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Copper catalyzed Heck-like cyclizations of oxime esters†

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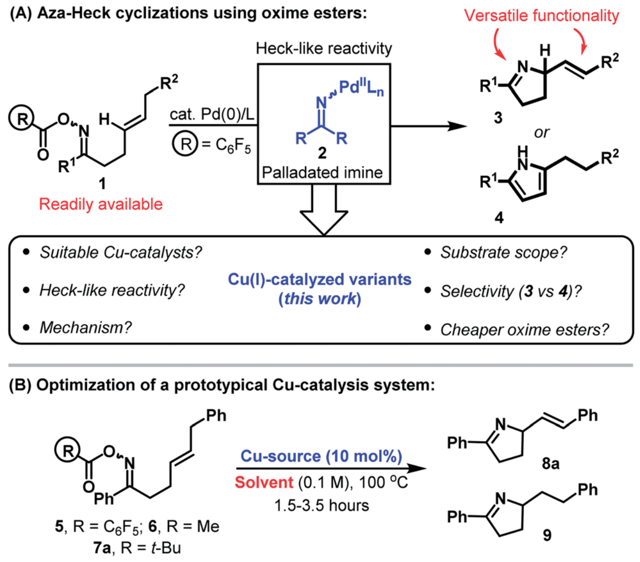
Copper catalyzed Heck-like cyclizations of oxime esters are described. Mechanistic studies indicate a reaction pathway that proceeds *via* the generation and cyclization of an intermediate that possesses iminyl radical character. To the best of our knowledge, this work encompasses the first examples of Cu-catalyzed aza-Heck reactions that proceed *via* oxidative initiation at nitrogen to generate products containing a new alkene. This new protocol is also an effective alternative to Pd-based systems and highlights the value of replacing precious metal catalysts with cheaper and more sustainable variants.

Introduction

The advent of catalysis based upon the oxidative generation and capture of aryl-Pd(II) intermediates has had a profound impact upon the field of organic synthesis. Accordingly, it is estimated that 20% of C–C bond forming reactions employed in the pharmaceutical sector are reliant upon this technology.[1] Given the privileged position of nitrogen in drug discovery, it is surprising that related processes involving the oxidative generation and capture of aza-Pd(II) species have been slow to emerge.[2] Seminal studies by Narasaka demonstrated that Pd(0)-catalysts undergo oxidative addition into the N–O bond of *O*-pentafluorobenzoyl oximes **1** to generate imino-Pd(II) intermediates **2** (Scheme 1A).[3,4] The reactivity of these species mirrors that of their aryl counterparts and migratory insertion of pendant alkenes provides an aza-variant of the Heck reaction.[5] This reactivity manifold is heavily underdeveloped and our studies have focused upon providing efficient catalysis systems that generate synthetically versatile chiral *N*-heterocyclic scaffolds (*e.g.* **3** rather than **4**).[6,7]

There is a growing interest in replacing Pd(0)-catalysts with more abundant and isoelectronic Cu(I)-variants.[2,8] Cu(I)-catalyzed aza-Stille and aza-Suzuki cross-couplings involving oxime esters have been reported by Liebeskind *et al.* but the corresponding aza-Heck processes have not been developed.[9,10] In this report we detail the discovery and mechanism of a Cu-catalyzed protocol for the aza-Heck cyclization of oxime esters. This provides a direct and economic alternative to Pd-based systems, and also addresses selectivity issues that hampered our earlier work (*e.g.* β-hydride elimination selectivity to **3** *vs.* **4**, Scheme 1A).[6a] To the best of our knowledge, the present study also encompasses the first examples of copper-catalyzed aza-Heck reactions that furnish products containing a new alkene by oxidative initiation at nitrogen (*i.e.* in terms of



Entry	R	Cu-source	Solvent	Yield (8a:9)^{a}
1	C_6F_5	CuOAc	DMF (0.1 M)	73% (73:27)
2	C_6F_5	$Cu(OAc)_2$	DMF (0.1 M)	56% (93:7)
3	C_6F_5	$Cu(acac)_2$	DMF (0.1 M)	21% (100:0)
4	C_6F_5	$Cu(OTf)_2$	DMF (0.1 M)	34% (100:0)
5	C_6F_5	$Cu(2\text{-ethylhexanoate})_2$	DMF (0.1 M)	70% (90:10)
6	C_6F_5	$Cu(2\text{-ethylhexanoate})_2$	PhCN (0.1 M)	79% (100:0)
7	Me	$Cu(2\text{-ethylhexanoate})_2$	PhCN (0.1 M)	65% (100:0)
8	*t*-Bu	$Cu(2\text{-ethylhexanoate})_2$	PhCN (0.1 M)	78% (100:0)

Scheme 1 Aza-Heck cyclizations of oxime esters and the development of a Cu-catalyzed protocol. ^{a} Isolated yield (product ratios were determined by ^{1}H NMR).

