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

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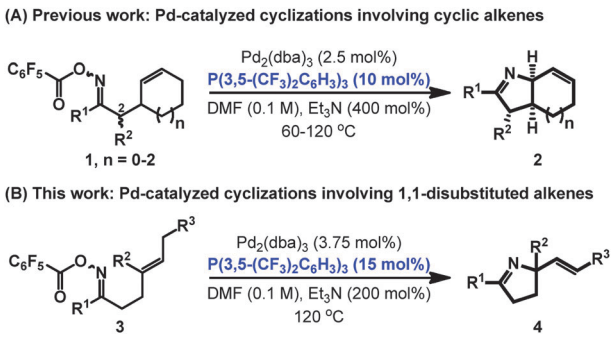
We report efficient Pd-catalyzed cyclizations of oxime esters with 1,1-disubstituted alkenes as the basis of a general entry to α,α-disubstituted pyrrolidine derivatives. We also demonstrate that catalytic asymmetric variants of this chemistry are feasible by employing a suitable chiral ligand.

As part of a programme directed towards the development of synthetic entries to chiral *N*-heterocyclic scaffolds,[1] we recently reported efficient conditions for the "Narasaka–Heck" cyclization[2,3] of pentafluorobenzoyl oxime esters with cyclic alkenes (Scheme 1A).[4,5] Here, following oxidative addition of Pd(0) into the oxime ester N–O bond,[6] C(sp^3)–N bond formation is enforced by the mechanistic requirements of *syn*-imino-palladation and *syn*-β-hydride elimination.[4,5] 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.[4] Key to the success of these diastereoselective processes was the identification of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as a privileged ligand.[4,7]



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

We reasoned that our catalytic system might also facilitate a direct entry to α,α-disubstituted dihydropyrroles **4** by 5-*exo* cyclizations involving 1,1-disubstituted alkenes **3** (Scheme 1B).[8] 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 α,α-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.[9] Auxiliary controlled trapping of iminium ions is also effective in certain cases.[10] More recently, approaches based upon enantioretentive [1,2]- or [1,3]-rearrangement have emerged.[11] Enantiopure *N*-Boc-2-phenylpyrrolidine has been converted to α,α-disubstituted derivatives by a stereoretentive lithiation-electrophile trapping sequence.[12] Spirocyclic systems can be accessed by intramolecular alkylidene carbene 1,5-C–H insertion reactions involving enantioenriched precursors.[13] 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.[14] Catalytic asymmetric phase transfer alkylation provides products where one of the substituents is limited to an ester.[15] 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,[16] aminooxygenation,[17] bromocyclization[18] and multicomponent coupling processes[19] are effective in certain cases.

Here, we report that using $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ 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 α,α-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^3)–N bond construction.[2,3,8]

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

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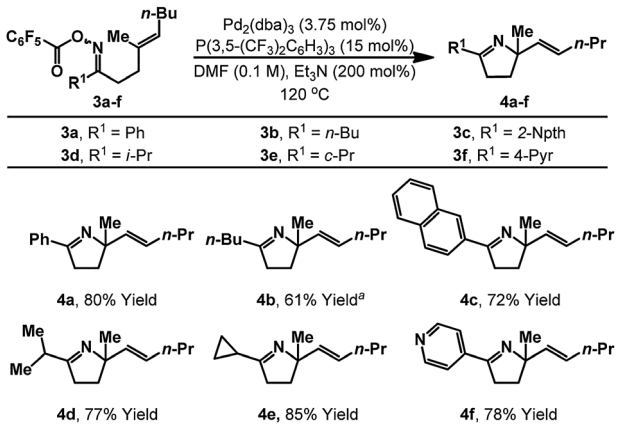
Table 1 Scope of the oxime ester



[a] $Pd_2(dba)_3$ (5 mol%) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20 mol%) were employed.

achiral catalysis system (Table 1). Here, we found that a slightly modified variant (7.5 mol% [Pd], 15 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, 200 mol% Et_3N) 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**[20] and products **4b–4f** were isolated in moderate to excellent yield.[21] 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^1 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.

