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Palladium-catalysed direct alkenylation of sydnones

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ABSTRACT

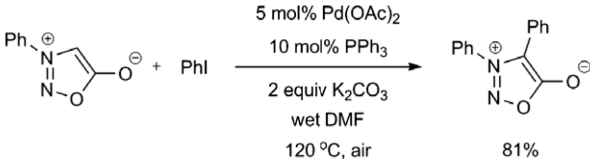
Sydnones have been directly functionalised with alkenyl halides and an alkynyl bromide under palladium catalysis.

The palladium-catalysed direct cross-coupling reaction of electron-rich heteroaromatics with aryl halides and pseudohalides has emerged as an incredibly useful and general synthetic technique to access biaryl structures.[1] These processes are superior to traditional cross-coupling techniques because a stoichiometric amount of an organometallic reagent is not required. This results in lower costs, less waste and, if the organometallic would need to be prepared, shorter syntheses. This concept has been applied successfully to the direct coupling of a range of heterocycles including furans,[2] oxazoles,[3] imidazoles,[4] triazoles,[5] purines,[6] indoles[7] and pyrroles.[8] Examples of intramolecular direct couplings have also been reported.[9]

Our research group recently reported the direct cross-coupling of aryl iodides and bromides with sydnones under palladium catalysis (e.g., in Scheme 1).[10] *N*-Phenyl and *N*-methyl sydnones were found to react efficiently with aryl iodides and bromides in the presence of palladium acetate (5 mol %), triphenylphosphine (10 mol %) and potassium carbonate (2 equiv) in wet *N*,*N*-dimethylformamide at reflux open to air. Sydnones are five-membered heterocycles which are part of an intriguing family of molecules termed mesoionic.[11] Sydnones have been investigated for their potential uses as therapeutic agents,[12] as liquid crystals[13] and as electrolytic solvents.[14] In synthesis, the principal reactions of sydnones are metallation,[15] electrophilic aromatic substitutions and 1,3-dipolar cycloadditions,[16] however little new reactivity has been revealed over the last few decades.[17] Kalinin and Min have shown that sydnones can be deprotonated at C-4 with butyllithium to form unstable species in solution. Subsequent addition of copper(I) bromide leads to the formation of relatively stable complexes that can take part in palladium-catalysed coupling reactions with iodoarenes and β-bromostyrene in excellent overall yields.[15a] A recent report by Harrity and co-workers has shown the application of the Suzuki cross-coupling reaction to functionalising 4-bromosydnones with a range of aryl boronic acids and with styrylboronic acid under palladium catalysis.[18]

We set out to increase the scope of the direct cross-coupling reaction with sydnones and investigated the reactivity of alkenyl halides under our optimised conditions.[19] We were pleased to find that α-bromostyrene coupled efficiently with *N*-phenyl sydnone providing the product in 78% yield (Table 1, entry 1).[20] Both (*E*)- and (*Z*)-β-bromostyrene coupled successfully with the sydnone (entries 2 and 3), however the latter product underwent slow (*Z*) to (*E*) alkene isomerisation at room temperature. After eight months at ambient conditions a 1:7 (*E*)/(*Z*) mixture had formed. The *para*-methyl-substituted (*E*)-β-bromostyrene derivative underwent clean conversion providing 62% of product (entry 4) and (*E*)-2-(2-bromovinyl)naphthalene furnished 65% of the coupled sydnone (entry 5). The trisubstituted vinyl bromide (entry 6) was coupled successfully albeit in somewhat lower yield of 42%. Surprisingly, 1-bromohex-1-ene and (3-bromoallyl)benzene failed to react under the reaction conditions returning starting materials (entries 7 and 8). However, the trisubstituted alkenyl iodide synthesised from cyclohexanone was coupled successfully in moderate yield (entry 9). *N*-Methyl sydnone also coupled with α-bromostyrene and (*Z*)-β-bromostyrene in moderate yields at the lower temperature of 80 °C (entries 10 and 11). In the latter case, very slow interconversion of the alkene from (*Z*) to (*E*) occurred with an 11:1 (*E*)/(*Z*) mixture being present after eight months. As with the arylation reaction, the *N*-methyl sydnone decomposes under the reaction conditions at 120 °C, so the reactions have to be run at 80 °C.

With these results in hand, the direct coupling of other electrophiles was investigated. Accordingly, under our standard conditions,



Scheme 1. An example of the direct arylation of *N*-phenyl sydnone with iodobenzene.

