Regioselective silyl installation for arene diversification

Jamie H. Docherty[1] and Igor Larrosa[2]

[1]Lancaster University, Lancaster, UK. [2]University of Manchester, Manchester, UK.

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Using a single ruthenium catalyst, site-selective C–H functionalization methods are developed for the installation of silylmethyl synthetic handles at either ortho or meta positions on diverse arenes, enabling a wide range of downstream transformations. Mechanistic studies highlight that biscyclometallated ruthenium(II) species are key to this reactivity, offering insight for future developments.

The Mission

Chemists have long sought robust methods to selectively install versatile functional handles onto aromatic rings to enable new synthetic routes to pharmaceuticals, agrochemicals and materials[1]. Although boron-based handles are widely established in cross-coupling and related transformations, their silicon analogues remain underexploited despite offering complementary reactivity. Metal-catalysed C–H functionalization has streamlined direct arene diversification; however, precise control of site-selectivity in complex molecules remains a challenge[2]. In particular, strategies for installing silicon-based handles – which can unlock further synthetic transformations and late-stage functionalizations – are still scarce. We envisioned addressing this gap by developing efficient, regiodivergent Ru-catalysed approaches to selectively install silylmethyl groups at both ortho and meta sites within arenes (Fig. 1), thus broadening synthetic possibilities.

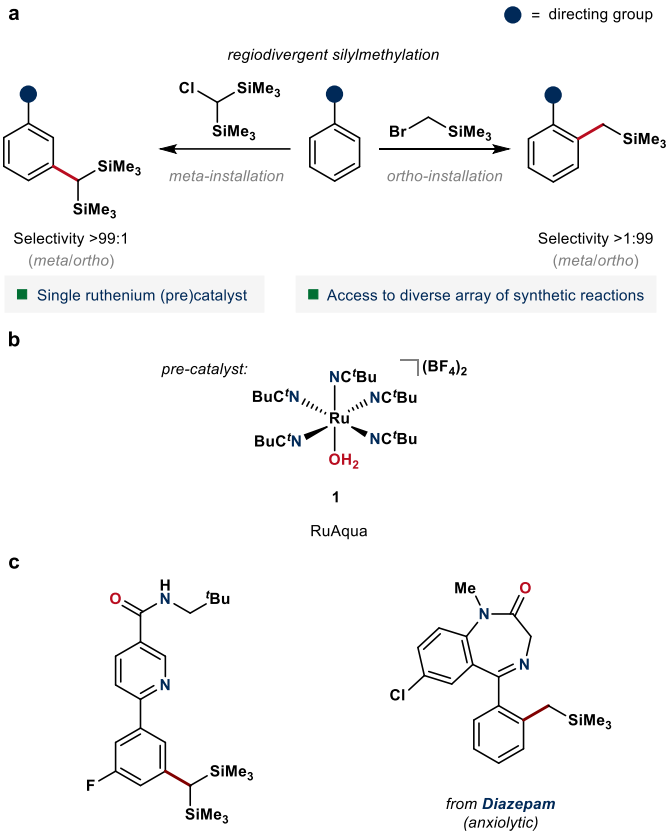

Fig. 1 | Accessing ortho- or meta-silylmethylation of arenes with a single ruthenium catalyst. a, Switching from a primary to a secondary silylmethyl halide reagent toggles regioselectivity between ortho and meta sites within arenes bearing N(sp^2)-directing groups. Specifically, the primary silylmethyl bromide reagent selectively gives ortho-functionalized products, whereas the secondary silylmethyl chloride reagent leads to meta addition. **b**, Structure of the air- and moisture-stable Ru(II) (pre)catalyst $(tBuCN)_5Ru(H_2O)_2$ (RuAqua), which facilitates both site-selective reactions. This single (pre)catalyst proved optimal for achieving high yields and selectivity in both protocols. **c**, Examples of products formed through the silylmethylation of different arenes. Compound **4ab** (right) was formed through the *ortho*-silylmethylation of Diazepam, a pharmaceutical. Compound **6x** (left) was formed through *meta*-silylmethylation and can undergo further transformations to give the pharmaceutical Losmapimod.

