

A silver-free system for the direct C–H auration of arenes and heteroarenes from gold chloride complexes†

Cite this: *Catal. Sci. Technol.*, 2013, 3, 2892Received 12th April 2013,
Accepted 13th June 2013

DOI: 10.1039/c3cy00240c

www.rsc.org/catalysis

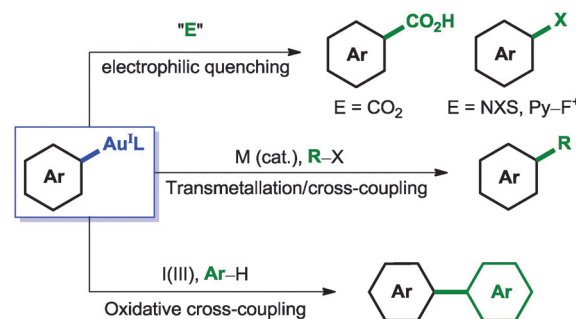
Nanna Ahlsten, Gregory J. P. Perry, Xacobe C. Cambeiro, Tanya C. Boorman and Igor Larrosa*

A new methodology for the direct C–H auration of electron-deficient arenes and heteroarenes with simple bases and readily available $[\text{Au}(\text{PR}_3)\text{Cl}]$ complexes is described. This system allows the preparation of a wide scope of aryl–Au(I) compounds without the need for using Ag(I) additives or preparing and isolating basic Au(I) hydroxide complexes.

Introduction

Direct functionalisation of arenes by metal-catalysed C–H activation is among the most active topics in organic synthesis. Although dominated by Pd, other metals such as Cu, Rh, Ru, Ir or Co have been shown in recent years to mediate this type of reaction.¹ Au(III) salts have also been used in C–H activation of electron-rich arenes under mild conditions.^{2,3} In contrast to Au(III), Au(I)-promoted C–H activation to afford (hetero)aryl–Au(I) compounds has been demonstrated only recently and is specific for electron-poor arenes.⁴

Studies on the chemistry of (hetero)aryl–Au(I) compounds (Scheme 1) have shown them to be suitable organometallic partners for Pd- or Ni-catalysed cross-coupling reactions,⁵ although systems catalytic in Au are scarce.⁶ These species have also been shown to react with appropriate electrophiles such as CO_2 ,⁷ electrophilic halogen sources⁸ or strong acids.^{6a,8b} Finally, oxidation with I(III) reagents has allowed their use in the direct C–H arylation of electron-rich arenes exploiting the orthogonal selectivity of both Au oxidation states towards C–H activation, which opens a path for the development of Au(I/III)-catalysed double C–H activation cross-coupling reactions.⁹

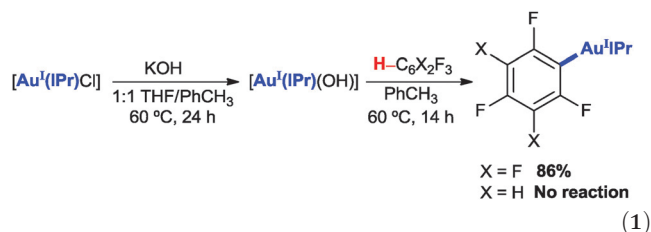


Scheme 1 Transformations of aryl–Au(I) compounds.

Aryl–Au(I) compounds are remarkably stable towards common decomposition pathways that affect related organometallic compounds.^{10,11} Thus, in addition to being air and moisture-stable, they do not participate in oxidative addition reactions,¹² undergo protodeauration only in the presence of relatively strong acids^{6a,8b,13} and, although one-electron reduction to Au(0) is possible with mild reductants such as Pd(0), this reaction is sufficiently slow to be outcompeted by other processes.^{6,14}

This combination of rich reactivity and stability towards undesired decomposition pathways makes aryl–Au(I) compounds extremely interesting intermediates in the design of metal-catalysed transformations.

