Peptide Coupling

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Oxidative Amidation of Nitroalkanes with Amine Nucleophiles using Molecular Oxygen and Iodine

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Abstract: *The formation of amides and peptides often necessitates powerful yet mild reagent systems. The reagents used, however, are often expensive and highly elaborate. New atom-economical and practical methods that achieve such goals are highly desirable. Ideally, the methods should start with substrates that are readily available in both chiral and non-chiral forms and utilize cheap reagents that are compatible with a wide variety of functional groups, steric encumberance, and epimerizable stereocenters. A direct oxidative method was developed to form amide and peptide bonds between amines and primary nitroalkanes simply by using I_2 and K_2CO_3 under O_2. Contrary to expectations, a 1:1 halogen-bonded complex forms between the iodonium source and the amine, which reacts with nitronates to form α-iodo nitroalkanes as precursors to the amides.*

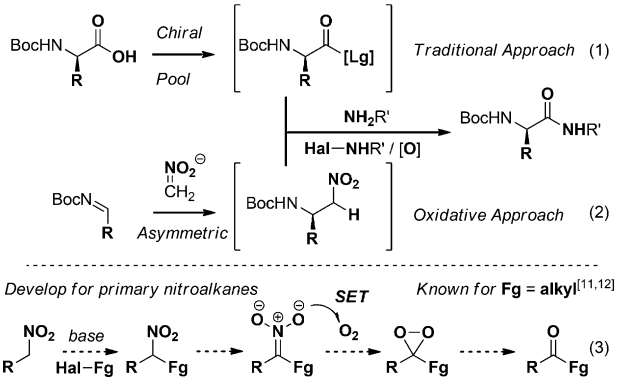

Figure 1. Traditional versus oxidative approaches to amide formation.

Traditional peptide and amide synthesis involves the electrophilic derivatization and activation of a carboxylic acid into an amine-selective acylating species (Eq. (1), Figure 1; Lg = leaving group).[1,2] There are, however, a few atypical cases of forming reactive *N*-acylating species in an oxidative manner from alcohols, aldehydes, and alkyne precursors.[3,4] Notably, pre-synthesized α-bromo substituted nitroalkanes have been oxidized with *N*-iodosuccinimide (NIS) and molecular oxygen in the presence of amines.[5–7] To account for the apparent umpolung in reactivity of the amine components, the intermediacy of electrophilic *N*-iodo amines and tetrahedral α-amino, α-bromo nitroalkanes were suggested.[5,6] From a synthetic point of view, however, methods to achieve direct asymmetric access to α-bromo nitroalkanes are relatively limited in substrate scope.[7,8] In comparison, there are a wide variety of catalytic asymmetric methods that adopt nitromethane as a simple, cheap pronucleophile to add to both alkyl and aryl aldehydes, imines, enals, enones, and so forth.[9,10] Herein, our interest was to exploit these readily available primary nitroalkane substrates (Eqs. (2) and (3)) and develop a direct oxidative method to form amide and peptide bonds in a most economical and practical manner.

Our inspiration for this study started after our 2013 total synthesis of prostaglandin A_1 and E_1 methyl esters.[11] Specifically, we discovered the base-promoted Nef conversion of a key nitroalkene into an enone product under aerobic conditions. In 2014, we extended this oxidative transformation to a wide range of nitroalkenes and nitroalkanes to produce enones and ketones, respectively (Eq. (3); Fg = alkyl).[12] Mechanistic insights were gained from ^{18}O-labeling, nitrite/nitrate ion analysis, intramolecular thioether trapping, and radical clock experiments. In short, the formation of ketones from secondary α-alkylated nitroalkanes was shown to be consistent with a single-electron transfer (SET) mechanism from a charged *aci*-nitronate electron donor to a triplet dioxygen molecule to afford an eventual dioxirane adduct after expelling a nitrite anion. The dioxirane subsequently acts as an electrophilic source of mono-oxygen[13] that can be captured by another nitronate anion in the surrounding basic medium.

