OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Benzoazepine-Fused Isoindolines via Intramolecular (3 + 2)-Cycloadditions of Azomethine Ylides with Dinitroarenes

Steven M. Wales,[†,⊥] Daniel J. Rivinoja,[†,⊥] Michael G. Gardiner,[‡] Melissa J. Bird,[†] Adam G. Meyer,[§] John H. Ryan,[§] and Christopher J. T. Hyland*[,†]

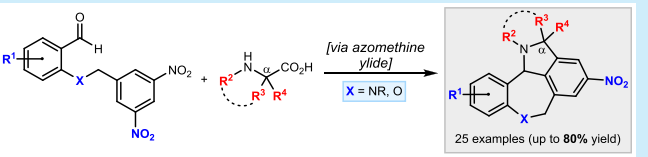
[†]School of Chemistry and Molecular Bioscience, University of Wollongong, Wollongong, NSW 2522, Australia

[‡]School of Natural Sciences − Chemistry, University of Tasmania, Hobart, Tasmania 7001, Australia

[§]CSIRO Biomedical Manufacturing, Ian Wark Laboratory, Bayview Avenue, Clayton, Victoria 3168, Australia

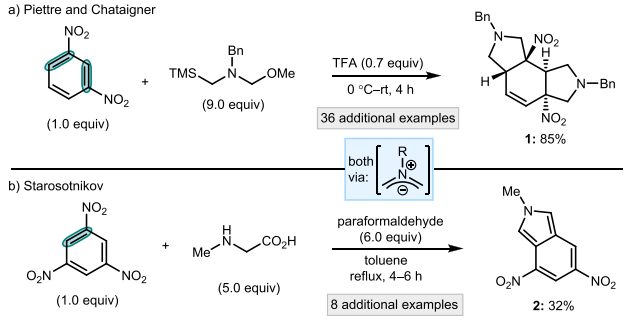
Supporting Information

ABSTRACT: Aminobenzaldehydes bearing a pendant 3,5-dinitrophenyl group react thermally with N-substituted α-amino acids to form unprecedented benzoazepine-fused isoindolines. The reaction proceeds via a dearomatization/rearomatization sequence involving an intramolecular (3 + 2)-cycloaddition between the in situ formed azomethine ylide and the dinitroarene. Various glycine derivatives are tolerated as well as branched substrates based on cyclic, α-mono-, and α,α-disubstituted amino acids, giving single diastereomers in many cases. The method is scalable and gives products with a nitro group ready for further manipulation.



Engaging π-bonds of benzene derivatives in cycloaddition processes is a powerful approach to generate poly(hetero)-cyclic compounds from readily available materials.[1] Prominent examples of complexity-building reactions of benzene derivatives that proceed through (formal) cycloadditions include cyclopropanations,[2] trimethylenemethane cycloadditions,[3] (4 + 3)-cycloadditions,[4] (hetero)-Diels−Alder reactions,[5] and photochemical variants.[6] A 1,3-dipolar cycloaddition between an azomethine ylide (AMY)[7] and a benzene-embedded dipolarophile is another efficient strategy for arene functionalization, providing access to isoindoline- or isoindole-containing structures.[8,9] The unique LUMO-lowering effect of the nitro-substituent has proven particularly effective in opening up this reactivity mode to common arene feedstocks (e.g., benzene, indole).[10] For example, Piettre and Chataigner reported efficient cycloadditions of a symmetrical *N*-benzyl AMY with (hetero)-arenes containing at least one nitro (or ester) substituent, giving mono- or bispyrrolidino adducts such as **1** (Scheme 1a).[11]

Scheme 1. Exemplary Previous Work



Conversely, Starosotnikov demonstrated that *N*-methylglycine reacted thermally with formaldehyde in the presence of polynitrobenzenes to give isoindoles (e.g., **2**) after rearomatization and oxidation of the initial cycloadducts (Scheme 1b).[12]