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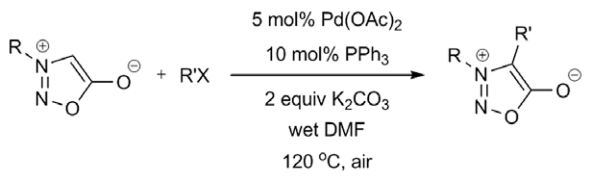
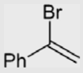
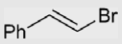
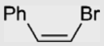
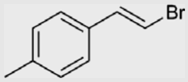
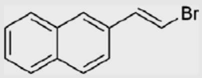
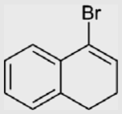
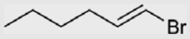
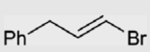
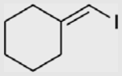
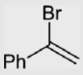
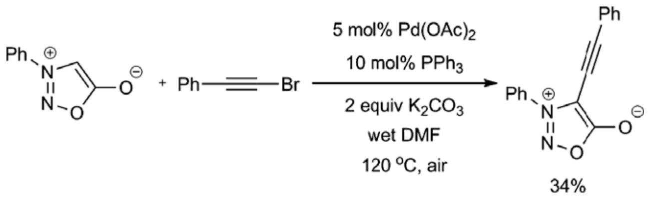
Table 1
Direct alkenylation of sydnones



Entry	R	R'X	Yield[a] (%)
1	Ph		78
2	Ph		76
3	Ph		74
4	Ph		62
5	Ph		65
6	Ph		42
7	Ph		0
8	Ph		0
9	Ph		57
10	Me		51[b]
11	Me		46[b]

[a] Yield of isolated product.
[b] Reaction run at 80 °C.

the coupling reactions of *N*-phenyl sydnone with benzyl bromide, benzyl chloride, allyl bromide and (bromoethynyl)benzene were explored.[21] In the event, only (bromoethynyl)benzene was coupled successfully although in modest yield (Scheme 2). Notably, to the best of the authors' knowledge, this represents the first example of a direct alkynylation of an aromatic molecule in the literature to date.



Scheme 2. Direct alkynylation of *N*-phenyl sydnone.

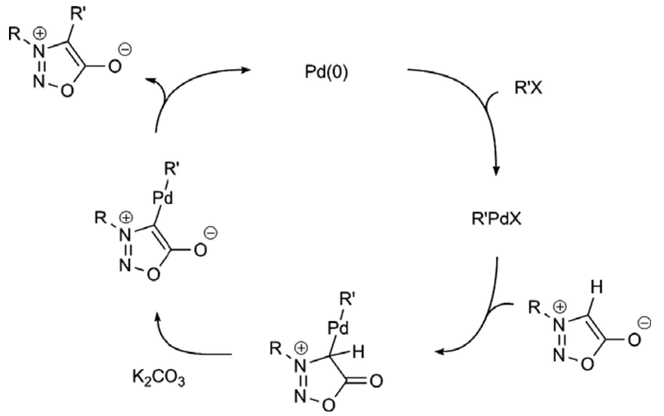


Figure 1. Postulated mechanism for the direct coupling reaction.

The mechanism of the coupling reaction is proposed to be oxidative addition of Pd(0) to the alkenyl halide, then electrophilic addition to the sydnone, followed by rearomatisation and reductive elimination to furnish the product and to regenerate the Pd(0) catalyst (Fig. 1).[10]

In conclusion, the palladium-catalysed direct alkenylation of sydnones with alkenyl halides has been achieved. The reaction was found to be successful with di- and tri-substituted alkenyl halides. In addition, the first reported example of a palladium-catalysed direct alkynylation of a heterocycle has been described.

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Supplementary data

Supplementary data (full characterisation data of novel compounds are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.075.

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20. *Representative procedure for the alkenylation of sydnones*: a flask was charged with 3-phenylsydnone (50 mg, 0.31 mmol, 1 equiv), $Pd(OAc)_2$ (4 mg, 0.016 mmol, 0.05 equiv), K_2CO_3 (86 mg, 0.62 mmol, 2 equiv), PPh_3 (8 mg, 0.031 mmol, 0.1 equiv), α-bromostyrene (61 μL, 0.47 mmol, 1.5 equiv) and wet DMF (1 mL) and was heated at reflux for 12 h open to air. Upon cooling, water (30 mL) was added to the reaction mixture that was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried with $MgSO_4$ and filtered. The volatiles were removed in vacuo and the mixture was purified by flash chromatography (5:1 PE/EtOAc on silica gel) to give 3-phenyl-4-(1-phenylvinyl)sydnone (64 mg, 78%).
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