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A general approach to intermolecular carbonylation of arene C–H bonds to ketones through catalytic aroyl triflate formation

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The development of metal-catalysed methods to functionalize inert C–H bonds has become a dominant research theme in the past decade as an approach to efficient synthesis. However, the incorporation of carbon monoxide into such reactions to form valuable ketones has to date proved a challenge, despite its potential as a straightforward and green alternative to Friedel–Crafts reactions. Here we describe a new approach to palladium-catalysed C–H bond functionalization in which carbon monoxide is used to drive the generation of high-energy electrophiles. This offers a method to couple the useful features of metal-catalysed C–H functionalization (stable and available reagents) and electrophilic acylations (broad scope and selectivity), and synthesize ketones simply from aryl iodides, CO and arenes. Notably, the reaction proceeds in an intermolecular fashion, without directing groups and at very low palladium-catalyst loadings. Mechanistic studies show that the reaction proceeds through the catalytic build-up of potent aroyl triflate electrophiles.

The generation of reactive electrophiles is one of the cornerstones of traditional synthetic chemistry. A powerful illustration of this is in Friedel–Crafts reactions, wherein the creation of sufficiently high-energy acylating reagents can lead to the functionalization of even the unactivated aromatic C–H bonds (Fig. 1a)[1,2]. The breadth and reliability of Friedel–Crafts acylations has made it a mainstay in the synthetic organic repertoire for the assembly of ketones, and recent advances have expanded the scope of these reactions, as well as offered novel approaches to control product selectivity[3–6]. Nevertheless, an intrinsic limitation of Friedel–Crafts chemistry is the required initial generation of the electrophilic acylating compounds themselves. This usually entails the use of reactive reagents (for example, $SOCl_2$, PCl_3 and strong Lewis acids) that are synthetic, high energy and create significant chemical waste. The reactivity of acylating reagents also leads to significant challenges in their handling and functional group compatibility. In this regard, transition-metal-catalysed C–H bond functionalization has rapidly evolved over the past decade to have tremendous impact[7–12]. Relative to stoichiometric Friedel–Crafts reactions, metal-catalysed approaches can use benign reagents to functionalize traditionally unreactive C–H bonds, generate minimal waste and often display high functional group compatibility.

Although metal-catalysed C–H functionalization can be advantageous, there remain a number of limitations in this chemistry relative to classical electrophilic substitution reactions. For example, the catalytic functionalization of simple arenes can often require substrate activation, high catalyst or substrate concentrations, or the presence of directing groups in order to proceed with high efficiency[13,14]. In addition, the incorporation of reactive functionalities into catalytic C–H derivatization platforms can be plagued by catalyst inhibition. An important example is in the carbonylative synthesis of ketones (Fig. 1b). The palladium-catalysed carbonylative C–H functionalization of arenes to form esters, amides and carboxylic acids was pioneered by Fujiwara and co-workers over two decades ago[15], and has seen significant recent progress[16–20]. In contrast, the intermolecular carbonylative coupling with simple arenes to generate valuable ketones is not known, and has to date required either intramolecular reactions or the use of acidic/activated substrates, as shown by the groups of Larock, Beller, Skrydstrup, Lei and others[21–26]. This has been attributed, in part, to the common mechanistic pathway for palladium-based C–H functionalization, in which the carboxylate reagents often used in the activation of C–H bonds can react with the palladium–acyl intermediate much more rapidly than with arenes (Fig. 1c). Instead, the formation of ketones by carbonylations typically requires coupling with pre-synthesized organometallic agents[27].

In considering these issues, we questioned if metal catalysed carbonylations might offer an alternative approach to arene C–H bond functionalization, in which, rather than using transition metals as the active bond-functionalizing agent, carbon monoxide might instead be employed to drive the build-up of potent organic electrophiles capable of reacting with arenes (Fig. 1d). This could provide a method to combine the attractive features of transition-metal catalysis (available reagents, functional group compatibility and atom economy) with that of Friedel–Crafts chemistry (high reactivity, intermolecular and electrophilic selectivity). The development of this transformation would require a catalyst that can mediate the currently unknown reductive elimination of an electrophile sufficiently reactive to functionalize simple arenes, in contrast with the highly favoured and well-established reverse oxidative addition of acylating electrophiles to palladium[28,29]. We describe below our studies towards this goal. These have led to the discovery of a palladium-catalysed platform to perform the carbonylative C–H functionalization of arenes to form ketones directly from broadly available and stable reagents (aryl halides, arenes and CO). This transformation occurs in common solvents, with low catalyst loadings, uses simple palladium catalysts and illustrates how carbonylation reactions can be employed efficiently to build-up potent electrophilic acylating agents: aroyl triflates.

