



C-H activation

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Synthesis of organic molecules carrying a number of functionalities relies on the conversion of functional groups that display high reactivity, into the target functional groups. Carbon–hydrogen (C–H) bonds are not classically considered functional groups within the context of functionalisation. Therefore introduction of a new bond requires the presence of either a heteroatom on the carbon backbone, a leaving group or unsaturation.[1]

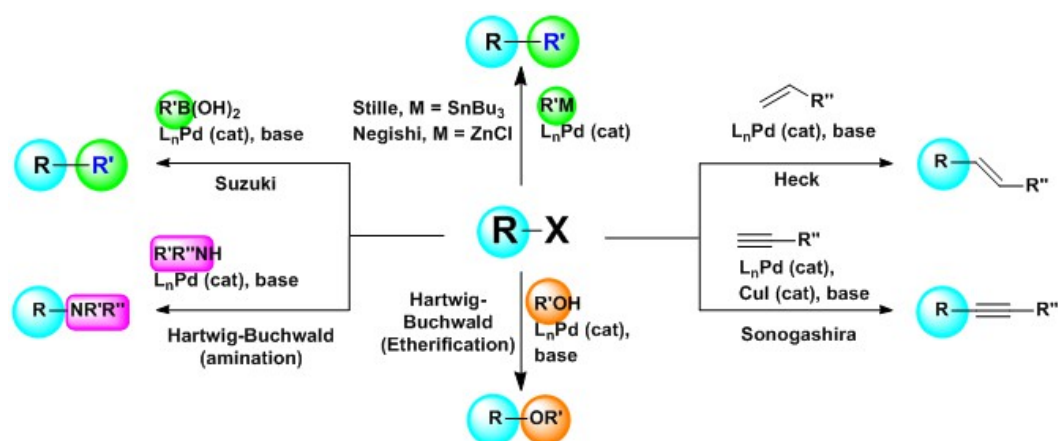
In the pharmaceutical industry new C–C and C–X (X= C, N, O) bonds are typically made by cross coupling reactions shown in Scheme 1. Of the methods highlighted, the Heck and Suzuki reactions are the most popular methods of C–C bond formation in the pharmaceutical industry, however as can be seen from Scheme 1, both systems require pre-functionalisation of one of the coupling partners with a halogen, while the other requires the presence of a terminal alkane (Heck) or a boronic acid (Suzuki).[2] Many synthetic intermediates do not lend themselves to the formation of terminal unsaturation, and boronic acids are synthesised from organometallic halides (e.g. Grignard reagents), which further adds to the complexity of what essentially is the formation of single bond. Aromatic and heteroaromatic groups are present in more than 75% of marketed pharmaceuticals, and their functionalisation represents a challenge to the synthetic community. The recent developments in cross-coupling reactions catalysed by transition

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metals have enabled a range of methods for introducing aryl functionality, although their versatility is limited by the availability of aryl halides.[3]



Scheme 1:

Common C-C coupling reactions used in the pharmaceutical industry

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The approach for the synthesis of new bonds via pre-functionalisation dictates the process of synthetic strategy; reactive sites are typically incorporated by a series of transformations and as a result the starting materials can be very different to the final product. Thus, the direct conversion of C–H bonds of organic compounds into desired functional groups without pre-activation represents a crucial field in green synthetic chemistry.[5] Such transformations have the potential to provide clean and economic methods for the preparation of a wide variety of important chemicals directly from hydrocarbons. Moreover, with such tools in the synthetic chemist's arsenal, new opportunities could present themselves that would have a significant impact on synthetic strategy.[5]

The challenge to direct C–H functionalisation stems from the high bond dissociation energy of the C–H bonds of aromatics and alkanes (H–C₆H₅: 460 kJ/mol; H₃C–H: 439 kJ/mol). [6] As such cleavage of these bonds requires high temperatures, the presence of strong oxidants and acidic or basic additives.[6] Such methods are incompatible for application with a significant number of functional groups, thus limiting their applicability.

