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[3 + 2]-Cycloadditions of Azomethine Imines and Ynolates

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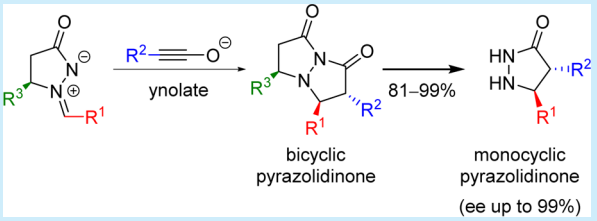
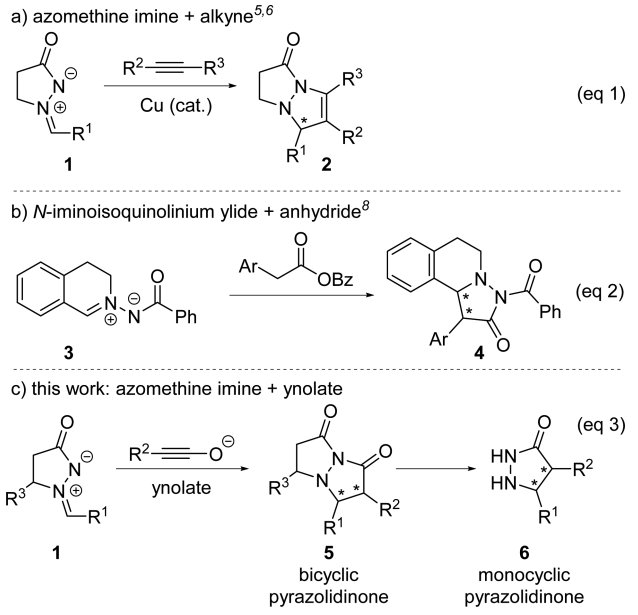
Supporting Information

ABSTRACT: A novel [3 + 2]-cycloaddition between azomethine imines and lithium ynolates is described to synthesize bicyclic pyrazolidinones. These bicyclic pyrazolidinones are versatile intermediates to form β-amino acids and monocyclic pyrazolidinones. High diastereoselectivity and stereospecificity allow access to optically active products.



1,3-Dipolar cycloadditions are useful reactions to synthesize five-membered heterocycles with high stereo- and regioselectivity in a single step.[1] A useful dipole for dipolar cycloadditions is the azomethine imine **1** due to its facile synthesis and benchtop stability.[2] Azomethine imines react with various dipolarophiles including olefins, alkynes, enones, isocyanides, and allenes to provide dinitrogen heterocycles.[3,4] Recently, Cu-catalyzed cycloadditions of alkynes with azomethine imines have been described. They involved either copper acetylides[5] or Lewis acid activation of alkynyl ketones[6] to form 3-pyrazolines **2** (Scheme 1, eq 1). These cycloadditions generate a new heterocyclic ring and one new stereocenter on the pyrazolines. Additionally, Studer and co-workers showed that the *N*-iminoisoquinolinium ylide **3** could participate in a [3 + 2]-cycloaddition with ketenes generated in situ (Scheme 1, eq 2).[7,8] These reactions involved *N*-heterocyclic carbene catalysts and formed pyrazolidinones **4** in high ee. However, the reaction is limited to forming isoquinoline-derived adducts.[8,9]

Scheme 1. Representative [3 + 2]-Cycloadditions of Azomethine Imines or *N*-Iminoisoquinolinium Ylides To Synthesize 3-Pyrazolines and Pyrazolidinones



Here, we report a general synthesis of pyrazolidinones involving a [3 + 2]-cycloaddition of azomethine imines with lithium ynolates[10,11] (Scheme 1, eq 3). Compared to previous cycloadditions between alkynes and azomethine imines, this transformation provides bicyclic pyrazolidinones **5**, which are at a higher oxidation state than the pyrazolines **2**. Moreover, the cycloaddition sets two contiguous stereocenters with high stereoselectivity. Additionally, our reaction design envisioned removing the three-carbon chain from the initial azomethine imine to form disubstituted pyrazolidinone products **6**. We reasoned that this strategy might enable a general enantioselective synthesis of pyrazolidinones **6** by starting with optically active azomethine imines (Scheme 1, eq 3, $R^3 \neq H$). In turn, we anticipated that the heterocyclic products could be useful in drug discovery given the high percentage of pharmaceutical agents that contain nitrogen heterocycles.[12] Indeed, pyrazolidinones are substructures within compounds displaying diverse biological properties.[13] Finally, optically active pyrazolidinones have found use as organocatalysts in Diels–Alder reactions[14] and in kinetic resolutions,[15] rendering methods for their synthesis valuable.