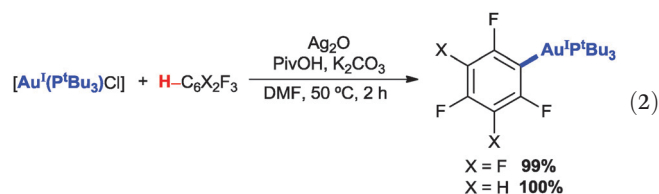
Two C–H auration systems have been reported to date by Nolan's group^{4b,c} (eqn (1)) and our group^{4a} (eqn (2)) based on the use of a $[\text{Au}(\text{IPr})(\text{OH})]$ or a $[\text{Au}(\text{PR}_3)\text{Cl}]$ – Ag_2O – K_2CO_3 – PivOH reagent system, respectively.



School of Biological and Chemical Sciences, Queen Mary University of London,
Joseph Priestley Building, Mile End Road, E1 4NS, London, UK.

E-mail: i.larrosa@qmul.ac.uk; Web: <http://webpace.qmul.ac.uk/ilarrosa/index.html>

† Electronic supplementary information (ESI) available: Experimental details, characterisation data and spectra of new compounds. See DOI: 10.1039/c3cy00240c



It is worth noting that the second of these systems, despite working in an overall less basic medium, shows a higher activity, as exemplified by the direct auration of 1,3,5-trifluorobenzene ($pK_a = 31.5$)¹⁵ which is not possible under the standard conditions reported for the $[\text{Au}(\text{IPr})(\text{OH})]$ system. The exact origin of this difference in activity has been a matter of discussion,^{4c,16} although no thorough mechanistic studies have been published to date.

We considered that the development of a system using a readily available $[\text{Au}(\text{PR}_3)\text{Cl}]$ starting complex and a simple base, without other additives, would not only be synthetically useful but also help us determine which are the real differences between the reactivity of phosphine- and NHC-ligated gold complexes towards C–H activation of electron-deficient arenes.

Results and discussion

We took as a starting point for this investigation our previously reported conditions for the direct auration of electron-deficient arenes ($[\text{Au}(\text{P}^t\text{Bu}_3)\text{Cl}]$, PivOH, Ag_2O and K_2CO_3 , eqn (2)) and studied the possibility of performing the reaction with only the base, in the absence of PivOH or Ag^+ salts. Unsurprisingly, K_2CO_3 alone was not able to promote the reaction by itself when applied to $[\text{Au}(\text{P}^t\text{Bu}_3)\text{Cl}]$ (**1a**) and 1,3-dinitrobenzene (**2a**) in DMF (Table 1, entry 1). However, shifting to the stronger, but

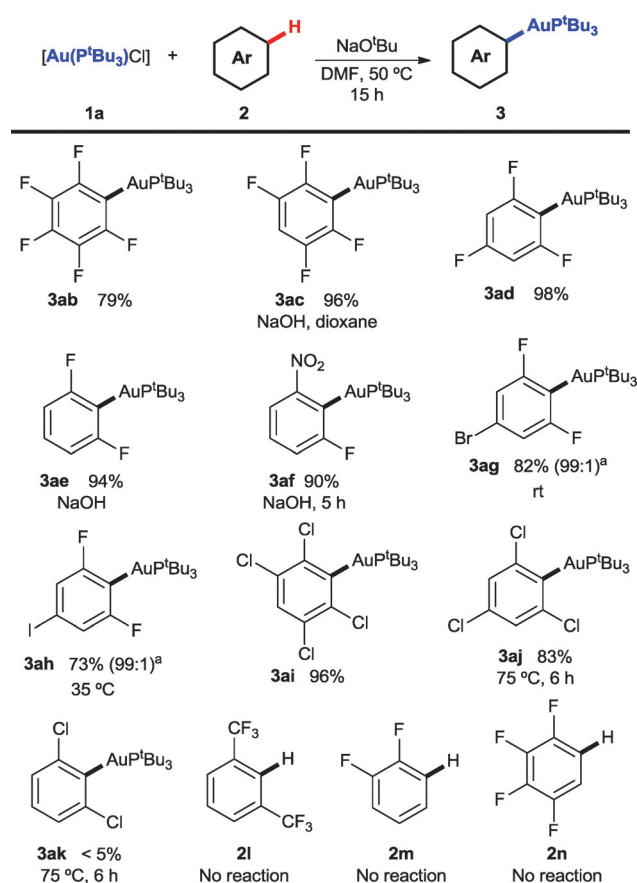
still simple, bases KOH (entry 2) or KO^tBu (entry 3) allowed us to obtain product **3aa** in 47 and 80% yields, respectively. Interestingly, use of the more soluble LiO^tBu (entry 4) resulted in a decreased yield, while the less soluble NaO^tBu (entry 5) gave a result comparable to that obtained with KO^tBu . Consistently, NaOH (entry 6) afforded a somewhat higher yield than KOH, although still lower than the *tert*-butoxide salts. The use of 4 equiv. of **2a** was necessary for optimal performance of the reaction, lower yields being obtained with smaller amounts of **2a** (entry 7).¹⁷ Less polar solvents, shown to be effective in direct auration with $[\text{Au}(\text{IPr})(\text{OH})]$, turned out to be detrimental in this case (entries 8 and 9), while dioxane (entries 10 and 11) afforded a yield very similar to that obtained in DMF. Finally, increasing the temperature to 75 °C in DMF with NaO^tBu (entry 12) allowed us to obtain the aured product in 82% yield after purification (90% NMR yield).

