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Catalytic sp^3-sp^3 functionalisation of sulfonamides: late-stage modification of drug-like molecules**

*Othman Abdulla, Adam D. Clayton, Robert A. Faulkner, Duncan M. Gill, Craig R. Rice, Scarlett M. Walton, and Joseph B. Sweeney**

Abstract: *A new application of Pd-catalysed allylation is reported which enables the synthesis of a range of branched sp^3-functionalised sulfonamides, a compound class for which few reported methods exist. By reacting benzyl sulfonamides with allylic acetates in the presence of Pd(0) catalysts and base at room temperature, direct allylation can be efficiently carried out, yielding products which are analogues of structural motifs seen in biologically active small molecules. The reaction is carried out under mild conditions and can be applied to nanomolar sigma-receptor binders, thus enabling a late-stage functionalisation and efficient expansion of drug-like chemical space.*

The difficulties in accessing non-planar 'hard-to-make' chemical matter for incorporation into drug molecules have been well-enumerated,[1] and in some therapeutic areas these difficulties have significant consequences. Thus there has been a drive to deliver novel small molecules with enhanced biological relevance, and a concomitant call for late-stage functionalisation[2] to enable improvements (such as the 'magic methyl' effect[3]) in pharmacological properties. Within the traditional chemical space of drug-like molecules, the sulfonamide motif is a frequently seen subunit of synthetic biologically-active molecules. The motif is a robust, pharmacologically-reliable unit which appears in both drug substances (**1a-c**, Figure 1a) and drug-like molecules (such as nanomolar receptor ligands **2a-d**, Figure 1b).[4] α-Substitution with alkyl groups can improve the binding properties,[5] however, despite the wide interest in the exploitation of sulfonamides, many of the compounds reported bear sparse substitution patterns adjacent to the sulfonyl moiety. Bearing this fact in mind, and in the context of the drive for late-stage molecular functionalisation, there has been a recent interest in the development of new methods for direct α-functionalisation of sulfonamides. However, despite the considerable effort directed towards de novo synthesis of sulfonamides,[6] there are still few generally applicable methods for the efficient preparation of α-branched sulfonamides.

Traditional methods (Figure 1c) for direct alkylations of sulfonamides[7] require strong bases, reactive electrophiles, low temperatures and the use of stoichiometric amounts of polar additives (such as TMEDA,[8] HMPA,[9] phenanthroline,[5]); several recent reports have described metal-catalyzed α-arylation of alkyl[10] sulfonamides (Figure 1c),[11] but only the methods from Zhou et al[11d] (who reported a single example of branched sulfonamide synthesis) and Knauber and Tucker[11a] deliver α-sp^3-substituted benzylsulfonamides as products. Furthermore, to date there have been few disclosures of methods to enable catalytic sp^3-sp^3 coupling to allow α-functionalisation of sulfonamides:[12] we report herein the first application of catalytic sulfonamide allylation, which can be applied to both simple substrates and also to drug-like receptor ligands.

