

# Palladium catalyzed cyclizations of oxime esters with 1,1-disubstituted alkenes: synthesis of $\alpha,\alpha$ -disubstituted dihydropyrroles and studies towards an asymmetric protocol†

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**We report efficient Pd-catalyzed cyclizations of oxime esters with 1,1-disubstituted alkenes as the basis of a general entry to  $\alpha,\alpha$ -disubstituted pyrrolidine derivatives. We also demonstrate that catalytic asymmetric variants of this chemistry are feasible by employing a suitable chiral ligand.**

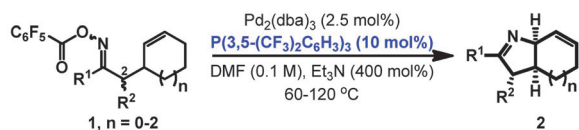
As part of a programme directed towards the development of synthetic entries to chiral *N*-heterocyclic scaffolds,<sup>1</sup> we recently reported efficient conditions for the “Narasaka–Heck” cyclization<sup>2,3</sup> of pentafluorobenzoyl oxime esters with cyclic alkenes (Scheme 1A).<sup>4,5</sup> Here, following oxidative addition of Pd(0) into the oxime ester N–O bond,<sup>6</sup> C(sp<sup>3</sup>)–N bond formation is enforced by the mechanistic requirements of *syn*-imino-palladation and *syn*- $\beta$ -hydride elimination.<sup>4,5</sup> The oxime ester starting materials **1** are easily accessed in enantioenriched form and cyclization of diastereomeric mixtures at C-2 provides stereoconvergent access to chiral heterocyclic targets **2** that retain synthetically flexible alkene and imine moieties.<sup>4</sup> Key to the success of these diastereoselective processes was the identification of P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub> as a privileged ligand.<sup>4,7</sup>

We reasoned that our catalytic system might also facilitate a direct entry to  $\alpha,\alpha$ -disubstituted dihydropyrroles **4** by 5-*exo* cyclizations involving 1,1-disubstituted alkenes **3** (Scheme 1B).<sup>8</sup> Here, an exciting possibility resides in utilizing appropriate chiral ligands to control the absolute stereochemistry of the newly formed *quaternary* amino-stereocentre of **4**. The synthesis of  $\alpha,\alpha$ -disubstituted pyrrolidine derivatives is synthetically challenging and highly flexible asymmetric methods have not been reported. Conventional strategies employ chirality transfer protocols to modify a pre-established enantioenriched core structure.<sup>9</sup> Auxiliary controlled trapping of iminium ions is also effective in certain cases.<sup>10</sup> More recently, approaches based upon enantioretentive [1,2]- or [1,3]-rearrangement have emerged.<sup>11</sup> Enantiopure *N*-Boc-2-phenylpyrrolidine has been converted to  $\alpha,\alpha$ -disubstituted derivatives by a stereoretentive lithiation-electrophile trapping sequence.<sup>12</sup> Spirocyclic systems can be accessed by intramolecular alkylidene carbene 1,5-C–H insertion reactions involving enantioenriched precursors.<sup>13</sup> Strategies based upon asymmetric catalysis, which do not rely on chiral starting materials, have also been reported but do not offer general substrate scope. In specific cases, catalytic enantioselective intra- or intermolecular trapping of transiently generated iminium ions is effective.<sup>14</sup> Catalytic asymmetric phase transfer alkylation provides products where one of the substituents is limited to an ester.<sup>15</sup> An alternative and very attractive approach involves enantioselective intramolecular amination of 1,1-disubstituted alkenes. Although efficient hydroamination protocols that achieve this have remained elusive,<sup>16</sup> aminoxygenation,<sup>17</sup> bromocyclization<sup>18</sup> and multicomponent coupling processes<sup>19</sup> are effective in certain cases.

