**Amides**

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# Sterically Demanding Oxidative Amidation of α-Substituted Malononitriles with Amines Using $O_2$

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**Abstract:** *An efficient amidation method between readily available 1,1-dicyanoalkanes and either chiral or nonchiral amines was realized simply with molecular oxygen and a carbonate base. This oxidative protocol can be applied to both sterically and electronically challenging substrates in a highly chemoselective, practical, and rapid manner. The use of cyclopropyl and thioether substrates support the radical formation of α-peroxy malononitrile species, which can cyclize to dioxiranes that can monooxygenate malononitrile α-carbanions to afford activated acyl cyanides capable of reacting with amine nucleophiles.*

Reaching high levels of cost economy and atom efficiency for an organic reaction is particularly challenging when faced with highly functionalized substrates and energetically demanding bond formations. This goal translates into finding simple reagent systems as well as practical reaction conditions and work-up procedures, so as to produce very little reagent-based byproducts and reaction-based side-products. There is thus a continual need to develop highly chemoselective methods with low-molecular-weight reagents to minimize side-reactions and thus the molecular wastes derived from both the reagents and the reactants. The efficient and rapid formation of amides and peptides falls into such a challenge. Indeed, although the amide bond plays a pivotal role in organic, biological, and materials chemistry,[1] it still presents a great synthetic challenge when confronted with sterically or electronically demanding substrates.[2] Seminal synthetic methods to making such challenging or complex amides have been reported by the groups of Bode, Rawal, Danishefsky, and Schafmeister.[3]

Adding to such challenges is a drive to develop new ways to make amide bonds by activating nontraditional substrates oxidatively, as represented by the methods from the groups of Milstein, Rovis, Johnston, Bode, Lei, and Garg, as well as ours.[4,5] Stemming from recent mechanistic insights[5c,d] into the umpolung amide synthesis (UmAS) method of Johnston and co-workers,[4c] we now present our oxidative advancement of the masked acyl cyanide (MAC) method to make amides, which was introduced by Yamamoto and co-workers[6] in 1990 and elegantly exploited in 2013 by the group of Rawal.[3c] Specifically, we disclose the direct, oxygen-based conversion of 1,1-dicyanoalkanes to make hindered amides and peptides in high yield and stereochemical integrity. This mild, yet powerful method simply entails stirring α-substituted malononitriles with chiral or nonchiral amines in acetonitrile under $O_2$ with a carbonate base.

The stimulus for this work began during our discovery and development of the base-promoted Nef oxidation of nitroalkenes or nitroalkanes to form their ketones with oxygen (Figure 1a).[5a,b] During the further development of a direct halogenative method to form amides under aerobic conditions,[5c] we isolated α,α-diiodinated nitroalkanes (Figure 1b) and recognized the mechanistic need to make intermediates that bear two electron-stabilizing groups, X and Y (Figure 1c).[5d] These substituents can thus not only stabilize transient radicals and anions, but also act as one- or two-electron leaving groups. We thus proposed to explore an oxidative amidation sequence via putative dioxirane intermediates, which can act as sources of electrophilic monooxygen and transform into reactive acyl derivatives to form amide bonds in a new powerful way.

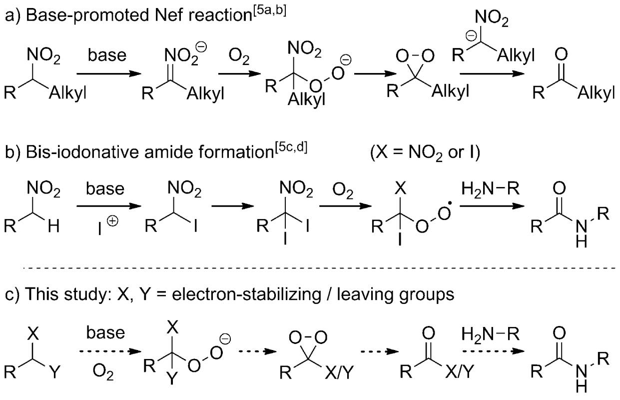

**Figure 1.** Mechanistic rationales for oxidative amidation.

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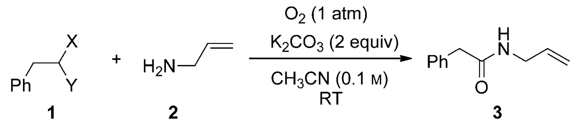
*Table 1:* Screening of functionality for oxidative amide formation.[a]