With these optimised conditions, we set out to explore the scope of the reaction, aiming to determine the reactivity of this system towards electron-poor arenes (Scheme 2). A variety of polyfluorinated benzenes **2b–e**, as well as 1-fluoro-3-nitrobenzene **2f**, reacted smoothly to afford the corresponding aryl–Au(i) compounds **3ab–3af** in excellent

Table 1 Optimisation of the reaction conditions^a

Entry	Base	Solvent	Yield (%)
1	K_2CO_3	DMF	0
2	KOH	DMF	47
3	KO^tBu	DMF	80
4	LiO^tBu	DMF	57
5	NaO^tBu	DMF	81
6	NaOH	DMF	64
7 ^b	NaO^tBu	DMF	31
8	NaO^tBu	THF	45
9	NaO^tBu	PhCH_3	30
10	NaO^tBu	1,4-Dioxane	80
11	NaOH	1,4-Dioxane	74
12 ^c	NaO^tBu	DMF	90 (82) ^d

^a Reactions carried out on the 0.03 mmol scale with **1a** as the limiting reagent, 4 equiv. of **2a**, 4 equiv. of base and 0.15 mL of solvent (0.2 M), at 50 °C for 18 h. Yields determined using ^1H NMR with an internal standard. ^b Reaction performed with 2 equiv. of **2a**. ^c Reaction at the 0.1 mmol scale, at 75 °C for 5 h. ^d Isolated yield.



Scheme 2 Scope of the direct C–H auration of arenes. Reactions carried out between the 0.06 and 0.1 mmol scale with **1a** as the limiting reagent, 4 equiv. of **2** and 4 equiv. of NaO^tBu in DMF (0.2 M) at 50 °C for 15 h, unless stated otherwise. Yields are of the pure isolated product. ^a Regioisomer ratios determined using ^1H NMR of the crude mixture.

