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Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation

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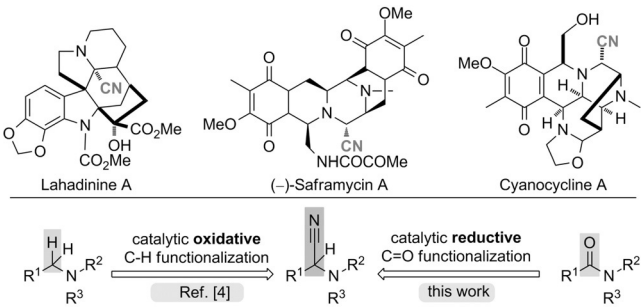
Abstract: *A new iridium-catalyzed reductive Strecker reaction for the direct and efficient formation of α-amino nitrile products from a broad range of (hetero)aromatic and aliphatic tertiary amides, and N-alkyl lactams is reported. The protocol exploits the mild and highly chemoselective reduction of the amide and lactam functionalities using $IrCl(CO)[P(C_6H_5)_3]_2$ (Vaska's complex) in the presence of tetramethyldisiloxane, as a reductant, to directly generate hemiaminal species able to undergo substitution by cyanide upon treatment with TMSCN (TMS = trimethylsilyl). The protocol is simple to perform, broad in scope, efficient (up to 99% yield), and has been successfully applied to the late-stage functionalization of amide- and lactam-containing drugs, and naturally occurring alkaloids, as well as for the selective cyanation of the carbonyl carbon atom linked to the N atom of proline residues within di- and tripeptides.*

Nitrile functionality is found in many bioactive natural products and, because of its high polarity, characteristic linear geometry, and hydrogen-bond-acceptor properties, it 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 five- and six-membered ring heteroaromatics by either cycloaddition or condensation reactions.[2] In addition, α-amino nitriles are a recurrent scaffold in many biologically active molecules and natural compounds.[1,3] *Aspidofractinine* and *Streptomyces* metabolites with antibiotic and antitumoral activities, for example, saframycin A or cyanocycline A and lahadinines A and *B*, extracted from *Kopsia pauciflora,* all 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 functionalization reactions of amines has attracted widespread attention as an alternative approach to classical routes.[4] In fact, great strides have been made in photochemical, electrochemical, and transition-metal-catalyzed sp^2 and sp^3 C–H cyanations.[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]



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

We recognized that an alternative, direct, and synthetically powerful solution for the synthesis of α-amino nitriles could arise from carboxamides by 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 which could efficiently and chemoselectively target such functional groups would likely find numerous applications in library generation, late-stage functionalization, and total synthesis alike.

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 preactivation (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 report our findings.

Our group recently reported that Vaska's complex in the presence of tetramethyldisiloxane (TMDS) catalyzed the intramolecular reductive nitro-Mannich reaction of lactam substrates possessing N-linked nitro-alkyl groups.[12] That

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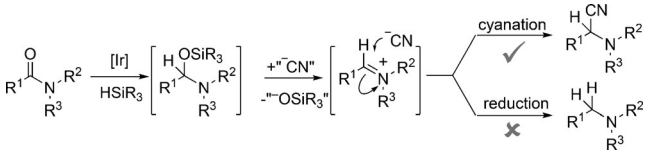
work demonstrated that reactive iminium species could be readily generated, then efficiently trapped by the pendant nitronate nucleophile to afford bicyclic tertiary amines. Furthermore, in a recent publication we have demonstrated a remarkable chemoselectivity of the Vaska's catalyst for lactam carbonyl groups over ester functionalities and C=C bonds.[13] We recognized the significant synthetic potential of opening up this chemistry to include external nucleophiles and cyanide was chosen for many of the reasons outlined above. Following the formation of an intermediate hemiaminal by the action of Vaska's complex and a silane reductant, our hope was that reaction conditions for an efficient intermolecular cyanation reaction which out-competed any over-reduction[14] of the reactive iminium species could be found (Scheme 2).

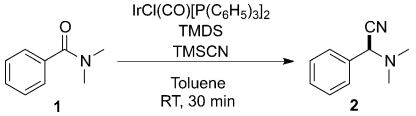


Scheme 2. Catalytic reductive cyanation for the synthesis of α-amino nitriles.

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% (entry 2). Either lowering the amount of catalyst or increasing the concentration proved to be detrimental for the yield (see the Supporting Information for further optimization experiments).

With optimized 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 a 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 adamantyl (**10**)] did not dramatically decrease the yield, and secondary and primary alkyl amides also worked well, thus showing that enolizable 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 **18** unambiguously established

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



Entry[a]	Mol% cat	TMDS (equiv)	TMSCN (equiv)	Yield [%][b]
1	1	1.1	1.1	43
2	1	2	2	92
3[c]	1	2	2	92
4[d]	1	2	2	58

[a] 0.3 mmol of **1**, $IrCl(CO)[P(C_6H_5)_3]_2$ (Vaska 's complex), TMDS, and TMSCN were mixed in toluene (6 mL) according to the general procedure. [b] Yield of isolated product. [c] 1 g scale. [d] 4 mg scale. TMDS = tetramethyldisiloxane, TMS = trimethylsilyl.