| Entry | X | Y | $t$ [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | $NO_2$ | $SO_2Ph$ | 12 | <5 |
| 2 | $NO_2$ | Cl | 12 | <5 |
| 3 | CN | CN | 3.5 | 96 |
| 4 | CN | $SO_2Ph$ | 90 | 70 |
| 5 | CN | $PO(OEt)_2$ | 60 | <5 |
| 6 | CN | COOMe | 60 | <5 |
| 7 | CN | OTs | 24 | <5 |

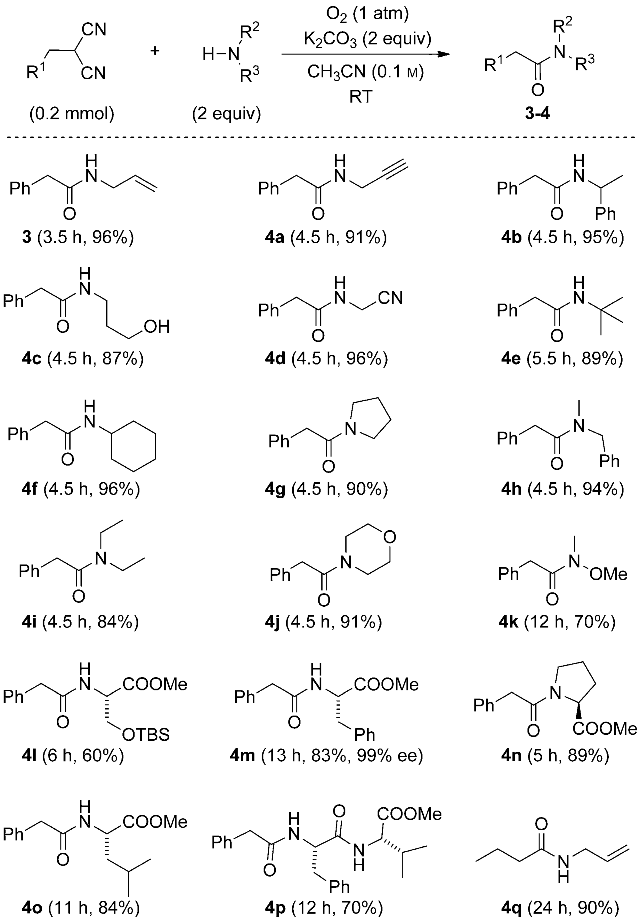
[a] Reactions were conducted with **1** (0.2 mmol), the allyl amine **2** (0.4 mmol), and $K_2CO_3$ (0.4 mmol) at room temperature under $O_2$ (1 atm). [b] Yield of the isolated product. Ts = 4-toluenesulfonyl.

First, we explored $NO_2$,[7] CN,[8] $SO_2R$,[9] and $PO(OR)_2$[10] as suitable X/Y groups for the proposed oxidative amidation sequence (Figure 1c). These studies are summarized in Table 1. Under our recently established oxidative conditions,[5c] reactions of either α-sulfonyl- or α-chloro-substituted nitroalkanes **1** with allylamine (**2**) did not produce the amide product **3** at all (entries 1 and 2). Suspecting the need for alternative electron-withdrawing groups to facilitate single-electron transfer (SET) mechanisms with $O_2$,[5b] we prepared and explored various α-substituted nitrile derivatives (**1**, X = CN). To our delight, when the 1,1-dicyanide **1** (X, Y = CN) was exposed to the amine **2** in the presence of $K_2CO_3$ under $O_2$, the desired amide was generated in 96% chemical yield within 3.5 hours at room temperature (entry 3). Further studies revealed the cooperative nature of CN and $SO_2Ph$ groups in **1**, which gave a 70% yield of **3**, albeit over three days (entry 4). Otherwise, only trace amounts of the amide **3** were observed (entries 5–7).

