Angewandte Communications

Oxidative Amidation

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Sterically Demanding Oxidative Amidation of α-Substituted Malononitriles with Amines using O_2**

Jing Li, Martin J. Lear, and Yujiro Hayashi**

Abstract: *An efficient amidation method between readily available 1,1-dicyanoalkanes and chiral or non-chiral 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 translates into finding simple reagent systems as well as practical 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 that 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 non-traditional substrates oxidatively, as represented by the methods of Milstein, Rovis, Johnston, Bode, Lei, Garg, and ours.[4,5] Stemming from recent mechanistic insights[5c,d] into Johnston's umpolung amide synthesis (UmAS),[4c] we now present our oxidative advancement of the masked acyl cyanide (MAC) method to make amides, which was introduced by Yamamoto[6] in 1990 and elegantly exploited in 2013 by 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 non-chiral 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 (Eq. (1), Figure 1).[5a,b] During the further development of a direct halogenative method to form amides under aerobic conditions,[5c] we isolated α,α-diiodinated nitroalkanes (Eq. (2)) and recognized the mechanistic need to make intermediates that bear two electron-stabilizing groups X and Y (Eq. (3)).[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 mono-oxygen and transform into reactive acyl derivatives to form amide bonds in a new powerful way.

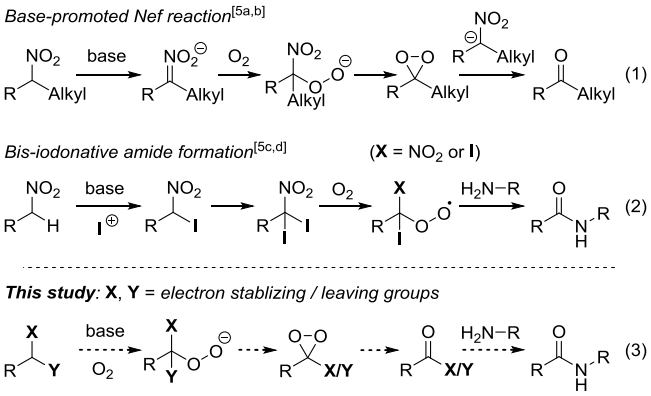

Figure 1. Mechanistic rationales for oxidative amidation.

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 (Eq. (3)). These studies are summarized in Table 1 (Eq. (4)). Under our recently established oxidative conditions,[5c] reactions of α-sulfonyl or α-chloro substituted nitroalkanes **1** with allylamine **2** produced no amide product **3** at all (entries 1–3). 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 h 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).

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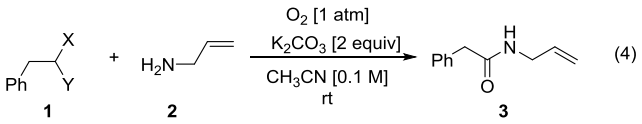
Table 1. Screening of functionality for oxidative amide formation.[a]



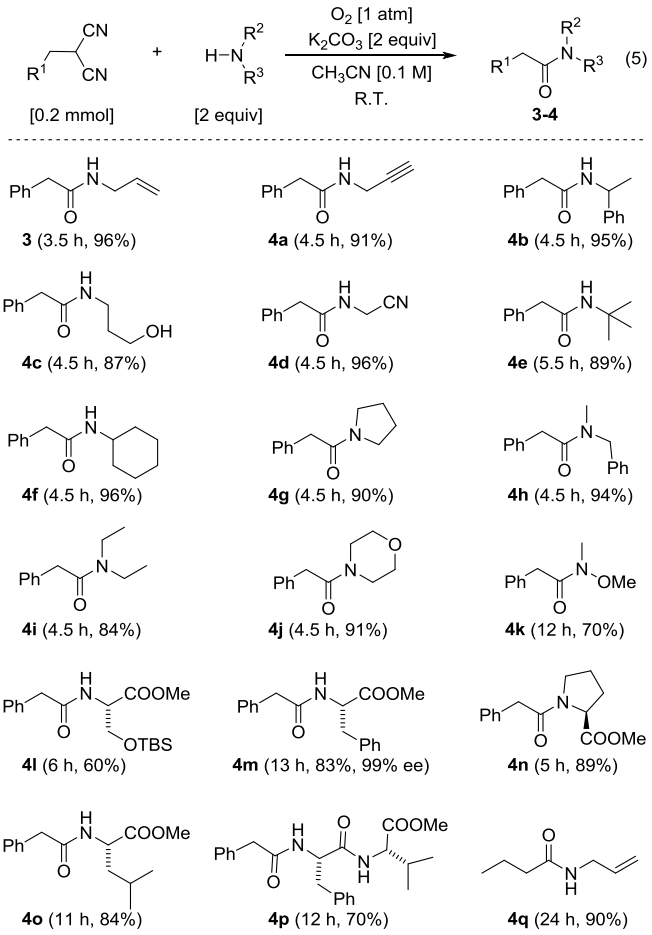
Entry	X	Y	Time [h]	Yield [%]
1	NO_2	SO_2Ph	12	< 5
2	NO_2	Cl	12	< 5
3	CN	CN	3.5	96
4	CN	SO_2Ph	90	70
5	CN	$PO(OEt)_2$	60	< 5
6	CN	COOMe	60	< 5
7	CN	OTs	24	< 5

