

Iridium Catalysed Reductive Strecker Reaction for Late Stage Amide and Lactam Cyanation

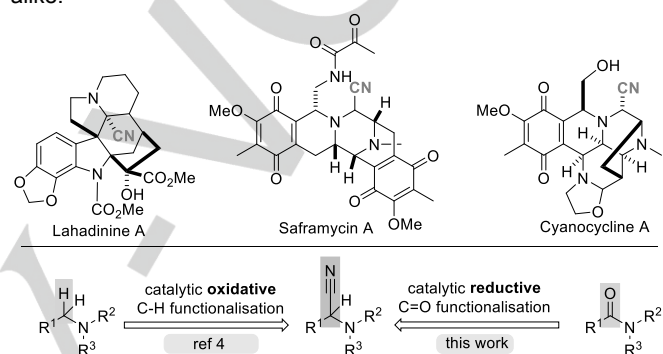
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Abstract: A new iridium catalysed reductive Strecker reaction for the direct and efficient formation of α -amino nitrile products from a broad range of (hetero)aromatic and aliphatic tertiary amides and *N*-alkyl lactams is reported. The protocol exploits the mild and highly chemoselective reduction of amide and lactam functionality by Vaska's complex in the presence of tetramethyldisiloxane as a reductant to directly generate hemiaminal species able to undergo substitution by cyanide on treatment with TMSCN. The protocol is simple to perform, broad in scope, efficient (up to 99% yield) and has been successfully applied to the late stage functionalisation of amide- and lactam-containing drugs and naturally occurring alkaloids as well as for the selective cyanation of the carbonyl carbon linked to the *N*-atom of proline residues within di- and tripeptides.

Nitrile functionality is found in many bioactive natural products and, due to its high polarity, characteristic linear geometry and hydrogen-bond acceptor properties, is common to numerous pharmaceutical compounds.^[1] Furthermore, the nitrile group is a valuable and versatile precursor to a wide range of functional groups including amines, amides, carbonyl compounds and carboxylic acid derivatives as well as 5-ring and 6-ring heteroaromatics via cycloaddition or condensation reactions.^[2] α -Amino nitriles in particular are a recurrent scaffold in many biologically active molecules and natural compounds^[1,3] *Aspidofractinine* and *Streptomyces* metabolites with antibiotic and antitumoral activities such as *Saframycin A* or *Cyanocycline A* and *Lahadinines A* and *B*, extracted from *Kopsia pauciflora*, all of them contain an α -amino nitrile moiety in their structure (Scheme 1, top).^[3] Accordingly in recent years much effort has been devoted to developing new and efficient ways for their preparation. In particular, direct α -C-H functionalisation reactions of amines has attracted widespread attention as an alternative approach to classical routes.^[4] In fact, great strides have been made in both sp^2 and sp^3 photochemical, electrochemical and transition-metal-catalyzed C-H cyanation procedures.^[5] However, significant challenges in relation to improvements to catalytic turnover, site selectivity and in particular substrate scope and functional group tolerance remain to be addressed for this approach to be generally applicable.^[4]

We recognised that an alternative, direct and synthetically powerful solution for the synthesis of α -amino nitriles could arise from carboxamides via the development of a reductive Strecker-type (reductive cyanation) reaction (Scheme 1, bottom). Owing

to the prevalence of amides and lactams in biologically active compounds, and the vast numbers of them contained within the suppliers' catalogues and the compound libraries of pharmaceutical and agrochemical companies, a mild reductive method that could efficiently and chemoselectively target such functional groups would likely find numerous applications in library generation, late stage functionalisation and total synthesis alike.



Scheme 1. (Top) Examples of natural products possessing an α -amino nitrile moiety. (Bottom) Catalytic reductive cyanation for the synthesis of α -amino nitriles.

