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Intramolecular Alkene Aminocarbonylation Using Concerted Cycloadditions of Amino-Isocyanates

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Dedicated to the memory of Professor Walter Lwowski

Abstract: The ubiquity of nitrogen heterocycles in biologically active molecules challenges synthetic chemists to develop a variety of tools for their construction. While developing metal-free hydroamination reactions of hydrazine derivatives, it was discovered that carbazates and semicarbazides can also lead to alkene aminocarbonylation products if nitrogen-substituted isocyanates (*N*-isocyanates) are formed in situ as reactive intermediates. At first this reaction required high temperatures (150–200 °C), and issues included competing hydroamination and *N*-isocyanate dimerization pathways. Herein, improved conditions for concerted intramolecular alkene aminocarbonylation with *N*-isocyanates are reported. The use of β*N*-benzyl carbazate precursors allows the effective minimization of *N*-isocyanate dimerization. Diminished dimerization leads to higher yields of alkene aminocarbonylation products, to reactivity at lower temperatures, and to an improved scope for a reaction sequence involving alkene aminocarbonylation followed by 1,2-migration of the benzyl group. Furthermore, fine-tuning of the blocking (masking) group on the *N*-isocyanate precursor, and reaction conditions relying on base catalysis for *N*-isocyanate formation from simpler precursors resulted in room temperature reactivity, consequently minimizing the competing hydroamination pathway. Collectively, this work highlights that controlled reactivity of aminoisocyanates is possible, and provides a broadly applicable alkene aminocarbonylation approach to heterocycles possessing the β-aminocarbonyl motif.

Introduction

The abundance and importance of nitrogen-containing functional groups in biologically active molecules such as natural products,[1] agrochemicals[2] and pharmaceuticals[3] cannot be overstated. It is therefore no surprise that numerous C–N bond-forming reactions of alkenes, such as aminohydroxylation, hydroamination, aziridination, aminocyanation, and aminoboration, have been developed to meet the synthetic demands of these increasingly complex nitrogen-rich products. Many of these synthetic transformations remain of high academic and industrial interest,[4] to improve the reaction scope for both intra- and intermolecular variants, increase reaction efficiency or develop enantioselective processes. While these processes have relied on a variety of activation modes, catalysis is generally required to overcome the high activation energy typically associated with amination reactions of alkenes. Conversely, metal-free reactions allowing effective C–N bond formation from simple and readily accessible reagents have also attracted significant interest in recent years.[5]

In our efforts to develop metal-free alkene amination reactions, we have demonstrated the utility of bifunctional reagents for the formation of C–N bonds from alkenes, alkynes and allenes under metal-free, thermal conditions.[6,7] In particular, hydroxylamines proved to be effective reagents for intra- and intermolecular Cope-type (concerted) alkene hydroaminations.[6] However, the instability of hydroxylamines upon heating at approximately 100 °C led to the development of related reactivity with other bifunctional reagents possessing increased thermal stability. This led to the discovery that hydrazine derivatives also engage in concerted, Cope-type hydroamination reactions of alkenes and alkynes.[7] However, the need to heat at higher temperatures (up to 200 °C) in some systems resulted in divergent reactivity:[7b] both alkene hydroamination and aminocarbonylation[8] reactions were observed with some hydrazine derivatives (Scheme 1).

Unexpectedly, at elevated temperatures, carbazate ($\mathbf{X}=OR^4$, Scheme 1) and semicarbazide ($\mathbf{X}=NR^3_2$) reagents generated a rare and highly reactive intermediate in situ. This nitrogen-substituted isocyanate (*N*-isocyanate) could then engage in a [3+2] cycloaddition reaction with the terminal alkene. From the perspective of the alkene, this reactivity is an intramolecular alkene aminocarbonylation[8] process, and synthetically this

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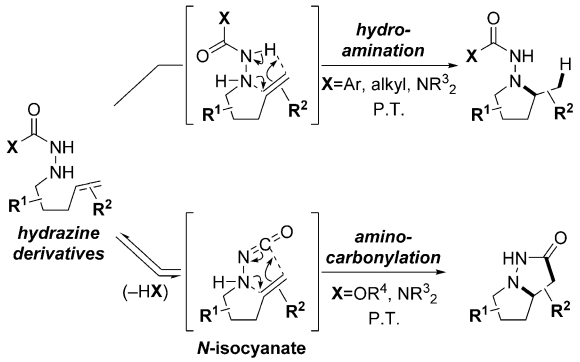


Scheme 1. Divergent reactivity of hydrazine derivatives: hydroamination (above) and aminocarbonylation (below) reactivity. P.T. = proton transfer.

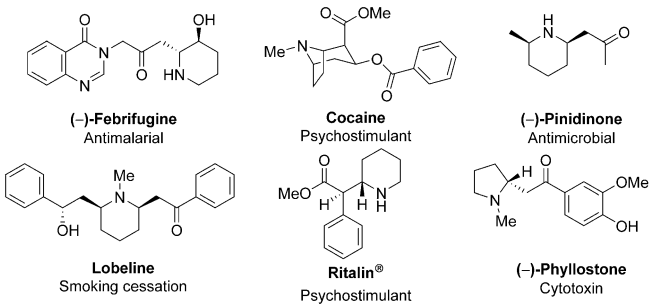
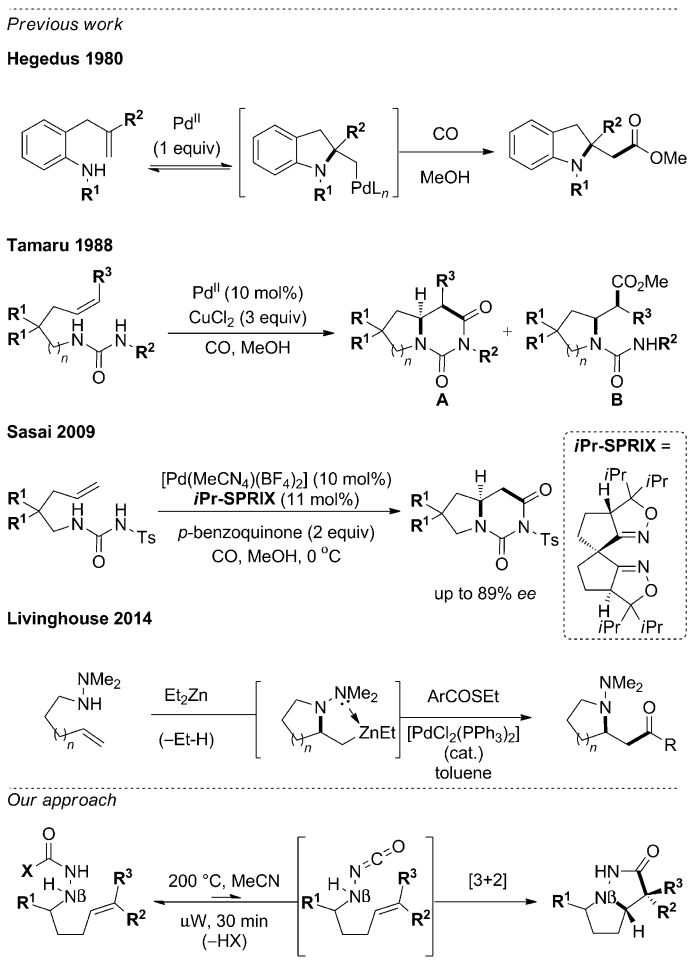


