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Direct Regioselective γ-Amination of Enones

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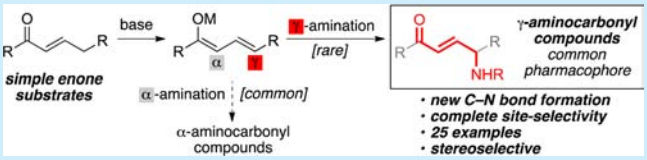
Supporting Information

ABSTRACT: Carbonyl compounds bearing a γ-amino group are valuable pharmacologically active targets. Regioselective γ-C−N bond formation is achieved with simple enone substrates through controlled dienolate reactivity toward azodicarboxylate electrophiles. The amination reaction occurs readily with sterically demanding nucleophiles and is stereoselective.



Whereas significant effort has been directed toward the synthesis of aminocarbonyl compounds bearing α- and β-relationships,[1] the range of available transformations that generate a C−N bond at the γ-position relative to the carbonyl remain limited. This shortage of reliable synthetic transformations stands as a significant limitation to access the many biologically active natural products bearing amino groups at this site efficiently (Figure 1), including the important class

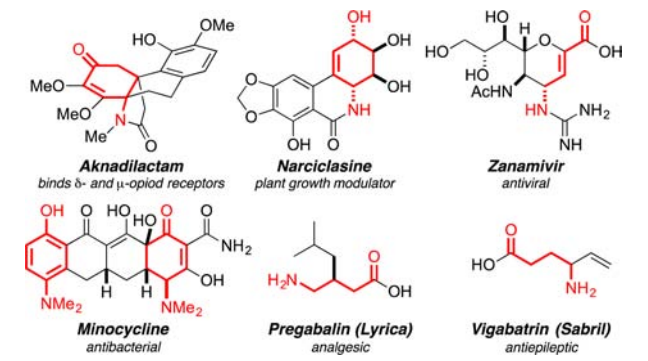
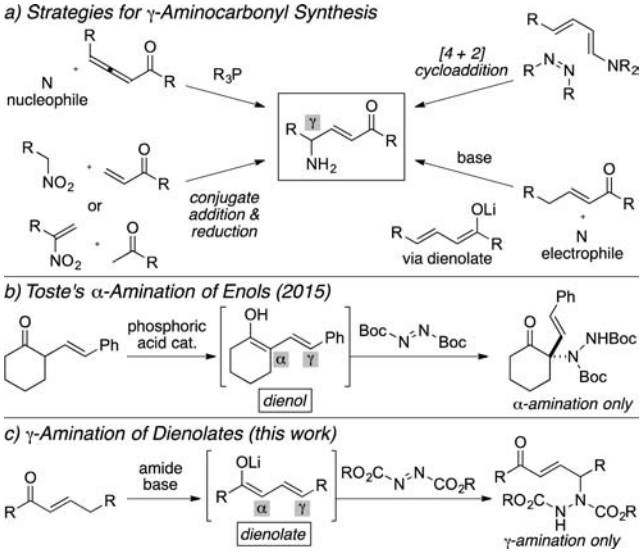


Figure 1. Bioactive molecules containing a γ-amino group.

of γ-aminobutyric acid (GABA) modulators.[2] Existing γ-aminocarbonyl syntheses include phosphine-catalyzed γ-activation of allenoates,[3] conjugate additions with acrylates or nitroalkenes,[4] and [4 + 2]-cycloadditions of azo and nitroso compounds[5] (Scheme 1a), each with specific substrate limitations. Although α-C−N bond formation via enol or enolate intermediates is well-established,[1a,6] the corresponding γ-reactivity of dienolates or comparable synthons is uncommon and limited in scope.[7] This approach to γ-aminoketones is complicated by competing, and often prevailing, α-amination of the dienol (e.g., Scheme 1b).[8] The scope of the few γ-selective amination reactions is limited, notably excluding simple ketones and many cyclic systems, and thus, γ-amination remains a significant unsolved synthetic problem. In light of these challenges, we have sought to develop a general, site-selective γ-amination reaction employing simple enone substrates.

We have recently undertaken a research program aimed at better understanding of the reactivity of dienolate systems and

Scheme 1. Amination Reactions of Dienolates



their derivatives.[9] Under carefully optimized reaction conditions, we have discovered that selective γ-halogenation of vinylogous esters[10] may be achieved en route to haloresorcinol derivatives.[9a] Whereas γ-oxidation reactions of dienolates are uncommon, and the generality of our system is unproven,[9a,11] we have sought to develop this area further toward the greater synthetic challenge of nonaromatic compounds. Herein, we disclose the first controlled γ-C−N bond formation protocol suitable for the synthesis of ketone-derived γ-aminocarbonyl systems.