[a] Reactions were conducted with **1** (0.2 mmol), allyl amine **2** (0.4 mmol) and K_2CO_3 (0.4 mmol) at room temperature under O_2 (1 atm).

With appropriate functionality and initial conditions in place for the 1,1-dicyanide **1** (X, Y = CN), the scope of the oxidative amidation method was 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 hydroxyl 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 *t*-butylamine, cyclohexylamine, pyrrolidine, *N*-methylbenzylamine diethylamine and morpholine, all gave the desired amides in greater than 80% yield (**4e**–**4j**). The 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% isolated yields (**4l**–**4p**) without epimerization. Also, 2-propylmalononitrile reacts with allylamine to give the desired amide **4q** in 90% yield.

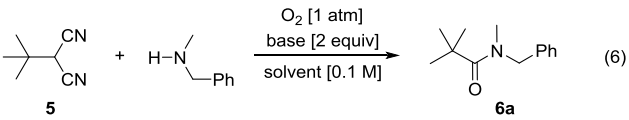
Next, our aim was to apply this oxidative method to more challenging amides. As a model system, we selected the α-*tert*-butyl malononitrile **5** and *N*-methylbenzylamine for optimization to the sterically hindered amide **6a** (Table 2, Eq. (6)). The reaction was very slow when K_2CO_3 was used as base, even at 50 ºC (entry 1). Changing the solvent from acetonitrile to THF or DMF, for example, gave no detectable product at all (entry 2). Eventually, Cs_2CO_3 was demonstrated to be superior to bases like K_2CO_3, KOAc, and K_3PO_4, as well as to stronger bases like KO^{t}Bu and CsOH (entries 3-7). Increasing the temperature to 50 °C slightly improved the reaction speed and gave a higher yield of 20% (cf. entries 7 and 8). During these optimization studies (entries 1–8), the major side product was identified as the corresponding carboxylic acid, presumably derived from **5** reacting with residual water. Therefore, strictly anhydrous conditions were adopted and pre-dried 4Å molecular sieves and Cs_2CO_3 dramatically improved the yield (60%; entry 9). Finally, for sterically demanding systems, it was optimal to adopt two equivalents of the *N*-methylbenzylamine. This gave the amide **6a** in 70% yield (entry 10).

With suitable conditions for a sterically demanding amidation to **6a** identified, we investigated the scope of this simple oxidative protocol to challenging amide and peptide systems (Scheme 2).



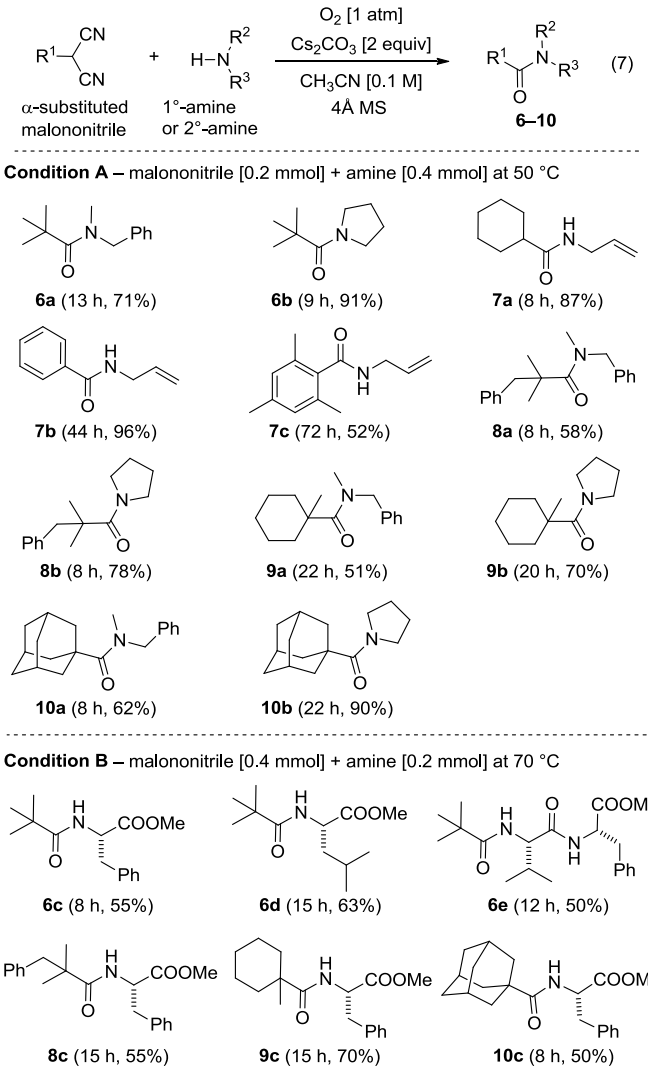
Scheme 1. Oxidative amidation of unhindered α-alkylated malononitriles.