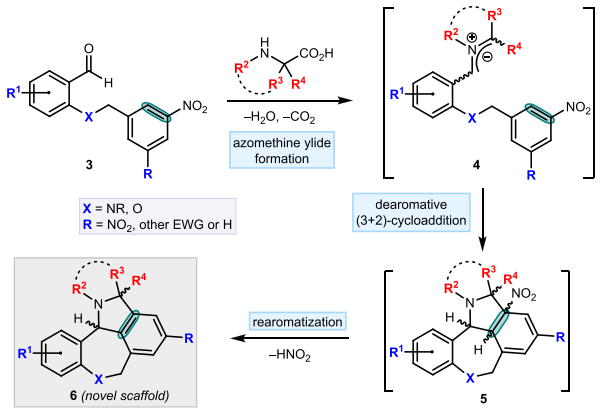
Although these developments (Scheme 1) demonstrate the potential of generating isoindoline (or isoindole) heterocycles through 1,3-dipolar cycloaddition of nonstabilized AMYs with electron-deficient benzene derivatives, the scope of accessible product types remains to be fully explored. This is especially the case for scarcely investigated intramolecular AMY−arene cycloadditions,[13,14] which present untapped opportunities to access more highly substituted isoindoline frameworks and to improve selectivity for a single cycloaddition to the benzene ring, where multiple additions[11,15] are undesired. Carefully designed intramolecular cycloaddition systems could therefore afford a more controlled process, while simultaneously providing novel polycyclic heterocycles. To be synthetically useful, such tethered substrates should be easily prepared from commercially available materials. We therefore designed readily prepared *ortho*-heterobenzaldehydes tethered to a nitrophenyl group as substrates to investigate in controlled, intramolecular AMY−arene cycloadditions (Scheme 2).

Thermal condensation of aldehyde **3** with *N*-substituted α-amino acids would be expected to generate dipole **4**, which was anticipated to undergo a regioselective, dearomatizing (3 + 2)-cycloaddition with the pendant nitroarene to generate cycloadduct **5**. Rearomatization under thermal conditions[10a,b,12,15a] would give the desired tetracycle **6**.

Received: May 5, 2019

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX−XXX

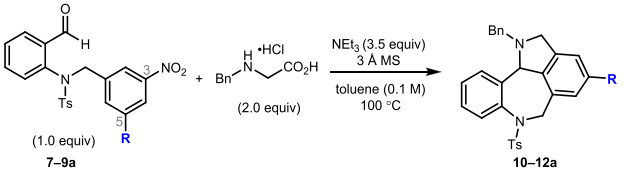
Scheme 2. Reaction Design Plan



As well as our interest in investigating the reactivity of α-substituted amino acids in this study (where R^3 and/or $R^4 \neq H$, Scheme 2), the concomitant formation of the benzoazepine ring system in **6** (where X = NR) during the cycloaddition process was compelling from a structural standpoint.[16] The 1-benzoazepine skeleton features in a range of bioactive molecules including agonists of *N*-methyl-D-aspartate[17] and Vasopressin V2 receptors.[18] Isoindolines are also highly privileged motifs, featured in a range of bioactive molecules.[19] Therefore, a new chemical entity (**6**) combining these two pharmacophores would be potentially of high importance.

Initially, three test substrates (**7**–**9a**) with a tosyl-protected amino linker were examined with variations in substitution at C-5 of the pendant 3-nitroarene (Table 1). These aldehydes were each treated with Bn-Gly-OH·HCl under typical conditions to promote AMY formation,[20] along with NEt_3 to neutralize HCl and any nitrous acid formed by rearomatization. The dependency of product formation on the pendant arene substitution (R) quickly became apparent: whereas substrates **7** and **8** bearing mononitro or fluoro/nitro activating groups, respectively, decomposed slowly and gave no traceable products (entries 1 and 2),[21a] the use of dinitro precursor **9a** gave the corresponding rearomatized cycloadduct **12a** in 74% isolated yield after 2 h (entry 3). Here, the only observed side product derived from **9a** was a trace of the corresponding isoindole oxidized form of **12a**, which was easily removed during purification.[21b] Encouraged by this result, we examined the effect of modifications to the reaction conditions including variations in temperature (80 or 120 °C), alternative heating via microwave at 100 °C, or increasing the relative stoichiometry of the amino acid to 5.0 equiv, all of which returned lower yields than the reaction conditions noted in Table 1.