For our initial experiments, azomethine imine **1a** was exposed to a lithium ynolate that was synthesized from phenylacetylene in a three-step, two-pot procedure[16] (Table 1). Specifically, lithium phenylacetylene was prepared and added to premade lithium *tert*-butyl peroxide (*t*-BuOOLi) to generate the ynolate. By quenching the cycloaddition with $NaHCO_3$, the desired bicyclic pyrazolidinone **8** was isolated, albeit in 30–40% yields (data not shown). However, despite the low yields, the reaction afforded bicycle **8** with 90:10

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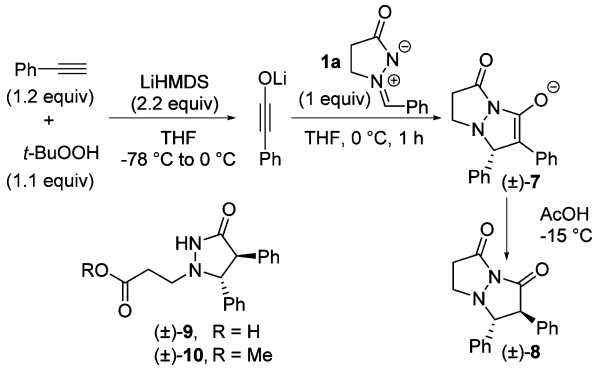
Table 1. Optimization of the [3 + 2]-Cycloaddition of 1a[a]



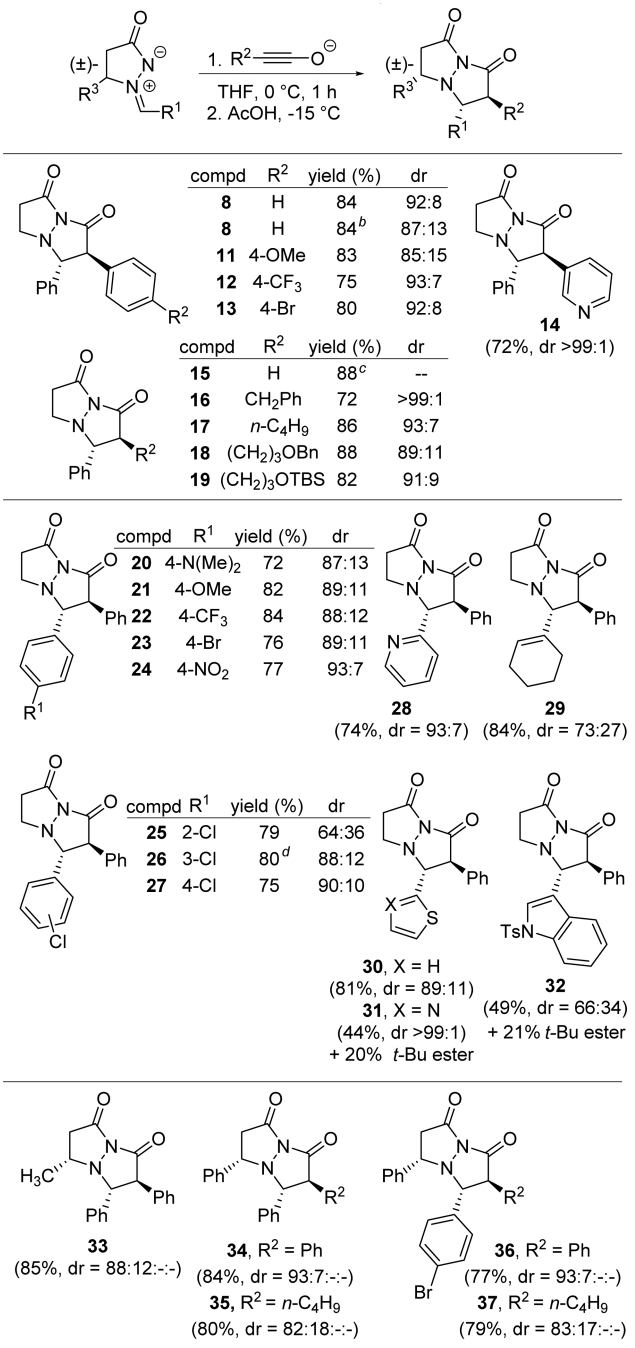
entry	variation from the "standard" conditions	yield of **8** (%)[b]
1	two pot: lithium phenylacetylide + *t*-BuOOLi instead of in situ formation	77
2	none	84
3	*n*-BuLi instead of LiHMDS	68
4	LDA instead of LiHMDS	66
5	1.2 equiv of *t*-BuOOH	58
6	1.2 equiv of azomethine imine	81
7	quench with $NaHCO_3$ instead of AcOH	54
8	quench with 1 M HCl instead of AcOH	58
9	quench with H_2O instead of AcOH	1
10	quench with MeOH instead of AcOH	3

