nature chemistry

ARTICLES

https://doi.org/10.1038/s41557-018-0078-8

Metathesis-active ligands enable a catalytic functional group metathesis between aroyl chlorides and aryl iodides

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Current methods for functional group interconversion have, for the most part, relied on relatively strong driving forces which often require highly reactive reagents to generate irreversibly a desired product in high yield and selectivity. These approaches generally prevent the use of the same catalytic strategy to perform the reverse reaction. Here we describe a catalytic functional group metathesis approach to interconvert, under CO-free conditions, two synthetically important classes of electrophiles that are often employed in the preparation of pharmaceuticals and agrochemicals—aroyl chlorides (ArCOCl) and aryl iodides (ArI). Our reaction design relies on the implementation of a key reversible ligand C–P bond cleavage event, which enables a non-innocent, metathesis-active phosphine ligand to mediate a rapid aryl group transfer between the two different electrophiles. Beyond enabling a practical and safer approach to the interconversion of ArCOCl and ArI, this type of ligand non-innocence provides a blueprint for the development of a broad range of functional group metathesis reactions employing synthetically relevant aryl electrophiles.

The efficient and safe transformation of one functional group into another is one of the pillars of organic synthesis. Countless efficient methods have been developed, which range from simple nucleophilic substitution reactions to highly designed catalytic systems for aromatic functional group exchange[1–3]. These methods have, for the most part, relied on relatively strong driving forces to irreversibly generate a desired product in high yield and selectivity (Fig. 1a). Although powerful, some important challenges arise from this approach: (1) these reactions often rely on highly unstable reactive reagents that have undesirable properties, such as a high toxicity (for example, carbon monoxide (CO))[4,5] or explosiveness (for example, diazonium)[6]; (2) because of the change in Gibbs free energy (ΔG) « 0, these reactions can only be performed in one direction (Fig. 1a, FG_1 to FG_2 (FG, functional group)), which inherently calls for the time- and resource-consuming development of a completely different reaction to perform the reverse reaction (Fig. 1a, FG_2 to FG_1). These two factors can often seriously limit the synthetic efficiency and flexibility of functional group manipulations. The development of a conceptually new approach that would allow for a facile and reversible ($\Delta G \approx 0$) functional group metathesis could possibly address these challenges.

Aroyl chlorides (ArCOCl) and aryl iodides (ArI) are two synthetically versatile intermediates that bear different functional groups (COCl and I) with complementary roles in the preparation of a wide range of pharmaceuticals and agrochemicals. ArCOCl can be accessed in certain cases from the corresponding ArI when a pressurized CO atmosphere and a sacrificial chloride source under Pd catalysis are used (Fig. 1b)[7,8]. In this kinetically controlled process, the thermodynamic and kinetic instability of CO serves as a powerful driving force to generate the reactive ArCOCl product. Unfortunately, the use of high pressures of toxic CO remains an important drawback for the widespread application of this method[4,5]. The reverse process, decarbonylative iodination of ArCOCl, is unknown, although synthetically related procedures that lead to aryl chlorides[9,10] or protocols that start from carboxylic acids or their derivatives[11–13] have been reported in certain instances. A challenge to the development of the decarbonylative iodination might arise from the thermodynamic preference for the oxidative addition of ArI over energetically disfavoured reductive elimination[11,14–16]. We envisaged that most of the challenges encountered in the desirable interconversion of ArCOCl and ArI could be addressed through a reversible metathesis reaction[17–21] because (1) no toxic CO would be employed nor produced as a by-product and (2) the formation of either product could be controlled with a single catalytic system to obtain either of the reactive electrophiles as the product (Fig. 1d).

Examples of catalytic functional group metathesis, wherein a $C–FG_1$ and $C–FG_2$ bond are reversibly exchanged (Fig. 1c), are very rare[22,23]. This probably stems from the challenge to identify a suitable catalyst system that is not only able to mediate the reversible cleavage of two distinct chemical bonds, but that can also provide a suitable platform for a productive ligand exchange. In addition, biaryl or benzophenone formation through the undesired dimerization of the electrophiles[24] must be prevented. For the reversible cleavage of an Ar–FG bond, oxidative addition and subsequent reductive elimination could be a potentially viable manifold in the case of ArCOCl and ArI. The reversibility of the oxidative addition for these two electrophiles is indirectly supported by many elegant studies in the literature that employ palladium-based catalytic systems[7,14,15]. However, a strategy to perform a rapid and reliable ligand exchange between the Pd–Ar intermediates generated catalytically, either through a CO/halide exchange or aryl exchange, remains challenging to realize.