Figure 1. Pharmaceuticals and natural products possessing cyclic β-aminocarbonyl motifs.

provides access to cyclic β-aminocarbonyl products. Such products are present in a variety of natural products and small-molecule drugs (Figure 1). β-Amino acids are also used as building blocks to assemble synthetic peptides.[9] In general, the usefulness of β-aminocarbonyl motifs, the scarcity of reactions allowing the transformation of alkenes into β-aminocarbonyls and the fact that reactions involving *N*-isocyanates are rare prompted further study of this alkene aminocarbonylation reactivity.

Despite the importance of the β-aminocarbonyl motif, intramolecular alkene aminocarbonylation reactions are quite rare: only few examples exist in the literature (Scheme 2). Hegedus reported the first examples, initially under conditions that required stoichiometric quantities of palladium.[10a,b] However, a subsequent report disclosed that a palladium-catalyzed variant was possible using olefinic tosylamides.[10c] Tamaru and Yoshida further improved this reactivity with the use of Wacker-type conditions, in which an external oxidant allowed the process to proceed with catalytic palladium and with a broader range of substrates.[11a] Continued work by this group led to the discovery of conditions for the synthesis of 6-membered rings, an important advance since all previous examples were limited to 5-membered products.[11b] Unfortunately, the reactions were difficult to control and a mixture of cyclic (**A**) and acyclic (**B**) aminocarbonylation products were often obtained. Recently, Sasai reported the first enantioselective intramolecular aminocarbonylation reaction using alkenylureas.[12] Alternatively, Livinghouse developed an approach by a metalloamination/cyclization reaction, which relies on an anionic mechanism for the cyclization step and on a subsequent Fukuyama coupling to provide the desired aminocarbonylation products.[13] A few other routes have also been studied,[14] and intramolecular aminocarbonylation reactions have even been the key step in syntheses of natural products[15] but as for the examples highlighted above, these reports typically necessitate the use of metal catalysis and an external source of CO for the carbonylation. To the best of our knowledge, the intramolecular aminocarbonylation reaction of *N*-isocyanates shown in Scheme 1 is unique as it relies on a concerted [3+2] cycloaddition to afford the aminocarbonylation products, and does not rely on external reagents or catalysts.

This concerted reactivity of *amino*-isocyanates is also a rare example of a reaction occurring through an *N*-isocyanate. There are only few reports in the literature of the reactivity of these amphoteric (ambident) isocyanates, probably due to their tendency to dimerize at temperatures as low as −40 °C if



Scheme 2. Review of intramolecular aminocarbonylation reactions.

the nitrogen atom is sp^3-hybridized.[16j] There are also important limitations on the methods to generate *N*-isocyanates. In a remarkable report however, Lwowski used an amino-isocyanate (Me_2N-NCO) in intermolecular alkyne aminocarbonylations.[13b] Since our initial report on alkene aminocarbonylation using amino-isocyanates,[7b] our group has expanded the use of blocked (masked) isocyanate precursors to form *N*-isocyanates in situ. This approach has led to increased control of *N*-isocyanate reactivity, and allowed their generation at lower temperatures. Synthetically, this enabled the development of intermolecular aminocarbonylation reactions of imino-isocyanates,[17] as well as many cascade reactions for the synthesis of NNCO-containing molecules.[18]

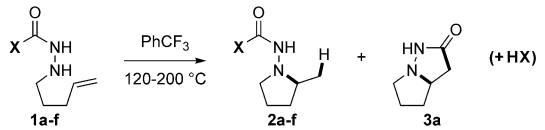
From a reaction development perspective, amino-isocyanates are probably the most difficult *N*-isocyanate reagents to work with due to the relatively high nucleophilicity of the β-nitrogen atom. Using hydrazine-derived amino-isocyanate precursors, efforts to expand the intramolecular aminocarbonylation reactivity shown in Scheme 1 were met with tremendous difficulty, due to competing homodimerization of the *N*-isocyanate or intramolecular hydroamination side-reactions. However, a thorough survey of blocked (masked) isocyanate precursors and milder conditions were expected to provide increased control of *N*-isocyanate formation, and consequently minimize dimerization. Herein, a detailed account of efforts to improve their intramolecular aminocarbonylation reactivity is provided. Specifically, improved reactivity proved possible through: 1) The use of *βN*-benzylated carbazates in an aminocarbonylation/1,2 benzyl shift cascade; 2) The use of *N*-isocyanate precursors with more labile leaving groups; and 3) The use of base catalysis to perform alkene aminocarbonylation at lower temperatures.

Results and Discussion

During the initial optimization of hydroamination reactivity with hydrazine derivatives, interesting results were obtained with carbazates **1 d** and **1 e** (Table 1). An unexpected compound formed in addition to the hydroamination products (**2 d**, **e**), and was later identified as aminocarbonylation product **3 a**. The formation of this product was hypothesized to occur from a reactive intermediate: a nitrogen-substituted isocyanate (*N*-isocyanate). Initial reaction optimization revealed that increased temperatures resulted in a higher yield of the aminocarbonylation product. Naturally, this provoked interest in the ability of semicarbazides to undergo a similar transformation, which led to the synthesis of semicarbazide **1 f**. Preliminary results suggested that semicarbazides were more stable aminocarbonylation precursors: hydroamination was more prevalent at 150 °C (entry 7), while aminocarbonylation was favored at 200 °C (entry 8).

Knowing that both carbazates and semicarbazides engaged in this aminocarbonylation reaction, the synthetic scope was explored with the hope of gaining insights into this unknown reactivity (Table 2). As such, a comparative study using several related substrates was first conducted with distinct carbonyl substituents (**LG** = O*t*Bu, and NH_2).