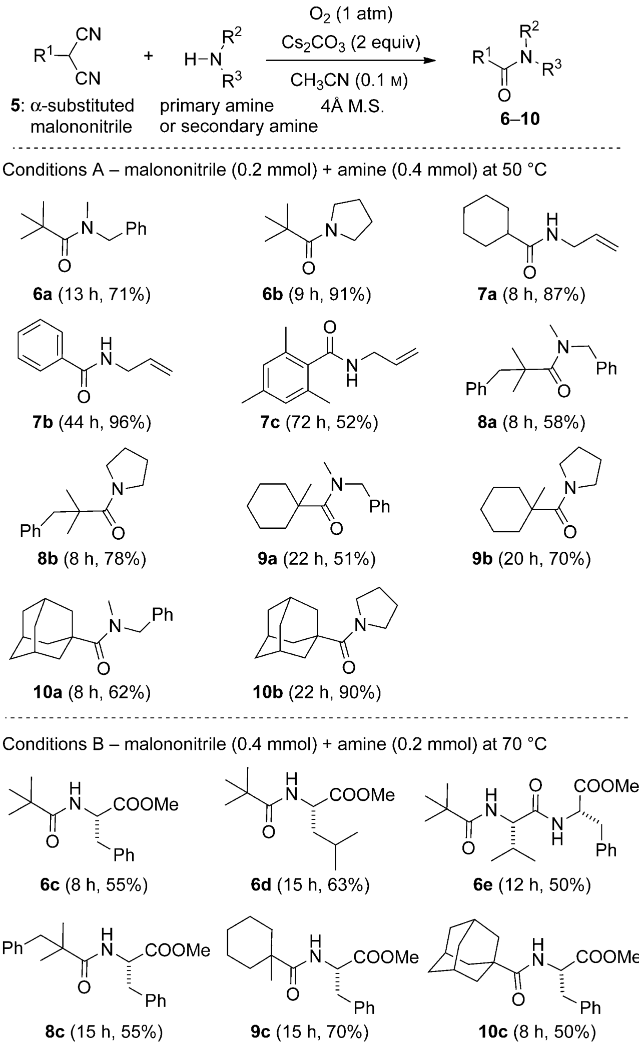
With appropriate functionality and initial reaction conditions in place for the 1,1-dicyanide **1** (X, Y = CN), the scope of the oxidative amidation method was first investigated by changing the amine component (Scheme 1). Common functional groups, such as allyl, propargyl and benzyl amines, displayed high reactivity to amide formation (**3**, **4a**/**b**). The unprotected hydroxy amine generated the corresponding amide **4c** chemoselectively in 87% yield and the electron-deficient 2-aminoacetonitrile gave the desired amide in 96% yield (**4d**). Amines with increasing steric hindrance, including *tert*-butylamine, cyclohexylamine, pyrrolidine, *N*-methylbenzylamine, diethylamine, and morpholine, all gave the desired amides in greater than 80% yield (**4e**–**j**). The reaction conditions were also found suitable for Weinreb amide formation (**4k**). Notably, coupling of **1** with amino-acid methyl esters or an amine-free dipeptide generated the corresponding amides and peptides in 70–84% yields upon isolation (**4l**–**p**) without epimerization. Also, 2-propylmalononitrile reacts with allylamine to give the desired amide **4q** in 90% yield.

