

Copper catalyzed Heck-like cyclizations of oxime esters†

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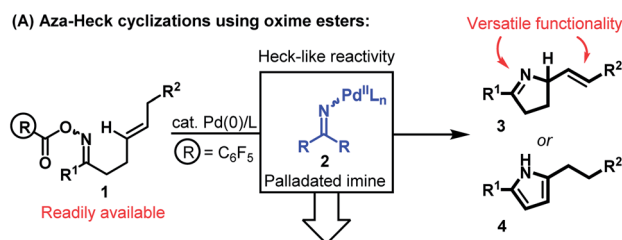
Introduction

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-Stillé 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

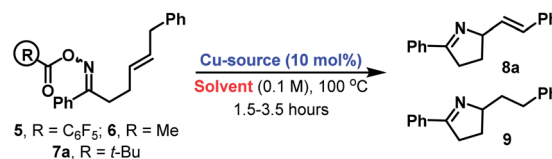
Copper catalyzed Heck-like cyclizations of oxime esters are described. Mechanistic studies indicate a reaction pathway that proceeds *via* the generation and cyclization of an intermediate that possesses iminyl radical character. To the best of our knowledge, this work encompasses the first examples 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.

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



- Suitable Cu-catalysts?
 - Heck-like reactivity?
 - Mechanism?
 - Substrate scope?
 - Selectivity (3 vs 4)?
 - Cheaper oxime esters?
- Cu(I)-catalyzed variants (this work)

(B) Optimization of a prototypical Cu-catalysis system:



Entry	R	Cu-source	Solvent	Yield (8a:9) ^a
1	C ₆ F ₅	CuOAc	DMF (0.1 M)	73% (73:27)
2	C ₆ F ₅	Cu(OAc) ₂	DMF (0.1 M)	56% (93:7)
3	C ₆ F ₅	Cu(acac) ₂	DMF (0.1 M)	21% (100:0)
4	C ₆ F ₅	Cu(OTf) ₂	DMF (0.1 M)	34% (100:0)
5	C ₆ F ₅	Cu(2-ethylhexanoate) ₂	DMF (0.1 M)	70% (90:10)
6	C ₆ F ₅	Cu(2-ethylhexanoate) ₂	PhCN (0.1 M)	79% (100:0)
7	Me	Cu(2-ethylhexanoate) ₂	PhCN (0.1 M)	65% (100:0)
8	<i>t</i> -Bu	Cu(2-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 ¹H 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-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

Table 1 Cyclizations involving 1,2-disubstituted alkenes

7a-l		8a-l
7a, R ¹ = Ph, R ² = Ph	7b, R ¹ = <i>i</i> -Pr, R ² = Ph	7c, R ¹ = 4-Pyridyl, R ² = Ph
7d, R ¹ = <i>t</i> -Bu, R ² = Ph	7e, R ¹ = 2-Naphthyl, R ² = Ph	7f, R ¹ = <i>n</i> -Bu, R ² = Ph
7g, R ¹ = Ph, R ² = Et	7h, R ¹ = 4-BrC ₆ H 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
Cu: 81% Yield Pd: 64% Yield (17:1) ^b		
Cu: 65% Yield Pd: 64% Yield (7:1) ^b		
Cu: 65% Yield ^c		
Cu: 69% Yield		
Cu: 67% Yield		
Cu: 54% Yield		
Cu: 70% Yield Pd: 60% Yield (3:1) ^b		
Cu: 64% Yield Pd: 46% Yield (3:1) ^b		
Cu: 82% Yield		
Cu: 26% Yield		
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. 6a). ^c The reaction was run at 120 °C.

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 2 Cyclizations involving 1,1-disubstituted alkenes

7m , R ¹ = CO ₂ Et, R ² = H 7p , R ¹ = Et, R ² = Et	7n , R ¹ = R ² = -(CH ₂) ₃ 7q , R ¹ = Me, R ² = H	7o , R ¹ = Me, R ² = <i>n</i> -Pr 7r , R ¹ = Ph, R ² = <i>i</i> -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. 6b). ^c Isolated as a 5 : 1 mixture of alkene regioisomers.

Table 3 Cyclizations involving cyclic alkenes

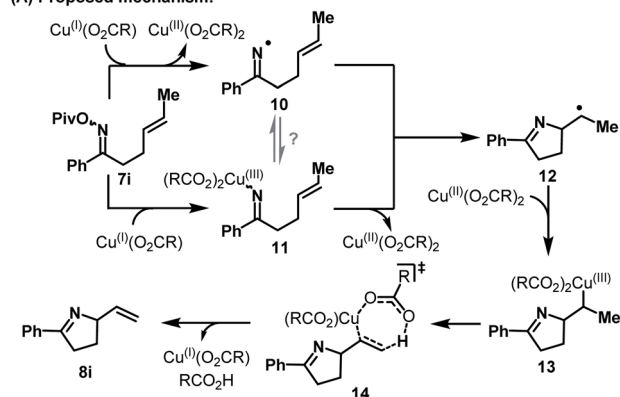
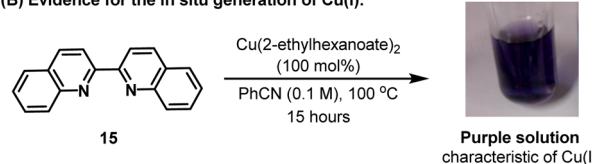
7s , R ¹ = H, R ² = H 7t , ^a R ¹ = H, R ² = Benzyl 7u , R ¹ = Me, R ² = Me	 8s Cu: 95% Yield Pd: 93% Yield ^b	 8t Cu: 55% Yield (10:1 d.r.) Pd: 76% Yield ^b (>19:1 d.r.)
 8u Cu: 75% Yield Pd: 89% Yield ^b		

^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. 6c).