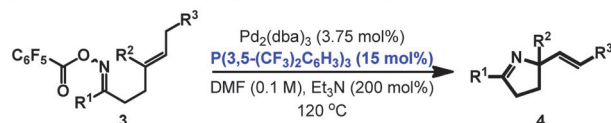
Here, we report that using P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub> as ligand enables highly efficient Pd-catalyzed 5-*exo* cyclizations of oxime esters with a wide range of representative 1,1-disubstituted alkenes. Additionally, we report studies towards an asymmetric protocol that provide the very same  $\alpha,\alpha$ -disubstituted derivatives with moderate enantioselectivity. To the best of our knowledge, these studies encompass the first *asymmetric* Narasaka–Heck cyclisations and thereby validate the potential of this reaction manifold for catalytic asymmetric C(sp<sup>3</sup>)–N bond construction.<sup>2,3,8</sup>

Our initial studies focused on evaluating the cyclization of aryl oxime ester **3a** to imine **4a** using our previously established

## (A) Previous work: Pd-catalyzed cyclizations involving cyclic alkenes



## (B) This work: Pd-catalyzed cyclizations involving 1,1-disubstituted alkenes



**Scheme 1** Synthesis of chiral *N*-heterocycles by Pd-catalyzed cyclization of oxime esters with alkenes.

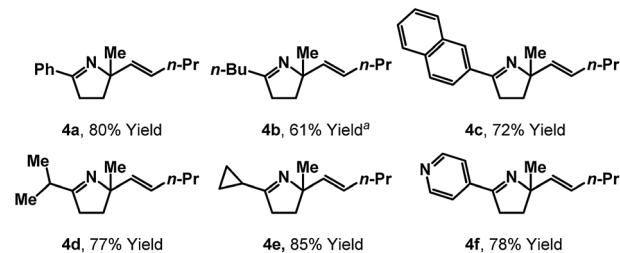
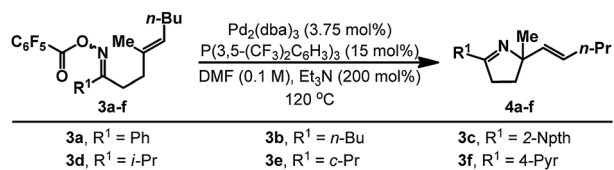
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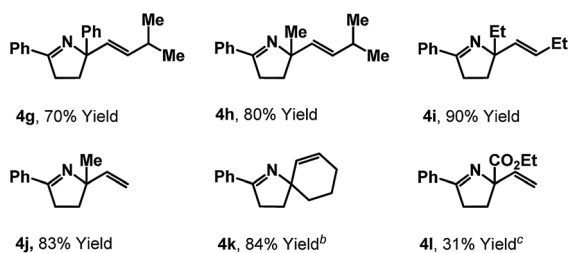
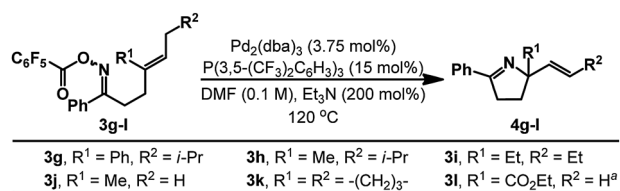


**Table 1** Scope of the oxime ester

<sup>a</sup> Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol%) and P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub> (20 mol%) were employed.

achiral catalysis system (Table 1). Here, we found that a slightly modified variant (7.5 mol% [Pd], 15 mol% P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub>, 200 mol% Et<sub>3</sub>N) of our earlier conditions was effective at generating the target compound in 80% yield. This protocol tolerates a wide range of ketoxime esters **3b–3f**<sup>20</sup> and products **4b–4f** were isolated in moderate to excellent yield.<sup>21</sup> In the case of **3b** a higher catalyst loading (10 mol% [Pd]) was required for efficient cyclization. For C–N bond formation to occur, the N–Pd(II) bond of the imino–Pd(II) intermediate must be oriented towards the alkene. Presumably, due to steric factors, smaller R<sup>1</sup> groups (e.g. *n*-Bu as in **3b**) are less effective at enforcing this configuration and, as such, substrates of this type cyclize with lower efficiency.

