

HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 953 - 960. © 2014 The Japan Institute of Heterocyclic Chemistry  
Received, 25th July, 2013, Accepted, 28th August, 2013, Published online, 2nd September, 2013  
DOI: 10.3987/COM-13-S(S)94

## A SIMPLE ROUTE TO FUNCTIONALIZED $\Delta^1$ -PYRROLINES

Matilda Bingham, Cécile Moutrille, and Samir Z. Zard\*

Department of Chemistry, Ecole Polytechnique, CNRS UMR 7652, 91128

Palaiseau, France

samir.zard@polytechnique.edu

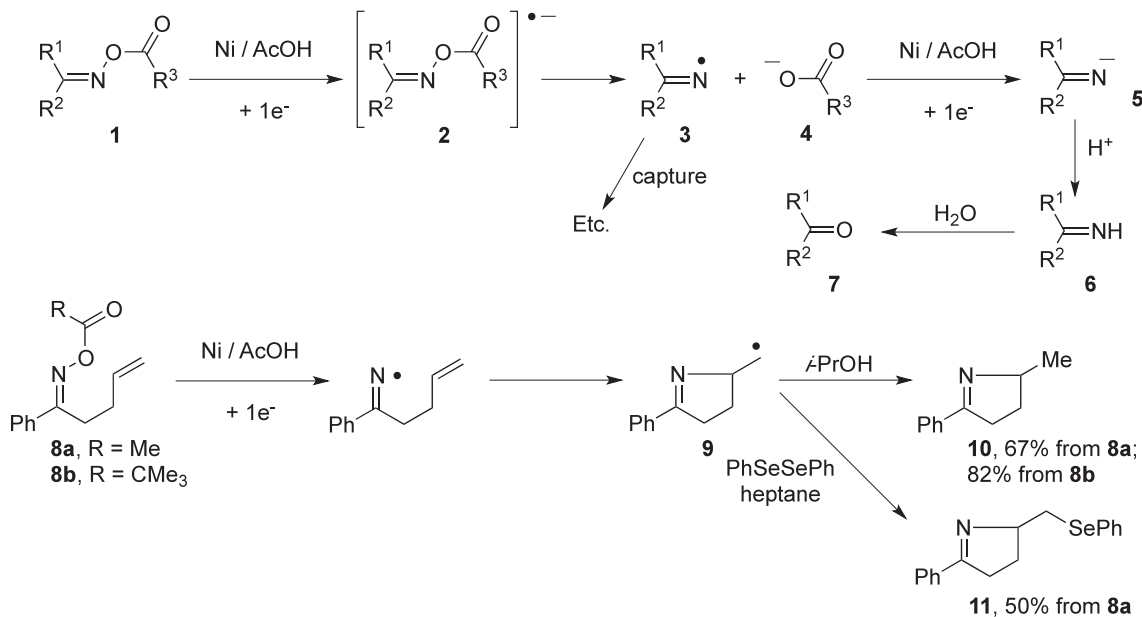
**Abstract** – Treatment of  $\gamma$ -unsaturated oxime esters with cupric acetate or ferric chloride in acetic acid / *t*-butanol or in *t*-butanol alone leads to the formation of vinyl- or chloroalkyl- substituted  $\Delta^1$ -pyrrolines in moderate to good yield.

New methods enabling the generation of reactive intermediates under mild conditions often open access to structures hitherto not readily available. In contrast to carbon-centered radicals, which continue to be extensively employed in organic synthesis, radicals centered on nitrogen have been much less exploited. This has been partly the result of a lack, until recent times, of convenient routes to these species. We and others have devised several new methods for producing nitrogen radicals, and some have been applied in the total synthesis of a number of alkaloids.<sup>1</sup>

