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Palladium Catalyzed Cyclizations of Oxime Esters with 1,2-Disubstituted Alkenes: Synthesis of Dihydropyrroles

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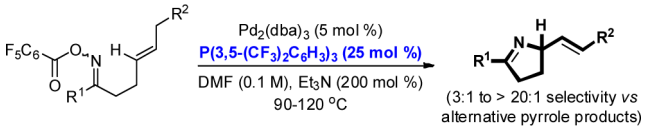
ABSTRACT



Pd-catalyzed cyclizations of oxime esters with 1,2-dialkylated alkenes provide an entry to chiral dihydropyrroles. Substrate and catalyst controlled strategies for selective product formation (vs alternative pyrroles) are outlined.

Robust and diversity oriented catalysis platforms are vital to drug discovery. Since the early 1990s, drug candidate library synthesis has relied heavily upon Pd(0)-catalyzed cross-couplings.[1] These processes convert readily available starting materials to a wide range of new products via a mechanistically common aryl-Pd(II) intermediate. This unified retrosynthetic blueprint, coupled with the operational simplicity and wide substrate scope offered by these methods, accounts for their popularity in medicinal chemistry. While particularly suited to the formation of new two-dimensional structures (e.g., biaryls), these processes are less applicable to the generation of chiral "3D" molecules. Consequently, over the past 20 years the average "chiral complexity" of drug candidate libraries has decreased significantly.[2−4] There is a growing realization that small molecule drug discovery programs can be enhanced by increasing the "chirality content" of compound libraries.[3,4] This, in turn, requires the development of catalysis platforms that not only retain the operational simplicity of Pd(0)-catalyzed cross-couplings but also provide direct access to privileged chiral scaffolds.

To address the issues outlined above, we have examined the possibility of exploiting palladated imines **1** as catalytic intermediates for accessing chiral N-heterocyclic systems (Scheme 1a).[5,6] Intermediates **1** are generated by oxidative addition of Pd(0) into the N−O bond of oxime esters and undergo Heck-like cyclization with pendant alkenes.[7,8] In general, this leads to heteroaromatic products (new $C(sp^2)$−N bond formed).[8c,d] However, in our previous studies, following 5-*exo* imino-palladation, the nature of the alkene acceptor controlled the direction of β-hydride elimination to generate *chiral* products **2a,b** (new $C(sp^3)$−N bond formed). The ligand requirements for these processes contrast those of the conventional Heck reaction, and we have found that electron deficient triarylphosphines are effective.[5,6]

Related cyclizations involving 1,2-dialkylated alkenes are known to generate preferentially pyrrole products and *do not* provide access to chiral targets. Narasaka has shown that cyclization of **3**, using PPh_3 as the ligand, generated pyrrole **4** with 8:1 selectivity over dihydropyrrole **5** (Scheme 1b).[8a,b,9] Selective product generation requires strategies to control the direction of β-hydride elimination

(1) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(2) "Compound chirality" correlates to the percentage of $C(sp^3)$ centers in a compound: Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405.

(3) There is a pressing demand for the development of efficient methodologies that target low molecular weight (200−350 Da), 3D (sp^3-rich) scaffolds: Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114.

(4) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(5) Faulkner, A.; Bower, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1675.

(6) Faulkner, A.; Scott, J. S.; Bower, J. F. *Chem. Commun.* **2013**, *49*, 1521.

(7) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(8) (a) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, *28*, 45. (b) Tsutsui, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451. For reviews, see: (c) Kitamura, M.; Narasaka, K. *Chem. Rec.* **2002**, *2*, 268. (d) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. Pentafluorobenzoyl oxime esters are usually employed for these processes because they are stable to Beckmann rearrangement.

(9) As far as we are aware, this is the only example where cyclization involving a linear 1,2-dialkylated alkene generates any dihydropyrrole.

