Ion-tagged π-acidic alkene ligands promote Pd-catalysed allyl–aryl couplings in an ionic liquid†

Patrick S. Bäuerlein,[ab] Ian J. S. Fairlamb,*[a] Amanda G. Jarvis,[a] Adam F. Lee,[a] Christian Müller,[b] John M. Slattery,*[a] Robert J. Thatcher,[a] Dieter Vogt[b] and Adrian C. Whitwood[a]

Received (in Cambridge, UK) 6th April 2009, Accepted 3rd August 2009
First published as an Advance Article on the web 2nd September 2009
DOI: 10.1039/b906823f

Ionic π-acidic alkene ligands based on chalcone and benzylidene acetone frameworks have been "doped" into ionic liquids to provide functional reaction media for Pd-catalysed cross-couplings of a cyclohexenyl carbonate with aryl siloxanes that allow simple product isolation, free from Pd (<50 ppm) and ligand contamination.

The importance of tuneable π-acidic alkene ligands, such as dibenzylidene acetone (dba-H), in Pd-catalysed couplings has recently been realised.[1] One of the drawbacks hindering the general use of alkene ligands is that they often share similar polarities to the desired reaction products, which complicates product separation and purification. In an elegant and comprehensive study, Denmark and Werner highlighted this as a problem for alkene ligands,[2] particularly dba-Z, in Pd-catalysed couplings of aromatic bromides with allylic silanolate salts, despite being promising ligands based on catalyst efficacy (yields and γ-selectivity). To address this key problem we have chosen to focus our alkene-ligand design strategy on ionic π-acidic alkene ligands based on simplified chalcone (**1**) and benzylidene acetone (**2**) frameworks (Fig. 1). These can be used to "dope" electron-deficient alkene functionality into common ionic liquids (ILs), which have been shown to be very promising reaction media for a range of Pd-catalysed coupling processes and other catalytic reactions.[3] Our hypothesis is that a remote ionic group can act as a "phase tag" to immobilise the alkene ligand in the IL, which can ultimately facilitate product recovery using biphasic IL–organic solvent conditions.

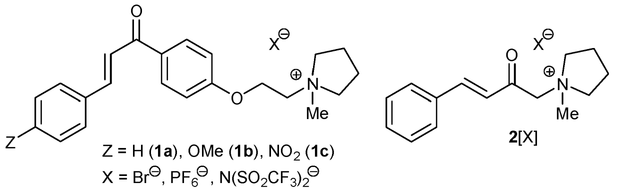
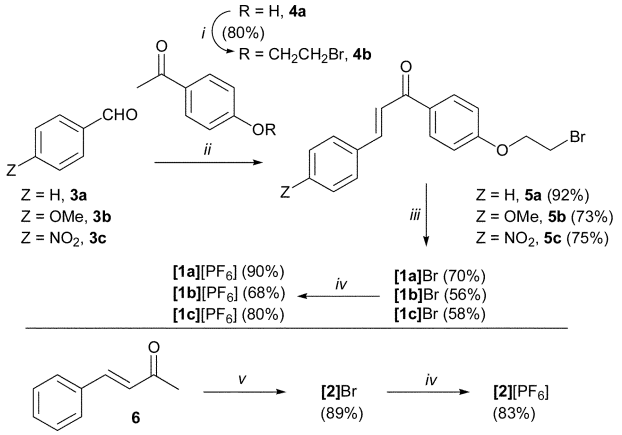


Fig. 1 Novel ion-tagged π-acidic alkene ligands.

To test this hypothesis, the ligands shown in Fig. 1 have been prepared using a general synthetic route (see ESI† for details). For example, in a typical synthesis, *p*-hydroxybenzophenone (**4a**) was reacted with 1,2-dibromoethane in the presence of K_2CO_3 to give 1-(4-(2-bromoethoxy)phenyl)ethanone (**4b**); the chalcone is then formed by subsequent reaction of **4b** with a *para*-substituted benzaldehyde (**3a–c**) under basic conditions to give **5a–c** in good yields. The final steps involve quaternisation of an amino functionality (*N*-methylpyrrolidine was selected as an arbitrary tertiary amine) with **5a–c** to give **1a–c**, respectively. Anion exchange is then possible, as necessary. The benzylidene acetone framework (**2**) was synthesised from **6** *via* a sequence of bromination, bromide displacement with *N*-methylpyrrolidine, and then anion exchange (Scheme 1).