Next, our aim was to apply this oxidative method to more challenging amides (see Table S2 in Supporting Information for optimization studies). In short, we studied the α-*tert*-butyl malononitrile **5** ($R^1$ = *t*Bu) and *N*-methylbenzylamine for optimization to the sterically hindered amide **6a**, whereby $Cs_2CO_3$ was demonstrated to be superior, at elevated temperatures, to bases like $K_2CO_3$, KOAc, and $K_3PO_4$, as well as to stronger bases like KO*t*Bu and CsOH (Scheme 2; Conditions A or B). To prevent carboxylic acid formation, presumably derived by **5** reacting with residual water, strictly anhydrous conditions were adopted and predried 4 Å molecular sieves and $Cs_2CO_3$ with two equivalents of amine gave the amide **6a** reliably in 71% yield. We thus explored the scope of these simple oxidative conditions for making other challenging amide and peptide systems (Scheme 2). Besides the notable formation of the congested aromatic amide **7c** with allylamine, the formation of the amides **6**–**10** proceeded in good yield at 50 °C, despite both sides of the amide bond being fully substituted (Conditions A). Furthermore, chiral amino-acid methyl esters and amides could be coupled with sterically hindered malononitriles in acceptable yields and reaction times at 70 °C (Conditions B) with complete stereochemical integrity in the amine component (see the Supporting Information).

On the basis of our previous mechanistic studies into making ketones[5b] and amides[5c,d] from nitroalkanes, one plausible pathway for the oxidative amidation of malononi-



*Scheme 1.* Oxidative amidation of unhindered α-alkylated malononitriles. TBS = *tert*-butyldimethylsilyl.



*Scheme 2.* Oxidative amidation of sterically hindered α-alkylated malononitriles and steric N-capping of amino-acid esters/peptides. M.S. = molecular sieves.

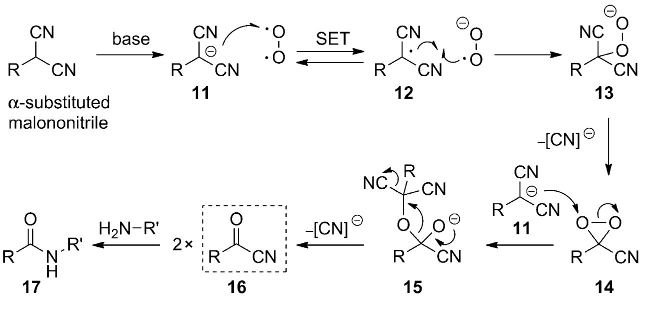
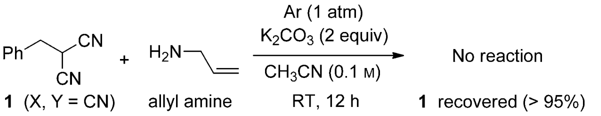


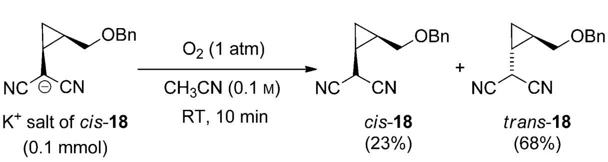
*Figure 2.* Proposed mechanism of amide formation via the acyl cyanide **16**.

triles with amines is proposed in Figure 2. Thus, the α-substituted malononitrile first deprotonates to generate the anion **11**, which is then capable of SET and addition with molecular oxygen, either directly or indirectly. If a radical pair is produced, they would couple to form the peroxide adduct **13**.[5,11] In either case, **13** can cyclize and expel cyanide anion to form the reactive dioxirane intermediate **14** (see the Supporting Information for an alternative $O_2$ addition pathway to eliminate cyanate anions via a four-membered adduct through **12** or **13**). In turn, electrophilic mono-oxygen transfer from **14** to another 1,1-dicyano carbanion (**11**) produces a bis(tetrahedral) adduct **15** which can fragment into two acylating species (**16**) capable of being intercepted by the amine nucleophile. It is conceivable that the initial steps between the intermediates **11**/**12** can be considered to be reversible. A selection of control reactions were carried out to evaluate this mechanistic proposal (also see the Supporting Information).