To this end, in recent years a handful of reports directed towards reductive cyanation reactions at the amide and lactam carbonyl carbon functionality have been described.^[6-11] However, to overcome the low inherent electrophilicity of the amide/lactam carbonyl group superstoichiometric amounts of powerful metal hydride reducing agents (such as DIBALH)^[9] or strong electrophiles for pre-activation (such as Tf_2O) were necessary to achieve reactivity.^[10,11] Such approaches bring with them issues of chemoselectivity and functional group intolerance and therefore we sought to develop a mild, catalytic, chemoselective and direct reductive cyanation reaction of carboxylic amides and lactams and herein we wish to report our findings.

Our group recently reported that Vaska's complex in the presence of tetramethyldisiloxane (TMDS) catalysed the intramolecular reductive nitro-Mannich reaction of lactam substrates possessing *N*-linked nitro-alkyl groups.^[12] That work demonstrated that reactive iminium species could be readily generated, then efficiently trapped by the pendant nitronate nucleophile to afford bicyclic tertiary amines. Furthermore, in a recent publication we have demonstrated a remarkable chemoselectivity of the Vaska's catalyst for lactam carbonyl groups over ester functionalities and C=C double bonds,^[13] however analogous reactions of acyclic carboxylic acid amides had not been explored. Following the formation of an intermediate hemiaminal by the action of Vaska's complex and a silane reductant, our hope was that conditions for an efficient intermolecular cyanation reaction that out-competed any over-reduction^[14] of the reactive iminium species could be found (Scheme 2).

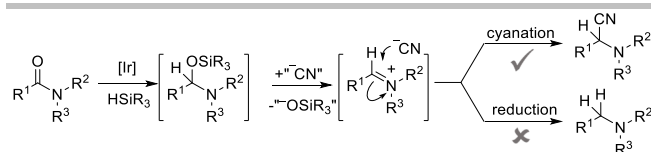
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Scheme 2. Catalytic reductive cyanation for the synthesis of α -amino nitriles.

N,N-Dimethylbenzamide was chosen as a model substrate to carry out feasibility studies and TMSCN as a convenient source of cyanide. Pleasingly, after addition of 1.1 equivalents of TMDS to a solution of **1** and 1 mol% Vaska's complex, followed by addition of 1.1 equivalents of TMSCN, the desired α -amino nitrile product **2** was isolated after 30 minutes in 43% yield (Table 1, entry 1). Increasing the amounts of TMDS and TMSCN to 2 equivalents each resulted in an increase in the yield to 92% (Table 1, entry 2). Lowering the amount of catalyst or increasing the concentration proved to be detrimental for the yield (see ESI for further optimisation experiments).

With optimised reaction conditions established, the scope of the reductive Strecker reaction with respect to the carboxylic acid moiety was studied (Figure 1). Pleasingly, the introduction of an additional aromatic ring in the naphthyl amide derivative increased the yield up to 98% (**3**). Both electron-rich and electron-deficient substituents were well-tolerated in the aromatic counterpart (**4–6**), although the yield was slightly lower for electron-deficient *N,N*-dimethyl-4-nitrobenzamide and unreacted starting material was recovered from the reaction mixture. The reaction proved to be applicable to furanyl heterocycle (**7**) as well as conjugated alkenes such as a cinnamic acid-derived amide (**8**) and also with aliphatic carboxylic acid moieties (**9–12**). Importantly, bulky substituents adjacent to the carbonyl group [such as *tert*-butyl (**9**) and

Table 1. Model reaction, scale-up and scale-down.

| Entry ^[a] | %mol cat | TMDS (eq) | TMSCN (eq) | Yield (%) |
|----------------------|----------|-----------|------------|-----------|
| 1 | 1 | 1.1 | 1.1 | 43 |
| 2 | 1 | 2 | 2 | 92 |
| 3 ^[b] | 1 | 2 | 2 | 92 |
| 4 ^[c] | 1 | 2 | 2 | 58 |