We selected vinylogous ester **1a** to explore our hypothetical C−N bond formation (Table 1). The extended enolates derived from these substrates presumably benefit from increased nucleophilicity at the γ-C owing to the addition of an electron-donating group affixed to the π-system.[9a,10] Our prior studies found that polar additives such as hexamethylphosphoramide (HMPA) dramatically influence regioselectivity

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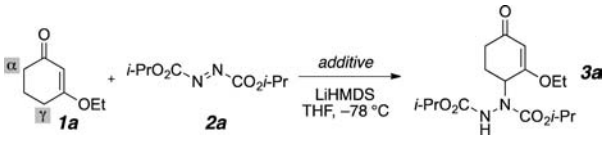
Table 1. Optimization of Reaction Conditions[a]



entry	additive	equiv	α/γ ratio	entry	additive	equiv	α/γ ratio
1	none		12:1	7	DMPU	2.5	1:8
2	TMEDA	2.5	3:1	8	DMPU	5.0	1:10
3	DMI	2.5	1.3:1	9	DMPU	10.0	1:25
4	$(EtO)_3PO$	2.5	1:1.4	10	DMPU	15.0	1:35
5	Ph_3PO	2.5	1:5	11	DMPU	18.0	1:50
6[b]	**HMPA**	**2.5**	**0:1**	**12**[c]	**DMPU**	**20.0**	**0:1**

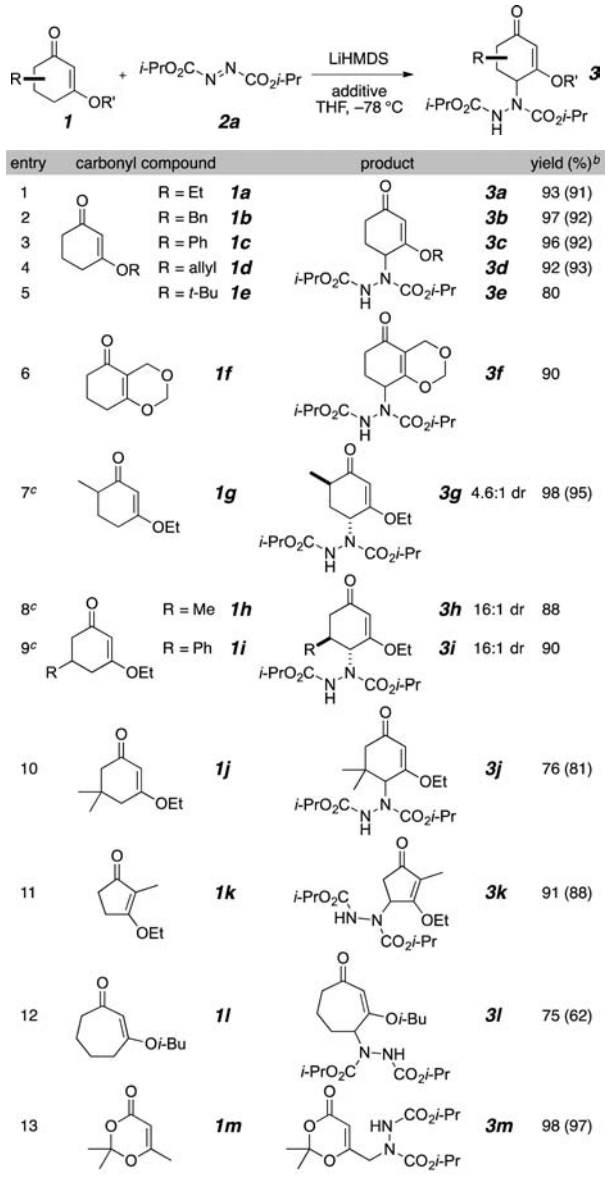
[a]Reaction performed with 0.5 mmol of vinylogous ester **1a**, DIAD (**2a**, 1.25 equiv), LiHMDS (0.99 equiv), and additive in THF (7 mL) at −78 °C for 5 min. The α/γ ratio was determined by ^{1}H NMR of the crude product. [b]93% isolated yield of **3a**. [c]91% isolated yield of **3a**. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DMI = 1,3-dimethylimidazolidin-2-one; DMPU = *N*,*N*′-dimethylpropyleneurea.

in these dienolate transformations.[12] We predicted that the electronics of the *N*-electrophile would be critical to regiocontrol in our system, leading us to select azodicarboxylates where modification of the carboxylate moiety could influence reactivity. Generation of the dienolate at low temperature followed by addition of diisopropylazodicarboxylate (DIAD, **2a**) was examined in the presence of a number of polar additives (entries 1−6). The proportion of the desired γ-adduct varied widely, with HMPA delivering the γ-aminoketone exclusively. Comparable regioselectivity was possible using DMPU, although significantly greater quantities were required as in earlier reports of substituting this additive for HMPA (entries 7−12).[12b,13]