Table 1. Thermolysis of hydrazine derivatives: hydroamination versus aminocarbonylation.[a]

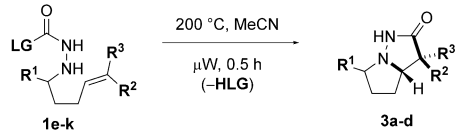


1a-f 2a-f 3a

Entry	X	*T* [°C]	*t* [h]	Product (yield [%])[b]
1	Ph (**1 a**)	120	18	**2 a** (93)
2	*t*Bu (**1 b**)	150	16	**2 b** (66)
3	2-pyridyl (**1 c**)	170	42	**2 c** (64)
4	OEt (**1 d**)	140	16	**2 d** (25) + **3 a** (6)
5	OEt (**1 d**)	200 (μW)	0.5	**2 d** (13) + **3 a** (46)
6	O*t*Bu (**1 e**)	200 (μW)	0.5	**2 e** (0) + **3 a** (71)
7	NH_2 (**1 f**)	150 (μW)	0.5	**2 f** (50) + **3 a** (20)[c]
8	NH_2 (**1 f**)	200 (μW)	0.25	**2 f** (10) + **3 a** (85)[c]

[a] Conditions: heating performed in $PhCF_3$ (0.05 M, sealed tube) using conventional heating or microwave irradiation (μW). [b] Isolated yield. [c] NMR yield using 1,4-dimethoxybenzene as internal standard.

Table 2. Preliminary substrate scope of aminocarbonylation reaction.[a,b]



1e-k 3a-d

LG = O*t*Bu, 70 % (**3 a**)
LG = NH_2, 86 % (**3 a**)

LG = O*t*Bu, 74 % (**3 b**)[c]
LG = NH_2, 84 % (**3 b**)[c]

LG = O*t*Bu, 66 % (**3 c**)
LG = NH_2, 52 % (**3 c**)[d]

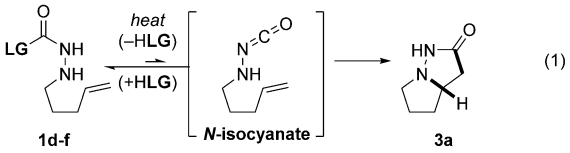
LG = O*t*Bu, 71 % (**3 d**)

[a] Conditions: heating performed in MeCN (200 °C, 0.5 h, 0.05 M, microwave reactor). [b] Isolated yield. [c] 2:1 d.r.; [d] NMR yield using 1,4-dimethoxybenzene as internal standard; 13 % of epimer **3 d** was also present.

It was noted that products **3 a**, **b** formed in higher yield from the corresponding semicarbazide precursors. Both precursors for **3 b** (**LG** = O*t*Bu and NH_2) provided the aminocarbonylation product **3 b** with very similar diastereoselectivity (ca. 2:1 d.r.), an observation that is again consistent with a common amino-isocyanate intermediate. The reaction also tolerated substitution at the alkene distal position (products **3 c**, **d**), with slight epimerization (4:1 d.r.) of product **3 c** when it was generated from the corresponding semicarbazide (**1 j**). The structure of **3 c** was unambiguously assigned through derivatization (see the Supporting Information). Interestingly, the reaction was stereospecific: the stereochemical information present in the *cis*- and *trans*-substituted alkene was transferred to the resulting aminocarbonylation product. *This observation is important as it provides insight towards the mechanism of the transforma-*

tion. Indeed, the stereospecificity of this reaction strongly suggested a concerted (*syn*) aminocarbonylation reaction.

In summary, two conclusions could be drawn from this initial survey. First, the convergent reactivity observed with both carbazate and semicarbazide reagents supported the involvement of a common intermediate. Second, the cycloaddition (aminocarbonylation) of this intermediate is likely concerted. A nitrogen-substituted isocyanate (amino-isocyanate) was suggested as the intermediate involved in the aminocarbonylation reaction [Eq. (1)].



(1)

To account for the observed stereospecificity, addition of the amino-isocyanate to the alkene was suggested to undergo a [3+2] cycloaddition. The possibility that a *N*-isocyanate would be formed upon thermolysis of carbazate or semicarbazide precursors was consistent with the literature on *N*-isocyanates,[16a,d,e] and Lwowski's prior report of intermolecular cycloadditions with electron-poor alkynes also supported this hypothesis.[16b] However, since *N*-isocyanates are reactive intermediates that are difficult to isolate,[16k,l] DFT calculations emerged as an ideal approach to probe this possibility. The results of exploratory calculations are shown in Figure 2.

Support for a concerted cycloaddition was obtained, indeed an asynchronous cycloaddition transition state was found to possess an activation energy of 19.1 kcal mol^{-1} from the *N*-isocyanate. In comparison to the *N*-isocyanate intermediate, the transient ammonium ylide intermediate is slightly less stable ($\Delta G = 2.4$ kcal mol^{-1}), but the overall reaction after proton transfer was found to be thermodynamically favorable by $\Delta G^{r} = -17.6$ kcal mol^{-1}. However, calculations also revealed the difficulty associated with an intramolecular proton-transfer

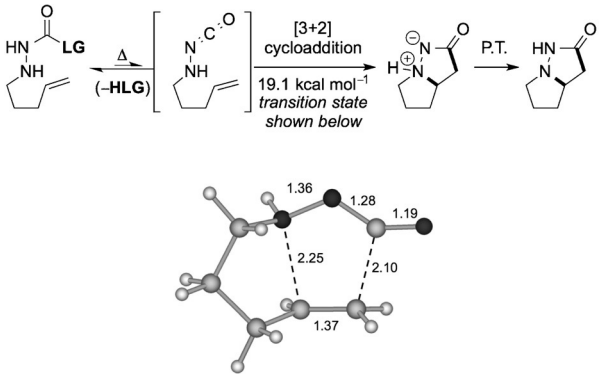
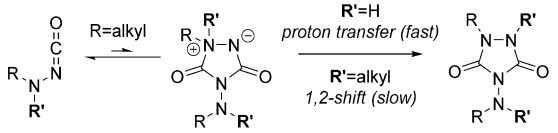


Figure 2. Proposed reaction pathway of intramolecular aminocarbonylation via a *N*-isocyanate intermediate investigated by DFT calculations (at the B3LYP/TZVP level of theory) including calculated gas-phase energies (above), and transition state structure for the intramolecular alkene aminocarbonylation with *N*-isocyanate (below). Internuclear distances [Å] are shown for relevant chemical bonds. P.T. = proton transfer.

step from the resulting aminocarbonylation dipole intermediate ($\Delta G^{\ddagger} = 33.3$ kcal mol^{-1}), which is reminiscent of studies performed on Cope-type hydroaminations.[7] However, only this difficult (intramolecular) proton-transfer pathway was investigated, and it is likely that more facile pathways are accessible. Overall, the DFT calculations suggested that despite the necessity for harsh thermal conditions to form the *N*-isocyanate (up to 200 °C), *the subsequent alkene cycloaddition (aminocarbonylation) should be quite favorable and could occur at room temperature.* Therefore, calculations also suggested that the generation of *N*-isocyanate was rate-determining for the transformation.