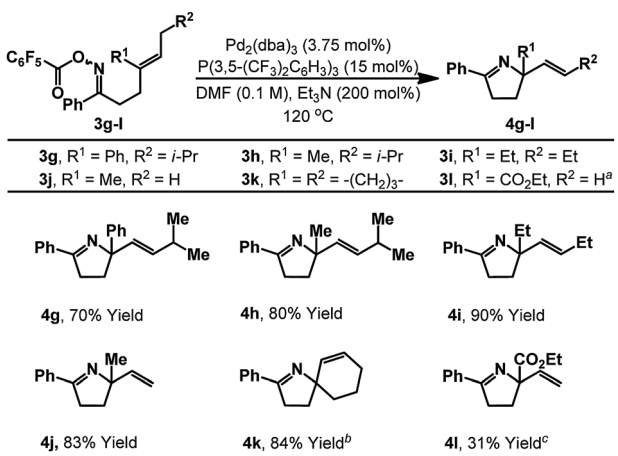
Variation of the alkene partner provides direct access to a wide range of representative scaffolds (Table 2). Cyclizations of **3g–i**, which contain sterically encumbered alkenes (*cf.* **3a**) were all efficient. In the case of **4g**, the formation of a challenging quaternary amino-substituted benzylic stereocentre is particularly noteworthy. Processes that generate terminal alkenes are also effective and the 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**.[22] 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.[23] This represents a very direct and flexible entry to complex proline derivatives[24] 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.[25]

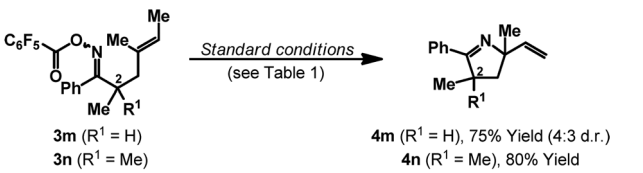
Having established an achiral catalyst system, we sought effective *chiral* ligands capable of mimicing the beneficial steric and electronic effects of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$. Accordingly, we evaluated an extensive range of commercial electron neutral/poor systems and established that TADDOL-derived phosphoramidite **L1** is unique at providing appreciable levels of asymmetry (Table 3).[26] Using this ligand, cyclizations of **3a**, **3c** and **3j** proceeded in moderate yield to provide adducts **4a**, **4c** and **4j** in 32–37% ee.[27] These results are significant because they provide compelling evidence for the close association of Pd during the C–N bond forming event[28,29] and, at the same time, establish the feasibility of *asymmetric* Narasaka–Heck cyclizations. Importantly, the TADDOL scaffold of **L1** is readily modified[30] 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.

Table 2 Scope of the alkene

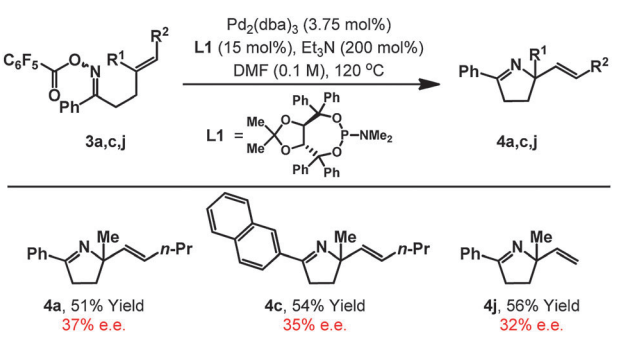


[a] R^1 and CH_2R^2 were *trans*. [b] Formed as a 5 : 1 mixture of alkene regioisomers. [c] $Pd_2(dba)_3$ (5 mol%) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20 mol%) were employed and the reaction was run at 135 °C.



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 α,α-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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Notes and references

1 There is a pressing demand for the development of efficient methodologies that target low molecular weight (200–350 Da), 3D (sp^3-rich) scaffolds: A. Nadin, C. Hattotuwagama and I. Churcher, *Angew. Chem., Int. Ed.*, 2012, **51**, 1114. Efficient chirality generating methods should facilitate an ''escape from flatland'': F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.

2 (*a*) H. Tsutsui and K. Narasaka, *Chem. Lett.*, 1999, 45; (*b*) H. Tsutsui, M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1451; For reviews, see: (*c*) M. Kitamura and K. Narasaka, *Chem. Rec.*, 2002, **2**, 268; (*d*) K. Narasaka and M. Kitamura, *Eur. J. Org. Chem.*, 2005, 4505.

