin chlorides **9** and **10**, respectively. ^{119}Sn NMR spectroscopy† could conveniently be used to compare the relative reactivity of the three reagents **1b**, **7** and **8** at 40 °C and at ambient temperature,[10] and all were within a factor of two in both internal and external competition experiments. This indicates that neither the change in basicity on going from **1b** to **7** (parent amines: pK_a = 4.83 and 8.91, respectively)[11] nor the increased steric crowding in going from **7** to **8** has much influence; the critical factor is the intramolecular availability of the N lone-pair. Comparison is complicated by the fact that **1b** has its N lone-pair constrained close to the Sn–N vector whereas **7** possesses greater flexibility. The reactivity of $MeSnPh_3$ towards furoyl chloride catalysed by palladium complex **4** was not enhanced in the presence of $PhCH_2NMe_2$, underscoring the intramolecular mechanism of amine-induced rate enhancement. Further, compound **11**, the analogue of compound **7** is quite unreactive to catalytic cross-coupling under the specified conditions. It is probable that the chosen systems do not represent an optimum in intramolecular reactivity enhancement; the acute C–Sn bond angle of 69° in **1a** indicates a strained chelate.

In an important recent study of reactivity in Pd-catalysed reactions of organostannanes,[12] Farina and Krishnan have systematically examined the effect of ligands, and discovered

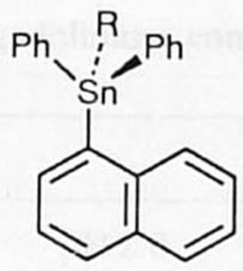
† ^{119}Sn data for key compounds (93.23 MHz, THF, relative to $SnMe_4$ = 0): δ **1b** −110.8 **2b** −98.2 **6** −88.1 **7** −115.9 **8** −123.5 **9** −108.8 **10** −119.3 **11** −91.5. Satisfactory elemental analyses were obtained for all $Ph_2Sn(Me)Ar$ compounds described.



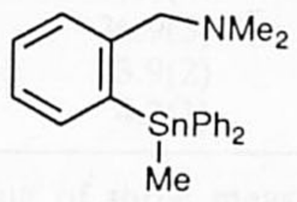
1a; R = Ph
b; R = Me



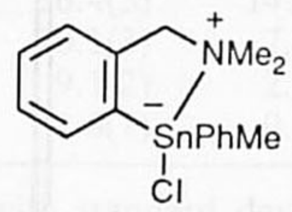
2a; R = Ph, X = Br
b; R = Me, X = Cl



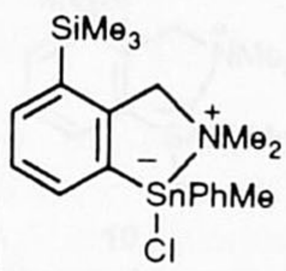
6



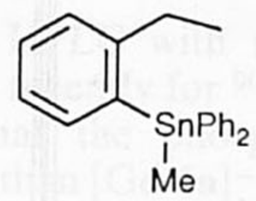
7



9



10



11

that the less basic ones, [$AsPh_3$ or $(2\text{-}C_4H_3O)_3P$] which were presumed to dissociate more readily from Pd, were superior to PPh_3. The key step in transmetallation was thought to involve a monoligated palladium complex produced by dissociation.[12] If the complex prepared *in situ* by reaction of $Pd(dba)_2$ with 4 equiv. of $AsPh_3$ was used as a catalyst, then the reaction of Scheme 1 went to completion in 30 h at 20 °C with compound **7** as substrate. Ph_3SnMe was unreactive under these conditions, although complete reaction was achieved at 40 °C, on the same timescale.

Hence, the intramolecular participation of a nitrogen lone-pair produces a *ca.* 10^2 enhancement of reactivity in Stille cross-coupling, and this effect can be further augmented by the correct choice of ligand. This paves the way for the development of tin-mediated cross-coupling with sp^3-carbon electrophiles, which is being actively pursued.

We thank the SERC (Quota studentship to M. P.) and the European Community (Grant CT000319) for support of this work, and Johnson-Matthey for the loan of precious metal salts.