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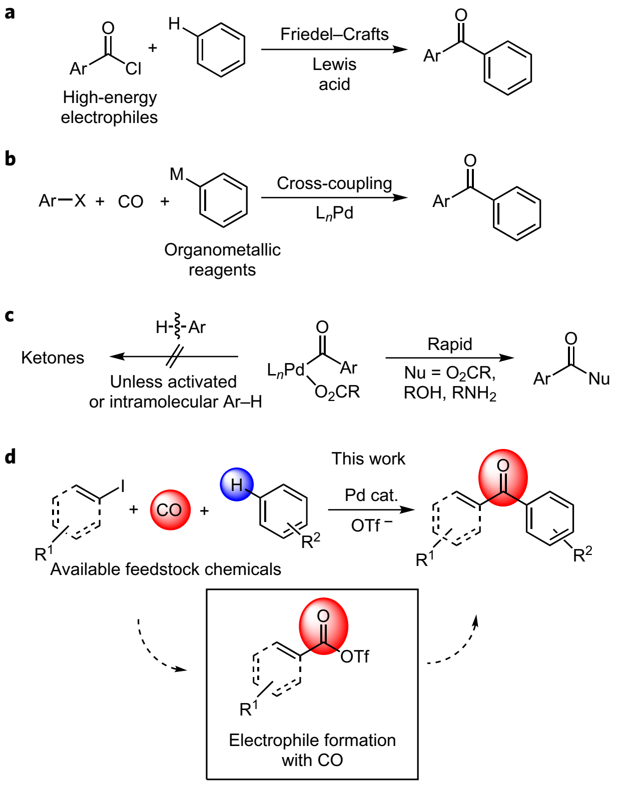


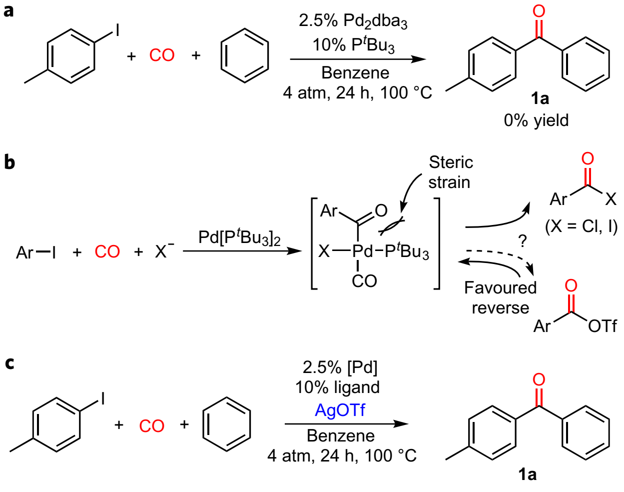
Figure 1 | Comparison of the classical approaches to ketone synthesis with the palladium-catalysed carbonylative C–H bond functionalization reaction described here. **a**, Typical synthetic approach to ketones by Friedel–Crafts reactions with synthetic electrophiles. **b**, Ketone synthesis by carbonylative cross-coupling reactions with organometallic reagents. Known for organometallic reagents (such as with M = R_3Sn or R_2B), not known for M = H. **c**, A challenge in applying palladium-catalysed C–H bond functionalizations to carbonylative ketone synthesis is the reaction of the palladium-acyl intermediate with bases, and typically requires the use of activated heteroarenes, acidic perfluoroarenes or intramolecular reactions. **d**, Concept reported here: the palladium-catalysed formation of high-energy aroyl electrophiles as an alternative approach to carbonylative arene C–H functionalization. Ar, aryl group; cat, catalyst; L, ligand; M, metal fragment; Nu, nucleophile; R, alkyl chains; R^1 and R^2, substituents; X, halogen.

Results and discussion

The catalytic formation of organic electrophiles sufficiently reactive to derivatize aromatic C–H bonds, yet doing so from stable and available substrates, at first glance appears energetically challenging. However, carbonylations may provide a unique entry to such systems. Carbon monoxide is an inexpensive feedstock chemical broadly employed in the assembly of carbonyl-containing products[30,31]. In addition, a less-appreciated feature of carbon monoxide is its energetics, in which the conversion of CO into a carbonyl-containing product is often highly exergonic (by up to 40 kcal mol^{-1}) (ref. 32). We have recently exploited this feature to generate aromatic acid chlorides and iodides from aryl halides and CO, with the latter having the ability to functionalize electron-rich N-heterocycles[33–35]. Morandi and co-workers have also shown that alkyl and vinyl acid chlorides can be generated by palladium-catalysed functional group exchange[36]. Based on these results, we questioned if the energetics of CO might be taken even further, and be employed to drive the generation of electrophilic acylating agents sufficiently reactive to directly derivatize simple arenes.