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substrate/product structure, the process is an exact aza-variant of the conventional Heck reaction where the oxime ester takes the place of the aryl halide).[10,11]

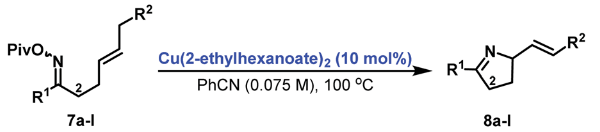
Results and discussion

At the outset of our studies, the prospect of replacing Pd-based systems with Cu(I)-variants was considered tentative. The generation of aza-copper intermediates by oxidative addition into N–O bonds has been invoked in a range of amination processes.[9,10,11d,g–j] However, reactions involving alkenes provide 1,2-difunctionalization processes and do not afford new alkene containing products.[11d,e,i] Consequently, the viability of a copper-catalyzed aza-Heck cycle that incorporates the key steps of oxidative initiation and β-hydride elimination was unclear. Our preliminary investigations involved exposing DMF solutions of *O*-pentafluorobenzoyl oxime **5** to a variety of commercial Cu-salts (Scheme 1B). Gratifyingly, both CuOAc and $Cu(OAc)_2$ provided the desired product **8a** with *complete* selectivity over the alternative pyrrole product (entries 1 and 2; *cf.* Scheme 1A). However, **8a** was accompanied by significant quantities of adduct **9**, which contains a saturated side chain. $Cu(acac)_2$ and $Cu(OTf)_2$ both suppressed the formation of this byproduct but provided only modest yields of the target **8a** (entries 3 and 4). However, good selectivity and yield was obtained using the more soluble $Cu(2\text{-ethylhexanoate})_2$, which provided adduct **8a** in 79% yield and as the only observable product when PhCN was used as solvent (entry 6). Pleasingly, this protocol also tolerates less activated oxime esters and acetyl and pivaloyl variants **6** and **7a** cyclized efficiently to provide **8a** in 65% and 78% yield respectively (entries 7 and 8). This facet is particularly striking and is in stark contrast to our work with Pd-systems, where *O*-pentafluorobenzoyl oximes are a requirement for efficient cyclization.[6]

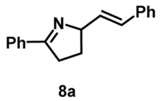
The ability to use acetyl or pivaloyl oxime esters is beneficial from the viewpoint of cost, starting material stability and atom economy. Consequently, we elected to explore scope using a range of pivaloyl oxime ester substrates **7a–l** that possess pendant 1,2-disubstituted alkenes (Table 1). In the majority of cases cyclization proceeded smoothly to generate the target dihydropyrroles **8a–j** in good to excellent yield and with *complete* selectivity over the alternative pyrrole products (*cf.* Scheme 1A). A range of alkyl and aryl oxime esters can participate in this process and cyclization efficiency is not adversely affected by sterically demanding oximes (*e.g.* **7d**). The successful cyclization of **7c**, which possesses a potentially problematic Lewis basic pyridyl moiety, is particularly noteworthy. For ease of comparison, and where determined, the results of the cyclization of the analogous *O*-pentafluorobenzoyl oxime esters with our best Pd-based systems are included.[6a] Note that in many cases (*e.g.* **8g** and **8i**) these Pd-catalyzed processes suffered from competing formation of significant quantities of pyrrole products (the ratios of dihydropyrrole to pyrrole products are given in parentheses). Another limitation of Pd-based systems is that aryl bromides are not well tolerated.[6c] For the copper catalyzed protocol this is not an issue and cyclization of **7h** provided **8h** in good yield and with Ar–Br bond still intact. This then opens up the option to modify further the initial scaffold using conventional Pd(0)-catalyzed cross-coupling reactions. Certain limitations are evident however, and alkynyl and aldoxime based systems **7k** and **7l** did not cyclize efficiently. In the former case the issue was the sensitivity of the product **8k** to conjugate addition by *in situ* generated pivalic acid. In the latter case (**8l**), decomposition of the oxime ester to the corresponding nitrile predominated.[12]