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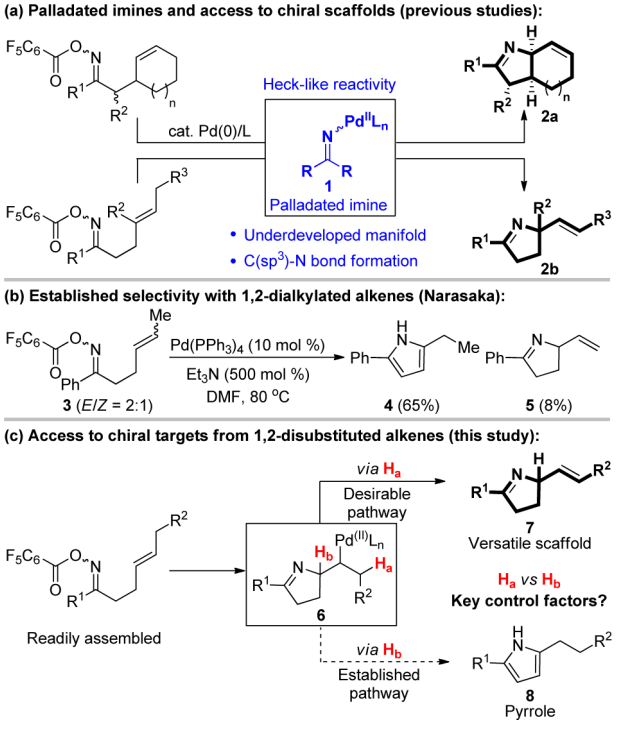
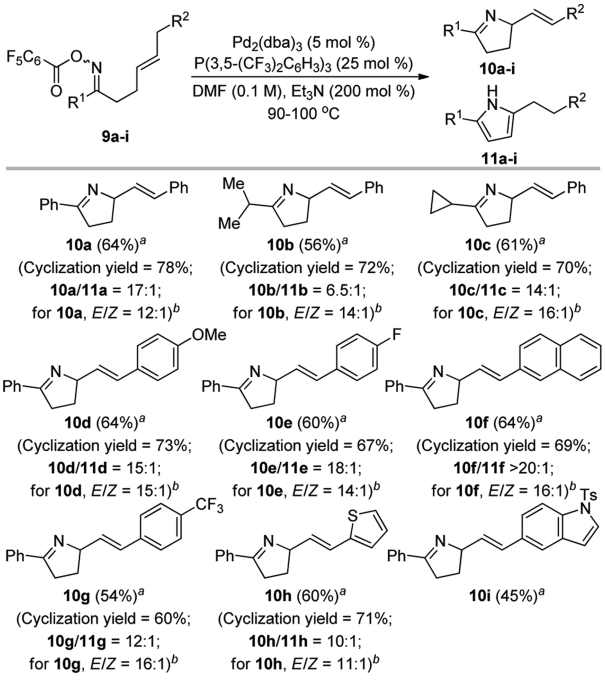
(H_a vs H_b) at the stage of alkyl-Pd(II) intermediate **6** (Scheme 1c). Elimination via H_a accesses directly chiral target **7**, whereas elimination via H_b affords an enamine intermediate that undergoes isomerization to the undesired pyrrole **8**.[8,10] In this study we outline (a) substrate and (b) catalyst controlled strategies that achieve selectivity for chiral products **7**. This provides a new class of cyclization and enhances further the scope of this catalysis platform for chiral scaffold generation. *The selectivity issues addressed here did not apply to our earlier work where the constraints of the alkene acceptor predetermined β-hydride elimination directionality*.[5,6]