The role of $O_2$ was considered first [Eq. (1)]. When **1** (X, Y = CN) was mixed with allyl amine in the presence of $K_2CO_3$ under argon, the amide **3** was not formed and **1** was recovered completely. This outcome is in stark contrast to when the reaction was conducted under $O_2$ (Scheme 1; 96 % yield of **3**). Next, the reaction of molecular oxygen with **11** was considered. Based on our Nef study to make ketones from secondary nitroalkanes,[5b] and related reports for ketone formation from monocyanide compounds using $O_2$,[11] processes involving SET were deemed feasible (Figure 2). Thus to determine the existence of a radical species like **12**, we prepared the α-cyclopropyl malononitrile *cis*-**18** as its pure *cis* isomer for suitable radical clock experiments.[12] Exposure of the preformed potassium salt of *cis*-**18** to $O_2$ for 10 minutes gave a 1:3 *cis*-**18**/*trans*-**18** mixture in 90 % yield [Eq. (2)]. Control experiments with added TEMPO (1.0 equiv) and under strictly $O_2$-free atmosphere gave near complete recovery of *cis*-**18** (around 90 %). Moreover, when *cis*-**18** was exposed to the allylamine in the presence of $K_2CO_3$ under $O_2$, the cyclopropyl amide was isolated as a 1:3.5 *cis*-**19**/*trans*-**19** mixture in 90 % yield after 4 hours [Eq. (3)]. Further experiments demonstrated a mixture of *cis*-**18** and *cis*-**19** to be isomerically stable to the reaction conditions under argon (see the Supporting Information). Collectively, these results support the anion **11** reacting reversibly with $O_2$ via SET to form the radical **12**, which can conceivably couple with superoxide to form the peroxide adduct **13** as shown in Figure 2.



(1)



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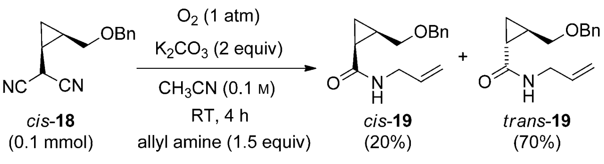
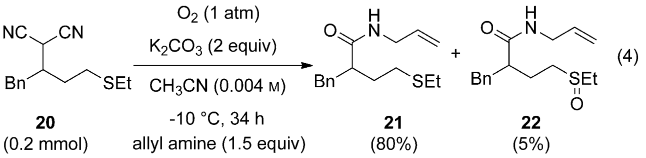


(3)

The fate of the cyano groups was also considered. Thus, the quantities of cyanide and cyanate anions were determined by ion chromatography as produced from the reaction given in the generation of **3** in Scheme 1. With respect to a total theoretical yield of 2 equivalents, cyanate ions were detected in low yield (7.6%), whereas cyanide ions were formed in high yield (84.8%; see the Supporting Information). On the basis of these results, we further suggest that **13** cyclizes to form the dioxirane intermediate **14**, thus releasing the first equivalent of cyanide, after which the second equivalent of cyanide would be generated after amine addition to the proposed acyl cyanide **16** to give the amide product **17** (Figure 2).

Next, to support the electrophilic dioxirane intermediate **14**, intramolecular thioether-trapping experiments were performed in $O_2$-saturated $CH_3CN$, such that the reaction of the anion **11** with molecular $O_2$ would be independent of the concentration of **11** [Eq. (4)].[5b] In the event, the δ-ethylsulfenyl β-benzyl malononitrile **20** was prepared and reacted under dilute conditions at −20 °C. This reaction gave the oxidized sulfinyl amide **22** reliably in 5% yield. The direct oxidation of **20** or the sulfide product **21** by $O_2$ was excluded by additional control experiments at room temperature for over 48 hours (see the Supporting Information).