We have also explored cyclizations of more heavily substituted 1,1-disubstituted alkenes **7m–r** to provide adducts **8m–r** that possess challenging quaternary amino-substituted stereocenters (Table 2). For **7m–q** cyclization was efficient independent of the nature of the alkene. For example, cyclization of **7m**, which involves an electron deficient acrylate, provided **8m** in 76% yield. Notably, under our best palladium catalyzed conditions, the analogous *O*-pentafluorobenzoyl oxime ester cyclized in only 31% yield.[6b] Some limitations do exist with respect to the alkene and cyclization of **7r**, which generates a benzylic C–N bond, was not efficient. Here, competing formation of the corresponding ketone (the formal hydrolysis product of the oxime ester) was problematic.[13]

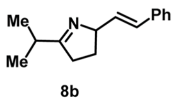
Table 1 Cyclizations involving 1,2-disubstituted alkenes



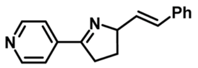
7a, R^1 = Ph, R^2 = Ph	**7b**, R^1 = *i*-Pr, R^2 = Ph	**7c**, R^1 = 4-Pyridyl, R^2 = Ph
7d, R^1 = *t*-Bu, R^2 = Ph	**7e**, R^1 = 2-Naphthyl, R^2 = Ph	**7f**, R^1 = *n*-Bu, R^2 = Ph
7g, R^1 = Ph, R^2 = Et	**7h**, R^1 = 4-BrC_6H_4, R^2 = Et	**7i**, R^1 = Ph, R^2 = H
7j, R^1 = Ph, R^2 = H[a]	**7k**, R^1 = 1-Pentynyl, R^2 = Et	**7l**, R^1 = H, R^2 = Ph



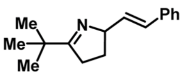
8a
Cu: 81% Yield
Pd: 64% Yield (17:1)[b]



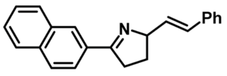
8b
Cu: 65% Yield
Pd: 64% Yield (7:1)[b]



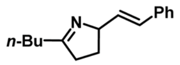
8c
Cu: 65% Yield[c]



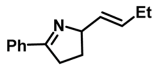
8d
Cu: 69% Yield



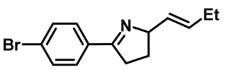
8e
Cu: 67% Yield



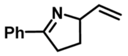
8f
Cu: 54% Yield



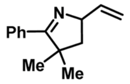
8g
Cu: 70% Yield
Pd: 60% Yield (3:1)[b]



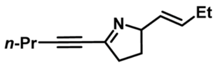
8h
Cu: 64% Yield



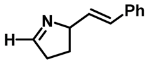
8i
Cu: 64% Yield
Pd: 46% Yield (3:1)[b]



8j
Cu: 82% Yield



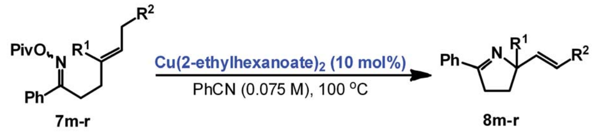
8k
Cu: 26% Yield



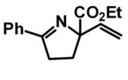
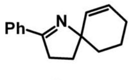
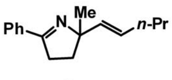
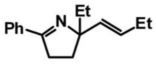
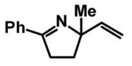
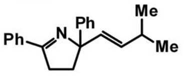
8l
Cu: <10% Yield

[a] **7j** was dimethylated at C-2. [b] Yield using optimized Pd-systems and the corresponding *O*-pentafluorobenzoyl oxime ester. The ratio of product *vs.* alternative pyrrole is given in parentheses (see ref. 6*a*). [c] The reaction was run at 120 °C.

Table 2 Cyclizations involving 1,1-disubstituted alkenes

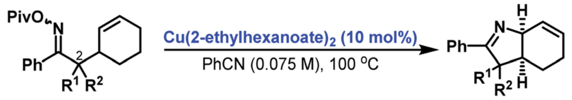


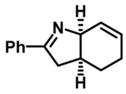
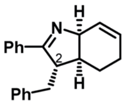
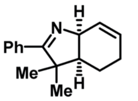
7m $R^1 = CO_2Et$, $R^2 = H$	**7n**, $R^1 = R^2 = \text{-(CH}_2)_3\text{-}$	**7o**, $R^1 = Me$, $R^2 = n\text{-Pr}$
7p, $R^1 = Et$, $R^2 = Et$	**7q**, $R^1 = Me$, $R^2 = H$	**7r**, $R^1 = Ph$, $R^2 = i\text{-Pr}$