[a]The reaction was conducted at 0.3 mmol. [b]Isolated yield.

diastereoselectivity favoring the trans configuration. The initial product was likely enolate **7**, which could have formed from either a stepwise or concerted process.[17] Protonation of the enolate upon workup afforded imide **8** and set the relative stereochemistry. To improve the yield, we optimized the quenching protocol to use acetic acid, and we modified the stoichiometry of phenylacetylene, *t*-BuOOH,[18] and LiHMDS to obtain pyrazolidinone **8** in 77% yield (Table 1, entry 1). While the three-step, two-pot ynolate procedure worked well, we developed a more convenient one-pot protocol with an improved yield (84%) (Table 1, entry 2). Thus, under optimized conditions, phenylacetylene and *t*-BuOOH were combined and treated with LiHMDS to form the ynolate in situ. Subsequent addition to azomethine imine **1a** yielded the cycloadduct **8** after quenching under mildly acidic conditions. When *n*-BuLi or LDA was used as the base instead of LiHMDS, the yield decreased due to incomplete conversion (Table 1, entries 3 and 4). Excess *t*-BuOOH decreased the yield substantially (Table 1, entry 5), while excess azomethine imine had no effect (Table 1, entry 6). We hypothesized that excess *t*-BuOOH provided a surplus of *t*-BuOOLi, which decreased the yield by reacting with enolate **7** and product **8**. Therefore, the precise stoichiometry of *t*-BuOOH was imperative for high yields.[18] Quenching with basic, acidic, or neutral aqueous solutions hydrolyzed the imide bond to form byproduct **9** (Table 1, entries 7–9). When methanol was used, methyl ester **10** was formed. Therefore, it was essential to use an acidic, nonaqueous reagent such as acetic acid to quench both the enolate and the lithium *tert*-butoxide.

With an optimized procedure for the [3 + 2]-cycloaddition, we next evaluated the scope of the method by examining various alkynes and aomethine imines (Scheme 2). Electron-donating, -withdrawing, and -neutral aromatic alkynes provided bicyclic pyrazolidinones in high yields and diastereoselectivities

Scheme 2. Substrate Scope of [3 + 2]-Cycloaddition[a]



[a]0.5 mmol scale reaction. Experimental details in Supporting Information. Yield of isolated product and the average of two experiments unless otherwise noted. Dr determined by ^{1}H NMR. [b]5 mmol scale. [c]From ethynyltrimethylsilane. [d]2 h for cycloaddition.

(**8**, **11**–**13**, 75–84%). The ynolate derived from 3-ethynylpyridine generated cycloadduct **14** in good yield and dr >99:1. Ethynyltrimethylsilane afforded the monosubstituted bicyclic pyrazolidinone **15** in 88% yield. In addition, the reaction proceeded smoothly with aliphatic alkynes, including those containing protected alcohols (**16**–**19**). After determining that aliphatic, aromatic, and pyridyl alkynes worked well in the [3 + 2]-cycloaddition, we next turned to varying the azomethine imine. The transformation tolerates a wide range of electronics for aromatic substituents on the azomethine imine, from

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strongly electron-donating (**20**, 4-NMe_2, 72%) to strongly electron-withdrawing (**24**, 4-NO_2, 77%) (**20**–**24**). *Ortho*-, *meta*-, and *para*-chloro substitution was tolerated (**25**–**27**, 75–80%), with the diastereoselectivity decreasing for the dipole derived from *o*-chlorobenzaldehyde due to sterics. Bicyclic pyrazolidinones with 2-pyridyl **28**, cyclohexene **29**, and thiophene **30** were isolated in good yields, while heteroaromatics (thiazole **31**, indole **32**) were isolated along with their respective *tert*-butyl esters. Aliphatic azomethine imines are not suitable reaction partners currently. The cycloaddition is scalable, with identical yields obtained on both 0.5 and 5 mmol scales (see pyrazolidinone **8**).