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1. K. Godula and D. Sames, **C-H bond functionalization in complex organic synthesis**, *Science*, 2006, **312**, 67-72.
2. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, **Analysis of the reactions used for the preparation of drug candidate molecules**, *Org. Biomol. Chem.*, 2006, **4**, 2337-2347.
3. D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. Johnnie L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, **Key green chemistry research areas-a perspective from pharmaceutical manufacturers**, *Green Chem.*, 2007, **9**, 411-420.
4. I. J. S. Fairlamb, **Pd-catalysed Cross-couplings for the Pharmaceutical Sector and a Move to Cutting-edge C-H Bond Functionalization: Is Palladium Simply Too Precious?**, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 11, pp. 129-139.
5. C. - J. Li and B. M. Trost, **Green chemistry for chemical synthesis**, *PNAS*, 2008, **105**, 13197-13202.
6. C. Jia, T. Kitamura and Y. Fujiwara, **Catalytic Functionalization of Arenes and Alkanes via C-H Bond Activation**, *Acc. Chem. Res.*, 2001, **34**, 633-639.

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Case studies

This case study was provided by [Ryan Gorman](#) during his time at the University of York.

Functionalisation and synthesis of substituted nitrogen containing compounds are one of the top chemical transformations used in industrial processes and medicinal chemistry.[1] In addition to this is the demand for the development of C-H activation methodologies that negate the need for halogenated starting materials. Nitrogen containing heterocycles represent an important class of biologically active molecules. Fused cyclic systems such as oxindoles are common structural motifs in pharmaceuticals such as the anticancer agent Sunitinib and the vasopressin V₂ receptor antagonist Satavaptan (**Figure 1**).[2]

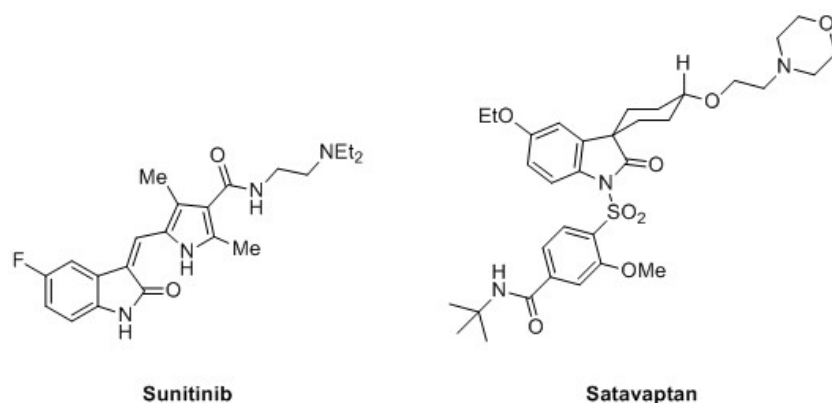


Figure 1: Pharmaceutical molecules carrying the oxindole motif

3,4-Dihydro-1*H*-quinolin-2-one ring systems also display potent biological activity and examples of pharmaceuticals carrying this functionality include the dopamine agonist aripiprazole, the renal deficiency drug trigolutesin A and meloscine used to treat meningitis and heart disease.[2] Added to this, is the extensive bioactivity of 1,2,3,4-tetrahydroquinolines, examples of biologically active molecules include argatroban (potent thrombin inhibitor) and strychnochromine.[2]

The development of synthetic routes to 1,2,3,4-tetrahydroquinolines has seen considerable interest by the synthetic organic community; there have been some recent representative examples for the formation of the C4-C4a bond in particular and these include a Pd⁰ catalysed cyclopropane C-H activation,[3][4] Povarov reaction,[5][6][7]

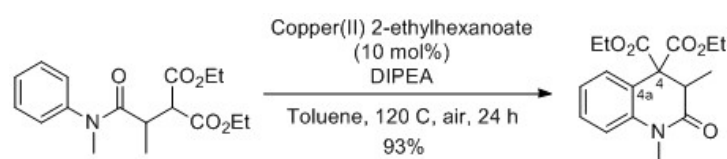
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intramolecular Heck reaction,[8][9] and Ni⁰ mediated cross coupling[10] among others. Although these methods involve C-H activation of one of the coupling partners, the efficient and direct synthesis of 1,2,3,4-tetrahydroquinolines remains a challenge.