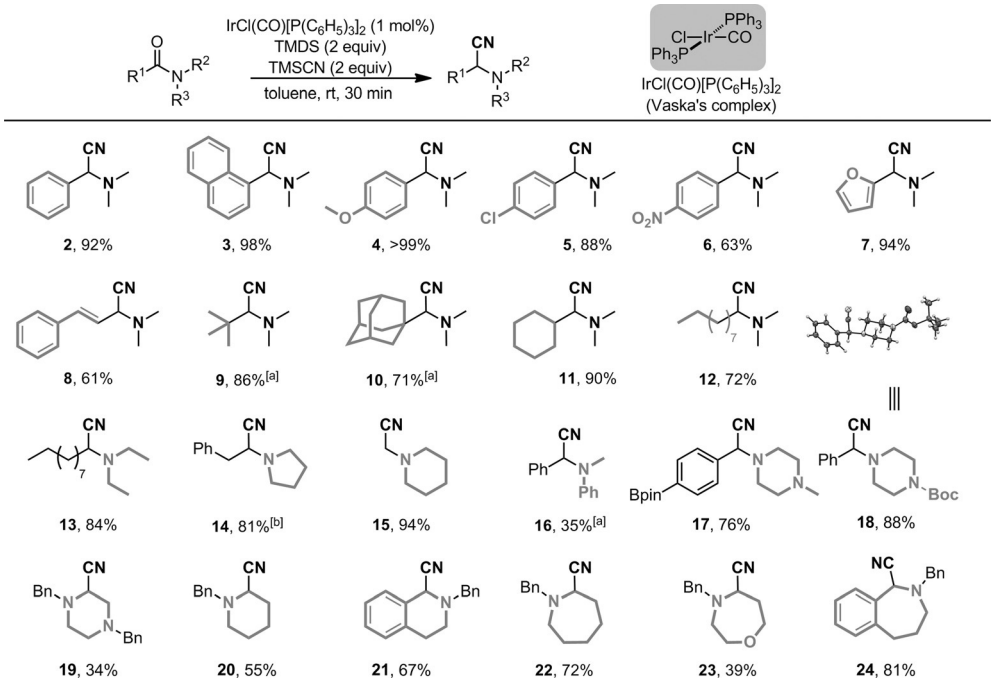
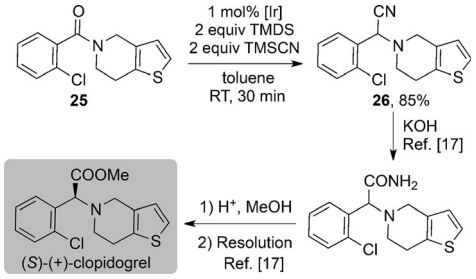


Figure 1. Scope of the reaction. [a] 2 mol% $IrCl(CO)[P(C_6H_5)_3]_2$ and 4 equiv of TMDS were used. [b] 4 equiv of TMSCN.

its structure as shown in Figure 1.[16] In contrast, a substrate possessing an aromatic amine resulted in a considerably reduced yield (**16**) 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 reaction (see the Supporting Information), and the lack of reactivity is likely a result of the lower Lewis basicity as compared with tertiary amides.[17] Importantly, however, their presence in the reaction media did not impede the cyanation of **1** (see the Supporting Information). A formic-acid-derived amide was a good substrate and afforded the 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.[12a] 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 **1** was readily scaled up to 1 gram with no loss of yield (Table 1, entry 3) and also readily scaled down (to 4 mg), and the product was still isolated in an acceptable yield (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 the 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 functionalize the carbonyl carbon atom 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

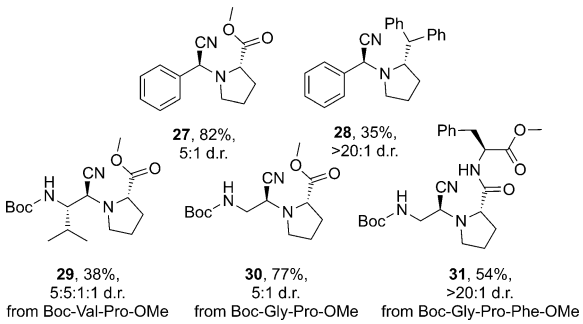


Figure 2. Cyanation of proline-containing di- and tripeptides. Boc = *tert*-butoxycarbonyl.

the formation of only one diastereomeric α-amino nitrile product, albeit with lower yield (**28**). 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 α-carbon atom of the valine residue. The 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, at the carbonyl carbon atom linked to the proline N-atom, in 54% yield, in a highly chemo- and diastereoselective fashion. This reaction is, to our knowledge, the first time that a peptide has been selectively functionalized with a CN group at the carbonyl group attached to a proline N atom. This significant result points to the possibility of allowing selective functionalization of tertiary amides within peptides and proteins.

