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# Chemoselective One-Pot Synthesis of Functionalized Amino-azaheterocycles Enabled by COware

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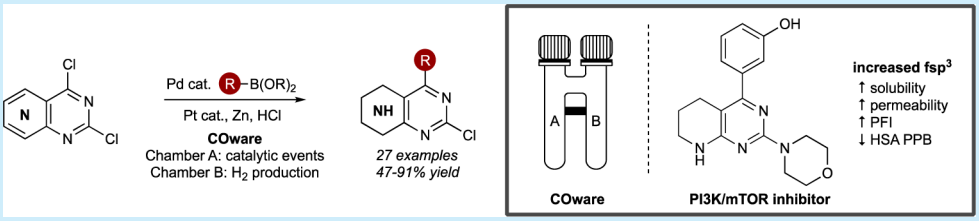
Supporting Information




**ABSTRACT:** Functionalized bicyclic amino-azaheterocycles are rapidly accessed in a one-pot cross-coupling/reduction sequence enabled by the use of COware. Incompatible reagents are physically separated in a single reaction vessel to effect two chemoselective transformations—Suzuki–Miyaura cross-coupling and heteroarene reduction. The developed method allows access to novel heterocyclic templates, including semisaturated Hedgehog and dual PI3K/mTOR inhibitors, which show enhanced physicochemical properties compared to their unsaturated counterparts.

The use of multistep, one-pot reactions has been widely adopted as a strategy for increasing the efficiency of chemical synthesis.[1] These approaches can be significantly less time- and resource-intensive due to the removal of intermediate isolation steps and subsequent reaction setup. A caveat to this strategy is potential incompatibilities of chemical reagents within the same reaction vessel. Consequently, methods to avoid reagent incompatibilities are desirable. One such solution is via the physical separation of mismatched reagents: an engineering solution to a chemical problem.

Encapsulated reagents have allowed separation of incompatible or sensitive reactants, rendering air-sensitive processes more achievable, as well as enabling the development of sequential one-pot processes. For example, seminal work on encapsulation from Taber allowed safer use of KH,[2] while catalytic processes using encapsulation of organometallic transition-metal catalysts from Taber,[3] Buchwald,[4] and Wu[5] have allowed olefin metathesis, C–X cross-couplings, and one-pot cross-coupling/thiophene ring annulations, respectively, avoiding catalyst degradation/poisoning.

A recent physical separation approach using reaction chambering has been developed through COware.[6] COware was initially developed for the in situ generation and use of low molecular weight gases such as carbon monoxide, ethene, and hydrogen.[7] Due to the safety issues associated with the use and storage of hydrogen, especially on discovery scale in industry, the ability to generate and use hydrogen in small volumes at a specific time point over the course of a reaction is an attractive concept.

Here we report the use of COware to enable a one-pot chemoselective Suzuki–Miyaura cross-coupling/heteroarene reduction sequence for the synthesis of novel heteroaromatic tetrahydropyridopyrimidine (THPP) derivatives (Scheme 1). We also show how the generated products align with medicinal chemistry design principles through the preparation of semisaturated Hedgehog and dual PI3K/mTOR inhibitors, which show improved physicochemical properties compared to their unsaturated counterparts.

**Scheme 1. (a) Pyridopyrimidines and the Unexplored THPP Template. (b) COware Approach to the THPP Scaffold**

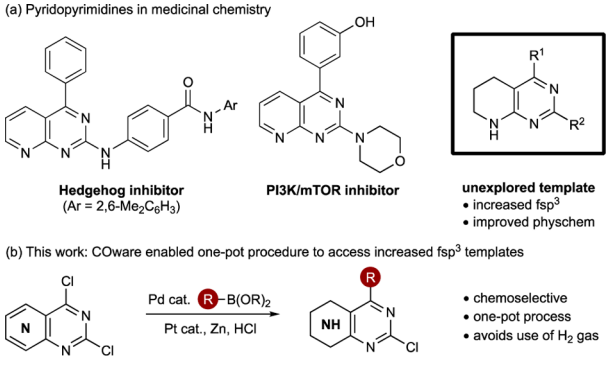



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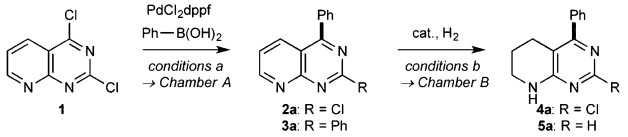
**Table 1. Reaction Development**[a]