We envisaged that the key to overcome the challenge of rapid ligand exchange would be to employ 'metathesis-active ligands' that mediate a new type of non-innocent ligand[25,26] behaviour wherein a phosphine ligand coordinated to a transition metal acts as a temporary aryl group storage unit through a rapid C–P bond metathesis event that proceeds at the ligand itself (Fig. 2a). The feasibility of this strategy is, in principle, supported by the possibility

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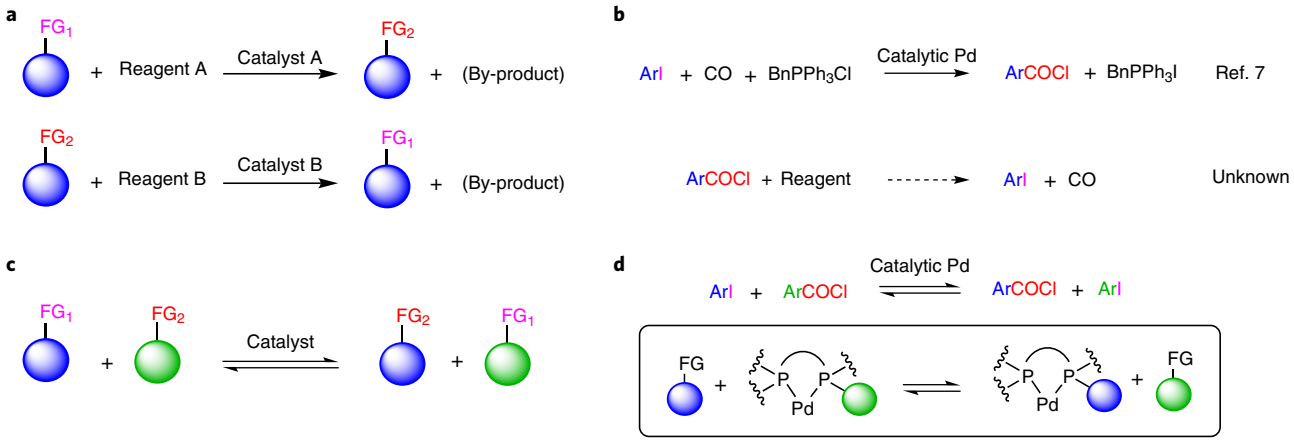


Fig. 1 | Conceptual blueprint for the development of a functional group metathesis reaction. a, Traditional approach for functional group interconversion in synthetic organic chemistry. Two completely different reaction protocols are usually required to interconvert two functional groups, FG_1 to FG_2 (top), and FG_2 to FG_1 (bottom), because these reactions rely on strong driving forces and are thus irreversible. **b**, The synthesis of ArCOCl (top) is known but uses toxic CO; the reverse reaction (bottom) has not been reported. **c**, The functional group metathesis concept introduced in this work. A single-reaction protocol is used for both processes in a reversible metathesis reaction. **d**, A functional group metathesis approach enabled by metathesis-active ligands that allow for a single reaction to interconvert ArI and ArCOCl in the absence of CO.

of using low valent transition metals as catalysts for C–P bond metathesis reactions[27–33]. In the proposed mechanism (Fig. 2a), the key exchange step proceeds through an initial oxidative addition of the corresponding electrophile (**I** to **II**), followed by an aryl group exchange with the phosphine ligand through reductive elimination[34] to form a phosphonium intermediate **III** followed by the oxidative addition of another C–P bond[35,36] to regenerate a different Pd–Ar species (**IV**). Reductive elimination then simultaneously generates an Ar–FG electrophile and a new Pd(0) species (**V**) that have swapped their aryl substituents in the overall process. The new Pd(0) species can now react with the next electrophile to undergo another aryl exchange process. If this mechanism, which does not involve any direct crossover step between two catalytically generated species, can be realized, a mixture of electrophiles should rapidly equilibrate to its thermodynamically most stable state, and so achieve the desired overall metathesis process of two different aryl electrophiles.

Results and discussion

Preliminary experiments demonstrated that the Ph groups present on a Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) ligand can be exchanged with the aryl group of either an ArI or ArCOCl electrophile in the presence of palladium (Fig. 2b). Further experiments that reacted both ArCOCl and ArI under optimized reaction conditions led to a full equilibration of the mixture within 12 hours, which proves the reversibility and high activity of the catalytic system (Fig. 2c). Notably, aryl chloride side-products, which could arise from the direct decarbonylation of ArCOCl[9,10], were not observed in this process.

