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Intermolecular Aminocarbonylation of Alkenes using Concerted Cycloadditions of Iminoisocyanates

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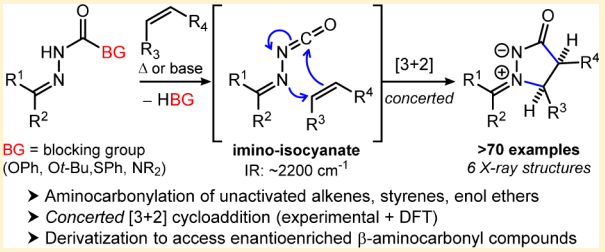
Supporting Information

ABSTRACT: The aminocarbonylation of alkenes is a powerful method for accessing the β-amino carbonyl motif that remains underdeveloped. Herein, the development of intermolecular aminocarbonylation reactivity of iminoisocyanates with alkenes is presented. This includes the discovery of a fluorenone-derived reagent, which was effective for many alkene classes and facilitated derivatization. Electron-rich substrates were most reactive, and this indicated that the LUMO of the iminoisocyanate is reacting with the HOMO of the alkene. Computational and experimental results support a concerted asynchronous [3 + 2] cycloaddition involving an iminoisocyanate, which was observed for the first time by FTIR under the reaction conditions. The products of this reaction are complex azomethine imines, which are precursors to valuable β-amino carbonyl compounds such as β-amino amides and esters, pyrazolones, and bicyclic pyrazolidinones. A kinetic resolution of the azomethine imines by enantioselective reduction (s = 13−43) allows access to enantioenriched products. Overall, this work provides a new tool to convert alkenes into β-amino carbonyl compounds.



INTRODUCTION

The β-amino carbonyl is a key structural motif in many biologically active acyclic and (hetero)cyclic compounds, most notably, β-amino acid derivatives and β-peptides. An additional methylene unit provides proteolytic stability to β-amino carbonyl compounds compared to that of their natural α-amino carbonyl analogues. This has made the β-amino carbonyl motif abundant in therapeutics, agrochemicals, peptidomimetics, and natural products.[1] Drugs such as metamizole, ondansetron, and β-lactam antibiotics are representative examples (Figure 1). β-Peptides have also become essential peptidomimetics, and the design of unique foldamer structures has made them exciting targets in drug discovery and proteomics.[2] The prevalence and importance of β-amino carbonyl compounds has resulted in intense research toward their synthesis.

The synthesis of β-amino carbonyl compounds from readily available starting materials has attracted considerable attention.[3,4] Many successful approaches use naturally abundant α-amino acids as substrates,[5] and many synthetic methodologies involve forming either the C−N or C_α−C_β bond.[6] The preparation of enantiopure β-amino carbonyl compounds has also stimulated intense research over the last three decades.[7,8] Many of these methods are useful if the products are simple and substrates are readily available. However, some strategic disconnections remain underdeveloped for the synthesis of β-amino carbonyl compounds, such as reactions involving C−H activation and the aminocarbonylation of alkenes. Alkenes are the substrates of choice in many amination reactions because they are abundant and generally inexpensive, but they are rarely used to form β-amino carbonyl compounds. This approach is simple yet potentially powerful in β-amino carbonyl synthesis with the potential to generate complexity rapidly.

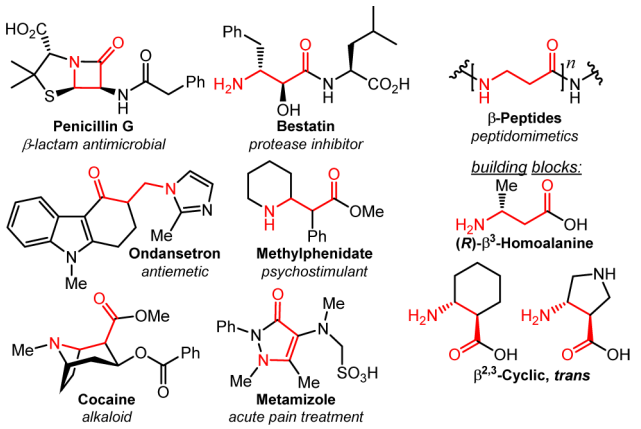


Figure 1. Examples of important β-amino carbonyl compounds.

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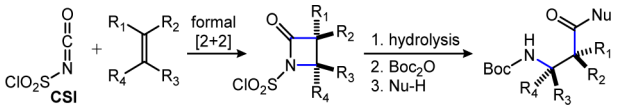
There are few methods available for the aminocarbonylation of alkenes, and intermolecular reactivity is quite rare. An early adopted and useful approach is the formal [2 + 2] cycloaddition of olefins with isocyanates to yield β-lactams (Scheme 1).

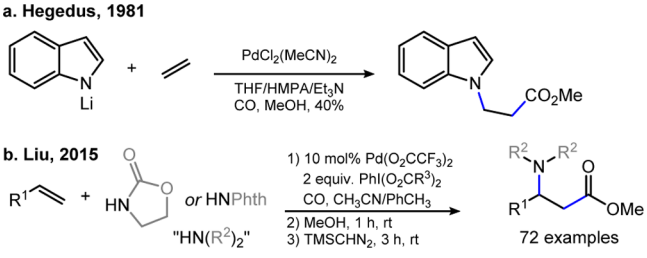
Scheme 1. Intermolecular [2 + 2] Aminocarbonylation Reactions of Alkenes with Chlorosulfonyl Isocyanate



Electron-rich alkenes react with many isocyanates, but unactivated alkenes require the use of the highly electrophilic chlorosulfonyl isocyanate (CSI).[9] Notably, this process is used in industry to synthesize diverse β-lactams that can be precursors to β-amino acids, agrochemicals, and drugs.[10] However, this approach has limitations, including the high reactivity of the cycloadducts and the toxicity and promiscuous reactivity of CSI.[9e,f]

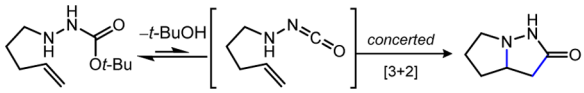
A more direct approach to alkene aminocarbonylation has been developed in *intramolecular* systems using palladium(II) catalysis.[11] Racemic reactions affording 5- and 6-membered azacycles are well developed and have been used in the synthesis of several natural products,[12] and a highly enantioselective variant has been developed by Sasai and co-workers.[13] An alternative was reported by Livinghouse et al.,[14] using an intramolecular amino-metalation approach followed by a subsequent acylation of the alkylzinc intermediate. However, there are few reports of *intermolecular* variants (Scheme 2) and

Scheme 2. Pd Assisted/Catalyzed Intermolecular Aminocarbonylation of Alkenes



no reports of enantioselective intermolecular alkene aminocarbonylation reactions. The palladium-assisted aminocarbonylation of alkenes was pioneered in the 1980s by Hegedus and co-workers.[15a] They found that stoichiometric Pd(II) enabled intramolecular aminopalladation, and that under appropriate conditions, CO insertion was favored over side reactions. The intermediate reacted with methanol to form β-amino methyl esters. Shortly after these studies, Hegedus reported the intermolecular aminocarbonylation of ethylene with the lithium salts of indole and skatole in the presence of CO and methanol (Scheme 2a).[15b−c] The yields of β-*N*-indolyl methyl esters were modest, and intermolecular reactivity with other olefins was not reported. In 2015, Liu communicated catalytic conditions for the intermolecular aminocarbonylation of unactivated alkenes and styrenes (Scheme 2b).[16] Stoichiometric hypervalent iodine is essential to the activation and turnover of the palladium catalyst, and this method gives a wide scope of racemic *N*-protected β-amino methyl esters. However, currently only terminal alkenes are reactive (providing β^3-substituted amino esters), and the reaction is limited to acidic nitrogen nucleophiles.

Our efforts toward alkene aminocarbonylation arose from our early interest in concerted, metal-free amination reactions with hydrazine derivatives.[17] While attempting an alkene hydroamination reaction with a Boc-protected hydrazide, an unexpected intramolecular aminocarbonylation reaction was observed (eq 1).[17b,f] Thermolysis of the hydrazide provided the



(1)

aminoisocyanate reactive intermediate,[18] which underwent a concerted [3 + 2] cycloaddition to give the β-amino carbonyl product. This highlighted the potential of this reactivity for the aminocarbonylation of alkenes using an amphoteric aminoisocyanate reagent that contains both the nitrogen and carbonyl functionalities. In contrast to common isocyanates, which are bulk industrial chemicals, *N*-isocyanates are quite rare in the literature (Figure 2).[19−21] Containing a nucleophilic amine and

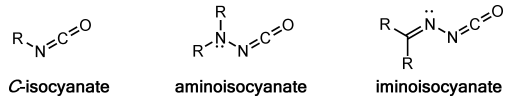


Figure 2. Amphoteric reactive intermediates.

an electrophilic isocyanate carbon, *N*-isocyanates are amphoteric reactive intermediates that typically cannot be isolated.[22] In fact, aminoisocyanates are known to dimerize at temperatures as low as −40 °C.[19a] We set out to develop *N*-isocyanates as bifunctional reagents for alkene aminocarbonylation.

This preliminary work with aminoisocyanates gave promising results for intramolecular reactions.[17b,f] However, intermolecular reactivity was very limited (e.g., norbornene as the substrate), and the high temperatures required (>150 °C) led mostly to isocyanate dimers and degradation of the reagent.[20b] In exploring other types of *N*-isocyanates, we became interested in intermolecular reactions of iminoisocyanates (containing an sp^2 nitrogen, Figure 2).[21] In contrast to aminoisocyanates, iminoisocyanates should show less propensity to dimerize because of the reduced nucleophilicity of the nitrogen atom. A single report from Jones describing the unexpected formation and reactivity of an iminoisocyanate with alkenes warranted further study (Scheme 3). Jones observed the intermolecular cycloaddition of one in situ-generated, hindered iminoisocyanate with four alkenes and an alkyne, but no yields were provided.[21b] Arguably, the potential of this reactivity as an alkene aminocarbonylation strategy was not demonstrated nor recognized until recently.

Herein, an in-depth study on the use of iminoisocyanates for metal-free, intermolecular alkene aminocarbonylation is presented. In contrast to Jones, our approach uses hydrazones as blocked (masked) *N*-isocyanate precursors[22] and allows for controlled formation of the reactive iminoisocyanate intermediate in situ. The scope of this cycloaddition has been thoroughly explored: many alkene classes react with a variety of hydrazones to provide complex azomethine imines. Both experimental results and DFT calculations are consistent with a concerted [3 + 2] cycloaddition. Importantly, these aminocarbonylation products are useful precursors to a variety

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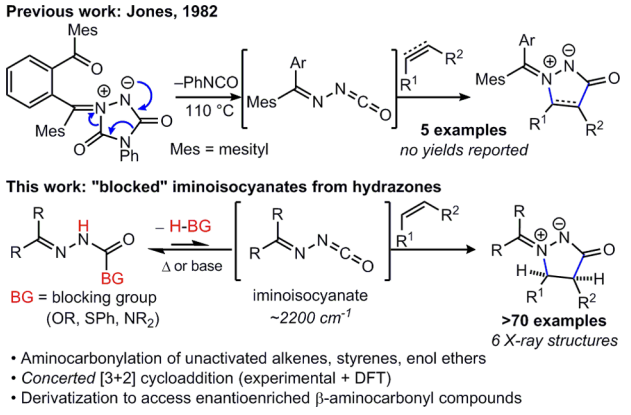
Scheme 3. Intermolecular Aminocarbonylation with Iminoisocyanates

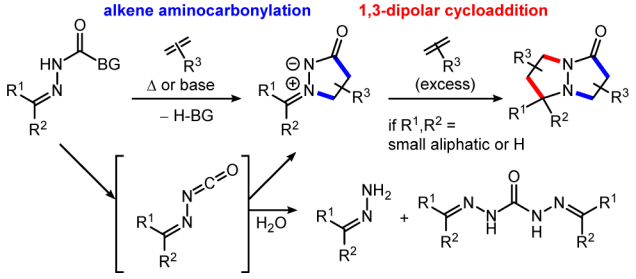


of valuable compounds possessing the β-amino carbonyl motif including complex hydrazines, pyrazolidinones, pyrazolones, and β-amino acid derivatives. The kinetic resolution of these racemic azomethine imines was also developed, allowing the conversion of alkenes into enantioenriched β-amino carbonyl compounds.

RESULTS AND DISCUSSION

Reaction Development and Optimization of *N*-Isocyanate Precursor.[23] In the development of a useful alkene aminocarbonylation reaction, our approach was to use hydrazones as stable and easily synthesized iminoisocyanate precursors.[21d−g] However, there are only a few accounts that describe the formation and reactivity of iminoisocyanates, and there were no reports using hydrazone precursors for *N*-isocyanate cycloaddition reactions. Thus, the basic structure of the hydrazone, such as the blocking group or the aldehyde or ketone precursor, were studied for their effect on overall aminocarbonylation reactivity. Early in this research, optimization of the hydrazone focused on preventing 1,3-dipolar cycloaddition of the product azomethine imine with excess alkene (Scheme 4). Initial studies showed that aldhydrazones were prone to such criss-cross cycloaddition processes,[24] forming diastereomeric mixtures and isocyanate degradation products.

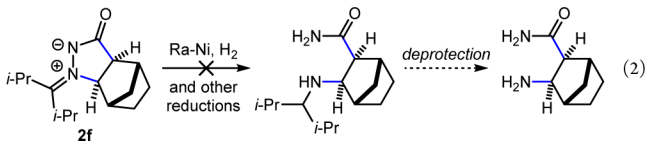
Scheme 4. Alkene Aminocarbonylation Reactions with Iminoisocyanates: Process and Possible Side Reactions



For simplicity and to prevent these side reactions, symmetrical ketones with increasing bulk were studied first. The reactivity of several *N*-Boc hydrazones (**1a**−**f**) was evaluated using norbornene as substrate (Table 1). Hydrazones with small R groups (**1a**, Me; **1b**, Et) provided the azomethine imine products in 67−70% isolated yield, but complete consumption of hydrazone was observed owing to competing side-reactions. Bulkier hydrazones derived from adamantanone (**1e**) and diisopropyl ketone (**1f**) gave excellent yields of the aminocarbonylation products. The bulky groups assist in shielding the dipole from a second cycloaddition and also help prevent self-reactions of the iminoisocyanate.

The study of iminoisocyanate precursors continued with investigation of the blocking group (BG). There are two steps in the overall aminocarbonylation reaction: (1) generation of the reactive iminoisocyanate by expulsion of the blocking group and (2) cycloaddition of the iminoisocyanate with the alkene. The nature of the blocking group will affect the concentration of iminoisocyanate formed in situ at a given temperature, and which step will be rate determining. Seven blocking groups were tested at a range of temperatures in the reaction of diisopropylketone-derived hydrazones with excess norbornene (Table 2). In this experiment, all hydrazones are precursors to the same iminoisocyanate and product. At 150 °C, all blocking groups performed comparably. As the reaction temperature was lowered, the different blocking groups had a large effect on the product yield. For example, hydrazone **1i** (BG = OPh) gave 84% yield of **2f** at 100 °C, whereas **1g** (BG = OEt) only provided an 8% yield. At 80 °C, low yields of **2f** were obtained with all hydrazones. This is attributed to the difficulty of forming the iminoisocyanate at low temperatures and to the intermolecular aminocarbonylation reaction also requiring higher temperatures. The blocking groups OPh (entry 4) and O*t*-Bu (entry 1) were chosen for further investigations of hydrazone structure.

The results with the first generation of hydrazones provided insight on blocking group trends, possible side reactions, and optimal solvent (see Table S1). However, reactions with reagent **1f** did not provide high yields of cycloadduct with unactivated alkenes (e.g., 1-hexene, cycloalkenes; see Table 4). In addition, azomethine imines (2) from these hydrazones were unsuitable as precursors to the desired β-amino acid derivatives. Unfortunately, we found that **2f** was resistant to a broad range of derivatization reactions, likely due to the high steric shielding that was installed to prevent unwanted dipolar cycloaddition (eq 2). Furthermore, the deprotection of the β-nitrogen atom



(2)

was expected to be an additional challenge due to the need for reducing conditions for N−N bond cleavage. A more versatile reagent was needed to access a variety of β-amino carbonyl compounds, ideally having a functional group on the nitrogen that could be easily removed or reduced to form a protecting group.

Second Generation Reagent Discovery and Advantages. With a growing understanding of the alkene aminocarbonylation reaction and iminoisocyanate intermediate (including DFT results presented below), studies to develop an improved reagent were initiated. Informative X-ray crystal structures of diispropyl (**2f**) and diphenyl (**3f**) azomethine imines showed a staggered (twisted) geometry of their respective groups,[23] which creates a highly shielded environment around the C=N bond, making these compounds resistant to N−N bond cleavage (Figure 3).