In summary, we have presented a new powerful way to construct challenging amide bonds between α-substituted malononitriles and amines under $O_2$. The oxidative amidation proceeds under mild reaction conditions, is highly practical, and simply employs cheap inorganic carbonate bases. Mechanistic studies support an initial SET pathway between the anion **11** of the α-substituted malononitrile and $O_2$ (via radical **12**) to form the α-peroxide adduct **13** as a precursor to the dioxirane **14**, which generates acyl cyanide (**16**) via the formation and fragmentation of bis(tetrahedral) adducts **15** (Figure 2). Notably, our method does not require the formation of either congested pre-oxidized hydroxy malononitriles as masked acyl cyanides (MAC)[3c,d,6] or congested halogenated nitroalkanes as precursors to activated esters,[4c,5c,d] and therefore offers good substrate scope for sterically hindered systems. It is thus reasoned that the SET induced addition of $O_2$ to **11** proceeds in a relatively unencumbered way to generate the acyl cyanide **16**, which is known to react readily with amines (or alcohols) in a mild manner.[13] This process compares favorably to either making and reacting acid chlorides with metal cyanides or by activating carboxylic acids with traditional reagents (e.g. with phosphorocyanidates).[2,14] Lastly, we anticipate this method to find wide synthetic use in difficult N-terminal capping amidations and throughout the chemical sciences.[1,2,15]

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*Angew. Chem.* **2016**, *128*, 9206–9210

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[1] a) N. Sewald, H. D. Jakubke in *Peptides*: *Chemistry and Biology*, Wiley-VCH, Weinheim, **2002**; b) "The Amide Linkage: Structural Significance": *Chemistry*, *Biochemistry and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley, New York, **2003**; c) *Peptide Drug Discovery and Development* (Eds.: M. Castanho, N. Santos), Wiley-VCH, Weinheim, **2011**.

[2] a) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631; b) A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, *111*, 6557–6602.

[3] Seminal methods to making challenging amide bonds: a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; b) G. Schäfer, C. Matthey, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9173–9175; *Angew. Chem.* **2012**, *124*, 9307–9310; c) K. S. Yang, A. E. Nibbs, Y. E. Turkmen, V. H. Rawal, *J. Am. Chem. Soc.* **2013**, *135*, 16050–16053; d) K. S. Yang, V. H. Rawal, *J. Am. Chem. Soc.* **2014**, *136*, 16148–16151; e) Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12924–12926; f) Z. Z. Brown, C. E. Schafmeister, *J. Am. Chem. Soc.* **2008**, *130*, 14382–14383.

[4] Leading oxidative methods to making amide bonds using alternative starting materials: a) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792; b) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; c) B. Shen, D. M. Makley, J. N. Johnston, *Nature* **2010**, *465*, 1027–1032; d) I. Pusterla, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 513–516; *Angew. Chem.* **2012**, *124*, 528–531; J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502–506; *Angew. Chem.* **2014**, *126*, 512–516; e) L. Hie, N. F. F. Nathel, X. Hong, Y.-F. Yang, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2016**, *55*, 2810–2814; *Angew. Chem.* **2016**, *128*, 2860–2864.

[5] Discovery, development, and mechanistic studies of the base-promoted Nef reaction and oxidative amidation of nitroalkanes by $O_2$: a) Y. Hayashi, S. Umemiya, *Angew. Chem. Int. Ed.* **2013**, *52*, 3450–3452; *Angew. Chem.* **2013**, *125*, 3534–3536; b) S. Umemiya, K. Nishino, I. Sato, Y. Hayashi, *Chem. Eur. J.* **2014**, *20*, 15753–15759; c) J. Li, M. J. Lear, Y. Kawamoto, S. Umemiya, A. Wong, E. Kwon, I. Sato, Y. Hayashi, *Angew. Chem. Int. Ed.* **2015**, *54*, 12986–12990; *Angew. Chem.* **2015**, *127*, 13178–13182; d) J. Li, M. J. Lear, E. Kwon, Y. Hayashi, *Chem. Eur. J.* **2016**, *22*, 5538–5542.