Table 2. Oxidative amidation study to form a sterically hindered amide.[a]



Entry	Base	Solvent	Conditions	4Å MS	Yield [%]
1	K_2CO_3	CH_3CN	rt, 24 h; or	-	15
			50 °C, 12 h	-	15
2	K_2CO_3	THF or DMF	rt, 24 h	-	< 5%
3	KOAc	CH_3CN	rt, 24 h	-	< 5%
4	K_3PO_4	CH_3CN	rt, 24 h	-	< 5%
5	KO^{t}Bu	CH_3CN	rt, 24 h	-	< 5%
6	CsOH	CH_3CN	rt, 24 h	-	< 5%
7	Cs_2CO_3	CH_3CN	rt, 24 h	-	15
8	Cs_2CO_3	CH_3CN	50 °C, 12 h	-	20
9[b]	Cs_2CO_3	CH_3CN	50 °C, 12 h	100 mg	60
10[b,c]	Cs_2CO_3	CH_3CN	50 °C, 12 h	100 mg	70

[a] Reactions were conducted with malononitrile **5** (0.2 mmol), *N*-methylbenzylamine (0.2 mmol), base (0.4 mmol) under O_2 atmosphere; [b] Cs_2CO_3 and 4Å MS were flame dried under vacuum and saturated with O_2 before use; [c] *N*-methylbenzylamine (0.4 mmol) was used.



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

Besides the notable formation of the congested aromatic amide **7c** with allylamine, the formation of 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 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 malononitriles with amines is proposed in Figure 2. Thus, the α-substituted malononitrile first deprotonates to generate an anion **11**, which is then capable of single-electron transfer (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, the dioxygenated adduct **13** can cyclize and expel cyanide anion to form the reactive dioxirane intermediate **14** (see Supportng Information for an alternative O_2 addition papthway to eliminate cyanate anions via a four-membered adduct via **12** or **13**). In turn, electrophilic mono-oxygen transfer from the dioxirane **14** to another 1,1-dicyano carbanion **11** produces a *bis*-tetrahedral adduct **15** that can fragment into two acylating species **16** capable of being intercepted by the amine nucleophile. It is conceivable that the intital 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 (Scheme 3; also see Supporting Information).

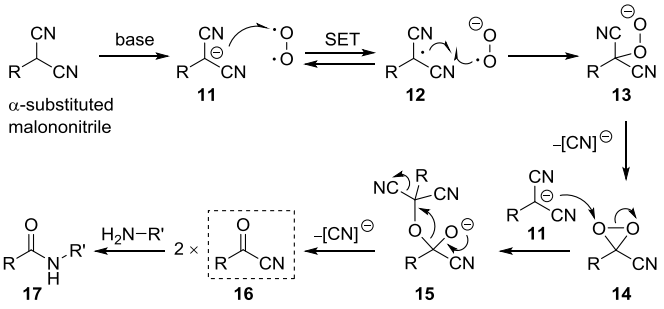
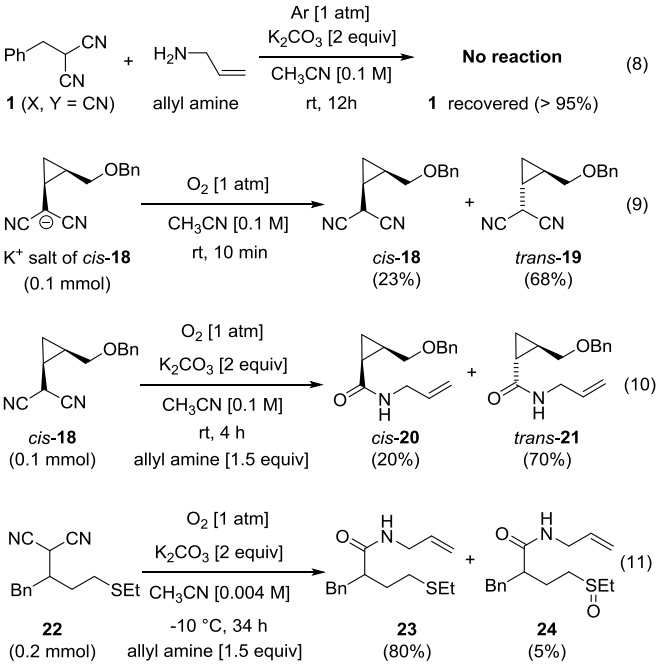


