



Cite this: *Green Chem.*, 2020, **22**, 5648

Mechanochemical synthesis of (hetero)aryl Au(I) complexes†

Fredric J. L. Ingner,^a Zachary X. Giustra,^a Sebastian Novosedlik,^a Andreas Orthaber,^b Paul J. Gates,^c Christine Dyrager^a and Lukasz T. Pilarski^{a*}

Growing demand for sustainable chemical syntheses casts mechanochemistry in a new light as an environmentally benign alternative to traditional solvent-based methods. Given recent interest in Au(I) complexes for catalytic, materials, and medicinal applications, we developed a mechanochemical protocol to prepare (hetero)aryl Au(I) complexes under green conditions. The procedure reported here uses C–H or C–B activation to afford the corresponding Au(I) complexes in high yields. Our approach bypasses external heating, long reaction times and the use of toxic solvents. We demonstrate that mechanochemical C–H auration can be used on highly functionalised bioactive substrates. Mechanistic aspects of the C–H auration are discussed.

Received 2nd July 2020,
Accepted 11th August 2020

DOI: 10.1039/d0gc02263b

rsc.li/greenchem

Introduction

Organogold compounds have demonstrated usefulness in a diverse range of research areas including synthetic,¹ physical,² and medicinal chemistry.³ An important subset of this class of compounds comprises neutral (hetero)aryl-ligated Au(I) complexes, which have attracted interest as mechanistic probes in organometallic catalysis,⁴ as luminescent⁵ and often mechano-chromic⁶ materials for optical devices and sensors, and as biologically active molecules for anticancer and antibacterial treatments.⁷

Despite the considerable level of attention garnered by these complexes, their preparation traditionally relies on the addition of reactive, unstable, or otherwise inconvenient-to-handle aryl organometallic reagents (*e.g.*, Grignards, lithiates, zincates) to a Au(I) source,^{1*i*,*n*,*5c*,*6a*,*8*} or transmetalation from toxic arylstannanes.^{5*e*,*9*} More recent reports describe the synthesis of aryl Au(I) complexes *via* transmetalation from various organoboron reagents^{5*b*,*f*,*5g*,*7a*,*10*} and organosilanes¹¹ or by direct C(sp²)–H activation.¹² While a handful of these methods

use so-called green solvents¹³ (*e.g.*, H₂O, EtOH),^{10*ef*} they still suffer from the need for extended reaction times or elevated temperatures. More generally, the problem of solvent waste remains an ongoing challenge for the greening of chemical synthesis, including that of organometallic species.¹⁴

We sought to address these issues by developing a method to synthesize (hetero)aryl Au(I) complexes using a mechanochemical ball milling approach.¹⁵ Ball milling uses the physical impact of ball bearings against the interior walls of reaction vessels to provide reagent mixing and activation energy. The generation of organometallic compounds under milling conditions has been reported previously for a number of transition metals.¹⁶ With respect to gold specifically, however, only a very small number of complexes, virtually all of them NHC-ligated, have hitherto been prepared mechanochemically,^{16*q*,*17*} the majority by manual grinding with a mortar and pestle.^{17*a*,*b*} The reproducibility of mortar-and-pestle techniques is conspicuously problematic due, in part, to variability in energy inputs delivered by different operators.^{16*a*}

Herein, we develop a standardized approach to the synthesis of a broad range of (hetero)aryl Au(I) complexes, *via* either transmetalation from organoboronic acids or by C–H auration (Fig. 1). In particular, our use of an automated mixer mill allows for the precise application of consistent mechanochemical force. We note that our method is applicable to the chemoselective auration of highly functionalized bioactive substrates. We also demonstrate direct C(sp²)–H auration to be reversible under milling conditions and investigate the implications this has for achieving chemoselectivity between different aryl moieties.

^aDepartment of Chemistry—BMC, Uppsala University, BOX 576, 75-123, Uppsala, Sweden. E-mail: lukasz.pilarski@kemi.uu.se

^bDepartment of Chemistry—Ångström, Uppsala University, BOX 523, 75-120, Uppsala, Sweden

^cSchool of Chemistry, University of Bristol, Cantock's Close, Clifton, Bristol, BS8 1TS, UK

†Electronic supplementary information (ESI) available: Experimental procedures, spectral characterization of new compounds, NMR spectra. CCDC 2007939 (3d) and 2007940 (3f). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0gc02263b



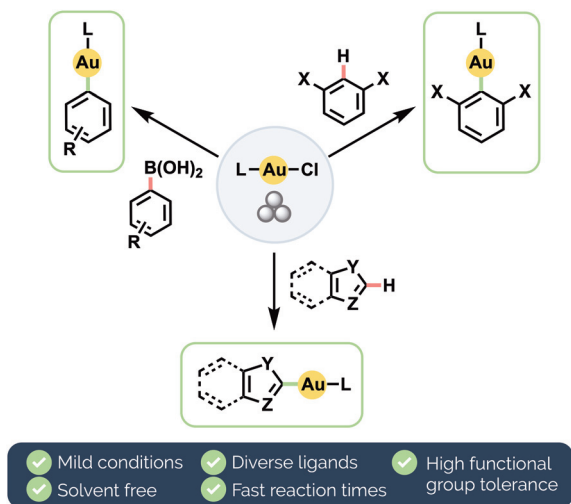


Fig. 1 This work: mechanochemical synthesis of diverse (hetero)aryl Au (I) complexes by ball milling.

Results and discussion

We initially investigated the possibility of using boronic acids as aryl sources, given that such compounds have been demonstrated to be competent reagents in several solvent-based methods.^{5g,10a-f} All reactions were conducted in a Teflon™ vessel loaded with one stainless steel ball bearing. Using 3-tolylboronic acid (**1a**) with (Ph₃P)AuCl as a model Au(I) precursor, we observed clean formation of the desired product, **2a**, by ³¹P NMR spectroscopy after milling for 1 h at 30 Hz in the presence of either 1.0 equiv. KOH or CsF (Table 1, entries 1 and 2).¹⁸ No product was observed without inclusion of a base (entry 3). Accordingly, the addition of a small volume of water to enable liquid-assisted grinding (LAG)¹⁹ was only effective when combined with a base additive (compare entries 4 and 5).

