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O-Isocyanates as Uncharged 1,3-Dipole Equivalents in [3+2] Cycloadditions

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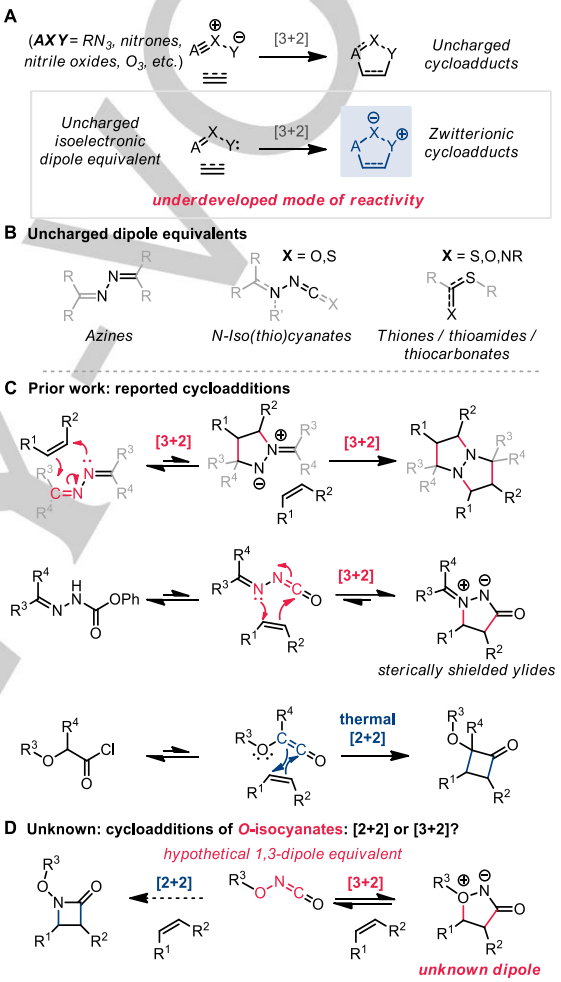
Abstract: 1,3-Dipoles are commonly used in [3+2] cycloadditions, whereas isoelectronic uncharged dipole variants remain underdeveloped. In contrast to conventional 1,3-dipoles, uncharged dipole equivalents form zwitterionic cycloadducts, which can be exploited to build further molecular complexity. Herein the first cycloadditions of oxygen-substituted isocyanates (*O*-isocyanates) are studied experimentally and by DFT calculations. This unique cycloaddition strategy allowed access to a novel class of heterocycle—aza-oxonium ylides via intramolecular and intermolecular cycloadditions with alkenes. This allowed a systematic study of the reactivity of the transient aza-oxonium ylide intermediate, which can undergo N-O bond cleavage followed by nitrene C-H insertion, and the formation of β-lactams or isoxazolidinones by varying the structure of the alkene or *O*-isocyanate reagents.

Introduction

Cycloadditions are an indispensable method for the synthesis of complex scaffolds through the concerted formation of two sigma bonds.[1] 1,3-Dipolar cycloadditions, systematically reviewed as a general class of reactivity by Huisgen's seminal overview in 1963, are a well-utilized variant to form 5-membered heterocycles (**Scheme 1A**).[2] Notable examples include the "click" reaction of azides and alkynes,[3] which transformed the field of biorthogonal chemistry, and stereoselective nitrone cycloadditions, often used in total syntheses of alkaloids.[4] [3+2] Cycloadditions can occur with a variety of 1,3-dipoles and dipolarophiles, however, they have several common features; 1) the dipole is charged, leading to; 2) an uncharged cycloadduct, and; 3) the dipole generally reacts through the HOMO (termed 'HOMO-controlled').[5] Using an uncharged isoelectronic species as a 1,3-dipole equivalent would lead to a predictably unstable zwitterionic cycloadduct (**Scheme 1A**). Despite decades of reports on dipolar cycloadditions, the related chemistry with uncharged dipole equivalents remains underdeveloped and the potential reactivity of the charged cycloadducts remains mostly untapped (**Scheme 1B**).[6]

The scarcity of uncharged dipole equivalents in the literature is likely a consequence of the unfavorable thermodynamic profile of the reaction. While pioneering work with azines demonstrated the potential of uncharged dipole equivalents to engage in [3+2] cycloadditions,[6n-x] the resulting ylide must be trapped by a subsequent cycloaddition reaction (**Scheme 1C**). In contrast, our lab developed intermolecular [3+2] cycloadditions of imino-isocyanates with alkenes to form stable cycloadducts, azomethine imines.[6k] Steric shielding of the dipole proved



Scheme 1. (A) Conventional and unconventional [3+2] cycloadditions; (B) Examples of uncharged 1,3-dipole equivalents.[6] (C) Cycloaddition reactivity of azines, *N*-isocyanates, and alkoxyketenes. (D) Potential cycloaddition reactivity of *O*-isocyanates.

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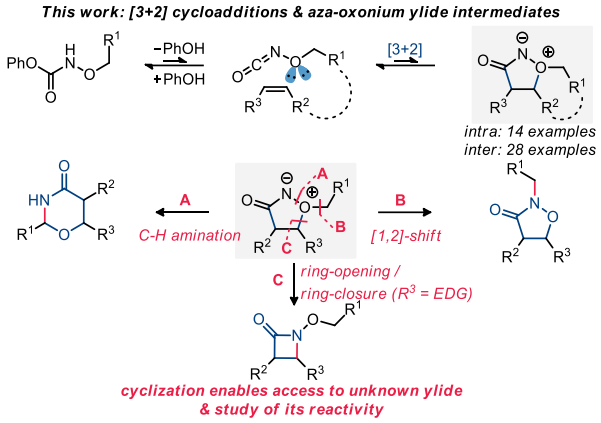


Scheme 2. Intra- and intermolecular *O*-isocyanate [3+2] cycloadditions and subsequent reactivity of the aza-oxonium ylide cycloadducts.

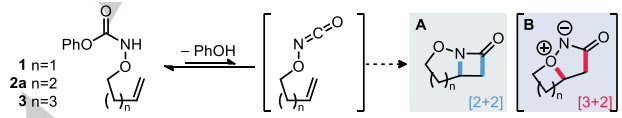
essential to allow isolation of the alkene aminocarbonylation products. The reaction was thermodynamically favorable and applicable to unbiased alkenes, as it involved a high energy heterocumulene as the 1,3-dipole equivalent, but crossover experiments showed that cycloreversion was still possible.[6k] To our knowledge, the reactivity of other heterocumulenes, such as *O*-isocyanates, as uncharged dipole equivalents has not been reported. [3+2] or [2+2] cycloaddition reactivity could be possible considering the reactivity of related heterocumulenes.[6] Given that alkoxy ketenes participate in [2+2] cycloadditions, we had initially anticipated structurally related *O*-isocyanates may react analogously.[7]

Herein we report the reactivity of *O*-isocyanates as novel uncharged 1,3-dipole equivalents, leading to reactive zwitterionic cycloadducts—aza-oxonium ylides—through intra- and intermolecular oxycarbonylative alkene [3+2] cycloadditions.[8] To our knowledge, the proposed aza-oxonium ylide has not been reported.[9,10] Therefore, the subsequent reactivity of the aza-oxonium was investigated. As expected based on similarity to other nitrene[11] and nitrenoid[12] precursors, aza-oxonium ylides provided C–H amination products following N-O bond cleavage (**Scheme 2**, path A). Examples of possible different reactivity include two other bond cleavages (paths B, C). Judicious choice of *O*-isocyanate and dipolarophile substitution for intermolecular cycloaddition allowed divergent reactivity of the aza-oxonium ylides to be achieved. Using strained alkenes, the corresponding aza-oxonium ylides spontaneously underwent N–O bond cleavage and selective nitrene C–H amination (**Scheme 2**, path A). Alternatively, using *O*-silyl *O*-isocyanate precursors, O–Si cleavage of the consequent aza-oxonium ylide led to the synthesis of an isoxazolidinone (**Scheme 2**, path B). Finally, using electron-rich alkenes, the synthesis of β-lactams was achieved by a [3+2] cycloaddition / ring contraction sequence (**Scheme 2**, path C). This work presents a rare, detailed study of the cycloaddition of a new uncharged 1,3-dipole equivalent and the resulting divergent reactivity of the previously unknown aza-oxonium ylide cycloadducts.