On the basis of these recent mechanistic findings,[12] we reasoned that secondary α-amino nitroalkanes could be formed in situ by reacting primary nitronates with electrophilic *N*-halo amines (Eq. (3); Hal = halogen, Fg = amine). These would be similarly oxidized with oxygen to afford peroxy adducts bearing amine groups and eventually trans-

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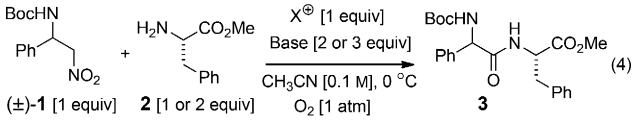
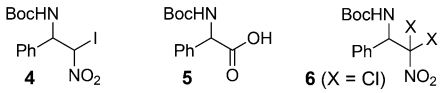
form into amides. At this juncture, among other mechanistic concerns, it was not certain whether the formation and reaction of *N*-iodo amines could be achieved in situ and thereby generate the requisite α-amino nitroalkane intermediates. This premise was, however, given credence by the suggestion of *N*-iodo amine and α-amino nitroalkane intermediates being reported in a series of oxidative umpolung amide synthesis (UmAS) studies.[5–7] Herein, during the course of developing an atom-economical, direct amidation procedure of readily prepared chiral nitroalkanes,[9,10] we describe our independent findings and ultimately propose new mechanistic aspects that have general implications both in amine/halogen-based chemistry and in UmAS chemistry.

Despite some mechanistic concerns regarding the amine component and the oxidative steps (Eq. (3)), we first elected to pursue the base-promoted oxidative coupling of the racemic nitroalkane **1**[9] with the hydrochloride salt of (*S*)-phenylalanine methyl ester **2** and NIS in acetonitrile (Table 1). Thus, the resultant 1:1 diastereomeric mixture of the dipeptide **3** could be checked for its stereochemical integrity by NMR and HPLC analysis. In the first instance, the base was varied (entries 1–7). This quickly demonstrated K_2CO_3 (entry 4) to be superior to weaker bases such as NaOAc, which gave the α-iodo nitroalkane **4** (entry 1). Stronger bases, such as Cs_2CO_3 and K_3PO_4, gave slightly lower yields of the dipeptide product **3** (entries 5 and 6). Soluble bases such as DBU were also found inferior to K_2CO_3 (cf. entries 4 and 7), but both conditions resulted in significant amounts of the carboxylic acid **5** (30–50% yields). The use of less electrophilic *N*-halosuccinamides did not improve the result (entries 8 and 9), and the α,α-dichloro nitroalkane **6** (X = Cl) was isolated in one case (entry 9). A change in the solvent system with NIS and adopting two equivalents of the free amine of **2** proved more successful (entries 10 to 15). In particular, the use of molecular I_2 or NIS at room temperature afforded optimal yields of dipeptide **3** (67%; entry 15). Generation of the carboxylic side-product **5** could not be avoided even under strictly anhydrous conditions.

Table 1: Optimization of oxidative peptide formation.[a]



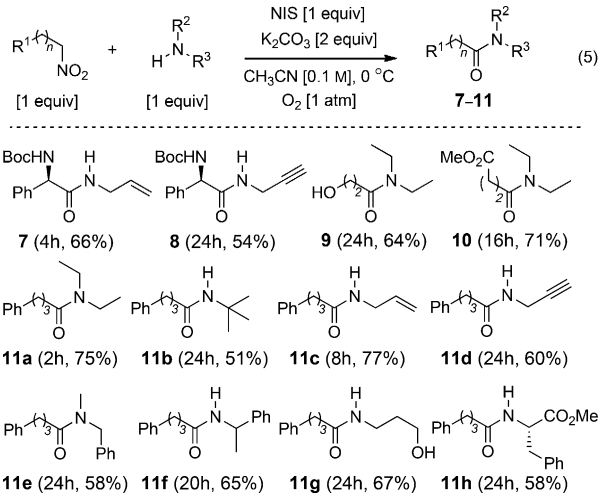


Entry	Base	X^+	Solvent (*t* [h])	**3**	**4**	**5**
1	NaOAc	NIS	CH_3CN (5)	–	5	–
2	KOAc	NIS	CH_3CN (5)	20	–	–
3	Na_2CO_3	NIS	CH_3CN (15)	5	–	–
4	K_2CO_3	NIS	CH_3CN (3)	49	–	30
5	Cs_2CO_3	NIS	CH_3CN (2)	30	–	–
6	K_3PO_4	NIS	CH_3CN (3)	42	–	–
7	DBU	NIS	CH_3CN (12)	30	–	50
8	K_2CO_3	NBS	CH_3CN (12)	20	–	–
9	K_2CO_3	NCS	CH_3CN (12)	–	–[b]	–
10[c]	K_2CO_3	NIS	CH_3CN (2.5)	51	–	–
11[c]	K_2CO_3	NIS	THF (7.5)	51	–	–
12[c]	K_2CO_3	NIS	$PhCH_3$ (48)	15	–	60
13[c]	K_2CO_3	NIS	DMSO (48)	15	–	30
14[c,d]	K_2CO_3	NIS	1:1 media (12)	59	–	30
15[c,e]	K_2CO_3	I_2	1:1 media (4)	67	–	25