 **8m** **Cu:** 76% Yield[a] **Pd:** 31% Yield[b]	 **8n** **Cu:** 72% Yield **Pd:** 84% Yield[b,c]	 **8o** **Cu:** 90% Yield **Pd:** 80% Yield[b]
 **8p** **Cu:** 86% Yield **Pd:** 90% Yield[b]	 **8q** **Cu:** 96% Yield **Pd:** 83% Yield[b]	 **8r** **Cu:** 35% Yield **Pd:** 70% Yield[b]

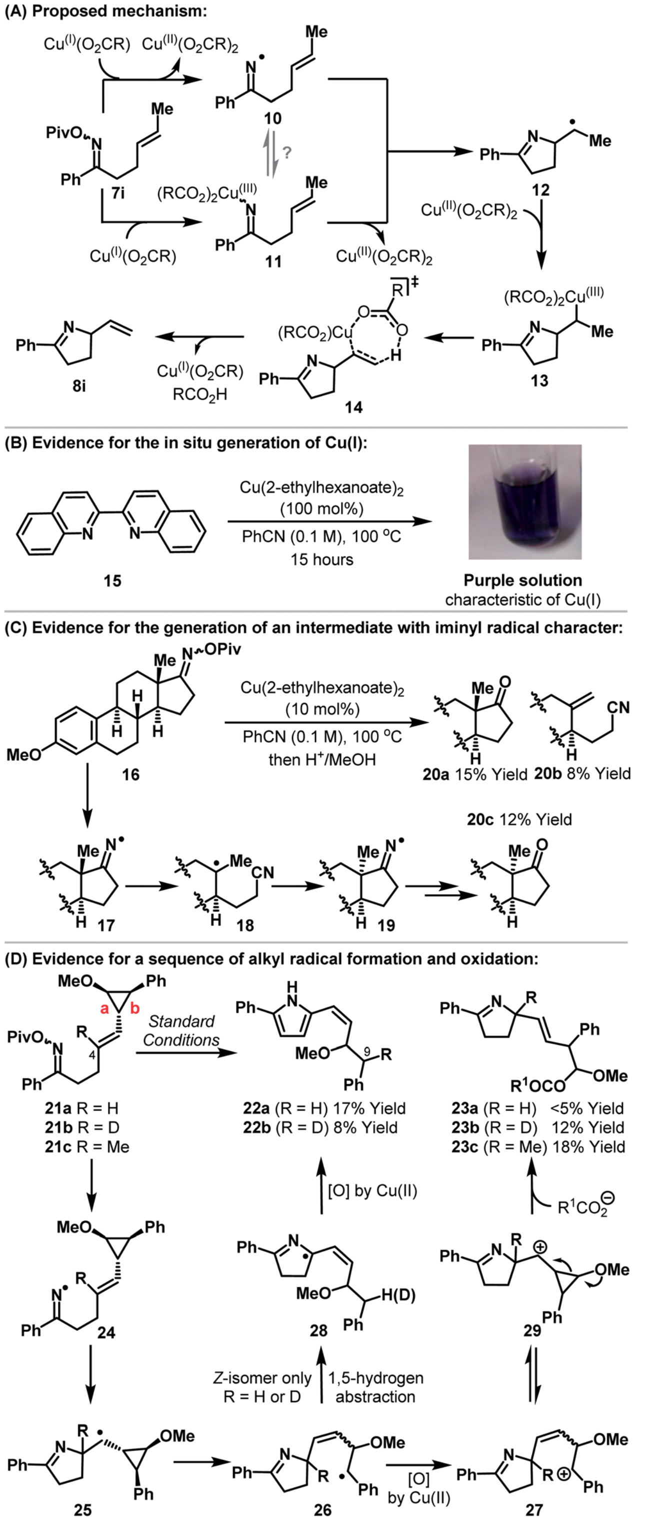
[a] The reaction was run at 120 °C. [b] Yield using optimized Pd-systems and the corresponding *O*-pentafluorobenzoyl oxime ester (see ref. 6*b*). [c] Isolated as a 5 : 1 mixture of alkene regioisomers.

Table 3 Cyclizations involving cyclic alkenes



7s, $R^1 = H$, $R^2 = H$	**7t**,[a] $R^1 = H$, $R^2 = \text{Benzyl}$	**7u**, $R^1 = Me$, $R^2 = Me$
 **8s** **Cu:** 95% Yield **Pd:** 93% Yield[b]	 **8t** **Cu:** 55% Yield (10:1 d.r.) **Pd:** 76% Yield[b] (>19:1 d.r.)	 **8u** **Cu:** 75% Yield **Pd:** 89% Yield[b]

[a] **7t** was a 1 : 1 mixture of diastereomers at C-2. [b] Yield using optimized Pd-systems and the corresponding *O*-pentafluorobenzoyl oxime ester (see ref. 6*c*).