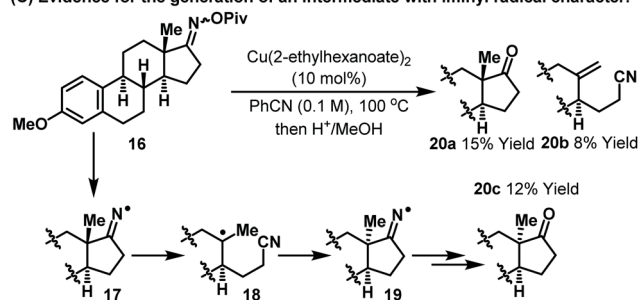
Cyclizations onto pendant cyclohexenes provide a direct entry to *cis*-configured heterobicycles **8s–u** (Table 3). Here, reaction efficiency is comparable to our best Pd-based systems.^{6c} In the case of **7t**, cyclization of a 1 : 1 mixture of diastereomers at C-2 provided **8t** as a 10 : 1 mixture 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

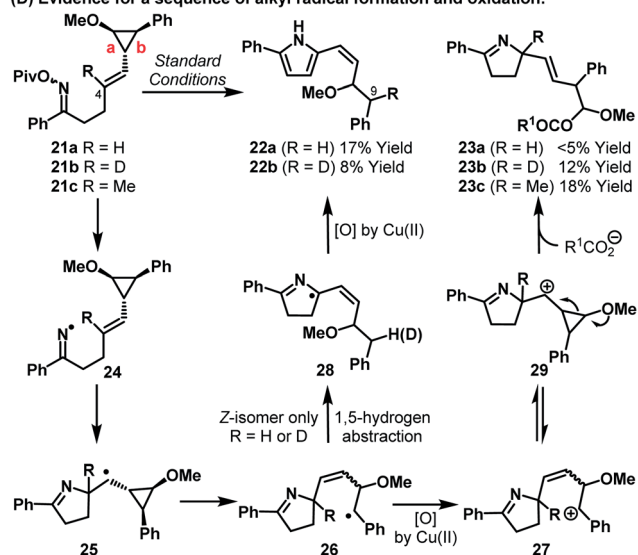
(A) Proposed mechanism:

(B) Evidence for the *in situ* generation of Cu(I):

(C) Evidence for the generation of an intermediate with iminyl radical character:



(D) Evidence for a sequence of alkyl radical formation and oxidation:



Scheme 2 Mechanistic analysis and supporting studies.

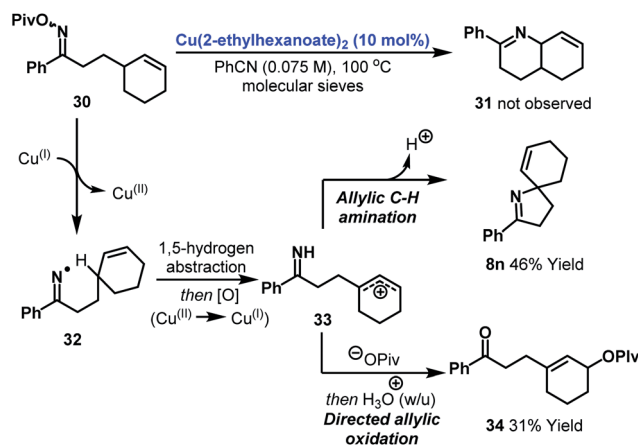
triggers cyclization to alkyl radical **12**. Pathways proceeding *via* either the generation of iminyl radical **10** or imino-Cu(III) intermediate **11** can be envisaged; in the latter case cyclization occurs by homolytic cleavage of the N–Cu bond.^{14,15} It is well established that alkyl radicals can undergo oxidative elimination upon exposure to cupric acetate.¹⁶ Accordingly, trapping of



alkyl radical **12** with Cu(II)-carboxylate¹⁷ 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-cupration¹⁶ 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



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

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.

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–Freitag 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.

Acknowledgements

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 - 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. 9a 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. 11i).
 - 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.
 - 20 Based upon the considerations outlined in ref. 18, we favor partial disproportionation to provide small quantities of Cu(I). For the reduction potentials of copper ions in benzonitrile, see: R. C. Larson and R. T. Iwamoto, *J. Am. Chem. Soc.*, 1960, **82**, 3239.
 - 21 J. Boivin, A. M. Schiano and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 7849.
 - 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.
 - 25 The fate of *trans*-**26** (R = H) is unknown. For examples of copper mediated additions of imines to alkenes that generate alkyl radicals, see: S. Sanjaya, S. H. Chua and S. Chiba, *Synlett*, 2012, **23**, 1657.
 - 26 For the relative stabilities of benzyl and cyclopropyl stabilized carbocations, see: J. P. Pezacki, D. Shukla, J. Luszyk 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. 6a for a discussion on mechanistic pathways to the ketone.