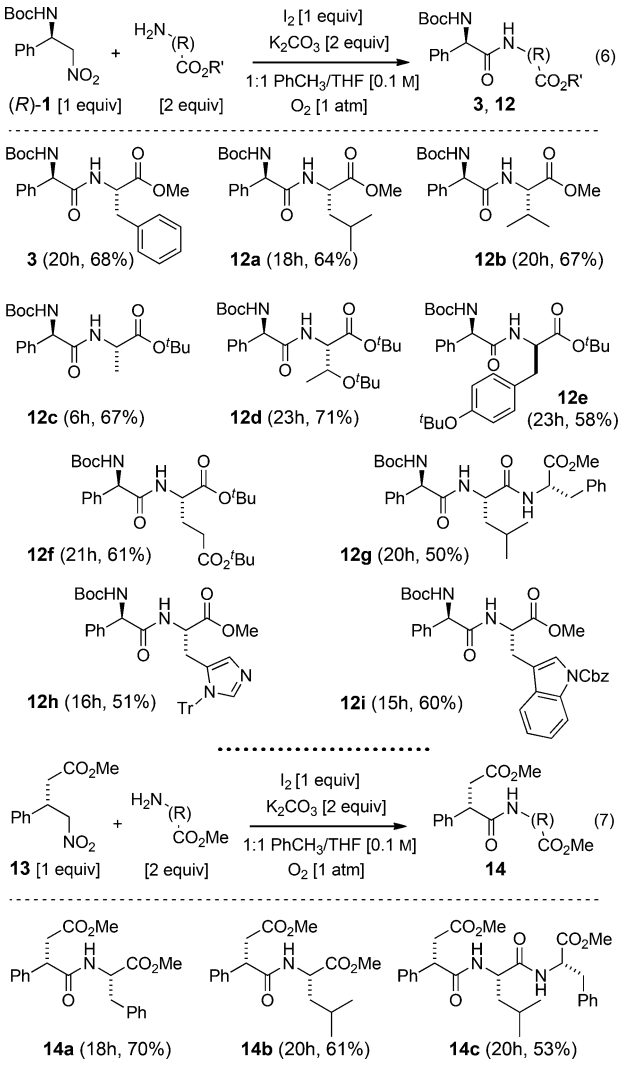
[a] Unless noted otherwise, all reactions were conducted with nitroalkane **1** [0.2 mmol], amine·HCl salt **2** [0.2 mmol], base [0.6 mmol], halonium (X^+) source [0.2 mmol] at 0°C in solvent [2 mL] under O_2 [1 atmosphere] and yields of isolated products (%) are given. [b] Dichlorinated nitroalkane **6** (X = Cl) was isolated in 10% yield. [c] For entries 10 to 15, two equivalents of the free amine **2** [0.4 mmol] and base [0.4 mmol] were used. [d] 1:1 toluene/THF mixture was used. [e] Reaction performed at room temperature with free amine **2** [0.4 mmol] and base [0.4 mmol]; a similar result was obtained with NIS [0.2 mmol] over 12 h.

Next, we investigated the scope of the oxidative amidation method with the use of NIS (Scheme 1) and I_2 (Scheme 2). The optimal solvent for primary and secondary alkyl amines was determined to be acetonitrile (Eq. (5)). Unsaturated functional groups, such as benzyl, allyl, and alkynyl groups, remained unreacted, and the amidation method also tolerated unprotected hydroxy groups (**9**, **11g**). Extension of the method to amino acid esters with (*R*)-**1**[14] was optimally performed with I_2 in 1:1 THF/toluene (Eq. (6)). Importantly, the dipeptide products (**3**, **12**) were produced with complete stereochemical integrity. No epimerization of potentially labile α-stereocenters was observed (Supporting Information). The same tolerances were found for readily prepared, chiral nitroalkyl Michael adducts[15] (**13**→**14**, Eq. (7)) and standard protecting groups (for example, *O*-*t*Bu, *N*-Tr, *N*-Cbz, *N*-Boc; Tr = trityl = triphenymethyl, Cbz = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl) were also found to be compatible.