Scheme 1 Synthesis of ion-tagged π-acidic alkene ligands (**1a–c**; **2**). *Reagents and conditions*: i, 1,2-DBE, K_2CO_3 (2 equiv.), 3-pentanone, 100 °C, 16 h; ii, NaOH (1.25 equiv.), EtOH–H_2O (1 : 2, v/v), 25 °C, 16 h; iii, *N*-methylpyrrolidine (excess), toluene, 60 °C, 16 h; iv, KPF_6 (1.1 equiv.), H_2O; v, pyrrolidone hydrotribromide (PHT) (1.2 equiv.), THF, 25 °C, then same as iii.

Single crystals of selected ionic alkene ligands were grown from dichloromethane–ether solutions at 5 °C and studied by X-ray diffraction (see ESI†), *e.g.* [**1a**]Br shown in Fig. 2.

The structural parameters can be compared to those of related neutral chalcones found in the Cambridge Structural Database, *e.g.* *E*-1-(4-(methoxyphenyl)-3-(phenyl)prop-2-en-1-one.[4] Inclusion of the cationic group does not substantially

---

[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: ijsf1@york.ac.uk, js633@york.ac.uk; Tel: +44 (0)1904 434091, +44 (0)1904 432610*
[b] *Department of Chemical Engineering and Chemistry, Schuit Institute of Catalysis, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands*

† Electronic supplementary information (ESI) available: Full synthetic details, X-ray crystal structure data, details of TEM measurements, kinetic studies and XRF measurements. CCDC 726739–726742. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b906823f

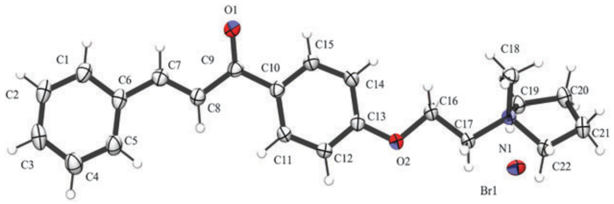
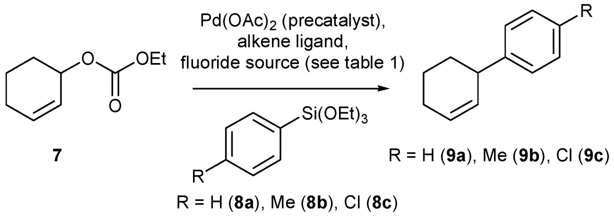


Fig. 2 Molecular structure of [**1a**]Br. Selected bonds (Å) and angles (°): C7–C8 1.342(4), C9–O1 1.235(3), C6–C7–C8 127.5(3), C7–C8–C9 119.3(2), C8–C9–C10 120.0(2), O1–C9–C10 119.7(2).

perturb the core α,β-unsaturated enone motif, suggesting that these ligands could behave similarly to neutral alkene ligands, *e.g.* dba-H and related, in Pd-catalysed coupling processes.

Alkene-doped ILs were prepared by the addition of the above ligands (2 equiv., based on the Pd loading of the reaction under study *vide infra*) into the ILs, 1-pentyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [C$_5$MIM][Tf$_2$N]) and 1-pentyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([C$_5$MPyrr][Tf$_2$N]) (see ESI† for synthesis). This strategy of "doping" functionality into common ILs has previously been used for strongly coordinating ligands (*e.g.* phosphine and *N*-heterocyclic carbenes),[5] but not for more labile ligands, such as π-acidic alkenes. The approach has significant benefits over the synthesis of ILs where the functionality of interest is incorporated into every ion pair, both in terms of cost and ease of formation of a material with suitable physical properties for metal catalysis, *e.g.* low melting point and relatively low viscosity.

The Hiyama-type cross-coupling of cyclohexenyl ethyl carbonate **7** with aryl siloxanes **8a–c** (shown in Scheme 2) was selected as a catalytic reaction for the alkene-doped ILs described above. Strong alkene-ligand effects are apparent in these couplings, and therefore it is a good benchmark.[6] To the best of our knowledge there are currently no reports of Hiyama-type couplings having been performed in ILs.