Table 1. Initial Results[a]

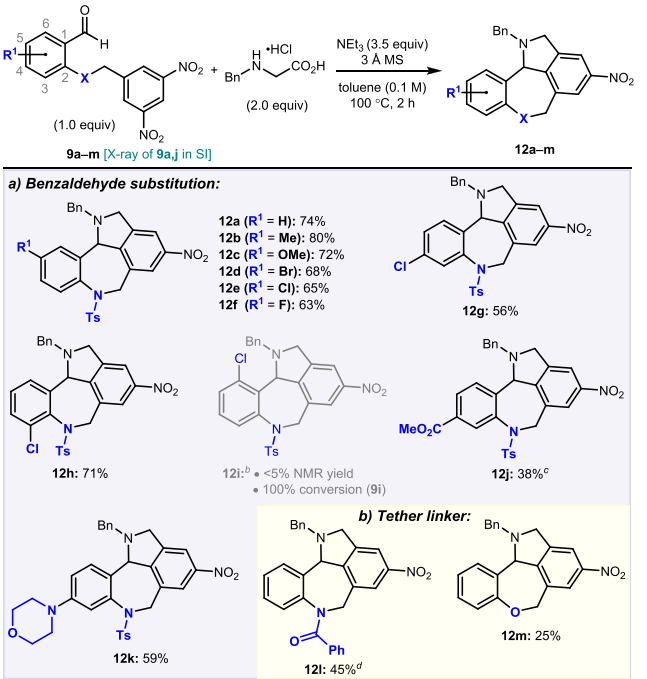


entry	R	product	time (h)	conv (%)[b]	yield (%)[b]
1	H (**7**)	**10**	24	79	<5
2	F (**8**)	**11**	24	89	<5
3	NO_2 (**9a**)	**12a**	2	100	74[c]

[a]Performed on a 0.10 mmol scale. [b]Determined by ^1H NMR spectroscopy with mesitylene as the internal standard. [c]Isolated yield.

In addition to the clear benefit in terms of reactivity observed with the symmetrical and doubly activated 3,5-dinitrophenyl derivative (Table 1, entry 3), the nitro group retained in the product (**12a**) represented a potentially valuable handle for downstream derivatization. Therefore, to assess the electronic and steric effect of benzaldehyde substitution, a series of *N*-tosyl-2-aminobenzaldehydes tethered to 3,5-dinitrobenzene (**9b**–**k**) were prepared and treated with Bn-Gly-OH·HCl under the standard reaction conditions (Scheme 3a). As with test substrate **9a**, these reactions required ≤2 h to reach completion in all cases. Substrates with methyl and methoxy substitution at C-5 reacted smoothly, giving **12b** and **12c** in 80 and 72% yields, respectively. Systematic evaluation of halogens at C-5 with increasing electronegativity resulted in slight incremental decreases in yield (**12d**–**f**: 68–63%). Benzaldehydes bearing chlorine at the *para*-position (C-4) or adjacent to the sulfonamide (C-3) were also amenable to the cycloaddition, giving **12g** and **12h** in 56 and 71% yields, respectively. In contrast, reaction of Bn-Gly-OH·HCl (or Me-Gly-OH) with a 6-chloro substrate failed to produce **12i**, leading only to decomposition, likely due to steric incompatibility of a C-6 substituent with the N-substituent of the amino acid. A mesomerically electron-withdrawing ester at C-4 had a detrimental effect on the efficiency of the process (**12j**: 38%), whereas cycloaddition with a *para*-electron-donating morpholino substituent gave **12k** in moderate yield (59%).

Scheme 3. Scope of Benzaldehydes[a]



[a]Reactions performed on a 0.10 mmol scale. Yields are of isolated products. [b]A similar result was obtained using 2.0 equiv of *N*-methylglycine (freebase) and 1.5 equiv of NEt_3 for 8 h. [c]Corresponding isoindole (**12j′**) was also isolated in 12% yield. [d]Performed on a 0.07 mmol scale. Reaction time was 3 h.

Linkers ("X") other than the *N*-Ts group were also briefly examined (Scheme 3b). The sulfonamide group could be successfully replaced with a benzoyl group, albeit at the expense

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX–XXX

of chemical yield (**12l** vs **12a**). Additionally, we demonstrated that an oxygen linker was feasible for the cycloaddition, isolating cyclic ether **12m** in a low, but repeatable, 25% yield.[22,23]