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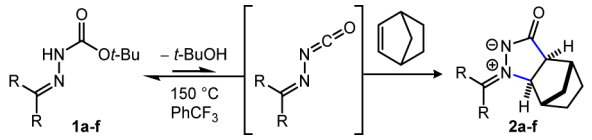
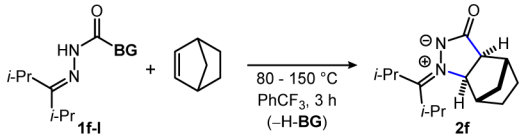
Table 1. Screening of Hydrazones (1a–f) with Increasing Bulk for the Aminocarbonylation of Norbornene[a]



Entry	R	Hydrazone	Product, Yield (%)[b]
1	Me	**1a**	**2a**, 70
2	Et	**1b**	**2b**, 67[c]
3	–$(CH_2)_4$–	**1c**	**2c**, 70
4	Ph	**1d**	**2d**, 70
5		**1e**	**2e**, 95
6	*i*-Pr	**1f**	**2f**, 95

[a]Conditions: hydrazone ([**1a–f**], 1 equiv) and norbornene (10 equiv) in $PhCF_3$ (0.05 M) heated in a sealed vial (microwave reactor, 150 °C, 3 h). [b]Isolated yield. [c]Fifteen equiv of norbornene.

Table 2. Survey of Blocking Groups for a First Generation Aminocarbonylation Reagent[a]



		yield (%)[b]			
entry	BG	150 °C	120 °C	100 °C	80 °C
1	**1f**: O*t*-Bu	99	69	23	7
2	**1g**: OEt	99	8	0	0
3	**1h**: OCH_2CF_3	82	55	30	9
4	**1i**: OPh	92	85	84	38
5	**1j**: SEt	98	64	46	11
6	**1k**: SPh	90	69	60	31
7	**1l**: $N(i\text{-}Pr)_2$	90	69	46	13

[a]Conditions: hydrazone (**1f–l**, 1 equiv) and norbornene (10 equiv) in $PhCF_3$ (0.05 M) heated in a sealed vial (microwave reactor, 80–150 °C, 3 h). [b]NMR yields using 1,3,5-trimethoxybenzene as internal standard.

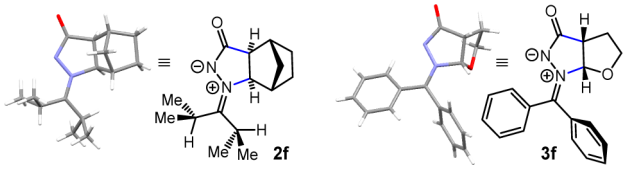


Figure 3. X-ray crystal structures of azomethine imines.

In designing a new reagent, planar systems were anticipated to provide an azomethine imine shielded from 1,3-dipolar cycloaddition but not from an approaching nucleophile. One of the first ketones explored with these criteria was fluorenone. Fluorenone-derived hydrazones are simple to prepare, and fluorenone is commercially available and inexpensive. Gratifyingly, hydrazone **4** (BG = OPh) showed excellent reactivity under standard conditions with norbornene at 100 °C, giving **5a** in 99% yield (Figure 4). The analysis of an X-ray structure of **5a** shows near coplanarity of the fluorenylidene with the dipolar pyrazolone core (torsion angle = −3.15°).[23] This allows delocalization of the dipole charge into the fluorenyl group, an effect that should stabilize the azomethine imine and prevent unwanted dipolar cycloaddition and also lower the cycloaddition transition state. The coplanarity also shields the dipole from a second cycloaddition, and a close CH···N proximity is observed in the crystal structure (Figure 4). This proton is

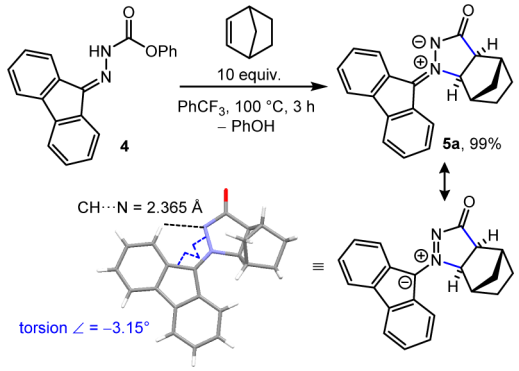
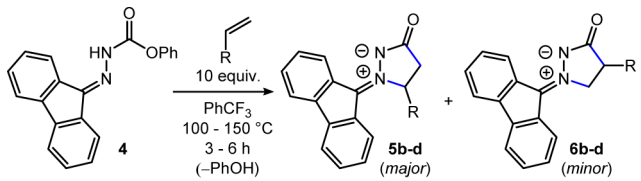


Figure 4. Reactivity of **4** with norbornene and single-crystal X-ray structure of cycloadduct **5a**.

observed by ^1H NMR to be shifted by +1 ppm (at ~9.0 ppm) from the other aromatic signals, an effect of the dipole charge delocalization.

When the initial reactivity of **4** was explored, it was found to out-perform all previously tested iminoisocyanate precursors. Reactivity was observed even with terminal aliphatic alkenes (Table 3, entries 1–7). The best yield and regioselectivity for

Table 3. Optimization of Reactivity with Unactivated Alkenes[a]



entry	R	[**4**] (M)	*t* (h)	*T* (°C)	yield (%)[b]	ratio (**5**:**6**)
1	*n*-C_4H_9	0.50	3	150	67 (**5b**)	25:1
2	*n*-C_4H_9	0.25	3	150	67	25:1
3	*n*-C_4H_9	0.10	3	150	67	25:1
4	*n*-C_4H_9	0.05	3	150	73	25:1
5	*n*-C_4H_9	0.05	3	100	57	50:1
6	$CH_2Si(Me)_3$	0.05	3	150	72 (**5c**)	>100:1
7	$CH_2Si(Me)_3$	0.05	3	100	81	>100:1
8	C_6H_5	0.05	3	100	40 (**5d**)	>100:1
9	C_6H_5	0.05	6	100	64	>100:1

[a]Conditions: hydrazone (**4**, 1.0 equiv) and alkene (10 equiv) in $PhCF_3$ (0.05–0.50 M) heated at 100–150 °C for 3–6 h. [b]^1H NMR yield of desired regioisomer using 1,3,5-trimethoxybenzene internal standard.

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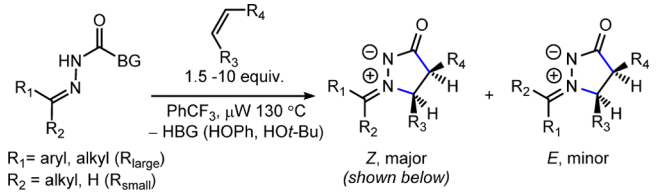
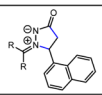
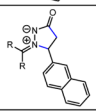
Table 4. Selected Scope of Alkene Aminocarbonylation[a]



Entry		Alkene (# equiv)		T (°C)	t (h)		Yield[b] (%)	
1	**1f**		(10)	100	3		**2f**	84[c]
2	**4**		(10)	100	3		**5a**	99
3			(2)	100	2			93
4	**1f**		(10)	80	3		**2g**	78
5	**4**		(10)	120	1		**5e**	86
6	**1f**		(10)	80	3		**2h**	60[d]
7	**4**		(10)	120	3		**5f**	52[d]
8	**1f**	X= 4-OMe	(10)	120	3		**2i**	43
9	**4**	4-OMe	(10)	100	3		**5g**	75
10		3-OMe	(5)	100	6		**5h**	29
11		 2-OMe	(5)	100	6		**5i**	72
12		H	(5)	100	6		**5d**	64
13		4-F	(10)	120	3		**5j**	54
14		Me	(10)	100	3		**5k**	48
15		2-Br	(5)	120	3		**5l**	48
16		3-Br	(5)	120	3		**5m**	43
17		4-CF_3	(10)	100	6		**5n**	23[g]
18	**4**	R_1= *n*-Bu	(10)	150	3		**5b**	73
19		*i*-Bu	(5)	150	3		**5o**	45
20		 Cy	(5)	120	3		**5p**	50
21		*t*-Bu	(10)	150	3		**5q**	38
22		CH_2TMS	(10)	100	3		**5c**	81
23		$(CH_2)_2OBn$	(10)	100	6		**5r**	52[e]
24	**4**		(5)	120	3		**5s**	66
25	**4**		(5)	120	3		**5t**	56
26	**4**		(1)	80	3		**5u**	93
27	**4**		(20)	150	0.3		**5v**	39
28	**4**	*n*=1	(10)	100	6		**5w**	76
29		 *n*=2	(>50[f])	150	3		**5x**	54
30		*n*=3	(10)	100	6		**5y**	40
31		*n*=4	(10)	100	6		**5z**	54
32	**4**		(5)	100	3		**5aa**	0
33	**4**		(10)	120	2		**5ab**	51[d,e]
34	**4**		(10)	120	3		**5ac**	31[d]

[a]Conditions: hydrazone (**1f** or **4**, 1.0 equiv), alkene (typically 5−10 equiv), $PhCF_3$ (entry 27: 1.0 M, entry 13: 0.5 M, entry 26: 0.2 M, entries 19 and 21, 24:0.1 M) or neat (entries 4, 6, 8, and 29) heated at 80−150 °C for 1−6 h. Reactions above 100 °C are heated in a sealed vial in a microwave reactor. [b]Isolated yields provided. [c]NMR yield. [d]Mixture of regioisomers (Z:E, **2h** = 7:1, **5f** = 14:1, **5ab** = 6:1, **5ac** = 1.5:1); major regioisomer (Z) is shown. The minimum regioselectivity for other regioisomers is 20:1. [e]X-ray crystal structure obtained for **5r** and **5ab**. [f]Cyclohexane used as solvent. [g]Regioisomer **6n** was also isolated in 5% yield.

Markovnikov product **5b** was obtained at a hydrazone concentration of 0.05 M. The resonance stabilized azomethine imine is effectively blocked from unwanted 1,3-dipolar cycloaddition, and this byproduct was never observed. Thus, an excess of less reactive alkenes can be used without loss of azomethine imine yield. Optimization revealed reactivity at 100

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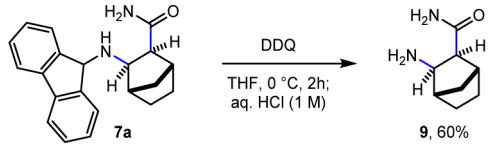
°C, which allowed longer reaction times (up to 6 h) without iminoisocyanate side reactions or degradation (entry 9) and thus maximization of the yield. In all cases, excellent selectivity for the formation of the Markovnikov product was obtained. Overall, this selected optimization data shows that hydrazone **4** proved more robust under the reaction conditions and could be recovered after the reaction with minimal loss of mass. This reagent was chosen to further evaluate the limits and scope of this alkene aminocarbonylation reactivity.

Aminocarbonylation of Alkenes: Scope and Trends. With the fluorenone-derived iminoisocyanate precursor **4** in hand, a large variety of alkene substrates were screened. A selected scope of the reaction is shown in Table 4, and for additional data and X-ray structures, see the Supporting Information. Initial optimized conditions for screening were 10 equiv of alkene, $PhCF_3$ (0.05 M), 100 °C, 3 h. Different classes of alkenes required further optimization of reaction conditions, to balance formation of the isocyanate with reactivity of the substrate. The substrates can be divided into "activated" alkenes, which are either electron rich or strained (e.g., enol ethers, norbornene) and other alkenes, which are monosubstituted or unstrained aliphatic alkenes and styrenes. Cyclic internal alkenes show generally good reactivity, whereas linear internal alkenes are less reactive. Surprisingly, a strained cyclopropane yielded no product, and no reactivity was observed with various alkynes, which may be attributed to steric hindrance caused by the planar fluorenone group. Overall, Table 4 shows a large scope of products (**5**) with unprecedented complexity from the intermolecular aminocarbonylation of alkenes with optimized reagent **4**. Synthetically useful yields were obtained for a variety of alkene classes, typically providing crystalline products with high selectivity for the formation of the Markovnikov-type products (typically >20:1). Results with first generation reagent **1f** are provided for comparison purposes.

Derivatization of the Cycloadducts. The azomethine imines synthesized from second generation reagent **4** could be converted into β-amino amides by reductive N−N cleavage (Table 5). This transformation was achieved with Raney nickel and required a borohydride reagent; no reaction was observed with Raney nickel and hydrogen gas. These β-amino amides can be transformed into β-amino esters (Table 5).[25a] Although this derivatization procedure proved efficient with adducts derived from both cyclic and acyclic alkenes, it should be noted that epimerization was observed for one of the three bicyclic substrates.

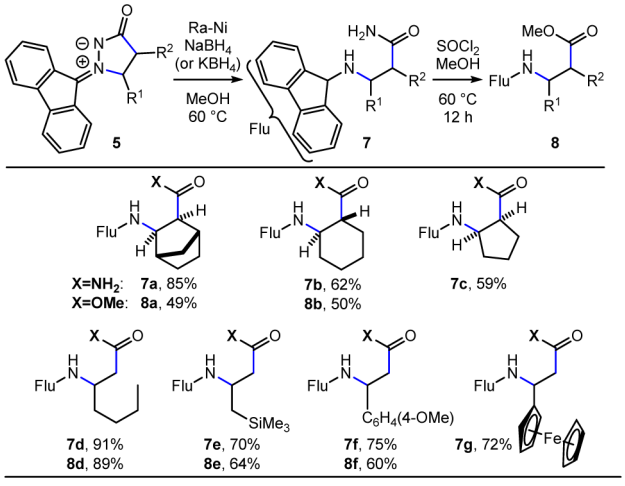
The *N*-fluorenyl group (Flu) is a known nitrogen protecting group and could be removed by oxidation with DDQ to access the free β-amino amide (eq 3).[25b]



(3)

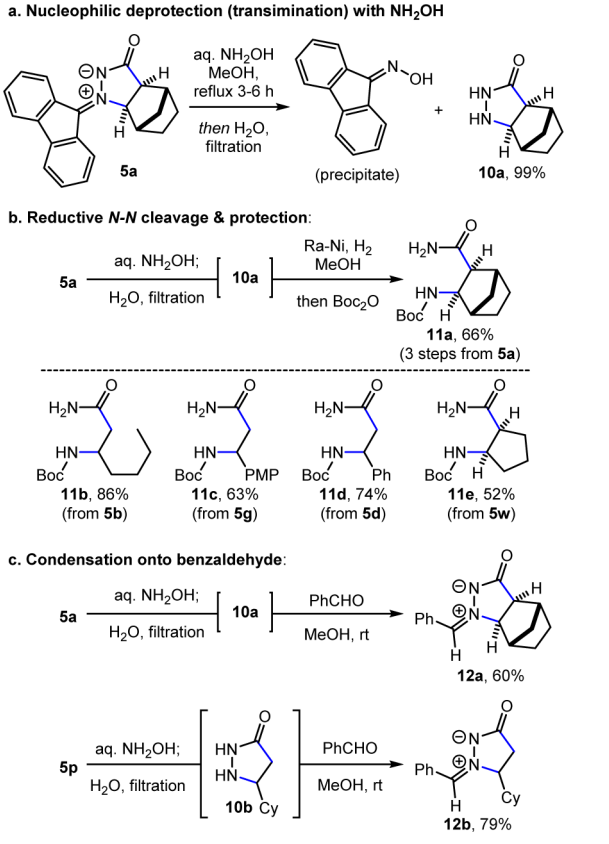
Following this work, simpler and milder derivatization protocols were developed. First, an alternative to the fluorenyl deprotection was pursued. Various nitrogen-based nucleophiles were screened for their ability to add to the dipole C=N bond and undergo transimination.[26] The desired transimination was achieved with aqueous hydroxylamine, and the resulting free pyrazolidinone is soluble in water and could be easily separated from the insoluble fluorenone oxime by filtration (Scheme 5a).

Table 5. Access to β-Amino Amides (7)[a] and Esters (8)[b]



[a]Conditions: azomethine imine (1 equiv), Raney nickel (slurry in water), methanol (0.1 M), and either $NaBH_4$ or KBH_4 (10.0 equiv) heated at 60 °C in a sealed screw-top flask. [b]Amide **7** added to a solution of $SOCl_2$ in MeOH at 0 °C and then heated at 60 °C for 12 h.