^[a] 0.3 mmol of **1**, Vaska's complex, TMDS and TMSCN were mixed in toluene (6 mL) according to the general procedure. ^[b] 1 g scale. ^[c] 4 mg scale.

adamantyl (**10**)] did not dramatically decrease the yield, and secondary and primary alkyl amides also worked well, showing that enolisable substrates did not derail the reductive cyanation reaction through possible irreversible formation of enamine intermediates.^[15] Different amines were also explored and the majority were well tolerated (Figure 1); diethyl amine (**13**), pyrrolidine (**14**) and Boc-piperazine (**18**) afforded the products with yields between 81–88%. Single crystal X-ray analysis studies of compound **18** unambiguously established its structure as shown in Figure 1.^[16] On the other hand, a substrate possessing an aromatic amine resulted in a considerably reduced yield (**16**, 35%), due to incomplete partial reduction to the intermediate hemiaminal, presumably because of the reduced Lewis basicity of the carboxylic amide group.^[17] Similarly, secondary amides did not undergo any observable

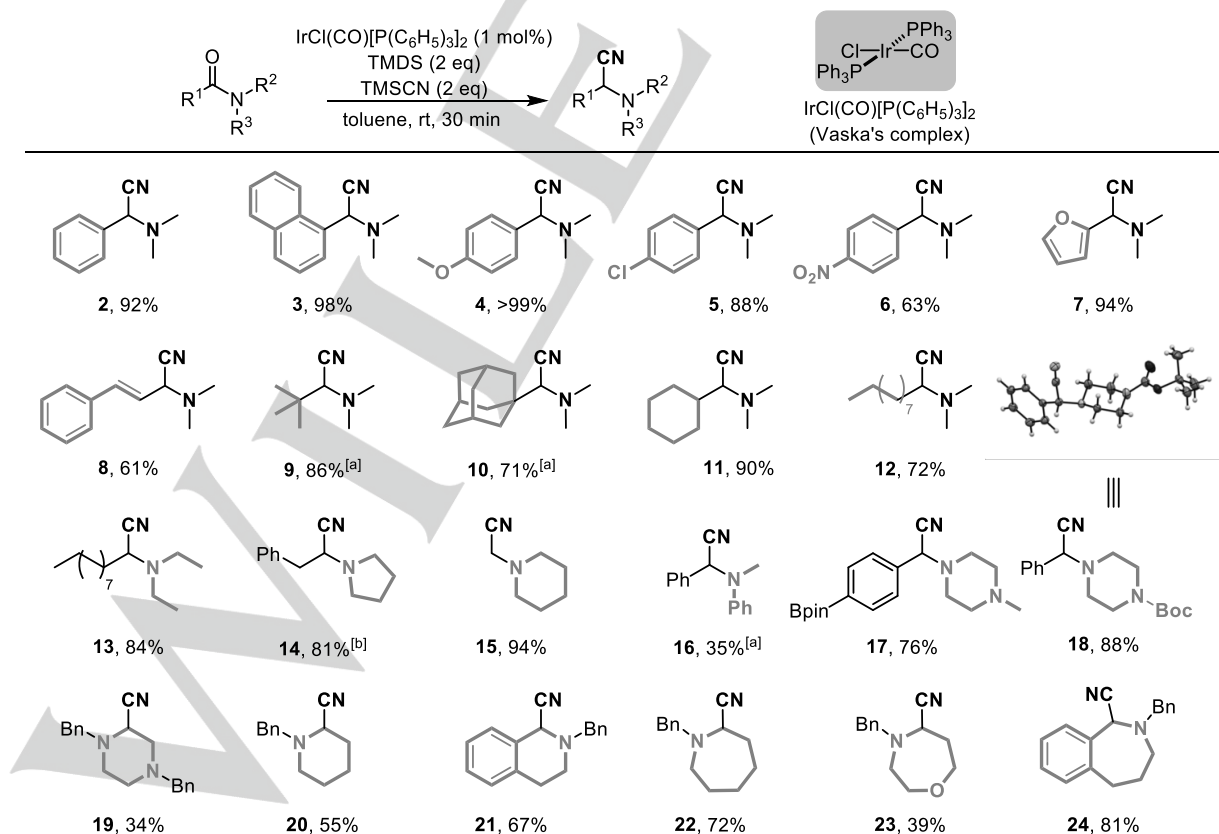
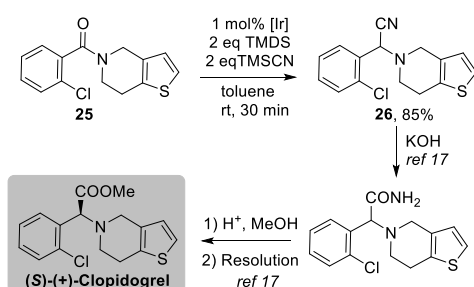


