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# Ammonium formate-based one-pot reductive Heck reactions for the construction of cyclic sulfonamides

Aisha Khalifa, Lorna Conway, Kimberly Geoghegan, Paul Evans *

*Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Dublin 4, Ireland*

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ABSTRACT

A modified method is reported for the conversion of unsaturated sulfonamides into their cyclic saturated counterparts. This method utilises a single palladium catalyst for an intramolecular Heck reaction and subsequent transfer hydrogenation, which is achieved in one-pot following the addition of ammonium formate. Accordingly, a range of fourteen structural variations are reported and under optimal conditions the adducts were generated in typically good to excellent yields. Notably, discrimination of differentially substituted dienes can be accomplished in the case of compounds **28** and **29** and the process was only observed to fail with the more sterically hindered precursor **32**.



The Heck reaction[1] is an important method for the formation of carbon–carbon bonds and one that we have exploited in its intramolecular guise for the synthesis of unsaturated cyclic sulfonamides (Scheme 1, 1 to 2),[2] the ultimate aim being to study how the sulfonamide motif behaved under reductive conditions. In relation to this we have demonstrated that under certain conditions both the nitrogen-sulfur and carbon–sulfur bonds undergo cleavage affording saturated *N*-heterocycles[3] of the type **4**. The 3-aryl pyrrolidine skeleton **4** is prevalent in a range of naturally occurring and/or pharmacologically interesting alkaloids (depicted in Scheme 1).[4] In order to achieve the key sulfonamide double reduction, the alkene (**2**), formed following the intramolecular Heck reaction, must be first saturated (**3**). Initially this was performed *via* a standard stop-go process, in which the reduction was accomplished with $H_2$ and Pd/C.[2a] Subsequently, we demonstrated that this overall process (**1** to **3**) may be achieved in one-pot, using the same palladium source,[5] simply by introducing $H_2$ gas following the Heck reaction.[6]

Although the overall yields for this one-pot process are somewhat lower than those observed in the two-pot process, use of the same catalyst for two different reactions and the requirement for only one purification process make it attractive. Notably, in the case of R = Me high levels of regioselectivity are encountered for the generation of the congested quaternary all-carbon centre[2d,e] and this overall synthetic sequence provided entry to compounds containing an aryl substituted octahydroindole skeleton, including mesembrine (Scheme 1).

Catalytic hydrogenation with hydrogen gas is a technology used globally within the chemical industry and academic research laboratories. However, the use of molecular hydrogen constitutes a potential hazard and requires the use/installation of specialist equipment for both its storage and usage. In this current study we demonstrate that the hydrogen gas previously used for alkene reduction can be effectively replaced with solid ammonium formate[7] and that, using this safer and operationally simpler hydrogen-transfer protocol, higher yields of the corresponding adducts are typically observed.

As shown in Scheme 2, for bromide **5** the traditional stop-go, two-pot Heck-hydrogenation process afforded **8**, *via* alkene **7**, in good yield over two-steps (Entry 1).[2a] In this case the palladium loading for both steps can be reduced to 1 mol% without a dramatically detrimental effect on the overall yield. Running the Heck reaction and the hydrogenation in the same pot gave **8** in 61% yield (Entry 2).[4] In contrast to Entry 1, results in this case indicate that the hydrogenation step only proceeds effectively if a higher loading of $Pd(OAc)_2$ is used – a finding which is likely to be linked to the nature of the Pd-species present post-Heck reaction.

Pleasingly, as shown in Entry 3, performing the Heck reaction with *N*-sulfonyl dihydropyrrole **5** in an identical manner but then adding ammonium formate (15 equiv.) generates **8** in comparable yield to the hydrogen-based process as long as the mixture is heated to approximately 65 °C (without heating no evidence of

* Corresponding author.
*E-mail address:* paul.evans@ucd.ie (P. Evans).