As this reaction is reversible and thus thermodynamically controlled, suitable strategies to drive the reaction to the desired product have to be found. We initially focused on designing suitable reagents for the transformation of ArI into ArCOCl. A nearly stoichiometric amount (1.5 equiv.) of sterically congested reagent **1** (ref. [14]) (Table 1), which is an inexpensive chemical, performed best for most of the chlorocarbonylation reactions. Alternatively, for some cases the purification of the products proved more challenging, and so the electron-deficient nitro derivative (**3**), which benefits from electronic destabilization as a driving force, was employed. Using this catalytic reaction, several electron-rich functional groups, such as the methoxy (**9**), thiomethoxy (**10**), benzyloxy (**21**) and alkyl (**18**) substituents were well tolerated and gave the corresponding products in high yields. Although most products were isolated after derivatization of the moisture-sensitive ArCOCl, we could show that methoxy compound **9** could be isolated in pure form on a larger scale. Electron-withdrawing ArI can also serve as substrates in this transformation, as illustrated by the tolerance to cyano (**20**), nitro (**14**), trifluoromethyl (**22**), esters (**15** and **23**), ketone (**16**) and even aldehyde (**17**) groups. The reaction could also be used to react the more electrophilic iodide site selectively, with other (pseudo)halogens, such as chloride (**12**), bromides (**13**, **24** and **28**) and triflate (**11**), left intact. Electron-rich and electron-poor heterocycles (**29**–**32**) were also good substrates for the transformation. More complex starting materials derived from natural products (oestrone (**34**) and δ-tocopherol (**35**)), a pharmaceutical intermediate (**36**) and a drug derivative (derived from adapalene (**37**)) were converted efficiently into the corresponding acid chloride products, which illustrates the excellent functional group tolerance of the reaction. The reaction of ArI substituted at the *ortho* position (**25**) and α-substituted heteroaromatic substrates resulted in poor conversions.

The reverse reaction, namely the conversion of an ArCOCl into an ArI, could also be performed using appropriately selected reagents (Table 2). Depending on the substrate, two different strategies were employed. Either the inexpensive phenyl iodide (**5**) was used in excess to drive the reaction to completion or an electron-rich iodide (**7**), from which the stabilized push–pull product **8** can be accessed as a by-product, could be employed in nearly stoichiometric amounts. Simple monosubstituted aromatics worked well under these conditions when either electron-rich or -deficient functional groups were present. In contrast to the forward reaction, a wide range of *ortho*-substituted aromatics (**49**–**55** and **63**) were tolerated in the reverse process. Although a range of heterocycles gave the desired ArI products (**56**–**60**) in good yields, the use of α-substituted heterocycles resulted in low conversions. To highlight the synthetic versatility of the reaction, we performed a late-stage functionalization of four structurally different drugs (**66**–**69**) that are commercially sold for diverse conditions, including acne, cancer, gout and osteoarthritis.

With the utility of this reaction demonstrated for the preparation of a broad range of useful aromatic products, we became interested in exploring the reaction mechanistically. In particular, due to its