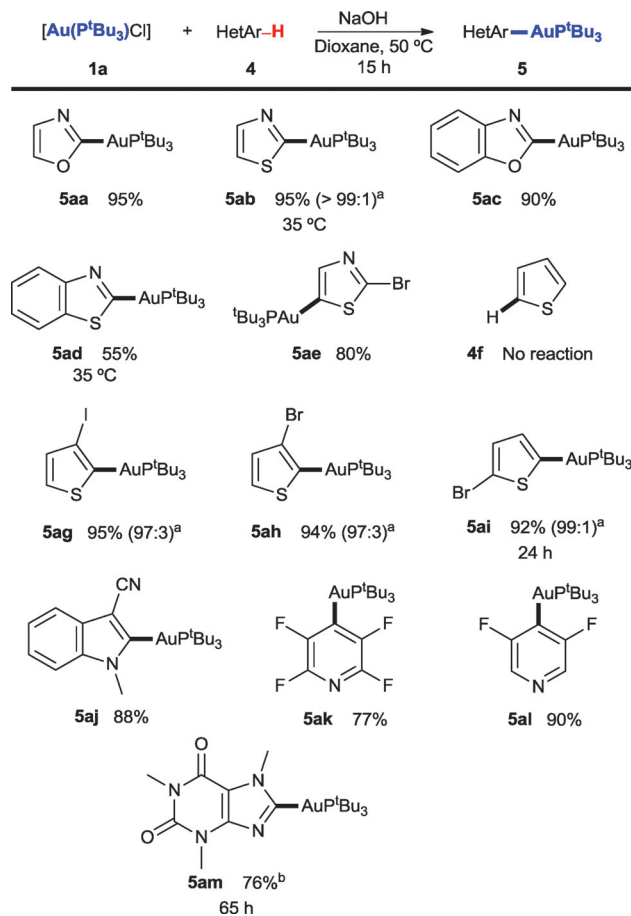


yields with only slight variations in the general procedure in some cases (use of NaOH as the base in 1,4-dioxane). Remarkably, even **2d** reacted at 50 °C without any additive. This contrasts with previous observations where [Au(IPr)(OH)] was not able to activate this substrate under the standard conditions (eqn (1)), requiring the use of a silver salt as an additive.¹⁶ A higher basicity of the active phosphine–Au(I) complex compared to that of [Au(IPr)(OH)] could explain this difference (*vide infra*). Benzene derivatives bearing two F atoms and another halogen such as Br or I (**2g–h**) reacted preferentially with the C–H bond *ortho* to the two F atoms, with virtually complete regioselectivity at nearly room temperature. These substrates are particularly interesting since, after functionalisation of the C–Au bond, they would give place to products bearing a useful functional group for further reactions *via* other metal-catalysed coupling processes.

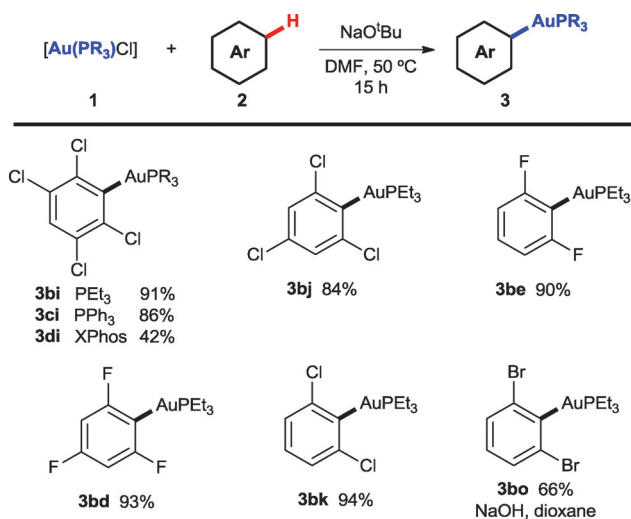
Polychlorinated benzenes **2i–k** were also reactive, although in this case at least three chlorine atoms were necessary for good yields. 1,3-Di(trifluoromethyl)benzene **2l** failed to afford any aured product, as well as benzenes without a C–H bond *ortho* to two electron-withdrawing groups (**2m–n**).

A wide scope was also observed for electron-deficient heteroarenes (Scheme 3), with a clear dependence of reactivity on the acidity of the C–H bond to be activated. A brief re-examination of the reaction conditions showed that NaOH in 1,4-dioxane consistently afforded higher yields in the case of heteroarenes. Under these conditions, oxazole (**4a**), thiazole (**4b**), benzoxazole (**4c**) and benzothiazole (**4d**) all reacted to afford the corresponding auration products **5aa–5ad** in good yields. In the case of thiazole, displaying two roughly equally acidic protons ($pK_a = 29.5$ for the C2 position and 29.6 for C4),¹⁵ selective C2-auration (>99:1) to give **5ab** could be achieved at 35 °C. Additionally, blocking the C2 position with a Br substituent allowed preparation of the C4-aured product **5ae**, keeping the Br intact and available for further functionalisation. The less acidic thiophene (**4f**, $pK_a = 32.5$)¹⁵ was found not to be active in the reaction, thus determining an upper limit for the activity of our system. However, the presence of just one halogen substituent lowered the pK_a sufficiently for the corresponding aured products **5ag–5ai** to be obtained in excellent yields and regioselectivities, with auration occurring selectively α to the sulfur. Similarly, just one strong electron-withdrawing group allowed C2-auration of indole-type substrates (pK_a of *N*-methylindole = 37.3)¹⁵ to obtain **5aj**, and two electron-withdrawing groups allowed preparation of pyridyl–Au(I) compounds **5ak–5al**. Finally, a stable, electron-deficient imidazole-type substrate such as caffeine (**4m**) could be used, affording product **5am** in good yield and using only 1.1 equiv. of the parent heteroarene.