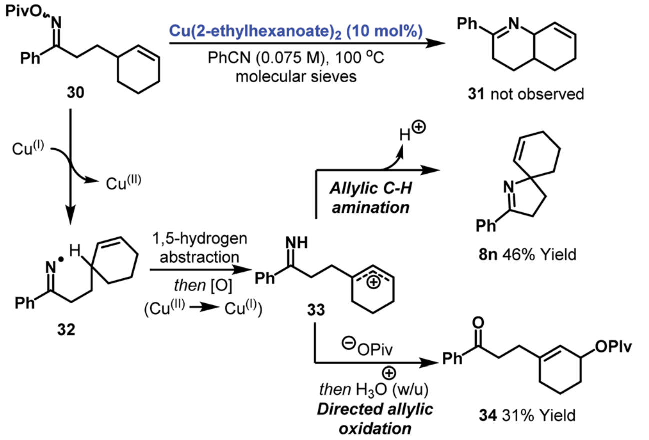
Scheme 2 Mechanistic analysis and supporting studies.

Cyclizations onto pendant cyclohexenes provide a direct entry to *cis*-configured heterobicycles **8s–u** (Table 3). Here, reaction efficiency is comparable to our best Pd-based systems.[6c] In the case of **7t**, cyclization of a 1 : 1 mixture of diastereomers at C-2 provided **8t** as a 10 : 1 mixture of diastereomers at C-2. By analogy with our earlier work,[6c] we favor epimerization of the C-2 stereocenter under the acidic reaction conditions *after* cyclization to provide the thermodynamically favored diastereomer **8t**.

Our studies indicate that the copper-catalyzed processes described here are distinct from Pd-catalyzed variants and most likely do not involve migratory insertion of the alkene component into an N–Cu bond. A working mechanistic hypothesis is outlined in Scheme 2A. *In situ* generation of Cu(I)-carboxylate triggers cyclization to alkyl radical **12**. Pathways proceeding *via* either the generation of iminyl radical **10** or imino-Cu(III) intermediate **11** can be envisaged; in the latter case cyclization occurs by homolytic cleavage of the N–Cu bond.[14,15] It is well established that alkyl radicals can undergo oxidative elimination upon exposure to cupric acetate.[16] Accordingly, trapping of alkyl radical **12** with Cu(II)-carboxylate[17] provides alkyl-Cu(III) intermediate **13**. Alkyl-Cu(III) species have significant carbocationic character and can undergo *syn*-elimination (as depicted) to generate alkene **8i**.[16] This process is known to favor formation of the less hindered alkene, which accounts for the observed regioselectivities. The minor quantities of saturated product (*e.g.* **9**) obtained during optimization are presumably the result of hydrogen atom abstraction by **12** from elsewhere in the reaction system.[18] Alkyl-Cu(III) carboxylates (*i.e.* **13**) are mechanistically promiscuous and undergo β-hydride elimination *or* reductive elimination of carboxylate (to generate an alkyl-O(CO)R bond) *or* solvolysis to a carbocation (which might lead to Ritter-type products).[16] It is noteworthy that the current protocol gives high selectivity for alkene **8i** over byproducts derived either from these latter two pathways or from alkyl radical **12**.

A series of experiments underpin the mechanism proposed in Scheme 2A. Heating a PhCN solution of Cu(II)(2-ethylhexanoate)$_2$ in the presence of cuproin **15** resulted in the *slow* evolution of a deep purple solution (Scheme 2B).[19] This is indicative of the formation of a Cu(I)–cuproin complex and is supportive of either reduction or disproportionation of Cu(II)(2-ethylhexanoate)$_2$ under the reaction conditions.[20] By way of comparison, exposure of Cu(I)OAc to analogous conditions resulted in the *immediate* formation of a similar purple solution (see the ESI†). The generation of an intermediate with significant iminyl radical character is evidenced using estrone derived oxime ester **16** (Scheme 2C). Upon exposure to Cu(II)(2-ethylhexanoate)$_2$ and subsequent hydrolysis (MeOH, aq. HCl) the formation of adducts **20a–c** was observed. The inversion of the methyl substituted stereocenter in **20c** is accounted for by reversible β-scission from iminyl radical **17** (or an imino-Cu(III) species with radical-like character; not depicted), which leads to the thermodynamically favored diastereomer **19**.[21,22] Multiple mechanistic pathways, including those based upon iminyl radicals, can account for the formation of **20a/b**.[23]