| entry | conditions a | conditions b | yield **2a**/**3a**[b] (%) | yield **4a**[b] (%) |
|---|---|---|---|---|
| 1 | $PdCl_2$dppf (4 mol %), $K_3PO_4$ (3 equiv), $H_2O$ (5 equiv), THF, 80 °C, 1 h | | 52:48[c] | |
| 2 | $PdCl_2$dppf (4 mol %), $K_3PO_4$ (3 equiv), $H_2O$ (5 equiv), THF, 40 °C, 1 h | | 60:4[d] | |
| 3 | $PdCl_2$dppf (4 mol %) $K_3PO_4$ (2 equiv) $H_2O$ (5 equiv) CPME, 40 °C, 16 h | | 89:9 | |
| 4 | | $H_2$, Pd/$Al_2O_3$ (5 mol %), THF, rt | | 0 |
| 5 | | $H_2$, $PtO_2$ (5 mol %), THF, rt | | 39[e] |
| 6 | | $H_2$, Pd/$Al_2O_3$ (5 mol %), CPME, rt | | 34[e] |
| 7 | | $H_2$, $PtO_2$ (5 mol %), CPME, rt | | 95[e] |
| 8 | $PdCl_2$dppf (4 mol %), $PtO_2$ (10 mol %), $K_3PO_4$ (2 equiv), $H_2O$ (5 equiv), CPME, 40 °C | HCl, Zn, rt | | 78[e] |

[a]Conditions a: **1** (1 equiv, 0.125 mmol), $PhB(OH)_2$ (1.05 equiv), $PdCl_2$dppf (4 mol %), $K_3PO_4$, $H_2O$, solvent, $N_2$. Conditions b: catalyst, $H_2$, rt. See the Supporting Information for full details. [b]Determined by HPLC analysis using an internal standard. [c]Using $PhB(OH)_2$ (1.5 equiv). [d]Mass balance is starting material. [e]Isolated yield.

Substituted pyridopyrimidine derivatives are important scaffolds in drug discovery.[8] However, there has been relatively little research into the biological activity of the related semisaturated tetrahydropyridopyrimidine (THPP) systems.[9]

As a benchmark reaction for the synthesis of functional THPPs, we envisioned the chemoselective cross-coupling of dichloropyridinopyrimidine **1** to generate **2a**,[10] which would then undergo a one-pot chemoselective hydrogenation to deliver **4a** (Table 1). Compound **4a** is an attractive product from a medicinal chemistry perspective due to the functional group handles embedded: the 2-chloropyrimidine is readily modifiable by cross-coupling or $S_NAr$ strategies, and the newly formed piperidine ring nitrogen provides a second flexible vector. Important to our objectives was the generation of both a practical as well as accessible method, with inexpensive catalysts and solvents more aligned with sustainable chemistry preferred.

Before undertaking the one-pot process, we first assessed the cross-coupling and hydrogenation reactions independently. Under conditions employed for similar processes using 2,4-dichloropyrimidine, chemoselective Suzuki–Miyaura cross-coupling of **1** with $PhB(OH)_2$ was poor at ca. 1:1 in favor of the desired product **2a**, with significant over-reaction observed producing **3a** (entry 1). Lowering the reaction temperature improved the **2a**:**3a** ratio but conversion was only moderate (entry 2). However, optimization of this step (see the Supporting Information for full details) delivered an effective set of reaction conditions where a good yield of **2a** was recorded (89%) while **3a** was minimized (entry 3).

Chemoselective hydrogenation of the pyridine ring while retaining the chloropyrimidine was then explored using a range of catalysts and solvents (entries 3–7; see the SI for full details). Low reactivity and issues with hydrogenation of the C-Cl bond (to deliver **5a**) were observed when Pd catalysts were used (entries 4 and 6). Poor conversion was also seen with $PtO_2$ when THF was used as the solvent (entry 5); however, full conversion and 95% isolated yield of **4a** were observed when $PtO_2$ in CPME was used (entry 7).