Scheme 2 Benchmark Pd-catalysed allyl–aryl coupling.

A range of conditions for the reaction of **7** + **8a** → **9a** (shown in Table 1; also see ESI†) were assessed. The initial reaction conditions (Pd loading, reaction time and temperature) used for the IL reactions (entries 1–9) are analogous to those used in related Hiyama couplings in conventional solvents and the yields obtained are equally good.[6] A test reaction using a neutral chalcone ligand in THF (entry 10) confirmed that the effectiveness of the doped IL reaction media is comparable to conventional solvents under these conditions. Subsequent experiments confirm that the Pd catalyst loading can be reduced to 4 mol%, retaining excellent product conversions for most of the alkene ligands tested (entries 11–14).

Table 1 Allyl–aryl coupling reaction conditions used (shown in Scheme 2; **7** + **8a** → **9a**)

Entry	Ligand	F$^-$ source	Solvent	Conv. (%)^d
1^a	[**1a**]Br	[Bu$^n_4$N]F	[C$_5$MIM][Tf$_2$N]	—
2^a	[**1a**]Br	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	>99
3^a	[**1a**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	>99
4^a	[**1b**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	(80)
5^a	[**1c**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	(60)
6^a	[**2**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	>99
7^a	None	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	Trace
8^a	[**1a**]Br	NaF, KF or CsF	[C$_5$MPyrr][Tf$_2$N]	—
9^a	[**1a**]Br	[Bu$^n_4$N][Ph$_3$SiF$_2$]	[C$_5$MPyrr][Tf$_2$N]	—
10^a	Neutral^e	[Bu$^n_4$N]F	THF	>99
11^b	[**1a**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	85
12^b	[**1b**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	99
13^b	[**1c**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	27
14^b	[**2**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	95
15^c	[**1a**][PF$_6$]	[Bu$^n_4$N]F	[C$_5$MPyrr][Tf$_2$N]	94

[a] Typical conditions: Pd(OAc)$_2$ (10 mol%), ligand (20 mol%), IL (4 mL), 55 °C, 16 h, cyclohex-2-enyl ethyl carbonate **7** (0.712 mmol), Si(Ph)(OEt)$_3$ (1.42 mmol), 1 M [Bu$^n_4$N]F in THF (2.84 mmol)—THF removed under vacuum after addition of IL (or equivalent CsF or [Bu$^n_4$N][Ph$_3$SiF$_2$] used). [b] Pd(OAc)$_2$ (4 mol%), ligand (8 mol%), IL (2 mL), 50 °C, 17 h, cyclohex-2-enyl ethyl carbonate **7** (0.44 mmol), Si(Ph)(OEt)$_3$ (0.71 mmol), [Bu$^n_4$N]F(H$_2$O)$_3$ (1.42 mmol); dried *in vacuo* prior to addition of IL. [c] As for b, but using 4 mol% ligand. [d] Conversion determined by ^{1}H NMR spectroscopy or GC analysis. Isolated yields given in brackets; reactions scaled up by a factor of 4. [e] Chalcone is *E*-1-(4-(piperidinophenyl)-3-(phenyl)prop-2-en-1-one.

In all cases, where coupling proceeded, Pd nanoparticles were formed in the reaction mixtures after *ca.* 15 min. After which time, a gradual darkening occurred, suggesting an increase in Pd nanoparticle (colloid) concentration, a finding that mirrors reported observations showing that such species effectively mediate Hiyama couplings.[7] On reaction completion, the products could be simply separated from the reaction mixture by washing with Et$_2$O or hexane followed by a quick filtration through a silica plug (1 g) (to remove any traces of IL and TBAF), giving **9a** with minimal Pd leaching (Pd content < 50 ppm—from XRF measurements). Kugelrohr distillation of the product from the essentially non-volatile IL is also very effective. Crucially, in all cases the product was free from chalcone ligand contamination (by ^{1}H NMR, 400 MHz). Thus, the strategy of alkene-ligand ion-tagging, and use of an ionic liquid solvent, simplifies product recovery in the reaction, which ordinarily requires time-consuming chromatographic separation of the product and ligand.