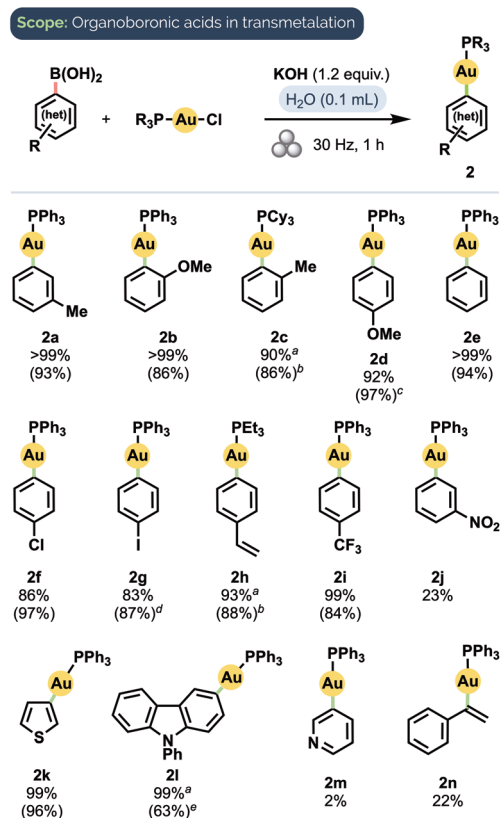
Table 1 Optimization of aryl boronic acid transmetalation

Entry	Additives	Yield ^a (%)
1	KOH (1.0 equiv.)	75
2	CsF (1.0 equiv.)	52
3	None	0
4	H ₂ O (0.1 mL)	0
5	KOH (1.0 equiv.) + H ₂ O (0.1 mL)	94
6	KOH (1.2 equiv.) + H ₂ O (0.1 mL)	>99
7 ^b	H ₂ O (0.1 mL)	84

^a Determined by ³¹P NMR spectroscopy for reactions conducted on 0.1 mmol scale in a 14 mL Teflon™ vessel with one stainless steel ball (15 mm, 13.6 g). ^b Using potassium 2-hydroxymethyl-2-methylpropane-1,3-diol borate in place of boronic acid.

In particular, product formation became effectively quantitative with a modest excess of KOH (entry 6). Substituting the separate boronic acid/KOH pairing for a pre-formed trialkoxyborate led to diminished yield (entry 7).

Having established a set of optimised conditions, we screened boronic acids to generate a variety of aryl Au(I) phosphine complexes (Scheme 1). Significantly, most of the product complexes could be isolated from the reaction mixture by extraction with EtOAc and a Celite filtration, which speaks to the overall ease of their synthesis using our procedure. The reaction did not appear significantly sensitive to the steric demands of *ortho*-substituted aryl groups; these transmetalated efficiently even when paired with a bulky²⁰ tricyclohexyl phosphine ligand (**2c**). In general, transmetalation of either electron-rich or electron-neutral aryl groups proceeded in excellent to quantitative yield (**2a–h**). Greater substituent dependence was observed, however, for electron-poor arylboronic acids: while 4-(trifluoromethyl)phenyl complex **2i** was obtained in very good isolated yield (84%), 3-nitrophenyl complex **2j** was observed to form in only 23% spectroscopic yield. A similar trend was found for heteroarene substrates: pleasingly, electron-rich moieties such as thiophene (**2k**) and



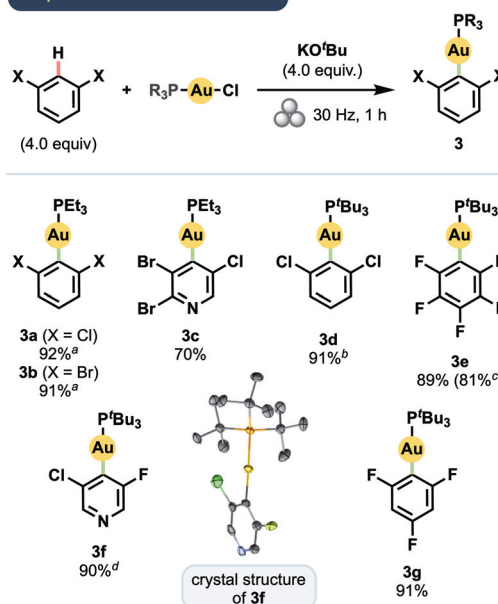
Scheme 1 Substrate scope for aryl boronic acid transmetalation to Au(I) phosphines. Yields determined by ³¹P NMR spectroscopy; values in parentheses are isolated yields using 1.2 equiv. Ar-B(OH)₂ and 1.5 equiv. KOH_(aq) (1.25 M) on 0.1 mmol scale. ^a 2.0 equiv. KOH_(s) ^b 3.0 equiv. KOH_(aq) (2.50 M), 25 Hz ^c 1.4 equiv. Ar-B(OH)₂ ^d 2.5 equiv. KOH_(aq) (2.50 M), 2 h, 25 Hz ^e 3.0 equiv. KOH_(aq) (2.50 M), 36 Hz.

9-phenyl-9*H*-carbazole (**2l**) – both motifs of significant interest in organic materials applications²¹ – transmetalated smoothly. In contrast, electron-poor 3-pyridineboronic acid afforded only trace amounts of product (**2m**). Lastly, although *p*-vinyl complex **2h** was obtained in very good yield (88%), the generation of an α -aurated styrenyl complex²² (**2n**) proved less efficient.

Our success with mechanically induced transmetalations from (hetero)arylboronic acids prompted us to attempt the more challenging²³ synthesis of (hetero)aryl Au(i) complexes directly *via* arene C–H activation. Specifically, we aimed to develop a general mechanochemical protocol for the generation of Au(i) complexes of significantly greater scope than the handful of polyfluoroarene derivatives generated manually so far.^{17b} With 1,3-dichlorobenzene as a model substrate, we determined that increasing the equivalents of arene relative to (Et₃P)AuCl led to steadily higher yields (Table 2, entries 1–4). Even at 4.0 equiv. of arene, however, product yield did not exceed 50%. In contrast to the boronic acids case, the addition of water to facilitate LAG proved detrimental (entry 5). Accordingly, by substituting the hydroxide base with KO^tBu – and thus establishing anhydrous conditions – the yield improved dramatically (entry 6).