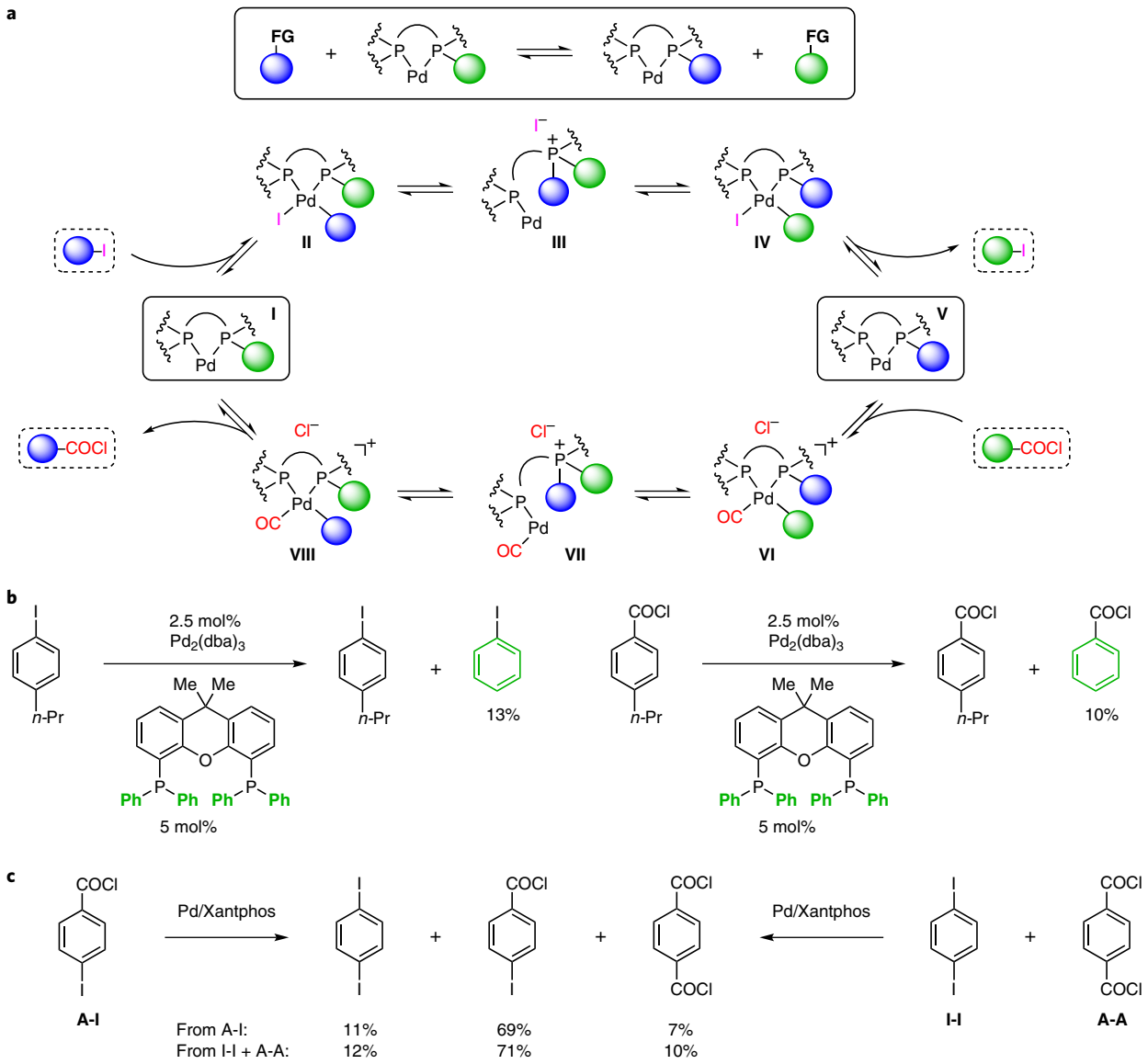
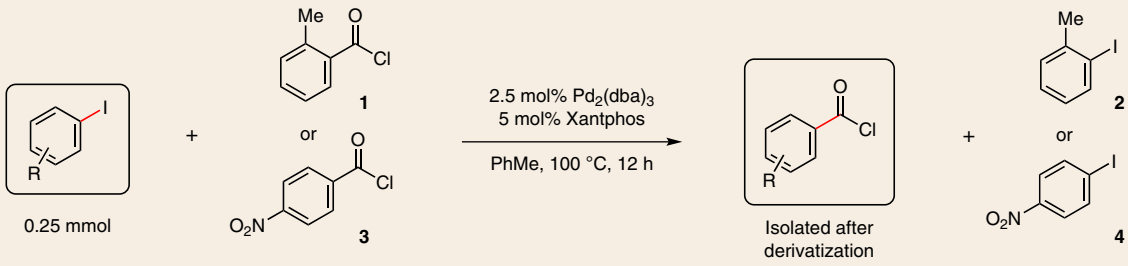