3 The Narasaka–Heck process has been used extensively for $C(sp^2)$–N bond formation in the context of heteroaromatic synthesis. Leading references: *Imidazoles:*(*a*) S. Zaman, K. Mitsuru and A. D. Abell, *Org. Lett.*, 2005, **7**, 609; *Azaazulenes:* (*b*) M. Kitamura, S. Chiba, O. Saku and K. Narasaka, *Chem. Lett.*, 2002, 606; (*c*) S. Chiba, M. Kitamura, O. Saku and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 785; *Isoquinolines and pyridines:* (*d*) H. Tsutsui and K. Narasaka, *Chem. Lett.*, 2001, 526; (*e*) M. Kitamura, D. Kudo and K. Narasaka, *ARKIVOC*, 2006, **iii**, 148; (*f*) J.-L. Zhu, Y.-L. Su, Y.-H. Chan, I.-C. Chen and C.-C. Liao, *Heterocycles*, 2009, **78**, 369; *Phenanthridines:* (*g*) T. Gerfaud, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2009, **48**, 572; (*h*) *Pyrroles*: J. Ichikawa, R. Nadano and N. Ito, *Chem. Commun.*, 2006, 4425, see also ref. 2.

4 A. Faulkner and J. F. Bower, *Angew. Chem., Int. Ed.*, 2012, **51**, 1675.

5 For an earlier example of a Narasaka–Heck cyclization involving a cyclic alkene, see: (*a*) A. Fürstner, K. Radkowski and H. Peters, *Angew. Chem., Int. Ed.*, 2005, **44**, 2777; (*b*) A. Fürstner, K. Radkowski, H. Peters, G. Seidel, C. Wirtz, R. Mynott and C. W. Lehmann, *Chem.–Eur. J.*, 2007, **13**, 1929.

6 The oxidative addition event has been confirmed by X-ray crystallographic analysis of an isolable imino-Pd(II) intermediate: Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676.

7 A similar catalyst system is effective for decarboxylative nitrene generation from oxime esters: K. Okamoto, T. Oda, S. Kohigashi and K. Ohe, *Angew. Chem., Int. Ed.*, 2011, **50**, 11470.

8 Cyclizations involving 1,1-disubstituted alkenes have been reported previously but *only* in the context of cascade processes: (*a*) M. Kitamura, S. Zaman and K. Narasaka, *Synlett*, 2001, 974; (*b*) S. Zaman, M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1055. These processes represent rare examples of the use of this reaction manifold for $C(sp^3)$–N bond formation.

9 Leading references: (*a*) D. Seebach, M. Boes, R. Naef and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390; (*b*) L. E. Burgess and A. I. Meyers, *J. Am. Chem. Soc.*, 1991, **113**, 9858.

10 See: J. C. Killen, J. Leonard and V. K. Aggarwal, *Synlett*, 2010, 579 and references cited therein.

11 Stereoretentive [1,2] Stevens rearrangement: (*a*) K. W. Glaeske and F. G. West, *Org. Lett.*, 1999, **1**, 31; (*b*) E. Tayama, S. Nanbara and T. Nakai, *Chem. Lett.*, 2006, **35**, 478; (*c*) P. Tuzina and P. Somfai, *Org. Lett.*, 2009, **11**, 919; (*d*) Stereoretentive [2,3] Sommelet–Hauser rearrangement: E. Tayam and H. Kimura, *Angew. Chem., Int. Ed.*, 2007, **46**, 8869(*e*) For a related approach involving SO_2 extrusion from *N*-sulfonyl proline derivatives: F. Foschi, D. Landini, V. Lupi, V. Mihali, M. Penso, T. Pilati and A. Tagliabue, *Chem.–Eur. J.*, 2010, **16**, 10667(*f*) For a mechanistically distinct process that proceeds *via* an ammomiun ylide, see: T. Igarashi, E. Tayama, H. Iwamoto and E. Hasegawa, *Tetrahedron Lett.*, 2011, **52**, 1819.

12 N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien and I. Coldham, *J. Am. Chem. Soc.*, 2012, **134**, 5300.

13 W. R. Esmieu, S. M. Worden, D. Catterick, C. Wilson and C. J. Hayes, *Org. Lett.*, 2008, **10**, 3045 and references cited therein.

