Palladium-Catalyzed Cyclization

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Highly Efficient Narasaka–Heck Cyclizations Mediated by $P(3,5\text{-}(CF_3)_2C_6H_3)_3$: Facile Access to N-Heterobicyclic Scaffolds**

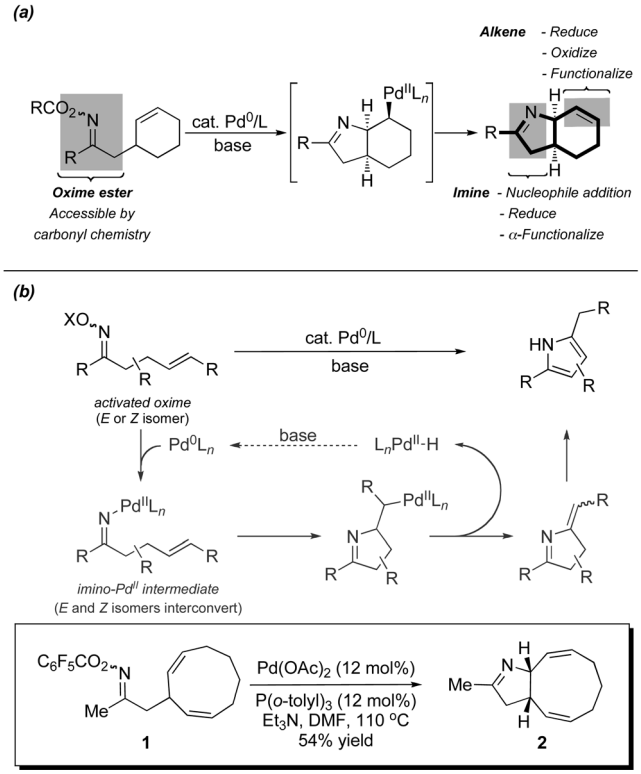
*Adele Faulkner and John F. Bower**

In recent years, the drive for more potent and selective drugs has seen medicinal chemistry move away from "flat" compounds and become increasingly interested in evaluating chiral "3D" drug candidates.[1] The complexities associated with accessing such molecules require the development of more efficient and versatile entries to chiral scaffolds. In this regard, and given the importance of nitrogen,[2] new methods for the efficient and controlled formation of $C(sp^3)$–N bonds, specifically those embedded within N-heterocyclic systems, are likely to be of great interest to the pharmaceutical sector.

With these considerations in mind, we initiated explorations into the Pd-catalyzed Heck-type cyclization of oxime esters[3] with cyclic alkenes. In this scenario the mechanistic requirements of *syn*-imino-palladation and *syn*-β-hydride elimination would be expected to mandate $C(sp^3)$–N bond formation (Scheme 1 a). Importantly, the oxime ester substrates are readily accessible and further derivatization of the cyclization products is possible by manipulation of either the imine or alkene functionalities.

The Pd-catalyzed cyclization of oxime esters with alkenes was first reported by Narasaka, et al. and provides an entry to pyrroles via the catalytic generation and trapping of an imino-Pd^{II} intermediate (Scheme 1 b).[3] Applications of the "Narasaka–Heck" method to other heteroaromatic classes[4] and cascade reactions[5] have been reported and the scope of the oxime activating group has been examined.[6] The catalytic generation and trapping of metalated imines has also been exploited in other contexts.[7–9]

In general, methods that are reliant upon this process produce $C(sp^2)$–N bonds and are therefore not applicable to the synthesis of chiral N-heterocycles.[3–5] Extension to the formation of $C(sp^3)$–N bonds is an attractive possibility but, cascade processes aside,[5a,b] general methods that achieve this have not been reported. Of particular relevance to this study is a single example by Fürstner, et al., who showed that cyclization of oxime ester **1** provided **2** in 54% yield.[10] However, high catalyst loadings and a symmetrical diene substrate were required for useful conversion. Indeed, reported conditions for the Narasaka–Heck process are highly sensitive to the electronic and steric demands of the oxime ester, with both hydrolysis and Beckmann rearrangement often competing.[3,10] This lack of generality has precluded the widespread use of the reaction in synthesis. Herein we show that efficient and general 5-*exo* cyclizations involving cyclic alkenes are achievable by employing $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as the ligand. The net result is a facile and asymmetric entry to perhydroindole and related scaffolds by formation of a key $C(sp^3)$–N bond. This work sets the stage for the development of other general entries to chiral N-heterocyclic architectures.