The Discovery

Our investigation began with the systematic assessment of conditions for direct arene silylmethylation using silylmethyl halide electrophiles and various Ru-based (pre)catalysts, bases, additives and solvents. We monitored product formation and identified the air- and moisture-stable (pre)catalyst $(tBuCN)_5Ru(H_2O)_2$ (RuAqua; Fig. 1b) as optimal in terms of yields and regioselectivity[3]. For example, in our model ortho-silylmethylation reaction between 2-phenylpyridine and (bromomethane)trimethylsilane, using tetrahydrofuran as solvent, RuAqua as the

(pre)catalyst with K_2CO_3 base and NaI and potassium phenylphosphonate additives, the benzyltrimethylsilane product was obtained in 93% yield. Switching to bis(trimethylsilyl)chloromethane in an isopropanol–water mixture directed the same catalyst to favour meta functionalization with similarly high efficiency. Thus, by changing the electrophile from a primary to a secondary halide, it is possible to tune the reaction to favour ortho or meta functionalization, respectively, enabling control of the site of installation (Fig. 1a).

This regiodivergence was confirmed across a range of arenes containing N(sp^2)-directing groups, including pharmaceuticals (Fig. 1c), demonstrating excellent compatibility with diverse functional groups. We subsequently examined the synthetic utility of the resulting benzyltrimethylsilane products, showing that they can serve as masked benzylic anions, enabling diverse late-stage functionalization reactions such as nucleophilic aromatic substitution, carbonyl addition and Peterson-type olefination.

Mechanistic investigations, namely stoichiometric studies and paramagnetic NMR observations with the meta-selective electrophile, pointed to the formation of biscyclometallated Ru(II) complexes – which can form transient Ru(III) species – as key intermediates. Observation of paramagnetic Ru(III) species indicates that the sterically encumbered secondary electrophile forms a radical that does not readily recombine with the metal centre, thus diverting the reaction path towards the meta site. By contrast, the less sterically hindered primary electrophile can recombine at the metal centre without generating a discrete Ru(III) species, leading to ortho addition. Simply put, the size of the alkyl halide determines whether the alkyl radical 're-binds' to Ru (ortho path) or remains free to attach the aromatic ring (meta path).

Future Directions

Our regiodivergent approach for installing silylmethyl handles offers late-stage diversification routes in fine and bulk chemical synthesis. In particular, precise ortho or meta functionalization offers the opportunity for building complex molecular libraries useful for discovery chemistry. Furthermore, the mechanistic insight garnered on biscyclometallated ruthenium intermediates can inform the design of catalytic systems, potentially expanding site-selective C–H functionalization beyond silylmethylation.

Despite the broad applicability of the developed methods, reliance on N(sp^2)-based directing groups limits their use in arenes lacking such functionality. Although our mechanistic evidence strongly supports our mechanistic conclusions, direct structural characterization of transient Ru(III) species remains a challenge. As with most late-stage functionalization strategies, refined optimization for specific targets might still be necessary when applying silylmethylation to high-complexity molecules.

The next frontier is to extend silylmethylation strategies to substrates beyond N(sp^2)-directed arenes by exploring alternative directing groups or ligands. We plan to capitalize on our mechanistic findings, particularly our understanding of how transient Ru(III) species and biscyclometallated species govern site-selectivity. The identification of alternative coupling partners and reaction conditions could expand the reactivity to access greater chemical space and enhance the versatility of Ru-catalysed C–H functionalization.

Expert Opinion

"Although in my opinion the synthetic value of this protocol is very good, it is the precious mechanistic investigations that raise the profile and general interest of this study for the entire field of C–H activation." **An anonymous reviewer.**

Behind the Paper

We first considered installing silylmethyl handles after previous successes in direct C–H arylation and alkylation[4,5], positing that silicon-based handles would enable diverse downstream transformations. However, both ortho and meta silylmethylation initially failed under our established Ru-catalysed conditions, giving only trace products and numerous byproducts. We initially attempted reaction discovery with standard solvents for this class of C–H activation reaction without success, until discovering that cosolvent mixtures of isopropanol and water combined with lithium bases and additives drastically increased the yields and selectivity. Another turning point came with the unexpected appearance of paramagnetic NMR signals in stoichiometric studies — our first strong evidence of Ru(III) intermediates. At the time, most mechanistic studies in the field suggested that monocyclometallated Ru(II) complexes were the primary reactive intermediates; thus, the identification of the biscyclometallated pathway challenged these assumptions. Ultimately, this insight and persistent reaction development enabled us to produce the regiodivergent protocols reported here. **J.D. & I.L.**

From the Editor

"The work by Docherty et al. stood out because it achieves the modulation of reactivity between ortho and meta aryl positions in ruthenium C(sp^2)–H functionalization. This regiodivergent installation of silyl handles will be an important contribution to the field, for the synthesis and late-stage functionalization of bioactive compounds." ***Editorial Team, Nature Catalysis***

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