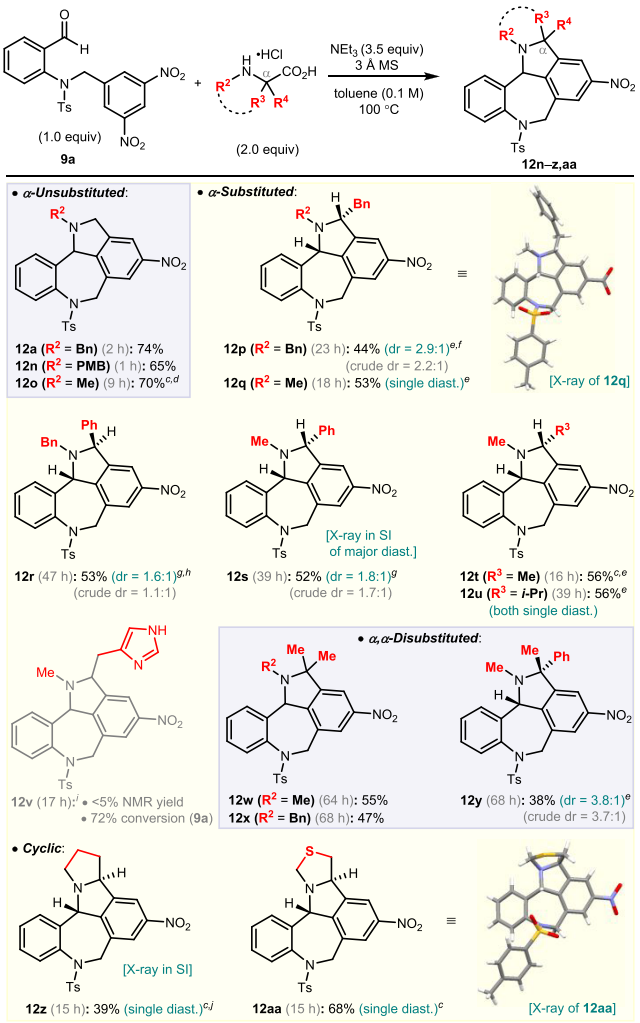
The scope of the cycloaddition with respect to N-substituted α-amino acids was investigated using **9a** as a model aldehyde, targeting a range of derivatives **12n−z,aa** (Scheme 4). Reaction times for full consumption of **9a** varied considerably (1−68 h) and were correlated to the degree of α-substitution. *N*-PMB and *N*-Me-glycine derivatives gave **12n** and **12o** in yields comparable to those of Bn analogue **12a**. α-Substituted *N*-Bn and/or *N*-Me amino acids bearing Bn, Ph, Me, and *i*-Pr α-groups (R^3) were successful, giving moderate yields of **12p−u** (44−56%) with a general preference for the *cis* diastereomer; the degree of *cis*-diastereoselectivity for these compounds (**12p−u**) was dependent on both the N-substituent (R^2) and the side chain (R^3). For example, whereas products **12q**, **12t**, and **12u** (derived from α-alkyl, *N*-Me amino acids) were obtained exclusively as *cis*-diastereomers, α-substitution with a Ph group resulted in a significant decrease in diastereoselectivity (**12s**: *cis*/*trans* = 1.7:1). Comparison of results for **12p** and **12q** obtained from *N*-Bn- and *N*-Me-phenylalanine, respectively, showed a decrease in *cis*-diastereoslectivity for the *N*-Bn substrate. *N*-Bn-α-Ph-glycine was the only chiral amino acid that reacted to give product **12r** with essentially no diastereochemical enrichment (crude dr [*trans*/*cis*] = 1.1:1). The only amino acid surveyed that did not react productively was *N*-Me-histidine (**12v**).

α,α-Disubstituted amino acids were also amenable to the cycloaddition (Scheme 4), as demonstrated with geminal dimethylated products **12w** and **12x**, as well as the *cis*-enriched α,α-Me-Ph derivative **12y** (38−55% yields). Finally, the reaction was extended to cyclic amino acids including proline and thiaproline to give pentacyclic products **12z** and **12aa** as exclusive *trans* stereoisomers.

The relative stereochemistry of products **12q**, **12s** (major), **12z**, and **12aa** were established by X-ray crystallography (Scheme 4 and Supporting Information). As expected, representative product **12q** of known *cis*-stereochemistry gave a NOE correlation between the methine hydrogens on the fused isoindoline ring system. The analogous NOE correlations between methine hydrogens were also observed for **12p** (major), **12t**, and **12u** and similarly between the methine hydrogen and *C*-methyl group of **12y** (major). These compounds were therefore assigned as *cis*-stereoisomers.