Phosphine ligands other than P^tBu_3 were also explored (Scheme 4). For the highly electron-deficient tetrachlorobenzene, both alkyl and aryl phosphines (**3ai–3ci**) afforded high yields, and only with the very bulky XPhos (**3di**) was the yield significantly reduced. Reaction of 1,3,5-trichloro- and 1,3-difluorobenzene with [Au(PEt₃)Cl] also led to excellent yields, comparable to those obtained with the P^tBu_3 ligand (compare

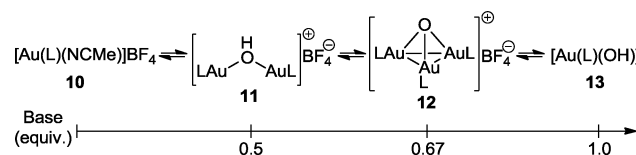


Scheme 3 Scope of the direct C–H auration of heteroarenes. Reactions carried out between the 0.06 and 0.1 mmol scale with **1a** as the limiting reagent, 4 equiv. of the corresponding heteroarene **4** and 4 equiv. of NaOH in 1,4-dioxane (0.2 M) at 50 °C for 15 h, unless stated otherwise. Yields are of the pure isolated product. ^a Regioisomer ratios determined using ¹H NMR of the crude product. ^b Reaction carried out with 1.1 equiv. of caffeine.



Scheme 4 Application of different phosphines. Reactions carried out between the 0.06 and 0.1 mmol scale with **1a** as the limiting reagent, 4 equiv. of **2** and 4 equiv. of NaOtBu in DMF (0.2 M) at 50 °C for 15 h, unless stated otherwise. Yields are of the pure isolated product.



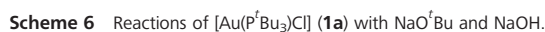


Scheme 7 Previously reported products obtained from basic treatment of [Au(L)(NCMe)]BF₄ complex **10**. L = XPhos or JohnPhos.²³

Trinuclear μ^3 -oxo Au(I) species with biphenyl(dialkyl)-phosphines (**12**, Scheme 7) have recently been shown to be related to **10**, **11** and **13** by an equilibrium which depends on the stoichiometry with respect to the base, as well as on the steric properties of the phosphine ligand.²³ The analogous compound **1d** (PR₃ = XPhos) was effective in the auration process under the conditions reported here (product **3di** in Scheme 4), leading us to hypothesise that a qualitatively similar situation could take place also with the other phosphines. Thus, *in situ* formation of a Au(I) hydroxide species, even as a minor component in the equilibrium mixture, can be hypothesised. Alternatively, direct deprotonation of the arene by the base followed by attack of the resulting aryl anion on an electrophilic gold(I) complex cannot be discarded either.²⁴

In summary, we have developed a simplified methodology for efficiently performing direct C–H auration of electron-deficient arenes and heteroarenes, combining readily available $[\text{Au}(\text{PR}_3)\text{Cl}]$ complexes and simple bases. This system shows excellent activity for a wide range of substrates without requiring the use of silver salts as additives or the preparation and isolation of Au(I) hydroxide complexes.

We gratefully acknowledge the Engineering and Physical Sciences Research Council for generous funding, the European Research Council for a Starting Research Grant (to I.L.),



the Marie Curie Foundation for an Intra-European Fellowship (to X.C.C.) and the EPSRC National Mass Spectrometry Service (Swansea).