Scheme 1. a) Proposed Pd-catalyzed approach to N-heterobicyclic scaffolds. b) The Narasaka–Heck pyrrole synthesis.

Our initial studies focused upon the cyclization of pentafluorobenzoyl oxime ester **3a** to imine **4a**.[11–13] Under conditions related to those employed by Fürstner, et al.,[10a] adduct **4a** was accessible in only 29% yield and hydrolysis of the oxime ester to the corresponding ketone and, to a lesser extent, oxime predominated (Table 1, entry 1). Improvements in yield were observed when the ligand was changed to xantphos (entry 2) and, using this as a basis, we were able to achieve a 58% yield of **4a** after the optimization of other parameters (entry 3). At this stage, a more thorough ligand screen was performed and we found that $P(p\text{-}FC_6H_4)_3$ allowed

[*] A. Faulkner, Dr. J. F. Bower
School of Chemistry, University of Bristol
Bristol, BS8 1TS (UK)
E-mail: john.bower@bris.ac.uk

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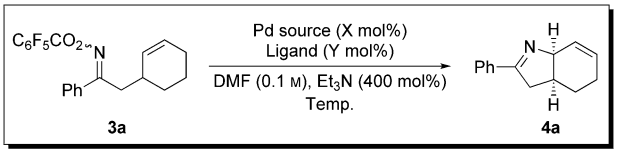
Table 1: Selected optimization results for the cyclization of **3a** to **4a**.[a]



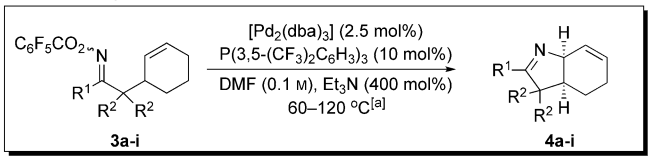
Entry	Pd-source (X mol%)	Ligand (Y mol%)	*T* [°C]	Yield %
1	$Pd(OAc)_2$ (10)	P(*o*-tolyl)$_3$ (10)	120	29
2	$Pd(OAc)_2$ (10)	xantphos (10)	120	52
3	$[Pd_2(dba)_3]$ (5)	xantphos (10)	100	58
4	$[Pd_2(dba)_3]$ (5)	P(2-furyl)$_3$ (20)	100	38
5	$[Pd_2(dba)_3]$ (5)	$P(C_6F_5)_3$ (20)	100	10
6	$[Pd_2(dba)_3]$ (5)	$P(p\text{-}FC_6H_4)_3$ (20)	100	76
7	$[Pd_2(dba)_3]$ (5)	$P(p\text{-}CF_3C_6H_4)_3$ (20)	100	85
8	$[Pd_2(dba)_3]$ (5)	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	100	90
9	$[Pd_2(dba)_3]$ (2.5)	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (10)	60	93
10	$[Pd_2(dba)_3]$ (5)	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	20	29

[a] dba = dibenzylideneacetone, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