Combining the insights gained from DFT calculations (Figure 2) with conclusions from pioneering work on the generation of *N*-isocyanates from the literature,[16] efforts were initiated towards an improved aminocarbonylation process. These targeted new aminocarbonylation precursors, and the study of their reactivity under thermolytic conditions, to identify milder aminocarbonylation conditions.

Due to the known propensity of *N*-isocyanates to undergo a competing dimerization at temperatures as low as −40 °C,[16j] minimizing this side reaction was considered to be crucial to achieve a milder, and a more broadly applicable aminocarbonylation reaction. Although *N*-isocyanate dimers can undergo cycloreversion and regenerate the reactive intermediate, this typically only occurs upon heating.[16i] With this in mind, the desired precursor would either need to be unlikely to undergo *N*-isocyanate dimerization; or readily undergo cycloreversion. Therefore, we turned our attention to the nature of *N*-alkyl substitution on *N*-isocyanate derivatives. The added steric hindrance of dialkyl *N*-isocyanates over their monoalkyl counterparts was expected to slow the rate of dimerization, thereby increasing the yields of aminocarbonylation products. Additionally, assessment of Lwowski's work[16b] suggested that hindered ammonium ylides undergo cycloreversion more readily to regenerate the reactive *N*-isocyanate [Eq. (2)].[19] Furthermore, the added *N*-alkyl substituent could increase the HOMO energy of the nitrogen atom participating in the cycloaddition, resulting in a more reactive aminocarbonylation reagent. Finally, substituting a hydrogen atom for an alkyl group would require the zwitterionic ammonium ylide generated from the intramolecular [3+2] to undergo a 1,2-alkyl-shift. βN-Benzyl carbazates emerged as an ideal candidate, fulfilling the steric and electronic demands above in conjunction with the fact that benzyl groups can undergo a 1,2-rearrangement under thermal conditions comparable to that of our initial aminocarbonylation process.[20]

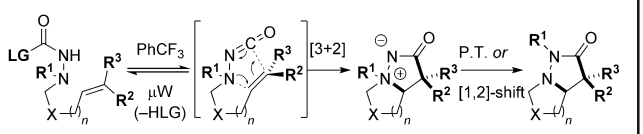


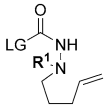
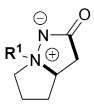
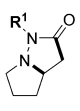
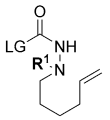
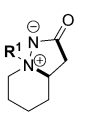
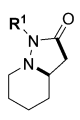
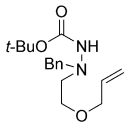
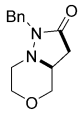
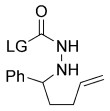
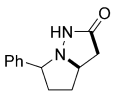
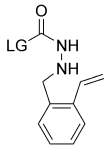
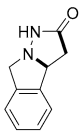
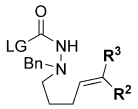
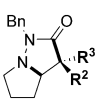
(2)

Presented in Table 3 is a comparison of the reactivity of monoalkenyl carbazates ($\mathbf{R^1} = H$) to that of βN-benzylated carbazates ($\mathbf{R^1} = Bn$). Under standard aminocarbonylation condi-

tions (200 °C), monoalkenyl carbazate **1e** provided the aminocarbonylation product **3a** in good yield (Table 3, entry 1). In turn, preliminary results from *N*-benzyl alkenyl carbazate **1l** provided excellent yield for the [3+2]/1,2-rearrangement sequence (**3e**) at 200 °C (entry 2).

Table 3. Aminocarbonylation with mono- and bisalkyl carbazate precursors.[a]



Entry	LG	R^1	T [°C]	Yield [%] (product)[b]	
					
1	OtBu	R^1 = H (**1e**)	200	0 (**4a**)	74 (**3a**)
2		R^1 = Bn (**1l**)	200	0 (**4e**)	90 (**3e**)
3		R^1 = Bn (**1l**)	150	49 (**4e**)	24 (**3e**)
					
4	OtBu	R^1 = H (**1m**)	200	0 (**4f**)	0 (**3f**)
5	NH_2	R^1 = H (**1n**)	200	0 (**4f**)	0 (**3f**)
6	OtBu	R^1 = Bn (**1o**)	200	0 (**4g**)	99 (**3g**)
7	OtBu	R^1 = Bn (**1o**)	150	0 (**4g**)	66 (**3g**)
					
8	OtBu	(**1p**)	200	82 (**3h**)	
9		(**1p**)	150[c]	98 (**3h**)	
					
10	OtBu	(**1q**)	200	76 (**3i**)[d]	
					
11	OtBu	(**1r**)	200	40 (**3j**)	
12		(**1r**)	200[e]	55 (**3j**)	
					
13	OtBu	R^3 = Me, R^4 = H (**1s**)	200	44[f] (**3k**)	
14		R^3 = H, R^4 = Me (**1t**)		43[f] (**3l**)	

[a] Conditions: heating performed in $PhCF_3$ (0.5 h, 0.05 M, microwave reactor) unless indicated otherwise. [b] Isolated yields unless noted otherwise. [c] Heated for 6 h. [d] Obtained as a mixture of diastereomers (3:2 d.r.). [e] Heated for 2 h. [f] NMR yield using 1,3,5-trimethoxybenzene as internal standard P.T. = proton transfer.

To gain insight on the 1,2-rearrangement step, the temperature was decreased to 150 °C with several substrates (Table 3, entries 3, 7 and 9). Using carbazate **1l** at 150 °C (entry 3), provided a mixture of the desired [3+2]/1,2-rearrangement cascade (**3e**) and the corresponding ammonium ylide precursor (**4e**). This provided the proof that this sequence could be used as a tool to improve aminocarbonylation reactivity. We questioned whether βN-benzyl substrates could enable more challenging reactions. In a prior survey, efforts were devoted to cyclizations forming 6,5-bicyclic ring systems. Unfortunately, monoalkenyl carbazates and semicarbazides (**1m** and **1n**) could not provide the desired 6,5-bicyclic product (entries 4 and 5), since aminations to form 6-membered ring systems are in general significantly more challenging than related 5-membered forming cyclizations. Comparatively, *N*-benzyl precursor **1o** cyclized in nearly quantitative yield to the desired 6,5-bicyclic product at 200 °C (entry 6). The temperature of the reaction was then lowered to 150 °C (entry 7), upon which only the desired product was obtained, albeit in lower yield, with no traces of the ammonium ylide. Encouragingly, βN-benzylation could expand the synthesis of 6,5-bicyclic substrates to include morpholine-based bicyclic derivative **3h** (entry 8 and 9) in excellent yield. In this case, generation of **3h** proved optimal at lower temperature (150 °C) and could be obtained in nearly quantitative yield (entry 9).