The reaction **7** + **8a** → **9a** proceeds well in the alkene-doped [C$_5$MPyrr][Tf$_2$N] ILs with all the ligands that were tested (entries 2–6), but intriguingly **9a** was not observed when [C$_5$MIM][Tf$_2$N] was used as the "base" IL (entry 1). We are currently investigating this effect, which may be related to carbene formation.

We have determined that the alkene functionality in the IL is essential for successful coupling, as only a trace amount of product was formed in the absence of the alkene ligand in [C$_5$MPyrr][Tf$_2$N] (entry 7). The fluoride source is also very important for successful coupling (entries 2, 8 and 9). When [Bu$^n_4$N]F was used, the reaction proceeded smoothly, whilst finely ground NaF, KF, CsF and [Bu$^n_4$N][Ph$_3$SiF$_2$] resulted in no product formation. The low solubility of the metal fluorides in the ILs explains the former result, however it is less clear why reactions involving [Bu$^n{}_4$N][Ph$_3$SiF$_2$] were unsuccessful. The relative "nakedness" of F$^-$ could be an important factor, as F$^-$ is already coordinated to a hypervalent Si center in [Bu$^n{}_4$N][Ph$_3$SiF$_2$]. In contrast, F$^-$ may be relatively poorly solvated, and thus more nucleophilic, in [Bu$^n{}_4$N]F dissolved in these ILs.

In order to probe any substituent effects in the alkene-doped ILs we have evaluated ionic chalcones [**1a**][PF$_6$], [**1b**][PF$_6$] and [**1c**][PF$_6$], which contain *para*-H, OMe and NO$_2$ groups, respectively. The data in Table 1 show that all three ligands give doped ILs with [C$_5$MPyrr][Tf$_2$N] that are active for the coupling reactions studied. However, the isolated yields from ligands [**1b**][PF$_6$] and [**1c**][PF$_6$] (80% and 60%, respectively) suggest that electron-donating or electron-withdrawing substituents on the ligand may significantly influence the reaction. In neutral alkenes, this has been linked to the relative σ-donor, π-acceptor properties of the alkenes when bound to Pd$^{0/\mathrm{II}}$ species.[1] In order to better understand this effect in the alkene-doped ILs the relative rates of reaction for the OMe and NO$_2$ substituted chalcones were measured by GC and found to be 1 and 0.12, respectively. These data suggest that the electron-releasing methoxy group (ligand [**1b**][PF$_6$]) promotes a significantly faster reaction than the electron-withdrawing NO$_2$ group (ligand [**1c**][PF$_6$]). Initial recycling experiments suggest that the IL–catalyst system is not catalytically active following extraction of the products. A build up of salt byproducts or Pd nanoparticle deactivation could explain this outcome. Work is in progress to address this issue.

TEM measurements were performed on the nanoparticulate Pd formed *in situ* in these reactions (see ESI†). Micrographs from the reactions involving ligands [**1b**][PF$_6$] and [**1c**][PF$_6$] are illustrated in Fig. 3. These micrographs, and others that we have collected during this study, show that the nanoparticulate Pd formed during the reactions in alkene-doped ILs have narrow size distributions. Of particular note is the relative size of the Pd nanoparticles. The nanoparticles formed from the IL doped with ligand [**1b**][PF$_6$] have sizes of 1–3 nm, whereas those from the [**1c**][PF$_6$]-doped IL have sizes of 10–15 nm. This suggests that the chalcone ligand could be involved in catalyst stability, nanoparticle formation or dissolution of mono-nuclear Pd^0 species, and that substituent effects are important in this process, akin to polyfluorinated-dba stabilised Pd nanoparticles (4–5 nm).[8] The difference in nanoparticle size in the two systems, for [**1b**][PF$_6$] and [**1c**][PF$_6$], can be compared to the relative rates of reaction for the two doped ILs and suggests that smaller nanoparticles lead to increased rates. A nanoparticle size of *ca.* 2 nm is optimal for related coupling processes.[9]

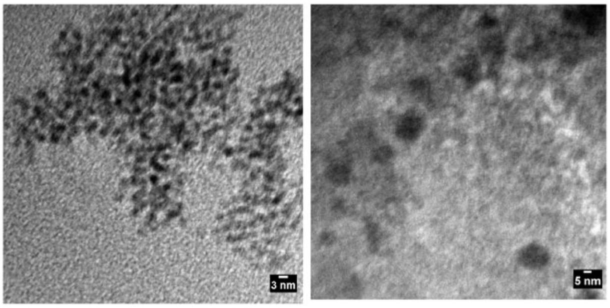


Fig. 3 TEM images of Pd nanoparticles formed during coupling reactions using conditions in Table 1 entry 4 (left) and entry 5 (right).