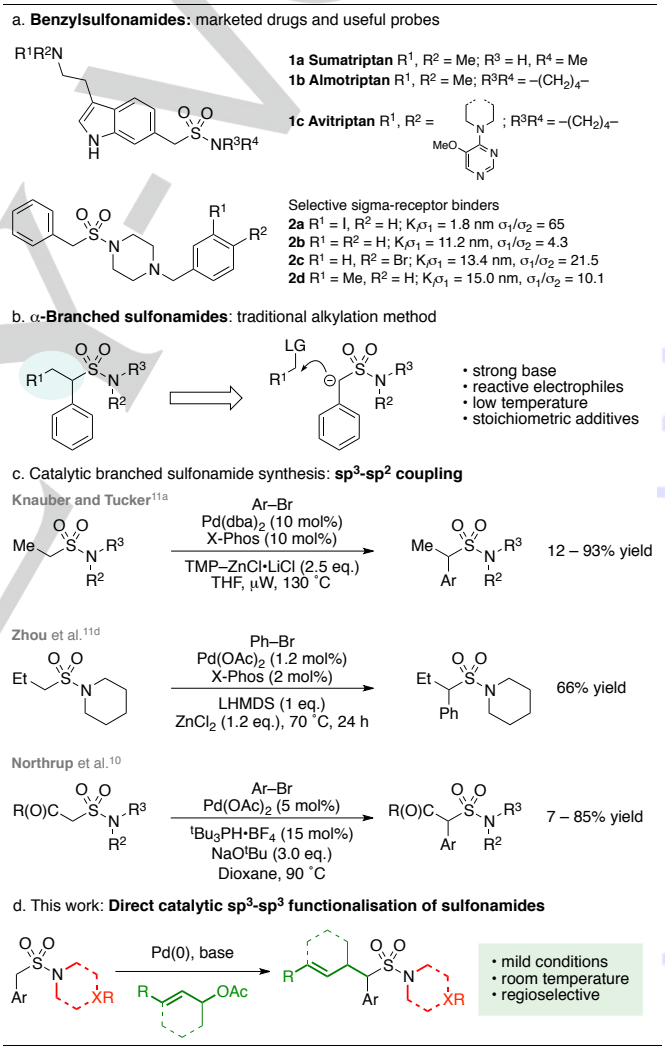

Figure 1. Bioactive benzylsulfonamides: properties and synthetic access.

We hypothesized that anions derived from benzyl sulfonamides would be amenable to palladium-catalyzed allylation (Figure 1d); however, there are relatively few reports of the use of nucleophiles other than carbonyl-stabilised carbanions in such reactions,[13] and fewer examples of the use of non-carbonyl α-branched anions.[13b] In addition, the pK_a of sulfonamide-derived anions is not definitively established: direct deprotonation even of benzyl sulfonamides often requires strong base,[6] suggesting that the anions thus obtained might be considered to be 'hard', and

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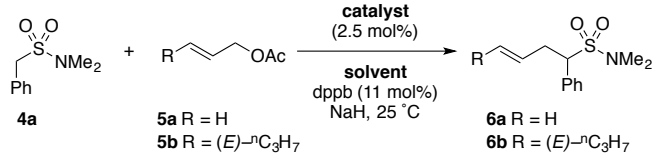
therefore likely to lead to products of inversion upon reaction with π-allylpalladium species.[14, 15] Thus, in addition to being an unknown process when we commenced our study, there was a mechanistic question to be answered about the proposed reaction.

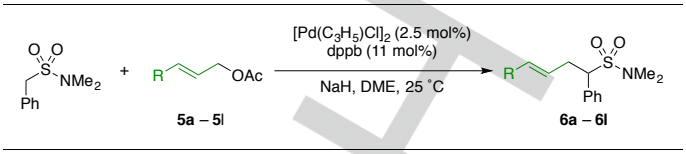
We commenced our study with an examination of the reaction of dimethylsulfonamide **4a** with allyl acetate **5a** under Pd-catalysed allylation conditions. Given that the transformation was previously unreported, we were gratified to observe that the reaction gave the desired sp^3-functionalised allylated product **6a**, in moderate yield (Table 1, entry 1); after an extensive catalyst and solvent screen (key experiments delineated in Table 1) we alighted upon the use of $[Pd(C_3H_5)Cl]_2$ and dppb ligand in DME solvent (Table 1, entries 9 and 10) as the most appropriate combination (featuring readily available catalyst and ligand, and low-boiling solvent, thereby facilitating work-up and product processing). The use of other bases (including NaOtBu, LHMDS, BTPP, and powdered NaOH) was not uniformly productive.



Entry	Acetate	Catalyst	Solvent	Yield/%[a]
1	**5a**	$[Pd(C_3H_5)Cl]_2$	THF	54
2	**5a**	$[Pd(C_3H_5)Cl]_2$	Dioxane	40
3	**5a**	$[Pd(C_3H_5)Cl]_2$	DMF	48
4	**5a**	$[Pd(C_3H_5)Cl]_2$	EtOAc	12
5	**5a**	$[Pd(C_3H_5)Cl]_2$	NMP	55
6	**5a**	$[Pd(C_3H_5)Cl]_2$	MeCN	30
7	**5a**	$[Pd(C_3H_5)Cl]_2$	CH_2Cl_2	27
8	**5a**	$[Pd(C_3H_5)Cl]_2$	PhH	11
9	**5a**	$[Pd(C_3H_5)Cl]_2$	DME	79
10	**5b**	$[Pd(C_3H_5)Cl]_2$	DME	96
11	**5b**	$Pd(OAc)_2$	DME	21
12	**5b**	$Pd_2(dba)_3$	DME	30
13	**5b**	$Pd(PPh_3)_4$	DME	43
14	**5b**	$PdCl_2(MeCN)_2$	DME	90
15	**5b**	-	DME	0

Table 1. Catalyst and solvent screen for sp^3-sp^3-sulfonamide coupling. Conditions: sulfonamide (0.5 mmol), acetate (0.55 mmol), catalyst (0.0125 mmol), ligand (0.055 mmol), NaH (3 mmol), DME (1 mL), 48h. a) Yields are quoted for isolated products.