Combining the Suzuki–Miyaura and hydrogenation processes into the COware setup proceeded smoothly: chamber A contained **1**, $PhB(OH)_2$, $PdCl_2$dppf, $PtO_2$, $K_3PO_4$, $H_2O$, and CPME, while chamber B contained Zn. Heating the mixture at 40 °C allowed chemoselective Suzuki–Miyaura cross-coupling. Upon completion of the cross-coupling, $H_2$ was generated in chamber B using Zn/HCl and allowed chemoselective hydrogenation of the pyridine ring. This ultimately provided 78% isolated yield of the desired product **3a** (entry 8).

Several points relating to the overall optimization are worth noting. Other catalyst types were effective (for example, PEPPSI-IPr; see the SI); however, $PdCl_2$dppf was selected as the more economical choice. Similarly, CPME offered both improved reactivity/selectivity at lower temperatures (entry 2 vs entry 3) and sustainability credentials over THF and was more economical vs competitor green solvents, such as 2-MeTHF.

With effective conditions for the benchmark reaction in place, we proceeded to assess the generality of the COware process by generation of a small collection of functionalized aza-heterocycle products accessed by variation of both the organoboron and chloroheterocycle components (Scheme 2).

Variation of the organoboron component was readily accommodated (Scheme 2a). Electron-rich and electron-deficient aryl groups, with varying regiochemistry, delivered the functionalized THPPs in generally good yield (**4a**–**j**). Similarly, heterocyclic organoboron components operated effectively (**4k**–**m**). The use of alkenyl organoborons resulted in hydrogenation of both the pyridine ring as well as the olefin to provide the products of formal $sp^2$–$sp^3$ cross-coupling in moderate overall yield (**4n**, **4o**).

Variation of the heterocyclic core was also possible to deliver both regioisomeric THPPs (**4a** vs **6e**, **6f**) as well as a series of analogues including regioisomeric tetrahydroquinolines (**6a**, **6c**, **6d**, **6g**, **6h**, **6i**, **6j**), piperazinopyrimidines (**6b**), and piperidinopyridines (**6k**, **6l**) in good yield (Scheme 2b).

The chemoselective hydrogenation step retains the 2-chloropyrimidine, allowing for subsequent functionalization. For example, a three-component process was developed where an additional $S_NAr$ event was coupled with the COware process to allow the one-pot synthesis of the semisaturated analogue of both a Hedgehog inhibitor **8**[11] and dual PI3K/mTOR inhibitor **9**[12] (Scheme 3).

The increased $fsp^3$ of **8** and **9** vs the parent compounds containing the pyridine ring (**10** and **11**, respectively) results in



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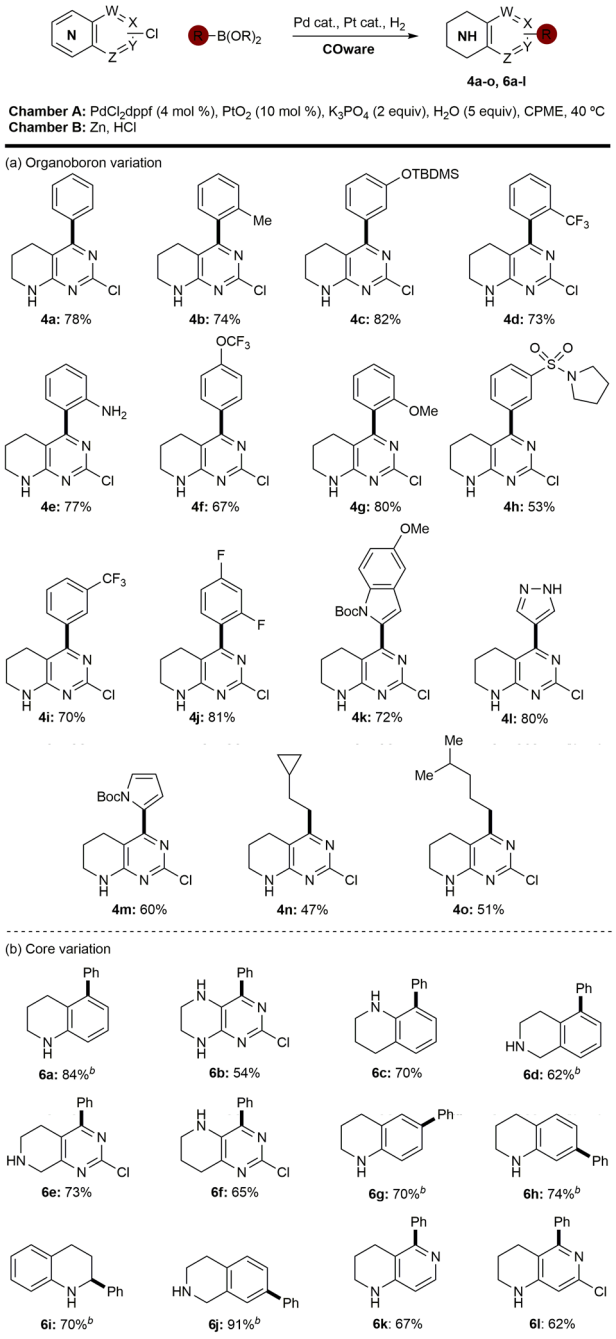
**Scheme 2. Scope of the COware Process**[a]