Using these optimized conditions, we were able to prepare a series of polyhaloaryl Au(i) phosphine complexes in very good to excellent yields (Scheme 2). The general effectiveness of our mechanochemical approach notably extended in this instance to the synthesis of pyridyl complexes both with (**3c**) and without (**3f**) steric hindrance about the nitrogen center. The required di-*ortho*-halide substitution pattern of the aryl group likewise did not appear to encumber the reaction and various combinations of F, Cl, and Br substituents were all well tolerated. Products also formed readily with bulky P^tBu₃ ligands. The formation of complex **3d**, for which solution-phase syntheses had previously proven unsuccessful,^{12d} proceeded in 91% isolated yield under our milling conditions. Moreover, the preparation of pentafluorophenyl complex **3e** could be scaled up by a factor of 5 without significant decrease

Scope: Haloarenes in C–H auration



Scheme 2 Substrate scope for haloarene C–H auration. Isolated yields on 0.1 mmol scale. ^a 1.5 h ^b 2 h, 36 Hz ^c 0.5 mmol scale ^d 4.0 equiv. KOH. For **3f** the crystal structure has ellipsoids set at 50% probability.

in yield. The structure of **3f** was confirmed by X-ray crystallographic analysis.²⁴

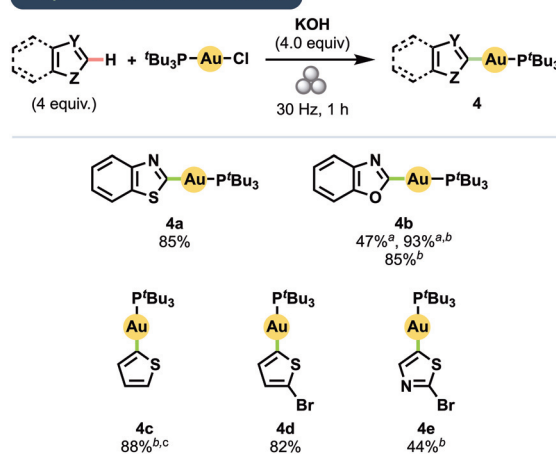
By a simple switch of base from KO^tBu to KOH, we could readily expand our C–H auration protocol to include a series of heteroarenes (Scheme 3).²⁵ Notably, benzothiazole complex **4a** was obtained in 85% isolated yield after milling for 1 h, compared to 55% yield obtained after stirring in 1,4-dioxane at 35 °C for 15 h.^{12d} (Temperature measurements of the interior of our reaction vessels and the balls using a laser thermometer immediately after the cessation of milling never exceeded

Table 2 Optimization of haloarene C–H auration

Entry	Arene equiv.	Base	Yield ^a (%)
1 ^b	2.0	NaOH	14
2 ^b	3.0	NaOH	26
3	4.0	NaOH	39
4	4.0	KOH	47
5	4.0	NaOH + H ₂ O (0.1 mL)	0
6	4.0	KO ^t Bu	88
7	4.0	None	0

^a Determined by ³¹P NMR spectroscopy for reactions conducted on 0.1 mmol scale. ^b 25 Hz.

Scope: Heteroarenes in C–H auration



Scheme 3 Substrate scope for heteroarene C–H auration. Isolated yields on 0.1 mmol scale. ^a Yield determined by ³¹P NMR spectroscopy ^b 36 Hz ^c 4.0 equiv. KO^tBu.



32 °C, even after milling for 60 min at 30 Hz.) Despite bearing a comparatively more acidic proton at C2,²⁶ benzoxazole ($pK_{\text{a(DMSO)}} = 24.8$) exhibited lower reactivity than benzothiazole ($pK_{\text{a(DMSO)}} = 27.3$), suggesting that C–H bond acidity may not be the sole determinant of the relative ease of auration in these cases. Specifically, we propose that initial S...Au interactions in the case of benzothiazole may pre-organise the reactants to better facilitate subsequent C–H auration to produce **4a**. Quantitative formation of benzoxazole complex **4b** could nevertheless be achieved by simply increasing the oscillation frequency of the mill to 36 Hz. High yield, and complete regioselectivity for C2 functionalization, were likewise observed for unsubstituted thiophene ($pK_{\text{a(DMSO)}} = 33.5$), in stark contrast to the reported difficulty of forming complex **4c** in solution.^{12d} 2-Bromo-substituted thiophene also underwent C–H auration to afford complex **4d** in high isolated yield.

Gratifyingly, our optimized mechanochemical conditions for preparing Au(I) phosphine complexes translated well to the complementary synthesis of NHC-ligated compounds (Scheme 4). Of particular note was that 2,4,6-trifluorophenyl complex **5a** was obtained in 82% isolated yield, whereas earlier attempts with mortar-and-pestle grinding produced only trace amounts.^{17b} Additionally, complex **5b**, isolated in 93% yield, has recently been demonstrated by Nolan and co-workers to serve as a versatile precursor to many other NHC–Au(I) species.^{10f}

To further demonstrate the general applicability of our milling conditions to the preparation of aryl Au(I) complexes, we attempted the C–H auration of highly functionalized, biologically active substrates (Fig. 2). Such late-stage derivatisation under mechanochemical conditions has not been demon-

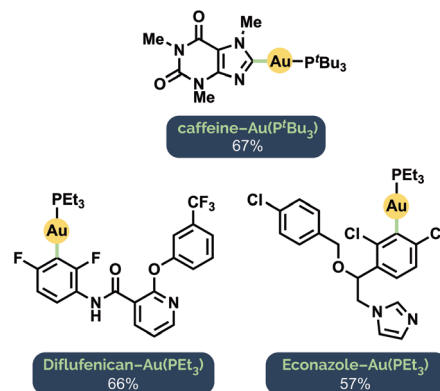
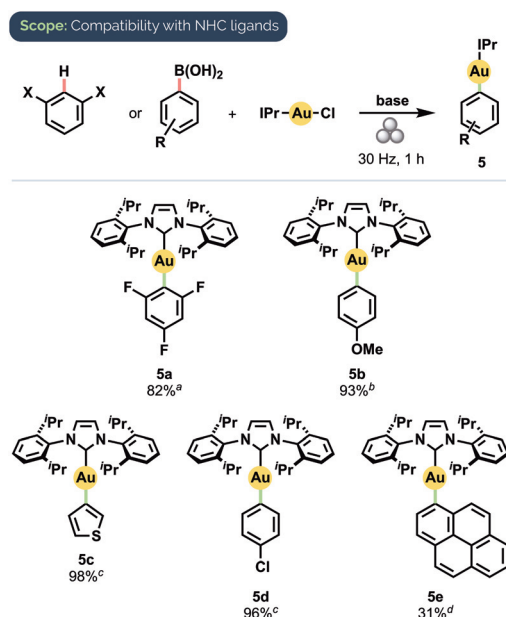


Fig. 2 Synthesized Au(I) phosphine complexes of biologically active compounds. See ESI† for reaction details.

strated previously. The C2–H auration of caffeine proceeded in 67% yield after milling for 1 h at 30 Hz (*cf.* 76% after 65 h stirring in 1,4-dioxane^{12d}). Interestingly, Diflufenican, a commercialized herbicide,²⁷ was selectively aured on the difluorophenyl group. This is complementary to analogous metalations with palladium and cobalt directed by the pyridyl moiety to the trifluoromethylated phenyl ring instead.²⁸ Functionalization of the commercial antifungal agent Econazole²⁹ also occurred exclusively on the 1,3-dichlorophenyl ring, despite the presence of a pendant imidazole group.