Results and Discussion

With the goal to use *O*-isocyanates for cycloadditions, the first problem encountered was their inherent instability. *O*-Isocyanates are unstable and prone to trimerization under mild conditions.[13] After decades of unsuccessful attempts to use *O*-isocyanates effectively, seminal work by BMS chemists demonstrated that blocked (masked) isocyanate precursors were suitable for controlled reactivity, efficiently undergoing substitution reactions with amines.[14] This blocking group strategy allows for a controlled concentration of isocyanate to be formed, decreasing the amount of trimerization.[15] Improvements on the thermal stability of the blocked isocyanate precursors led us to use *N*-oxycarbamates (blocking group = alcohols/phenols). Carbamate blocked precursors have previously enabled the use of *O*-isocyanates in cascade reactions to form heterocyclic derivatives.[16] The cycloaddition reactivity of *O*-isocyanates, however, has yet to be reported. Carbon isocyanates have been used in thermal [2+2] cycloadditions to form β-lactams.[17] Conversely, nitrogen-substituted isocyanates preferentially undergo [3+2] cycloadditions, acting as uncharged 1,3-dipole equivalents.[6] *O*-Isocyanates, with predictably intermediate HOMO and LUMO energies, could undergo either pathway. As such, when exploring the cycloaddition reactivity of *O*-isocyanates using blocked precursors, suitable substrates (**1**, **2a**, **3**) were chosen for both [2+2] and [3+2] reactivity (**Table 1**).

Table 1. Selected optimization of *O*-isocyanate cycloaddition[a]



Entry	Carbamate	Solvent (0.05 M)	Temp (°C)	Time (h)	Yield (%)[b]
1	1	MeCN	180	2	0
2	2a	MeCN	180	2	90 (**B**)
3	3	MeCN	180	2	0
4	2a	DMSO	180	2	0
5	2a	DMF	180	2	0
6	2a	$PhCF_3$	180	2	47[c] (**B**)
7	2a	toluene	180	2	0
8	2a	MeCN	120	6	0
9	2a	MeCN	150	4	5 (**B**)
10[d]	2a	MeCN	120	2	36[e] (**B**)

[a] Conditions: carbamate (1.0 equiv., 0.1-0.2 mmol), under Ar, and heated in a microwave reactor. [b] ^{1}H NMR yield for cycloaddition products **A** or products derived from intermediate **B** using 1,3,5-trimethoxybenzene as an internal standard (identity of the product- *A or B* - noted in parentheses). [c] 20% SM remaining. [d] 20 mol% *i*-Pr_2NEt added. [e] 50% SM remaining.

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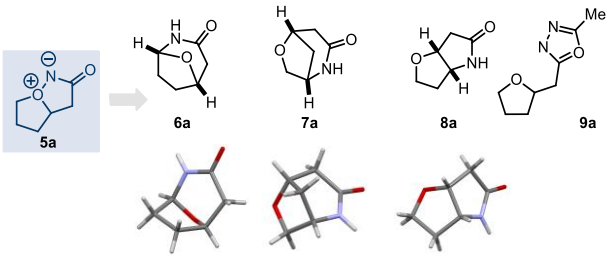
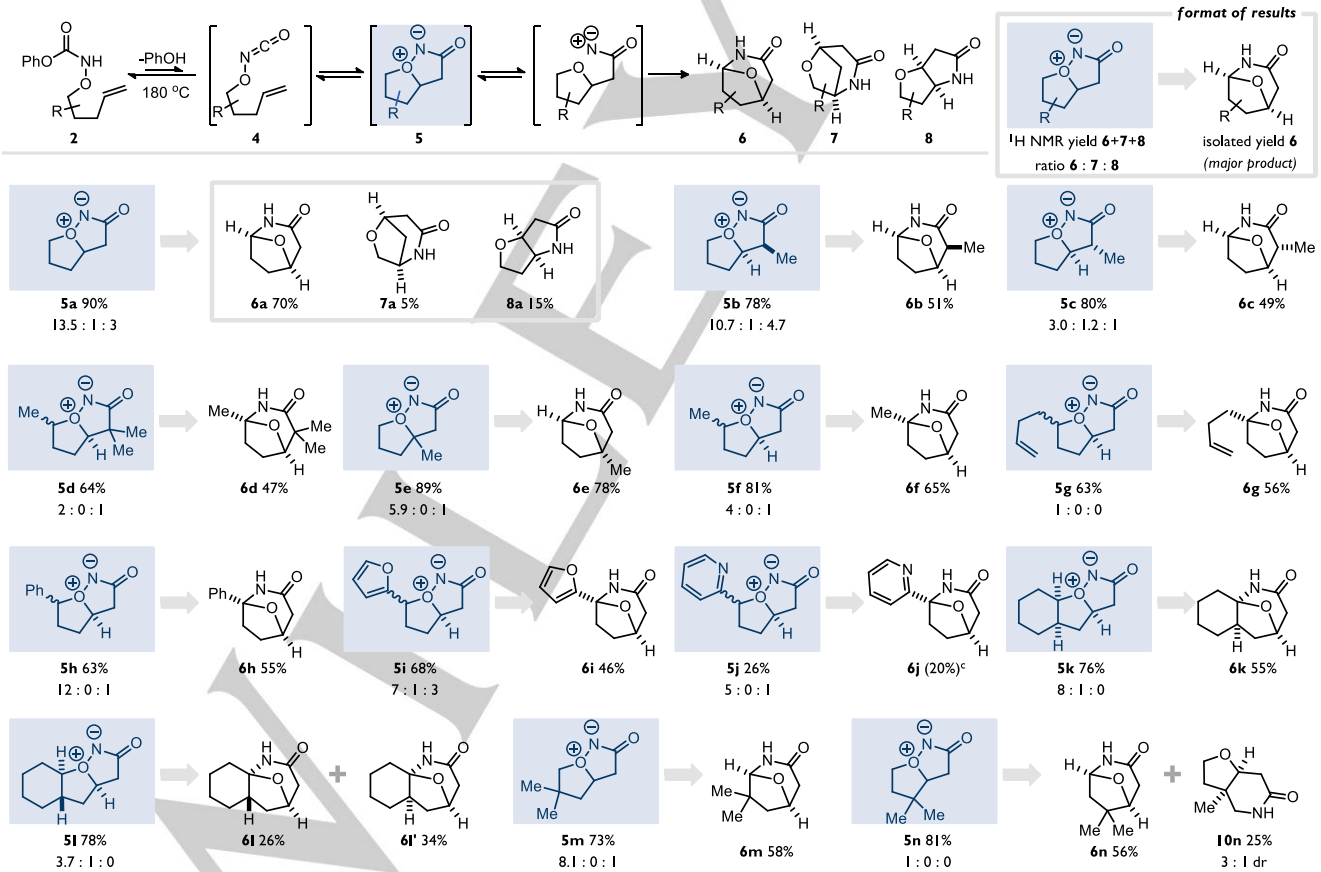
Figure 1. Structures of bicyclic lactam isomers **6a**, **7a**, **8a** with X-ray structures[18] obtained and oxadiazole **9a**.



Based on previous work using blocked isocyanates, phenol was chosen as a blocking group to begin exploring the cycloaddition reactivity of *O*-isocyanates.[6,16] Using thermal deblocking conditions for several phenol-blocked *O*-isocyanates (**1**, **2a**, **3**), it rapidly became clear that [3+2] was the favoured cycloaddition pathway (entries 1-3). Near quantitative cycloaddition can be inferred from the isolation of isomeric lactam products (**6a**, **7a**, **8a**) and aromatic cycloaddition product **9a** (**Figure 1**). Structural determination was completed using X-ray[18] and NMR spectroscopy. The mechanism will be discussed in detail below. In order to survey the efficacy of the cycloaddition step alone, the combined yields of lactam products derived from cycloadduct **5a** were used for reaction optimization. The product distribution will be discussed below. High solvent dependence was observed, as only MeCN and $PhCF_3$ proved suitable (entries 2-7). High temperature was required for effective isocyanate formation and the cycloaddition sequence (entries 8-9).[19] Using base catalysis to lower the temperature required for deblocking consumed the *O*-isocyanate precursor but compromised the formation of lactam products (entry 10).[20] Heating at high temperature (180 °C) in a microwave reactor was found to provide the best yield of intramolecular [3+2] cycloaddition products (entry 2). With an adequate procedure in hand, the scope of the [3+2] cycloaddition was evaluated using the inferred yield of cycloadduct intermediates **5** (**Scheme 3**) using the ^{1}H NMR yield of related lactam isomers which have diagnostic signals.

In general, substitution on the alkyl backbone was well tolerated with a few exceptions. Substitution at the terminal position of the alkene led to high yields of the corresponding cycloadducts (**5b, 5c**). [6i] Notably, the *cis* and *trans* methyl-substituted *O*-isocyanates



Scheme 3. Scope of intramolecular *O*-isocyanate cycloaddition[a] (yield derived from common intermediate **5** shown for clarity[b]). [a] Conditions: carbamate (1.0 equiv., 0.38-1.0 mmol) and MeCN (0.05 M), under Ar, and heated at 180 °C for 4-10 h in a microwave reactor (see SI for details); [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard for the inferred yield of common intermediate **5** based on the sum of ^{1}H NMR yields of products **6**, **7**, **8** (ratio **6**:**7**:**8** shown below). The major product **6** was isolated for each entry (isolated yield shown). [c] ^{1}H NMR yield of product **6i** shown in parentheses. 17% of starting material formed *O*-isocyanate trimer.