Next, we examined 5-substituted azomethine imines (R^3 = phenyl or methyl) in the cycloaddition. These dipoles provided bicyclic pyrazolidinones **33**–**37** in excellent yields and high diastereoselectivities. The major diastereomers were the *trans* and *cis* isomers involving R^1 and R^2; we only observed products with a cis relationship between R^1 and R^3. The [3 + 2]-cycloaddition yielded bicyclic pyrazolidinones with an average diastereoselectivity of 90:10 (*trans*:*cis*). Higher diastereoselectivity was achieved through epimerization with DBU. For example, the diastereoselectivity of bicyclic pyrazolidinone **34** increased from dr 81:19:–:– to a higher 95:5:–:– in the presence of DBU. The *cis* stereochemical relationship between R^1 and R^3 was determined by X-ray crystallography (Figure 1a).

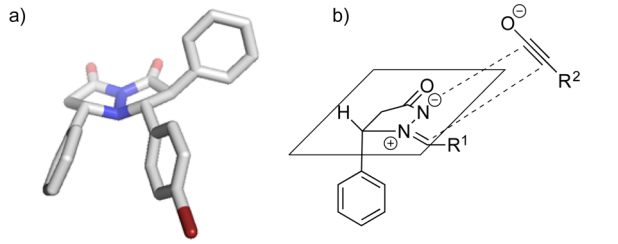


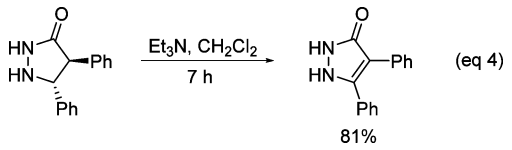
Figure 1. (a) Crystal structure of **36**. (b) Stereochemical model of [3 + 2] cycloaddition.

To obtain this stereochemistry, the ynolate must approach from the less hindered face of the azomethine imine ring (Figure 1b). Therefore, the substituent on the 5-position of the azomethine imine controls the stereochemical outcome of the cycloaddition. This observation suggested that optically active dipoles would give rise to nonracemic pyrazolidinones. For maximum synthetic utility, however, the chiral controller should be removable to convert the bicyclic pyrazolidinones to their monocyclic derivatives. To that end, we next turned to removing the three-carbon bridge from the original dipole (Table 2).

We envisioned that the imide bond would readily hydrolyze and the C(R^3)–N bond could cleave upon protonation of the nitrogen, followed by elimination. In this regard, we discovered that heating bicyclic pyrazolidinones to 100 °C in 37% HCl/H_2O or a 1:1 mixture of 37% HCl/H_2O/AcOH provided their respective monocyclic pyrazolidinones in excellent yields (81–99%) (Table 2). The C–N bond cleavage proved general and has been applied to bicyclic pyrazolidinones containing either aliphatic or aromatic moieties at R^2. The diphenyl pyrazolidinone **38** was synthesized from both the unsubstituted (Table 2, entry 1) and substituted dipoles (Table 2, entry 2). Fortunately, several bicyclic pyrazolidinones with low diastereoselectivities epimerized during the hydrolysis to give monocyclic products with higher diastereomer ratios. Most notably, a 3:2 mixture of the triphenyl-substituted bicycle **34** provided the product **38** with dr >99:1 (Table 2, entry 2). To our knowledge, this is the first example in which the three bridging carbons of the azomethine imine are completely removed following cycloaddition.[19]

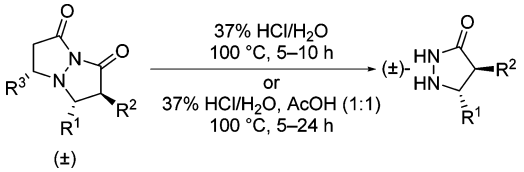
During hydrolysis of the bicyclic pyrazolidinones, we observed some oxidation to the corresponding pyrazolones (see Table 2, product **41**). Taking advantage of this reactivity, we identified optimal conditions for aerobic oxidation. Specifically, stirring the monocyclic pyrazolidinones with Et_3N under air provided pyrazolones in good yield (Scheme 3, eq 4).