One method we devised for the generation of iminyl radicals consisted in the reduction of oxime esters **1** with a combination of plain nickel powder and acetic acid in an organic solvent.<sup>2</sup> Electron transfer from the nickel gives rise to a radical anion **2**, which rapidly fragments into an iminyl radical **3** and a carboxylate anion **4**. The former can capture a second electron to furnish iminyl anion **5**. This is immediately protonated and the hydrolytically labile unsubstituted imine **6** converted into the corresponding ketone **7** (Scheme 1). However, owing to the weak reducing nature of the nickel, the iminyl radical **3** survives long enough to be intercepted by a well-positioned internal alkene. This is illustrated by the transformation of oxime acetate **8a** or the more robust pivalate **8b** into pyrroline **10** by quenching the intermediate primary cyclized carbon radical **9** by hydrogen abstraction from isopropanol. The radical nature of the process was confirmed by trapping radical **9** with diphenyldiselenide, which is compatible with the mild reducing system, to give selenide **11** in a useful yield.<sup>2</sup>

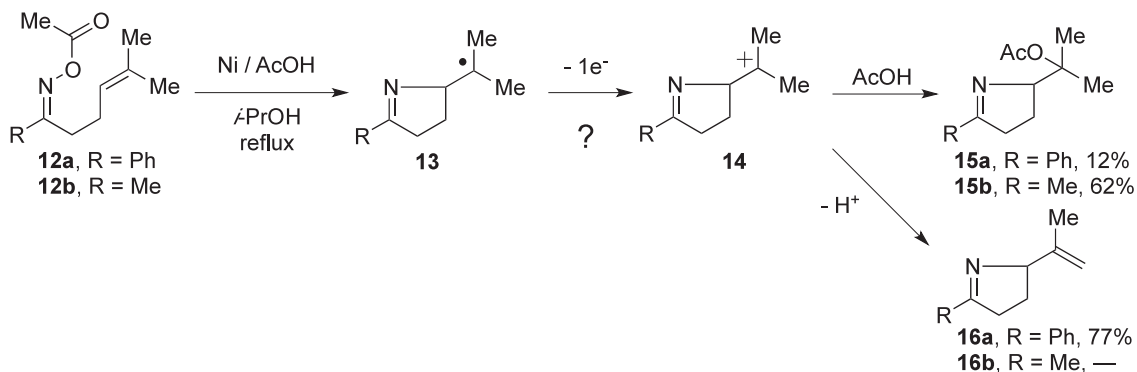
---

This paper is dedicated with respect and admiration to Prof. Victor Snieckus on the occasion of his 77<sup>th</sup> birthday.



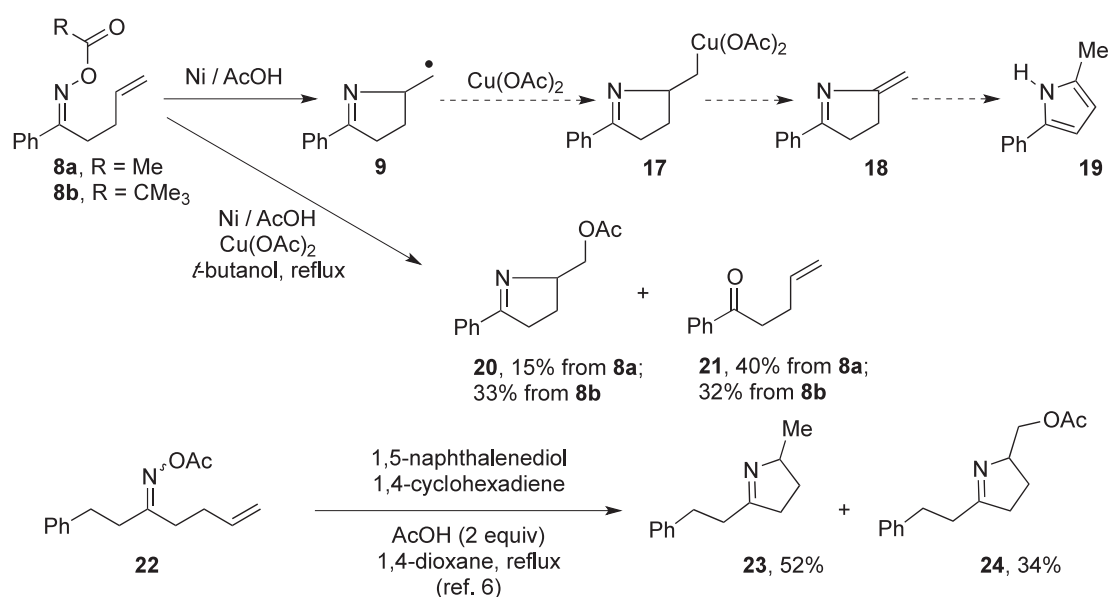
Scheme 1. Dissolving nickel metal mediated generation of iminyls from oxime esters