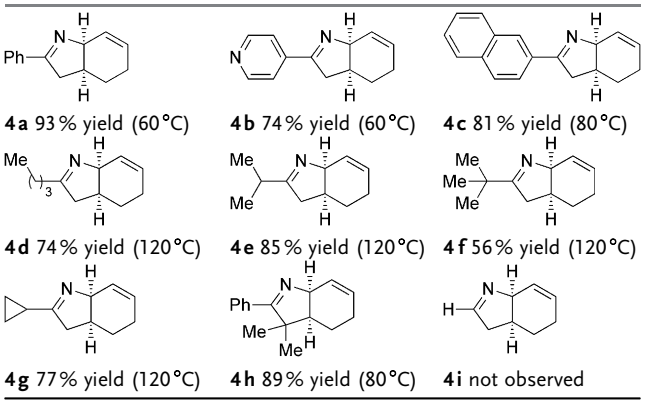
the generation of **4a** in 76% yield (entry 6). Further sequential improvements were observed upon switching to $P(p\text{-}CF_3C_6H_4)_3$ (85%; entry 7) and then $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (90%; entry 8). Using this ligand, we were able to decrease both the catalyst loading and the reaction temperature such that **4a** became accessible in 93% yield using 2.5 mol% $[Pd_2(dba)_3]$ at 60°C (entry 9). Indeed, under these conditions, significant conversion to **4a** was observed even at room temperature (entry 10). It should be recognised that other electron deficient phosphines, such as $P(C_6F_5)_3$ and P(2-furyl)$_3$ (entries 4 and 5), were not effective for this transformation.[14] The relative stereochemistry of **4a** was determined by NOE analysis, according to the method of Butts et al.[15] and was later confirmed by X-ray crystallography (see below).

Having established suitable conditions on model substrate **3a**, we investigated the scope of the process with respect to the oxime ester (Table 2). The reaction conditions tolerate both electron deficient and electron rich aryl groups and both **4b** and **4c** were formed in good yield. Cyclizations involving alkyl-substituted substrates were more challenging. For example, cyclization of **3d** was not efficient at 60°C and significant hydrolysis to the corresponding ketone (40%) was observed. However, increasing the reaction temperature to 120°C resulted in an efficient and fast cyclization to **4d** with only minimal quantities (< 15%) of ketone formed; similar trends were seen with cyclopropyl variant **3g**.[16] Isopropyl substrate **3e**, which is sterically less susceptible to hydrolysis, cyclized in excellent yield at 120°C, and even the hindered *tert*-butyl variant **3f** underwent cyclization in moderate yield. The reaction also proceeds when the oxime ester is α-trisubstituted (for example, **3h** to **4h**); this demonstrates that cyclization does not require prior tautomerization to a palladated enamine. As expected,[17] the method does not tolerate aldoxime ester substrates, and the cyclization of **3i** did not afford target **4i**. In this case, Beckmann rearrangement predominated to deliver the corresponding nitrile; this byproduct was also observed, to a lesser extent (28%), in the cyclization of **3f** to **4f**.[17] The stereochemical outcomes of all of the cyclizations shown in Table 2 were assigned by analogy

Table 2: Scope of the oxime ester.[a]



3a: R^1 = Ph, R^2 = H; **3b**: R^1 = 4-Py, R^2 = H; **3c**: R^1 = 2-Npth, R^2 = H; **3d**: R^1 = *n*Bu, R^2 = H; **3e**: R^1 = *i*Pr, R^2 = H; **3f**: R^1 = *t*Bu, R^2 = H; **3g**: R^1 = *c*-Pr, R^2 = H; **3h**: R^1 = Ph, R^2 = Me; **3i**: R^1 = H, R^2 = H



4a 93% yield (60°C); **4b** 74% yield (60°C); **4c** 81% yield (80°C)

4d 74% yield (120°C); **4e** 85% yield (120°C); **4f** 56% yield (120°C)

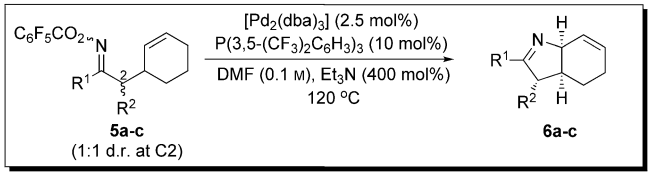
4g 77% yield (120°C); **4h** 89% yield (80°C); **4i** not observed

[a] Reaction temperatures are specified in parentheses. Npth = naphthyl, Py = pyridyl.