Aryl siloxane substituent effects are also seen; alkene-doped ILs (with **1a**) used in this study were tested against *para*-H, Me and Cl substituted siloxanes (as shown in Scheme 2). The relative rates of reaction in a competition experiment involving all three siloxanes were measured using HRGC (1, 0.5 and 3.7, respectively). As in DeShong's work,[6] *para* electron-withdrawing substituents in aryl siloxanes increase the rate of reaction, suggesting that the results obtained from the coupling in alkene-doped ILs exhibit similar trends to comparable reactions in conventional solvents.

In summary, alkene-doped, functional ILs are excellent reaction media for Pd-catalysed allyl–aryl couplings, simplifying product recovery. The presence of alkene functionality in the IL is essential for the formation of the cross-coupled product and alkene-ligand substituent effects, similar to those seen using neutral alkene ligands, are operative in these systems. These effects can be related to the Pd nanoparticle size formed during the reaction, although a more subtle effect at Pd$^{\mathrm{II}}$ cannot be ruled out. Investigations to determine whether these ligands can be used as probes to help with the elucidation of catalytic mechanisms using mass spectrometric methods are in progress.

The authors thank the University of York (J.M.S), the Royal Society and Astra Zeneca (I.J.S.F), the NRSCC and ERASMUS (P.S.B.) and the Netherlands Organization for Scientific Research (NWO) (C.M.) for financial support. We thank C. Biewer for starting material syntheses.

Notes and references

1 I. J. S. Fairlamb, *Org. Biomol. Chem.*, 2008, **6**, 3645–3656; H. Zhang, X. Luo, K. Wongkhan, H. Duan, Q. Li, L. Zhu, J. Wang, A. S. Batsanov, J. A. K. Howard, T. B. Marder and A. Lei, *Chem.–Eur. J.*, 2009, **15**, 3823–3829.
2 S. E. Denmark and N. S. Werner, *J. Am. Chem. Soc.*, 2008, **130**, 16382–16393.
3 R. Singh, M. Sharma, R. Mamgain and D. S. Rawat, *J. Braz. Chem. Soc.*, 2008, **19**, 357–379; V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615–2665; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772–3789; J. Dupont, R. F. d. Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667–3692; P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, New York, 2007; C. E. Song, *Chem. Commun.*, 2004, 1033–1043; T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083; T. Welton, *Coord. Chem. Rev.*, 2004, **248**, 2459–2477; J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223–226.
4 L. Zhengdong, H. Liangren and S. Genbo, *Acta Crystallogr., Sect. C*, 1992, **48**, 751.
5 S.-G. Lee, *Chem. Commun.*, 2006, 1049–1063; R. Šebesta, I. Kmentovàb and Š. Toma, *Green Chem.*, 2008, **10**, 484–496.
6 K. H. Shukla and P. DeShong, *J. Org. Chem.*, 2008, **73**, 6283–6291.
7 L. D. Pachón, M. B. Thathagar, F. Hartl and G. Rothenberg, *Phys. Chem. Chem. Phys.*, 2006, **8**, 151–157; E. Alacid and C. Nájera, *Adv. Synth. Catal.*, 2006, **348**, 945–952; D. Srimani, S. Sawoo and A. Sarkar, *Org. Lett.*, 2007, **9**, 3639–3642.
8 M. Tristany, J. Courmarcel, P. Dieudonné, M. Moreno-Mañas, R. Pleixats, A. Rimola, M. Sodupe and S. Villarroya, *Chem. Mater.*, 2006, **18**, 716–722.
9 J. Liu, Y. Deng, H. Wang, H. Zhang, G. Yu, B. Wu, H. Zhang, Q. Li, T. B. Marder, Z. Yang and A. Lei, *Org. Lett.*, 2008, **10**, 2661–2664.