Given the prevalence of biologically active compounds bearing both halo- and heteroaryl motifs (*vide supra*), we were interested to investigate the degree to which our mechanochemical C–H activation conditions would afford chemoselectivity between auration of these two groups. To that end, a series of competition experiments was conducted using equimolar amounts of haloarene and heteroarene substrates with $(t\text{Bu}_3\text{P})\text{AuCl}$ and excess KO^tBu .³⁰ As shown in Scheme 5A, combining pentafluorobenzene ($\text{C}_6\text{F}_5\text{H}$) and benzothiazole resulted in the formation of complexes **3e** and **4a** in an 11 : 1 ratio under conditions analogous to those for their separate synthesis. Lower ratios were observed with $\text{C}_6\text{F}_5\text{H}$ and benzoxazole (Scheme 5B, **3e/4b** = 4 : 1) and trifluorobenzene and benzothiazole (Scheme 5C, **3g/4a** = 1 : 1). In all cases, analysis by ^{31}P NMR spectroscopy indicated complete consumption of the $(t\text{Bu}_3\text{P})\text{AuCl}$ starting material after 1 h. Effectively the same product ratios were also obtained in each case upon milling for a longer period (2 h).

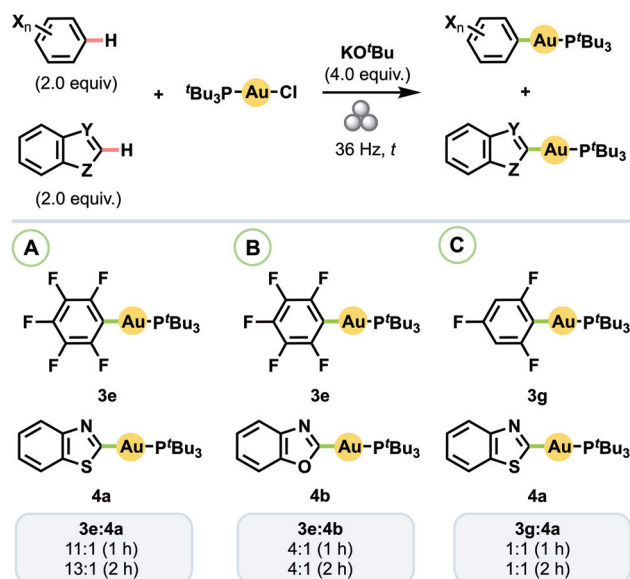
To determine if the origin of the product ratios was thermodynamic or kinetic in nature, we carried out additional experiments in which a pre-formed complex was subjected to milling in the presence of another arene substrate, with or without base present (Scheme 6). (An equivalent of free arene corresponding to the aryl group of the complex was also added so that the total number of equivalents of each aryl group present would be the same as in the prior competition experiments.) When complex **3e** was milled together with benzothiazole and excess KO^tBu , only partial conversion to benzothiazole complex **4a** was observed and the ratio of product com-



Scheme 4 Synthesis of NHC-ligated complexes. Isolated yields on 0.1 mmol scale. ^a 4.0 equiv. arene, 4.0 equiv. KO^tBu ^b 1.4 equiv. Ar-B(OH)_2 , 1.5 equiv. $\text{KOH}_{(\text{aq})}$ (1.25 M) ^c 1.5 equiv. $\text{KOH}_{(\text{aq})}$ (1.25 M) ^d 1.0 equiv. Ar-B(OH)_2 , 2.0 equiv. $\text{KOH}_{(\text{s})}$.

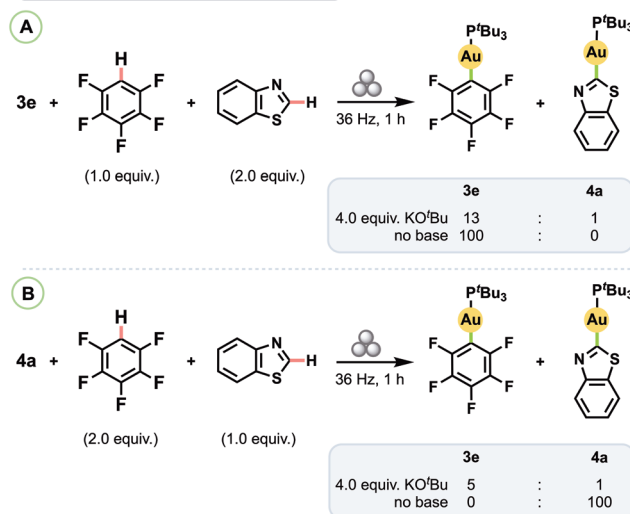


Mechanistic insights: Competition experiments



Scheme 5 Haloarene/heteroarene C–H auration competition experiments. Product ratios determined by ^{31}P NMR spectroscopy.

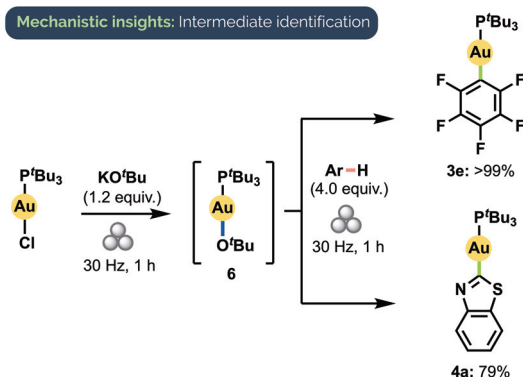
Mechanistic insights: Aryl ligand exchange



Scheme 6 Aryl group exchange experiments. Final complex ratios determined by combined ^{31}P and ^{19}F NMR analysis, see ESI† for details.

plexes was $3\text{e}/4\text{a} = 13:1$ (Scheme 6A).³¹ Starting instead from pure **4a** and free $\text{C}_6\text{F}_5\text{H}$ also favoured **3e** ($3\text{e}/4\text{a} = 5:1$; Scheme 6B). These results indicate the C–H auration is reversible and that the product ratios from the competition experiments reflect an overall equilibrium between different aryl Au(I) complexes. DFT (PBE0/TZVP/SDD) calculations also point to the major species in the mixtures from the competition experiments as being the more thermodynamically stable complex (see ESI† for details).