Received, 12th June 1992; Com. 2/031011

References

1 K. Tamao and M. Kumada, *The Chemistry of the Metal-Carbon Bond*, ed. F. R. Hartley, John Wiley and Sons, Chichester, 1987, vol. 4, pp. 820; J. K. Stille, 1985, vol. 2 pp. 625.
2 N. Miyura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314; A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178; see C. M. Unrau, M. G. Campbell and V. Snieckus, *Tetrahedron Lett.*, 1992, **33**, 2773; W-C. Shieh and J. A. Carlson, *J. Org. Chem.*, 1992, **57**, 379, for recent examples.
3 *E.g.* J. M. Saa, G. Martorell and A. Garcia-Raso, *J. Org. Chem.*, 1992, **57**, 678; D. A. Elsley, D. McLeod, J. A. Miller, P. Quayle and G. M. Davies, *Tetrahedron Lett.*, 1992, **33**, 409.
4 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508.
5 Ag and Cu compounds can accelerate Stille cross-couplings, possibly by transmetallation: L. Liebeskind and R. W. Fengl, *J. Org. Chem.*, 1990, **55**, 5359; C. R. Johnson, J. P. Adams, M. P. Braun and C. B. W. Senanayake, *Tetrahedron Lett.*, 1992, **33**, 919; J. Malm, P. Björk, S. Gronowitz and A. B. Hörnfeldt, *Tetrahedron Lett.*, 1992, **33**, 2199.
6 I. P. Beletskaya, *J. Organomet. Chem.* 1983, **250**, 551.
7 E. Wehman, G. van Koten, D. M. Knotter, H. Spelten, D. Heindenrijk, A. N. S. Mak and C. H. Stam, *J. Organomet. Chem.*, 1987, **325**, 293; E. Wehman, G. van Koten, J. T. B. H. Jastrezebski, H. Ossor and M. Pfeffer, *J. Chem. Soc., Dalton Trans.*, 1988, 2975; G. P. C. M. Dekker, A. Buijs, C. J. Elsevier, K. Vrieze, P. W. N. M. van Leeuwen, W. J. J. Smeets, A. L. Spek, Y. F. Wang and C. H. Stam, *Organometallics*, 1992, **11**, 1937.
8 J. T. B. H. Jastrezebski, J. Boersma, P. M. Esch and G. van Koten, *Organometallics*, 1991, **10**, 930.
9 F. M. Menger, *Acc. Chem. Res.*, 1985, **18**, 128.
10 J. T. B. H. Jastrezebski, D. M. Grove, J. Boersma, G. van Koten and J. M. Ernsting, *Magn. Reson. Chem*, 1991, **29**, S25.
11 D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths, London, 1965.
12 V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585; V. Farina, S. R. Baker, D. A. Benigni, S. I. Hauck and C. J. Sapino, *J. Org. Chem.*, 1990, **55**, 5833.
13 *Note added in proof*: an elegant alternative approach to Sn activation in cross-coupling is reported by, E. Vedejs, A. R. Haight and W. O. Moss, *J. Am. Chem. Soc.*, 1992, **114**, 6556.

Stable Anionic, Neutral and Cationic Complexes of Gadolinium with Functionalised Amino-phosphinic Acid Macrocyclic Ligands

David Parker,*[a] Kanthi Pulukkody,[a] Timothy J. Norman,[a] Alice Harrison,[b] Louise Royle[a,b] and Carol Walker[b]

[a] *Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*
[b] *MRC Radiobiology Unit, Harwell, Didcot OX11 0RD, UK*

The synthesis and stability of anionic, neutral and cationic gadolinium complexes based on tetraazaphosphinic acid ligands is compared: lipophilic anionic complexes show biliary rather than renal clearance.

There are two major applications for those complexes of yttrium and gadolinium that are kinetically stable *in vivo*. The first involves the development of therapeutic radiolabelled conjugates of tumour-localising molecules (*e.g.* monoclonal antibodies labelled with ^{90}Y)[1] and the second concerns the clinical use of gadolinium complexes as paramagnetic contrast agents in magnetic resonance imaging.[2] In both situations, the metal complex must be stable with respect to acid- (or cation-) catalysed dissociation pathways in order to avoid the premature loss of the potentially lethal and bone-seeking 'free' ^{90}Y or of the highly toxic 'free' gadolinium ion. The most successful ligands, which have been used for this purpose, are based on the 1,4,7,10-tetraazacyclododecane skeleton, the ligand DOTA,† **1a**, being pre-eminent in this respect.[3] Having recently demonstrated that ^{90}Y-labelled antibody conjugates of **1a** and of the tetraphosphinic acid analogue **1b** (as *C*-, *N*- or *P*-functionalised derivatives) are sufficiently stable *in vivo* for therapeutic applications,[4,5] the problem of preparing stable gadolinium complexes is now being addressed. In an attempt to determine the structural features that define either the clearance pathway of the complex *in vivo* (*i.e.* renal or biliary

† DOTA = 1,4,7,10-tetrazacyclodecane-1,4,7,10-tetraacetic acid.