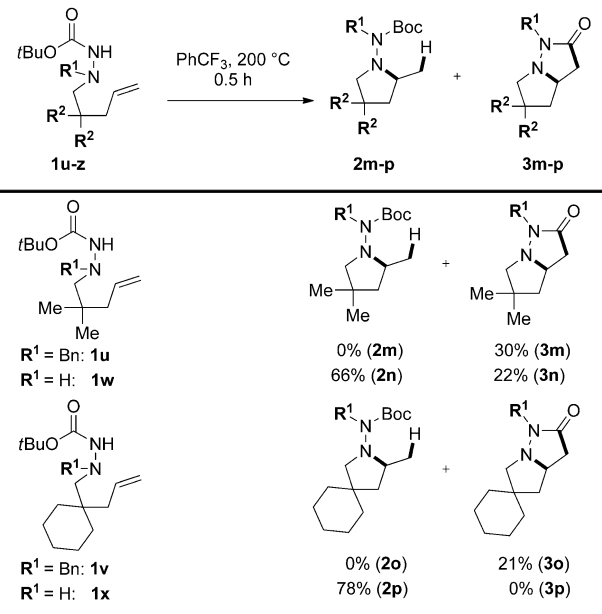
To elucidate the effects of βN-benzylation on aminocarbonylation, the reactivity was expanded to other benzylic substrates (entries 10–12). Investigations began with monoalkenyl carbazate **1q**. Arguably this carbazate allows to probe the electronic and steric influence of the benzyl group also present in benzylic precursors such as **1l**. Encouragingly, the 2-phenyl substituted product **3i** could be obtained in good yield (76%, entry 10), a result similar to that of unsubstituted product **3a** (74%, entry 1). Carbazate **1r** also provided its aminocarbonylation product **3j** (entry 11), albeit in modest yield after heating for 30 min and improved yield after 2 h (entry 12). It should be noted that solubility issues could have contributed to the diminished reactivity of **1r**, and this limits the conclusions that could be drawn from entries 11 and 12. The investigation was then expanded to substrates possessing internal alkenes. In our initial survey, yields were fairly consistent with these substrates (**3c**, **d**, Table 2). In contrast, βN-benzylated *cis* and *trans* methyl-alkenyl carbazates **1s** and **1t** cyclized in modest yields (**3k**, **l**, entries 13 and 14), despite several optimization attempts. However, again the aminocarbonylation event in this reaction sequence proved stereospecific.

Overall, the data shown in Table 3 show that the [3+2]/1,2-rearrangement sequence developed with *N*-benzyl substrates is more efficient for challenging reactions. Possible explanations for this improved reactivity include that substitution is increasing the HOMO of the β-nitrogen, minimizing *N*-isocyanate dimerization, and/or favoring cycloreversion of an isocyanate dimer similar to Equation (2) above. A more facile cycloreversion is an attractive explanation, as it would allow the dimer to reform the reactive *N*-isocyanate and undergo aminocarbonyla-

tion. Wentrup has shown that dimerization of sp^3-hydridized *N*-isocyanates occurs at low temperatures (−40 °C).[13j] Lwowski also reported that cycloreversion of hindered *N*,*N*-dialkyl aminimides [Eq. (2)] occurs at appreciable rates between 60 and 110 °C.[16b] The observation of the ammonium ylide (**4e**, entry 3) at 150 °C suggests that the 1,2-benzyl migration is relatively slow, and this could allow for cycloreversion to the *N*-isocyanate to occur. Finally, the lower efficiency of the reaction with internal alkenes could also be rationalized by invoking the stability of the parent ammonium ylide intermediate. Indeed, DFT calculations indicated that forming this intermediate was already thermodynamically uphill with a terminal alkene (by 2.4 kcal mol^{-1}, see Figure 2) and would therefore be more difficult with more stable, internal alkenes. This implies more reversibility for the alkene aminocarbonylation step relative to the 1,2-rearrangement, and could allow for other side-reactions to compete with the desired reaction sequence.

Although βN-benzylated substrates provided access to more complex aminocarbonylation products, additional complications arose as more complex substrates were synthesized. Presented in Table 4 are substrates that failed to perform a *selective* aminocarbonylation reaction. Indeed, Cope-type hydroamination (hydro-hydrazination[8]) proved to be a competing side-reaction with select substrates.

Table 4. Selected reactions showcasing hydroamination as a significant side-reaction.[a]



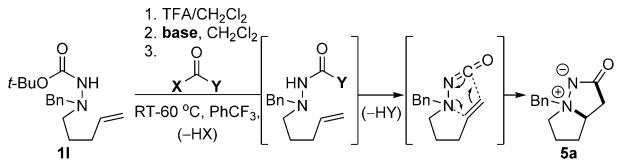
[a] Conditions: heating performed in $PhCF_3$ (200 °C, 0.5 h, 0.05 M, microwave reactor), NMR yields using 1,3,5-trimethoxybenzene as internal standard.

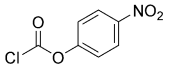
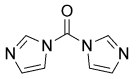
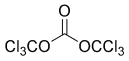
In general, hydroamination was a competing side-reaction for substrates possessing exhibiting a strong conformational bias (Table 4). For the case of βN-benzyl Thorpe–Ingold biased substrates **1u** and **1v**, the yield of aminocarbonylation was improved over their monoalkenyl equivalents (**1w** and **1x**, respectively). More specifically, 30% aminocarbonylation was observed with **1u** and 21% with **1v**, while Thorpe–Ingold influenced monoalkenyl carbazates **1w** and **1x** only showed 22 and 0% aminocarbonylation, respectively. Since a modest increase of aminocarbonylation was observed with βN-benzylation and no evidence of hydroamination was detected by NMR spectroscopy, we were initially excited to have apparently suppressed the competing hydroamination reaction. This excitement dissipated proceeding exhaustive attempts to further increase the yield of the aminocarbonylation reaction. This indicated that, although βN-benzylation could increase aminocarbonylation, indiscriminately favoring cyclization ultimately could not provide a broadly applicable aminocarbonylation reaction (see Supporting Information, Table S6 for a full list of failed attempts). Collectively, these examples of failed reactions demonstrate the need for new aminocarbonylation reagents that could react below the threshold temperatures required for hydro-hydrazination (roughly 80 °C),[7c,18a] or decomposition pathways that are consistent with uncontrolled benzyl-group-transfer reactions.