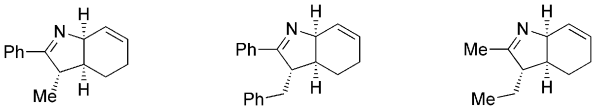
to **4a** and, in several cases, were confirmed by NOE analysis (see the Supporting Information).

Access to higher substitution patterns is facilitated by increasing the substitution at C2 (Table 3). Oxime esters **5a–c**

Table 3: Cyclization of C2-disubstituted substrates.



5a, R^1 = Ph, R^2 = Me; **5b**, R^1 = Ph, R^2 = Bn; **5c**, R^1 = Me, R^2 = Et



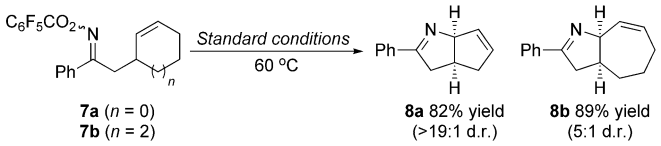
6a 88% yield[a] (>19:1 d.r.); **6b** 76% yield (>19:1 d.r.); **6c** 55% yield (10:1 d.r.)

[a] **6a** was obtained in 88% yield and 7:2 d.r. when the reaction was run at 60°C.

were synthesized as 1:1 mixtures of diastereomers at C2, but this lack of selectivity was inconsequential, as cyclization at 120°C delivered heterocyclic adducts **6a–c** in moderate to excellent yield and in high diastereomeric purity. When the cyclization of **5a** to **6a** was performed at 60°C, lower diastereoselectivity (7:2 vs. > 19:1) was observed. Resubjecting this mixture to the reaction conditions at 120°C led to the isolation of **6a** in greater than 19:1 d.r. and this supports base-mediated equilibration to the major diastereomer after

cyclization. The relative stereochemistry of **6a–c** was confirmed by NOE analysis (see the Supporting Information).

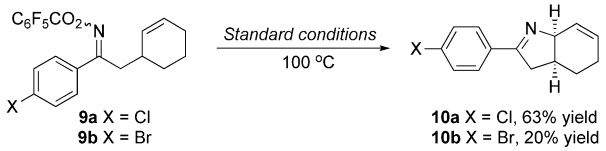
This method is also efficient for 5-*exo* cyclizations onto other cyclic alkenes (Scheme 2). For example, cyclization of



Scheme 2. Cyclizations involving five- and seven-membered-ring alkenes. For standard conditions, see Table 2.

7a, which involves a five-membered-ring alkene, generated **8a** in 82% yield and as a single diastereomer, the stereochemistry of which was determined by NOE analysis (see the Supporting Information). Cyclization of **7b** delivered adduct **8b** in high yield and as a 5:1 mixture of diastereomers; the imperfect selectivity observed here may be a consequence of the less conformationally rigid seven-membered-ring cyclic alkene.

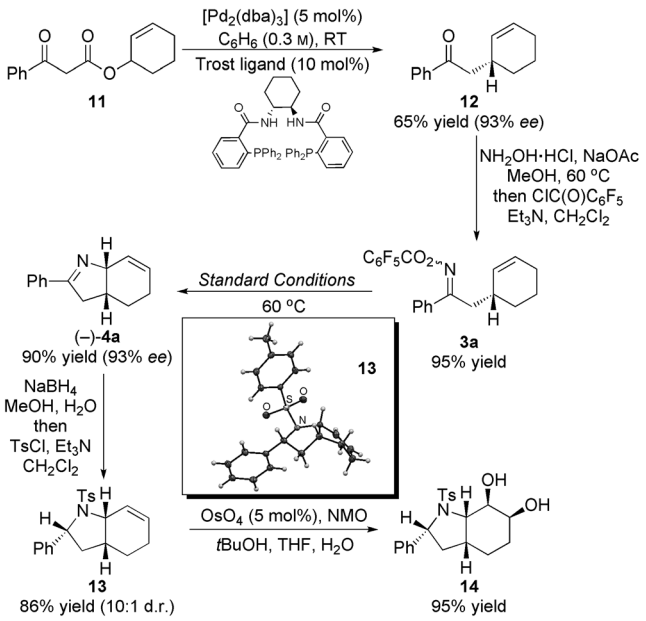
We were interested in evaluating whether the process could tolerate aryl bromides and chlorides, as these have an obvious sensitivity to the Pd-catalyzed conditions but provide a potentially useful handle for further manipulation. We therefore synthesized substrates **9a** and **9b**, which possess relatively activated aryl halides (Scheme 3). Cyclization of