To evaluate whether our initial mechanistic idea was in keeping with prior studies,[12] we began to explore the first α-amination step of our proposal (Eq. (3)). In short, all attempts to prepare, infer, or observe the anticipated *N*-iodo amines,[5–7] were not confirmed in our hands. Instead, we interpret our NMR data to show that amines like allylamine and α-methyl benzyl amine form a complex readily with NIS and precipitate, and these precipitates behave chemically as sources of electrophilic iodine and nucleophilic amine. For



Scheme 1. Oxidative amidation using NIS/O_2.



Scheme 2. Oxidative peptide formation using I_2/O_2.

example, these 1:1 NIS/amine precipitates can be employed directly in our base-promoted nitroalkane amidation procedure with similar success (cf. Eq. (4)), and they also react with electrophilic Boc_2O to form standard NH-Boc amides slowly (Supporting Information). Eventually, we were able to obtain a single-crystal X-ray crystallographic structure for the allylamine/NIS complex **15** (Figure 2).

This evidence of a halogen bonded amine complex **15** and isolating an α-iodo nitroalkane **4** (Table 1, entry 1) clearly puts our proposed α-amination (Eq. (3), Fg = NHR) into question. Suspecting α-iodination was occurring first, and thus the mono-iodide **4** as an early intermediate, we first checked for its formation by reacting the *aci*-nitronate anion of **1** with **15** or NIS alone (Scheme 3). This being the case in

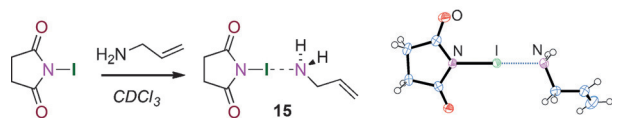
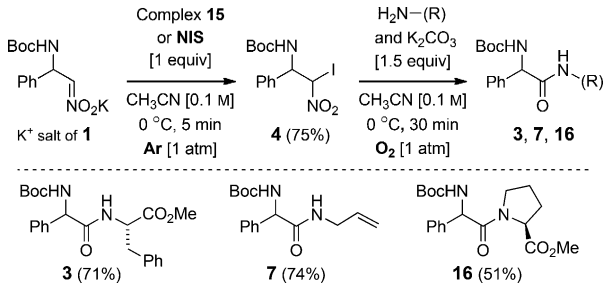


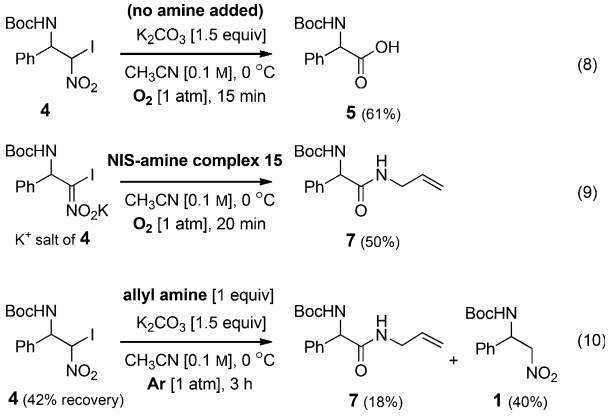
Figure 2. ORTEP X-ray crystal structure of 1:1 NIS·allylamine (**15**) with ellipsoids set at 30% probability level.



Scheme 3. Formation and oxidative amidation of α-iodo nitroalkane **4**.

75% yield, pre-prepared **4** was tested for its ability to form amides directly. Electrophilic halogen sources were omitted and **4** was reacted in the presence of K_2CO_3, O_2, and a slight excess of allylamine or phenylalanine methyl ester **2**. The anticipated amides were isolated in good yields at 0 °C within 30 min. The iodo nitroalkane **4** was even reactive enough to couple with the methyl ester of L-proline, a secondary amino ester often displaying unique reactivity, giving its respective dipeptide **16** in 51% yield.