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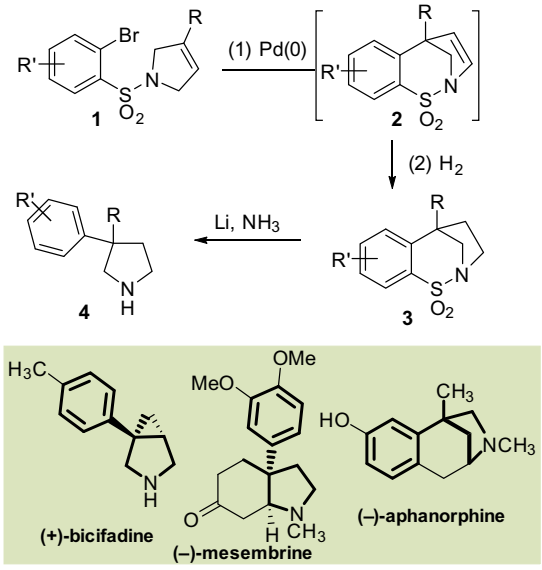
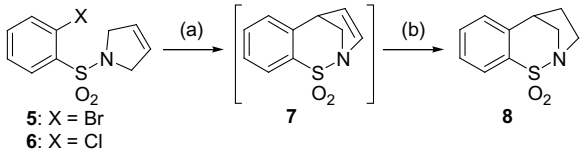



**Scheme 1.** One-pot intramolecular Heck reaction-reduction sequence for the synthesis of saturated cyclic sulfonamides **3** and their subsequent double reduction to 3-aryl pyrrolidines **4**.




**5**: X = Br
**6**: X = Cl

| Entry | X | Cond. | Yield **8**[a] |
|---|---|---|---|
| 1[b] | Br | (a) $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; (b) Pd/C (10 mol%), **$H_2$** (1 atm), EtOH, rt, 15 h | 81% |
| 2[c] | Br | $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; then **$H_2$** (1 atm), rt, 12 h | 61% |
| 3 | Br | $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; then **$NH_4HCO_2$** (15 equiv.), 65 °C, 15 h | 45% |
| 4 | Br | $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; then **$NH_4HCO_2$** (55 equiv.), 80 °C, 15 h | 91% |
| 5 | Cl | $Pd(OAc)_2$ (10 mol%), $PPh_3$ (20 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; then **$NH_4HCO_2$** (55 equiv.), 80 °C, 15 h | 0%[d] |
| 6 | Cl | $Pd(OAc)_2$ (10 mol%), BrettPhos (10 mol%), $K_2CO_3$, DMF, 110 °C, 15 h; then **$NH_4HCO_2$** (55 equiv.), 80 °C, 15 h | 53% |

[a]Isolated yields following purification by flash column chromatography; [b]Two-pot from ref. 2a; [c]One-pot process using $H_2$ from ref. 6; [d]**6** was recovered (72%)

**Scheme 2.** Optimisation of the one-pot Heck-hydrogen transfer reaction for the formation of cyclic sulfonamide **8**.

hydrogen transfer was observed and **7** was isolated). Further optimisation indicated that if the hydrogen transfer process was conducted with a larger excess of ammonium formate (55 equiv.) and at 80 °C excellent yields of **8** were obtained (Entry 4).[8]

Next the use of aryl chloride **6** was considered. Aryl chlorides are attractive substrates for this type of chemistry since they tend to be cheaper and have a lower molecular weight than the corresponding bromides and iodides. Unfortunately, this protocol does not transfer directly to chloride **6** and, under the conditions identified in Entry 4, only starting material **6** was recovered (Entry 5). This failure stems directly from the reduced reactivity of the C ($sp^2$)–Cl bond in the oxidative addition step of the Heck reaction, under our reaction conditions. Related to this we have shown that chlorides like **6** may be effectively used in this type of intramolecular Heck reaction when Buchwald's BrettPhos is used as the ligand.[2e] Thus, we investigated whether under these conditions chloride **6** could be used to prepare **8** by introducing ammonium formate to the post-Heck reaction mixture (Entry 6). This was achieved to a degree, however, both the hydrogenation and the Heck reactions did not reach completion and consequently, in addition to **8**, a mixture of compounds were present necessitating a difficult purification.