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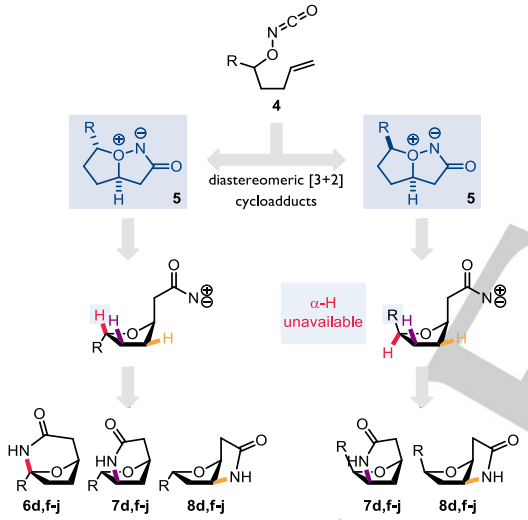
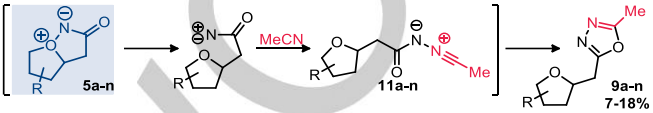
underwent stereospecific cycloadditions to form the corresponding *syn* and *anti* lactam products (**6b**, **6c**) respectively, providing evidence that the cycloaddition is concerted. Terminal disubstitution on the alkene led to somewhat lower yield (**5d**), whereas substitution at the internal position was well tolerated (**5e**). Substitution alpha to the oxygen atom was well tolerated (**5f**, **5g**). Aromatic substitution was also tolerated at the alpha position (**5h**, **5i**), however, basic substituents led to lower yields (**5j**). Both the *syn* and *anti* 2-allyl cyclohexyl substrates underwent cycloaddition readily leading to a mixture of tricyclic products (**5k, 5l**). Two geminal dimethyl substrates were also tested and led to slightly lower yields relative to the unsubstituted alkyl chain (**5m, 5n**). In the analogous intramolecular alkene cycloaddition of *N*-isocyanates, substrates with a Thorpe-Ingold bias reacted at room temperature and high yields of the products could be obtained as low as 50 °C with catalytic base (unbiased substrates reacted at 120-200 °C).[6i] However, in the current cycloaddition reaction with *O*-isocyanates, we observed no benefit from a Thorpe-Ingold effect and found that lower temperatures lead to no product formation. The mechanistic implication of this observation is that the cycloaddition is likely not the rate determining step of this reaction sequence.



Scheme 4. Substitution effects on mixtures of lactam products **6**-**8**: Rational for observed diastereomeric ratio for minor products.

A more rigorous examination of the reaction sequence is required to rationalize the observed product distribution resulting from aza-oxonium ylide **5**. Once the intramolecular [3+2] cycloaddition occurs and aza-oxonium ylide **5** is formed, several pathways are possible. The formation of an acyl nitrene accounts for all isolated products (**Scheme 3**). In stark contrast to recent reports, we found that the aza-oxonium ylide does not require stabilization as a metal-nitrene to avoid 1,2-rearrangement to the corresponding isocyanate.[21] Bicyclic lactams **6**-**8** are proposed to be the C-H insertion products of the acyl nitrene. In line with regular reactivity trends of nitrene C-H insertions, the most activated C-H bond, at the ethereal methylene position, leads to the major product **6** (**Scheme 4**).[11,12] Minor lactam products (**7**, **8**) result from the other two *C-H* insertions possible. For several substrates, diastereomers of lactam products are also observed. Diastereomers are observed for the minor lactam products for α-substituted *O*-isocyanates (**7d,f-j**, **8d,f-j**), although expectedly, not for the major lactam product **6d,f-j** (**Scheme 4**). A detailed scheme of the products formed in each reaction is available in the SI (**Scheme S1**). Oxadiazole **9** (**Scheme 5**) is proposed to be the product of the cyclization of the acyl nitrene/acetonitrile adduct **10**. Acetonitrile has been previously reported to react with acyl nitrenes and subsequently undergo cyclization to form analogous oxadiazole products.[22] Acetonitrile, nonetheless, remains the optimal solvent for this cycloaddition despite this competing oxadiazole formation pathway (**Table 1**).



Scheme 5. Acetonitrile as an acyl nitrene trap.

To gain further insight into this novel reactivity, the intramolecular [3+2] cycloaddition of *O*-isocyanates was studied by density functional theory (DFT) calculations. Minimal computational work related to the [3+2] cycloadditions of uncharged 1,3-dipole equivalents has been reported previously.[6i] DFT studies were primarily directed at (1) mapping the potential energy surface of isocyanate **4a** cycloaddition and of the following steps leading to the lactams (**6**-**8a**), including activation energies, and thus allow comparison with the observed product distribution; (2) studying the nature of the cycloaddition transition state structure.

Initial calculations were aimed at probing the reaction mechanism and examining the cause of the observed product distribution. The relative energies of intermediates and products, as well as transition states for each step were calculated using the B3LYP functional and the 6-311+G(2d,p) basis set (**Figure 2A**). The B3LYP functional has been previously found to produce results in accordance with experimental trends of uncharged 1,3-dipole equivalents.[6i] Although the deblocking mechanism of the precursor *O*-isocyanate **2a** was not modelled, it was calculated that this step is endergonic by 9.1 kcalmol^{-1}. The rest of the DFT results are relative to the energy of *O*-isocyanate **4a**, not including the PhOH present from deblocking. The cycloaddition was found to have a transition state energy of +15.9 kcalmol^{-1} (**TS1**) relative to *O*-isocyanate **4a**. Interestingly, the expectedly unstable aza-oxonium ylide cycloadduct **5a** is +1.2 kcalmol^{-1} higher in energy than *O*-isocyanate **4a**, speaking to the instability of *O*-isocyanates and the importance of controlled *in-situ* formation from blocked precursors. It is expected that the stability of aza-oxonium ylide **5a** would also benefit from hydrogen bonding, but this was not explored computationally. On a broader scale, it can be reasoned that the use of an unstable heterocumulene allows this cycloaddition (**TS1**) to be thermodynamically feasible, which can be applied to the development of other uncharged 1,3-dipole equivalents. The following N-O bond cleavage step to form the acyl nitrene (**TS2**) was found to have the highest transition state energy ($\Delta G^{\ddagger}$ = +21.5 kcalmol^{-1}). This process forms the highest energy intermediate (acyl nitrene **IN1**) and is therefore predictably the rate-determining step (RDS). The final C-H insertion step then

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requires +23.6 kcalmol^{-1} for the major product (**TS3**). The cause of the observed product distribution remains unclear after DFT analysis of nitrene C-H insertion transition state energies for each bicyclic lactam product (**TS3**, **TS3'**, **TS3''**, see SI for DFT calculations for minor lactam products **7a**, **8a**).

The acetonitrile-nitrene adduct cyclization has previously been studied experimentally in detail, and as such, this step was not analysed computationally.[22e] The reaction of acetonitrile with the acyl nitrene and subsequent cyclization to form oxadiazole **9a** is a thermodynamically favourable process, though is not kinetically favourable. Previous work by Jenks found a rapid rate of reaction between acyl nitrenes and acetonitrile (10^5 - 10^6 $M^{-1}s^{-1}$), though, a slower rate of cyclization (10^4 s^{-1}) was observed. These results are in agreement with previous studies of acyl nitrenes with acetonitrile. This slow rate of oxadiazole formation supports the low yield observed from ylide **11a** even with the thermodynamic driving force associated with aromatization.

The nature of the *O*-isocyanate cycloaddition transition state structure, including bond lengths and bond angles, was then analyzed. The transition state was compared to known dipolar cycloadditions in an attempt to classify the uncharged dipole equivalent within the propargyl or allyl anion type dipole categories.[2a] The calculated *O*-isocyanate cycloaddition transition state closely resembles the analogous structure for amino-isocyanate cycloaddition (**Figure 2B**).[6i] Both cycloadditions are concerted, though asynchronous in favour of C-C bond formation suggesting a LUMO-controlled cycloaddition. The *O*-isocyanate cycloaddition is, however, distinctly more asynchronous than that of the amino-isocyanate, which is a likely effect of the more electronegative oxygen atom. While most electronically biased charged 1,3- dipoles (e.g. nitrones, nitrile oxides) have concerted, but asynchronous cycloaddition transition state structures, this feature is exaggerated in the studied heteroatom-substituted isocyanates.[23] Additionally, the distortion of the dipole prior to the transition state ($\Delta E_d^{\ddagger}$) is an effective predictor of reactivity, as described by Houk, and can be qualitatively assessed using the change in bond angles during cycloaddition.[24] The distortion of *O*-isocyanates during cycloaddition, assessed as the change in bond angles (α, β, γ), exhibits differences to both propargyl and allyl anion type 1,3-dipoles (**Figure 2C**). The model for the *O*-isocyanate cycloaddition transition state structure has minimal distortion of the dipole equivalent based on changes in bond angle β (119.9° (**I**); 108.1° (**II**)), similar to allyl anion (bent) type charged dipoles. Although, a large distortion of the isocyanate moiety before the transition state occurs based on changes in bond angle γ (171.3° (**I**); 139.2° (**II**)), common among propargyl anion (linear) type 1,3-dipoles such as azides and nitrile oxides.[25] Another distinguishing feature of propargyl and allyl anion type dipolar