However, when oxime acetate **12a** was exposed to the action of nickel powder / acetic acid in refluxing isopropanol, we were surprised to find that the major product was in fact alkene **15a** (77%) accompanied by a small amount of tertiary acetate **16a** (12%).<sup>2</sup> We initially believed that the intermediate tertiary radical **13** abstracted hydrogen too slowly from the solvent and was oxidized into cationic species **14** by electron transfer, possibly to the starting oxime acetate **12a** (Scheme 2). In the case of **12b**, only the tertiary acetate **15b** was isolated in 62% yield. While we were pleased by the relatively clean formation of more functionalized and therefore more useful products, we were nevertheless puzzled by the mechanism. Subsequent experiments, summarized hereafter, revealed that the reaction of oxime acetate **12**, in contrast to congeners **8a** and **8b**, is in fact *ionic* and *not radical* in nature.<sup>3</sup>



Scheme 2. Unexpected transformations of an unsaturated oxime acetate

Still under the impression of a radical based mechanistic hypothesis, we attempted to obtain alkene **18** or the corresponding pyrrole **19** starting from oxime esters **8a** and **8b** by oxidizing the intermediate primary radical **9** with cupric acetate (Scheme 3). The latter's ability to capture primary and secondary carbon radicals is well known and the transient Cu(III) intermediate thus generated (e.g. **17**) decomposes to furnish in most cases the least substituted alkene.<sup>4</sup> In a related study on trichloroacetamides, we had found that the mildly reducing nickel/acetic acid system was compatible with the presence of the mildly oxidizing cupric acetate and alkenes could indeed be formed upon trapping the intermediate carbon radicals.<sup>5</sup>