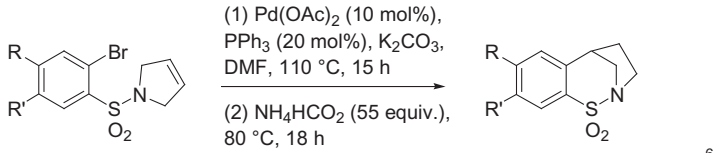
Following identification of the optimal reaction conditions discussed above a range of 2-bromo-substituted, unsaturated sulfonamide Heck reaction precursors were prepared and studied in their respective one-pot reductive Heck reactions.[9] The substrates originate from the corresponding 2-bromo substituted benzenesulfonyl chlorides. The non-commercially available substituted 2-bromobenzenesulfonyl chlorides used in this study were either prepared by electrophilic aromatic substitution (chlorosulfonic acid),[2a,g] or from a Meerwein's diazotisation/Cu(I)-$SOCl_2$ sequence.[10] As shown in Scheme 3, *N*-sulfonyl dihydropyrroles **9** to **14** were converted into the corresponding saturated cyclic sulfonamides **15** to **20**. The yields obtained for adducts **15** to **17** demonstrate that under the optimal conditions, electron releasing oxygen substituents are well-tolerated. The 4-chloro substituent in substrate **13** was predominantly preserved over the course of the reaction and **19** was isolated in reasonable yield (67%). Compound **8**, the product of hydrogen-chloride exchange, was also isolated in 20% yield following purification from this particular reaction.

As anticipated, 4-nitro substituted dihydropyrrole **14** underwent both the expected reductive Heck process but also nitro reduction generating compound **20** (R = $NH_2$). Additional unidentified products are present in the crude reaction mixture, serving to reduce the yield of **20**. As a comparison, using hydrogen gas at room temperature, rather than ammonium formate at 80 °C, the nitro group was largely preserved, and **21** (R = $NO_2$) was isolated in 43% yield. These complementary outcomes demonstrate that functional group selectivity may be achieved using the two methods.

3-Methyl substituted dihydropyrroles **22** to **24**, in which additional steric functionality is introduced into the alkene, were next studied (Scheme 4). As expected, based on our previous work,[2d,e] high levels of regioselectivity in the Heck reaction were observed and good yields of the adducts **25** to **27** were obtained after purification by flash column chromatography. Notably, in these examples, better yields of the saturated cyclic sulfonamides were obtained than the corresponding processes using $H_2$ (values in parentheses).

Building upon this selectivity and efficiency we were also interested to study how dienes **28** and **29**, prepared by enyne metathesis,[2h] would behave. It is worth mentioning that intermolecular Heck processes with 1,3-dienes are known to occur at the terminal, rather than internal, positions.[11] In contrast to these intermolecular examples, compounds **28** and **29** generated partially saturated cyclic sulfonamides **30** and **31** in good yield (Scheme 5). This outcome is of interest and was not anticipated since the yields obtained demonstrate that high levels of regioselectivity for carbon–carbon bond formation in the intramolecular Heck reaction and chemoselectivity in the reduction of the endocyclic alkene over the exocyclic iso-propenyl group, have taken place. As shown, X-ray crystallography confirmed this outcome for compound **30**.[9]

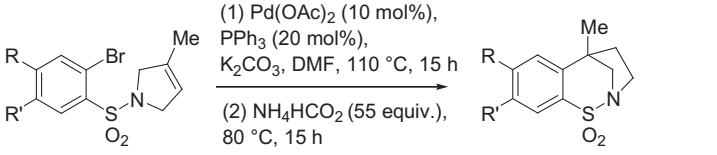
Finally, we investigated *N*-sulfonyl hexahydroindole **32**, which was an intermediate in our synthesis of mesembrane.[2d] Using the previously published Heck-hydrogenation process with hydrogen




**9**: R = R' = OMe
**10**: R = R' = $OCH_2O$
**11**: R = OMe, R' = H
**12**: R = H, R' OMe
**13**: R = Cl, R' = H
**14:** R = $NO_2$, R' = H

**15**: R = R' = OMe, 85% ($H_2$: 52%)[6]
**16**: R = R' = $OCH_2O$, 87%
**17**: R = OMe, R' = H, 87%
**18**: R = H, R' OMe, 92%
**19**: R = Cl, R' = H, 67% (**8**: 20%)
**20:** R = $NH_2$, R' = H, 65%
**21**: R = $NO_2$, R' = H, 43% ($H_2$)