Scheme 3. Cyclization of substrates containing aryl halides. For standard conditions, see Table 2.

chloride **9a** was reasonably efficient and adduct **10a** was formed in 63% yield. However, the reaction was much slower than, for example, the cyclization of **3a** to **4a** and so required higher temperatures for reasonable rates. This observation, in conjunction with the lower yield of **10a** (vs. **4a**), suggests competitive Pd insertion into the aryl chloride bond. Cyclization of bromide **9b** was not efficient and **10b** was isolated in only 20% yield.[18]

As alluded to in the introduction, oxime ester substrates are highly flexible because they are synthesized by established carbonyl α-functionalization strategies. As such, the methodology presented herein is readily translated to asymmetric synthesis. To demonstrate this, we have prepared adduct **4a** in enantioenriched form (Scheme 4). Accordingly, decarboxylative Tsuji–Trost cyclohexenylation of **11**, following the method of Tunge and Burger,[19] delivered ketone **12** in good yield and with high levels of enantioenrichment (93% *ee*). Advancement to oxime ester **3a** was then readily achieved and cyclization under standard conditions (see



Scheme 4. Asymmetric synthesis of (−)-**4a** and downstream manipulations of the imine and alkene functional groups. For standard conditions, see Table 2. dba = dibenzylideneacetone, NMO = *N*-methylmorpholine *N*-oxide, Ts = tosyl.

Table 2; 60 °C) provided (−)-**4a** in high yield and without erosion of enantiopurity (as determined by chiral HPLC analysis of **12** and (−)-**4a** using the corresponding racemates as standards; see the Supporting Information).

To demonstrate potential manipulations of the imine and alkene functionalities, we reduced (−)-**4a** with $NaBH_4$ and, upon N-tosylation, sulfonamide **13** was obtained in high diastereoselectivity. That the reduction occurred preferentially from the least hindered imine face was confirmed by X-ray crystallographic analysis of the major diastereomer of **13**.[20] This also served to confirm both the relative stereochemical outcome of the Pd-catalyzed cyclization and the absolute stereochemical outcome of the asymmetric Tsuji–Trost process. Upjohn dihydroxylation[21] of **13** then occurred from the convex face to provide diol **14** as a single diastereomer and in high yield. Thus, compound **14** is accessible in over 40% yield from **11** with control over both the absolute and relative stereochemistry of all five stereocenters.

The origins of the high efficiency of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ in the reactions presented herein remain to be rigorously determined. However, beneficial effects upon both the lifetime and reactivity of the putative imino-Pd^{II} intermediate can be envisaged. Electron deficient phosphine ligands may enhance the stability of this species by rendering the Pd center more electron-deficient. This, in turn, would be expected to lead to greater σ donation from the imine moiety and the resulting stronger imino-Pd bond should be less susceptible to protodepalladation (which would lead to ketone hydrolysis products).[22] Furthermore, a more electron-deficient imino-Pd^{II} intermediate may enhance the rate of iminopalladation. Recent computational and experimental studies by Hartwig on the migratory insertion of alkenes into related Pd–NPh_2

bonds have shown that electron-deficient phosphine ligands accelerate this process.[23]

In summary, we present highly efficient palladium-catalyzed cyclizations of oxime esters with cyclic alkenes as the basis of a general entry to perhydroindole and related scaffolds. The chemistry is reliant upon the use of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ for the key $C(sp^3)$–N bond-forming process and this facilitates cyclizations with enhanced levels of efficiency across a range of sterically and electronically distinct substrates. The rigid N-heterobicyclic products arising from these studies can easily be accessed in enantioenriched form and are readily manipulated through both the imine and alkene functionalities. Future studies will focus upon the development of enhanced catalyst systems and applications to the synthesis of other chiral N-heterocyclic classes.