Mechanistic insights: Intermediate identification



Scheme 7 Synthesis of Au(I) alkoxide complex **6** and subsequent aryl C–H activation. Yields determined by ^{31}P NMR spectroscopy.

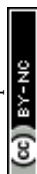
The actual mechanism of the observed aryl exchange remains to be elucidated fully. The complete lack of reactivity of **3e** and **4a** with benzothiazole and $\text{C}_6\text{F}_5\text{H}$, respectively, in the absence of KOtBu rules out the possibility of a direct meta-thesis-type process. Larrosa and co-workers have proposed that aryl C–H auration is mediated in solution by a gold alkoxide species when KOtBu is used as base.^{12d} Indeed, upon milling $(\text{tBu}_3\text{P})\text{AuCl}$ together with KOtBu, we observed complete conversion to a single species that we assigned as $(\text{tBu}_3\text{P})\text{AuO}^t\text{Bu}$ (**6**) on the basis of ^1H , ^{13}C , ^{31}P , DOSY NMR spectroscopy and HRMS analysis (Scheme 7).³² Significantly, this material demonstrated competency equal to that of $(\text{tBu}_3\text{P})\text{AuCl}$ in forming **3e** and **4a** under standard milling conditions. If formed in catalytic amounts *in situ*, **6** could thus also potentially facilitate the observed aryl exchange between these complexes. At this time, however, we cannot discount the possibility of an exchange proceeding directly through the reaction with a deprotonated aryl species.

Conclusions

We have developed a green protocol for the preparation of (hetero)aryl Au(I) complexes by leveraging the practical advantages of automated mechanochemical synthesis. Specifically, the method reported herein generates products with greater overall expediency than previous syntheses while avoiding the need for prolonged heating or environmentally hazardous solvents. Under our mechanochemical regime, Au(I) complexes can be formed by either transmetalation from readily available aryl boronic acids or direct C–H activation of various halo- and heteroarenes. The method allows the synthesis of several previously challenging compounds and demonstrates, for the first time, the viability of a mechanochemical approach to the late-stage C–H auration of biologically active substrates.

Conflicts of interest

There are no conflicts to declare.



Acknowledgements

We are grateful to the Swedish Research Council (Vetenskapsrådet) and the Carl Trygger Foundation for financial support. We also thank Dr. Johanna Larsson and Prof. Graham Budd for help with proof-reading the manuscript.