The search for milder aminocarbonylation conditions led to the consideration of other methods of isocyanate formation. Phosgenation of hydrazine was attractive given that the subsequent acylation products are known to release isocyanates at room temperature.[21] Unfortunately, hydrazine synthesis can be challenging due to chemoselectivity issues inherent to possessing two nucleophilic nitrogen atoms.[22] Gratifyingly, TFA-induced Boc-deprotection of the βN-benzyl carbazate precursors provided the required unsymmetrical hydrazines, which in turn could be treated with phosgene equivalents. These substrates allowed *N*-isocyanate formation under mild conditions, due to the lability of the resultant blocking group following acylation. Results from this survey are presented in Table 5.

As predicted by DFT, mild *N*-isocyanate formation enabled room temperature aminocarbonylation. The products were obtained in the form of zwitterionic dipole **5a** since 1,2-benzyl migration could not occur at room temperature (Table 5). Oxalyl chloride provided a modest yield of the desired aminocarbonylation product (entry 1) whereas no product could be observed upon treatment of bisalkyl hydrazine with *p*-nitrophenyl chloroformate (entry 2). Other phosgene equivalents reacted more effectively. Carbonyldiimidazole (CDI) resulted in an excellent yield of product **5a** at room temperature (entry 3). Compared to other acylating agents, CDI was slower to form the *N*-isocyanate. To overcome the long reaction time, temperature was increased, but this resulted in lower yields (entry 4 and 5). This negative effect could be explained either by a reversible aminocarbonylation reaction or by a higher *N*-isocyanate concentration, making the reaction more prone to isocyanate dimerization. Triphosgene provided excellent yield of the desired product (entry 6). Excess DMAP was used both as a base (given the formation of two equivalents of HCl upon reaction with phosgene) and as a potential catalyst.[21a] Unfortunately, this method used to achieve room temperature reactivity is not practical. For one, Boc-deprotection with TFA is difficult to control given the resulting product's ability to undergo

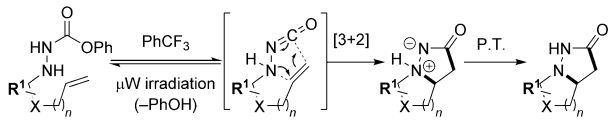
Table 5. Intramolecular aminocarbonylation by acylation of a *N*,*N*-dialkyl hydrazine.[a]

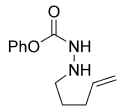
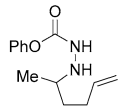
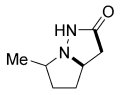
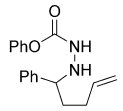
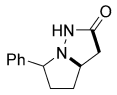
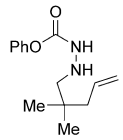
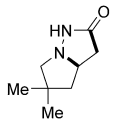
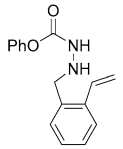
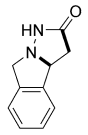
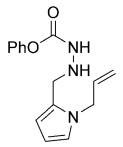
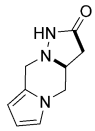


Entry	Reagent	*T* [°C]	*t* [h]	Yield [%][c]
1		RT	1	32
2		RT	1	0
3		RT	12	81
4		40[b]	12	62
5		60[b]	3	16
6[d]		RT	1	93

[a] Conditions: performed in $PhCF_3$ in a sealed tube (0.05 M). [b] Conventional heating was used. [c] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [d] 5.0 equivalents of DMAP was added to the reaction.

Table 6. Scope of intramolecular alkene aminocarbonylation with *O*-Ph carbazates.[a]



Entry	Substrate		*T* [°C]	Products	Yield [%][b]
1		**1 y**	120		(**3 a**) 28
2		**1 z**	120		(**3 b**) 70
3		**1 aa**	120		(**3 i**) 60
4		**1 bb**	120		(**3 n**) 35
5		**1 cc**	120		(**3 j**) 20[c]
6			150		(**3 j**) 50[c]
7			200[d]		(**3 j**) 75
8		**1 dd**	200[d]		(**3 q**) 95

[a] Conditions: heating performed in $PhCF_3$ (2 h, 0.05 M, microwave reactor) unless indicated otherwise. [b] Isolated yields. [c] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [d] Heating for 0.5 h. P.T. = proton transfer.

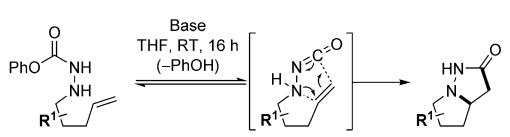
side-reactions (such as acid-catalyzed hydroamination). Ultimately, TFA deprotection followed by basic quench of the reaction could only provide moderate yield of the corresponding free hydrazine. Additionally, the resulting dipole product from this aminocarbonylation sequence could not be isolated by chromatography.

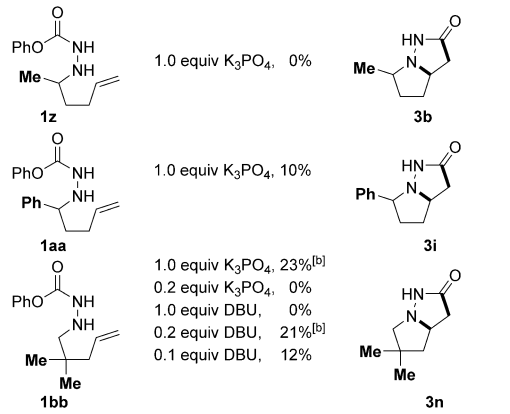
The study of intramolecular alkene aminocarbonylation led to the realization that although the objectives initially established were achieved, the reactivity developed still had important synthetic limitations. However, several conclusions regarding the use of β*N*-benzyl carbazates could be made: 1) They are more reactive than their monoalkyl counterparts under thermolysis; 2) They are capable of achieving room temperature reactivity with suitable *N*-isocyanate precursors; and 3) They have enabled the synthesis of 6,5-bicyclic systems by alkene aminocarbonylation. However, the reaction still suffered from a relatively limited scope, and difficult synthesis of the required starting materials. With these issues in mind, carbazate precursors with more labile leaving groups (e.g., **LG** = *O*-Ph) were targeted. Such carbazates would be less susceptible to hydroamination side-reactions, since milder formation of the *N*-isocyanate would allow exploration of the aminocarbonylation reactivity of monoalkyl *N*-isocyanates at lower temperatures (Table 6).