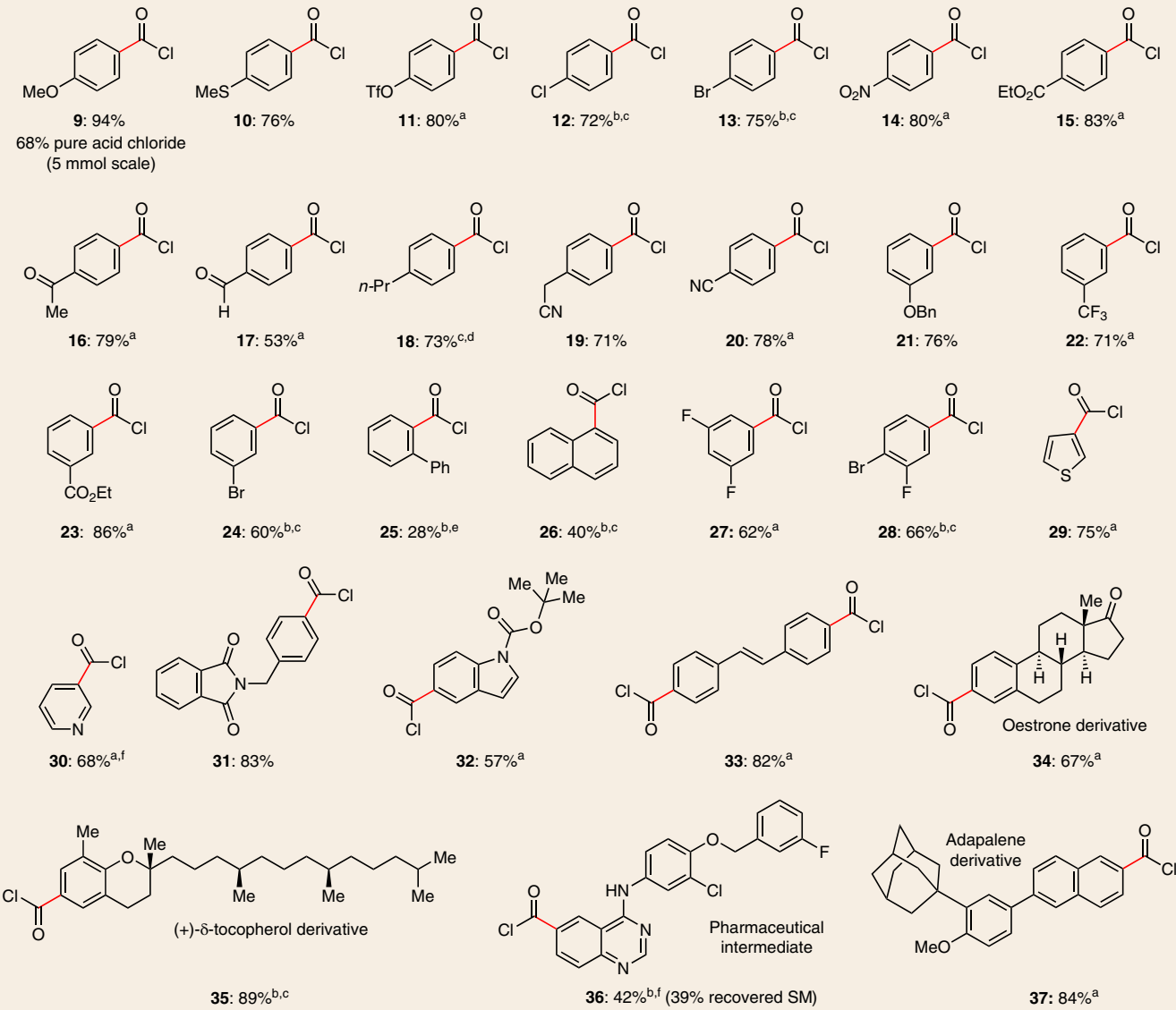