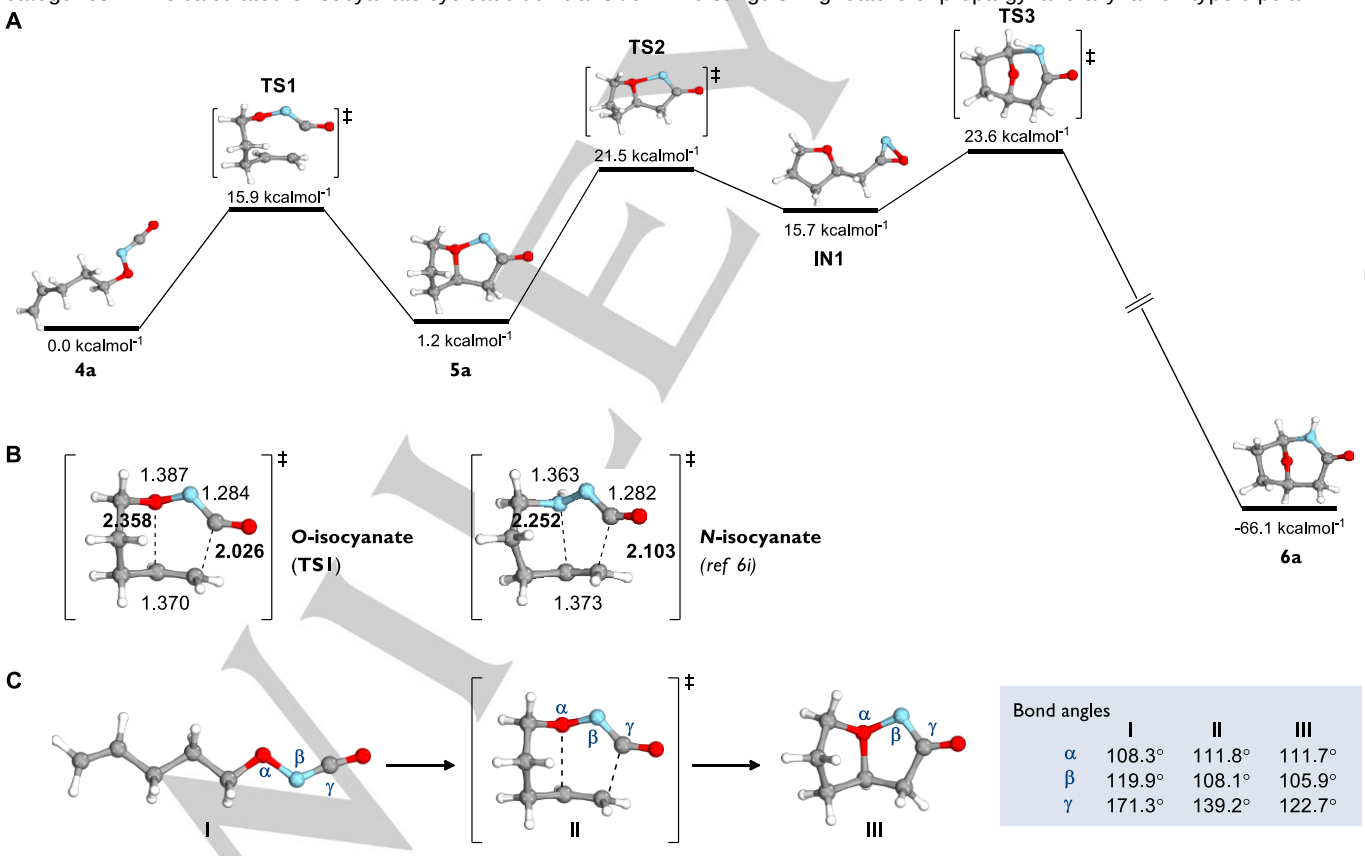

Figure 2. (A) DFT calculations for O-isocyanate **4a** intramolecular alkene cycloaddition; (B) Cycloaddition transition state structures of *O*-isocyanates in comparison to *N*-isocyanates (distance in Angstroms); (C) *O*-isocyanate cycloaddition bond angles. Calculations completed using B3LYP 6-311+G(2d,p).

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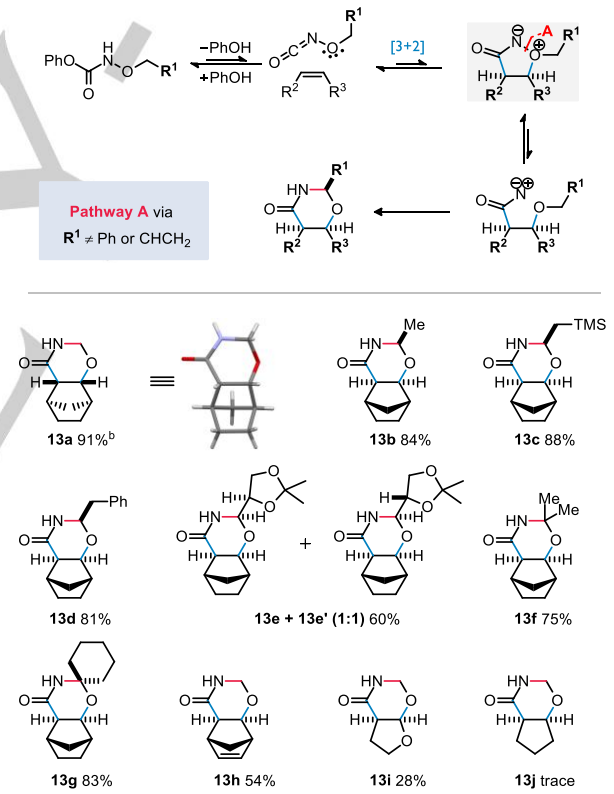
cycloadditions, is the shape of the 5-membered transition state (planar and envelope respectively). The calculated planar transition state more closely resembles those of the propargyl anion type 1,3-dipoles. As *O*-isocyanates appear to have features of both propargyl and allyl anion type dipoles, they cannot be clearly classified within either dipole category.

Unlike many charged 1,3-dipoles, *O*-isocyanate cycloaddition reactivity appears to be controlled by the LUMO (type III by Sustmann defined categories).[5] The other exclusively LUMO-controlled 1,3-dipoles are ozone and nitrous oxide, both of which are unable to undergo intramolecular cycloadditions. In related intermolecular systems, however, LUMO-controlled cycloadditions of ozone or nitrous oxide form unstable intermediates (molozonide and 4,5-dihydro[1,2,3]oxadiazole respectively), in part, due to the inclusion of weak heteroatom-heteroatom bonds in the starting dipole.[26] It appears that choosing an unstable heterocumulene dipole equivalent allowed for a similarly low-lying LUMO and analogous cycloadduct reactivity.

While the intramolecular [3+2] cycloaddition of *O*-isocyanates clearly demonstrates an efficient cycloaddition process (average aza-oxonium ylide yield of 72% for 14 examples above), the poor selectivity of the subsequent C–H amination diminished the synthetic applicability of the transformation. However these products have only been accessed through aza-oxyallylic cation [4+3] cycloadditions after a reductive work-up.[27] We therefore sought to extend this reactivity to intermolecular cycloadditions, with the hope that substrate modification may lead to a suitable *O*-isocyanate precursor that could control the fate of the aza-oxonium ylide. Moreover, intermolecular reactivity further bolsters the synthetic applicability of the transformation of this novel [3+2] cycloaddition. Ultimately, improved reaction conditions could lead to the use of simple hydroxylamine derivatives as effective synthons in diastereoselective difunctionalization of commercially available and abundant alkenes for heterocycle synthesis.

The first objective was to assess the feasibility of the intermolecular *O*-isocyanate cycloaddition. Analogous nitrogen-substituted isocyanates (*N*-isocyanates) have served as 1,3-dipole equivalents in intermolecular [3+2] cycloadditions with π-systems, notably forming stable azomethine imines, unlike the unisolable aza-oxonium ylide.[6i-l,28] Since reactivity through pathway A (**Scheme 2**) was validated in the corresponding intramolecular reaction, it was logical to target this pathway first in an intermolecular system. Reasoning that small alkyl groups would be reluctant to undergo [1,2]-rearrangement based on analogous reactivity with *N*-isocyanates,[6i-j] phenol-blocked methoxycarbamate **12a** was selected as an *O*-isocyanate precursor (**Scheme 6**). Norbornene was selected as the alkene reagent given its favourable strain energy, which we reasoned could be leveraged against the increased entropic cost of the intermolecular cycloaddition.[29] When **12a** was reacted in the presence of excess norbornene, the reaction was selective for the exo cycloaddition / nitrene C–H amination cascade (pathway A, **eq 1**). A sole C–H amination product was obtained in excellent yield (**Scheme 6**, **2a**). The structure of the product was confirmed by single X-ray crystallography.[18]

To probe substituent effects on the cycloaddition, a variety of *O*-isocyanate precursors were reacted in the presence of excess norbornene to produce the corresponding 1,3-oxazinan-4-ones (**Scheme 6**, **13a-g**) in excellent yields. Methoxycarbamate precursor (**12a**) provided the product in the highest yield (91%), while isopropyl and cyclohexyl cycloadducts **13f** and **13g** were obtained in 75% and 83% respectively. These results suggest that the cycloaddition is only moderately sensitive to steric hindrance.[30] However, the decrease in yield obtained with ketal derivatives **13e** and **13e'** suggests that electronic effects may impact the cycloaddition. Cycloaddition / C–H amination products were obtained using norbornadiene (**13h**) and dihydrofuran (**13i**) as the alkenes, but unfortunately attempts to extend this reactivity beyond strained / electronically activated alkenes were unsuccessful (**13j**). However, this initial survey of *O*-isocyanate substituent effects revealed that precursors containing suitable groups to undergo either [1,2]-shift (**14a**, **14b**) or [2,3]-sigmatropic rearrangement (**14c**) provided a mixture of C–H amination / rearranged products (**Scheme 7**).