Notes and references

- For reviews of various facets of modern organogold homogeneous catalysis, see: (a) A. Nijamudheen and A. Datta, *Chem. – Eur. J.*, 2020, **26**, 1442–1487; (b) X. Zhao, M. Rudolph and A. S. K. Hashmi, *Chem. Commun.*, 2019, **55**, 12127–12135; (c) V. Pirovano, *Eur. J. Org. Chem.*, 2018, **2018**, 1925–1945; (d) S. Kramer, *Chem. – Eur. J.*, 2016, **22**, 15584–15598; (e) M. N. Hopkinson, A. Tlahuext-Aca and F. Glorius, *Acc. Chem. Res.*, 2016, **49**, 2261–2272; (f) W. Zi and F. D. Toste, *Chem. Soc. Rev.*, 2016, **45**, 4567–4589; (g) B. Ranieri, I. Escofet and A. M. Echavarren, *Org. Biomol. Chem.*, 2015, **13**, 7103–7118; (h) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358–1367. For examples of organometallic gold complexes used as stoichiometric reagents, see: (i) M. Contel, M. Stol, M. A. Casado, G. P. M. van Klink, D. D. Ellis, A. L. Spek and G. van Koten, *Organometallics*, 2002, **21**, 4556–4559; (j) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi and F. Rominger, *Angew. Chem., Int. Ed.*, 2009, **48**, 8243–8246; (k) S. Yili, S. D. Ramgren and S. A. Blum, *Organometallics*, 2009, **28**, 1275–1277; (l) M. Peña-López, M. Ayán-Varela, L. A. Sarandeses and J. P. Sestelo, *Chem. – Eur. J.*, 2010, **16**, 9905–9909; (m) J. J. Hirner and S. A. Blum, *Organometallics*, 2011, **30**, 1299–1302; (n) M. Hejda, L. Dostál, R. Jambor, A. Růžicka, R. Jirásko and J. Holeček, *Eur. J. Inorg. Chem.*, 2012, **2012**, 2578–2587; (o) M. Peña-López, L. A. Sarandeses and J. P. Sestelo, *Eur. J. Org. Chem.*, 2013, **2013**, 2545–2554.
- (a) M. Enomoto, A. Kishimura and T. Aida, *J. Am. Chem. Soc.*, 2001, **123**, 5608–5609; (b) A. Kishimura, T. Yamashita and T. Aida, *J. Am. Chem. Soc.*, 2005, **127**, 179–183; (c) M.-C. Tang, D. P.-K. Tsang, M. M.-Y. Chan, K. M.-C. Wong and V. W.-W. Yam, *Angew. Chem., Int. Ed.*, 2013, **52**, 446–449; (d) W.-X. Ni, M. Li, J. Zheng, S.-Z. Zhan, Y.-M. Qiu, S. W. Ng and D. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 13472–13476; (e) M.-C. Tang, D. P.-K. Tsang, Y.-C. Wong, M.-Y. Chan, K. M.-C. Wong and V. W.-W. Yam, *J. Am. Chem. Soc.*, 2014, **136**, 17861–17868; (f) S. T. Madrahimov, T. A. Atesin, O. Karagiari, A. A. Sarjeant, O. K. Farha, J. T. Hupp and S. T. Nguyen, *Cryst. Growth Des.*, 2014, **14**, 6320–6324; (g) V. W.-W. Yam, V. K.-M. Au and S. Y.-L. Leung, *Chem. Rev.*, 2015, **115**, 7589–7728; (h) E. Y.-H. Hong, C.-T. Poon and V. W.-W. Yam, *J. Am. Chem. Soc.*, 2016, **138**, 6368–6371; (i) N. B. Jayaratna, M. M. Olmstead, B. I. Kharisov and H. V. R. Dias, *Inorg. Chem.*, 2016, **55**, 8277–8280; (j) J. Cored, O. Crespo, J. L. Serrano, A. Elduque and R. Giménez, *Inorg. Chem.*, 2018, **57**, 12632–12640; (k) M. B. E. Griffiths, Z. S. Dubrawski, G. Bačić, A. Japahuge, J. D. Masuda, T. Zeng and S. T. Barry, *Eur. J. Inorg. Chem.*, 2019, **2019**, 4927–4938; (l) L.-K. Li, M.-C. Tang, S.-L. Lai, M. Ng, W.-K. Kwok, M.-Y. Chan and V. W.-W. Yam, *Nat. Photonics*, 2019, **13**, 185–191.
- For general reviews, see: (a) M. Mora, M. C. Gimeno and R. Visbal, *Chem. Soc. Rev.*, 2019, **48**, 447–462; (b) T. Zou, C. T. Lum, C.-N. Lok, J.-J. Zhang and C.-M. Che, *Chem. Soc. Rev.*, 2015, **44**, 8786–8801; (c) B. Đ. Glišić and M. I. Djuran, *Dalton Trans.*, 2014, **43**, 5950–5969; (d) C. F. Shaw, *Chem. Rev.*, 1999, **99**, 2589–2600. For selected recent studies: (e) J. Weaver, S. Gaillard, C. Toye, S. Macpherson, S. P. Nolan and A. Riches, *Chem. – Eur. J.*, 2011, **17**, 6620–6624; (f) E. Schuh, C. Pflüger, A. Citta, A. Folda, M. P. Rigobello, A. Bindoli, A. Casini and F. Mohr, *J. Med. Chem.*, 2012, **55**, 5518–5528; (g) H. Bjelosevic, I. A. Guzei, L. C. Spencer, T. Persson, F. H. Kriel, R. Hewer, M. J. Nell, J. Gut, C. E. J. van Rensburg, P. J. Rosenthal, J. Coates, J. Darkwa and S. K. C. Elmroth, *J. Organomet. Chem.*, 2012, **720**, 52–59; (h) A. Gutiérrez, I. Marzo, C. Cativiela, A. Laguna and M. C. Gimeno, *Chem. – Eur. J.*, 2015, **21**, 11088–11095; (i) S. Vanicek, H. Kopacka, K. Wurst, S. Vergeiner, S. Kankowski, J. Schur, B. Bildstein and I. Ott, *Dalton Trans.*, 2016, **45**, 1345–1348; (j) A. Luengo, V. Fernández-Moreira, I. Marzo and M. C. Gimeno, *Inorg. Chem.*, 2017, **56**, 15159–15170; (k) V. G. Reddy, T. S. Reddy, S. H. Privér, Y. Bai, S. Mishra, D. Wlodkowic, N. Mirzadeh and S. Bhargava, *Inorg. Chem.*, 2019, **58**, 5988–5999; (l) J. Oberkofler, B. Aikman, R. Bonsignore, A. Pöthig, J. Platts, A. Casini and F. E. Kühn, *Eur. J. Inorg. Chem.*, 2020, **2020**, 1040–1051; (m) A. P. A. Oliveira, J. T. J. Freitas, R. Diniz, C. Pessoa, S. S. Maranhão, J. M. Ribeiro, E. M. Souza-Fagundes and H. Beraldo, *ACS Omega*, 2020, **5**, 2939–2946.
- (a) K. E. Roth and S. A. Blum, *Organometallics*, 2010, **29**, 1712–1716; (b) D. Weber and M. R. Gagné, *Chem. Commun.*, 2011, **47**, 5172–5174; (c) M. T. Johnson, J. M. J. van Rensburg, M. Axelsson, M. S. G. Ahlquist and O. F. Wendt, *Chem. Sci.*, 2011, **2**, 2373–2377; (d) K. E. Roth and S. A. Blum, *Organometallics*, 2011, **30**, 4811–4813; (e) M. S. Winston, W. J. Wolf and F. D. Toste, *J. Am. Chem. Soc.*, 2014, **136**, 7777–7782; (f) J. J. Hirner and S. A. Blum, *Tetrahedron*, 2015, **71**, 4445–4449; (g) S. Taschinski, R. Döpp, M. Ackermann, F. Rominger, F. de Vries, M. F. S. J. Menger, M. Rudolph, A. S. K. Hashmi and J. E. M. N. Klein, *Angew. Chem., Int. Ed.*, 2019, **58**, 16988–16993.
- (a) R. Bayón, S. Coco and P. Espinet, *Chem. – Eur. J.*, 2005, **11**, 1079–1085; (b) D. V. Partyka, A. J. Esswein, M. Zeller, A. D. Hunter and T. G. Gray, *Organometallics*, 2007, **26**, 3279–3282; (c) C. R. Wade, A. A. Yakovenko and F. P. Gabbaï, *New J. Chem.*, 2010, **34**, 1646–1651; (d) Y. Ogino, T. Kusamoto, Y. Hattori, M. Shimada, M. Tsuchiya, Y. Yamanoi, E. Nishibori, K. Sugimoto and H. Nishihara, *Inorg. Chem.*, 2017, **56**, 3909–3915; (e) T. G. Do, E. Hupf, E. Lork, J. F. Kögel, F. Mohr,