To probe this potential, our initial studies examined the functionalization of benzene with the Pd/P^tBu_3 catalyst system found to allow the formation of acid halides (ArCOX, X = Cl, I). However, no evidence for benzene functionalization was observed, and we instead simply recovered the starting materials (Fig. 2a). This reactivity mirrors that of aroyl iodides, the presumed intermediate generated from the carbonylation of aryl iodide, which also cannot directly react with benzene (Supplementary Fig. 1). In considering approaches to enhance the electrophilicity, one possibility would be to employ anions that are even more ionizable, such as triflate. Aroyl triflates are exceptionally potent electrophiles that are typically generated *in situ* for aroylation reactions[37]. Unfortunately, their high reactivity would not only make their reductive elimination challenging, but also lead to their much more rapid re-addition to Pd(0) than that of the aryl halide reagent (Fig. 2b). The screening of many triflate salts in this catalytic reaction did not lead to any reaction (Supplementary Table 1). However, we were pleased to find that the addition of silver triflate resulted in the carbonylative functionalization of benzene into ketone **1a** in low yield (12%, Fig. 2c).

Interestingly, further studies showed that a number of phosphine ligands can be employed in this catalytic reaction to generate ketone in comparable yields (Fig. 2c, entries 2–5). This contrasts with the catalytic formation of acid chlorides and iodides, in which the sterically encumbered P^tBu_3 ligand is critical to drive reductive elimination as a mechanism to relieve strain[38]. The origin of the lack of ligand influence can be seen by monitoring the catalytic reaction with P^tBu_3 by ^1H and ^{31}P NMR analysis, which shows that P^tBu_3



Entry	[Pd]	Ligand	Yield **1a**
1	Pd_2dba_3	P^tBu_3	12%
2	Pd_2dba_3	PPh_3	31%
3	Pd_2dba_3	P^oTol_3	9%
4	Pd_2dba_3	PCy_3	21%
5	Pd_2dba_3	$P(C_6F_6)_3$	29%
6	$[Pd(allyl)Cl]_2$	–	99%
7	5% $PdCl_2$	–	92%
8	0.0075% $[Pd(allyl)Cl]_2$	–	95%

Figure 2 | Palladium-catalyst development for the intermolecular carbonylative coupling of aryl iodide and benzene into ketones. **a**, Attempt at benzene carbonylation by *in situ* aroyl iodide generation leads to no product. **b**, Mechanism of catalytic acid halide formation, and the challenge of generating even more potent aroyl triflate electrophiles. **c**, Catalyst design for arene carbonylation into ketones with AgOTf: *p*-tolyl iodide (55 mg, 0.25 mmol); Pd_2dba_3 (6 mg, 0.0062 mmol); ligand (0.025 mmol); AgOTf (97 mg, 0.375 mmol); benzene (2 ml); and 4 atm CO. ^1H NMR yield. Entry 8 performed in DCE solvent. Cy, cyclohexyl; dba, dibenzylideneacetone.