Scheme 1



We initially explored scenarios where R^2 = aryl because secondary orbital interactions ($\pi_{(aryl)} \rightarrow \sigma^*_{(C-H)}$) should weaken the C−$H_a$ bond of **6** and increase its propensity to β-hydride elimination.[11] In the event, **9a** (R^2 = Ph) underwent efficient and selective cyclization, when treated with a P(3,5-$(CF_3)_2C_6H_3)_3$ ligated Pd(0)-system, to provide a 17:1 mixture of **10a**:**11a** in 78% overall yield, as determined by ^{1}H NMR analysis of the crude mixture (Scheme 2). **10a** was formed as a 12:1 mixture of geometric isomers, and chromatographic purification afforded readily the major *E*-isomer in 64% yield. The product ratio of **10a**:**11a** was constant over the course of the cyclization process, and resubmission of **10a** to the reaction conditions did not result in significant isomerization to **11a**.[12] These observations are indicative of kinetic product selection. In our previous studies, we delineated the scope of this type of process with respect to substituents on the oxime.[5,6] The present class of cyclization demonstrates similar tolerances, and alkyl and cyclopropyl substituted systems **9b**/**c** underwent smooth cyclization to afford **10b** and **10c** respectively.[13] In both cases, the phenyl group enforced good selectivity for the chiral targets over the corresponding pyrroles **11b/c**.

Scheme 2. Scope of the R^1 and R^2 Groups



[a] Isolated yield of the major *E*-alkene isomer. [b] Total cyclization yields and selectivities were determined by ^{1}H NMR of the crude reaction mixture (vs trimethoxybenzene as a standard).

The success of these cyclizations mirrors our previous observations that electron deficient Pd-systems enhance reaction efficiency.[5,6] This is likely due to beneficial effects upon the properties of the key imino-Pd(II) intermediate **1**. Presumably, an electron deficient Pd(II)-center enhances σ-donation from the imine moiety which increases the N−Pd bond strength and decreases N-lone pair basicity. This then suppresses competitive protodepalladation to the corresponding NH imine. Additionally, a more electrophilic Pd-center may increase the rate of imino-palladation via increased coordination of the pendant alkene.[14] By way of comparison, use of PPh_3 as the ligand for the cyclization of **9a** provided a 12:1 mixture of **10a**:**11a** but in only 45% overall yield. Here, significant quantities of the corresponding ketone

(10) Isomerization may be promoted either by acid generated during the aza-Heck process or by Pd(II)-hydride.

(11) For studies that delineate factors responsible for β-hydride elimination selectivity from alkyl-Pd(II) intermediates, see: (a) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692. (b) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981.

(12) Product ratios have been determined by ^{1}H NMR at various time points during the cyclization of **9a**.

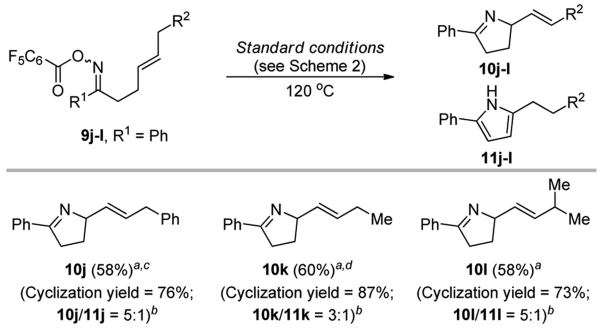
(13) Aldoxime esters are challenging substrates due to competitive Beckmann rearrangement to the corresponding nitrile. Studies to address this issue are ongoing.

(14) Electron-deficient ligand systems may also accelerate migratory insertion of the alkene. For studies on alkene insertion into Pd-NPh_2 bonds, see: (a) Hanley, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15661. See also: (b) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *Organometallics* **2011**, *30*, 1269 and references cited therein.

were isolated, and our studies indicate that this forms by hydrolysis of the NH imine protodepalladation product.[15]

We have undertaken an assessment of the scope of the aryl moiety to determine its effects upon product selection (Scheme 2).[16] A range of electron-rich and -poor aryl groups gave good selectivity for the target dihydropyrroles **10d**–**i** (10:1 to >20:1 vs **11d**–**i**).[17] In all cases, the major *E*-alkene isomer was isolated easily in moderate to good yield (45–64%). For **10i**, the crude reaction mixture was not readily analyzed by ^{1}H NMR and so *in situ* selectivities have not been determined.