Using *O*-Ph as the *N*-isocyanate blocking group, efficient intramolecular aminocarbonylation reactions were achieved with several substrates (Table 6). The reactions of α-substituted substrates were more efficient at a lower temperature (120 °C, entries 2 and 3), and increased yields at higher temperature were observed for substrates possessing less conformational freedom (entries 7 and 8). The remaining mass balance for most entries in Table 6 was found to be *N*-isocyanate dimers. The use of more labile blocking groups (i.e., *O*-Ph vs. O*t*Bu) would facilitate *N*-isocyanate formation and potentially increase their concentration, thus promoting isocyanate dimerization. Under these milder conditions, a large dependence on steric hindrance of the *N*-isocyanate intermediate was noted (**3 a** vs. **3 b** and **3 i**). A high-yielding, selective aminocarbonylation reaction with Thorpe–Ingold biased substrate (entry 4) was still impossible, since hydroamination reactivity was operating at lower temperatures than *N*-isocyanate formation in this system. However, the yield of styrene-derived carbazate was increased to afford the fused tricyclic core in 20% higher yield than using O*t*Bu carbazate (Table 3, entries 11 and 12). Furthermore, the use of *O*-Ph carbazate also enabled the efficient synthesis of tricyclic product **3 q** through a challenging cyclization forming the 6,5-ring system, a cyclization that was impossible from the corresponding O*t*Bu carbazates.

With more control over *N*-isocyanate generation and reactivity, efforts were devoted to explore recently developed base-catalyzed *N*-isocyanate formation procedures of *O*-Ph substituted carbazates (Table 7).[18e] The optimization of room temperature reactivity began with methyl-substituted carbazate **1z**, and a variety of organic and inorganic bases were screened (see Supporting Information Table S2). Although several bases were able to form the *N*-isocyanate under catalytic or stoichiometric conditions, only dimerization was observed. Under conditions where the dimerization reaction would be operating (i.e., lower temperatures) it was hypothesized that more sterically hindered *N*-isocyanates would be less prone to dimerize. Encouragingly, using a substrate with a larger substituent at the R^1 position (R^1 = Ph, carbazate **1aa**) led to a 10% aminocarbonylation yield at room temperature with 1.0 equiv K_3PO_4 (Table 7). This result supported that steric hindrance near the β-nitrogen of the *N*-isocyanate could help minimize dimerization and promote aminocarbonylation.

Table 7. Base-catalyzed aminocarbonylation of *O*-Ph derived monoalkenyl carbazates.[a]





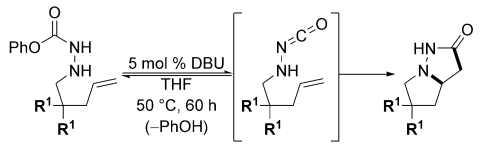
[a] Conditions: performed in THF (RT, 16 h, 0.05 M); NMR yields using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield.

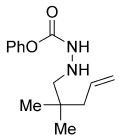
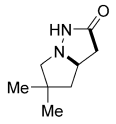
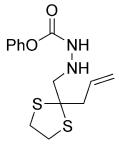
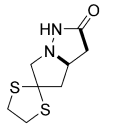
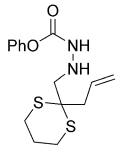
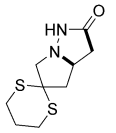
Despite providing a low yield, this preliminary result proved that it was possible to achieve aminocarbonylation at temperatures far below typical hydroamination conditions with βN–H carbazate precursors. However, the substrate needed to be capable of outcompeting the intermolecular dimerization reaction. It was expected that a Thorpe–Ingold biased substrate could selectively perform the aminocarbonylation reaction. This would be significant, because under thermolytic conditions the hydroamination reaction outcompetes the aminocarbonylation reaction with all other carbazate substrates (see Table 4 and Table 6). Pleasingly, a modest yield of 23% of the corresponding cycloaddition was observed at room temperature using 1.0 equiv K_3PO_4 with substrate **1bb** displaying a Thorpe–Ingold bias and, importantly, *no competing hydroamination was observed* (Table 7, entry 4). From this point, bases were further screened and 20 mol% DBU emerged as an additive that provided a similar yield to the reaction with K_3PO_4 (see Supporting Information Table S3). The following trends were noted: when loadings of base increased or when stronger bases were used, the amount of the *N*-isocyanate dimerization byproduct increased; however, when the loadings of base were decreased starting material remained. This was expected, since increased base loadings or the use of stronger bases would increase the concentration of *N*-isocyanates in situ, resulting in increased isocyanate dimerization. Gratifyingly, dimerization was minimal at lower base loadings (e.g., 5 mol% DBU) resulting in only the aminocarbonylation product and the starting material present in the reaction media. This reinforced the need for controlling the concentration of these amphoteric intermediates. Mild heating was needed to promote the cyclization, since base-induced formation of the intermediate at room temperature proved too slow. At 50 °C and with 5 mol% DBU, a selective aminocarbonylation reaction proceeded with the *gem*-dimethyl carbazate **1bb** to yield product **3n** in 82% yield. It should be noted that this transformation required a long reaction time (60 h), which further highlights the need for a carefully controlled concentration of *N*-isocyanate. These mildly basic conditions in THF facilitate the slow release of the *N*-isocyanate, while the thermal energy provided from heating in conjunction with a Thorpe–Ingold effect provide a basis for the intramolecular cycloaddition to occur rather than the intermolecular dimerization. From this point, the scope of the reaction was expanded to a subset of Thorpe–Ingold biased aminocarbonylation substrates (Table 8).

Pleasingly, the yields remained consistent for these reactions and control experiments confirmed the need for base catalysis. This included the synthesis of substrates possessing 5- and 6-membered thioketals (entries 4 and 6, respectively). By performing the reaction at low temperature the competing hydroamination reaction could be avoided; however, if the substrates did not possess a Thorpe–Ingold bias, dimerization was the major pathway (see Supporting Information Table S1).