14 Chiral hydrogen-bond donor catalysts and chiral Brønsted acids promote enantioselective Pictet–Spengler type cyclizations to provide structures containing embedded α,α-disubstituted pyrrolidine motifs: (*a*) I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404; (*b*) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796; (*c*) C. A. Holloway, M. E. Muratore, R. I. Storer and D. J. Dixon, *Org. Lett.*, 2010, **12**, 4720; (*d*) A. Gómez-SanJuan, N. Sotomayor and E. Lete, *Tetrahedron Lett.*, 2012, **53**, 2157. Related intermolecular processes: (*e*) X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, *Eur. J. Org. Chem.*, 2011, 3060; (*f*) E. Aranzamendi, N. Sotomayor and E. Lete, *J. Org. Chem.*, 2012, **77**, 2986.

15 T. Kano, R. Sakamoto, H. Mii, Y.-G. Wang and K. Maruoka, *Tetrahedron*, 2010, **66**, 4900.

16 Intramolecular asymmetric hydroamination involving 1,1-dialkylated alkenes generates the corresponding pyrrolidines in up to 55% ee.: Y. Chapurina, H. Ibrahim, R. Guillot, E. Kolodziej, J. Collin, A. Trifonov, E. Schulz and J. Hannedouche, *J. Org. Chem.*, 2011, **76**, 10163.

17 (*a*) Chiral hypervalent iodine reagents promote enantioselective intramolecular aminooxygenation of 1,1-disubstituted styrene derivatives: U. Farid and T. Wirth, *Angew. Chem., Int. Ed.*, 2012, **51**, 3462(*b*) Copper catalyzed intramolecular aminooxygenation encompassing 1,1-dialkylated alkenes: P. H. Fuller, J.-W. Kim and S. R. Chemler, *J. Am. Chem. Soc.*, 2008, **130**, 17638.

18 Amino-thiocarbamate catalyzed bromoaminocyclization: L. Zhou, J. Chen, C. K. Tan and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2011, **133**, 9164.

19 Catalytic asymmetric coupling of alkenyl isocyanates and alkynes provides substrates containing embedded α,α-disubstituted pyrrolidines: (*a*) E. E. Lee and T. Rovis, *Org. Lett.*, 2008, **10**, 1231; (*b*) R. K. Friedman and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 10775.

20 Previous studies have established that oxime ester geometry does not affect the efficiency of cyclization and facile interconversion likely occurs at the stage of the putative imino-Pd(II) intermediate (see ref. 2).

21 Aldoxime esters are challenging substrates due to competing Beckmann rearrangement (for example, see ref. 8*b*).

22 Efforts to suppress isomerization are ongoing. This is a particularly problematic side reaction in Heck-type processes involving cycloalkenes: C. G. Hartung, K. Köhler and M. Beller, *Org. Lett.*, 1999, **1**, 709.

23 5-*exo* cyclization requires imino-palladation to occur with the opposite regioselectivity to that normally favoured for Heck-type reactions involving acrylates. For related examples in the conventional Heck reaction that involve cyclization onto the α-position of acrylamides, see: A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer and M. M. Weiss, *J. Am. Chem. Soc.*, 2003, **125**, 6261.

24 For a review on the synthesis of quaternary proline analogues, see: M. I. Calaza and C. Cativiela, *Eur. J. Org. Chem.*, 2008, 3427.

25 In our previous studies (see ref. 4) equilibration of the C-2 stereocentre of the product was observed under the cyclization conditions.

26 This ligand has been used in conventional asymmetric intramolecular Heck reactions: R. Imbos, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2002, **124**, 184.

27 The corresponding *cis*-olefinic isomers cyclize with lower enantioselectivity but with the same sense of stereoinduction.

28 For studies on the insertion of alkenes into N–Pd bonds see: (*a*) P. S. Hanley and J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 15661; (*b*) J. D. Neukom, N. S. Perch and J. P. Wolfe, *Organometallics*, 2011, **30**, 1269 and references cited therein.

29 Alkene insertion into the N–Pd bond of Pd(II)-sulfonamidates is reversible: P. B. White and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 18594. Product e.e. is constant over the course of the reactions outlined in Table 3.

30 (*a*) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346; (*b*) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486; (*c*) H. W. Lam, *Synthesis*, 2011, 2011.