Fig. 2 | Mechanistic hypothesis and preliminary experiments. a, Proposed mechanism based on metathesis-active ligands to facilitate a fast aryl group transfer between electrophiles. C–P metathesis acts as a key transfer step. **b**, Proof of concept for the Ar group exchange between Xantphos and each electrophile. Ligand-scrambling experiments demonstrated the feasibility of the mechanism. Reaction conditions: aryl electrophiles (0.25 mmol, 1 equiv.), $Pd_2(dba)_3$ (2.5 mol%) (dba, dibenzylideneacetone), Xantphos (5 mol%), toluene, 100 °C, 12 h. **c**, Preliminary FG metathesis experiments demonstrated the equilibration process and the thermodynamic bias of the reaction. Reaction conditions: **A-I** (1 equiv.), **I-I** (0.5 equiv.), **A-A** (0.5 equiv.), $Pd_2(dba)_3$ (0.5 mol%), Xantphos (1 mol%), toluene, 100 °C, 12 h. Yields were determined by GC analysis versus *n*-dodecane as an internal standard.

potential broad applications in homogeneous catalysis, we wanted to investigate whether the postulated ligand metathesis occurred under our reaction conditions. Initially, we performed some simple control experiments to test whether CO was generated in our reaction. The reaction performed in an open system with continuous argon purging resulted in the same yield as in the normal reaction, a result that makes the involvement of free CO unlikely (Fig. 3a). Additionally, the reaction shut down when an atmosphere of CO was employed, probably due to the formation of a catalytically inactive species (Fig. 3b)[37]. To support our proposed C–P bond metathesis mechanism (Fig. 2a), we wondered if the postulated phosphonium intermediate could be isolated from the reaction of an aryl electrophile with a Pd–Xantphos species. A Pd-catalysed reaction between PhI and Xantphos (Fig. 3c) led to the precipitation and isolation of a 55% yield of the corresponding phosphonium under highly concentrated conditions (>3 M)[34]. Critically, when this phosphonium species was used as a ligand instead of Xantphos under the normal reaction conditions, similar yields of products were obtained (Fig. 3d). This result shows that the phosphonium is a catalytically competent species that could be involved as an intermediate in the process. These experiments also show that C–P bond metathesis at the ligand can take place under our reaction conditions. To provide further support for this mechanism, we performed qualitative kinetic experiments with a wide range of different substrates (Fig. 3e,f). The central question we wanted to answer with these studies is whether C–P bond metathesis at the ligand was possible with a broad range of substrates and, more importantly, whether the relative rate of C–P bond metathesis for different aryl substrates correlated with the overall rate of the catalytic reaction using the same substrates. For that purpose, we initially measured the amount