Scheme 5. Derivatization by Transimination with NH_2OH



The pyrazolidinone then undergoes reductive ring opening with Raney nickel and H_2, and Boc protection allows for easy isolation of the protected β-amino amide (Scheme 5b). The crude pyrazolidinone can also be used directly to synthesize unsymmetrical azomethine imines by condensation onto aldehydes following the traditional approach for their synthesis

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(Scheme 5c). The latter derivatization to form azomethine imines allows a comparison with other common approaches for the formation of such 1,3-dipoles.[27] Besides similar condensations, azomethine imines have also been formed by the deprotonation of hydrazonium salts,[28] oxidation of hydrazine derivatives,[29] *N*-alkylation of hydrazone precursors,[30] Cope-type hydroamination of alkynes,[17d] or generated in situ by a 1,2-proton shift from a suitable hydrazone.[31] The cycloaddition reaction of alkenes and iminoisocyanates presented herein thus constitutes a complementary route to synthesize these useful 1,3-dipoles.

Overall, we have demonstrated the value of alkene aminocarbonylation reactions with iminoisocyanates for the synthesis of azomethine imines, β-amino amides, and other compounds possessing the β-amino carbonyl motif. This was accomplished by the development of efficient derivatization protocols. The methods are simple and use inexpensive reagents but can only provide racemic products. To access enantioenriched β-amino carbonyl compounds from alkenes, we investigated the kinetic resolution of azomethine imines by enantioselective reduction.[32]

Kinetic Resolution of Azomethine Imines by Enantioselective Reduction. Alkene aminocarbonylation with iminoisocyanates provides complex azomethine imines, which are valuable precursors to β-amino amides through reduction. However, the intermolecular aminocarbonylation step is not enantioselective, and thus, the products are racemic. This is not a new problem: there are no reports of enantioselective intermolecular alkene aminocarbonylation reactions in the literature. Thus, the synthesis of enantioenriched β-amino carbonyls from the alkene aminocarbonylation reaction discussed above required the development of new chemistry. We envisioned a kinetic resolution of azomethine imines by enantioselective reduction[32] using a chiral Brønsted acid to allow controlled 1,2-reduction of the C=N bond. A similar concept was demonstrated by Maruoka for nucleophilic additions to *acyclic* azomethine imines,[33] but there were no reports for the activation of *N,N′*-cyclic azomethine imines by Brønsted acids or reports on their enantioselective reduction. Consequently, this reactivity was explored by screening chiral phosphoric acid organocatalysts with the Hantzsch ester as a reductant. From the initial screening, we found that only (*R*)-TRIP provided sufficient yields of reduced product and high enantioselectivity. This kinetic resolution by reduction showed high selectivity (s = 13−43) for 15 examples (Figures 5 and 6), typically providing the enantioenriched azomethine imine in >90% ee.

The reduced product (pyrazolidinone) was often isolated at lower enantiomeric purity and recrystallized to high ee. This method was applicable for fluorenone-derived azomethine imines (obtained by alkene aminocarbonylation, Figure 5) and for a variety of ketone and aldehyde-derived substrates (Figure 6), including those synthesized by the transimination protocol described above.

A model of the pretransition state complex accurately predicts enantioselectivity (Scheme 6), which arises from the sterically favorable approach, featuring dual activation of the rigid azomethine imine (by the Brønsted acid) and the Hantzsch ester (by the Brønsted base, P=O).[34] This method provides unreacted azomethine imine in high ee (e.g., **12b**) and an enantioenriched pyrazolidinone (e.g., **13b**), which can be recrystallized to high ee. Further reduction offers opposite

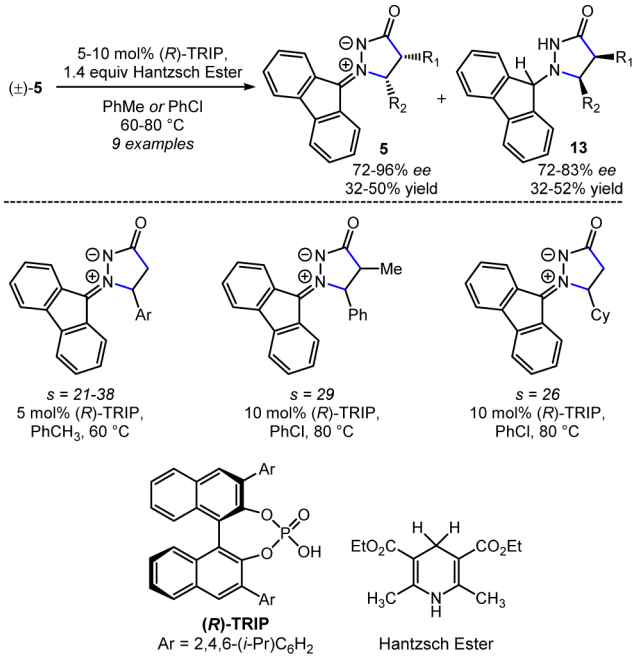


Figure 5. Kinetic resolution of azomethine imines derived from fluorenone by enantioselective reduction with (*R*)-TRIP.

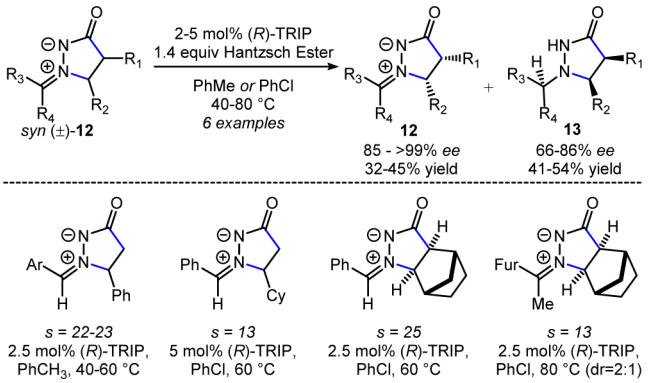
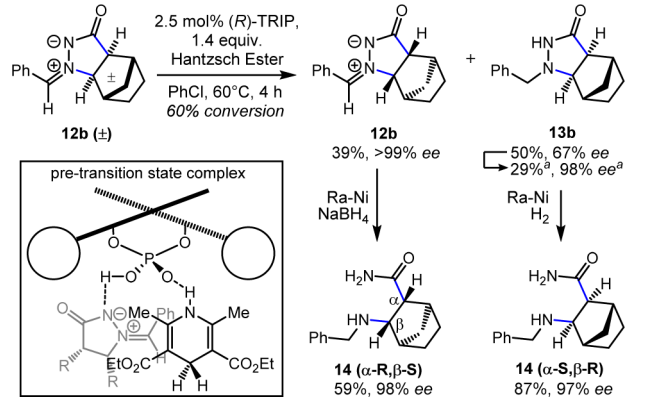


Figure 6. Kinetic resolution of unsymmetrical azomethine imines derived from aldehydes and ketones.

Scheme 6. From a Racemic Azomethine Imine to Enantioenriched β-Amino Amides



[a]Recrystallization provided reduced compound **13b** in 98% ee and 58% yield (overall 29% yield from (±)-**12b**).

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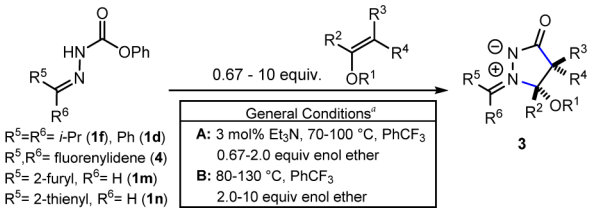
Table 6. Selected Scope of Enol Ethers with Various Iminoisocyanate Precursors[a]



Entry	Equiv	Enol Ether		R^5, R^6	Cat[a]	T (°C)	t (h)	Product, Yield (%)[b]
1	10			**1f**	-	80	3	**3a**, 81
2	2			**4**	-	100	2	**3b**, 75
3	0.67			**4**	Et_3N	70	3	68
4	10			**1f**	-	80	3	**3c**, 87
5	2			**4**	-	100	2	**3d**, 68
6	10			**1f**	-	80	3	**3e**, 99
7	10			**1d**	-	100	3	**3f**, 75
8	2			**1m**	-	130	1	**3g**, 82
9	2			**1n**	-	130	1.5	**3h**, 90
10	2			**4**	-	100	2	**3i**, 57
11	0.67				Et_3N	70	2.5	95
12	10			**1f**	-	80	3	**3j**, 70
13	2			**4**	-	100	2	**3k**, 77
14	0.67				Et_3N	100	3	81
15	0.67				Et_3N	70	2.5	38
16	0.68			**4**	Et_3N	70	3	**3l**, 69
17	2			**4**	-	100	2	**3m**, 70[c]
18	0.67		*n*=1	**4**	-	100	3	**3n**, 63
19	0.67		*n*=2	**4**	-	100	3	**3o**, 25
20	0.5		*n*=3	**4**	-	100	3	**3p**, 57
21	2		*n*=1	**4**	-	100	1	**3q**, 98[d]
22	2.5		*n*=2	**4**	-	100	3	**3r**, 86[d]
23	0.67			**4**	Et_3N	100	3	**3s**, 76[e]

[a]Conditions A: hydrazone, enol ether (0.67−2.0 equiv) and Et_3N (3 mol %) in $PhCF_3$ (0.1 M) heated at 70−100 °C for 1−3 h; B: hydrazone and alkene (2−10 equiv) in $PhCF_3$ (0.1 M) heated at 80−130 °C for 1−3 h. [b]Isolated yields provided are calculated based on the limiting reagent. [c]Enol ether is a mixture of cis/trans; final product is 16:1 *anti*/*syn*. [d]Ring junction hydrogens are *anti* to the bridge. [e]Ring junction hydrogens are *syn* to the CH_2OBn.

enantiomers of the same *β*-amino amide with no loss of enantiopurity (Scheme 6).

When combined, the intermolecular alkene aminocarbonylation reaction and derivatization methodologies are a versatile approach toward enantioenriched azomethine imines, pyrazolidinones, *β*-amino amides, and other compounds containing the *β*-aminocarbonyl motif.

Aminocarbonylation of Enol Ethers: Scope and Catalysis.[35] Enol ethers have electron-rich C═C bonds and were quickly discovered to undergo facile intermolecular aminocarbonylation with iminoisocyanates. With reagent **4**, reactivity with a variety of enol ethers was observed at 100 °C (Table 6, conditions B). The high reactivity of enol ethers was used to develop conditions for catalysis of the reaction. It is possible to catalyze the formation of the iminoisocyanate using a base,[36] and catalysis of the overall reaction at 70 °C was successful in cases where *N*-isocyanate formation is the rate-determining step (Table 6, conditions A). In contrast, there was little effect of adding base when the reaction temperature was 100 °C. Base catalysis enabled the use of new iminoisocyanate precursors, including aldehyde-derived hydrazones, without unwanted dipolar cycloadditions. In turn, this strategy allowed the synthesis of enol ether adducts, which are inaccessible under normal thermal conditions because enol ethers are often sensitive and can degrade under mildly acidic conditions. These results are shown in Table 6.

Synthetic Applications: Pyrazolones. The azomethine imines provided by aminocarbonylation reactions of enol ethers (**3**) are closely related to pyrazolones (**15**): aromatic heterocycles with applications in medicinal chemistry and agrochemistry.[37] Pyrazolones are typically synthesized from hydrazines and unsaturated carbonyl compounds or through variations relying on the same retrosynthetic disconnection.[38] In contrast, we envisioned access to pyrazolones from our azomethine imines by a one-pot reduction/aromatization sequence to provide a new approach starting from simple alkenes. The reduction of azomethine imines derived from enol ethers was first explored using sodium borohydride. Typically, the pyrazolidinone could not be isolated, and an aqueous NH_4Cl workup allowed aromatization by expelling the intrinsic alcohol R_1OH (Figure 7). For hindered substrates, brief heating in the presence of an acid catalyst was required to obtain the fluorenyl-protected pyrazolone.

The fluorenyl protecting group was readily removed from **15a** by reduction with Pd/C and H_2 (eq 4). In addition, the hydroxylamine transimination protocol (described above) could be applied to provide free pyrazolone **16b** in one step directly from the azomethine imine (eq 5).

In summary, we developed a two-step reaction sequence to convert enol ethers into pyrazolones. The first step is the aminocarbonylation of enol ethers with iminoisocyanates, which occurs under relatively mild conditions and could be catalyzed by base. To our knowledge, this is the first report on

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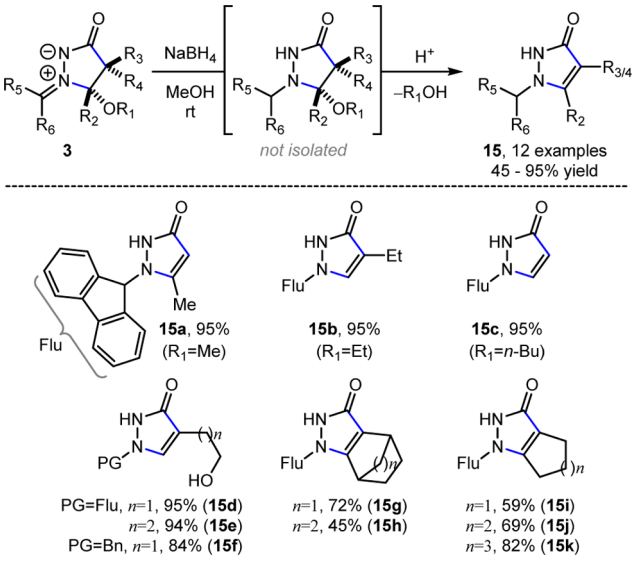
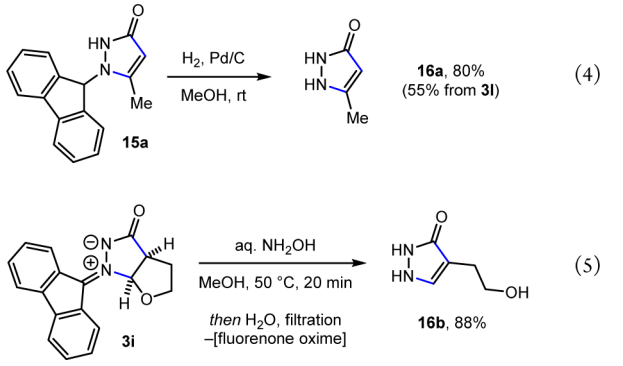


Figure 7. Synthesis of pyrazolones (**15**) from azomethine imines (**3**).

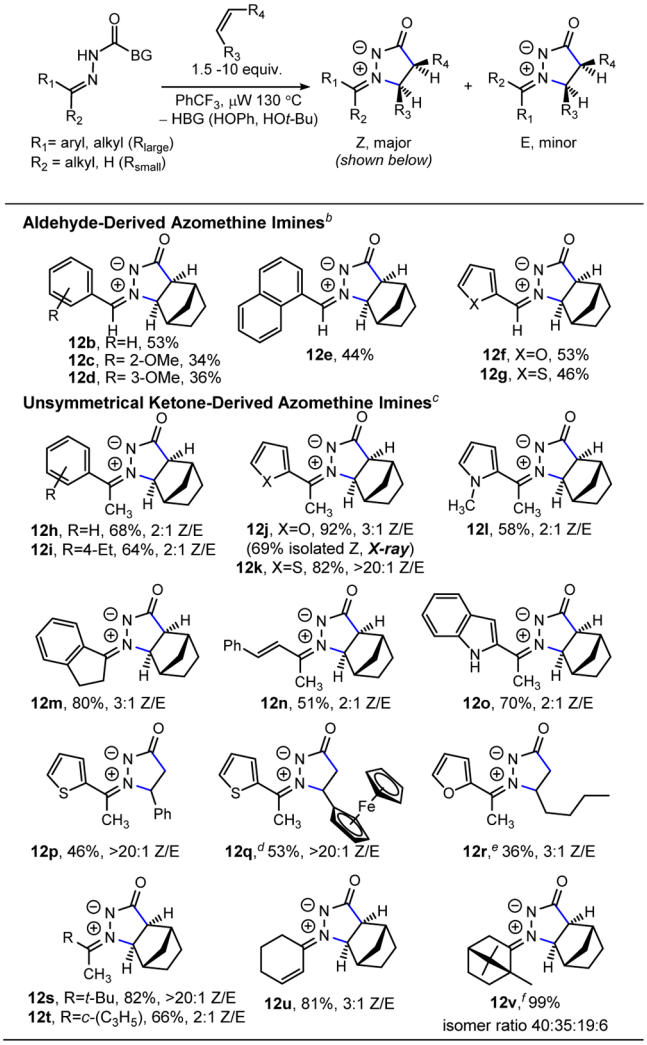


the use of base catalysis to accelerate the release of an *N*-isocyanate from a blocked precursor.[21e−g] This method enabled the synthesis of complex azomethine imines from enol ethers, which are then readily converted to pyrazolones by reduction or nucleophilic addition followed by in situ aromatization.