A diverse set of vinylogous ester substrates (**1**) function in our amination reaction (Table 2). Excellent yields are observed for various oxygen substituents, including sterically demanding *tert*-butyl esters, with no evidence of competing amination elsewhere in the molecule (entries 1−5).[14] This high selectivity was maintained across many substrates when DMPU was used as the polar additive in place of HMPA. Substitutions about the six-membered ring do not perturb the transformation, and even neopentylic amines (e.g., **3j**) are accessible in high yield (entries 6−10). The presence of stereocenters around the ring influences the configuration of the aminated carbon substantially, although the effect is less pronounced when the existing asymmetric center is more remote (entries 7−9). Both cyclopentanone and cycloheptanone derivatives are also viable amine precursors (entries 11 and 12). Amination achieved at an exocyclic site when vinylogous carbonate **1m** is engaged in the amination, delivering near quantitative yield of hydrazide **3m**. The successful amination of a dienolate constrained in an *s-trans* conformation notably precludes the [4 + 2]-cycloaddition mechanism suggested for some related transformations.[5]

We sought to expand the scope of our protocol to enones lacking the β-alkoxy group that was integral to our initial regiocontrol hypothesis (Table 3). As an initial test, we employed unsubstituted cyclohexenone (**4**) under our typical reaction conditions. This simple substrate performed exceptionally well when moderately higher reaction concentration was employed, and the corresponding amination product (**5**) was isolated in 90% yield (entry 1). Using DMPU as the polar additive led to a somewhat lower yield but maintained the

Table 2. Scope of Vinylogous Esters[a]



[a]Isolated yield (average of two runs) from reaction of 0.5 mmol of vinylogous ester **1a**, DIAD (**2a**, 1.25 equiv), LiHMDS (0.99 equiv), and HMPA (2.5 equiv) as additive in THF (7 mL) at −78 °C for 5 min. [b]The value in parentheses is the isolated yield for reaction with DMPU (20 equiv) in place of HMPA. [c]The dr was determined by ^{1}H NMR of the crude reaction mixture, and the configuration was assigned by NOE experiments on purified product.

desired regioselectivity. Stereoselectivity with 6-benzylcyclohexenone was comparable to the vinylogous ester case (entry 2). Isophorone (**9**) and verbenone (**11**) were each aminated in excellent yield, and DMPU could be substituted for HMPA with minimal effect on overall efficiency (entries 4 and 5). Octalone **13** undergoes amination with high diastereoselectivity, delivering hydrazine derivative **14** as a single isolated diastereomer (entry 6). Acyclic α,β-unsaturated carbonyls were also explored: ethyl crotonate (**15**) and aliphatic enone **17** each performed well in the reaction (entries 7 and 8).

We next examined a range of azo electrophiles bearing various carboxylate moieties (entries 1−4, Table 4). These *N*-electrophiles performed well even when sterically demanding

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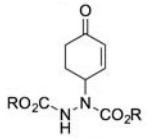
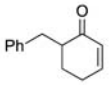
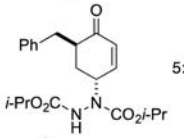
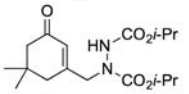
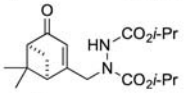
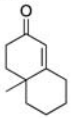
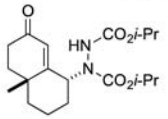
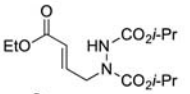
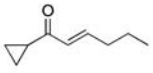
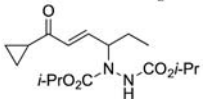
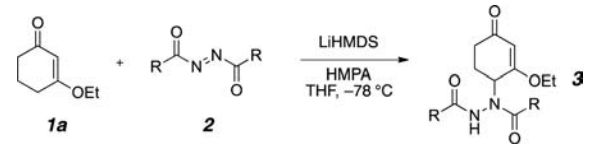
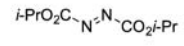
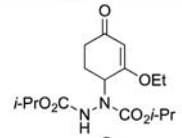
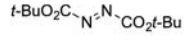
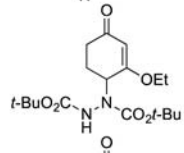
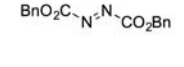
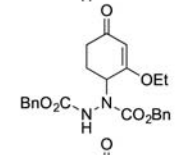
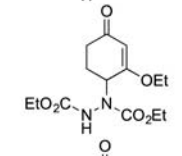
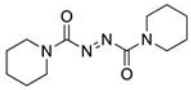
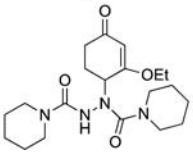
Table 3. Amination of Simple Enones and Enoates[a]

entry	enone compound		product		yield (%)[b]
1		**4**	 R = *i*-Pr	**5**	90 (75)
2[c]		**4**	R = *t*-Bu	**6**	82
3[d]		**7**	 5:1 dr	**8**	82
4		**9**		**10**	95 (97)
5		**11**		**12**	94 (92)
6[d]		**13**		**14**	62
7		**15**		**16**	78
8		**17**		**18**	56