After successful investigations with amino-acid derivatives, the late-stage cyanation of a selection of alkaloids and drugs possessing either tertiary amide or lactam residues was approached (Figure 3). Good yields were obtained in all cases and the reductive cyanation reaction proved to be diastereo-

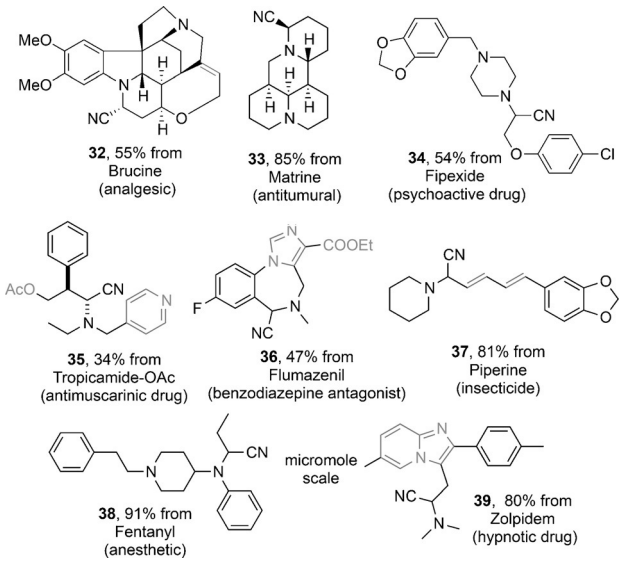
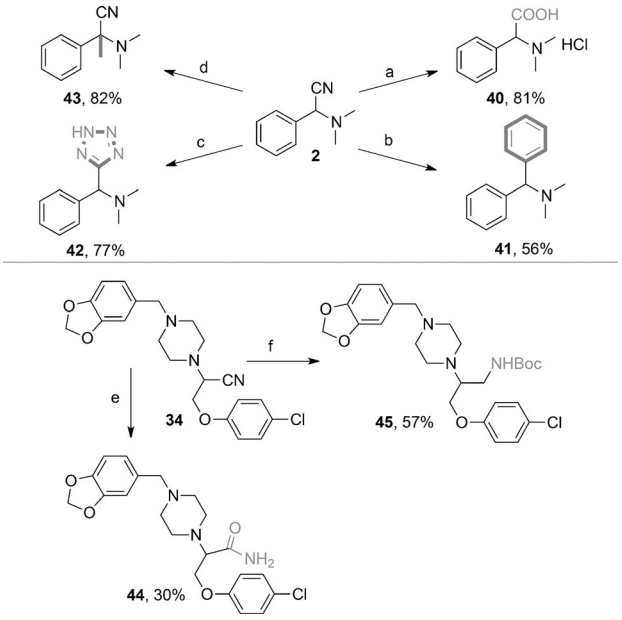


Figure 3. Late-stage cyanation of alkaloids and drugs. Tolerated functional groups are highlighted in grey.

selective 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 at the micromole 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 derivatizations of **2** were carried out (Scheme 4, top). The



Scheme 4. Derivatization of **2** and **34**. a) HCl conc, reflux, 24 h; b) PhMgBr (2 equiv), THF, RT, 3 h; c) $TMSN_3$ (10 equiv), Bu_2SnO (0.6 equiv), toluene, 70 °C, 4 d; d) KHMDS (1 equiv), MeI (1.2 equiv), THF, RT, 30 min; e) K_2CO_3, H_2O_2, DMSO, RT, 24 h; f) $NiCl_2{\cdot}6H_2O$ (2 equiv), $NaBH_4$ (14 equiv), Boc_2O (2 equiv), MeOH, 0 °C, 1 h. DMSO = dimethylsulfoxide, KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran.

nitrile group was hydrolyzed to the carboxylic acid in high yield (**40**). It was also successfully substituted by a phenyl ring upon reaction with PhMgBr (**41**) and transformed into a tetrazole (**42**) when reacted with $TMSN_3$. 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, **2** was efficiently methylated using KHMDS and MeI (**43**).[20] In a similar vein, a more complex molecule, the cyanated Fipexide **34**, was converted into the amide **44** through partial hydrolysis, and into the N-Boc-protected amine **45** by a reduction/protection sequence (Scheme 4, bottom).

In conclusion, a new iridium-catalyzed 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 micromole scale synthesis and has been applied to the selective cyanation of the carbonyl carbon atom 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 micromole scale.

Experimental Section

General procedure for the synthesis of α-amino nitrile compounds. To a solution of the amide/lactam (0.3 mmol) in anhydrous toluene (6 mL), Vaska's catalyst (1 mol%) was added. The resulting suspension was stirred for 5 minutes, giving a yellow solution. TMDS (2 equiv) was added in one portion and the reaction mixture stirred for 5 minutes until H_2 gas evolution had ceased and the solution turned colorless, then TMSCN (2 equiv) was added in one portion and stirred for 30 minutes or overnight. The solution was then washed with 1M NaOH, extracted with EtOAc, dried over Na_2SO_4, and concentrated under reduced pressure. Pure α-amino nitrile samples were obtained after flash column chromatography on silica gel.

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Conflict of interest

The authors declare no conflict of interest.

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