Scheme 6 Intermolecular *O*-isocyanate [3+2] cycloaddition of strained alkenes [a] Conditions: alkoxycarbamate (1.0 equiv), alkene (50 equiv) in MeCN (0.2 M) at 180 °C via microwave irradiation for 2 hours. Major diastereomer shown for **2b-2g'** (d.r. by ^{1}H NMR are typically ~10:1, see SI for exact values). [b] 30 equiv alkene used.

These rearrangement products provided experimental evidence that N–O bond cleavage or C–H amination could be rate limiting, and that these rearrangements offer lower-energy pathways from the aza-oxonium ylide. Notably, the substrates that underwent

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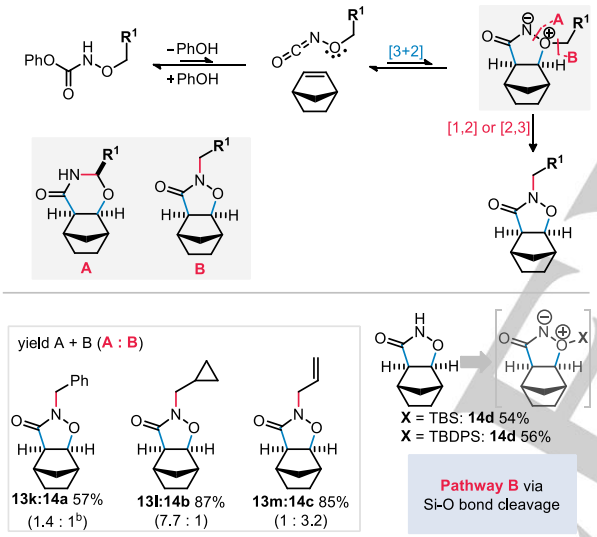
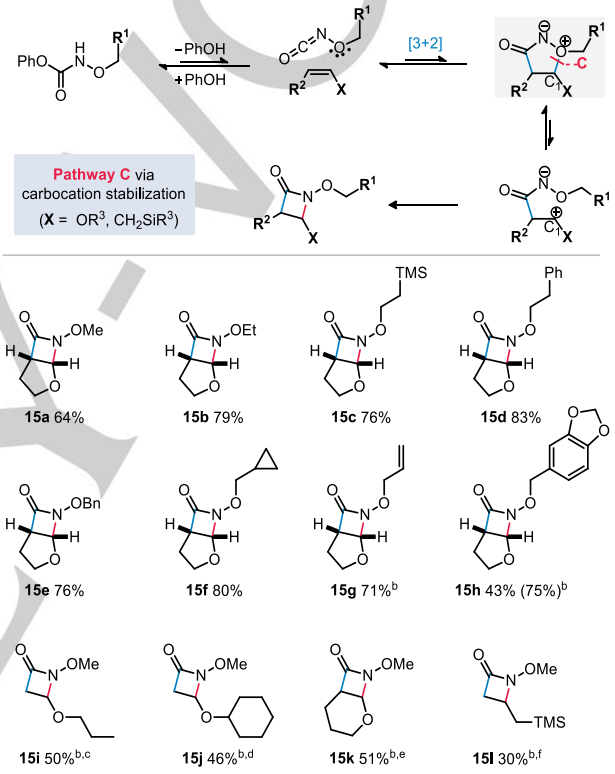
rearrangement demonstrated the first examples of non-nitrene reactivity of an aza-oxonium ylide (**Scheme 2**, path B). Encouraged by the ability to direct some aza-oxonium ylide reactivity towards C–O cleavage (**Scheme 2**, pathway B), we speculated that continued substrate modification could enhance this type of reactivity. We reasoned that an *O*-silyl derivative could selectively react via pathway B (**Scheme 2**), either through O–Si bond cleavage of the aza-oxonium ylide, or perhaps [1,2]-silyl shift and subsequent N–Si cleavage. In either mechanistic scenario, it is likely that phenol would participate in the silyl deprotection step. Silyl-derived *O*-isocyanate precursors **11k** and **12l** provided the isoxazolidinones **14d** in good yield validating our initial hypothesis. Importantly, these *O*-silyl substrates allow for selective and direct synthesis of N–H unprotected isoxazolidinones via concerted cycloaddition. However, at this time the *O*-silyl isocyanate cycloaddition remains limited by the reliance on strained alkenes as reaction partners. Nonetheless, the isolation of the rearrangement products in **Scheme 7** further supports the proposed mechanism invoking a [3+2] cycloaddition forming an aza-oxonium ylide intermediate.



Scheme 7 Intermolecular *O*-isocyanate [3+2] cycloaddition with O-CH_2R^1 / silyl migration [a] Conditions: alkoxycarbamate (1.0 equiv), alkene (50 equiv) in MeCN (0.2 M) at 180 °C via microwave irradiation for 2 hours. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. Major diastereomer shown for **2k-2m** (d.r. by ^{1}H NMR are typically ~10:1, see SI for exact values).

With conditions developed to selectively enable pathway A and B, attention was directed to pathway C (**Scheme 2**). We hypothesized that the ability to selectively achieve pathway C hinged on stabilizing the carbocation formed as a result of O–C_1 cleavage (**Scheme 8**). To probe this hypothesis, enol ethers were implemented as reaction partners. Strategically, lone pair donation from the enol ether oxygen atom to the σ* of the adjacent O–C_1 bond on the aza-oxonium ylide could selectively accelerate pathway C and show better cycloaddition reactivity since the π-bond is electron-rich. Initially, the reaction with 2,3-dihydrofuran led to a complex mixture of products (see SI for details). However, β-lactam **15a**, a predicted product of pathway C, was identified as a minor product of the thermal reaction (180 °C). Conditions were developed to optimize β-lactam formation (see SI). Efficient and selective generation of β-lactams was accomplished at a lower temperature (120 °C) using catalytic *i*-Pr_2NEt. Complete suppression of N–O bond cleavage (pathway A), and [2,3]-sigmatropic rearrangement / 1,2-shift (pathway B) was achieved and high yields of β-lactams were obtained. β-Lactam products were formed in similar yields irrespective of the *O*-isocyanate precursors used (**15a**-**15h**). Acyclic enol ethers formed β-lactams in modest yields (**15i**, **15j**), and larger cyclic enol ethers were also competent reaction partners in higher alkene loadings (**15k**). Preliminary results with allylsilanes (**15l**) are encouraging for the expansion of this reactivity beyond enol ethers.



Scheme 8 Intermolecular *O*-isocyanate [3+2] cycloaddition of enol ethers [a] Conditions: alkoxycarbamate (1.0 equiv), alkene (20 equiv), *i*-Pr_2NEt (0.20 equiv) in MeCN (0.2 M) at 120 °C via microwave irradiation for 2.5 hours. [b] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard. [c] 30 equiv alkene used. [d] 10 equiv alkene used. [e] 100 equiv alkene used. [f] 75 equiv alkene used at 150 °C.

β-Lactams are routinely formed by [2+2] cycloadditions of isocyanates and enol ethers[31] / enol esters.[32] Therefore, an important endeavour of this study was to provide evidence for a [3+2] or [2+2] reaction pathway. In an effort to establish if these reactions operate via thermal [3+2] cycloaddition / ring opening and closing sequence—rather than a [2+2] cycloaddition—the substrates were modified to undergo pathway B-type rearrangements from the proposed aza-oxonium ylide more readily. Substrates bearing allyl substituents provided mixtures of the [2,3]-sigmatropic rearrangement and β-lactam products (**14e-14f** and **15m-15n**), supporting that these reactions likely operate via [3+2] cycloaddition (**Scheme 9**).