[a]Isolated yield (average of two runs) from reaction of 0.5 mmol of vinylogous ester **1a**, DIAD (**2a**, 1.25 equiv), LiHMDS (0.99 equiv), and HMPA (2.5 equiv) in THF (3 mL) at −78 °C for 5 min. [b]The value in parentheses is the isolated yield for reaction with DMPU (20 equiv) in place of HMPA. [c]Di(*tert*-butyl)azodicarboxylate (**2b**) was used in place of DIAD. [d]The dr was determined by ^{1}H NMR of the crude reaction mixture and the configuration was assigned by NOE experiments on purified product.

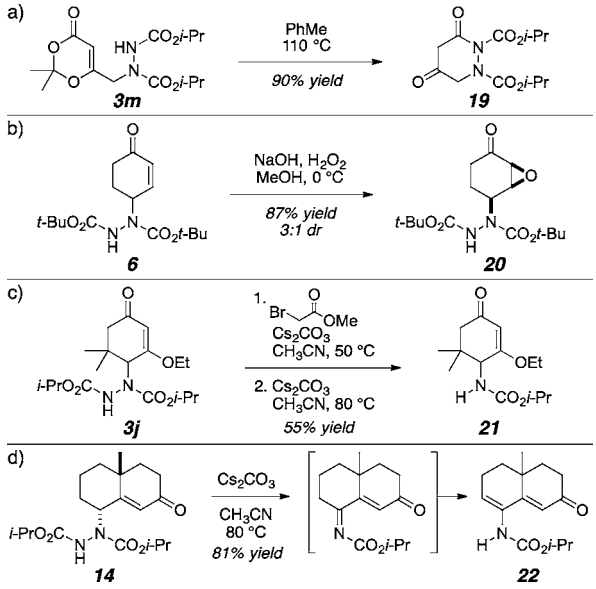
Table 4. Scope of Azodicarboxylates[a]



entry	azo compound		product		yield (%)
1		**2a**		**3a**	93
2		**2b**		**3n**	94
3		**2c**		**3o**	84
4		**2d**		**3p**	96
5		**2e**		**3q**	82

[a]Isolated yield (average of two runs) from reaction of 0.5 mmol of vinylogous ester **1a**, azodicarboxylate **2** (1.25 equiv), LiHMDS (0.99 equiv), and HMPA (2.5 equiv) in THF (7 mL) at −78 °C for 5 min.

Scheme 2. Synthetic Applications of Hydrazide Products



tert-butyl groups were present. An azodicarbonamide participated in the reaction with comparable results as well, indicating a measure of electronic flexibility in the electrophile (entry 5).

Turning to the use of our hydrazine derivatives, hydrazide **3m** was transformed into hexahydropyridazine **19** under thermal conditions, presumably proceeding through a ketene intermediate (Scheme 2a).[15] Aminated enone **6** undergoes directed alkene epoxidation with moderate diastereoselectivity (Scheme 2b). Cleavage of the hydrazine N−N bond is achieved by alkylation of the N−H functional group of enone **3j** and subsequent basic elimination to furnish *N*-protected γ-amino ketone **21** (Scheme 2c).[16] In a related transformation, the N−N bond is cleaved directly by exposure of amination product **14** to basic conditions, likely through an E1cb-type mechanism forming conjugated enecarbamate **22** in good yield (Scheme 2d).[16] This transformation is notable as an overall double oxidation of the γ-carbon.

In conclusion, we have developed a versatile system for regiocontrolled synthesis of γ-amino carbonyl compounds via reactive dienolate intermediates. This method represents the first direct γ-amination of ketone-derived dienolates. Our protocol utilizes commercially available reagents, proceeds in high yield, and exhibits good stereoselectivity. The scope of the transformation suggests that, unlike several related methods, a different mechanism of bond formation is likely operative and as a result a significantly increased range of γ-amino carbonyl compounds are accessible. The hydrazide products are versatile synthetic building blocks, and we anticipate that this straightforward method will significantly contribute to target-directed synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03689.

Experimental procedures and characterization data (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) We define "vinylogous ester" as a 3-alkoxyenone owing to the similarity in electronic structure between these and simple esters. For a review of the vinylogy concept, see: Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1−27.

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