Table 1 | Substrate scope for the transformation of ArI into ArCOCl

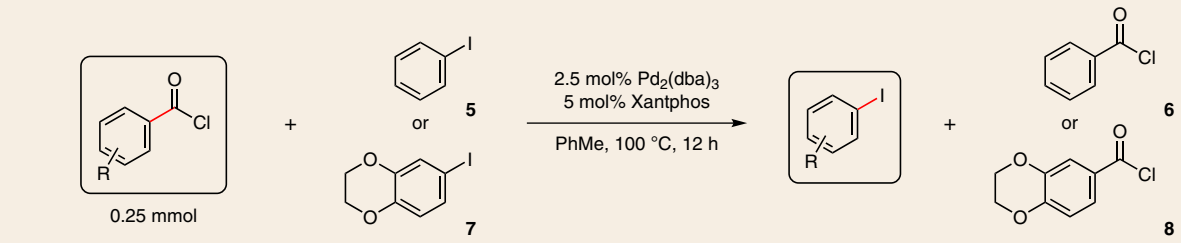


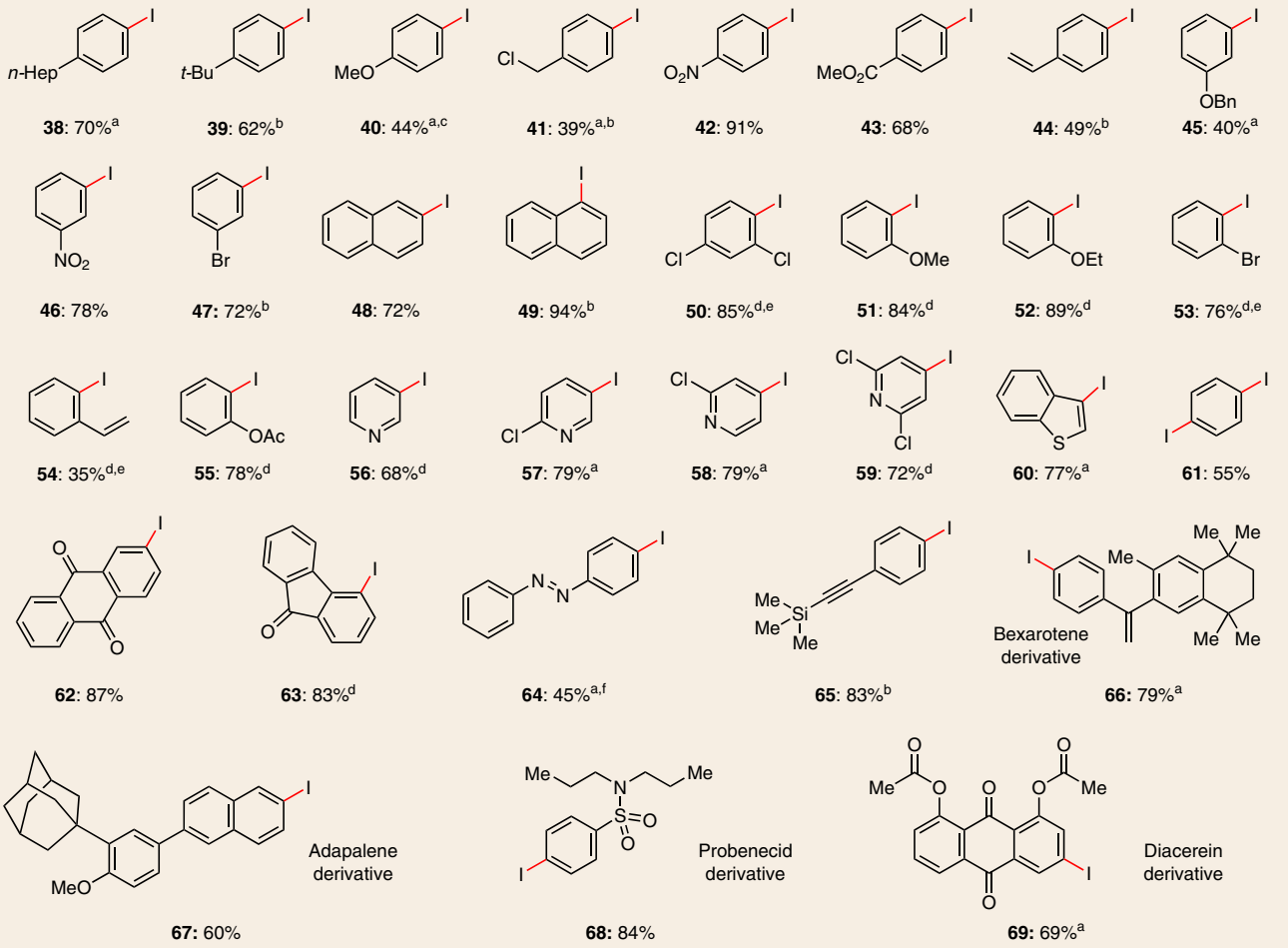


Yields (%) refer to isolated products after in situ derivatization of the ArCOCl product (Supplementary Section 9). Reaction conditions: ArI (0.25 mmol), **1** (1.5 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), toluene, 100 °C, 12 h. [a]**1** (3 equiv.). [b]**3** (1.3 equiv,). [c]125 °C. [d]**3** (1.1 equiv.). [e]Mesitylene, 180 °C. [f]o-xylene, 150 °C. For **9**, a pure acid chloride was isolated on a larger scale. TfO, trifluoromethanesulfonate; Bn, benzyl.

of combined PhI and PhCOCl yield formed under the normal reaction conditions starting from different starting materials that did not contain any Ph substituents (Fig. 3e). Under such conditions, all the Ph groups found in the products must arise from ligand metathesis and the subsequent statistical incorporation of the Ph substituents initially present in the Xantphos ligand. Experimentally, we determined that all the substrates gave substantial amounts of the Ph-containing products, which clearly shows that the ligand metathesis is a general pathway. When looking at the amount of these Ph-containing products formed at an earlier time point, it became evident that some functional groups, for example, NO_2 or 3,5-diF (3,5-difluoro), triggered a much slower exchange process

Table 2 | Substrate scope for the transformation of ArCOCl into ArI





All yields are isolated yields (%). Reaction conditions: ArCOCl (0.25 mmol), **5** (5 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), toluene, 100 °C, 12 h. [a]125 °C. [b]**7** (2 equiv.). [c]**7** (3 equiv.). [d]*o*-xylene, 150 °C. [e]**5** (2 equiv.). [f]**5** (10 equiv.). For **56**, a HCl salt of the substrate was used with DABCO (1,4-diazabicyclo[2.2.2]octane (0.5 equiv.)).

when compared to other groups, such as 4-Me or 4-MeO. We next qualitatively measured the rate of the ArCOCl/ArI metathesis reaction by monitoring the disappearance or formation of 1-iodo-4-propylbenzene (4-*n*-PrPhI) by quantitative gas chromatography (GC) analysis in both the forward (Fig. 3f) and reverse (Supplementary Fig. 18) reactions. Qualitatively, it is evident that most of the substituents that enable a fast C–P metathesis process are also those that lead to a faster overall metathesis between ArCOCl and ArI. The two clear outliers in this correlation are the *ortho*-substituted substrates (Supplementary Section 7)—in these cases, it is possible that the mechanism competes with a more traditional transfer mechanism, for example, a sequence of CO and halide exchanges. Overall, the excellent correlation between the rate of the C–P bond metathesis at the ligand and the overall rate of the reaction provides clear circumstantial evidence that our proposed mechanism (Fig. 2a) is the main pathway that occurs with the majority of the substrates studied.

Conclusion

We present a new approach for functional group manipulation, functional group metathesis, which offers great promise for more flexible and safer target-oriented syntheses. The unique type of ligand non-innocence demonstrated here, which employs metathesis-active ligands, is poised to provide a platform for the development of reversible arylation reactions.

Data availability. All data generated and analysed during this study are included in this article and its Supplementary Information,