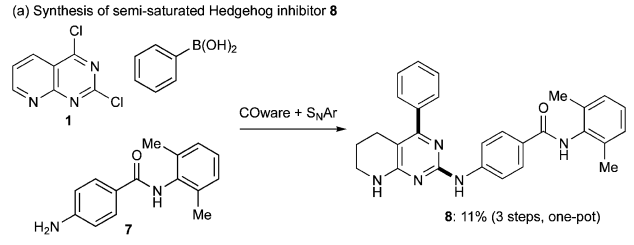


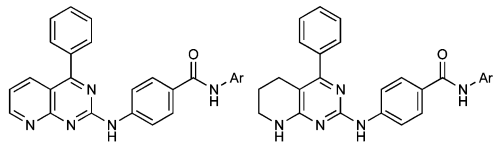

[a]Isolated yields. [b] $Pd(OAc)_2$ (4 mol %), XPhos (8 mol %) catalyst system used.

significant improvements in physicochemical properties of these compounds, in alignment with medicinal chemistry strategy (Figure 1).[13] For example, the solubility, permeability, human serum albumin plasma protein binding (HSA PPB), and property forecast index (PFI)[14] are all markedly improved in comparison to the progenitor compounds.

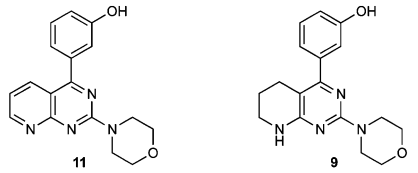
In summary, we have developed a one-pot chemoselective cross-coupling/hydrogenation protocol using COware for the expedient preparation of a diverse set of pharmaceutically relevant aza-heterocycles. The utility of both the COware process and the generated products can be expanded by inclusion of an additional functionalization event using the chloropyrimidine motif. This allows access to semisaturated derivatives of patented drug molecules that display enhanced physicochemical properties vs the parent compounds.

**Scheme 3. Synthesis of Semisaturated Analogues of Hedgehog and PI3K/mTOR Inhibitors**



| Property | 10 | 8 |
|---|---|---|
| $fsp^3$ | 0.07 | 0.18 |
| solubility (μg/mL) | 3 | 31 |
| permeability (nm/sec) | 375 | 815 |
| HSA PPB (%) | 97.70 | 93.30 |
| PFI | 10.84 | 9.70 |



| Property | 11 | 9 |
|---|---|---|
| $fsp^3$ | 0.24 | 0.41 |
| solubility (μg/mL) | 14 | 308 |
| permeability (nm/sec) | 150 | 395 |
| HSA PPB (%) | 90.13 | 89.22 |
| PFI | 5.89 | 5.53 |

**Figure 1.** Physicochemical property comparison of semisaturated derivatives of Hedgehog and PI3K/mTOR inhibitors. Ar = 2,6-$Me_2C_6H_3$. $fsp^3$, fraction $sp^3$ atoms; HSA PPB, human serum albumin plasma protein binding; PFI, property forecast index.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03214.

Experimental procedures, characterization data, and NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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