Alkene Aminocarbonylation with Unsymmetrical Iminoisocyanate Precursors.[39] For accessing a wider scope of complex azomethine imines and overcoming steric limitations of the fluorenone reagent, the reactivity of unsymmetrical hydrazones was studied (Table 7). Aldehyde-derived hydrazones were a particular challenge because they give more reactive azomethine imines that can undergo unwanted 1,3-dipolar cycloaddition with excess alkene.

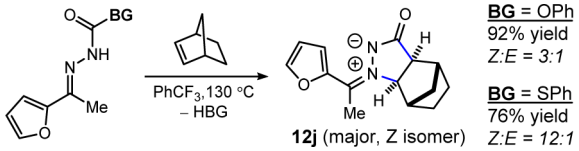
With careful optimization of reaction conditions,[39] modest to good yields of aromatic aldehyde-derived azomethine imines were obtained (**12b−g**). A variety of unsymmetrical ketone-derived hydrazones were also explored as iminoisocyanate precursors. These provided good to high yields of complex ketone-derived azomethine imines (**12h−v**), which are shielded from unwanted dipolar cycloaddition. Although only one stereoisomer was obtained with aldehyde-derived reagents, most reactions with ketone-derived reagents provided stereoisomeric mixtures of azomethine imines (*Z*:*E* = 2:1 to 6:1) with the exception of *t*-butyl methylketone and 2-thiophenyl ketone derived hydrazones providing (*Z*:*E* = >20:1; **12k,p,q,s**). The latter observation may be due to a unique chalcogen bonding effect between sulfur and nitrogen,[40] favoring this stereoisomeric product.[40d]

Table 7. Aminocarbonylation of Unsymmetrical Iminoisocyanate Precursors[a]



[a]Major isomer (*Z*) is shown, and isolated yields are provided. Hydrazone (BG = OPh, 1.0 equiv) and alkene. [b]Using 1.5−5.0 equiv or [c]10 equiv in $PhCF_3$ (0.05 M) at 130 °C for 1−3 h (microwave). [d]Using 5.0 equiv of vinyl ferrocene. [e]1-Hexene used as solvent. [f]Hydrazone (BG = O*t*-Bu) was used; *T* = 150 °C.

A mixture of stereoisomers is obtained with most unsymmetrical ketone derivatives, which is expected because two iminoisocyanate stereoisomers can be formed under the reaction conditions. As illustrated below, the reaction is also influenced by the blocking group released during *N*-isocyanate formation (eq 6). Improved selectivity is obtained for the *Z*



isomer of **12j** in the presence of PhSH rather than PhOH as a blocking group. Control experiments performed with pure *E* and *Z* isomers show that isomerization occurs under the reaction conditions even in the absence of PhXH.[39] These results show that this reaction is influenced by the presence of additives and suggests the reaction could be improved.

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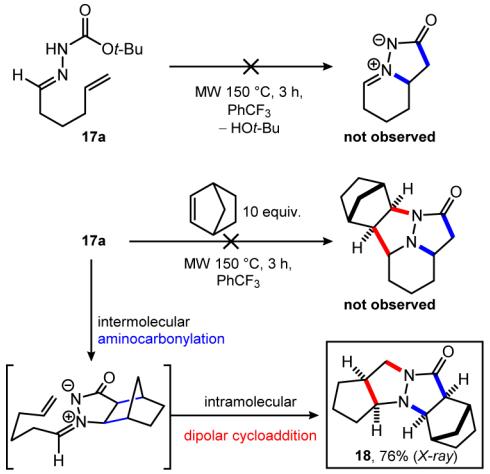
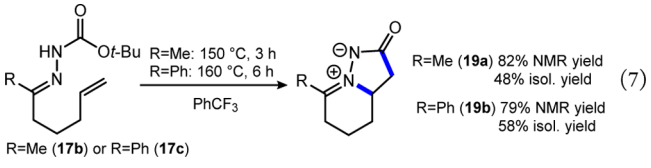
The ability of unsymmetrical iminoisocyanate precursors to react efficiently also provided the opportunity to explore intramolecular alkene aminocarbonylation. To our knowledge, examples of intramolecular aminocarbonylation reactions involving sp^2 nitrogen atoms have not been reported. Intramolecular reactivity was first tested with readily available *N*-Boc hydrazone **17a**. The reaction gave none of the desired azomethine imine product, and byproducts were observed that result from side reactions of the azomethine imine with the reactive iminoisocyanate. Norbornene was added to the reaction in an attempt to trap the azomethine imine in situ by 1,3-dipolar cycloaddition (Scheme 7). This strategy also

Scheme 7. Intermolecular vs Intramolecular Aminocarbonylation Competition Experiment



served as a competition experiment to evaluate intermolecular relative to intramolecular aminocarbonylation reactivity. Intramolecular aminocarbonylation followed by intermolecular cycloaddition with the dipolarophile norbornene was expected. Surprisingly, the major product was from an initial intermolecular reaction with norbornene, followed by an intramolecular dipolar cycloaddition. The structure of **18** was confirmed by X-ray crystallography.[39]

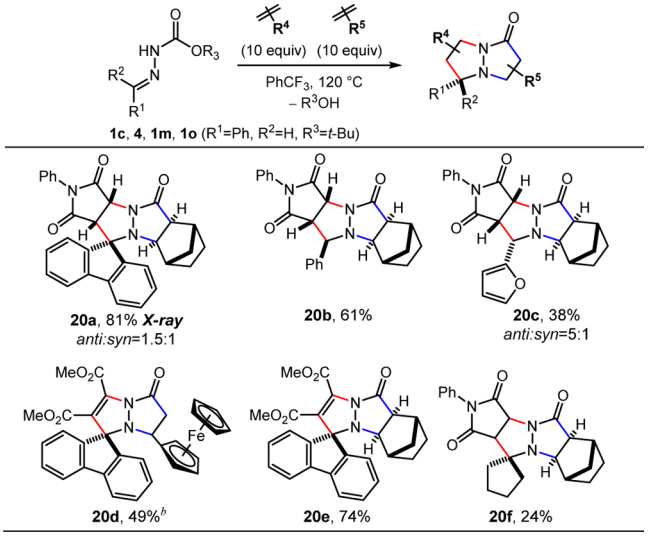
Conversely, intramolecular aminocarbonylation was observed with related ketone-derived hydrazones (eq 7). The products of these reactions are bicyclic azomethine imines, which proved difficult to isolate due to their instability on silica gel.



(7)

Given the complexity of the azomethine imines formed with this method and our interest in reaction cascades, this provided the opportunity to explore their cycloaddition reactivity further. Azomethine imines are well-known for reactivity in 1,3-dipolar cycloadditions, typically proceeding faster with electron-poor dipolarophiles.[41] Because intermolecular alkene aminocarbonylation reactions are more favorable with electron-rich alkenes, this allowed for alkene aminocarbonylation/1,3-dipolar cycloaddition cascades in which both partners can be added at the beginning of the reaction (Table 8). This approach proved efficient when electronically differentiated reagents were used

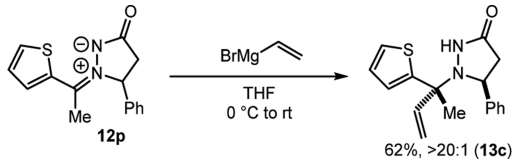
Table 8. Cascade Alkene Aminocarbonylation/1,3-Dipolar Cycloaddition[a]



[a]Hydrazone (1.0 equiv), electron-rich alkene (10 equiv norbornene or [b]1 equiv vinyl ferrocene) and dipolarophile (*N*-phenyl maleimide or dimethyl acetylenedicarboxylate, 10 equiv) in $PhCF_3$ (0.05 M) at 120 °C for 6–12 h (microwave). Isolated yields and *anti*:*syn* stereochemistry are provided.

to give products **20a–f** in 24–81% yields. The structure of **20a** was confirmed by X-ray crystallography.[23]

Various nucleophilic additions to the C=N bond of the azomethine imine were also studied. Vinyl magnesium bromide was added to **12p** with high diastereoselectivity with the formation of a fully substituted carbon center alpha to the pyrazolidinone ring system to give 62% yield of **13c** (eq 8).



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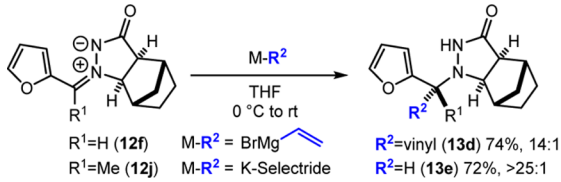
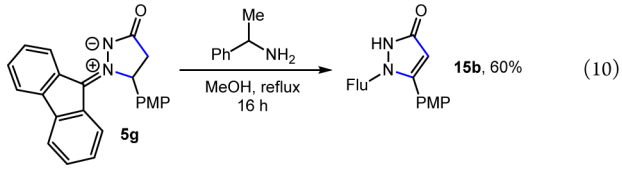
Grignard addition to the aldehyde-derived substrate **12f** also proceeded with good diastereoselectivity and yield (eq 9). In addition, K-Selectride was found to be effective for a highly diastereoselective reduction (>25:1) to give **13e** in 72% yield.



(9)

Finally, treatment of azomethine imines with a Brønsted base (secondary or primary amine) and heat provides pyrazolones (eq 10). This likely occurs through isomerization of the



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azomethine imine followed by favorable aromatization and has been reported with other *N,N′*-cyclic azomethine imines when using *t*-BuOK.[42]

Visualization of the Iminoisocyanate by IR Spectroscopy. To visualize the iminoisocyanate and obtain direct support of its involvement in the proposed cycloaddition, we became interested in reaction monitoring with IR spectroscopy. Isocyanates have signature peaks in the infrared sp region, typically from 2200 to 2300 cm^{-1}, and IR spectroscopy is a valuable tool to study the reactivity of carbon-substituted isocyanates, such as the kinetics of deblocking (isocyanate release) or polymerization (isocyanate consumption).[18c,43] However, this has not been applied to iminoisocyanates due to several challenges: detection of the iminoisocyanate at the low concentration during the reaction and side-reactions such as dimerization that occur at higher concentrations. In fact, only a few *N*-isocyanates have been observed experimentally in matrices at low temperatures,[19b,44] but some hindered *N*-isothiocyanates show moderate stability at room temperature and have thus been characterized by IR and NMR spectroscopy.[45]

For performing the analysis, a flow-IR instrument equipped with an injector was used, which is designed for analysis of liquid solutions and reaction mixtures. The entire analysis was performed in a glovebox for control of moisture and oxygen. The study began with first generation reagent **1f** under conditions of base catalysis. The spectra of **1f** at room temperature with or without Et_3N showed no significant differences. The reagent was then heated to 90 °C in the presence of Et_3N, and samples of the mixture were injected into the IR detector. Upon heating, the colorless mixture became dark orange, which suggests formation of a conjugated π system. The first sample after 17 min at 90 °C showed a new peak corresponding to the NCO asymmetric stretch at 2201 cm^{-1} (Figure 8). This peak is in good agreement with the

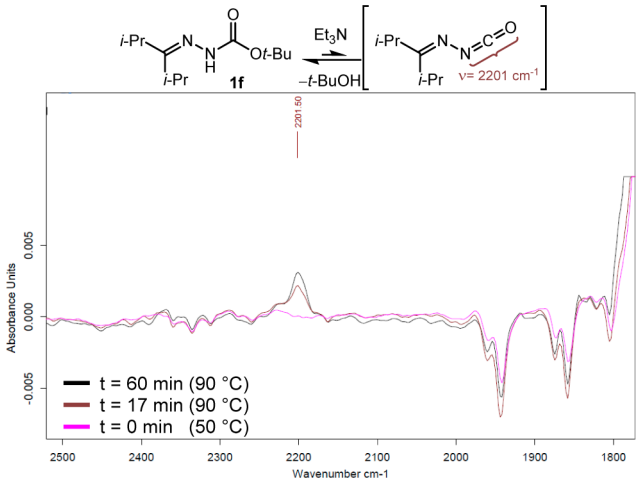
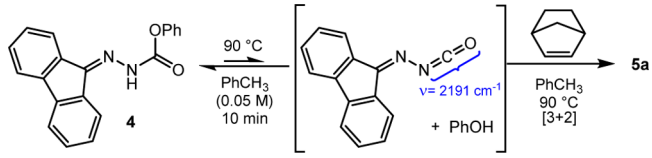


Figure 8. IR visualization of iminoisocyanate formation from **1f**.

reported values of 2220 cm^{-1} for Me_2N-NCO and 2221 cm^{-1} for N_3-NCO in Argon matrices[19b,44c] and does not correspond to CO_2 (2337 cm^{-1}) or CO (2138 cm^{-1}), both being possible products of iminoisocyanate degradation.

Fluorenone-derived reagent **4** was then studied (Scheme 8). The hydrazone solubilized to a yellow solution upon heating at 90 °C and then became dark ruby red. Analysis of the sample after 10 min showed a new peak at 2191 cm^{-1}, corresponding

Scheme 8. IR Visualization of Iminoisocyanate from Reagent 4



to the asymmetric NCO stretch of the conjugated iminoisocyanate (see Supporting Information). This peak does not match the expected frequency of the fluorenone azine (1600–1650 cm^{-1}), a red byproduct that is observed in reactions at higher temperatures.[46] Norbornene was added to the reaction mixture after 20 min, and the mixture immediately returned to a pale yellow solution. Prompt analysis of the reaction mixture revealed no peak at 2191 cm^{-1}.

This study provided the first direct evidence for the intermediacy of the iminoisocyanate in alkene aminocarbonylation reactions and the first characterization of such species by IR spectroscopy. More broadly, this method has the potential to be a valuable technique for studying the formation of *N*-isocyanates in other cycloadditions or cascade reactions.[21f,g]

Mechanistic Studies and DFT Calculations. In this research on alkene aminocarbonylation, it became clear that cycloaddition reactions of iminoisocyanates are unique in their reactivity preferences and in the products formed. In comparison to chlorosulfonyl isocyanate, which is purely electrophilic, iminoisocyanates are amphoteric and exhibit moderate electrophilicity and nucleophilicity. In addition, the literature shows that other isoelectronic reactants (e.g., azides, nitrones) undergo different cycloaddition reactivities compared to iminoisocyanates.[47] For example, nitrones preferably undergo 1,3-dipolar cycloadditions with electron-deficient dipolarophiles employing the HOMO of the nitrone and LUMO of the alkene. The transition state for alkene aminocarbonylation is similar to the 1,3-dipolar cycloaddition: the iminoisocyanate cycloaddition is concerted and asynchronous (see below for computational and experimental evidence), and partial charges exist on the amphoteric reactant. However, the iminoisocyanate cycloaddition occurs preferentially with electron-rich alkenes, signifying that the LUMO of the iminoisocyanate is important.

Given the novelty of the cycloaddition, the reaction was studied both computationally and experimentally. Computational results were obtained early in the reaction development process to provide further information about the geometry of the aminocarbonylation transition state and help guide the survey of the reaction scope. The lowest energy transition state structures for the reactions of both ethylene and norbornene with the simple iminoisocyanate derived from acetone are shown below (Figure 9).

A concerted asynchronous transition state is observed in both models with the C–C bond more formed than the N–C bond. This result is in agreement with the preference for the formation of Markovnikov products observed experimentally. Insight into the potential energy surface of the reaction was also acutely needed because this cycloaddition has the peculiarity of forming a dipole from a neutral isocyanate reactive intermediate. These types of cycloadditions should be less thermodynamically favorable when compared to dipolar cycloadditions and could consequentially be more limited from a synthetic perspective. The calculated potential energy surface for the reaction of dimethyl iminoisocyanate with

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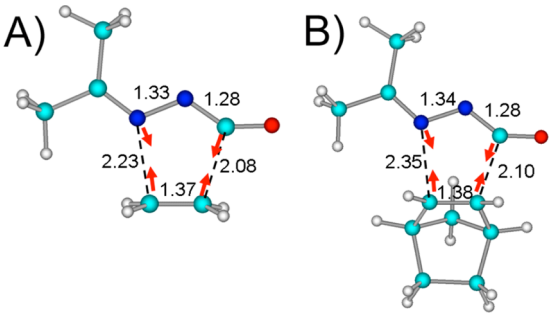


Figure 9. Calculated transition states (B3LYP/TZVP) for the intermolecular aminocarbonylation of dimethyl iminoisocyanate with (A) ethylene and (B) norbornene. Bond distances are shown in angstroms.

norbornene is shown in Figure 10. Gibbs free energies of activation were calculated to be 35.5 kcal/mol in vacuum and

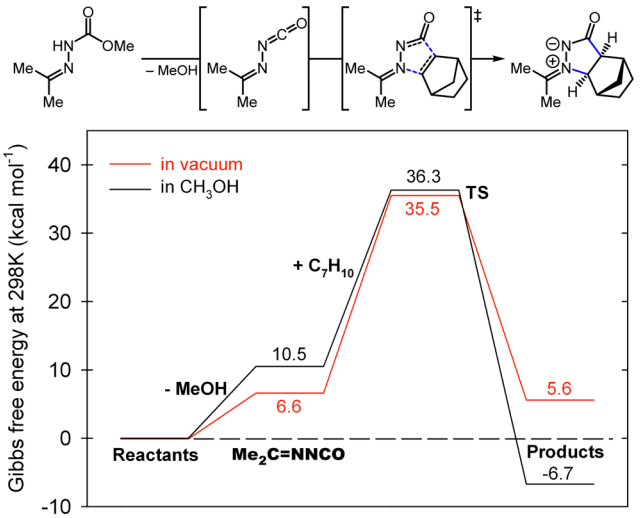
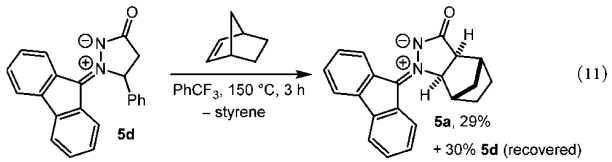


Figure 10. Gibbs free energies (kcal/mol, 298 K) for the reaction of norbornene (C_7H_{10}) and dimethyl iminoisocyanate in vacuum (red line) and in methanol (black line). TS = transition state.