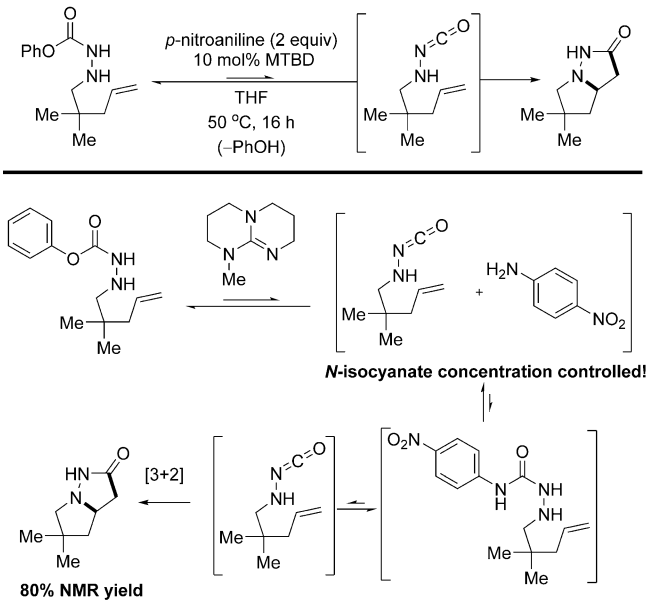
To avoid the necessity of lengthy reaction times, additives could be used. Experimentation revealed that *p*-nitroaniline was an excellent additive (see Supporting Information, Tables S4 and S5 for other additives tested), presumably by controlling the concentration of *N*-isocyanate in situ. Excess *p*-nitroaniline used in tandem with 10 mol% MTBD at 50 °C could provide, overnight, reactivity in comparable yield (Scheme 3) to a 60 h reaction with 5 mol% DBU for the *gem*-dimethyl carbazate **1bb**. This increased yield can be attributed to the ability of *p*-nitroaniline to reversibly add to the *N*-isocyanate under the reaction conditions, thereby effectively minimizing the concentration of reactive intermediate in situ. The exploration of this effect in other reactions, as well as extrapolations of the strategies discussed above that enable new reactivity of amino-isocyanates are currently ongoing and will be reported in due course.

Table 8. Base-catalyzed aminocarbonylation of Thorpe–Ingold biased carbazates.[a]



Entry	Additive	Carbazate	Product	Yield [%][b]
1	none			n.r.
2	DBU			82
		1 bb	**3 n**	
3	none			n.r.
4	DBU			81
		1 ee	**3 r**	
5	none			n.r.
6	DBU			83
		1 ff	**3 s**	

[a] Conditions: heating performed in the presence of 5 mol% DBU in THF (60 h, 0.05 M) in a sealed tube. [b] Isolated yields are shown. n.r. = no reaction. DBU = 1,8-diazabicycloundec-7-ene.



Scheme 3. The use of additives as a method to control for *N*-isocyanate concentration. A representative scheme using *p*-nitroaniline as additive in base-catalyzed intramolecular aminocarbonlyation sequence is shown. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Conclusions

A variety of cyclic β-aminocarbonyl motifs can be accessed using novel intramolecular alkene aminocarbonylation reactivity of amino-isocyanate intermediates. Support for the involvement of transient *N*-isocyanates in a 5-membered concerted aminocarbonylation transition state was obtained by DFT calculations, and experimentally by the stereospecificity observed with internal alkenes. Several reactions were developed using hydrazine derivatives such as carbazates and semicarbazides as blocked (masked) *N*-isocyanate precursors, allowing the formation of the reactive *N*-isocyanate in situ upon heating or using a base as catalyst. Complementary methodologies were developed to overcome side reactions, such as hydroamination and *N*-isocyanate dimerization, which were observed depending on the substrate. Initially, the reaction of βN–H carbazates (**LG** = O*t*Bu) and semicarbazides (**LG** = NH_2) required heating at 200 °C to form the *N*-isocyanate and subsequent pyrazolidinones after aminocarbonylation and proton-transfer steps. An alternative, related approach was developed: the thermolysis of *βN*-benzyl carbazates. Using these substrates in an alkene aminocarbonylation/*N*-benzyl 1,2-rearrangement sequence typically afforded the desired products in higher yields, and enabled the synthesis of 6,5-bicyclic ring systems. These increased yields were attributed to the minimization of *N*-isocyanate dimerization, and/or to a more facile cycloreversion of these isocyanate dimers. Alternatively, a transacylation sequence of *βN*-benzyl carbazates (Boc cleavage followed by reaction with phosgene equivalents such as CDI) provided a method to form the *N*-isocyanate at lower temperatures, and led to room temperature aminocarbonylation reactivity. However, since the 1,2-rearrangement could not occur at room temperature, the resultant dipole could not be isolated. The combined insights from these two strategies led to the use of hemilabile *N*-isocyanate precursors. *O*-Ph substituted carbazates enabled aminocarbonylation by thermolysis of monoalkenyl carbazates at lower temperatures (ca. 120 °C). Encouragingly, base-catalyzed *N*-isocyanate formation occurred at even lower temperatures (RT to 50 °C), which resulted in high yielding aminocarbonylation reactions for substrates containing a Thorpe–Ingold (which were problematic under previously established thermolytic conditions). Lastly, *p*-nitroaniline as an additive was shown to provide control of *N*-isocyanate concentration, allowing for faster reactions with higher base loadings and the prevention of *N*-isocyanate dimerization. Collectively, these results demonstrate the unique reactivity of *N*-isocyanates as reactive intermediates in intramolecular alkene aminocarbonylations. This work also presents several strategies and tools to achieve controlled reactivity using these amphoteric (ambident) intermediates, and prevent the *N*-isocyanate dimerization pathway which has been a major hindrance to the development of new reactions involving these rare isocyanates.

Experimental Section

General procedure: intramolecular aminocarbonylation by thermolysis

To an oven-dried 5–20 mL μW tube, a stir bar was added and the vial was capped with a septum and purged with argon for 5 min. The carbazate (1.00 equiv) dissolved in solvent (acetonitrile or α,α,α-trifluorotoluene, 0.05 M) was added to the sealed tube. The tube was then sealed with a microwave cap and heated for the time specified at the temperature indicated. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and then purified by silica gel chromatography to give the corresponding pure aminocarbonylation products.

General procedure: intramolecular aminocarbonlyation by base catalysis

To an oven-dried 5–20 mL μW tube, a stir bar was added and the vial was capped with a septum and purged with argon for 5 min. The corresponding carbazate (1.00 equiv) dissolved in THF (0.05 M) was added to the sealed vial. To this solution was added DBU (0.05 equiv). The reaction vessel was sealed with a microwave cap and heated in an oil bath at 50 °C for 60 h. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and then purified by silica gel chromatography to give the corresponding pure aminocarbonylation products.

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Keywords: amination · amphoteric molecules · intramolecular aminocarbonylation · nitrogen-substituted isocyanates · synthetic methods

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