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[10] a) A. Fürstner, K. Radkowski, H. Peters, *Angew. Chem.* **2005**, *117*, 2837; *Angew. Chem. Int. Ed.* **2005**, *44*, 2777; b) A. Fürstner, K. Radkowski, H. Peters, G. Seidel, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 1929. The sensitivity and volatility of cyclization product **2** were noted as complicating factors in its isolation. For the observation of $C(sp^3)$–N bond formation as a minor byproduct under Narasaka–Heck conditions, see reference [3a].

[11] The oxime esters employed in this study were synthesized in high yield from the corresponding carbonyl compounds. These, in turn, were prepared by alkylation of the corresponding β-keto ester or hydrazone with the appropriate cyclic allylic bromides; details are provided in the Supporting Information. Pentafluorobenzoyl esters were chosen, as they have been established to be largely resistant to Beckmann rearrangement (see reference [3]). We have also evaluated other oxime ester derivatives (for example, benzoyl, pivaloyl, and picalinoyl), but these were less effective; full details will be reported in due course.

[12] Oxime ester starting materials were usually obtained as a mixture of geometric isomers. Previous studies have established that this is inconsequential, as interconversion occurs at the stage of the imino-Pd^{II} intermediate (see reference [3]). Unambiguous assignment of oxime ester geometry by NMR is not readily achievable.

[13] Reactions were monitored by TLC until full consumption of starting material occurred. Under optimized conditions, prolonged reaction times do not adversely affect product yield.

[14] In the case of $P(2\text{-furyl})_3$, complete consumption of **3a** occurred, but significant quantities of ketone hydrolysis product were observed. When $P(C_6F_5)_3$ was used, the conversion of **3a** was low. These observations point to a potentially narrow steric and/or electronic window for effective ligands for these specific processes.

[15] a) C. P. Butts, C. R. Jones, E. C. Towers, J. L. Flynn, L. Appleby, N. J. Barron, *Org. Biomol. Chem.* **2011**, *9*, 177; b) C. P. Butts, C. R. Jones, J. N. Harvey, *Chem. Commun.* **2011**, *47*, 1193; details are given in the Supporting Information.

[16] At lower temperatures, the rate of hydrolysis is competitive with the rate of cyclization in these cases. Our observations are that aryl-substituted oxime esters undergo cyclization at faster rates than alkyl-substituted variants. After oxidative addition, there is a requirement for the imino-Pd^{II} moiety to be oriented towards the alkene. Geometric interconversion to this configuration is likely enhanced by higher reaction temperatures and bulkier R^1 substituents. The comparatively low steric bulk of the alkyl substituent of **3d** may explain the inefficiencies observed at lower temperatures for this substrate; this will be a focus of future studies. It is unclear whether hydrolysis to the corresponding ketone occurs directly from the oxime ester or via the presumed imino-Pd^{II} intermediate. Reactions run in the absence of palladium result in minimal oxime ester hydrolysis, but these conditions do not exactly mimic a catalytically active system. The use of drying agents (for example, molecular sieves or Na_2SO_4) was only marginally beneficial. Taken together, these observations suggest that the ketone is formed by protodepalladation to the corresponding imine and subsequent hydrolysis upon workup.

[17] For a review of the Beckmann rearrangement, see: R. E. Gawley, *Org. React.* **1988**, *35*, 1; for similar observations see, for example, reference [5b]. Compound **3i** is relatively unstable and undergoes normal Beckmann rearrangement (to the corresponding amide) slowly at room temperature. Compound **3f** is stable to the reaction conditions in the absence of palladium; this implicates a Pd-mediated Beckmann rearrangement pathway in this case.
[18] In these reactions, dehalogenated cyclization products (such as **4a**) are not observed. The mass balance of the reactions is low, and we suspect this is due to polymerization of aryl-Pd^{II} intermediates via Heck-type pathways.
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[21] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973.
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