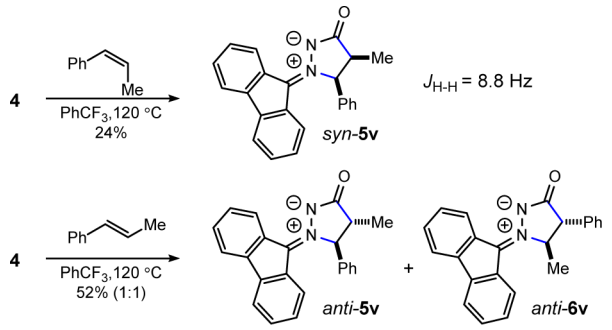
36.3 kcal/mol in MeOH solvent. These values are relative to the reactants, and the calculations suggest that formation of the iminoisocyanate is endergonic. From this intermediate, activation energies for the cycloaddition were calculated to be 28.9 kcal/mol in the gas phase and 25.8 kcal/mol in MeOH. These values are consistent with reactions requiring heating to proceed. The results also show the iminoisocyanate is destabilized in MeOH compared to vacuum, whereas the dipole product is stabilized. Qualitatively, this result is significant because one equivalent of a blocking group is released under the reaction conditions and able to engage in hydrogen bonding. This result is also consistent with the changes in azomethine imine ratios observed in the presence of PhSH or PhOH additive (eq 6). Given this, the driving force for the reaction calculated in MeOH (ΔG_r = −6.7 kcal/mol) is likely more appropriate than the value determined in the gas phase (ΔG_r = 5.6 kcal/mol). Because these values were determined for the reaction of norbornene, which benefits from some strain release, this suggests that the reaction is close to thermoneutrality, an observation that could be important if more stable alkenes are used as reagents. In agreement with this, some crossover was observed in a cycloreversion/aminocarbonylation experiment (eq 11).



(11)

In addition to the computational studies,[23] stereospecific reactions of *cis*- and *trans*-β-methylstyrene provided experimental support for a concerted cycloaddition reaction (Scheme 9). The aminocarbonylation of *cis*-β-methylstyrene provided

Scheme 9. Reactions with *cis*- and *trans*-β-Methylstrene Provide Experimental Support for a Concerted Cycloaddition



the *syn* product (**5v**) in 24% yield, whereas *trans*-β-methylstyrene gave a 1:1 mixture of *anti* adducts **5v** and **6v** in 52% combined yield.

Beyond providing strong support for a concerted cycloaddition, these results highlight that more stable alkenes can react with reagent **4**. In fact, many of the alkenes surveyed in the context of exploratory studies provided the alkene aminocarbonylation products, which testifies to the reliability of this approach. Extensions of this reactivity, including the cycloaddition reactions of iminoisocyanates with imines and of iminoisothiocyanates with alkenes and imines were not included in this article due to space considerations.[40d] Overall, these results indicate a strong propensity of amphoteric isocyanates to engage in concerted cycloaddition reactions.

■ CONCLUSIONS

The aminocarbonylation reaction of iminoisocyanates with alkenes is a powerful strategy for accessing many complex azomethine imines and β-amino carbonyl compounds from simple starting materials. An advantage to this approach is that it yields stable, isolable, and typically crystalline azomethine imines. Systematic variations on the hydrazone reagent allowed the identification of aminocarbonylation reagent **4**, possessing OPh as an optimal blocking group to form the iminoisocyanate in situ, and a planar fluorenylidene group that provides sufficient steric shielding to prevent [3 + 2] reactions of the desired azomethine imine product with excess alkene. Gratifyingly, this reactivity proceeds with a wide range of alkenes and hydrazones, and for reactive alkenes, tertiary amine bases were found to accelerate the formation of *N*-isocyanate and the overall process. Perhaps more importantly, the fluorenone-derived reagent allows for a variety of derivatization reactions, including reductive protocols for N−N bond cleavage and

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transformation of the cycloadducts into β-amino carbonyl compounds. There are several ways to remove the fluorenyl auxiliary, including by oxidation with DDQ or via a transimination procedure using NH_2OH. Other derivatization reactions include the transformation of azomethine imines into pyrazolones and a kinetic resolution of the azomethine imines by enantioselective reduction. The latter is crucial as it allows the synthesis of enantioenriched β-amino carbonyl compounds from alkenes. Mechanistically, the direct observation of iminoisocyanates was achieved by infrared spectroscopy under the reaction conditions. To our knowledge, this is the first example of the observation of iminoisocyanates by IR. Finally, the nature of the transition state was explored experimentally and by DFT calculations. These results provide support for a concerted, asynchronous transition state for the aminocarbonylation event, a finding that is aligned with the observation of Markovnikov products in reactions of unsymmetrical alkenes. Calculations on the potential energy surface support a reaction forming an iminoisocyanate intermediate, requiring heating to undergo a concerted aminocarbonylation and a slightly exothermic overall process. In conclusion, this work is a complete study on the generation and reactivity of rare amphoteric isocyanates, which establishes their synthetic potential in the context of cycloaddition reactions. Efforts to develop new reactivity of amphoteric reagents is ongoing and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All commercially available materials were used without further purification unless otherwise noted. Solvents for reactions were obtained from solvent system or dried over 4 Å molecular sieves. Microwave reactions were performed using a Biotage Initiator Eight microwave reactor and microwave vials. Reactions were monitored by analytical thin layer chromatography (TLC), using glass- or aluminum-backed plates cut to size. TLC visualization was achieved by UV and stain (such as $KMnO_4$, vanillin, and ninhydrin). Flash column chromatography was carried out using 40−63 μm SiliCycle silica gel. ^1H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers at ambient temperature except where noted. Spectral data are reported in ppm using solvent as the reference. ^1H NMR: $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), DMSO-d_6 (2.50 ppm), toluene-d_8 (2.08 ppm), CD_3OD (3.31 ppm). ^{13}C NMR: $CDCl_3$ (77.16 ppm), C_6D_6 (128.06 ppm), DMSO-d_6 (39.52 ppm), CD_3OD (49.00 ppm). ^1H data are reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, appt = apparent triplet), coupling constants (J) in Hz, and integration. Infrared (IR) spectra were obtained as thin films or as neat solids on FTIR instruments. High resolution mass spectroscopy (HRMS) was performed by electron impact (EI) or Q-TOF electrospray ionization (ESI).

Hydrazones (**1a−l**) were synthesized according to known procedures.[23,39] General procedures for alkene aminocarbonylation and characterization data for new azomethine imines are provided. Compounds **5a-g**, **5j**, **5r**, **5u**, **5v**, **5x**, **5ab**, and **5ac** were previously reported.[23,32a]

Phenyl Hydrazinecarboxylate. Hydrazine hydrate (30 mL, 50−60 wt % solution in H_2O, 0.60 mol, 3 equiv) was diluted in CH_2Cl_2 (250 mL). A solution of diphenyl carbonate (43 g, 0.20 mol, 1 equiv) in CH_2Cl_2 (250 mL) was added dropwise over 2 h while stirring at room temperature. Immediately after the addition was complete, the mixture in concentrated in vacuo. The crude product was isolated by column chromatography (gradient, 50% EtOAc, and 50% hexanes to 100% EtOAc). Fractions contaminated with PhOH were recrystallized in CH_2Cl_2/hexane. The title compound was obtained as a white solid in 14.6 g (48% isolated yield). ^1H NMR spectrum was in agreement with the literature.[23,48c]

*Phenyl 2-(9H-Fluoren-9-ylidene)hydrazine-1-carboxylate (**4**).* Phenyl hydrazinecarboxylate (2.43 g, 16.0 mmol), fluorenone (2.90 g, 16.0 mmol), and AcOH (0.20 mL) in MeOH (35 mL) were heated to reflux for 6 h. The mixture was cooled to rt, and the product was crystallized from the crude mixture. The product was obtained as a yellow solid (4.0 g, 80% yield). Mp 178−180 °C. TLC R_f = 0.31 in 20% EtOAc/hexanes. ^1H NMR (400 MHz, CDCl3) δ 9.18 (s, 1H), 7.91 (d, J = 7.48 Hz, 1H), 7.82 (d, J = 7.63 Hz, 1H), 7.66 (d, J = 7.51 Hz, 1H), 7.56 (d, J = 7.43 Hz, 1H), 7.47−7.21 (m, 9H). ^{13}C NMR (100 MHz, CDCl3) δ 152.1(C), 150.6 (C), 142.6 (C), 139.5 (C), 136.8 (C), 131.4 (CH), 130.3 (CH), 129.7 (C), 129.6 (CH), 128.4 (CH), 128.1 (CH), 126.0 (CH), 125.6 (CH), 122.6 (CH), 121.5 (CH), 121.0 (CH), 119.7 (CH). IR (film) 1716, 1735, 1490, 1471, 1219, 1171, 772 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{14}N_2O_2$ $[M]^+$ 314.1050; found 314.1056.

General Procedure A for the Intermolecular Aminocarbonylation of Alkenes (Microwave Conditions).[23,39] The hydrazone and corresponding alkene (1−10 equiv) were added to an oven or flame-dried microwave vial with a stir bar. The mixture was diluted with α,α,α-trifluorotoluene ($PhCF_3$, 0.5 to 0.05 M) unless noted otherwise (e.g., neat conditions or solvent optimization). The vial was sealed with a septum and purged with argon. The mixture was heated at the specified temperature in a microwave reactor for the given time. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure, and analyzed by ^1H NMR using 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene as an internal standard. The azomethine imine product was isolated using silica gel column chromatography.

General Procedure B for the Intermolecular Aminocarbonylation of Alkenes (reflux conditions)..[23,39] The hydrazone, corresponding alkene (1−10 equiv), and α,α,α-trifluorotoluene ($PhCF_3$, 0.5 to 0.05 M) were added to an oven or flame-dried flask with a stir bar. The flask was equipped with a reflux condenser and purged with argon. The mixture was heated to 100 °C in an oil bath. The mixture was then cooled to ambient temperature; the stir bar was removed, and the solvent was evaporated to give the crude product. The azomethine imine product was isolated using silica gel column chromatography.

*2-(9H-Fluoren-9-ylidene)-3-(3-methoxyphenyl)-5-oxopyrazolidin-2-ium-1-ide (**5h**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.157 g, 0.500 mmol) and 3-methoxystyrene (0.35 mL, 2.5 mmol, 10 equiv) in $PhCF_3$ (10 mL). The reaction was heated at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:3 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 20:1 MeOH/CH_2Cl_2 to elute the product). The product was obtained as a yellow solid (0.051 g, 29% yield). TLC R_f = 0.24 in EtOAc. ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (d, J = 7.4 Hz, 1 H), 7.65−7.54 (m, 2 H), 7.50−7.34 (m, 3 H), 7.33−7.24 (m, 3 H), 7.12−7.03 (m, 1 H), 6.91−6.77 (m, 3 H), 6.30 (dd, J = 1.7, 9.4 Hz, 1 H), 3.74 (s, 3 H), 3.47 (dd, J = 9.4, 16.2 Hz, 1 H), 2.74 (dd, J = 2.0, 16.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 160.6, 141.7, 141.2, 140.2, 139.4, 132.2, 131.7, 131.0, 130.9, 130.9, 129.4, 129.2, 128.0, 125.8, 120.8, 119.7, 116.8, 113.5, 110.8, 72.0, 55.3, 40.7. IR (ATR): 3071, 2982, 2939, 1658, 1605, 1550, 1274 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{18}N_2O_2$ $[M]^+$ 354.1368; found 354.1396.

*2-(9H-Fluoren-9-ylidene)-3-(2-methoxyphenyl)-5-oxopyrazolidin-2-ium-1-ide (**5i**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.157 g, 0.500 mmol) and 2-methoxystyrene (0.34 mL, 2.5 mmol, 10 equiv) in $PhCF_3$ (10 mL). The reaction was heated at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:4 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.128 g, 72% yield). TLC R_f = 0.31 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J = 7.3 Hz, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.2 Hz, 1 H), 7.45−7.32 (m, 2 H), 7.29−7.20 (m, 2 H), 7.17 (d, J = 8.0 Hz, 1 H), 7.06−6.90 (m, 3 H), 6.83−6.72 (m, 1 H), 6.49 (dd, J = 2.0, 9.2 Hz, 1 H), 4.02 (s, 3 H), 3.43 (dd, J = 9.2, 16.6 Hz, 1 H), 2.57 (dd, J = 2.3, 16.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 155.0, 141.5, 140.4, 140.1, 132.0, 131.6, 131.4, 130.7, 130.0, 129.5, 129.0, 127.9, 126.0, 125.3, 124.1,

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121.8, 120.6, 119.6, 110.5, 67.6, 55.8, 39.4. IR (ATR): 3062, 2930, 2840, 1670, 1544 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{18}N_2O_2$ $[M]^+$ 354.1368; found 354.1383.

*2-(9H-Fluoren-9-ylidene)-5-oxo-3-(p-tolyl)pyrazolidin-2-ium-1-ideide (**5k**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.159 g, 0.504 mmol) and 4-methylstyrene (0.66 mL, 5.0 mmol, 10 equiv) in $PhCF_3$ (10 mL). The reaction was heated at 100 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:1 Et_2O/CH_2Cl_2 and then 9:1 Et_2O/MeOH to elute the product). The product was obtained as a yellow solid (0.083 g, 48% yield). TLC R_f = 0.20 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 7.5 Hz, 1 H), 7.61 (dd, J = 4.1, 7.2 Hz, 2 H), 7.51−7.35 (m, 3 H), 7.34−7.28 (m, 1 H), 7.16 (s, 4 H), 7.12−7.03 (m, 1 H), 6.33 (dd, J = 1.5, 9.2 Hz, 1 H), 3.50 (dd, J = 9.3, 16.3 Hz, 1 H), 2.77 (dd, J = 1.8, 16.3 Hz, 1 H), 2.30 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 141.9, 141.5, 140.4, 138.8, 135.1, 132.4, 131.9, 131.8, 131.2, 130.5, 129.5, 129.4, 128.1, 126.2, 124.7, 120.9, 119.8, 72.2, 41.0, 21.2. IR (ATR): 3095, 1699, 1616, 1570, 1320 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{18}N_2O$ $[M]^+$ 338.1419; found 338.1414

*3-(2-Bromophenyl)-2-(9H-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (**5l**).* This compound was synthesized according to general procedure A using **4** (62.9 mg, 0.200 mmol) and1-bromo-2-vinylbenzene (0.13 mL, 1.0 mmol, 5 equiv) in $PhCF_3$ (4.0 mL). The reaction was heated at 120 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (30−80% EtOAc/hexanes and then 5% MeOH/EtOAc). The product was obtained as a yellow solid (39.1 mg, 48% yield). TLC R_f = 0.08 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 7.4, 1H), 7.70−7.67 (m, 1H), 7.62−7.58 (m, 2H), 7.49−7.46 (m, 1H), 7.41 (td, J = 1.2, 7.6 Hz, 1H), 7.30 (ddd, J = 2.0, 6.0, 7.7 Hz, 1H), 7.20 (dt, J = 3.0, 6.6 Hz, 2H), 7.12−7.06 (m, 3H), 6.51 (dd, J = 2.1, 9.3 Hz, 1H), 3.56 (dd, J = 9.3, 16.6 Hz, 1H), 2.67 (dd, J = 2.2, 16.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3 (C), 142.1 (C), 141.4 (C), 140.6 (C), 137.3 (C), 133.7 (CH), 132.8 (CH), 132.1 (CH), 131.8 (C), 131.5 (CH), 130.8 (CH), 129.62 (CH), 129.57 (C), 129.47 (CH), 128.6 (CH), 125.74 (CH), 125.59 (CH), 121.8 (C), 121.2 (CH), 120.1 (CH), 72.5 (CH), 39.6 (CH_2). IR (film) 1734, 1661, 1647, 1605, 1545, 1448, 1290, 1269, 1248 cm^{-1}. HRMS (EI): exact mass calcd for $C_{22}H_{15}BrN_2O$ $[M]^+$ 402.0368; found 402.0399.