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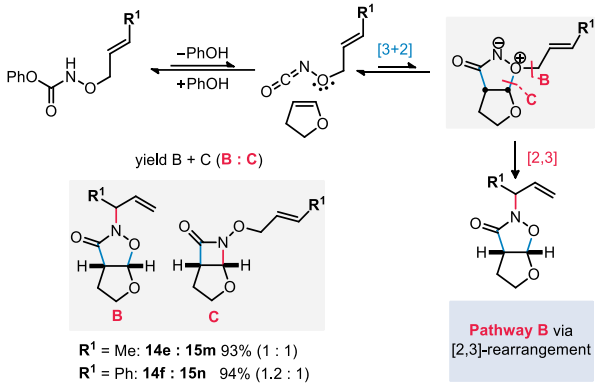
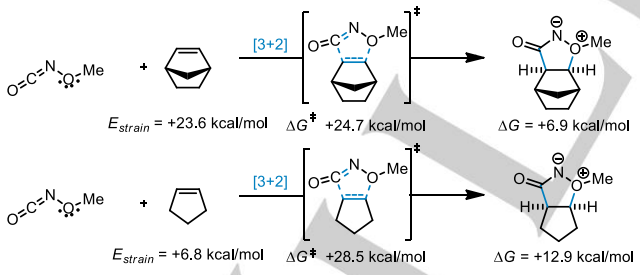


Scheme 9 Intermolecular *O*-isocyanate [3+2] cycloaddition of enol ethers with subsequent [2,3] rearrangement [a] Conditions: alkoxycarbamate (1.0 equiv), alkene (20 equiv), *i*-Pr_2NEt (0.20 equiv) in MeCN (0.2 M) at 120 °C via microwave irradiation for 2 hours. ^1H NMR yields using 1,3,5-trimethoxybenzene as internal standard.

Given the apparent limitations of this intermolecular cycloaddition reaction, we sought to investigate the activation energy of the cycloaddition by density function theory (DFT) calculations. Using the B3LYP exchange-correlation functional and the 6–311+G(d,2p) basis set, the transitions states for the cycloadditions of different alkenes were studied. As seen in **Scheme 10**, the computed activation energy for the cycloaddition with norbornene is 24.7 kcalmol^{-1}; however, with cyclopentene (**13j**, trace) a higher energy transition state was calculated (28.5 kcalmol^{-1}). Thus, it is hypothesized at this time that the cycloaddition reaction is teetering on the energetic boundary of the forward reaction. It is imperative to note that these energies are calculated from the *O*-isocyanate, which is an exceptionally reactive intermediate that is only formed in sufficient quantities thermally (typically above ~120 °C).



Scheme 10 Computed activation energies for the intermolecular *O*-isocyanate [3+2] cycloaddition on strained and unstrained alkenes.

Therefore, these cycloadditions occur at a calculated transition state that is 20-30 kcalmol^{-1} above the initial formation of the reactive *O*-isocyanate. Moreover, in comparison to the intramolecular system, where the cycloaddition was calculated to be only mildly endergonic (+6.9 kcalmol^{-1}), the intermolecular reaction appears to be much more unfavourable (+12.9 kcalmol^{-1}). These factors cumulatively provide an explanation for the lower reactivity of unactivated alkenes. Combining these findings with the more detailed DFT study of the intramolecular system, which revealed rate determining C–H amination, it is hypothesized that thermodynamically unfavourable formation of the aza-oxonium ylide coupled with a high energy irreversible final step (C–H amination) ultimately limits this reactivity. While we had some success circumventing these challenges through the development of novel *O*-isocyanate precursors which would not undergo C–H amination (e.g. **Scheme 7-9**), we were unable to extend this reactivity more broadly to unbiased alkenes (**Scheme 6**). Therefore, the key to improve this reactivity appears to lie in the catalysis of the C–H amination step, or in the development of improved *O*-isocyanate precursors that can either stabilize the aza-oxonium ylide or cycloaddition transition state (e.g. by hydrogen bonding) or establish a more favourable equilibrium with the *O*-isocyanate intermediate.[33] Nevertheless, this work clearly establishes the current applicability of this new cycloaddition in intermolecular reactions to form oxycarbonylation products from strained alkenes and to form β-lactams from enol ethers.

Conclusion

The use of *O*-isocyanates as uncharged 1,3-dipole equivalents offered a rare opportunity in the development of unusual reactivity. This work provided the first example of cycloaddition reactivity for *O*-isocyanates and one of few examples of isocyanates reacting in [3+2] cycloadditions rather than in the [2+2] pathway typically favoured by isocyanates. The aza-oxonium ylide cycloadduct was an unexplored reactive intermediate and nitrene precursor. Like many free nitrenes, the acyl nitrene formed was unselective for C-H activation, but surprisingly, did not undergo 1,2-rearrangement to the corresponding carbon isocyanate. Instead, the C-H insertion led to the formation of lactam products in good yields. DFT computational results provided a potential energy surface for the cycloaddition sequence of isocyanate **4a**, establishing that a concerted and asynchronous cycloaddition pathway was possible and suggesting that nitrene C-H insertion was the rate-determining step, albeit close in energy to the N-O bond cleavage. From a synthetic perspective, the intramolecular reactivity established that the cycloaddition was efficient, and formed the aza-oxonium ylides in high overall yields for substrates bearing various alkene substitution patterns. Combined with the DFT results this suggest that the synthetic efficiency of this alkene oxy-carbonylation process would benefit from milder, controlled reactivity of aza-oxonium ylides. Preliminary studies demonstrate that the intermolecular cycloaddition of *O*-isocyanates is also possible, leading to analogous nitrene C-H insertion products and isoxazolidinone and β-lactam products via divergent aza-oxonium ylide reactivity. Considering the large impact of [3+2] cycloadditions on the chemical landscape, an additional isoelectronic uncharged example of uncharged dipole equivalent warrants further studies. Efforts to improve the cycloaddition reactivity of *O*-isocyanates, the reactivity of aza-oxonium ylides and develop milder conditions are actively being pursued to address current synthetic limitations. This will be reported in due course.

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Conflicts of Interest

The authors declare no conflicts of interest.

Keywords: [3+2] cycloaddition • β-lactam • C-H amination • isocyanate • nitrene • oxycarbonylation

[1] a) S. Kobayashi, K. A. Jorgensen in *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2001**; b) N. Nishiwaki in *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Hoboken, **2014**.

[2] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604; *Angew. Chem. Int. Ed.* **1963**, *2*, 565; For a review of intramolecular 1,3-dipolar cycloadditions, see: (b) A. Padwa, *Angew. Chem.* **1976**, *88*, 131; *Angew. Chem. Int. Ed.* **1976**, *15*, 123; For a recent review of asymmetric 1,3-dipolar cycloadditions, see: c) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 9653.

[3] For reviews of Huisgen click reactions, see: a)H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; b) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128; c) V. D. Bock, H. Hiemstra, J. H. van Marreveen, *Eur. J. Org. Chem.* **2006**, *51*; d) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952; e) E. Haldon, M. C. Nicasio, P. J. Perez, *Org. Biomol. Chem.* **2015**, *13*, 9528.

[4] For select examples of nitrone cycloaddition as a key step in total syntheses, see: a) F.-X. Wang, J.-Y. Du, H.-B. Wang, P.-L. Zhang, G.-B. Zhang, K.-Y. Yu, X.-Z. Zhang, X.-T. An, Y.-X. Cao, C.-A. Fan, *J. Am. Chem. Soc.* **2017**, *139*, 4282; b) J. M. E. Hughes, J. L. Gleason, *Angew. Chem.* **2017**, *129*, 10970; *Angew. Chem. Int. Ed.* **2017**, *56*, 10830; c) J. K. Kerkovius, M. A. Kerr, *J. Am. Chem. Soc*. **2018**, *140*, 8415.

[5] R. Sustmann, *Pure Appl. Chem.* **1974**, *40*, 569.