Armed with these initial data, we proceeded next to probe the scope of the reaction with regard to the allyl component (Table 2), using a range of commercial or easily prepared substrates. It quickly transpired that the catalytic allylation reaction proceeded in generally good yield under mild conditions, using a diverse range of allyl donors, to give α-substituted sulfonamides **6a-6l**. Both acyclic and cyclic acetates delivered the corresponding C-allylated sulfonamides efficiently, and where present alkene stereochemistry was generally retained (for compounds **6b**, **6e-f**, and **6k**). Exclusive *cis*-stereoselectivity was observed in the synthesis of cyclohexenyl sulfonamide **6l**; in addition to providing an excellent exemplar of the reaction scope, this product also enabled confirmation of the stereochemical course of the allylation process (*vide infra*, Scheme 3).



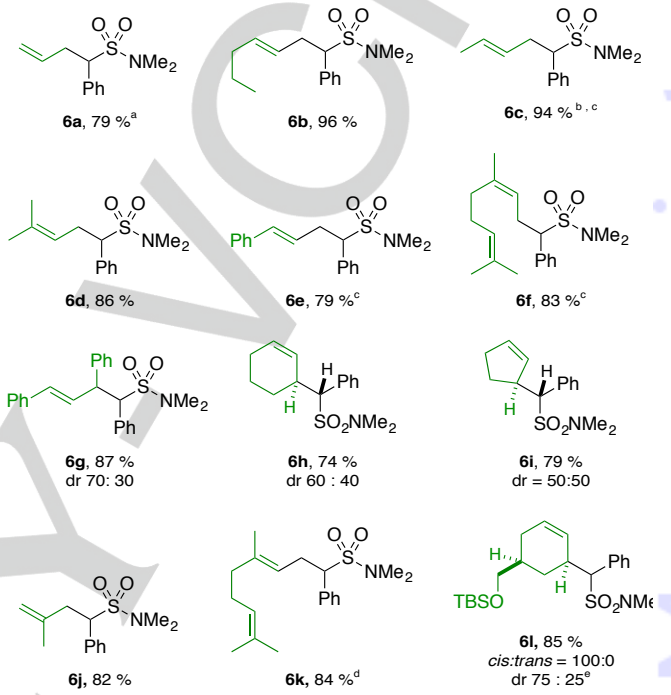
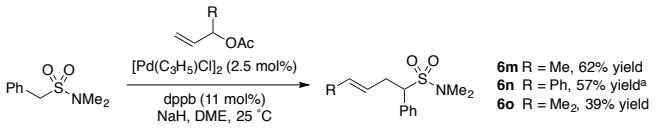


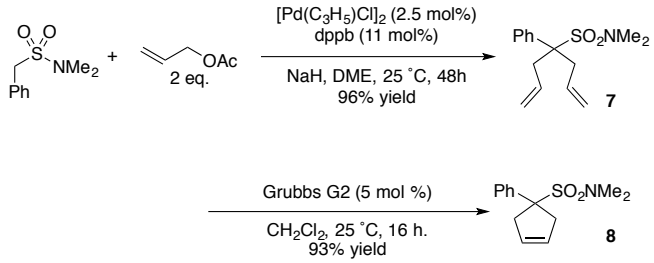
Table 2. Substrate scope in allyl component for the catalytic sulfonamide allylation reaction. Conditions: sulfonamide (0.5 mmol), acetate (0.55 mmol), catalyst (0.0125 mmol), ligand (0.055), NaH (3 mmol), DME (1 mL), 48h. a) obtained as a 67:33 *E*:*Z* mixture. b) Yields are quoted for isolated compounds. c) dppe used as ligand. d) dppf used as ligand. e) dr refers to relative configuration at exocyclic stereogenic centre

In all cases where isomerism was possible, linear products was exclusively favoured over branched isomers (giving compounds **6m-o**, Scheme 1)



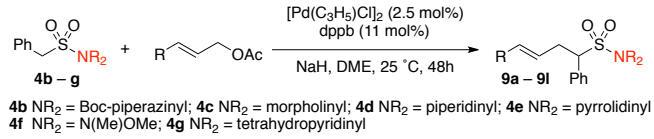
Scheme 1. Linear isomers are preferred over branched. Conditions: sulfonamide (0.5 mmol), acetate (0.55 mmol), catalyst (0.0125 mmol), ligand (0.055 mmol), NaH (4 mmol), DME (1 mL), 48h. a) dppf used as ligand.