Notably, we did not observe the intermediacy or isolate any α-amino nitroalkane product, as either we proposed in Equation (3)[12] or as reported in umpolung amide synthesis (UmAS) studies.[5–7] This was the case even by directly reacting pre-formed *N*-bromo amines (or **15**, see above) with the *aci*-nitronate of **1**; in fact, this generated the α-bromo analogue of **4** in good yields.[16] Having confirmed the α-iodide **4** as the primary intermediate, two possible pathways to form the amide product **7** were considered; one pathway being where an oxygen molecule first reacts with **4** before the amine component, and in the other pathway the amine reacts with **4** first. Thus, the relative reactivities of the amine and oxygen components were investigated through a set of control experiments (Scheme 4). Here, we found the α-iodide **4** reacted readily with O_2 within 15–20 min, giving good yields of the oxidized products **5** or **7** (cf. Eq. (8) and (9)). In the absence of O_2, the amine reacts with **4** relatively slowly and inefficiently over 3 h (cf. Eq. (10)). These results support the



Scheme 4. Control experiments to discern relative reactivity of **4** to O_2 and amine components.

initial reaction of O_2 with **4**, as opposed to the α-iodide **4** first reacting with the amine component.[17]

Collectively, our findings are consistent with the reaction sequence as illustrated in Figure 3. We thus propose an *aci*-nitronate anion, once formed under the basic conditions from

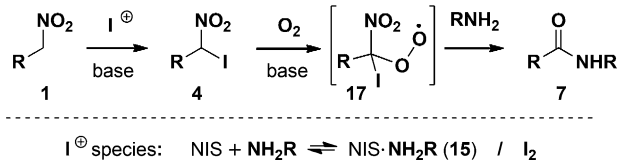


Figure 3. Proposed oxidative conversion of nitroalkanes **1** into amide products **7** by α-iodinated intermediates **4**.

the primary nitroalkane **1**, will first become α-iodinated with NIS from the halogen bonded amine complex **15** or I_2, to afford the mono-iodide **4**. From this intermediate onwards, several addition-elimination pathways, under either radical or ionic reaction modes, can be proposed to afford the amide product **7**.[5–7] Among such possibilities, we currently favor the formation of a peroxy radical[18] **17**, which can cyclize and expel a mono-iodine or nitrite radical to form a reactive dioxirane intermediate (cf. Eq. (3)).[12] Further mechanistic evidence is being actively pursued in our group to provide a more complete and consistent picture of this non-trivial oxidative process.[17,19]

In closing, several synthetic virtues of this oxidative amidation method are noteworthy (Schemes 1, 2, and 3). The method is straightforward in operation, chemoselective in functional group tolerance, and stereochemically robust to potentially epimerizable substrates and products. Importantly, a whole range of primary nitroalkane starting materials for our reaction method can be readily prepared in chiral form through a plethora of asymmetric methods.[9,10,14,15] Further improvements and extension of the mechanistic rationales presented herein to construct more challenging amide bonds are ongoing in our laboratories.[17,19] The implications of amine-complexed, halogen bonded, electrophilic iodine species to our understanding of amine-based, asymmetric catalytic events will be published in due course.[20,21]

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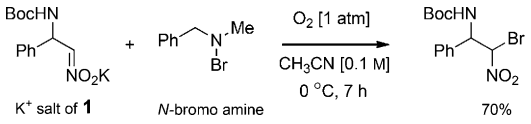

[17] As insightfully suggested by the reviewers, additional halogenation could be occurring on **4** (cf. Eqs. (9) and (10), Scheme 4) and extra iodonium sources could be regenerated under the aerobic conditions. These possibilities, and the potential for catalysis in the iodine component, are being further explored. For mechanistically related iodine catalyzed and promoted coupling reactions, see: a) D. Liu, A. Lei, *Chem. Asian J.* **2015**, *10*, 806–823; b) S. Tang, K. Liu, Y. Long, X. Qi, Y. Lan, A. Lei, *Chem. Commun.* **2015**, *51*, 8769–8772; c) S. Tang, K. Liu, Y. Long, X. Gao, M. Gao, A. Lei, *Org. Lett.* **2015**, *17*, 2404–2407; d) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu, A. Lei, *Chem. Commun.* **2014**, *50*, 4496–4499.
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[19] Besides UmAS and other possibilities, see Refs. [5,6,7a,12,17,18], the exact mechanistic details and sequence of events for the addition of dioxygen and the exact stage of introduction of the amine component to an α-iodo nitroalkane **4**, for example, through a peroxy species like **17,** remains to be elucidated.

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