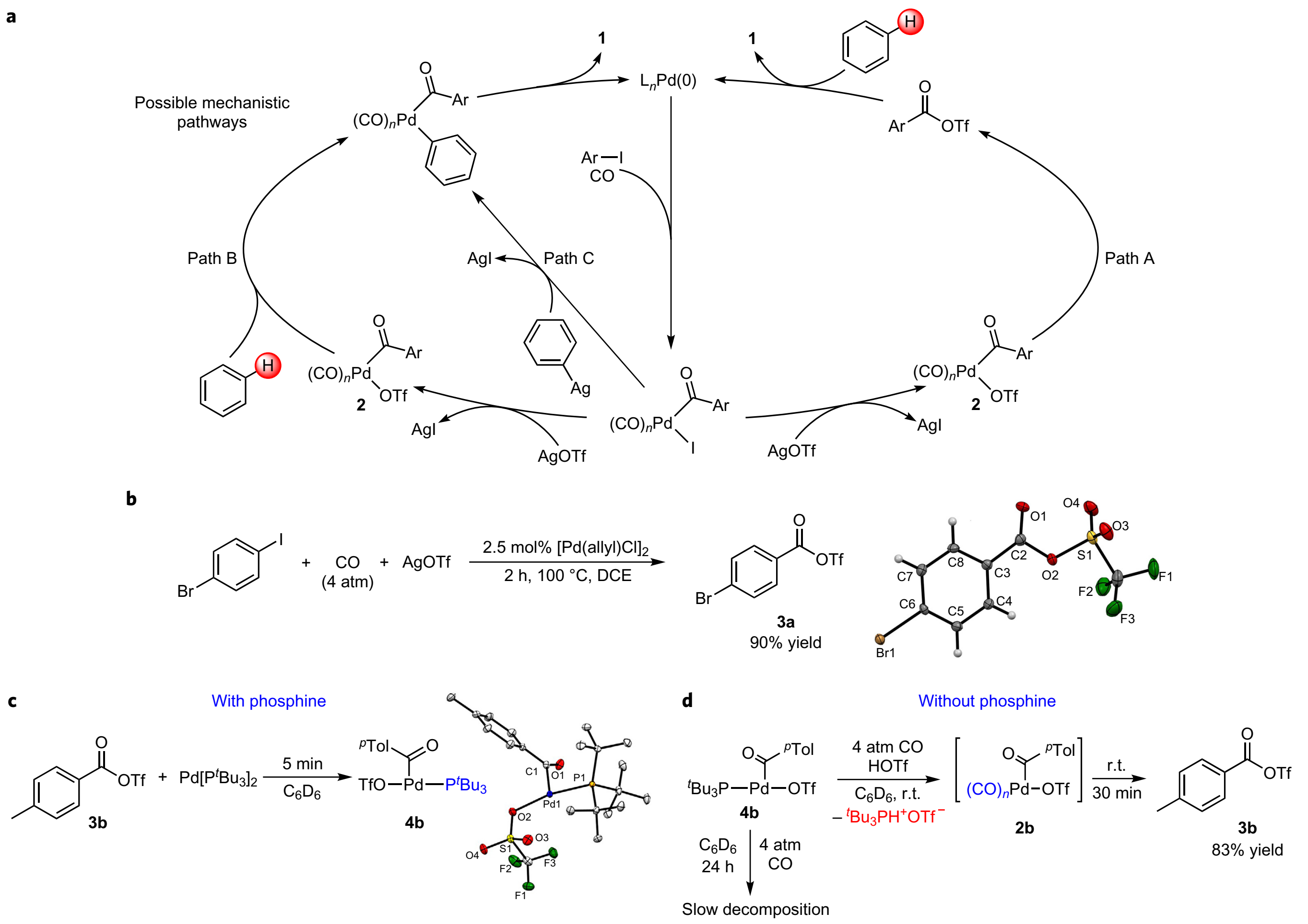


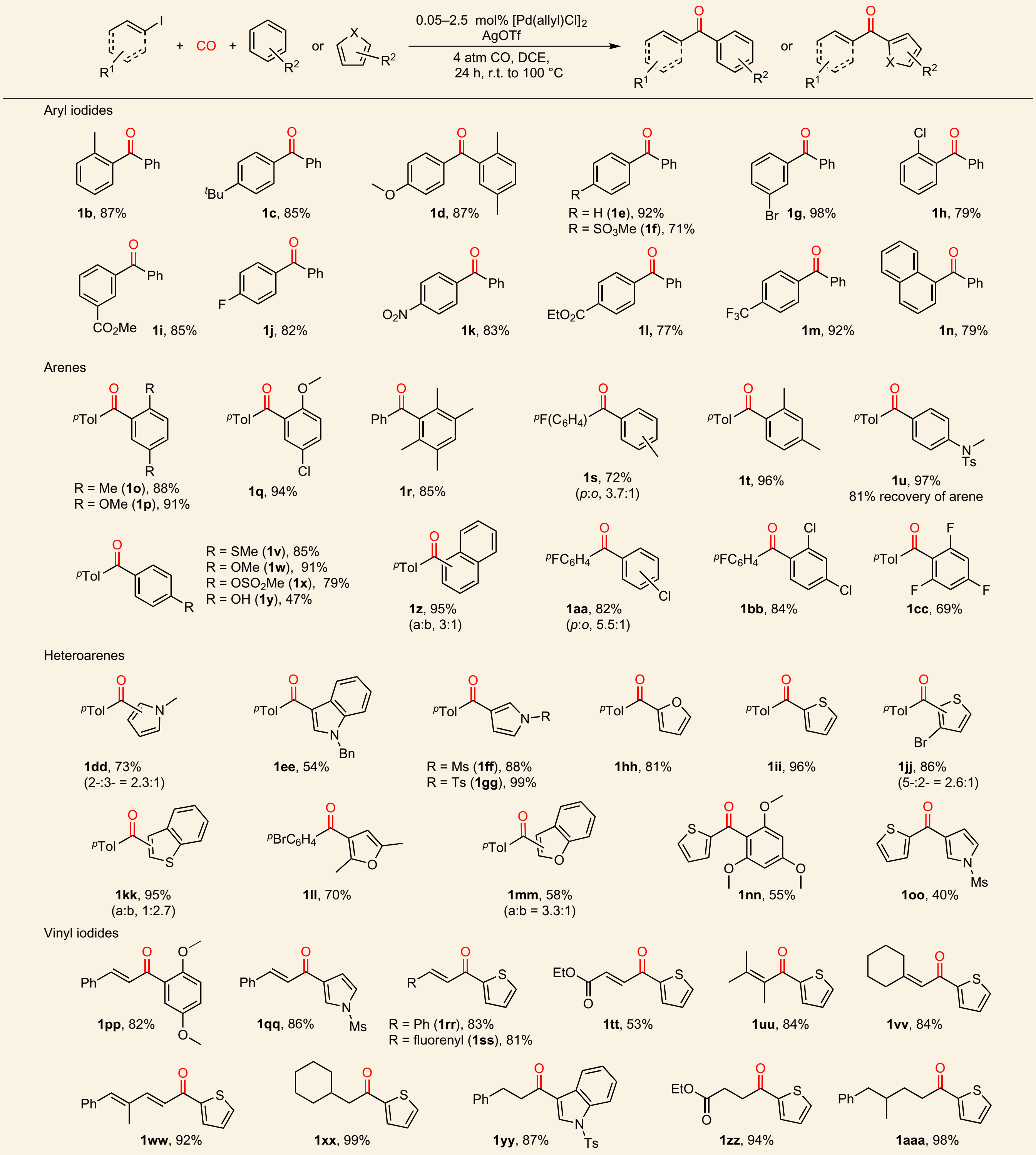
Figure 3 | Mechanistic studies demonstrate this transformation proceeds through the novel catalytic formation of aroyl triflate electrophiles. a, Plausible mechanisms for ketone formation include the *in situ* formation of aroyl triflate electrophiles (path A), palladium-based arene functionalization (path B) or the formation of a silver–aryl intermediates (path C). Ar, aryl group; L, ligand. **b**, Removal of benzene from the catalytic reaction leads to the formation of aroyl triflate (ORTEP-style ellipsoids drawn at 50% probability). **c**, Aroyl triflates undergo rapid oxidative addition to P^{t}Bu$_3$-coordinated palladium. **d**, The sequestration of P^{t}Bu$_3$ with HOTf addition leads to the rapid, near-quantitative elimination of aroyl triflate from palladium. r.t., room temperature.