To gain insights into the sequence of events after cyclization we have prepared cyclopropyl substrates **21a–c** (Scheme 2D). The substituted cyclopropane moiety is based upon Newcomb's design, which enables differentiation of radical *vs.* carbocation-like intermediates;[24] the latter would be indicative of pathways involving either alkene imino-cupration[16] or Lewis acid activation of the oxime ester.[10] Because the mechanism proposed in Scheme 2A involves both radical *and* carbocation-like intermediates, careful analysis of the products arising from cyclization of all three substrates **21a–c** was required. Cyclization of **21a** resulted in the formation of the unstable *cis*-configured vinyl pyrrole **22a** as the only observable product. This indicates that alkyl radical **25** forms and then rearranges, *via* cleavage of bond b, to the more stable benzylic radical **26**. 1,5-Hydrogen atom abstraction (*cis*-alkene isomer of **26** only)[25] then leads, after *in situ* oxidation by Cu(II)(carboxylate)$_2$, to pyrrole **22a**. Alternatively, benzylic oxidation of **26** followed by 1,5-hydride transfer (not depicted) could also generate **22a**. Cyclization of *deuterio*-variant **21b** revealed full deuterium transfer from C-4 of the starting material to C-9 of product **22b**. In this case, the formation of adduct **23b**, which results from cleavage of bond a, was *also* observed. For methyl-substituted analogue **21c**, only product **23c** was observed. Presumably, at the stage of **26**, Cu(II)(carboxylate)$_2$ promotes oxidation to benzylic carbocation **27** [16] which undergoes ring-closure to cyclopropyl stabilized carbocation **29**.[26] Methoxy-triggered cleavage of bond a generates an oxocarbenium ion which is trapped by carboxylate ($R^1CO_2^-$ = pivalate or 2-ethylhexanoate) to afford adduct **23b,c** (R = D or Me).[27] Overall, these results support initial cyclization to an alkyl radical and subsequent Cu(II)-promoted oxidation to an alkene. A pathway based upon migratory insertion of the alkene into the N–Cu bond of an imino-Cu(III) intermediate is discounted as this should lead solely to dihydropyrroles **23a–c**. An ionic mechanism, involving Lewis acid activation of the oxime ester by Cu(II)(carboxylate)$_2$, is not consistent with the results presented here.



Scheme 3 Attempted 6-ring cyclization and mechanistic pathways to allylic C–H functionalization products.

As further support for the mechanism outlined in Scheme 2A, it is pertinent to consider the results of an attempted 6-ring cyclization (Scheme 3). Exposure of oxime ester **30** (the homologue of **7s**) to optimized conditions did not result in the formation of Heck-type product **31**. Instead, adducts **8n** and **34** were generated in 46% and 31% yield respectively. The formation of these products can be accounted for by copper-catalyzed generation of iminyl radical **32** (or an imino-Cu(III) species with radical like character). 1,5-Hydrogen atom abstraction then generates an allylic radical which undergoes copper-catalyzed oxidation to the corresponding cation **33**. This is trapped by either the imine moiety or pivalate to provide **8n** or **34**. These processes represent interesting approaches to allylic C–H amination or oxidation. The generation of **8n** can be viewed as a copper-catalyzed variant of the Hofmann–Löffler–Freytag reaction and further investigations into the scope of this process are ongoing.[28–30]

Conclusions

In summary, we demonstrate that simple copper salts can replace phosphine ligated palladium catalysts for aza-Heck cyclizations of oxime esters. The Cu-catalyzed protocol proceeds *via* a mechanistically distinct pathway involving radical-based

C–N bond formation and does not involve migratory insertion of the alkene into the N–Cu bond of an imino-Cu(III) intermediate. The net result is an easy catalytic entry to a range of synthetically flexible pyrrolidine derivatives that seem well suited to applications in medicinal chemistry. Key synthetic benefits of the current work include (a) the replacement of expensive Pd-based systems with more economical Cu-variants, (b) the use of cheap pivaloyl oxime esters instead of *O*-pentafluorobenzoyl variants, (c) complete selectivity for chiral products over the corresponding pyrroles for processes involving 1,2-disubstituted alkenes and (d) a catalyst system that tolerates aryl bromides. In a broader context, these studies also provide unique examples of Cu-catalyzed aza-Heck reactions that proceed *via* oxidative initiation at nitrogen to generate new alkene containing products. Replacing precious metal catalysts with cheaper and more sustainable variants is an important goal and this study highlights a case where this can be achieved in a particularly effective manner.