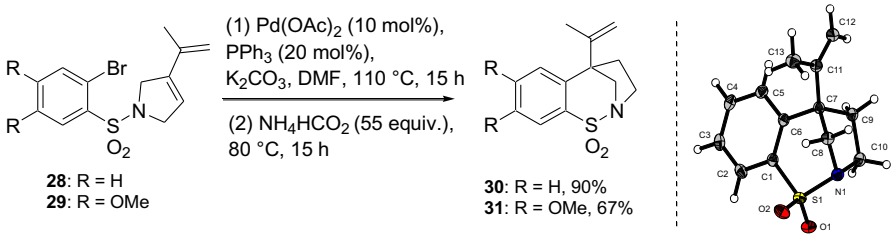
**Scheme 3.** Synthesis of benzo-substituted cyclic sulfonamides **15**–**21** using the one-pot Heck-hydrogen transfer protocol.




**22**: R = R' = H
**23**: R = R' = OMe
**24**: R = OMe, R' = H

**25**: R = R' = H, 93% (67%)[6]
**26**: R = R' = OMe, 70% (58%)[6]
**27**: R = OMe, R' = H, R'' = Me, 92%

**Scheme 4.** Synthesis of substituted cyclic sulfonamides **25**–**27** using the one-pot Heck-hydrogen transfer protocol (values in parentheses, yields for the corresponding process conducted with $H_2$, see Ref. 6).




**28**: R = H
**29**: R = OMe

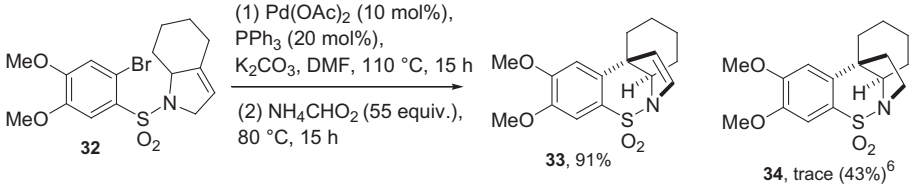
**30**: R = H, 90%
**31**: R = OMe, 67%

**Scheme 5.** Synthesis of substituted cyclic sulfonamides **30** and **31** using the one-pot Heck-hydrogen transfer protocol. Single crystal X-ray structure of *iso*-propenyl containing sulfonamide **30** (ellipsoids shown at 50% probability).

gas a 43% yield of **34** has been obtained.[6] However, several attempts to replicate this result with ammonium formate led only to the formation of traces of **34**. The main product for this reaction proved to be intermediate alkene **33** resulting from a regioselective intramolecular Heck reaction (Scheme 6).

We reason that the failure of the hydrogenation stems from the alkene being too sterically encumbered which is evident from the X-ray crystal structure of **33** (see ESI). This failure, and also the selectivity encountered with dienes **28** and **29**, demonstrates that sterically hindered alkenes are more difficult to reduce under the reported Pd-$NH_4HCO_2$ conditions.

In summary, we have reported that a range of intramolecular Heck reactions to form cyclic sulfonamides can be telescoped with a hydrogen transfer reaction upon the addition of ammonium formate. Reactions were performed on scales ranging from 0.1 to 5.5 mmol and employ the same palladium source in two distinct reactions, which typically generate the saturated products in high isolated yields. Additionally, it should be noted that the use of ammonium formate as the hydrogen source is operationally easy and avoids the direct use of hydrogen gas and the potential hazards associated with its use. Further studies, employing these adducts in our double reduction chemistry, are underway.




**32**

**33**, 91%

**34**, trace (43%)[6]

**Scheme 6.** Attempted synthesis of substituted cyclic sulfonamides **34** using the one-pot Heck-hydrogen transfer protocol (value in parentheses, yield for the corresponding process conducted with $H_2$, see Ref. 6).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.053.

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8. Treatment of **5** with 1 mol% $Pd(OAc)_2$, and 2 mol% $PPh_3$, under otherwise identical conditions to Entry 4, led to full conversion of **5** but incomplete formation of **8** (**7**:**8**; 80:20 judged by $^1H$ NMR spectroscopy).
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