is rapidly consumed by the strong electrophiles generated in catalysis to form protonated phosphine and various degradation products (Supplementary Fig. 2). As a result, simply removing the phosphine ligand from the reaction and employing palladium(II) salts as catalyst leads to the intermolecular derivatization of benzene in near-quantitative yield (Fig. 2c, entries 6 and 7).

The unusual ability of simple palladium salts with no added ligands to catalyse the high-yield intermolecular functionalization of benzene with CO, aryl iodide and a triflate source raises a number of mechanistic questions. The transformation presumably proceeds through the formation of a palladium–aroyl intermediate from oxidative addition followed by CO insertion (Fig. 3a). One possibility is that this palladium intermediate may undergo reductive elimination of an aroyl triflate electrophile (path A). However, in the absence of any phosphine to favour elimination, we also considered the potential that the non-phosphine coordinated Pd–COAr intermediate **2** may be sufficiently electrophilic to palladate benzene (path B), or the silver complex could itself be involved in C–H bond activation (path C), similar to recent results of Hartwig[39], Larossa[40] and Sanford[41] and their co-workers. To gain some insight into which pathway is operative, a series of mechanistic studies were performed. The competition kinetic isotope effect (KIE) for the reaction is 1.24 (Supplementary Fig. 3), which is much lower than that previously observed for arene palladation or the formation of a silver–aryl intermediate (KIE = ~4.5 and 2.3, respectively)[39,40,42]. However, it is in line with common C–H/D isotope effects in Friedel–Craft acylations with aroyl triflates (KIE = 1.1–1.4) (ref. 43). Even greater evidence for the mechanism can be seen by monitoring the catalytic reaction by NMR analysis. As illustrated in Fig. 3b, removing benzene from the [Pd(allyl)Cl]$_2$-catalysed reaction of aryl iodide, CO and silver triflate leads to the high-yield generation of the potent electrophile aroyl triflate **3a** as an isolable product.

As far as we are aware, aroyl triflates have not been observed before as products of palladium catalysis or carbonylation chemistry. The identity of this product was confirmed by both *in situ* multinuclear NMR analysis and, as shown in Fig. 3b, X-ray crystallography. The subsequent reaction of this aroyl triflate with benzene occurs in the absence of any catalyst, and with the same KIE as noted above ($k_H/k_D = 1.27$ (Supplementary Fig. 3)), which confirms the viability of path A as the mechanism for the catalytic reaction. The actual build-up and isolation of **3a** is surprising, as its potent electrophilicity would normally be thought to result in its more favoured re-oxidative addition to palladium. For example, the addition of **3b** to Pd(P^{t}Bu$_3$)$_2$ leads to the quantitative formation of the oxidative addition product **4b** within minutes at ambient temperature (Fig. 3c). However, such a rapid oxidative addition is not necessarily the case with the more electron-deficient, non-ligated palladium salt used as catalyst. By itself, the P^{t}Bu$_3$-coordinated palladium–aroyl triflate complex **4b** does not eliminate

Table 1 | Scope of the carbonylative C–H functionalization of arenes and heteroarenes.