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Notes and references

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

2 Review: I. P. Beletskaya and A. V. Cheprakov, *Organometallics*, 2012, **31**, 7753. We refer specifically to processes that rely upon an internal oxidant (*cf.* oxidative addition of Pd(0)-catalysts into aryl-halide bonds).

3 (*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. Pentafluorobenzoyl oxime esters are usually employed for these processes because they are stable to Beckmann rearrangement.

4 Imino-Pd(II) intermediates have been characterized and exploited in catalytic C–H amination: (*a*) Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676; see also: (*b*) W. P. Hong, A. V. Iosub and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 13664.

5 Previous studies are consistent the direct insertion of the alkene component into the N–Pd(II) bond in a manner that is analogous to the conventional Heck reaction (see ref. 6*b* and *c*).

6 (*a*) N. J. Race and J. F. Bower, *Org. Lett.*, 2013, **15**, 4616; (*b*) A. Faulkner, J. S. Scott and J. F. Bower, *Chem. Commun.*, 2013, **49**, 1521; (*c*) A. Faulkner and J. F. Bower, *Angew. Chem., Int. Ed.*, 2012, **51**, 1675.

7 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.

8 Selected examples of copper catalyzed Heck-like couplings: (*a*) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773; (*b*) V. Declerck, J. Martinez and F. Lamaty, *Synlett*, 2006, 3029; (*c*) Y. Peng, J. Chen, J. Ding, M. Liu, W. Gao and H. Wu, *Synthesis*, 2011, 213; (*d*) V. Calò, A. Nacci, A. Monopoli, E. Ieva and N. Cioffi, *Org. Lett.*, 2005, **7**, 617; (*e*) J.-H. Li, D.-P. Wang and Y.-X. Xie, *Tetrahedron Lett.*, 2005, **46**, 4941.

9 (*a*) S. Liu, Y. Yu and L. S. Liebeskind, *Org. Lett.*, 2007, **9**, 1947; (*b*) S. Liu and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2008, **130**, 6918. These processes are proposed to involve oxidative addition of Cu(I) into the N–O bond. For mechanistically similar processes that involve O-acyl hydroxylamine derivatives, see: (*c*) Z. Zhang, Y. Yu and L. S. Liebeskind, *Org. Lett.*, 2008, **10**, 3005. For examples of mechanistically similar processes that involve N–Cl bonds, see: (*d*) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2008, **47**, 6414 and references cited therein. Copper can catalyze S_N2 substitutions of N–O bonds. For example, see: (*e*) M. J. Campbell and J. S. Johnson, *Org. Lett.*, 2007, **9**, 1521.

10 Zard has reported recently two examples of cyclizations of oxime esters that are stoichiometric in $Cu(OAc)_2$ and provide aza-Heck-type products by an ionic mechanism that involves Lewis acid activation of the oxime ester: M. Bingham, C. Moutrille and S. Z. Zard, *Heterocycles*, 2014, **88**, 953.

11 Intramolecular copper-catalyzed alkene difunctionalization reactions that use external oxidants: (*a*) T. W. Liwosz and S. R. Chemler, *J. Am. Chem. Soc.*, 2012, **134**, 2020; (*b*) P. H. Fuller, J. W. Kim and S. R. Chemler, *J. Am. Chem. Soc.*, 2008, **130**, 17638; (*c*) M. C. Paderas, J. B. Keister and S. R. Chemler, *J. Org. Chem.*, 2013, **78**, 506, Intramolecular copper-catalyzed alkene difunctionalization reactions that use internal oxidants: (*d*) alkene amino-hydroxylation: M. Noack and R. Göttlich, *Chem. Commun.*, 2002, 536; (*e*) alkene amino-chlorination: G. Heuger, S. Kalsow and R. Göttlich, *Eur. J. Org. Chem.*, 2002, 1848. Intermolecular oxidative aza-Heck reactions that employ an external oxidant and do not rely on oxidative initiation at nitrogen: (*f*) T. W. Liwosz and S. R. Chemler, *Chem.–Eur. J.*, 2013, **19**, 12771. The activation of oxime ester N–O bonds with catalytic Cu(I) to form new C–N bonds has been employed in various contexts. For leading references, see: (*g*) aza-copper enolate generation: Y. Wei and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 3756; (*h*) aryl-C–H amination: K. Tanaka, M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1659; (*i*) alkene imino-bromination: Y. Koganemaru, M. Kitamura and K. Narasaka, *Chem. Lett.*, 2002, 784; For the activation of oxime ester N–O bonds

with catalytic Cu(I) to form new N–N bonds, see: (*j*) M.-N. Zhao, H. Liang, Z.-H. Ren and Z.-H. Guan, *Synthesis*, 2012, **44**, 1501.