Figure 1. Scope of the reaction. ^[a] 2 mol% $\text{IrCl(CO)[P(C}_6\text{H}_5)_3]_2$ and 4 eq of TMDS were used. ^[b] 4 eq TMSCN.

reaction (see ESI) – and the lack of reactivity is likely due to a lower Lewis basicity as compared with tertiary amides.^[17] Importantly, however, their presence in the reaction media did not impede the cyanation of compound **1** (see ESI). A formic acid-derived amide was a good substrate and afforded product **15** in near quantitative yield. Furthermore, lactams were generally well-tolerated with product yields ranging from modest to high (**19–24**). Diminished yields were attributed to competitive formation of undesired enamine / iminium condensation products.^[12] Notably, chloro substituents, nitro groups, alkenes, esters, carbamates and boronate esters remained essentially untouched under the reaction conditions, clearly demonstrating the wide functional group tolerance of this transformation. Moreover, the reaction with model amide **1** was readily scaled up to 1 g with no loss of yield (92%, Table 1, entry 3) and also readily scaled down (to 4 mg) and the product was still isolated in an acceptable yield (58%, Table 1, entry 4). Thus as well as for preparative scale synthesis this new transformation could be deployed for the late stage cyanation of small amounts of complex and/or precious materials. The synthetic utility of our method was proven in the reductive cyanation of amide **25** (Scheme 3). The cyanated product **26**, a known precursor of the antiplatelet agent Clopidogrel, was obtained in 85% yield.^[18]



Scheme 3. Application of the iridium catalyzed reductive cyanation to the synthesis of Clopidogrel.

To further demonstrate the robustness of the reductive cyanation protocol and its general applicability, more challenging substrates of biological and medicinal interest were tackled. We envisioned that our chemoselective cyanation of tertiary amides could potentially functionalise the carbonyl carbon linked to the *N*-atom of a proline residue within a peptide in a selective way, as proline is the only proteinogenic amino acid which forms tertiary amides.^[19]

First we tested our reaction on a simple benzoylated proline methyl ester, and very pleasingly the cyanated product **27** was obtained as a 5:1 mixture of diastereomers in 82% yield (Figure 2). The introduction of a bulkier benzhydryl group in place of the methyl ester resulted in the formation of only one diastereomeric α -amino nitrile product, albeit with lower yield (**28**, 35%). Importantly, the presence of a 'free' NH in the dipeptide Boc-Val-Pro-OMe did not prevent the reaction from proceeding; the nitrile product **29** was formed in 38% yield as a mixture of diastereomers, likely as a result of iminium-enamine interconversion with concomitant epimerization of the former valine residue α -carbon. Boc-Gly-Pro-OMe dipeptide yielded again a 5:1 mixture of diastereomers **30** with good yield. Interestingly, the tripeptide Boc-Gly-Pro-Phe-OMe generated the cyanation product **31** exclusively in the carbonyl carbon linked to the proline *N*-atom in 54% yield, in a completely chemo- and diastereoselective fashion. This is, to our knowledge, the first time that a peptide has been selectively functionalised with a CN group in the carbonyl group attach to a proline *N*-atom. This