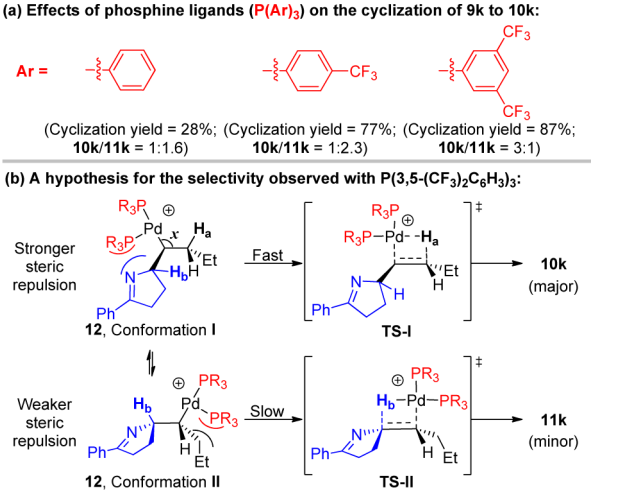
Scheme 3. Cyclizations Generating 1,2-Dialkylated Alkenes



[a] Isolated yield of the major *E*-alkene isomer; only *E*-alkene products were observed. [b] Total cyclization yields and selectivities were determined by ^{1}H NMR of the crude reaction mixture (vs trimethoxybenzene as a standard). [c] Isolated as a 6:1 mixture of alkene regioisomers. [d] Isolated as a 12:1 mixture of alkene regioisomers.

In the cyclizations presented in Scheme 2, product selectivity is dictated by the strategic installation of an aryl group although the ligand may also play a role (*vide infra*). Consequently, in cases where C–H_a is not benzylic (see Scheme 1c), it was unclear whether cyclizations could be selective for chiral products. Pleasingly, using the same reaction conditions as outlined in Scheme 2, cyclization of **9j**–**l** afforded dihydropyrroles **10j**–**l** with between 3:1 and 5:1 selectivity over the undesired pyrroles **11j**–**l** (Scheme 3). Here, the lower product selectivities are offset by the more efficient cyclizations (73–87% total cyclization yield), and so the targets could still be isolated in synthetically useful yields (58–60%).[18] In the case of **10j**, some alkene isomerization to the corresponding styrenyl derivative was observed (6:1 regioisomer ratio).[19] As before, product ratios were largely constant over the time frame of the reaction, which supports kinetic product selection.

Scheme 4



In the cyclizations outlined in Scheme 3, the R^2 group seemingly provides no significant activation of C–H_a (vs C–H_b) for β-hydride elimination (see Scheme 1c). We have carried out an assay of ligand effects (PPh_3 vs P(4-$CF_3C_6H_4)_3$ vs P(3,5-$(CF_3)_2C_6H_3)_3$) on the cyclization of **9k** to uncover the origins of product selection in these cases (Scheme 4a). As expected, overall cyclization efficiency improves as the ligand becomes more electron deficient. However, both PPh_3 and P(4-$CF_3C_6H_4)_3$ afforded predominantly the undesired pyrrole **11k**.[20] These data indicate that P(3,5-$(CF_3)_2C_6H_3)_3$ is able to enforce selective β-hydride elimination because of the steric effects of the *meta*-CF_3 substituents (i.e., larger cone angle vs P(4-$CF_3C_6H_4)_3$).[21] It is generally accepted that β-hydride elimination proceeds through a planar 4-centered transition state.[22] This requires alkyl-Pd(II) intermediate **12** to adopt transiently a high energy conformation where angle *x* deviates from ideality (Scheme 4b). We suggest that selective β-hydride elimination is facilitated by the interplay of the sterically demanding ligand system (PR_3 = P(3,5-$(CF_3)_2C_6H_3)_3$) with the bulky dihydropyrrole moiety (vs the smaller propyl group) (conformation **I** vs **II**). In conformation **I**, steric repulsion between these two groups is alleviated by progressing to **TS-I** en route to the desired dihydropyrrole **10k**. In conformation **II**, the smaller propyl group suffers less severe steric interactions with the ligand, and so progression to **TS-II**, and ultimately **11k**, is

(15) In the absence of palladium, pentafluorobenzoyl oxime esters are stable to the reaction conditions (see ref 5).