[6] There are limited uncharged dipole equivalents that may undergo [3+2] cycloaddition. For examples of thioamide, thione or thiocarbamate, see: a) D.B. J. Easton, D. Leaver, *Chem. Commun.* **1965**, *22*, 585; b) B. R. O'Connor, F. N. Jones, *J. Org. Chem.* **1970**, *35*, 2002*;* c) J. E. Oliver, R. T. Brown, *J. Org. Chem.* **1974**, *39*, 2228; d) M. V. Lakshmikantham, M. P. Cava, *J. Org. Chem.* **1976**, *41*, 879; e) J. Nakayama, A. Kimata, H. Taniguchi, F. Takahashi, *Chem. Commun.* **1996**, 205; f) J. R. Hwu, Y. C. Hsu, *Chem. Eur. J.* **2011**, *17*, 4727; g) J. Zhang, A. C. S. Page, V. Palani, J. Chen, T. H. Hoye, *Org. Lett.* **2018**, *20*, 5550; For examples of amino-isocyanates, see: h) J. G. Roveda, C. Clavette, A. D. Hunt, S. I. Gorelsky, C. J. Whipp, A. M. Beauchemin, *J. Am. Chem. Soc.* **2009**, *131*, 8740; i) R. A. Ivanovich, C. Clavette, J.-F. Vincent-Rocan, J.-G. Roveda, S. I. Gorelsky, A. M. Beauchemin, *Chem. Eur. J.* **2016**, *22*, 7906; j) R. A. Ivanovich, J. A. M. Quartus, N. Das Neves, F. Loiseau, M. Raymond, A. M. Beauchemin, *J. Org. Chem.* **2019**, *84*, 9792; For examples of imino-isocyanates, see: k) C. Clavette, W. Gan, A. Bongers, T. Markiewicz, A. Toderian, S. I. Gorelsky, A. M. Beauchemin, *J. Am. Chem. Soc.* **2012**, *134*, 16111; l) A. B. Bongers, C. Clavette, W. Gan, S. I. Gorelsky, L. Betit, K. Lavergne, T. Markiewicz, P. J. Moon, N. Das Neves, N. K. Obhi, A. B. Toderian, A. M. Beauchemin, *J. Org. Chem.* **2017**, *82*, 1175. For examples of imino-isothiocyanates, see: m) A. Bongers, I. Ranasinghe, P. Lemire, A. Perozzo, J.-F. Vincent-Rocan, A. M. Beauchemin, *Org. Lett.* **2016**, *18*, 3778; For examples of azines, see: n) J. R. Bailey, N. H. Moore, *J. Am. Chem. Soc.* **1917**, *39*, 279; o) J. G. Schantl, H. Gstach, P. Hebeisen, N. Lanznaster, *Tetrahedron* **1985**, *41*, 5525; p) J. G. Schantl, P. Nadenik, *Synlett* **1998**, 786; q) R. J. Cremlyn, R. M. Ellam, S. Farouk, *Phosphorous, Sulfur and Silicon* **2000**, *161*, 213; r) J. Verner, J. Taraba, M. Potacek, *Tetrahedron Lett.* **2002**, *43*, 4833; s) H. Zachova, S. Man, M. Necas, M. Potacek, *Eur. J. Org. Chem.* **2005**, 2548; t) K. Burger, L Hennig, O. Zeika, A. Lux, *Heterocycles* **2006**, *67*, 443; u) J. Verner, M. Potacek, *Molecules* **2006**, *11*, 34; v) S. Man, M. Necas, J.-P. Bouillon, C. Portella, M. Potacek, *Eur. J. Org. Chem.* **2006**, 3473.

[7] The retro [3+2] cycloaddition of an oxonium ylide has been reported previously, suggesting the microscopic reverse *e.g.* the [3+2] cycloaddition of an alkoxy ketene, is possible. To date, only [2+2] reactions have been reported. a) A. Oku, S. Ohki, T. Yoshida, K. Kimura, *Chem. Commun.* **1996**, 1077; b) A. Oku, Y. Sawada, M. Schroeder, I. Higashikubo, T. Yoshida, S. Ohki, *J. Org. Chem.* **2004**, *69*, 1331; For other examples of oxonium ylides as intermediates, see: c) S. Muthusamy, J. Krishnamurthi, E. Suresh, *Chem. Commun.* **2007**, 861; d) D. M. Jaber, R. N. Burgin, M. Helper, P. Zavalij, M. R. Doyle, *Chem. Commun.* **2011**, *47*, 7623; e) G. K. Murphy, G. Stewart, F. G. West, *Tetrahedron* **2013**, *13*, 2667; f) L. Liu, C. Chen, H. Jiang, B. Yin, *J. Org. Chem.* **2018**, *83*, 14385.

[8] For examples of metal-catalyzed oxycarbonylation reactions of alkenes, see: a) T. Taniguhi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem.* **2010**, *122*, 10352; *Angew. Chem. Int. Ed.* **2010**, *49*, 10154; b) W. Liu, Y. Li, K, Liu, Z. Li, *J. Am. Chem. Soc.* **2011**, *133*, 10756; c) M. Li, F. Yu, X. Qi, P. Chen, G. Liu, *Angew. Chem.* **2016**, *128*, 14047; *Angew. Chem. Int. Ed.* **2016**, *55*, 13843; d) G. T. Hoang, D. J. Walsh, K. A. McGarry, C. B. Anderson, C. J. Douglas, *J. Org. Chem.* **2017**, *82*, 2972; e) J.-K. Cheng, L. Shen, L.-H. Wu, X.-H. Hu, T.-P. Loh, *Chem. Commun.* **2017**, *53*, 12830; For an example of a formal metal-free oxycarbonylation reactions of alkenes, see: f) R. K. Quinn, V. A. Schmidt, E. J. Alexanian, *Chem. Sci.* **2013**, *4*, 4030; For the use of oxycarbonylation of an alkene as a key step in total synthesis, see: g) L. Lv, B. Shen, Z. Li, *Angew. Chem.* **2014**, *126*, 4248; *Angew. Chem. Int. Ed.* **2014**, *53*, 4164; h) F. Manoni, C. Rumo, L. Li, P. G Harran, *J. Am. Chem. Soc.* **2018**, *140*, 1280.

[9] To our knowledge there are two examples of structurally distinct aza-oxonium ylides postulated as potential intermediates, though in each case they were discounted as unlikely pathways in the reactions studied. a) M. Ochiai, S. Yamane, M. M. Hoque, M. Saito, K. Miyamoto, Chem. Commun. **2012**, *48*, 5280; b) J. Escudero, V. Bellosta, J. Cossy, *Angew. Chem.* **2018**, *130*, 583; *Angew. Chem. Int. Ed.* **2018**, *57*, 574.

[10] Attempts to study pentafluorophenylnitrene in neat THF via laser flash photolysis (LFP) resulted in tentative structural assignment of a structurally distinct aza-oxonium ylide: R. Poe, K. Schnapp, M. J. T. Young, J. Grayzar, M. S. Platz, *J. Am. Chem. Soc.* **1992**, *114*, 5054.

[11] For a review of free nitrene reactions, see: R. A. Abramovitch, B. A. Davies, *Chem. Rev.* **1964**, *64*, 149.

[12] For examples of carbamate nitrenoid precursors, see: a) H. Lebel, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198; b) R. P. Peddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013; For examples of sulfamide nitrenoid precursors, see: c) R. Breslow, S. H. Gellman, *J. Chem. Soc., Chem. Commun.* **1982**, 1400; d) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6729; For examples of sulfamate ester nitrenoid precursors, see: e) Y. Cui, C. He, *Angew. Chem.* **2004**, *116*, 4306; *Angew. Chem. Int. Ed.* **2004**, *43*, 4210; f) E. Milczek, N. Boudet, S. Blakey, Angew. Chem. **2008**, *120*, 6931; *Angew. Chem. Int. Ed.* **2008**, *47*, 6825; g) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036; h) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; For an example of diaoxazolone nitrenoid precursors, see: i) V. Bizet, L. Buglioni, C. Bolm, *Angew. Chem.* **2014**, *126*, 5745; *Angew. Chem. Int. Ed.* **2014**, *53*, 5639. For an example of sulfimine nitrenoid precursors, see: j) C. Liang, F. Robert-Peillard, C. Fruit, P Muller, R. H. Dodd, P. Dauban, *Angew. Chem.* **2006**, *118*, 4757; *Angew. Chem. Int. Ed.* **2006**, *45*, 4641.

[13] For unsuccessful attempts synthesizing and isolating *O*-isocyanates, see: a) V. D. Sheludyakov, A. B. Dmitrieva, A. D. Kirilin, E. A. Chernyshev, *Zh. Obshch. Khim.* **1983**, *53*, 2051; *J. Gen. Chem. USSR* **1983**, *53*, 1851.

b) W. Mormann, G. Leukel, *Synthesis* **1988**, 990; For early studies of *O*-isocyanates, see: c) J. U. Nef, *Liebigs Ann. Chem.* **1894**, *280*, 263; d) L. W. Jones, *J. Am. Chem. Soc.* **1898**, *20*, 1; e) L. W. Jones, L. Neuffer, *J. Am. Chem. Soc.* **1917**, *39*, 652; For a review of heteroatom-substituted heteroallenes, including heteroatom-substituted isocyanates, see: f) W. Reichen, *Chem. Rev.* **1978**, *78*, 569; For examples of trimerization of *O*-isocyanate intermediates, see: g) A. F. McKay, D. L. Garmaise, G. Y. Paris, S. Gelblum, *Can. J. Chem.* **1960**, *38*, 343; h) H. A. Staab, *Angew. Chem.* **1962**, *74* 407; *Angew. Chem. Int. Ed.* **1962**, *1*, 351; i) M. T. Randolph, T. J. Hendrick, *J. Org. Chem.* **1965**, *30*, 1268; d) U. Heep, *Tetrahedron* **1975**, *31*, 77; j) I. Butula, M. J. M. Takac, *Croat. Chem. Acta* **2000**, *73*, 569; k) I., Kos, M. J. M. Takac, I., Butula, M. Birus, G., Maravič-Vlahoviček, S. Dabelic˘, Acta Pharm. **2013**, *63*, 174.