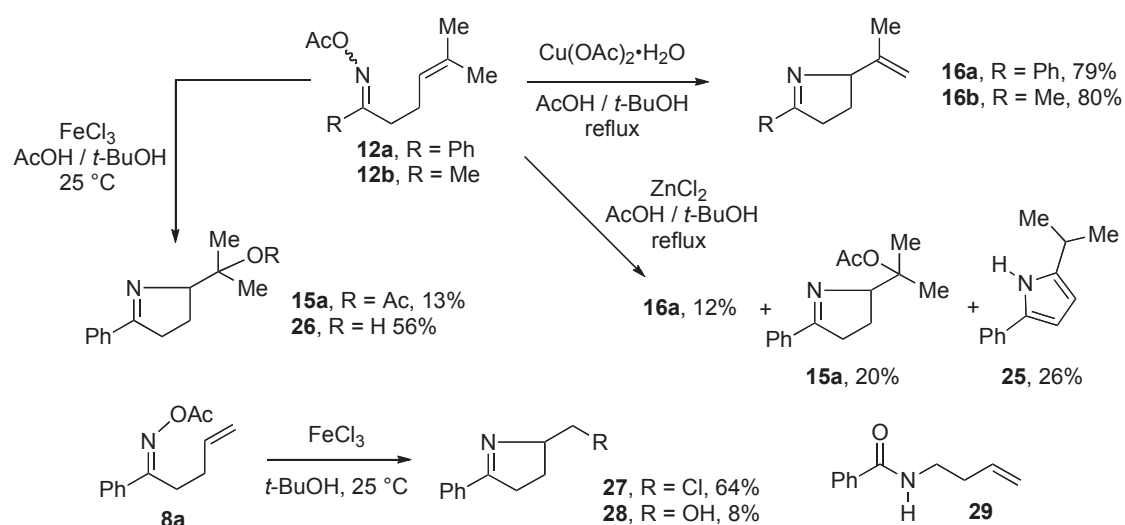


Scheme 3. Unusual reactions of unsaturated oxime esters

We therefore treated oxime esters **8a** and **8b** with a combination of nickel powder, cupric acetate monohydrate and acetic acid in refluxing *t*-butanol. The choice of *t*-butanol to replace isopropanol was made to avoid possible hydrogen atom abstraction from the solvent. In the event, the reaction led to the formation of acetate **20** and the parent ketone **21** in rather modest yield (Scheme 3). No alkene **18** or pyrrole **19** was observed. Ketone **21** is presumably the result of cupric acetate promoted hydrolysis of the starting oxime esters; however, the formation of acetate **20** instead of alkene **18** or pyrrole **19** is not compatible with a radical mechanism. We therefore embarked on a series of blank experiments to acquire some insight into the process.

Under the same conditions, *but in the absence of nickel powder*, oxime acetate **8b** furnished acetate **20** in 43% yield along with ketone **21** (36%). *Even cupric acetate was not strictly necessary*: the same products were obtained by simply heating **8b** in acetic acid / *t*-butanol, albeit in lower yield (27% and 13% for **20** and **21** respectively) and longer reaction time. No reaction occurred in *t*-butanol alone. It is interesting to

note that Narasaka and co-workers have reported that treatment of oxime acetate **22** with a combination of 1,5-naphthalenediol, 1,4-cyclohexadiene, and acetic acid in refluxing 1,4-dioxane resulted in the formation of pyrrolines **23** and **34** in excellent combined yield (Scheme 3).<sup>6</sup> The former clearly arises from a typical iminyl radical cyclization, with the cyclohexadiene acting as the final hydrogen atom donor, whereas the latter derives from an ionic reaction induced by the presence of acetic acid. In our original experiments, the trisubstituted alkene in **12a,b** is sufficiently nucleophilic to allow the ionic process to compete favorably against the radical cyclisation observed with **8a,b**, where the unsubstituted terminal alkene is only poorly nucleophilic.

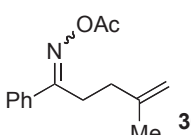
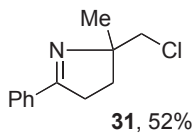
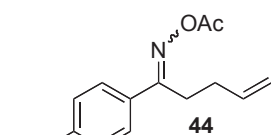
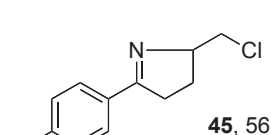
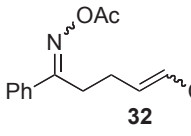
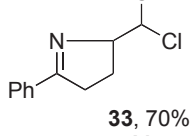
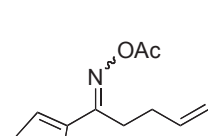
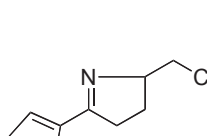
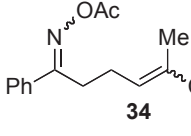
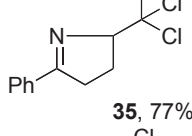
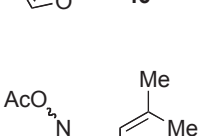
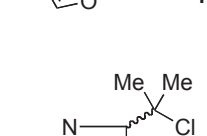
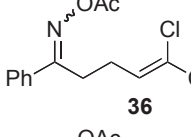
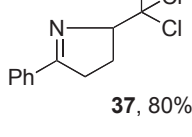
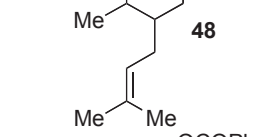
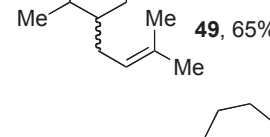
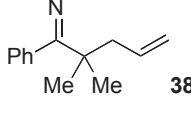
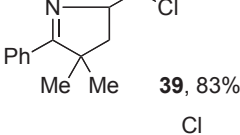
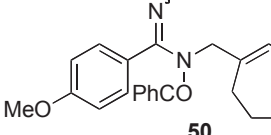
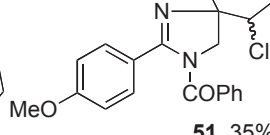
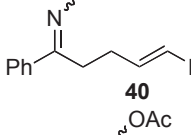
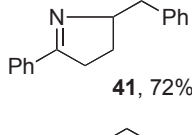
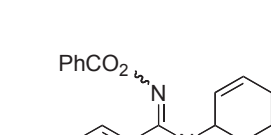
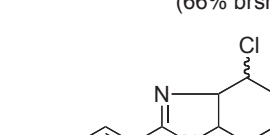
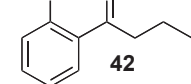
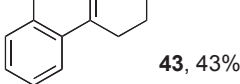
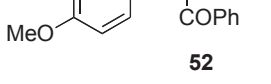
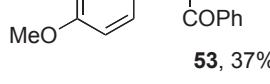