Aryl iodides: **1b**, 87%; **1c**, 85%; **1d**, 87%; R = H (**1e**), 92%; R = SO_3Me (**1f**), 71%; **1g**, 98%; **1h**, 79%; **1i**, 85%; **1j**, 82%; **1k**, 83%; **1l**, 77%; **1m**, 92%; **1n**, 79%

Arenes: R = Me (**1o**), 88%; R = OMe (**1p**), 91%; **1q**, 94%; **1r**, 85%; **1s**, 72% (*p*:*o*, 3.7:1); **1t**, 96%; **1u**, 97%, 81% recovery of arene; R = SMe (**1v**), 85%; R = OMe (**1w**), 91%; R = OSO_2Me (**1x**), 79%; R = OH (**1y**), 47%; **1z**, 95% (a:b, 3:1); **1aa**, 82% (*p*:*o*, 5.5:1); **1bb**, 84%; **1cc**, 69%

Heteroarenes: **1dd**, 73% (2-:3- = 2.3:1); **1ee**, 54%; R = Ms (**1ff**), 88%; R = Ts (**1gg**), 99%; **1hh**, 81%; **1ii**, 96%; **1jj**, 86% (5-:2- = 2.6:1); **1kk**, 95% (a:b, 1:2.7); **1ll**, 70%; **1mm**, 58% (a:b = 3.3:1); **1nn**, 55%; **1oo**, 40%

Vinyl iodides: **1pp**, 82%; **1qq**, 86%; R = Ph (**1rr**), 83%; R = fluorenyl (**1ss**), 81%; **1tt**, 53%; **1uu**, 84%; **1vv**, 84%; **1ww**, 92%; **1xx**, 99%; **1yy**, 87%; **1zz**, 94%; **1aaa**, 98%

Ar–I (1 mmol), arene (2 mmol), $[Pd(allyl)Cl]_2$ (0.2 mg, 5×10^{-4} mmol, from stock solution), AgOTf (385 mg, 1.5 mmol), 4 ml DCE, 4 atm CO, 100 °C, 24 h. 1uu–1ww and 1u formed with 2,6-di-*t*-butylpyridine (50 mg, 0.30 mmol). Electron-rich arenes (<80 °C) and vinyl iodides (r.t.) react at lower temperatures; heterocycle added after aroyl triflate formation for 1dd, 1ee, 1hh, 1ll and 1mm (Supplementary Information gives full details). Excess arene can be recovered (for example, 1u). 1xx–aaa are generated by hydrogenation of the vinyl ketone (0.15 mmol), Pd/C (38 mg, 5% w/w Pd), 3 atm H_2, 55 °C, 16 h. X = N, O, S; Bn = benzyl; Ts = *p*-toluenesulfonyl; Ms = methanesulfonyl.

aroyl triflate, and slowly decomposes into a range of products in the presence of CO. In contrast, the addition of HOTf to protonate the phosphine and generate *in situ* a presumably CO-bound palladium intermediate **2b** leads to the rapid, near-quantitative elimination of aroyl triflate **3b** as a product together with protonated P^tBu_3 (Fig. 3d). As such, we postulate that the catalytic generation of aroyl triflate in this system is facilitated by the electron-deficient Pd(II) catalyst generated in the presence of CO that can undergo a rapid reductive elimination of even a highly electrophilic product such as **3**.

In addition to offering a method to generate high-energy aroyl triflate electrophiles as the products of carbonylation, a notable