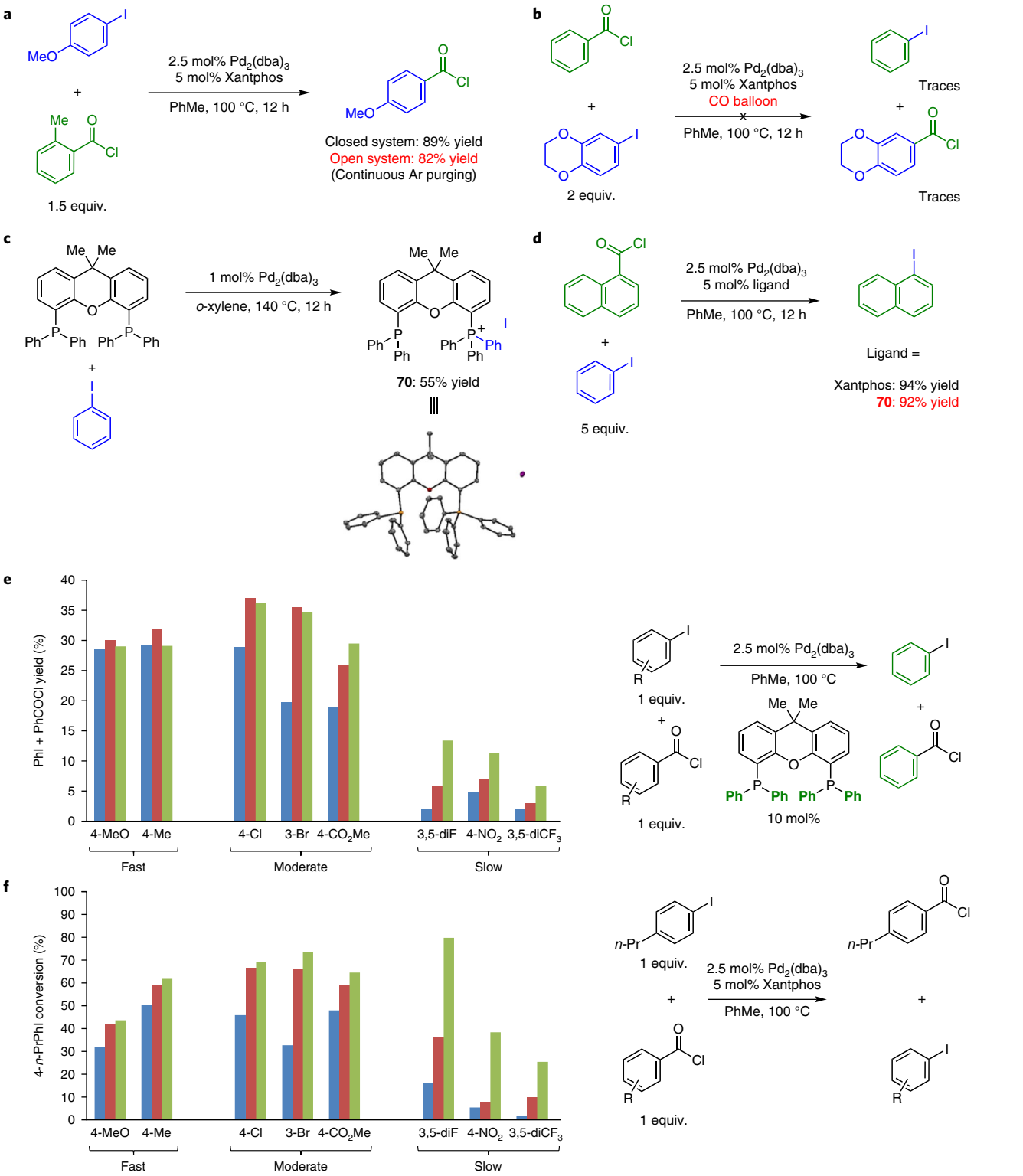


Fig. 3 | Experimental evidence for the proposed functional group metathesis mechanism based on metathesis-active ligands. a, Ar purging experiments make the involvement of free CO unlikely (Supplementary Section 6). **b**, A CO atmosphere shuts down the exchange process (Supplementary Section 6). **c**, Mechanistic experiments show the isolation of the postulated phosphonium intermediate under the reaction conditions (Supplementary Section 6). **d**, The phosphonium is catalytically competent (Supplementary Section 6). **e**, The rate of the C–P bond metathesis shows a strong rate dependence on the substitution pattern. Reaction conditions: ArI (1 equiv.), ArCOCl (1 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (10 mol%), toluene, 100 °C, 0.5 h (blue), 2 h (red) and 12 h (green) (Supplementary Fig. 17). **f**, The rate of the overall reaction shows a strong rate dependence on the substitution pattern and a qualitative correlation between the rate of the reaction and the rate of C–P metathesis. Reaction conditions: 4-*n*-PrPhI (1 equiv.), ArCOCl (1 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), toluene, 100 °C, 0.5 h (blue), 2 h (red) and 12 h (green) (Supplementary Fig. 18). Yields and conversions in **d**–**f** were determined by GC analysis based on the corresponding ethyl ester and ArI versus *n*-dodecane as an internal standard. 3,5-diCF3 = 3,5-bis(trifluoromethyl).

and also available from the authors upon request. Crystallographic data for compound **70** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1829364) and can be obtained free of charge from the CCDC via https://www.ccdc.cam.ac.uk/structures.

Received: 14 September 2017; Accepted: 2 May 2018;
Published online: 06 August 2018

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Acknowledgements

We thank Z. K. Wickens (Harvard University) for a critical proofreading of this manuscript. Generous funding from the Max-Planck-Society, the Max-Planck-Institut für Kohlenforschung and LG Chem (fellowship to Y.H.L.) is acknowledged. We thank B. List for sharing analytical equipment, and our NMR spectroscopy, mass spectrometry and X-ray departments for technical assistance.

Author contributions

Y.H.L. and B.M. conceived the project and prepared the manuscript. B.M. directed the work. Y.H.L. developed and studied the reaction experimentally. Both the authors analysed the data.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41557-018-0078-8.

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