Scheme 4. Cupric acetate and ferric chloride mediated cyclizations of unsaturated oxime acetates

In the case of oxime acetates **12a** and **12b** containing an isopropylidene group, the action of cupric acetate and acetic acid in refluxing *t*-butanol provided cleanly  $\Delta^1$ -pyrrolines **16a** and **16b** with an isopropenyl side-chain (Scheme 4). This again proceeded clearly through an ionic mechanism promoted by the cupric acetate. We further examined briefly the action of other metallic salts. Thus, zinc chloride and acetic acid in refluxing *t*-butanol converted oxime acetate **12a** into cyclized products **15a**, **16a**, and pyrrole **25** in the yields indicated in Scheme 4. Under similar conditions, ferric chloride proved more interesting. It gave rise to only two products: acetate **15a** and its corresponding alcohol **26**, with the latter dominating (13% and 56% yield respectively). In the absence of acetic acid, and at room temperature (25 °C), the reaction of oxime **8a** with ferric chloride in *t*-butanol furnished chloride **27** in 64% yield, along with a small amount of the corresponding alcohol **28** (ca 8%). No reaction occurred in acetonitrile or DMF under otherwise identical conditions. These are coordinating solvents and almost certainly deactivate the ferric chloride. At reflux in acetonitrile, the reaction gave a small yield of the chloride **27** (23%) in addition to the parent ketone **21** (60%) and amide **29** (14%) resulting from a Beckmann rearrangement. In

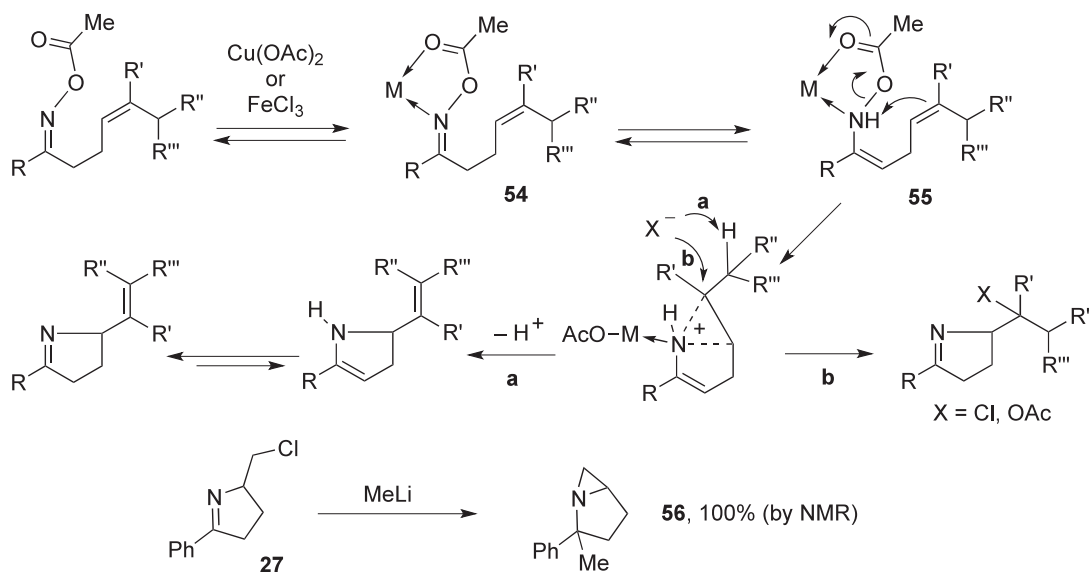
dichloromethane, but at room temperature, only the desired chloride **27** (59%) and Beckmann derived amide (40%) were formed in nearly quantitative combined yield.