*3-(3-Bromophenyl)-2-(9H-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (**5m**).* This compound was synthesized according to general procedure A using **4** (62.9 mg, 0.200 mmol) and 1-bromo-3-vinylbenzene (0.18 g, 1.0 mmol, 5.0 equiv) in $PhCF_3$ (4.0 mL). The reaction was heated at 120 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (30−50% EtOAc/hexanes, then EtOAc, and then 5% MeOH/EtOAc). The title compound was obtained as a yellow solid (34.6 mg, 43% yield). TLC R_f = 0.48 (EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 9.10−9.08 (m, 1H), 7.58 (dd, J = 0.6, 7.4 Hz, 2H), 7.47−7.42 (m, 3H), 7.38 (td, J = 1.2, 7.6 Hz, 1H), 7.33−7.28 (m, 2H), 7.23−7.18 (m, 2H), 7.11−7.07 (m, 1H), 6.32 (dd, J = 1,4, 9.3 Hz, 1H), 3.49 (dd, J = 9.4, 16.3 Hz, 1H), 2.72 (dd, J = 1.9, 16.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3, 142.2, 141.9, 140.6, 140.4, 132.8, 132.4, 132.1, 131.84, 131.70, 131.64, 129.61, 129.46, 128.4, 128.1, 126.0, 124.2, 123.6, 121.3, 120.1, 71.7, 40.9. IR (film) 1653, 1607, 1549, 1450, 1342, 1275, 1246 cm^{-1}. HRMS (EI): exact mass calcd for $C_{22}H_{15}BrN_2O$ $[M]^+$ 402.0368; found 402.0375.

*2-(9H-Fluoren-9-ylidene)-5-oxo-3-(4-(trifluoromethyl)phenyl)-pyrazolidin-2-ium-1-ide (**5n**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.157 g, 0.500 mmol) and 4-(trifluoromethyl)styrene (0.74 mL, 5.0 mmol, 10 equiv) in $PhCF_3$ (10 mL). The reaction was heated at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:4 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.045 g, 23% yield). TLC R_f = 0.17 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.24−8.96 (m, 1 H), 7.75−7.54 (m, 4 H), 7.53−7.36 (m, 4 H), 7.36−7.28 (m, 1 H), 7.26 (m, 1 H), 7.13−7.02 (m, 1 H), 6.46 (d, J = 8.4 Hz, 1 H), 3.57 (dd, J = 9.5, 16.4 Hz, 1 H), 2.74 (dd, J = 2.0, 16.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 141.8, 141.7, 141.4, 140.2, 132.5, 131.6, 131.4, 131.3, 131.0 (q, J_{C-F} = 33.0 Hz), 129.2, 129.0, 128.0, 126.8 (q, J_{C-F} = 3.7 Hz, 2C), 125.5, 125.3 (2C), 123.5 (q, J_{C-F} = 271 Hz), 121.0, 119.8, 71.4, 40.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ 62.8. IR (ATR) 3095, 1992, 1733, 1695, 1623, 1577, 1456, 1372 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{15}F_3N_2O$ $[M]^+$ 392.1136; found 392.1138.

*2-(9H-Fluoren-9-ylidene)-5-oxo-4-(4-(trifluoromethyl)phenyl)-pyrazolidin-2-ium-1-ide (**6n**).* Following the same procedure as above for product **5n**, product **6n** was also isolated as a yellow solid (9.8 mg, 5% yield). TLC R_f = 0.49 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 7.7 Hz, 1 H), 7.71 (d, J = 7.3 Hz, 1 H), 7.69−7.58 (m, 4 H), 7.55−7.43 (m, 4 H), 7.37 (ddd, J = 1.1, 7.7, 7.7 Hz, 1 H), 7.33−7.27 (m, 1 H), 5.38 (dd, J = 9.9, 13.5 Hz, 1 H), 4.86 (dd, J = 5.6, 13.5 Hz, 1 H), 4.37 (dd, J = 5.6, 9.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 142.1, 142.0, 141.2, 140.3, 132.6, 131.7, 131.4, 131.2, 130.4, 130.3 (q, J_{C-F} = 32.0 Hz), 129.4, 129.2, 128.5, 128.4, 126.4 (q, J_{C-F} = 4.0 Hz, 2C), 125.7, 124.5, 124.1 (q, J_{C-F} = 270 Hz), 121.5, 120.5, 120.1, 64.5, 47.5. IR (ATR) 3136, 1699, 1634, 1581, 1410, 1395 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{15}F_3N_2O$ $[M]^+$ 392.1136; found 392.11375.

*2-(9H-Fluoren-9-ylidene)-3-isobutyl-5-oxopyrazolidin-2-ium-1-ide (**5o**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.159 g, 0.506 mmol) and 4-methyl-1-pentene (0.32 mL, 2.5 mmol, 5 equiv) in $PhCF_3$ (5 mL). The reaction was heated by microwave irradiation at 150 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:3 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.069 g, 45% yield). TLC R_f = 0.23 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 7.6 Hz, 1 H), 7.71 (d, J = 7.0 Hz, 1 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.48−7.39 (m, 2 H), 7.39−7.30 (m, 2 H), 5.51−5.30 (m, 1 H), 3.11 (dd, J = 8.2, 16.3 Hz, 1 H), 2.76 (d, J = 16.4 Hz, 1 H), 2.05−1.88 (m, 2 H), 1.87−1.77 (m, 1 H), 1.15 (d, J = 6.3 Hz, 3 H), 1.00 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.4, 142.2, 140.1, 140.0, 132.1, 132.0, 131.7, 131.2, 129.7, 129.4, 128.1, 125.5, 121.3, 119.8, 67.9, 42.8, 35.8, 26.1, 23.7, 21.5. IR (ATR) 3003, 2847, 1699, 1615, 1566, 1326 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{20}N_2O$ $[M]^+$ 304.15756; found 304.15719.

*3-Cyclohexyl-2-(9H-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (**5p**).* This compound was synthesized according to general procedure A using **4** (0.063 g, 0.20 mmol) and vinylcyclohexane (0.14 mL, 1.0 mmol, 5 equiv) in $PhCF_3$ (4 mL). The reaction was heated by microwave irradiation at 120 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:1 EtOAc/hexane and then 20:1 EtOAc/MeOH). The product was obtained as a yellow solid (0.033 g, 50% yield). TLC R_f = 0.33 in EtOAc. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06−9.04 (m, 1H), 7.74−7.72 (m, 1H), 7.65 (d, J = 7.1, 1H), 7.47−7.43 (m, 3H), 7.36 (dtd, J = 1.3, 7.7, 9.0 Hz, 2H), 5.32−5.30 (m, 1H), 2.95 (dd, J = 8.9, 16.6 Hz, 1H), 2.73 (dd, J = 1.8, 16.6 Hz, 1H), 2.26−2.19 (m, 1H), 1.86 (t, J = 10.2, 2H), 1.75−1.66 (m, 2H), 1.55 (d, J = 12.6, 1H), 1.31−1.02 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 142.3, 139.9, 139.5, 132.09, 132.07, 131.7, 131.1, 130.2, 129.5, 128.6, 125.1, 121.4, 119.9, 72.8, 41.0, 32.4, 29.9, 26.3, 26.1, 25.6, 24.3. IR (film) 2928, 2854, 1659, 1605, 1541, 1448, 1255 cm^{-1}. HRMS (EI): exact mass calcd for $C_{22}H_{22}N_2O$ $[M]^+$ 330.1732; found 330.1734.

*3-(tert-Butyl)-2-(9H-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (**5q**).* This compound was synthesized according to general procedure A using **4** (0.600 g, 1.91 mmol) and 3,3-dimethylbut-1-ene (1.60 g, 19.1 mmol, 10 equiv) in $PhCF_3$ (15.0 mL). The reaction was heated by microwave irradiation at 150 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (50% EtOAc/hexanes, then EtOAc, and then 10% MeOH/EtOAc). The product was obtained as a yellow solid (0.222 g, 38% yield). R_f = 0.24 (2% MeOH/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 9.13−9.11 (m, 1H), 7.79 (d, J = 8.1, 1H), 7.68 (dd, J = 0.6,

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7.5 Hz, 1H), 7.63−7.61 (m, 1H), 7.46−7.43 (m, 1H), 7.39 (ddd, J = 0.6, 7.7, 15.5 Hz, 2H), 7.30 (dd, J = 1.2, 7.9 Hz, 1H), 5.50 (d, J = 7.7, 1H), 3.02 (dd, J = 7.9, 16.0 Hz, 1H), 2.73 (dd, J = 0.3, 16.1 Hz, 1H), 1.08 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.7, 143.0, 142.4, 140.2, 132.40, 132.37, 132.33, 131.5, 131.2, 129.5, 127.9, 126.5, 121.3, 119.8, 76.5, 38.7, 35.5, 27.3. IR (film) 2964, 1734, 1663, 1605, 1533, 1448, 1294, 1273 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{20}N_2O$ $[M]^+$ 304.1576; found 304.1578.

*2-(9H-Fluoren-9-ylidene)-3-(naphthalen-1-yl)-5-oxopyrazolidin-2-ium-1-ide (**5s**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.400 g, 1.27 mmol) and 1-vinylnapthalene (0.98 g, 6.4 mmol, 5 equiv) in $PhCF_3$ (13 mL). The reaction was heated at 120 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (2:1 EtOAc/hexane and then 20:1 EtOAc/MeOH). The product was obtained as a yellow solid (0.247 g, 66% yield). TLC R_f = 0.33 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (dd, J = 0.5, 7.6 Hz 1H), 7.99 (appt, J = 9.3 Hz, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.75 (td, J = 1.1, 7.7 Hz, 1H), 7.68−7.64 (m, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.45 (dtd, J = 1.2, 7.5, 22.6 Hz, 2H), 7.30 (appt, J = 7.8 Hz, 1H), 7.22−7.17 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.75−6.71 (m, 1H), 3.72 (dd, J = 9.3, 16.3 Hz, 1H), 2.80 (dd, J = 2.1, 16.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.9, 141.9, 141.6, 140.6, 134.4, 133.2, 132.6, 131.97, 131.95, 131.3, 130.1, 129.82, 129.75, 129.58, 129.2, 128.4, 128.0, 126.9, 126.3, 125.6, 121.87, 121.82, 121.1, 120.1, 70.6, 40.3. IR (film) 1663, 1605, 1553, 1450, 1288, 1269, 1232, 1124, 1091, 1018, 802, 773, 711 cm^{-1}. HRMS (EI): exact mass calcd for $C_{26}H_{18}N_2O$ $[M]^+$ 374.1419; found 374.1405.

*2-(9H-Fluoren-9-ylidene)-3-(naphthalen-2-yl)-5-oxopyrazolidin-2-ium-1-ide (**5t**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.063 g, 0.20 mmol) and 2-vinylnapthalene (0.154 g, 1.0 mmol, 5 equiv) in $PhCF_3$ (4 mL). The reaction was heated at 120 °C for 3 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (2:1 EtOAc/hexane and then 9:1 EtOAc/MeOH). The product was obtained as a yellow solid (0.042 g, 56% yield). TLC R_f = 0.21 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22−9.20 (m, 1H), 7.91 (d, J = 8.5, 1H), 7.83−7.80 (m, 1H), 7.76−7.74 (m, 1H), 7.68 (d, J = 1.0 Hz, 1H), 7.62−7.56 (m, 2H), 7.51−7.39 (m, 6H), 7.29−7.25 (m, 1H), 7.01 (td, J = 7.8, 0.9 Hz, 1H), 6.55−6.53 (m, 1H), 3.63 (dd, J = 9.3, 16.4 Hz, 1H), 2.90 (dd, J = 1.9, 16.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7, 142.1, 141.8, 140.7, 135.5, 133.7, 133.3, 132.7, 132.12, 132.06, 131.4, 130.5, 129.66, 129.60, 128.50, 128.38, 128.1, 127.36, 127.20, 126.2, 123.7, 122.8, 121.2, 120.1, 72.7, 41.1. IR (film) 1734, 1663, 1609, 1544, 1506, 1450, 1292 cm^{-1}. HRMS (EI): exact mass calcd for $C_{26}H_{18}N_2O$ $[M]^+$ 374.1419; found 374.1444.

*syn-1-(9H-Fluoren-9-ylidene)-3-oxohexahydro-1H-cyclopenta[c]-pyrazol-1-ium-2-ide (**5w**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.316 g, 1.01 mmol) and cyclopentene (0.92 mL, 10 mmol, 10 equiv) in $PhCF_3$ (20 mL). The reaction was heated by microwave irradiation at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:4 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.220 g, 76% yield). TLC R_f = 0.10 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 7.8 Hz, 1 H), 7.68−7.51 (m, 3 H), 7.39 (ddd, J = 1.1, 7.5, 7.5 Hz, 2 H), 7.34−7.23 (m, 2 H), 5.59−5.36 (m, 1 H), 3.41 (dd, J = 7.7, 7.7 Hz, 1 H), 2.46−2.51 (m, 1 H), 2.32−2.16 (m, 2 H), 1.93−1.74 (m, 2 H), 1.64−1.45 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 141.6, 139.5, 138.9, 131.7, 131.5, 130.9, 130.8, 129.9, 129.0, 127.9, 124.9, 120.9, 119.5, 73.0, 47.2, 36.0, 30.3, 23.1. IR (film) 3114, 2992, 1696, 1619, 1570, 1315 cm^{-1}; HRMS (EI): exact mass calcd for $C_{19}H_{16}N_2O$ $[M]^+$ 288.1263; found 288.1246.

*syn-1-(9H-Fluoren-9-ylidene)-3-oxooctahydro-1H-cyclohepta[c]-pyrazol-1-ium-2-ide (**5y**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.079 g, 0.25 mmol) and cycloheptene (0.29 mL, 2.5 mmol, 10 equiv) in $PhCF_3$ (5 mL). The reaction was heated by microwave irradiation at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:4 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.032 g, 40%). TLC R_f = 0.27 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.3 Hz, 1 H), 7.58 (d, J = 7.3 Hz, 1 H), 7.48−7.36 (m, 3 H), 7.36−7.28 (m, 2 H), 5.40−5.24 (m, 1 H), 3.33 (ddd, J = 5.4, 8.9, 11.1 Hz, 1 H), 2.35 (ddd, J = 5.5, 8.7, 14.6 Hz, 1 H), 2.23−2.08 (m, 2 H), 2.05−1.90 (m, 2 H), 1.90−1.75 (m, 2 H), 1.64−1.36 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 141.8, 139.4, 139.1, 131.7, 131.6, 131.2, 130.6, 129.6, 129.0, 128.1, 125.1, 121.0, 119.4, 73.5, 45.5, 31.0, 30.6, 26.5, 26.5, 26.4. HRMS (EI): exact mass calcd for $C_{21}H_{20}N_2O$ $[M]^+$ 316.15756; found 316.16049.

*syn-1-(9H-Fluoren-9-ylidene)-3-oxodecahydrocycloocta[c]-pyrazol-1-ium-2-ide (**5z**).* This compound was synthesized according to general procedure A using hydrazone **4** (0.079 g, 0.25 mmol) and cyclooctene (0.30 mL, 2.5 mmol, 10 equiv) in $PhCF_3$ (5 mL). The reaction was heated by microwave irradiation at 100 °C for 6 h. The crude mixture was concentrated in vacuo, and the product was isolated by column chromatography (1:4 EtOAc/CH_2Cl_2 to remove excess alkene and byproducts and then 9:1 EtOAc/MeOH to elute the product). The product was obtained as a yellow solid (0.045 g, 54%). TLC R_f = 0.42 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 7.7 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H), 7.62−7.55 (m, 2 H), 7.43−7.37 (m, 2 H), 7.36−7.27 (m, 2 H), 5.45−5.30 (m, 1 H), 2.86 (ddd, J = 2.0, 8.5, 12.1 Hz, 1 H), 2.55−2.42 (m, 1 H), 2.24−2.10 (m, 1 H), 2.10−1.96 (m, 3 H), 1.94−1.54 (m, 5 H), 1.34−1.20 (m, 1 H), 1.17−1.03 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 141.7, 139.5, 139.3, 132.0, 131.7, 131.4, 130.8, 129.9, 129.2, 128.0, 124.7, 121.0, 119.5, 73.8, 45.6, 31.9, 29.7, 28.1, 26.0, 24.8, 21.8. HRMS (EI): exact mass calcd for $C_{22}H_{22}N_2O$ $[M]^+$ 330.1732; found 330.1730.