[6] Seminal development of masked acyl cyanides (MAC): H. Nemoto, Y. Kubota, Y. Yamamoto, *J. Org. Chem.* **1990**, *55*, 4515–4516.

[7] R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.

[8] A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117.

[9] M. Y. Chang, C. Y. Tsai, *Tetrahedron Lett.* **2014**, *55*, 5548–5550.

[10] J. Motoyoshiya, T. Ikeda, S. Tsuboi, T. Kusaura, Y. Takeuchi, S. Hayashi, S. Yoshioka, Y. Takaguchi, H. Aoyama, *J. Org. Chem.* **2003**, *68*, 5950–5955.

[11] Related reports on ketone formation from alkylnitriles using $O_2$: a) S. S. Kulp, M. J. McGee, *J. Org. Chem.* 1983, 48, 4097–4098; b) N. Rabjohn, C. A. Harbert, *J. Org. Chem.* 1970, 35, 3240–

3243; c) S. H. Kim, K. H. Kim, J. N. Kim, *Adv. Synth. Catal.* **2011**, *353*, 3335 – 3339.

[12] a) E. L. Spence, G. J. Langley, T. D. H. Bugg, *J. Am. Chem. Soc.* **1996**, *118*, 8336 – 8343; b) T. Benkovics, J. Du, I. A. Guzei, T. P. Yoon, *J. Org. Chem.* **2009**, *74*, 5545 – 5552; c) J. F. Van Humbeck, S. P. Simonovich, R. R. Knowles, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 10012 – 10014; d) E. Arceo, I. D. Jurberg, A. Alvarez-Fernandez, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750 – 756.

[13] Current oxidative methods to acyl cyanide intermediates are limited to unhindered mono- or bisnitriles and use peroxy reagents: a) Y. Sugiura, Y. Tachikawa, Y. Nagasawa, N. Tada, A. Itoh, *RSC Adv.* **2015**, *5*, 70883 – 70886; b) M. Brünjes, M. J. Ford, H. Dietrich, K. Wilson, *Synlett* **2015**, *26*, 1365 – 1370; c) X. Chen, T. Chen, Q. Li, Y. Zhou, L.-B. Han, S.-F. Yin, *Chem. Eur. J.* **2014**, *20*, 12234 – 12238; for amide and ester formations, see: d) S.-I. Murahashi, T. Naota, N. Nakajima, *Tetrahedron Lett.* **1985**, *26*, 925 – 928; e) S. Förster, O. Tverskoy, G. Helmchen, *Synlett* **2008**, 2803 – 2806; f) T. Arai, T. Moribatake, H. Masum, *Chem. Eur. J.* **2015**, *21*, 10671 – 10675.

[14] For classical and emerging methods to acyl cyanides, see: a) S. Hünig, R. Schaller, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36 – 49; *Angew. Chem.* **1982**, *94*, 1 – 15; b) S. Takuma, Y. Hamada, T. Shioiri, *Chem. Pharm. Bull.* **1982**, *30*, 3147 – 3135; c) S. Lundgren, E. Wingstrand, C. Moberg, *Adv. Synth. Catal.* **2007**, *349*, 364 – 372; d) H. H. Choi, Y. H. Son, M. S. Jung, E. J. Kung, *Tetrahedron Lett.* **2011**, *52*, 2312 – 2315.

[15] For peptide N-terminal capping, see: A. J. Doig, R. L. Baldwin, *Protein Sci.* **1995**, *4*, 1325 – 1336; Ongoing work pertains to preventing β-amino epimerization of chiral malononitriles (see Ref. [13e,f]) prior to acyl cyanide formation. Also oxidative esterification studies with $O_2$ show promise. For example, the reaction of **1** (as in Table 1, entry 3) with methanol (5 equiv) instead of allyl amine **2** proceeds in 85 % yield.

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