(16) For the synthesis of oxime esters employed here see the Supporting Information. Oxime ester geometry does not affect the efficiency of cyclization, and facile interconversion likely occurs at the stage of the imino-Pd(II) intermediate (see ref 8).

(17) A strong trend between the electronics of the aryl moiety and product selectivity is not evident. However, the importance of the aryl group is underscored by comparing the cyclization results of **9a** and **9k** using PPh_3 as the ligand (12:1 vs 1:1.6 selectivity; see text and Scheme 4).

(18) We have also explored the cyclization of compound **3**. Under our optimized conditions we have been able to obtain a 62% overall yield and 1:3 ratio of **4**:**5**. However, control experiments indicate that dihydropyrrole **5** is not stable to the reaction conditions and so yields and selectivities are variable in this particular case.

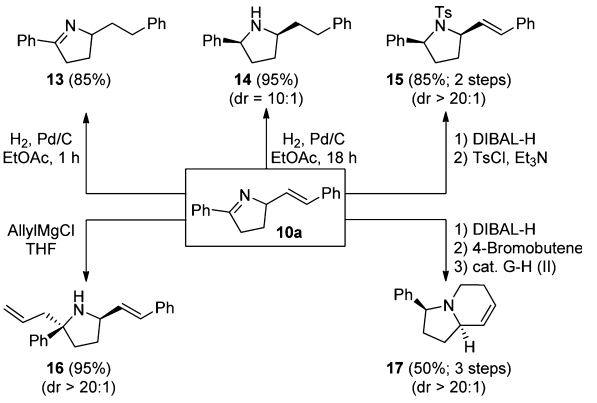
(19) The regioisomer ratio of **10j** is constant over the course of the reaction suggesting that isomerization occurs prior to dissociation of Pd–H. For related observations, see: Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.

(20) In all cases, the ratio of **10k**:**11k** was largely constant over the time frame of the reaction, thereby supporting kinetic product selection.

(21) The cone angle for P(3,5-$(CF_3)_2C_6H_3)_3$ has been determined as 160° *vs* 155° for PPh_3 and P(4-$CF_3C_6H_4)_3$: Howell, J. A. S.; Fey, N.; Lovatt, J. D.; Yates, P. C.; McArdle, P.; Cunningham, D.; Sadeh, E.; Gottlieb, H. E.; Goldschmidt, Z.; Hursthouse, M. B.; Light, M. E. *J. Chem. Soc., Dalton Trans.* **1999**, 3015.

(22) Koga, N.; Obara, S.; Kitaura, K.; Morokuma, K. *J. Am. Chem. Soc.* **1985**, *107*, 7109.

Scheme 5. Synthetic Manipulations of Cyclization Product **10a**



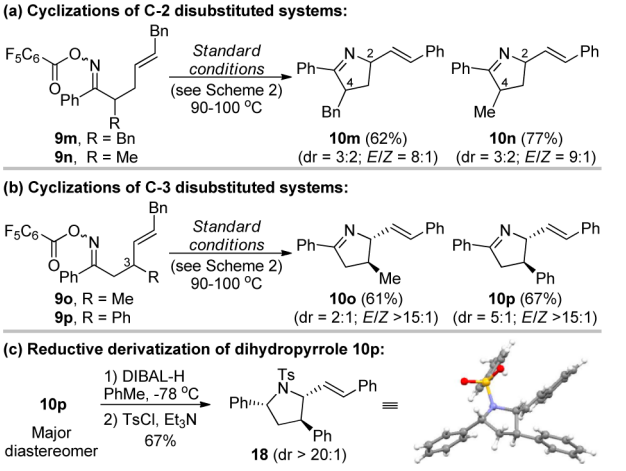
kinetically less favorable.[23] The steric and electronic properties of $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ are able therefore to effect *both* efficient cyclization *and* selective chiral product formation.