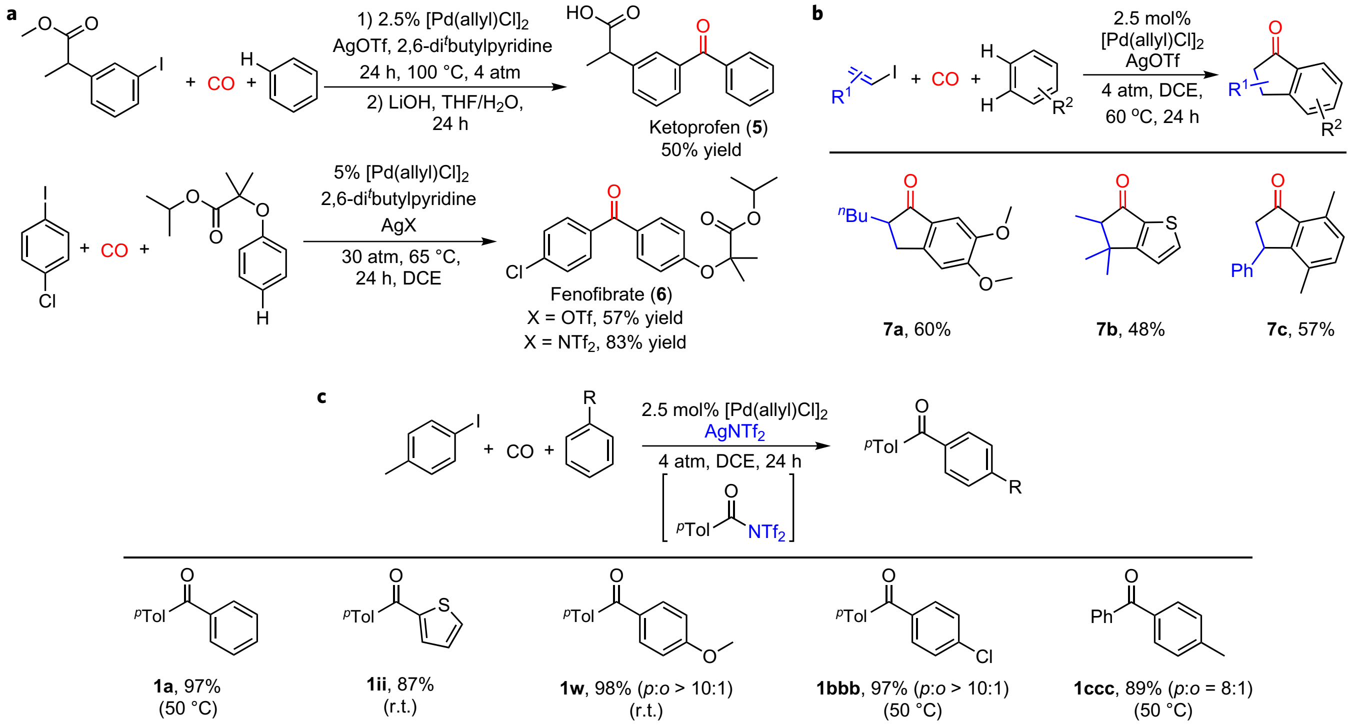


Figure 4 | Applications of this general methodology to the synthesis of pharmaceutically relevant molecules, double C–H bond functionalization and low-temperature C–H bond functionalization. **a**, Synthesis of ketoprofen and fenofibrate by arene carbonylation. **b**, Palladium-catalysed double C–H functionalization and indanone synthesis with vinyl iodides by *in situ* acid-mediated cyclization. **c**, Generation of the even-more electrophilic aroyl triflimides allows the carbonylative C–H functionalization of arenes to proceed at ambient temperature and with high regioselectivity (*p*:*o* selectivity with AgOTf: **1bbb**, 6:1; **1ccc**, 5:1).

feature is that the catalytic formation of **3** is more rapid than its subsequent reaction with benzene (Fig. 3b and Supplementary Fig. 4). The decoupling of the low-concentration palladium catalyst from the bond-functionalization step leads to a number of useful features. For example, it is straightforward to perform benzene C–H functionalization in common organic solvents (such as 1,2-dichloroethane (DCE) and dichloromethane), rather than in neat arene solvent, because the arene can react with the organic aroyl triflate product built up during catalysis (Supplementary Table 2). The catalyst loadings for arene functionalization can also be significantly lowered, and the reaction proceeds in near-quantitative yields with as little as 0.0075 mol% catalyst (or 150 ppm Pd (Fig. 2c, entry 8)). As far as we are aware, this represents one of the lowest catalyst loadings known for intermolecular arene C–H functionalization[44–46].

We next examined the generality of this approach to ketone synthesis. Examples are shown in Table 1. A wide range of aryl iodides are compatible with this reaction, including those with electron-donating (**1a**–**1d**) and electron-withdrawing (**1f**–**1m**) substituents. Potentially reactive functionalities can be incorporated, such as esters (**1i** and **1l**) and nitro substituents (**1k**), and the chemoselectivity for aryl iodide oxidative addition makes this chemistry tolerant of other halogen-containing substituents (**1g** and **1h**). Benzylic C–H bonds, which often exhibit a higher reactivity than arenes in many C–H functionalization systems, are readily tolerated (**1a**, **1b** and **1d**). The reactions can be performed with an equimolar amount of arene with a slightly lower yield (80% **1a** (Supplementary Fig. 5)). It is also straightforward to tune the arene that is derivatized. Examples include benzene and various electron-rich arenes (**1o**–**1z**). With more-elevated temperatures, deactivated arenes can also be employed, such as chlorobenzenes (**1aa** and **1bb**) and trifluorobenzene (**1cc**), with the selectivity mirroring that of Friedel–Crafts chemistry[1,2]. The electrophilicity of the aroyl triflate intermediates in this chemistry can also be applied to functionalize heterocycles, such as pyrroles and indoles, which can react to generate **1dd** and **1ee**, respectively. Less-activated heterocycles can be similarly functionalized, including furan (**1hh**), substituted furans (**1ll**), thiophenes (**1ii**–**1kk**) or heterocycles with electron-withdrawing substituents (**1ff** and **1gg**). Heteroaryl iodides are also viable reagents in this reaction to build-up diheteroaryl ketones (**1oo**).