Since the allylated products still bear an acidic α-proton, the possibility exists for a second functionalization. Thus, when reacted with excess allyl acetate, sulfonamide **4a** was directly converted to the doubly-allylated product **7** (93% yield), which could converted by ring-closing metathesis[16] in high yield into the previously unreported[17] tertiary sulfonamide **8** (Scheme 2).



Scheme 2. Access to novel tertiary sulfonamides via catalytic double allylation. Conditions: 1. sulfonamide (0.5 mmol), acetate (2.5 mmol), catalyst (0.0125 mmol), ligand (0.055 mmol), NaH (4 mmol), DME (1 mL), 48h; 2. sulfonamide (0.36 mmol) Grubbs G2 (0.018 mmol), CH_2Cl_2 (6 mL,) 25 °C, 16h.

Having conclusively demonstrated the feasibility of the sulfonamide allylation reaction, our attention turned to an examination of the structural scope possible in the nitrogen subunit: again we observed generally efficient reaction of sulfonamides **4b-g** under the catalytic allylation conditions, leading to novel sulfonamides **9a-9l** (Table 2).



4b NR_2 = Boc-piperazinyl; **4c** NR_2 = morpholinyl; **4d** NR_2 = piperidinyl; **4e** NR_2 = pyrrolidinyl
4f NR_2 = N(Me)OMe; **4g** NR_2 = tetrahydropyridinyl

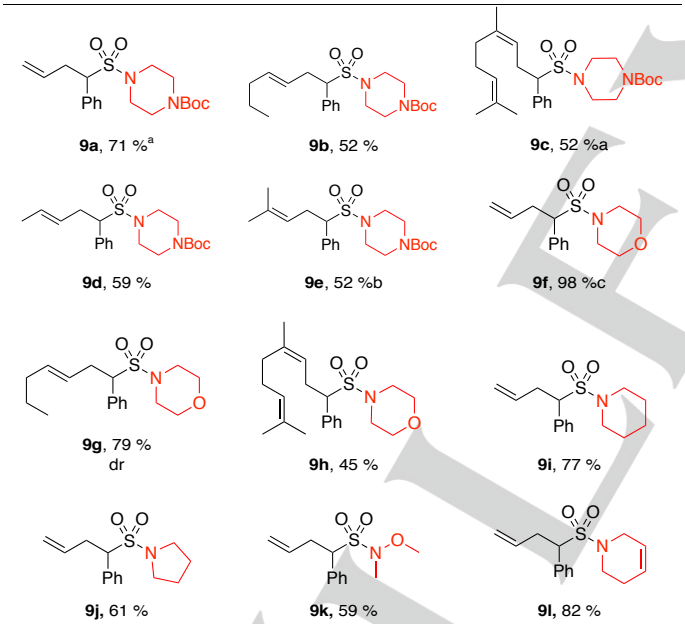
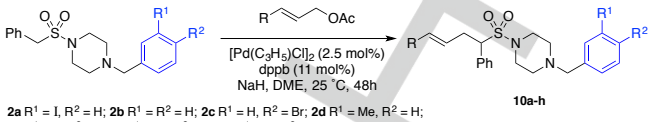


Table 2. Substrate scope in amide component for the catalytic allylation reaction. sulfonamide (0.5 mmol), acetate (0.55 mmol), catalyst (0.0125 mmol), ligand (0.055 mmol), NaH (4 mmol), DME (1 mL), 48h. a) Yields are quoted for isolated products..

To probe the suitability of the reaction as a late-stage functionalisation tool, we next examined nanomolar receptor ligands as substrates. Thus, sigma-receptor binding sulfonamides **2a-g** reacted smoothly under the reaction conditions, to give novel α-functionalised products **10a-h** (Table 3). It is noteworthy that reaction with cinnamyl acetate gave both linear and branched products (**10c** and **10d**, respectively, 60:40 ratio), whereas reactions with hexenyl and crotyl acetates gave only linear products **10e**, **10f** and **10g**.

The mildness of the method is emphasised by the fact that, where present, halogeno substituents are tolerated, allowing for subsequent synthetic development.