Variation of the alkene partner provides direct access to a wide range of representative scaffolds (Table 2). Cyclizations of **3g–i**, which contain sterically encumbered alkenes (cf. **3a**) were all efficient. In the case of **4g**, the formation of a challenging quaternary amino-substituted benzylic stereocentre is particularly noteworthy. Processes that generate terminal alkenes are also effective and the

**Table 2** Scope of the alkene

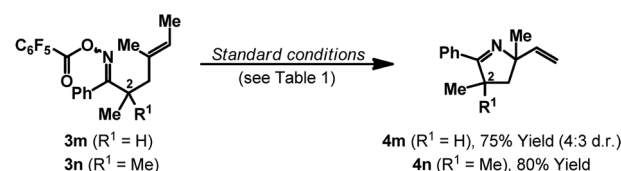
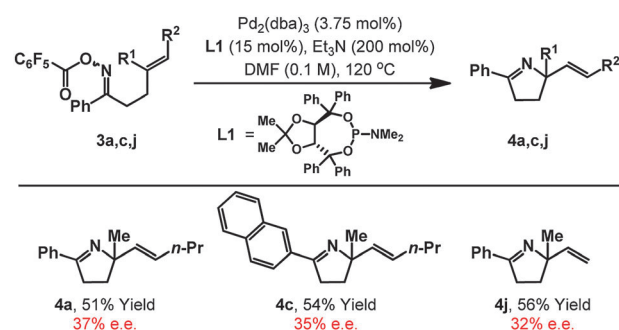
<sup>a</sup> R<sup>1</sup> and CH<sub>2</sub>R<sup>2</sup> were *trans*. <sup>b</sup> Formed as a 5 : 1 mixture of alkene regioisomers. <sup>c</sup> Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol%) and P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub> (20 mol%) were employed and the reaction was run at 135 °C.

potentially vulnerable olefinic moiety of **4j** was stable to the reaction conditions. Cyclization of **3k**, which involves a 1,1-disubstituted cyclic alkene, generated spirocycle **4k** in 84% yield. Here, small amounts of the corresponding alkene regioisomer (5 : 1 regioisomeric ratio) were also formed, presumably *via* Pd-hydride mediated isomerization of the initial adduct **4k**.<sup>22</sup> Electron deficient alkenes participate using this protocol but cyclize less efficiently. Substrate **3l**, which requires 5-*exo* cyclization onto the α-position of a pendant acrylate, generated dihydropyrrole **4l** in 31% yield.<sup>23</sup> This represents a very direct and flexible entry to complex proline derivatives<sup>24</sup> and studies to optimize this class of cyclization are ongoing.

More complex pyrrolidine derivatives are accessible by employing C-2 di- or tri-substituted oxime esters (Scheme 2). Cyclizations involving both **3m** and **3n** were efficient and the target heterocycles **4m** and **4n** were isolated in good yield. In the former case, relative stereochemistry was not readily controlled (4 : 3 dr); this is either reflective of non-diastereoselective cyclization or the lability of the C-2 stereocentre of the product.<sup>25</sup>

Having established an achiral catalyst system, we sought effective *chiral* ligands capable of mimicking the beneficial steric and electronic effects of P(3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)<sub>3</sub>. Accordingly, we evaluated an extensive range of commercial electron neutral/poor systems and established that TADDOL-derived phosphoramidite **L1** is unique at providing appreciable levels of asymmetry (Table 3).<sup>26</sup> Using this ligand, cyclizations of **3a**, **3c** and **3j** proceeded in moderate yield to provide adducts **4a**, **4c** and **4j** in 32–37% ee.<sup>27</sup> These results are significant because they provide compelling evidence for the close association of Pd during the C–N bond forming event<sup>28,29</sup> and, at the same time, establish the feasibility of *asymmetric* Narasaka–Heck cyclizations. Importantly, the TADDOL scaffold of **L1** is readily modified<sup>30</sup> and, in the longer term, fine tuning of steric and electronic properties should facilitate provision of a more effective chiral ligand.

In summary, efficient conditions for the Pd-catalyzed cyclization of oxime esters with 1,1-disubstituted alkenes are described.

**Scheme 2** Cyclizations of C-2 di- and tri-substituted oxime esters.**Table 3** Preliminary asymmetric results

These are the first examples of this class of cyclization, and this provides an approach to synthetically challenging  $\alpha,\alpha$ -disubstituted pyrrolidine derivatives. The method is operationally simple and has wide scope with respect to both the oxime ester and alkene. Additionally, we have established for the first time the feasibility of asymmetric cyclizations based upon the use of a chiral ligand system. This has important ramifications for the further development and utility of this type of process. More efficient chiral ligands and other classes of cyclization are currently being developed.

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