Table 1. Formation of chloroalkyl- $\Delta^1$ -pyrrolines from unsaturated oxime acetates

Oxime Acetate	$\Delta^1$ -Pyrroline	Oxime Acetate	$\Delta^1$ -Pyrroline
	 <b>31</b> , 52%		 <b>45</b> , 56%
	 <b>33</b> , 70%		 <b>47</b> , 55%
	 <b>35</b> , 77%		 <b>49</b> , 65%
	 <b>37</b> , 80%		 <b>51</b> , 35% (66% brsm)
	 <b>39</b> , 83%		 <b>53</b> , 37%
	 <b>41</b> , 72%		
	 <b>43</b> , 43%		

Since no Beckmann rearrangement was observed in *t*-butanol using ferric chloride as the promoter, the remainder of this study was conducted in this solvent, sometimes in combination with acetic acid. The results are collected in Table 1. The un-optimized yields are moderate to good. Various substitution patterns on the side chains are tolerated, and the aromatic ring can be substituted with various group or replaced by a heteroaromatic motif such a furan as in **47**. In the case of compound **41**, only one diastereoisomer is apparently formed but its stereochemistry was not unambiguously established. A mixture of *t*-butanol and acetic acid was used as the solvent in this example. The same combination of solvents was employed in the case of aliphatic substrate **48**. In these two instances, and for reasons which are not yet clear, the presence of acetic acid did not lead to complications from a Beckmann

rearrangement. Curiously, however, complex mixtures were sometimes obtained when the starting oxime acetate was derived from aliphatic rather than from aromatic ketones. It is not clear at this stage what is at the origin of the complications with purely aliphatic substrates. Finally, the present transformation could be extended to the synthesis of imidazolines, as illustrated by compounds **51** and **53**, even if the yields at this stage are still modest.<sup>7</sup>



Scheme 5. Possible mechanism and example of a further transformation

A plausible mechanism for this transformation is outlined in Scheme 5, even if the details are still not clear. The metal could presumably complex both to the nitrogen of the oxime and to an oxygen from the ester leading to a structure such as **54**, which is likely in equilibrium with the enamine form **55**. This equilibrium explains why the initial geometry of the oxime is of little consequence in most cases even if, as would be expected, the isomer with the ester and the allyl side chain in a *trans* arrangement is better disposed for cyclization. Nucleophilic attack by the alkene results in rupture of the relatively weak N-O bond, and the more electron-rich the alkene the better the reaction. Depending on the metal used and the type of nucleophile present, an alkene is formed by removal of a proton (with cupric acetate; path **a**) or a chloride is finally obtained following nucleophilic substitution by a chloride anion (with ferric chloride; path **b**). Acetic acid can also act as a nucleophile and acetates are hence sometimes observed.

In summary, we have described a simple, practical route to functionalized  $\Delta^1$ -pyrrolines using cheap, readily available starting materials and reagents.<sup>8</sup> The allyl ketone precursors can be made by numerous standard textbook methods, in particular by direct allylation of enolates or by the very powerful Claisen sigmatropic rearrangement.<sup>9</sup> The  $\Delta^1$ -pyrrolines products can be further modified in many ways. One especially interesting transformation is exemplified in the lower part of Scheme 5 and concerns the

addition of a methyllithium to chloromethyl derivative **27** to give bicyclic aziridine **56** in an essentially quantitative yield (by NMR).<sup>10</sup> Nevertheless, much work remains to be done to improve the yields, to better delineate and expand the scope, and to explore possible synthetic applications. Indeed, 5-membered-ring nitrogen heterocycles, represented by pyrroles, pyrrolines, and pyrrolidines, are ubiquitous among alkaloids.<sup>11</sup>

## ACKNOWLEDGEMENTS

We thank Dr Haiwen Zhang for a few preliminary experiments. One of us (C. M.) thanks Rhodia for a scholarship.