Notes and references

- For recent reviews on C–H activation, see: (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (b) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (c) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (d) *Modern Arylation Methods*, ed. L. Ackermann, 1st edn, Wiley-VCH, Weinheim, 2009; (e) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (f) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (g) C–H Activation in *Topics in Current Chemistry*, ed. J.-Q. Yu and Z. Shi, Springer, Heidelberg, 1st edn, 2010, vol. 292; (h) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761.
- (a) M. S. Kharasch and H. S. Isbell, *J. Am. Chem. Soc.*, 1931, **53**, 3053–3059; (b) M. S. Kharasch and T. M. Beck, *J. Am. Chem. Soc.*, 1934, **56**, 2057–2060; (c) K. S. Liddle and C. Parkin, *J. Chem. Soc., Chem. Commun.*, 1972, 26a; (d) F. Calderazzo and D. B. Dell'Amico, *J. Organomet. Chem.*, 1974, **76**, C59–C60; (e) P. W. J. de Graaf, J. Boersma and G. J. M. van der Kerk, *J. Organomet. Chem.*, 1976, **105**, 399–406.
- For reviews on Au-catalysed C–H activation: (a) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910–1925; (b) H. A. Wegner and M. Auzias, *Angew. Chem., Int. Ed.*, 2011, **50**, 8236–8247; (c) T. De Haro and C. Nevado, *Synthesis*, 2011, 2530–2539; (d) R. Skouta and C.-J. Li, *Tetrahedron*, 2008, **64**, 4917–4938.
- (a) P. Lu, T. C. Boorman, A. M. Z. Slawin and I. Larrosa, *J. Am. Chem. Soc.*, 2010, **132**, 5580–5581; (b) S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2010, **46**, 2742–2744; (c) S. Gaillard, C. S. J. Cazin and S. P. Nolan, *Acc. Chem. Res.*, 2012, **45**, 778–787.
- Metal-catalysed coupling reactions with stoichiometric organo-Au(I) complexes: (a) Y. Shi, S. D. Ramgren and S. A. Blum, *Organometallics*, 2009, **28**, 1275–1277; (b) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi and F. Rominger, *Angew. Chem., Int. Ed.*, 2009, **48**, 8243–8246; (c) A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel and F. Rominger, *Adv. Synth. Catal.*, 2010, **352**, 1307–1314; (d) M. Peña-López, M. Ayán-Varela, L. A. Sarandeses and J. Pérez-Sestelo, *Chem.–Eur. J.*, 2010, **16**, 9905–9909; (e) J. J. Hirner, Y. Shi and S. A. Blum, *Acc. Chem. Res.*, 2011, **44**, 603–613; (f) J. J. Hirner and S. A. Blum, *Organometallics*, 2011, **30**, 1299–1302.
- For a Pd/Au dual-catalysed Stille coupling proceeding through an aryl-Au(I) intermediate, see: (a) J. Delpozo, D. Carrasco, M. H. Pérez-Temprano, M. García-Melchor, R. Alvarez, J. A. Casares and P. Espinet, *Angew. Chem., Int. Ed.*, 2013, **52**, 2189–2193. For other dual Au/TM catalytic systems, see: (b) L. A. Jones, S. Sanz and M. Laguna, *Catal. Today*, 2007, **122**, 403–406; (c) Y. Shi, S. M. Peterson, W. W. Haberaecker and S. A. Blum, *J. Am. Chem. Soc.*, 2008, **130**, 2168–2169; (d) Y. Shi, K. E. Roth, S. D. Ramgren and S. A. Blum, *J. Am. Chem. Soc.*, 2009, **131**, 18022–18023; (e) B. Panda and T. K. Sarkar, *Tetrahedron Lett.*, 2010, **51**, 301–305; (f) J. J. Hirner, K. E. Roth, Y. Shi and S. A. Blum, *Organometallics*, 2012, **31**, 6843–6850; (g) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. De Buck Becker, M. Rudolph, C. Scholz and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 133–147; (h) B. Sahoo, M. N. Hopkinson and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 5505–5508.
- I. I. F. Boogaerts and S. P. Nolan, *J. Am. Chem. Soc.*, 2010, **132**, 8858–8859.
- (a) A. S. K. Hashmi, T. D. Ramamurthi and F. Rominger, *J. Organomet. Chem.*, 2009, **694**, 592–597; (b) J. Cornella, M. Rosillo-Lopez and I. Larrosa, *Adv. Synth. Catal.*, 2011, **353**, 1359–1366.
- X. C. Cambeiro, T. C. Boorman, P. Lu and I. Larrosa, *Angew. Chem., Int. Ed.*, 2013, **52**, 1781–1784.
- Some of the aryl-Au(I) compounds described herein have been stored under bench conditions for up to two years without any observable decomposition.
- K. E. Roth and S. A. Blum, *Organometallics*, 2010, **29**, 1712–1716.
- T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet and A. M. Echavarren, *Org. Lett.*, 2010, **12**, 3006–3009.
- For other preparation processes and properties of aryl-Au(I) compounds, see: (a) J. M. Forward, J. P. Fackler and R. J. Staples, *Organometallics*, 1995, **14**, 4194–4198; (b) A. Sladek, S. Hofreiter, M. Paul and H. Schmidbaur, *J. Organomet. Chem.*, 1995, **501**, 47–51; (c) E. J. Fernández, A. Laguna and M. E. Olmos, *Adv. Organomet. Chem.*, 2004, **52**, 77–141; (d) H. Schmidbaur and A. Schier, in *Comprehensive Organometallic Chemistry III*, ed. R. Crabtree and M. Migos, Elsevier, New York, 2006, vol. 2, Section 2.05; (e) D. V. Partyka, M. Zeller, A. D. Hunter and T. G. Gray, *Angew. Chem., Int. Ed.*, 2006, **45**, 8188–8191.
- D. Weber and M. R. Gagné, *Chem. Commun.*, 2011, **47**, 5172–5174.
- K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576.
- Nolan and coworkers have reported that the addition of Ag(I) salts to their system allows the auration of 1,3,5-trifluorobenzene: S. R. Patrick, I. I. F. Boogaerts, S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Beilstein J. Org. Chem.*, 2011, **7**, 892–896.
- This is likely due to side reactions between the arene and the base competing with the auration process.
- Similar behaviour has been recently reported in solid-phase reactions with IPrAuCl. J. D. Egbert, A. M. Z. Slawin and S. P. Nolan, *Organometallics*, 2013, **32**, 2271–2274.
- The exact nature of the active Au species is, however, not clear. In the case of NHC-ligated complexes with NaOH as the base, the similarity between our reaction conditions and the ones employed by Nolan suggests that