Figure 2. Proposed mechanism of amide formation via acyl cyanides **16**.



Scheme 3. Experiments to probe intermediates of oxidative amidation process.

The role of O_2 was considered first (Eq. (8)). When the malononitrile **1** (X, Y = CN) was mixed with allyl amine in the presence of K_2CO_3 under Ar, no amide **3** formed and **1** was recovered completely. This 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 the 1,1-dicyano carbanion **11** was considered. Based on our Nef study to make ketones from secondary nitroalkanes,[5b] and related reports for ketone formation from mono-cyanide compounds using O_2,[11] processes involving single-electron transfer (SET) were deemed feasible (Figure 2). Thus to determine the existence of radical species like **12**, we prepared the α-cyclopropyl malononitrile *cis*-**18** as its pure isomer for suitable radical clock experiments.[12] Exposure of the pre-formed potassium salt of *cis*-**18** to O_2 for 10 minutes gave a 1:3 *cis*-**18**/*trans*-**19** mixture in 90% yield (Eq. (9)). Control experiments with added TEMPO (1.0 equiv) and under strictly O_2-free atmospheres gave near complete recovery of the *cis* starting material (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*-**20**/*trans*-**21** mixture in 90% yield after 4 h (Eq. (10)). Further experiments demonstrated a mixture of the *cis* starting material **18** and *cis* amide product **20** to be isomerically stable to the reaction conditions under Ar (see Supporting Information). Collectively, these results support the anion **11** reacting reversibly with O_2 via SET to form a radical **12**, which can conceivably couple with superoxide to form a peroxide adduct **13** as shown in Figure 2.

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 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 Supporting Information). On the basis of these results, we further suggest the peroxide adduct **13** cyclizes to form a dioxirane intermediate **14**, 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** (see 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. 11).[5b] In the event, the δ-ethylsulfenyl β-benzyl malononitrile **22** was prepared and reacted under dilute conditions at –20 °C. This gave the oxidized sulfinyl amide **24** reliably in 5% yield. The direct oxidation of the sulfide starting material **22** or sulfide product **23** by O_2 was excluded by additional control experiments at room temperature over 48 h (see 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 an α-peroxide adduct **13** as a precursor to the dioxirane **14**, which generates acyl cyanides **16** via the formation and fragmentation of *bis*-tetrahedral adducts **15** (Figure 2). Notably, our method does not require the formation of congested pre-oxidized hydroxyl 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 1,1-dicyanide anions **11** proceeds in a relatively unencumbered way to form sterically hindered acyl and aroyl cyanides **16**, which are known to react readily with amines (or alcohols) in a mild manner.[13] This compares favourably to 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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Keywords: amides • malononitriles • peroxides • radical reactions • dioxiranes

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[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 [cf. ref. 13e,f] prior to acyl cyanide formation. Also oxidative esterification studies with O_2 show promise; for example, the reaction of **1** in Eq. (4) with methanol [5 equiv] instead of allyl amine **2** proceeds in 85% yield.

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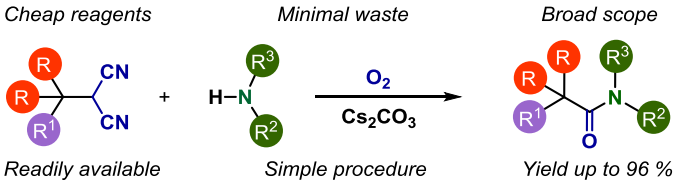

Simply mix and stir: With just O_2 and base, the direct coupling of readily available malononitriles and amines provides an efficient way to make sterically hindered amides. A radical mechanistic pathway via dioxirane intermediates is proposed, which is supported by cyclopropane-based radical-clock experiments.