- A. Brown, R. Toyoda, R. Sakamoto, H. Nishihara, S. Mebs and J. Beckmann, *Eur. J. Inorg. Chem.*, 2019, **2019**, 647–659; (f) J. J. Mihaly, D. J. Stewart, T. A. Grusenmeyer, A. T. Phillips, J. E. Haley, M. Zeller and T. G. Gray, *Dalton Trans.*, 2019, **48**, 15917–15927; (g) T. Li, D. S. M. Ravinson, R. Haiges, P. I. Djurovich and M. E. Thompson, *J. Am. Chem. Soc.*, 2020, **142**, 6158–6172. For a recent review, see: (h) J. M. López-de-Luzuriaga, M. Monge and M. E. Olmos, *Dalton Trans.*, 2017, **46**, 2046–2067; (i) T. Seki, C. Feng, K. Kashiya, S. Sakamoto, Y. Takasaki, T. Sasaki, S. Takamizawa and H. Ito, *Angew. Chem., Int. Ed.*, 2020, **59**, 8839–8843.
- 6 (a) T. Seki, Y. Takamatsu and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 6252–6260; (b) T. Seki, M. Jin and H. Ito, *Inorg. Chem.*, 2016, **55**, 12309–12320; (c) K. Sakurada, T. Seki and H. Ito, *CrystEngComm*, 2016, **18**, 7217–7220; (d) T. Seki, N. Tokodai, S. Omagari, T. Nakanishi, Y. Hasegawa, T. Iwasa, T. Taketsugu and H. Ito, *J. Am. Chem. Soc.*, 2017, **139**, 6514–6517; (e) T. Seki, K. Kashiya, S. Yagai and H. Ito, *Chem. Lett.*, 2017, **46**, 1415–1418; (f) T. Seki, K. Kobayashi, T. Mashimo and H. Ito, *Chem. Commun.*, 2018, **54**, 11136–11139; (g) T. Seki, K. Ida, H. Sato, S. Aono, S. Sakaki and H. Ito, *Chem. – Eur. J.*, 2020, **26**, 735–744.
- 7 (a) S. Craig, L. Gao, I. Lee, T. Gray and A. J. Berdis, *J. Med. Chem.*, 2012, **55**, 2437–2451; (b) M. Frik, J. Jiménez, I. Gracia, L. R. Falvello, S. Abi-Habib, K. Surriel, T. R. Muth and M. Contel, *Chem. – Eur. J.*, 2012, **18**, 3659–3674; (c) S. K. Verma, S. N. Ansari, P. Kumari and S. M. Mobin, *Organometallics*, 2019, **38**, 2591–2596.
- 8 C. Croix, A. Balland-Longeau, H. Allouchi, M. Giorgi, A. Duchêne and J. Thibonnet, *J. Organomet. Chem.*, 2005, **690**, 4835–4843.
- 9 (a) N. Meyer, C. W. Lehmann, T. K.-M. Lee, J. Rust, V. W.-W. Yam and F. Mohr, *Organometallics*, 2009, **28**, 2931–2934; (b) N. Meyer, S. Sivanathan and F. Mohr, *J. Organomet. Chem.*, 2011, **696**, 1244–1247.
- 10 (a) D. V. Partyka, M. Zeller, A. D. Hunter and T. G. Gray, *Angew. Chem., Int. Ed.*, 2006, **45**, 8188–8191; (b) D. V. Partyka, J. B. Updegraff III, M. Zeller, A. D. Hunter and T. G. Gray, *Organometallics*, 2009, **28**, 1666–1674; (c) S. Dupuy, L. Crawford, M. Bühl, A. M. Z. Slawin and S. P. Nolan, *Adv. Synth. Catal.*, 2012, **354**, 2380–2386; (d) H. K. Lenker, T. G. Gray and R. A. Stockland Jr., *Dalton Trans.*, 2012, **41**, 13274–13276; (e) F. J. L. Ingner, A. C. Schmitt, A. Orthaber, P. J. Gates and L. T. Pilarski, *ChemSusChem*, 2020, **13**, 2032–2037; (f) N. V. Tzouras, M. Saab, W. Janssens, T. Cauwenbergh, K. Van Hecke, F. Nahra and S. P. Nolan, *Chem. – Eur. J.*, 2020, **26**, 5541–5551.
- 11 S. Dupuy, A. M. Z. Slawin and S. P. Nolan, *Chem. – Eur. J.*, 2012, **18**, 14923–14928.
- 12 (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. R. Patrick, I. I. F. Boogaerts, S. Gaillard, A. M. Z. Slawin and S. P. Nolan, *Beilstein J. Org. Chem.*, 2011, **7**, 892–896; (d) N. Ahlsten, G. J. P. Perry, X. C. Cambeiro, T. C. Boorman and I. Larrosa, *Catal. Sci. Technol.*, 2013, **3**, 2892–2897.
- 13 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
- 14 (a) C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800; (b) K. L. Wilson, J. Murray, H. F. Sneddon, K. M. P. Wheelhouse and A. J. B. Watson, *Chem*, 2017, **3**, 365–368; (c) C. P. Ashcroft, P. J. Dunn, J. D. Hayler and A. S. Wells, *Org. Process Res. Dev.*, 2015, **19**, 740–747.
- 15 (a) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094; (b) D. Tan and T. Friščić, *Eur. J. Org. Chem.*, 2018, **2018**, 18–33; (c) I. N. Egorov, S. Santra, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. Majee, B. C. Ranu, V. L. Rusinov and O. N. Chupakhin, *Green Chem.*, 2020, **22**, 302–315; (d) J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435–1443; (e) J.-L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, **3**, 13–19; (f) M. Leonardi, M. Villacampa and J. C. Menéndez, *Chem. Sci.*, 2018, **9**, 2042–2064; (g) D. Tan and F. García, *Chem. Sci.*, 2019, **48**, 2274–2292; (h) J. M. Andersen and J. Mack, *Chem. Sci.*, 2017, **8**, 5447–5453.
- 16 For representative examples, see: (a) V. D. Makhaev, A. P. Borisov and L. A. Petrova, *J. Organomet. Chem.*, 1999, **590**, 222–226; (b) V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *Chem. Commun.*, 2002, **2**, 1606–1607; (c) D. Braga, S. L. Gialfreda, F. Grepioni, A. Pettersen, L. Maini, M. Curzi and M. Polito, *Dalton Trans.*, 2006, **60**, 1249–1263; (d) J. G. Hernández, I. S. Butler and T. Friščić, *Chem. Sci.*, 2014, **5**, 3576–3582; (e) J. G. Hernández, N. A. J. Macdonald, C. Mottillo, I. S. Butler and T. Friščić, *Green Chem.*, 2014, **16**, 1087–1092; (f) M. Ferguson, N. Giri, X. Huang, D. Apperley and S. L. James, *Green Chem.*, 2014, **16**, 1374–1382; (g) M. Juribašić, K. Užarević, D. Gracin and M. Ćurić, *Chem. Commun.*, 2014, **50**, 10287–10290; (h) N. R. Rightmire, T. P. Hanusa and A. L. Rheingold, *Organometallics*, 2014, **33**, 5952–5955; (i) C. S. B. Gomes, P. T. Gomes and M. T. Duarte, *J. Organomet. Chem.*, 2014, **760**, 101–107; (j) D. W. Peters and R. G. Blair, *Faraday Discuss.*, 2014, **170**, 83–91; (k) C. J. Adams, M. Lusi, E. M. Mutambi and A. G. Orpen, *Chem. Commun.*, 2015, **51**, 9632–9635; (l) J. G. Hernández and C. Bolm, *Chem. Commun.*, 2015, **51**, 12582–12584; (m) J. Wang, R. Ganguly, L. Yongxin, J. Díaz, H. S. Soo and F. García, *Dalton Trans.*, 2016, **45**, 7941–7946; (n) D. H. Woen, C. M. Kotyk, T. J. Mueller, J. W. Ziller and W. J. Evans, *Organometallics*, 2017, **36**, 4558–4563; (o) D. V. Aleksanyan, S. G. Churusova, R. R. Aysin, Z. S. Klemenkova, Y. V. Nelyubina and V. A. Kozlov, *Inorg. Chem. Commun.*, 2017, **76**, 33–35; (p) A. Beillard, X. Bantreil, T.-X. Métro, J. Martinez and F. Lamaty, *New J. Chem.*, 2017, **41**, 1057–1063; (q) H. Cheng, J. G. Hernández and C. Bolm, *Adv. Synth. Catal.*, 2018, **360**, 1800–1804; (r) T. E. Shaw, L. R. Shultz, L. R. Garayeva, R. G. Blair, B. C. Noll and T. Jurca, *Dalton Trans.*, 2018, **47**,