## REFERENCES AND NOTES

1. For a recent review on the generation and use of nitrogen-centered radicals, see: S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603.
2. J. Boivin, A.-M. Schiano, S. Z. Zard, and H. Zhang, *Tetrahedron Lett.*, 1999, **40**, 4531; J. Boivin, A.-M. Schiano, and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 7849.
3. There are several reports on related reactions involving oxime esters, ethers, and related derivatives: T. Wagner-Jauregg and M. Roth, *Helv. Chim. Acta*, 1962, **45**, 771; K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, 1998, 1261; K. Uchiyama, Y. Hayashi, and K. Narasaka, *Tetrahedron*, 1999, **55**, 8915; M. Yoshida, M. Kitamura, and K. Narasaka, *Chem. Lett.*, 2002, 144; Y. Kognemaru, M. Kitamura, and K. Narasaka, *Chem. Lett.*, 2002, 784; K. Narasaka, *Pure Appl. Chem.*, 2003, **75**, 19 and references cited therein; M. Yoshida, M. Kitamura, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2003; M. Kitamura, M. Yoshida, T. Kikuchi, and K. Narasaka, *Synthesis*, 2003, 2415; T. Nishimura, Y. Nishiguchi, Y. Maeda, and S. Uemura, *J. Org. Chem.*, 2004, **69**, 5342; M. Kitamura, M. Yoshida, T. Kikuchi, and K. Narasaka, *Tetrahedron Lett.*, 2005, **46**, 2373; K. Narasaka and M. Kitamura, *Eur. J. Org. Chem.*, 2005, 4505; T. D. Wahyuningsih, K. Pchalek, N. Kumar, and D. Black, *Tetrahedron*, 2006, **62**, 6343; T. D. Wahyuningsih, N. Kumar, and D. Black, *Tetrahedron*, 2006, **62**, 6713; C. G. Savarin, C. Gris , J. A. Murry, R. A. Reamer, and D. L. Hughes, *Org. Lett.*, 2007, **9**, 981; M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 539; N. Chandan, A. L. Thompson, and M. G. Moloney, *Org. Biomol. Chem.*, 2012, **10**, 7863; I. Deb and N. Yoshikai, *Org. Lett.*, 2013, **15**, 4254.
4. J. K. Kochi and R. V. Subramanian, *J. Am. Chem. Soc.*, 1965, **87**, 4855; E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.*, 1971, **93**, 524; B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.
5. J. Cassayre, D. Dauge, and S. Z. Zard, *Synlett*, 2000, 471.
6. M. Yoshida, M. Kitamura, and K. Narasaka, *Chem. Lett.*, 2002, 144.

7. For a synthesis of dihydroimidazoles from amidoxime esters, see: D. Gennet, S. Z. Zard, and H. Zhang, *Chem. Commun.*, 2003, 1870; S. Zaman, K. Mitsuru, and A. D. Abell, *Org. Lett.*, 2005, **7**, 609.
8. A typical experimental procedure is as follows: The substrate oxime ester (1.0 equiv) is dissolved in *t*-BuOH (8.0 mL/mmol) and AcOH (optional, 2.7 mL/mmol) and is stirred at room temperature under an inert atmosphere. The metal salt (1.25 equiv) is then added in one lot and the resulting mixture stirred at room temperature until complete consumption of the starting material (ca 1 h). The reaction is then quenched by the addition of water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts are washed with aq. NaHCO<sub>3</sub> (optional –dependent on the use of AcOH), brine, and dried over MgSO<sub>4</sub>. The crude reaction mixture is concentrated in vacuo and purified by flash column chromatography to afford the products.
9. For a recent review of the Claisen rearrangement, see: J. Rehbein and M. Hiersemann, *Synthesis*, 2013, **45**, 1121.
10. For an analogous transformation, see: K. E. Harding and S. R. Burks, *J. Org. Chem.*, 1984, **49**, 40 and references cited therein.
11. E. Fatturoso and O. Taglilatela-Scafati, Eds., ‘Modern Alkaloids’, Wiley-VCH, Weinheim, 2008.