Scheme 3. Pyrazolone Formation



With a protocol to hydrolyze the bicyclic cycloadducts, the azomethine imine can act as a chiral auxiliary to access optically active cycloadducts. Thus, a diastereoselective [3 + 2]-cycloaddition with optically active azomethine imines was followed by removal of the azomethine imine skeleton. Several chiral nonracemic 5-phenyl azomethine imines[14] were used in

Table 2. C–N Bond Cleavage of Bicyclic Pyrazolidinones[a]



entry	product	R^1	R^2	R^3	yield (%)[b]	dr[c]	S.M. dr[c]
1	**38**	Ph	Ph	H	81	90:10	90:10:–:–
2	**38**	Ph	Ph	Ph	85	>99:1	61:39:–:–
3	**39**	Ph	*n*-C_4H_9	Ph	87	91:9	86:14:–:–
4	**40**	4-BrC_6H_4	Ph	Ph	99	92:8	87:13:–:–
5	**41**	4-BrC_6H_4	*n*-C_4H_9	Ph	84[d]	91:9	90:10:–:–

[a]0.2 mmol scale reaction in a sealed vial at 100 °C. Expemental details in Supporting Information. [b]Isolated yield. [c]Dr determined by ^{1}H NMR. [d]95% yield of a 7.6:1 mixture with the corresponding pyrazolone. S.M. = starting material.

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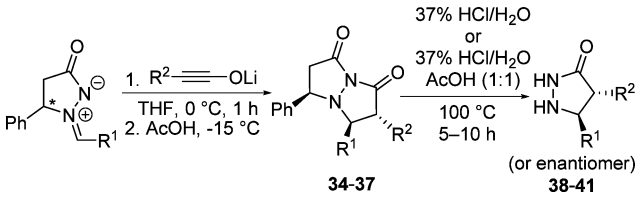
the [3 + 2]-cycloaddition to obtain bicyclic pyrazolidinones **34**−**37** with high enantiomeric excesses (Table 3). The azomethine imine auxiliary was sequentially removed to yield monocyclic pyrazolidinones without loss of optical activity (**38**−**41**).

Table 3. [3 + 2]-Cycloaddition with Optically Active Azomethine Imines and C−N Cleavage to Remove Auxiliary[a]



34-37 38-41

compd	R^1	R^2	yield (%)[b]	dr[c]	ee (%)[d]
(−)-**34**	Ph	Ph	84	79:21:−:−	nd
(−)-**35**	Ph	n-C_4H_9	92	83:17:−:−	nd
(+)-**36**	4-BrC_6H_4	Ph	86	76:24:−:−	nd
(+)-**37**	4-BrC_6H_4	n-C_4H_9	83	85:15:−:−	nd
(−)-**38**	Ph	Ph	95	91:9	>99[f]
(−)-**39**	Ph	n-C_4H_9	86	87:13	99[f]
(+)-**40**	4-BrC_6H_4	Ph	85	90:10	94[g]
(+)-**41**	4-BrC_6H_4	n-C_4H_9	78[e]	88:12	95[g]

[a]Expemental detail in Supporting Information. [b]Isolated yield. [c]Dr determined by ^{1}H NMR. [d]ee determined by HPLC. nd = not determined. [e]88% yield of a 8.8:1 mixture with the corresponding pyrazolone. [f]Azomethine imine ee >99%. [g]Azomethine imine ee 92%.

In summary, we developed a novel [3 + 2]-cycloaddition of ynolates and azomethine imines to synthesize bicyclic pyrazolidinones in high yields and diastereoselectivities. At this time, it is not clear if the reaction is stepwise or concerted.[17] Nonetheless, this is the first example in which the azomethine imine acts as a chiral auxiliary to control the cycloaddition. We have defined conditions for its removal to yield optically active monocyclic pyrazolidinones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01104.

X-ray crystal data for (−)-**36** (CIF)
Experimental methods, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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