The dihydropyrrole products described here are well suited to further manipulations, and we have demonstrated this using adduct **10a** (Scheme 5). Mild hydrogenation of the alkene moiety afforded **13** in good yield. Longer hydrogenation times resulted in the reduction of both the alkene and imine to generate pyrrolidine **14** (10:1 dr). Reduction of solely the imine moiety was achieved using DIBAL-H, and, after N-tosylation, pyrrolidine **15** was isolated in greater than 20:1 diastereoselectivity. The diastereofacial bias associated with **10a** makes it well suited to other imine 1,2-addition processes. Exposure to allyl magnesium chloride afforded **16**, which contains a challenging quaternary amino-stereocenter, in excellent diastereoselectivity. Access to more complex heterocyclic scaffolds is also possible. For example, diastereoselective imine reduction of **10a**, followed by N-alkylation with 4-bromobutene, enabled an efficient ring closing metathesis reaction to generate indolizidine bicycle **17**.

We have also explored cyclizations of more heavily substituted systems. Cyclizations of **9m** and **9n** proceeded smoothly to generate targets **10m** and **10n** in good yield (Scheme 6a). Here, the more bulky dihydropyrrole moiety (vs **9a** to **10a**) enforces perfect selectivity for β-hydride elimination and no traces of pyrrole products were observed (*cf.* Scheme 4b). Enhancement of the diastereomer ratios of **10m** and **10n** by epimerization of the C-4 stereocenter was investigated without success. Under equilibrating conditions (e.g., HCl/MeOH or NaOMe/MeOH) no diastereoenrichment was evident. Alternative strategies, based upon the formation of an aza-enolate and kinetic reprotonation, were complicated by the relatively high acidity of the C-2 proton. Substitution at C-3 of the starting material shows more promise for stereoselective synthesis

(23) We favor a cationic aza-Heck pathway as depicted in Scheme 4b because electron deficient leaving groups are required for efficient cyclization. The corresponding benzoyl oxime esters are active for oxidative addition (see: Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342) but provide traces of cyclization product under the conditions described here.

Scheme 6



(Scheme 6b). In the cyclizations of **9o** and **9p** the size of the C-3 substituent controls the diastereoselectivity associated with dihydropyrroles **10o** and **10p**. The *trans*-isomer was favored in both cases, but the larger phenyl group provided greater levels of diastereocontrol (5:1 dr for R = Ph vs 2:1 dr for R = Me). Once again, these cyclizations were chemically efficient and exhibited high selectivity for dihydropyrroles **10o** and **10p** over the corresponding pyrroles (> 20:1 selectivity). Diastereoselective reduction of the imine moiety (DIBAL-H) of the major diastereomer of **10p** provided, after N-tosylation, trisubstituted pyrrolidine **18** (characterized by X-ray diffraction) (Scheme 6c).

The present study outlines, for the first time, substrate and, perhaps more importantly, catalyst controlled strategies to reverse the established product selectivity for aza-Heck cyclizations of oxime esters with 1,2-dialkylated alkenes. The net result is a direct and flexible entry to chiral dihydropyrrole targets that are then well suited to further elaboration. In combination with earlier work, we have now demonstrated that a simple and commercial catalyst system enables efficient access to a wide range of chiral pyrrolidine derivatives. These studies will feed into the design of effective chiral ligands and the development of complexity generating cascade reactions.

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Supporting Information Available. Experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.