- 16876–16884; (s) K. Kubota, R. Takahashi and H. Ito, *Chem. Sci.*, 2019, **10**, 5837–5842. For a review, see: (t) N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352–2362.
- 17 (a) A. Zhdanko, M. Ströbele and M. E. Maier, *Chem. – Eur. J.*, 2012, **18**, 14732–14744; (b) J. D. Egbert, A. M. Z. Slawin and S. P. Nolan, *Organometallics*, 2013, **32**, 2271–2274; (c) A. Beillard, E. Golliard, V. Gillet, X. Bantreil, T.-X. Métro, J. Martinez and F. Lamaty, *Chem. – Eur. J.*, 2015, **21**, 17614–17617; (d) J.-L. Do, D. Tan and T. Friščić, *Angew. Chem., Int. Ed.*, 2018, **57**, 2667–2671; (e) G. N. Hermann, M. T. Unruh, S.-H. Jung, M. Krings and C. Bolm, *Angew. Chem., Int. Ed.*, 2018, **57**, 10723–10727.
- 18 CsF-mediated reactivity is surprising here given that, in the analogous boron-to-palladium transmetalation, fluoride coordination to boron has been demonstrated to have an inhibitory effect on the process: (a) C. Amatore, A. Jutand and G. Le Duc, *Angew. Chem., Int. Ed.*, 2012, **51**, 1379–1382. Also, the intermediacy of a Au-F complex in boron-to-gold transmetalation has, to our knowledge, only been reported for Au(III) species: (b) J. Miró and C. del Pozo, *Chem. Rev.*, 2016, **116**, 11924–11966.
- 19 (a) N. Shan, F. Toda and W. Jones, *Chem. Commun.*, 2002, **2**, 2372–2373; (b) F. C. Stobridge, N. Juda and T. Friščić, *CrystEngComm*, 2010, **12**, 2409–2418; (c) E. A. Losev and E. V. Boldyreva, *CrystEngComm*, 2014, **16**, 3857–3866.
- 20 C. A. Tolman, *Chem. Rev.*, 1977, **77**, 313–348.
- 21 (a) R. Kroon, D. A. Mengistie, D. Kiefer, J. Hynnen, J. D. Ryan, L. Yu and C. Müller, *Chem. Soc. Rev.*, 2016, **45**, 6147–6164; (b) C. Rodríguez-Seco, L. Cabau, A. Vidal-Ferran and E. Palomares, *Acc. Chem. Res.*, 2018, **51**, 869–880.
- 22 To our knowledge, only three examples of this type of compound have been isolated previously: (a) J. A. Akana, K. X. Bhattacharyya, P. Müller and J. P. Sadighi, *J. Am. Chem. Soc.*, 2007, **129**, 7736–7737; (b) M. Joost, P. Gualco, S. Mallet-Ladeira, A. Amgounne and D. Bourissou, *Angew. Chem., Int. Ed.*, 2013, **52**, 7160–7163; (c) T. Seki, T. Mashimo and H. Ito, *Chem. Sci.*, 2019, **10**, 4185–4191. For isolations of the corresponding β -aurated species, see: ref. 1k and. (d) A. S. K. Hashmi, T. D. Ramamurthi and F. Rominger, *J. Organomet. Chem.*, 2009, **694**, 592–597; (e) T. P. Cornell, Y. Shi and S. A. Blum, *Organometallics*, 2012, **31**, 5990–5993.
- 23 These protocols require extended reaction times and/or the use of hazardous solvents, i.e., DMF or 1,4-dioxane (ref. 12a and d).
- 24 See ESI† for details.
- 25 As with haloarenes, existing solution-phase methods to prepare these complexes require long reaction times and hazardous solvents (ref. 12d).
- 26 K. Shen, Y. Fu, J.-N. Li and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576.
- 27 M. C. Cramp, J. Gilmour, L. R. Hatton, R. H. Hewett, C. J. Nolan and E. W. Parnell, *Pestic. Sci.*, 1987, **18**, 15–28.
- 28 (a) S.-J. Lou, Q. Chen, Y.-F. Wang, D.-Q. Xu, X.-H. Du, J.-Q. He, Y.-J. Mao and Z.-Y. Xu, *ACS Catal.*, 2015, **5**, 2846–2849; (b) Q. Gou, X. Tan, M. Zhang, M. Ran, T. Yuan, S. He, L. Zhou, T. Cao and F. Luo, *Org. Lett.*, 2020, **22**, 1966–1971.
- 29 R. C. Heel, R. N. Brogden, T. M. Speight and G. S. Avery, *Drugs*, 1978, **16**, 177–201.
- 30 Although KOH was ultimately found to be the optimal base for heteroarene C–H auration, comparable activity was also observed with KO^tBu.
- 31 Similar reactivity was also observed in solution; see ESI† for details.
- 32 Despite extensive efforts, we were unable fully to isolate this species from remaining KO^tBu. For reported preparation and characterization of related (R₃P)Au(I) alkoxide complexes, see: (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.