Vinyl halides were also explored as substrates. Unlike aryl-substituted acid triflates, vinoyl triflates are often highly labile and difficult to generate by traditional methods[47]. As shown in Table 1, these electrophiles can be formed *in situ* through palladium-catalysed carbonylations and allow the formation of synthetically useful α,β-unsaturated ketones **1pp**–**1ww** with electron-rich arenes. In the case of **1uu**–**1ww**, a bulky 2,6-di-*t*-butylpyridine base is required to remove HOTf. The formation of these products can also be combined with their subsequent reactivity. As an example, coupling the catalytic formation of these α,β-unsaturated ketones with hydrogenation can provide an overall approach to prepare alkyl-substituted ketones (**1xx**–**1aaa**). As such, this offers a general method to perform carbonylative arene C–H bond functionalization to generate ketones.

Ketones are valuable building blocks in synthetic chemistry, as well as useful products themselves in many areas of application. The ability to generate these compounds from stable and broadly available aryl iodides, CO and arenes can therefore provide an attractive alternative to classical synthetic methods. As an illustration, this transformation can be applied to the targeted formation of pharmaceuticals such as ketoprofen, an effective non-steroidal anti-inflammatory drug[48], from simply benzene, CO and an aryl iodide in the presence of base to inhibit ester decomposition (Fig. 4a). Similarly, fenofibrate, a triglyceride and cholesterol regulator[49], can be generated by the carbonylative coupling of 4-chloroiodobenzene and the appropriate arene. Alternatively, the catalytic formation of ketones can also be coupled with their subsequent reactivity. Performing the carbonylation of arenes with vinyl iodides under mild heating in the absence of base leads to the formal double C–H functionalization of arenes (Fig. 4b). The latter presumably proceeds through subsequent Friedel–Crafts cyclization from the α,β-unsaturated ketone product under the acidic reaction conditions[50], and offers a direct method to form indanones from arenes.

Finally, we have probed if this approach can offer a method to build-up electrophiles that are even more reactive. Relative even to triflates, triflimides are exceptional leaving groups. Thus, performing the catalytic carbonylation of aryl iodides in the presence of a triflimide salt can allow the intermolecular carbonylative functionalization of arenes into ketones at ambient temperature (Fig. 4c). To our knowledge, electrophilic aroyl triflimides have not been reported. Although these electrophiles are more labile, their formation through carbonylation can even allow the derivatization of deactivated aromatic substrates at temperatures as low as 50 °C and with high regioselectivity. The latter presumably arises from a combination of the lower reaction temperatures and larger triflimide anion that directs this chemistry towards the selective formation of *para*-derivatized arenes in high yield and under mild conditions.

Conclusions

In summary, we have developed a conceptually new approach to intermolecular arene C–H functionalization to form ketones. The reaction proceeds through the unprecedented palladium-catalysed formation of aroyl triflates, and demonstrates how carbonylations can be employed to drive the formation of exceptionally reactive electrophiles from available reagents. This opens a method to couple metal-catalysed arene C–H bond functionalization with electrophilic substitution chemistry to generate ketones in high yield with low palladium loadings, and from aryl iodides, CO and arenes. Considering the diverse reactivity of the high-energy acylating agents, we anticipate this approach will find utility as a general platform to functionalize unreactive bonds by carbonylation chemistry.

Methods

General procedure. Under an inert nitrogen atmosphere, silver triflate (386 mg, 1.5 mmol) was transferred to a Teflon sealed thick-walled 50 ml glass reaction vessel equipped with a stir bar, followed by aryl iodide (1.0 mmol), arene (2.0 mmol), DCE (4 ml) and then a freshly prepared stock solution of $[Pd(allyl)Cl]_2$ (0.2 mg, 5×10^{-4} mmol). The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 °C for 24 h with stirring, the reaction was cooled to room temperature and carbon monoxide was released. The reaction mixture was filtered through Celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane/ethyl acetate 0 to 20%) to afford the pure ketone product.

Data availability. All data generated and analysed during this study are included in this article and its Supplementary Information files, and are also available from the authors on reasonable request. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as CCDC 1513679 (3a) and 1554343 (4b) and can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/getstructures.

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Author contributions

B.A.A. and R.G.K. conceived the project. R.G.K. conducted the majority of the experiments. J.T. assisted in the early experiments. G.M.T. conducted the mechanistic experiments with **4b** and assisted with Table 1 and Fig. 4b. N.I.L. and O.K. assisted with Table 1. B.A.A. and R.G.K. prepared the manuscript with feedback from all of the authors.

Additional information

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Competing financial interests

The authors declare no competing financial interests.