[14] a) J. L. Romine, S. W. Martin, N. A. Meanwell, J. R. Epperson, *Synthesis* **1994**, 846; For selected examples of other *O*-isocyanate syntheses, see: b) R. E. Wilde, T. K. K. Srinivasan, W. Lwowski, W. *J. Am. Chem. Soc.* **1971**, *93*, 860; c) V. D. Sheludyakov, A. B. Dmitrieva, A. D. Kirilin, E. A. Chernyshev, *Zh. Obshch. Khim.* **1983**, *53*, 706; d) W. Mormann, G. Leukel, *Synthesis* **1988**, 990; e) J. H. Teles, G. Maier, *Chem. Ber.* **1989**, *122*, 745; f) S. Hanessian, S. Johnstone, *J. Org. Chem.* **1999**, *64*, 5896; g) S. Fioravanti, F. Marchetti, A. Morreale, L. Pellacani, P. A. Tardella, *Org. Lett.* **2003**, *5*, 1019; h) J. G. Krause, B. D. Leskiw, M. L. Emery, M. E. McGahan, M. P. McCourt, R. Priefer, *Tetrahedron Lett.* **2010**, *51*, 3568; i) T. Baburaj, S. Thambidurai, *Synlett* **2011**, 1993; For the correction, see: T. Baburaj, S. Thambidurai, *Synlett* **2015**, 1137; j) T. Baburaj, S. Thambidurai, *Tetrahedron Lett.* **2012**, *53*, 2292; For the correction, see: T. Baburaj, S. Thambidurai, *Tetrahedron Lett.* **2014**, *54*, 561. k) T. A. Chavez, Y. Liu, J. P. Toscano, *J. Org. Chem.* **2016**, *81*, 6320; l) H. Wan, J. Xu, Q. Liu, H. Li, Y. Lu, M. Abe, X. Zeng, *J. Phys. Chem.* **2017**, *121*, 8604; m) H. Li, Z. Wu, D. Li, H. Wan, J. Xu, M. Abeb, X. Zeng, *Chem. Commun.* **2017**, *53*, 4783.

[15] For an entry into the blocked isocyanate literature, see: a) D. A. Wicks, Z. W. Wicks, *Prog. Org. Coat.* **1999**, *36*, 148; b) D. A. Wicks, Z. W. Wicks, *Prog. Org. Coat.* **2001**, *41*, 1; c) E. Delebecq, J.- P. Pascault, B. Boutevin, F. Ganachaud, *Chem. Rev.* **2013**, *113*, 80; d) M. S. Rolph, A. L. J. Markowska, C. N. Warriner, R. K. O'Reilly, *Polym. Chem.* **2016**, *7*, 7351.

[16] a) M. A. Allen, R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Org. Lett.* **2017**, *19*, 6574; b) R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Adv. Synth. Catal.* **2017**, *359*, 4289; c) Q. Wang, J. An, H. Alper, W.-J. Xiao, A. M. Beauchemin, *Chem. Commun.* **2017**, *53*, 13055.

[17] a) J. K. Rasmussen, A. Hassner, *Chem. Rev.* **1976**, *3*, 389; b) F. P. Cossio, G. Roa, B. Lecea, J. S. Ugalde, *J. Am. Chem. Soc.* **1995**, *117*, 12306.

[18] Deposition Number 1949772 (**6a**), 1949771 (**7a**), 1949770 (**8a**), and 1949773 (**13a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[19] A "deblocking temperature" is often quoted in the blocked isocyanate literature to denote the temperature of reactivity for a masked isocyanate. For *O*-isocyanates, like other isocyanates, this temperature varies depending on the reactivity following the deblocking equilibrium and the choice of measurement. In general, however, satisfactory substitution reactivity of *O*-isocyanates with good nucleophiles occurs around 70˚C with catalytic base and cycloaddition/nitrene reactivity can proceed without base around 150˚C. For an entry into the blocked isocyanate literature, see references 14a-d.

[20] Brønsted bases are well-known catalysts for isocyanate deblocking. Their use generally allows for a lower "deblocking temperature". Base catalysis of isocyanate deblocking is discussed in references 14a-d.

[21] S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik, S. Chang, *Science* **2018**, *359*, 1016.

[22] a) W. Lwowski, A. Hartenstein, C. deVita, R. L. Smick, *Tetrahedron Lett.* **1964**, *5*, 2497; b) E. Eibler, J. Sauer, *Tetrahedron Lett.* **1974**, *15*, 2569; c) K.-U. Clauss, K. Buck, W. Abraham, *Tetrahedron* **1995**, *51*, 7181 d) E. A. Pritchina, N. P. Gritsan, A. Maltsev, T. Bally, T. Autrey, Y. Liu, Y. Wang, J. P. Toscano. *Phys. Chem. Chem. Phys.* **2003**, *5*, 1010; e) V. Desikan, Y. Liu, J. P. Toscano, W. S. Jenks, *J. Org. Chem.* **2007**, *72*, 6848; This cycloaddition is also known for acyl carbenes via the analogous ylide. For examples, see: f) R. Huisgen, H. J. Sturm, G. Binsch, *Chem. Ber.* **1964**, *97*, 2865; g) N. T. Buu, J. T. Edward, *Can. J. Chem.* **1972**, *50*, 3730; h) M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliott, J. W. Hoekstra, M. Oppenhuizen, *J. Org. Chem.* **1980**, *45*, 366; i) R. Connell, F. Scavo, P. Helquist, B. Akermark, *Tetrahedron Lett.* **1986**, *27*, 5559; j) R. Connell, M. Tebbe, R. Helquist, B. Akermark, *Tetrahedron Lett.* **1991**, *32*, 17; k) K. J. Doyle, C. J. Moody, *Tetrahedron* **1994**, *50*, 3761; l) K. J. Doyle, C. J. Moody, *Synthesis* **1994**, 1021.

[23] L. Xu, C. H. Doubleday, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 3029.

[24] a) S. Nagase, K. Morokuma, *J. Am. Chem. Soc.* **1978**, *100*, 1666; b) F. M. J. Bickelhaupt, *Comput. Chem.* **1999**, *20*, 114 c) D. E. Hess, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 10646 d) D. E. Hess, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10187.

[25] D. E. Hess, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 10646.

[26] A. Padwa in *1,3-Dipolar Cycloaddition Chemistry*, Wiley: New York, **1984**.

[27] a) A. Acharya, J. A. Eickhoff, C. S. Jeffrey, *Synthesis (Stuttg).* **2013**, *45*, 1825–1836; b) A. Acharya, J. A. Eickhoff, K. Chen, V. J. Catalano, C. S. Jeffrey, *Org. Chem. Front.* **2016**, *3*, 330–334.

[28] a) W. J. S. Lockley, W. Lwowski, *Tetrahedron Lett.* **1974**, *15*, 4263–4266; b) W. Lwowski, S. Kanemasa, R. A. Murray, V. T. Ramakrishnan, T. K. Thiruvengadam, K. Yoshida, A. Subbaraj, *J. Org. Chem.* **1986**, *51*, 1719–1723; c) D. W. Jones, *J. Chem. Soc. Chem. Commun.* **1982**, 766–768.

[29] X. Hong, Y. Liang, A. K. Griffith, T. H. Lambert, K. N. Houk, *Chem. Sci.* **2014**, *5*, 471–475.

[30] Higher alkene loadings were required to increase yields with all other carbamates other than *N*-methoxycarbamate affording product **13a.**

[31] a) R. Łysek, B. Furman, M. Cierpucha, B. Grzeszczyk, Ł. Matyjasek, M. Chmielewski, *European J. Org. Chem.* **2002**, *2002*, 2377–2384; b) M. Chmielewski, Z. Kałuża, B. Furman, *Chem. Commun.* **1996**, 2689–2696; c) Z. Kałuza, W. Fudong, C. Bełzecki, M. Chmielewski, *Tetrahedron Lett.* **1989**, *30*, 5171–5172.

[32] S. De Bernardo, J. P. Tengi, G. J. Sasso, M. Weigele, *J. Org. Chem.* **1985**, *50*, 3457–3462.

[33] Current efforts include catalysing the cycloaddition and subsequent steps. Already, base catalysis is demonstrated herein to provide milder conditions, and alternative reaction pathways with vinyl ethers enabling access to synthetically useful β-lactams. We also have other preliminary results with ZnO as an additive with norbornene showing reactivity at 110 °C. While preliminary, this important rate acceleration is an encouraging hit for further development, and better reaction scope.

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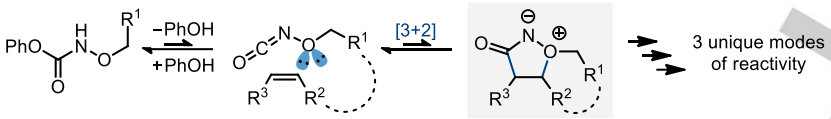

Cycloadducts charged with intent to aminate. *O*-Isocyanates undergo a novel [3+2] cycloaddition to form a zwitterionic cycloadduct — an aza-oxonium ylide. The aza-oxonium ylide undergoes divergent reactivity enabling the synthesis of a variety of saturated *N*-containing heterocycles via nitrene C-H insertion, formal ring contraction, and [1,2] shift from the ylide cycloadduct.