[Au(IPr)(OH)] could be formed, while when NaO^tBu was used as the base, [Au(IPr)(O^tBu)] or [Au(IPr)(OH)] could be present.

- 20 (a) B. R. Sutherland, K. Folting, W. E. Streib, D. M. Ho, J. C. Huffman and K. G. Caulton, *J. Am. Chem. Soc.*, 1987, **109**, 3489–3490; (b) S. Komiya, M. Iwata, T. Sone and A. Fukuoka, *J. Chem. Soc., Chem. Commun.*, 1992, 1109–1110.
- 21 A. Kolb, P. Bissier and H. Schmidbaur, *Inorg. Chem.*, 1993, **32**, 5132–5135.
- 22 (a) H. Schmidbaur, A. Kolb, E. Zeller, A. Schier and H. Beruda, *Z. Anorg. Allg. Chem.*, 1993, **619**, 1575–1579; (b) K. I. Grandberg and V. P. Dyadchenko, *J. Organomet. Chem.*, 1994, **474**, 1–21.
- 23 A. Zhdanko, M. Ströbele and M. E. Maier, *Chem.-Eur. J.*, 2012, **18**, 14732–14744.
- 24 Both hypotheses would explain the need for excess base, due to its influence on the equilibrium between 12 and 13 in one case, or between arene and aryl anions in the other.