significant result points to the possibility of allowing selective

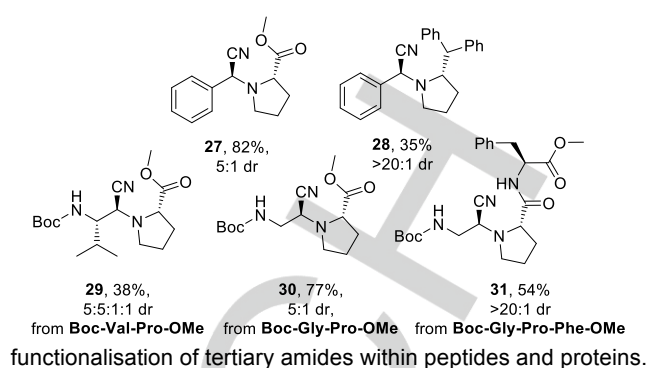


Figure 2. Cyanation of proline, di- and tripeptides derivatives

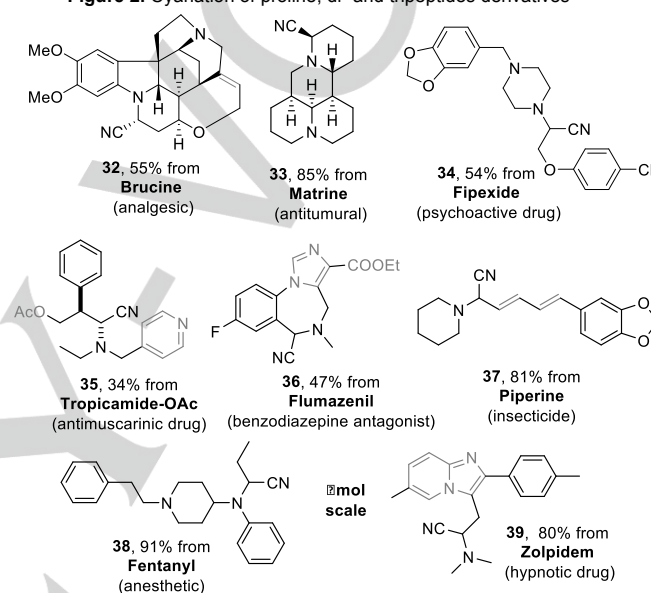
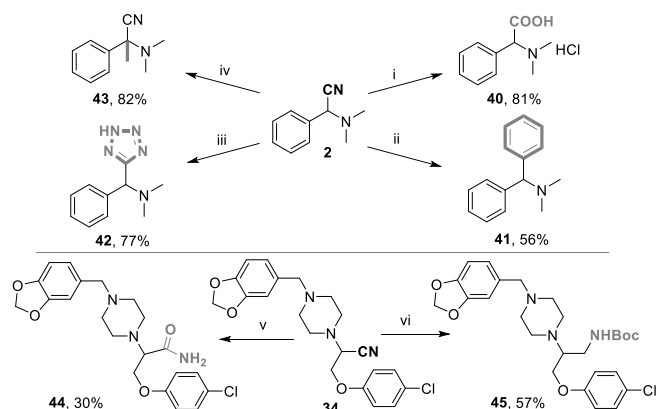


Figure 3. Late stage cyanation of alkaloids and drugs. Tolerated functional groups are highlighted in grey.