In an effort to develop such a method in an efficient and sustainable manner, CHEM21 researchers developed a simple copper(II) catalysed method for the synthesis of oxindoles, thio-oxindoles, 3,4-dihydro-1*H*-quinolin-2-ones and 1,2,3,4-tetrahydroquinolines from linear starting materials by direct C-H, Ar-H coupling (**Scheme 1**). The method boasts of broad scope in substrate and is carried out in open air using ambient oxygen as the oxidant and thus does not require air and moisture exclusion. The method is shown to be superior to existing methods including protocols mediated by manganese catalysts.[2]



Scheme 1: Copper mediated C-H activation for the synthesis of 1,2,3,4-tetrahydroquinolines (Taylor et al., 2014[2])

1. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, **Analysis of the reactions used for the preparation of drug candidate molecules**, *Org. Biomol. Chem.*, 2006, **4**, 2337-2347.
2. T. E. Hurst, R. M. Gorman, A. Drouhin Pauline and Perry and R. J. K. Taylor, **A direct C-H/Ar-H coupling approach to oxindoles, thio-oxindoles, 3,4-dihydro-1 H-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines**, *Chemistry*, 2014, **20**, 14063–14073.
3. S. Rousseaux, B. Liegault and K. Fagnou, **Palladium(0)-catalyzed cyclopropane C-H bond functionalization: synthesis of quinoline and tetrahydroquinoline derivatives**, *Chemical Science*, 2012, **3**, 244-248.
4. T. Saget and N. Cramer, **Palladium(0)-Catalyzed Enantioselective C-H Arylation of Cyclopropanes: Efficient Access to Functionalized Tetrahydroquinolines**, *Angew. Chem.*, 2012, **124**, 13014-13017.
5. G. Dagousset, J. Zhu and G. Masson, **Chiral Phosphoric Acid-Catalyzed Enantioselective Three-Component Povarov Reaction Using Enecarbamates as Dienophiles: Highly Diastereo- and Enantioselective Synthesis of Substituted 4-Aminotetrahydroquinolines**, *J. Am. Chem. Soc.*, 2011, **133**, 14804-14813.

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6. A. Mahadev Jadhav, V. Vishnu Pagar and R. - S. Liu, **Development of a Povarov Reaction/Carbene Generation Sequence for Alkenyldiazocarbonyl Compounds**, *Angew. Chem.*, 2012, **124**, 11979-11983.
7. P. M. Truong, M. D. Mandler, P. Y. Zavalij and M. P. Doyle, **Tetrahydroquinolines and Benzazepines through Catalytic Diastereoselective Formal [4 + 2]-Cycloaddition Reactions between Donor–Acceptor Cyclopropenes and Imines**, *Org. Lett.*, 2013, **15**, 3278-3281.
8. Z. Lu, Y. Cui and Y. Jia, **Palladium-Catalyzed Domino Heck/C-H Activation/Intermolecular Direct Arylation Reactions**, *Synthesis-Stuttgart*, 2011, 2595-2599.
9. J. E. Wilson, **Diastereoselective synthesis of tetrahydroquinolines via a palladium-catalyzed Heck–Suzuki cascade reaction**, *Tetrahedron Lett.*, 2012, **53**, 2308-2311.
10. C. - S. Yan, Y. Peng, X. - B. Xu and Y. - W. Wang, **Nickel-Mediated Inter- and Intramolecular Reductive Cross-Coupling of Unactivated Alkyl Bromides and Aryl Iodides at Room Temperature**, *Chem. Eur. J.*, 2012, **18**, 6039-6048.

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Summary and further reading

C–H bond functionalisation has been a subject of vigorous research over the last 20 years, and more recently with respect to the development of methods that overcome the drawbacks highlighted.

Recommended reading:

I. J. S. Fairlamb, [Pd-catalysed Cross-couplings for the Pharmaceutical Sector and a Move to Cutting-edge C–H Bond Functionalization: Is Palladium Simply Too Precious?](#), in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 11, pp. 129-139.

J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, [Towards mild metal-catalyzed C-H bond activation](#), *Chem. Soc. Rev.*, 2011, **40**, 4740-4761.

S. Hwan Cho, J. Young Kim, J. Kwak and S. Chang, [Recent advances in the transition metal-catalyzed twofold oxidative C-H bond activation strategy for C-C and C-N bond formation](#), *Chem. Soc. Rev.*, 2011, **40**, 5068-5083.

S. Chandra Pan,

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