2a R^1 = I, R^2 = H; **2b** R^1 = R^2 = H; **2c** R^1 = H, R^2 = Br; **2d** R^1 = Me, R^2 = H;
2e R^1 = F, R^2 = H; **2f** R^1 = Cl, R^2 = H; **2g** R^1 = H, R^2 = OMe;

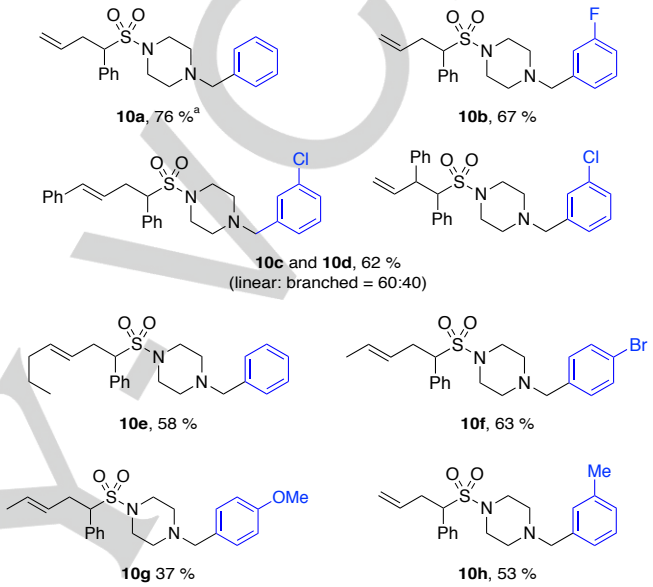
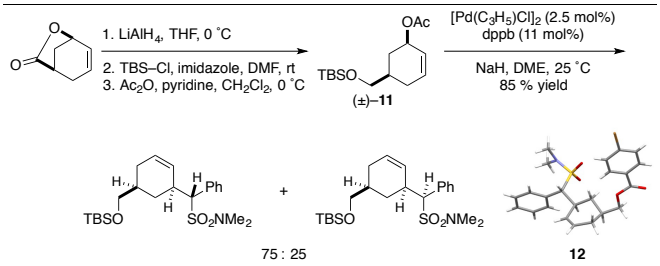


Table 3. Late-stage functionalisation of sigma-receptor binding sulfonamides. Conditions: sulfonamide (0.5 mmol), acetate (0.55 mmol), catalyst (0.0125 mmol), ligand (0.055 mmol), NaH (4 mmol), DME (1 mL), 48h. a) Yields are quoted for isolated products.

The mechanism of Pd-catalysed allylation reactions is well-predicated to occur by one of two pathways, depending on the polarisation of the nucleophile component.[10] When the allylation reaction was carried out with *cis*-cyclohexenyl acetate **11**,[18] the *cis*-products **6l** were obtained exclusively (as confirmed by x-ray analysis of a single crystal of a *p*-bromobenzoyl derivative, **12**, of the major product, Scheme 3). Since obtention of *cis*-configured products indicates direct attack at carbon rather than palladium, this confirms that the anions derived from benzylsulfonamides can be considered to be 'soft' reagents, at least in the context of palladium catalysis.



Scheme 3. Stereochemical course of the catalytic allylation reaction. Conditions: sulfonamide (1 mmol), acetate (1.1 mmol), catalyst (0.0125 mmol), ligand (0.055), NaH (4 mmol), DME (1 mL), 48h.

The use of asymmetric protocols[19] (likely to be challenging given the inherent difficulties of asymmetric α-functionalisation of S=O bonds[20], [21]) in this process have, to date, proved non-productive, delivering allylated products in variable yields and with no discernable enantioselectivity. This matter is currently the focus of intense interest in our laboratories.

In summary, we have developed a new application of Pd-catalysed allylation for direct sp^3- sp^3 coupling of sulfonamides, and demonstrated that the reaction is applicable to late-stage functionalisation of bioactive small molecules. The transformation takes place at ambient temperature, is tolerant to a wide range of functional groups and provides ready access to novel compounds in good yields. We believe that this method will be of utility to a range of academic and industrial chemists.

Keywords: • Late-stage functionalisation • sulfonamide • sigma receptor • catalytic • palladium

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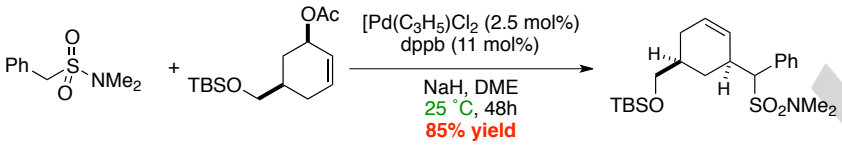

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