12 The mechanism for nitrile formation is not clear. Possible pathways include (but are not limited to) Lewis acid promoted Beckmann type-II rearrangement of the oxime ester or β-hydride elimination from an imino-Cu(III) intermediate (*vide infra*). See also ref. 9*a*.

13 Addition of molecular sieves to the reaction mixture did not suppress the formation of this byproduct. Consequently, we favor a pathway involving decomposition of the oxime ester to the corresponding NH-imine and hydrolysis to the ketone during work-up or chromatography. The NH-imine may form *via* either an imino-Cu(III) intermediate or an iminyl radical (*vide infra*).

14 For a review on the one electron reduction of oxime derivatives, see: K. Narasaka and M. Kitamura, *ARKIVOC*, 2006, **vii**, 245.

15 Iminyl radical and imino-Cu(III) intermediates may exist in equilibrium as depicted in Scheme 2A. Imino-Cu(III) intermediates have been proposed previously (for example, see ref. 9*a* and *b*). An alternative possibility is that a radical anion of the oxime ester is generated which then cyclizes, with concomitant loss of pivalate, to generate an alkyl radical (see ref. 11*i*).

16 (*a*) J. K. Kochi, *J. Am. Chem. Soc.*, 1962, **84**, 3271; (*b*) J. K. Kochi, A. Bemis and C. L. Jenkins, *J. Am. Chem. Soc.*, 1968, **90**, 4616; (*c*) J. K. Kochi and C. L. Jenkins, *J. Am. Chem. Soc.*, 1972, **94**, 843; (*d*) J. K. Kochi and C. L. Jenkins, *J. Am. Chem. Soc.*, 1972, **94**, 856.

17 "Carboxylate" refers to either pivalate or 2-ethylhexanoate.

18 Even though we propose a Cu(I)-initiated process, Cu(II)-salts are preferred. Higher concentrations of Cu(II) may increase the efficiency of oxidative elimination from secondary alkyl radical **12**.

19 J. Hoste, *Anal. Chim. Acta*, 1950, **4**, 23. For an application of this method as a mechanistic probe in Cu-catalysis, see: T. P. Lockhart, *J. Am. Chem. Soc.*, 1983, **105**, 1940.

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22 It is unclear whether the processes described here proceed *via* an imino-Cu(III) species or the direct formation of an iminyl radical or, indeed, a radical anion of the oxime ester. To date, all attempts to isolate an imino-Cu(III) intermediate have been unsuccessful.

23 **20a,b** are formally hydrolysis and Beckmann rearrangement products of **16**: C. Wang, X. Jiang, H. Shi, J. Lu, Y. Hu and H. Hu, *J. Org. Chem.*, 2003, **68**, 4579. Both products may arise also *via* an iminyl radical or imino-Cu(III) intermediate.

24 (*a*) M. Newcomb and D. L. Chestney, *J. Am. Chem. Soc.*, 1994, **116**, 9753; (*b*) M. H. Le Tadic-Biadatti and M. Newcomb, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1467. For an application of this type of probe to a copper catalyzed Heck reaction, see ref. 8a.

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26 For the relative stabilities of benzyl and cyclopropyl stabilized carbocations, see: J. P. Pezacki, D. Shukla, J. Lusztyk and J. Warkentin, *J. Am. Chem. Soc.*, 1999, **121**, 6589.

27 A mixture of diastereomeric products arising from trapping of the oxocarbenium ion with pivalate or 2-ethylhexanoate was observed (see the ESI†).

28 (*a*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 558; (*b*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 5; (*c*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 109; (*d*) M. E. Wolff, *Chem. Rev.*, 1963, **63**, 55.

29 For a mechanistically similar process that employs an amidoxime ester, see: H. Chen and S. Chiba, *Org. Biomol. Chem.*, 2014, **12**, 42.

30 Exposure of the analogous *O*-pentafluorobenzoyl oxime ester to our optimized Pd-based systems (see ref. 6) did not result in the formation of **8n** or products related to **34** and only formal hydrolysis to the corresponding ketone was observed. See ref. 6*a* for a discussion on mechanistic pathways to the ketone.