Representative procedures for reductive N−N cleavage and characterization data for new products are provided. Compounds **7a**, **7b**, **7d−g**, **8a**, **8b**, and **8d−f** were previously reported.[23]

*Representative Procedure for N−N Cleavage:[23] 2-((9H-Fluoren-9-yl)amino)cyclopentane-1-carboxamide (**7c**).* Azomethine imine **5w** (0.213 mmol, 0.0613 g), Raney nickel (1 mL, slurry in MeOH), $NaBH_4$ (1.7 mmol, 0.064 g), and methanol (30 mL) were added to a 100 mL screw-top flask. Care must be taken in choosing the size of the flask to allow a large empty volume of headspace once sealed. The flask was sealed, and the reaction mixture was stirred at 60 °C for 6 h. The mixture was concentrated under reduced pressure and then quenched with saturated aq. NH_4Cl (30 mL). The product was extracted with dichloromethane (3 × 20 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (EtOAc) and recrystallization from EtOAc/hexanes gave the target compound as a white solid (0.0365 g, 59%). TLC R_f = 0.25 in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.72 (m, 3 H), 7.57 (d, J = 7.4 Hz, 1 H), 7.61 (d, J = 7.5 Hz, 1 H), 7.38 (dd, J = 7.4, 7.4 Hz, 2 H), 7.30 (ddt, J = 1.0, 2.9, 7.4 Hz, 2 H), 5.80 (br s, 1 H), 4.93 (s, 1 H), 3.19 (**M1**, td, J = 6.7, 8.4 Hz, 1 H, NOE with **M2**), 2.47−2.40 (**M2**, m, 1 H, NOE with **M1**), 2.33 (br s, 1 H), 2.13−2.01 (m, 1 H), 1.77−1.41 (m, 5 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.0, 145.9, 145.2, 140.7, 140.5, 128.3, 128.3, 127.4 (2C), 125.1, 124.8, 120.0, 120.0, 62.5, 58.2, 48.0, 32.1, 27.6, 21.2. IR (ATR): 3487, 3329, 3175, 2840, 1733, 1520 cm^{-1}. HRMS (EI): exact mass calcd for $C_{19}H_{20}N_2O$ $[M]^+$ 292.1576, not found. Exact mass calcd for $C_6H_{11}N_2O$ $[M$ − fluorenyl$]^+$ and $C_{13}H_9$ [fluorenyl]$^+$: 127.0871 and 165.0704; found 127.0865 and 165.0710.

*Representative Procedure for β-Aminoester Synthesis:[23] Methyl 3-((9H-Fluoren-9-yl)amino)bicyclo[2.2.1]heptane-2-carboxamide (**8a**).* This compound was synthesized according to the procedure taken from Zhu et al.[25a] $SOCl_2$ (0.50 mL, 6.9 mmol, 35 equiv) was added to cooled methanol (3 mL, 0 °C) in a 15 mL vial, and the mixture was stirred at 0 °C for 10 min. Compound **7a** (0.064 g, 0.20 mmol) was then added to the solution at ∼0 °C. The vial was sealed, and the reaction mixture was stirred at 60 °C for 12 h. The mixture was concentrated under reduced pressure and quenched with saturated aqueous NH_4Cl (10 mL). The product was extracted with dichloro-

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methane (10 mL × 3), and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by a silica gel chromatography (EtOAc) gave the target compound as a colorless solid (0.032 g, 48% yield).

*General Procedure C: Cleaving the Azomethine Imine Substituent with Hydroxylamine (**10a**).* Azomethine imine **5a** (0.298 g, 0.943 mmol, 1 equiv) was diluted in MeOH (40 mL), and aqueous NH_2OH (1 mL, 50 wt % in H_2O) was added. The mixture was heated to reflux for 2 h when TLC showed complete consumption of **5a**. After cooling to rt, 80 mL of H_2O was added, and the mixture was cooled in an ice bath to precipitate the fluorenone oxime. The mixture was filtered, rinsing with H_2O. The filtrate was concentrated in vacuo to give the product as a white solid (0.143 g, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (br s, 1 H), 5.32 (br s, 1 H), 2.41 (d, J = 8.1 Hz, 1 H), 2.34 (d, J = 4.0 Hz, 1 H), 2.13 (d, J = 4.4 Hz, 1 H), 1.54−1.29 (m, 3 H), 1.22−1.12 (m, 1 H), 1.09 (td, J = 1.4, 10.1 Hz, 1 H), 1.07−0.97 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.6, 61.4, 50.4, 43.6, 38.6, 32.6, 27.2, 24.5. IR (ATR): 3681, 3389, 2977, 1885, 1395 cm^{-1}. HRMS (EI): exact mass calcd for $C_8H_{12}N_2O$ $[M]^+$ 152.09496; found 152.09580.

The synthesis and characterization of **10b**, **12a**, and **12b** using condensation chemistry were described in a prior communication.[32a]

*General Procedure D: N-Boc-β-amino Amides including tert-Butyl (3-Carbamoylbicyclo[2.2.1]heptan-2-yl)carbamate (**11a**).*[48b] A mixture of azomethine imine **5a** (0.50 g, 1.6 mmol, 1 equiv), aqueous hydroxylamine (0.126 mL, 1.91 mmol, 1.2 equiv), and MeOH (32 mL, 0.05 M) was heated for 16 h at 60 °C. The resulting concentrated crude mixture was diluted in EtOH (3.2 mL) and subjected to reductive cleavage with Raney nickel under hydrogen atmosphere at 45 °C for 16 h. The mixture was cooled to room temperature and filtered through Celite while washing with MeOH. The filtrate was concentrated under reduced pressure. *tert*-Butanol (1.6 mL, 1 M) was added followed by di-*tert*-butyl carbonate (0.693 g, 3.18 mmol, 2 equiv) and a solution of 5 M aq. NaOH (0.064 mL, 0.318 mmol, 0.2 equiv), and the mixture was stirred at room temperature for 16 h. The precipitate was refluxed in 60% EtOAc in hexanes and filtered when hot to yield the product as a white solid (0.288 g, 65%). TLC R_f = 0.35 (7% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 3.85−3.70 (br d, J = 8.0 Hz, 1 H), 3.63−3.50 (br d, J = 8.0 Hz, 1 H), 2.33 (m, 1 H), 2.08 (m, 1 H), 1.99−1.87 (m, 1 H), 1.63−1.49 (m, 1 H), 1.41 (s, 9 H), 1.30−1.15 (m, 4 H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 156.3, 78.9, 56.1, 51.9, 42.2, 40.5, 28.4, 27.3, 26.0. IR (film): 3411, 3300, 3215, 2967, 2930, 2867, 1676, 1654, 1624, 1550, 1360, 1308, 1281, 1251, 1063, 1022, 834, 703 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{13}H_{22}N_2O_3Na$ $[M + Na]^+$ 277.1523; found 277.1525.

*tert-Butyl (1-Amino-1-oxoheptan-3-yl)carbamate (**11b**).* This compound was prepared according to general procedure D using **5b** (0.50 g, 1.64 mmol, 1 equiv), aqueous hydroxylamine (0.13 mL, 1.97 mmol, 1.2 equiv), and MeOH (33 mL, 0.05 M) heated for 16 h at 70 °C. Following the reductive cleavage step, *tert*-butanol (1.64 mL, 1 M), di-*tert*-butyl carbonate (0.715 g, 3.28 mmol, 2 equiv), and 5 M NaOH (0.066 mL, 0.328 mmol, 0.2 equiv) were added. The precipitate was filtered to yield the product as a white solid (0.377 g, 86%). TLC R_f = 0.33 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 3.90−3.80 (m, 1 H), 2.32 (m, 2 H), 1.59−1.25 (m, 6 H), 1.43 (s, 9 H), 0.91 (t, J = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, CD_3OD) δ 175.2, 156.5, 78.5, 40.9, 34.2, 27.9, 27.4, 22.1, 13.0 IR (film): 3397, 3352, 3191, 2928, 2861, 1682, 1652, 1530, 1442, 1369, 1346, 1295, 1280, 1247, 1175, 1083, 1021, 861, 778, 698 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{12}H_{24}N_2O_3Na$ $[M + Na]^+$ 267.1679; found 267.1685.

*tert-Butyl (3-Amino-1-(4-methoxyphenyl)-3-oxopropyl)carbamate (**11c**).* This compound was prepared according to general procedure D using **5g** (0.50 g, 1.41 mmol, 1 equiv), aqueous hydroxylamine (0.131 mL, 1.97 mmol, 1.4 equiv), and methanol (33 mL, 0.06 M) in a pressure flask by heating for 16 h at 60 °C. Following the reductive cleavage step, *tert*-butanol (1.4 mL, 1 M), di-*tert*-butyl carbonate (0.615 g, 2.82 mmol, 2 equiv), and 5 M NaOH (0.056 mL, 0.282 mmol, 0.2 equiv) were added. The precipitate was refluxed in 60% EtOAc in hexanes and filtered when hot to yield the product as a white solid (0.288 g, 63%). TLC R_f = 0.23 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (d, J = 9.0 Hz, 2 H), 7.17- 7.10 (m, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 6.69−6.54 (m, 1 H), 4.87−4.67 (m, 1 H), 3.73 (s, 3 H), 2.45 (t, J = 6.0 Hz, 2 H), 1.34 (s, 9 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 158.6, 155.2, 136.2, 114.0, 78.2, 55.6, 51.5, 42.8, 28.7. IR (film): 3417, 3374, 3185, 2976, 2835, 1682, 1649, 1614, 1513, 1459, 1430, 1409, 1390, 1367, 1354, 1327, 1301, 1251 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{15}H_{22}N_2O_4Na$ $[M + Na]^+$ 317.1472; found 317.1477.

*tert-Butyl (3-Amino-3-oxo-1-phenylpropyl)carbamate (**11d**).* Prepared according to general procedure D using **5d** (1.0 g, 3.1 mmol, 1 equiv), aqueous hydroxylamine (0.246 mL, 3.72 mmol, 1.2 equiv), and MeOH (62 mL, 0.05 M) heated for 16 h at 70 °C. Following the reductive cleavage step, *tert*-butanol (3 mL, 1 M), di-*tert*-butyl carbonate (1.29 g, 5.93 mmol, 2 equiv), and 5 M NaOH (0.119 mL, 0.593 mmol, 0.2 equiv) were added. The precipitate was filtered to yield the product as a white solid (0.61 g, 74%). TLC R_f = 0.20 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29−7.09 (m, 5 H), 3.96−3.80 (m, 1 H), 2.50−2.38 (m, 2 H), 1.31 (s, 9 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 154.8, 142.5, 127.6, 125.6, 77.8, 51.1, 41.6, 27.1. IR (film): 3413, 3371, 3181, 2978, 1681, 1655, 1625, 1519, 1431, 1407, 1391, 1362, 1322, 1292, 1269, 1251 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{14}H_{20}N_2O_3Na$ $[M + Na]^+$ 287.1366; found 287.1372.

*tert-Butyl (syn-2-Carbamoylcyclopentyl)carbamate (**11e**).* Prepared according to general procedure D using **5w** (0.50 g, 1.73 mmol, 1 equiv), aqueous hydroxylamine (0.137 mL, 2.08 mmol, 1.2 equiv), and MeOH (35 mL, 0.05 M) heated for 4 h at 70 °C. Following the reductive cleavage step, *tert*-butanol (1.7 mL, 1 M), di-*tert*-butyl carbonate (0.745 g, 3.42 mmol, 2 equiv), and 5 M NaOH (0.068 mL, 0.342 mmol, 0.2 equiv) were added. This was concentrated and resubjected to protection conditions for 16 h. The precipitate was filtered to yield the product as a white solid (0.21 g, 52%). TLC R_f = 0.26 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 4.16−4.05 (m, 1 H), 2.96−2.83 (m, 1 H), 2.02−1.52 (m, 6 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, CD_3OD) δ 177.2, 156.2, 78.8, 54.1, 32.4, 27.7, 27.6, 22.2. IR (film): 3464, 1671, 1450, 1365 cm^{-1}. HRMS (ESI): exact mass calcd for $C_{11}H_{20}N_2O_3Na$ $[M + Na]^+$ 251.1366; found 251.1374.

Unsymmetrical azomethine imines from Table 7 (**12**) were synthesized according to general procedure A as described in a prior communication.[39]

*General Procedure F: Aminocarbonylation of Enol Ethers with Base Catalysis Conditions A (**3**).*[35] To an oven-dried vial was added hydrazone **4** (1.0−1.5 equiv), $PhCF_3$ (0.1 M), the enol ether (1.0−2.0 equiv), and then Et_3N (3 mol %). The vial was then sealed and purged with argon, and the reaction mixture was then heated for 1−3 h at 70 °C. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude mixture was purified by column chromatography over silica gel. The azomethine imine product (**3**) was isolated using silica gel column chromatography.

*General Procedure G: Pyrazolones from Azomethine Imines (**15**).*[35] To a round-bottom flask with a stir bar were added the azomethine imine (1 equiv) and methanol (0.02−0.05 M). If the azomethine imine is *syn*-disubstituted (e.g., **3q**), the reaction was cooled (−20 to 0 °C). Sodium borohydride (1−6 equiv) was added, and the mixture was stirred at room temperature until full conversion by TLC. The reaction was quenched with aq. NH_4Cl and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give the crude product. The product (**15**) was isolated after purification using trituration with EtOAc if necessary. For *syn*-disubstituted azomethine imines, the reaction was extracted with $CHCl_3$ and dried with Na_2SO_4; catalytic *p*-TsOH was added, and the mixture was heated at 60 °C for 3 h. Then, the product was isolated as described above.

*1-(9H-Fluoren-9-yl)-5-(4-methoxyphenyl)-1,2-dihydro-3H-pyrazol-3-one (**15b**).* As shown in eq 10, azomethine imine **5g** (0.060 g, 0.17 mmol) and 1-phenylethan-1-amine (0.2 mL, 1.6 mmol, 9 equiv) were combined in MeOH (3 mL) under argon, and the mixture was

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heated at reflux for 16 h. The crude mixture was filtered to isolate the product as a white solid precipitate (0.036 g, 60% yield). TLC R_f = 0.8 (Et_2O). This isomerization/aromatization was also observed with other amine bases. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.77 (br s, 1 H), 7.84 (d, J = 7.5 Hz, 2 H), 7.74−7.50 (m, J = 7.8 Hz, 2 H), 7.50−7.34 (m, 2 H), 7.34−7.19 (m, 4 H), 7.19−6.97 (m, J = 8.6 Hz, 2 H), 6.17 (s, 1 H), 5.69 (s, 1 H), 3.81 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.2, 159.6, 146.7, 143.5, 140.1, 130.3, 128.6, 127.5, 124.4, 122.7, 120.3, 114.5, 92.0, 62.2, 55.3. HRMS (EI): exact mass calcd for $C_{23}H_{18}N_2O_2$ $[M]^+$ 354.1368; found 354.1374.

The synthesis and characterization of **16a** and **16b** are described in a prior communication,[35] and the synthesis and characterization of **17a**, **17b**, **18**, and **19a** are described in another prior communication.[39]

*tert-Butyl (Z)-2-(1-Phenylhex-5-en-1-ylidene)hydrazine-1-carboxylate (**17c**).* 1-Phenylhex-5-en-1-one was synthesized according to Schore et al.[48d] A solution of ethyl benzoylacetate (14.41 mL, 83.2 mmol) in dry DMF (51 mL) was added dropwise via cannulation to a suspension of NaH (3.86 g, 96.6 mmol) in dry DMF (57 mL). The mixture was stirred for 1 h at rt. Homoallyl bromide (8.87 mL, 87.4 mmol) in dry DMF (22 mL) was then added dropwise, and the mixture was stirred for 20 h at rt. The reaction was quenched with H_2O and neutralized with 10% aq. HCl. The mixture was extracted 3× with EtOAc, and the combined organic layer was washed with 1:1 water/brine, dried with Na_2SO_4, and concentrated in vacuo. To the crude ethyl 2-benzoyl-5-hexenoate were added H_2O (3.35 mL, 184.0 mmol), LiBr (14.53 g, 167.3 mmol), and DMF (71 mL). The reaction mixture was heated at 200 °C for 72 h. The mixture was cooled, diluted with H_2O (125 mL), and extracted 3× with EtOAc. The combined organic layer was back washed with 1:1 water/brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (5% EtOAc/Hex) yielded 1-phenyl-5-hexen-1-one as an orange oil (3.25 g, 22% yield).