After the successful investigations with amino acid derivatives the late stage cyanation of a selection of alkaloids and drugs possessing tertiary amide or lactam residues was approached (Figure 3). Good yields were obtained in all cases and the reductive cyanation reaction proved to be diastereoselective for chiral alkaloids brucine (**32**) and matrine (**33**). Drug molecules containing various heterocycles were well-tolerated (**35**, **36**, **39**). Also, alkene (**32**, **37**) and ester (**35–36**) functionalities proved to be inert under the reaction conditions. Interestingly, the reaction was successful even working at μ mol scale, and Fentanyl and Zolpidem were cyanated in 91 and 80% yield (**38–39**), respectively. To show the synthetic versatility offered by the CN group, various derivatisations of compound **2** were carried out (Scheme 4, top). The nitrile group was hydrolyzed to the carboxylic acid in high yield (**40**). It was also successfully substituted by a phenyl ring on reaction with PhMgBr (**41**) and transformed into a tetrazole (**42**) when reacted with TMSN₃. Furthermore, it is known that the acidic α -proton can be substituted with a multitude of different groups by, for example, deprotonation/alkylation strategies. Following this approach, compound **2** was efficiently methylated using KHMDS and MeI (**43**).^[20] In a similar vein, a more complex molecule, cyanated Fipexide **34**, was converted to amide **44** through partial hydrolysis, and into *N*-Boc-protected amine **45** via a reduction/protection sequence (Scheme 4, bottom).



Scheme 4. Derivatization of compounds **2** and **34**. i) HCl conc, reflux, 24 h; ii) PhMgBr (2 eq), THF, rt, 3 h; iii) TMSN₃ (10 eq), Bu₂SnO (0.6 eq), toluene, 70 °C, 4 d; iv) KHMDS (1 eq), MeI (1.2 eq), THF, rt, 30 min; v) K₂CO₃, H₂O₂, DMSO, rt, 24 h; vi) NiCl₂·6H₂O (2 eq), NaBH₄ (14 eq), Boc₂O (2 eq), MeOH, 0 °C, 1 h.

In conclusion, a new iridium catalysed reductive Strecker reaction for the introduction of a nitrile residue into amide and lactam containing substrates has been developed. The reaction is simple to perform, chemoselective, functional group tolerant, requires low catalyst loading, and has proven to be successful with a broad range of tertiary (hetero)aromatic and aliphatic amides and lactams. The method is appropriate to both gram and μ mol scale synthesis and has been applied to the selective cyanation of the carbonyl carbon linked to the *N*-atom of a proline residue in di- and tripeptides with good yields and selectivities. Finally, late stage cyanation of amide and lactam containing drugs has been effectively developed and proven to be high yielding even at μ mol scale.

Experimental Section

General procedure for the synthesis of α -amino nitrile compounds. To a solution of the amide/lactam (0.3 mmol) in dry toluene (6 mL), Vaska's catalyst (1 mol%) was added. The resulting suspension was stirred for 5 minutes giving a yellow solution. TMDS (2 eq) was added in one portion and the reaction mixture stirred for 5 minutes until H₂ gas evolution had ceased and the solution turned colourless, then TMSN₃ (2 eq) was added in one portion and stirred for 30 minutes or overnight. The solution was then washed with 1 M NaOH, extracted with EtOAc, dried over Na₂SO₄ and concentrated under reduced pressure. Pure α -amino nitrile samples were obtained after flash column chromatography on silica gel.

Acknowledgements

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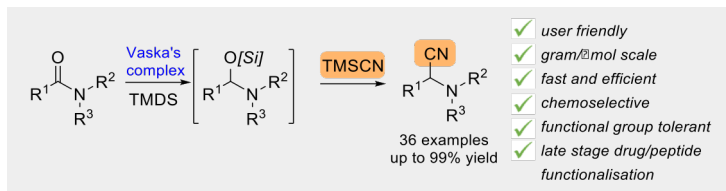
Keywords: amide cyanation • Strecker • iridium catalysed reduction • late stage functionalisation • peptide.

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Layout 2:

COMMUNICATION



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A magic nitrile bullet! A highly chemoselective iridium catalysed reductive Strecker reaction of tertiary amides and lactams has been developed. The protocol is simple to perform, broad in scope, highly efficient (up to 99% yield) and has been successfully applied to the late stage functionalisation of tertiary amides in drugs, naturally occurring alkaloids and peptides.