To the crude ketone (1.00 g, 5.7 mmol) in methanol (19 mL) was added *tert*-butyl carbazate (0.76 g, 5.7 mmol), and the mixture was stirred at reflux until consumption of the aldehyde by TLC. The product was directly recrystallized from the crude mixture. Title compound **17c** was obtained as a white solid (1.63 g, 99% yield, E/Z ratio = 1:1). TLC R_f = 0.25 in 5% EtOAc/95% hexane. ^{1}H NMR (400 MHz, $CDCl_3$, both isomers) δ 7.81−7.78 (m, 2H), 7.51−7.47 (m, 3H), 7.38−7.36 (m, 2H), 7.23−7.20 (m, 2H), 5.93−5.67 (m, 2H), 5.15−5.09 (m, 4H), 5.00−4.95 (m, 4H), 2.66−2.57 (m, 4H), 2.19−2.17 (m, 2H), 2.10−2.07 (m, 2H), 1.72−1.67 (m, 4H), 1.57 (s, 9H), 1.47 (s, 9H). ^{13}C NMR (400 MHz, CDCl3) δ 155.62 (C), 147.9 (C), 144.6 (C), 129.6 (C), 128.6 (CH), 126.9 (CH), 126.3 (CH), 114.9 (CH2), 80.7 (C), 37.7 (CH2), 33.19 (CH2), 28.31 (CH3), 24.9 (CH2). IR (film) 3188, 1726, 1699, 1537, 1269, 1252 cm^{-1}. HRMS (EI): exact mass calcd for $C_{17}H_{24}N_2O_2$ $[M]^+$ 288.1838; found 288.1822.

*2-Oxo-7-phenyl-2,3,3a,4,5,6-hexahydropyrazolo[1,5-a]pyridin-8-ium-1-ide (**19b**).* Hydrazone **17c** (0.15 g, 0.5 mmol) was diluted in $PhCF_3$ (10.4 mL) and heated at 160 °C for 6 h under microwave irradation. The crude mixture was purified by column chromatography using 10% MeOH/CH_2Cl_2. The product was obtained as a white solid (0.64 g, 58% isolated yield, 79% NMR yield using 1,4-dimethoxybenzene as an internal standard). TLC R_f = 0.29 in 7% MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.02 (m, 2H), 7.45−7.42 (m, 3H), 4.4 (br d, J = 8.9 Hz, 1H), 3.14−3.00 (m, 2H), 2.93−2.87 (m, 1H), 2.65−2.58 (m, 1H), 2.46−2.41 (m, 1H), 2.11−1.96 (m, 2H), 1.88−1.82 (m, 1H). ^{13}C NMR (400 MHz, CDCl3) δ 181.7 (C), 145.5 (C), 132.4 (C), 131.1 (CH), 129.4 (CH), 128.3 (CH), 65.9 (CH), 36.7 (CH2), 28.8 (CH2), 27.3 (CH2), 18.3 (CH2). IR (film) 1655, 1651, 1587, 1568, 1446, 1328 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{14}N_2O$ $[M]^+$ 214.1106; found 214.1128.

The synthesis and characterization of **13b**[32a] and **13d** and **13e**[39] are described in prior communications.

*5-Phenyl-1-(2-(thiophen-2-yl)but-3-en-2-yl)pyrazolidin-3-one (**13c**).* Azomethine imine **12p** (0.14 g, 0.5 mmol) was dissolved in dry THF (2.5 mL) in a flame-dried round bottomed flask purged with argon. The flask was cooled in an ice bath at 0 °C, and a solution of vinylmagnesium bromide in THF (0.7 M, 2.14 mL, 1.5 mmol) was added dropwise. The flask was removed from the ice bath and left to stir for 1 h. The reaction mixture was quenched using saturated aq. NH_4Cl and extracted 3× with EtOAc, and the combined organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The reaction mixture was purified by silica gel chromatography. The product was obtained as an orange oil (0.090 g, 62% yield, >20:1 dr). TLC R_f = 0.30 in 60% EtOAc/hexanes. ^{1}H NMR (400 MHz, C_6D_6) δ 7.23−7.21 (m, 2H), 7.12−7.04 (m, 3H), 6.83−6.80 (m, 2H), 6.68−6.65 (m, 1H), 6.08 (dd, J = 17.5 Hz, 10.9 Hz, 1H), 5.14 (dd, J = 17.5 Hz, 0.9 Hz, 1H), 4.97 (dd, J = 10.9 Hz, 0.9 Hz, 1H), 4.32 (dd, J = 9.6 Hz, 1.8 Hz, 1H), 2.33 (dd, J = 16.9 Hz, 9.6 Hz, 1H), 1.97 (dd, J = 16.8 Hz, 2.1 Hz, 1H), 1.47 (s, 3H). ^{13}C NMR (400 MHz, C_6D_6) δ 174.9 (C), 146.9 (C), 144.4 (C), 141.3 (CH), 128.9 (CH), 126.9 (CH), 126.4 (CH), 125.9 (CH), 125.8 (CH), 116.5 (CH2), 67.7 (CH), 60.9 (C), 39.2 (CH2), 24.8 (CH3). IR (film) 3168, 3066, 2985, 1685, 1558, 1494, 1448, 1417, 1373, 1242 cm^{-1}. HRMS (EI): exact mass calcd for $C_{17}H_{18}N_2OS$ $[M]^+$ 298.1140; found 298.1153.

*General Procedure H: Cascade Aminocarbonylation and Dipolar Cycloaddition,[23,48d] including 2,11-Diphenyloctahydro-5H-6,9-methanopyrrolo[3′,4′:3,4]pyrazolo[1,2-a]indazole-1,3,5(2H,3aH)-trione (**20b**).* Hydrazone **1o**[39] (0.070 g, 0.290 mmol, 1 equiv), norbornene (0.27 g, 2.9 mmol, 10 equiv), *N*-phenyl maleimide (0.50 g, 2.9 mmol, 10 equiv), and $PhCF_3$ (6 mL, 0.05 M) were combined in a 10−20 mL microwave vial. The reaction was heated at 120 °C for 12 h. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure, and analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. The product was purified by column chromatography and obtained as a yellow solid (0.179 g, 61%, >20:1 dr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.61 (m, 10H), 4.63 (d, J = 7.5 Hz, 1H), 3.91 (d, J = 6.7 Hz, 1H), 3.60 (t, J = 7.12 Hz, 1H), 3.08 (d, J = 7.64 Hz, 1H), 2.80 (d, J = 7.64 Hz, 1H), 2.64 (br s, 1H), 2.32 (br s, 1H), 1.85 (d, J = 10.62 Hz, 1H), 1.37−1.65 (m, 2H), 1.11−1.32 (m, 3H), 0.99 (d, J = 10.24 Hz, 1H), 0.87 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (C), 172.7 (C), 167.7 (C), 137.0 (C), 131.3 (C), 129.1 (2CH), 129.0 (2CH), 128.8 (CH), 128.7 (CH), 127.5 (2CH), 126.4 (2CH), 73.2 (CH), 66.4 (CH), 57.1 (CH), 56.8 (CH), 52.7 (CH), 42.7 (CH), 39.7 (CH), 33.6 (CH2), 27.8 (CH2), 25.1 (CH2). IR (film) 3067, 2959, 2878, 2367, 2331, 1778, 1699, 1373, 1184, 1095 cm^{-1}. HRMS (EI): exact mass calcd for $C_{25}H_{23}N_3O_3$ $[M]^+$ 413.17394; found 413.17420.

Compound **20a** was synthesized according to general procedure H and characterized in a prior communication.[39]

*11-(Furan-2-yl)-2-phenyloctahydro-5H-6,9-methanopyrrolo-[3′,4′:3,4]pyrazolo[1,2-a]indazole-1,3,5(2H,3aH)-trione (**20c**).* This compound was synthesized according to general procedure H using **1m**[39] (0.069 g, 0.30 mmol), norbornene (0.28 g, 3.0 mmol, 10 equiv), and *N*-phenyl maleimide (0.52 g, 3.0 mmol, 10 equiv) in $PhCF_3$ (6 mL). The reaction was heated at 120 °C for 6 h. The product was isolated by column chromatography (40:60 hexane/EtOAc) as an off-white solid (0.046 g, 38% yield). TLC R_f = 0.22 in 60% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) 7.30−7.55 (m, 5 H), 6.38−6.44 (m, 1 H), 6.33 (d, J = 3.16 Hz, 1 H), 5.26 (d, J = 7.70 Hz, 1 H), 4.68 (s, 1 H), 3.78 (d, J = 9.0 Hz, 1 H), 3.04 (d, J = 6.0 Hz, 1 H), 2.49 (br s, 1 H), 2.33 (br s, 1 H), 2.25 (br s, 1 H), 1.94 (d, J = 7.57 Hz, 1 H), 1.76 (d, J = 10.73 Hz, 1 H), 1.38−1.58 (m, 2 H), 1.15 (d, J = 10.73 Hz, 1 H), 0.94−1.10 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) 174.7 (C), 174.3 (C), 171.0 (C), 148.8 (C), 143.8 (CH), 131.3 (C), 129.2 (CH), 128.9 (CH), 126.4 (CH), 111.2 (CH), 111.0 (CH), 63.5 (CH), 61.9 (CH), 55.0 (CH), 52.5 (CH), 51.3 (CH), 39.4 (CH), 33.6 (CH2), 27.7 (CH2), 25.4 (CH2). IR (film) 2959, 2874, 2363, 2327, 1715, 1385, 1200, 1092 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{21}N_3O_4$ $[M]^+$ 403.1532; found 403.1537.

*Dimethyl 5′-Oxo-7′-ferrocenyl-6′,7′-dihydro-5′H-spiro[fluorene-9,1′-pyrazolo[1,2-a]pyrazole]-2′,3′-dicarboxylate (**20d**).* This compound was synthesized according to general procedure H using **4** (0.094 g, 0.30 mmol), vinyl ferrocene (0.64 g, 0.3 mmol, 1 equiv), and dimethyl acetylenedicarboxylate (0.42 g, 3.0 mmol, 10 equiv) in $PhCF_3$ (6 mL). The reaction was heated at 120 °C for 6 h. The product was obtained as a yellow solid (0.084 g, 49% yield). TLC R_f = 0.33 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) 7.70 (d, J

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= 7.43 Hz, 1 H), 7.42−7.53 (m, 4 H), 7.39 (d, J = 7.43 Hz, 1 H), 7.08−7.26 (m, 2 H), 4.08−4.20 (m, 1 H), 4.04 (s, 3 H), 3.92 (s, 5 H), 3.84 (d, J = 7.29 Hz, 2 H), 3.61 (br s, 1 H), 3.35 (s, 3 H), 3.20 (d, J = 11.97 Hz, 1 H), 3.06 (d, J = 7.43 Hz, 1 H), 2.85 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) 162.4 (C), 161.7 (C), 159.6 (C), 145.3 (C), 140.8 (C), 140.0 (C), 139.4 (C), 133.8 (C), 130.2 (CH), 128.8 (CH), 127.7 (CH), 127.2 (CH), 125.7 (CH), 125.2 (CH), 120.6 (CH), 119.3 (CH), 118.5 (C), 81.7 (C), 78.4 (C), 68.9 (CH), 68.3 (CH), 68.2 (2 CH3), 67.3 (CH), 65.2 (2 CH), 57.4 (CH), 53.6 (2 CH), 51.6 (2 CH), 42.7 (CH2). IR (film) 1751, 1714, 1606, 1429, 1348, 1260, 1219, 740, 427 cm^{-1}. HRMS (EI): exact mass calcd for $C_{32}H_{26}N_2O_5Fe$ $[M]^+$ 574.1191; found 574.11871.

*Dimethyl 9′-Oxo-4a′,5′,7′,8′,8a′,9′-hexahydro-6′H-spiro-[fluorene-9,3′-[5,8]methanopyrazolo[1,2-a]indazole]-1′,2′-dicarboxylate (**20e**).* This compound was synthesized according to general procedure H using **4** (0.094 g, 0.30 mmol), norbornene (0.28 g, 3.0 mmol, 10 equiv), and dimethyl acetylenedicarboxylate (0.43 g, 3.0 mmol, 10 equiv) in $PhCF_3$ (6 mL). The reaction was heated at 120 °C for 6 h. The product was isolated by column chromatography (80:20 to 70:30 hexane/EtOAc) as a yellow solid (0.101 g, 74% yield). TLC R_f = 0.32 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) 7.57−7.80 (m, 3 H), 7.20−7.57 (m, 5 H), 4.00 (s, 3 H), 3.37 (s, 3 H), 2.54−2.83 (m, 3 H), 1.85 (d, J = 10.73 Hz, 1 H), 1.70 (d, J = 4.13 Hz, 1 H), 1.33−1.56 (m, 1 H), 1.12−1.29 (m, 2 H), 0.93−1.11 (m, 1 H), 0.66 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), 168.4 (C), 161.8 (C), 159.8 (C), 144.9 (C), 141.3 (C), 140.6 (C), 140.2 (C), 134.9 (C), 130.2 (CH), 129.4 (CH), 128.1 (CH), 128.0 (CH), 125.3 (CH), 124.6 (CH), 120.9 (C), 120.5 (CH), 119.8 (CH), 80.7 (C), 62.1 (CH), 56.3 (CH), 53.5 (CH3), 51.7 (CH3), 43.4 (CH), 39.9 (CH), 34.3 (CH2), 28.2 (CH2), 23.5 (CH2). IR (film) 3064, 2955, 2875, 1736, 1611, 1422, 1394, 1338, 1257 cm^{-1}. HRMS (EI): exact mass calcd for $C_{27}H_{24}N_2O_5$ $[M]^+$ 456.1685; found 456.16747.

*2′-Phenyloctahydro-1′H,5′H-spiro[cyclopentane-1,11′-[6,9]-methanopyrrolo[3′,4′:3,4] pyrazolo[1,2-a]indazole]-1′,3′,5′(2′H)-trione (**20f**).* This compound was synthesized according to general procedure H using **1c**[23] (0.059 g, 0.30 mmol), norbornene (0.282 g, 3.0 mmol, 10 equiv), and *N*-phenyl maleimide (0.52 g, 3.0 mmol, 10 equiv) in $PhCF_3$ (6 mL). The reaction was heated at 120 °C for 6 h. The product was isolated by column chromatography (70:30 to 80:20 hexane/EtOAc) as a brown solid (0.028 g, 24% yield). TLC R_f = 0.37 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) 7.35−7.56 (m, 3 H), 7.26−7.35 (m, 2 H), 4.78 (d, J = 8.80 Hz, 1 H), 3.88 (d, J = 8.94 Hz, 1 H), 3.16 (d, J = 8.67 Hz, 1 H), 2.91 (d, J = 8.67 Hz, 1 H), 2.70 (br s, 1 H), 2.24 (br s, 1 H), 2.03−2.22 (m, 2 H), 1.09−2.03 (m, 14 H). ^{13}C NMR (75 MHz, $CDCl_3$) 172.3 (C), 167.6 (C), 165.2 (C), 130.9 (C), 129.2 (2 CH), 128.9 (CH), 126.3 (2 CH), 73.3 (C), 60.8 (CH), 59.0 (CH), 56.7 (CH), 54.4 (CH), 43.7 (CH), 39.5 (CH), 36.7 (CH2), 34.2 (CH2), 28.1 (CH2), 27.0 (CH2), 26.4 (CH2), 24.6 (CH2), 24.3 (CH2). IR (film) 2971, 2874, 2359, 2331, 1723, 1381, 1091 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{25}N_3O_3$ $[M]^+$ 391.1896; found 391.1918.

IR Study. Liquid measurement FTIR spectrometer with flow cell (100 um, ZnSe). The analysis was performed in a glovebox for control of moisture and oxygen. A flow IR instrument equipped with an injector was used, which is designed for analysis of liquid solutions and reaction mixtures. Procedure: Hydrazone **1f** in toluene (0.05 M) was first injected at room temperature with and without triethylamine, and the spectra showed significant differences. The mixture of **1f** and Et_3N was then heated to 90 °C, and samples of the reaction mixture were injected into the detector. For detecting reactive intermediates, the samples were immediately analyzed before the mixture cooled. Upon heating, the colorless mixture became dark orange. The first sample after 17 min at 90 °C showed a new peak at 2201 cm^{-1}. This peak became more prominent in the analysis at 60 min (see Figure 8).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02713.

Optimization tables, X-ray ellipsoid plots of compounds **2f**, **3f**, **5a**, **5r**, **5ab**, **12j**, **18**, and **20a**, and NMR spectra for all new compounds (PDF)

X-ray crystallographic file of **5r** (CIF)

X-ray crystallographic file of **5ab** (CIF)

X-ray crystallographic file of **12j** (CIF)

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Notes

The authors declare no competing financial interest.

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