Previous computational studies have concluded that cycloadditions of nonstabilized AMYs and nitroarenes occur through an irreversible, concerted process.[11b] It is also known that nonstabilized AMYs form from α-amino acids via stereospecific decarboxylation of oxazolidinone intermediates and that the derived AMYs can undergo isomerization before cycloaddition in the absence of highly reactive dipolarophiles (e.g., maleimides).[24] Based on those studies,[11b,24] the divergent diastereoselectivity of the current cycloaddition can be rationalized by considering the preferred geometry of the dipole undergoing the cycloaddition (Figure 1). The predominant *cis*-stereoselectivity observed with acyclic amino acids presumably arises from reaction of a W-shaped ylide **4a**. When switching from *N*-Me to *N*-Bn amino acids, we believe that steric interactions between R^2 and R^3 become more apparent, causing partial adoption of a reactive S-shaped *anti*-configuration **4a′**, which results in a greater relative degree of *trans* isomer formation. This effect appears to be more pronounced when a Ph group occupies R^3, regardless of R^2, but we cannot rule out nonsteric interactions (e.g., Ph-nitroarene π-stacking) playing a role. Due to geometrical constraints, pentacyclic *trans* products

Scheme 4. Scope of Amino Acids[a,b]



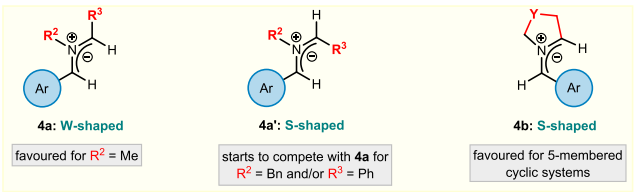


Figure 1. Proposed reactive ylide geometries.

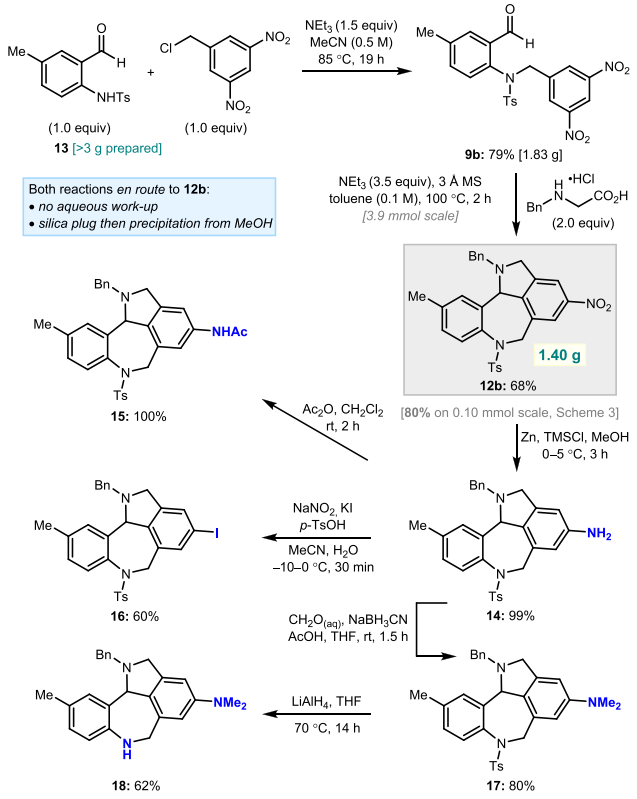
[a]Reactions performed on a 0.10 mmol scale. Yields are of isolated products. [b]Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. Isolated samples are enriched in the same epimers as the crude mixtures. The relative configurations of the major epimers are shown. [c]Using 2 equiv of amino acid freebase and 1.5 equiv of NEt_3. [d]Isolated with 5 mol % of the corresponding isoindole **12o′**. [e]Relative configuration determined by NOE NMR spectroscopy. [f]Isolated with ∼10 mol % of an unknown side product. [g]Diastereomers were partially separated. Yield and dr represent that of the combined isolates. [h]Relative configuration determined by ^{1}H NMR spectral comparison with **12s** and **12y**. See the Supporting Information. [i]Using 2.0 equiv of Me-His-OH·2HCl and 5.5 equiv of NEt_3. [j]Isolated with 10 mol % of the corresponding isoindole **12z′**.

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX−XXX

12z and **12aa** must arise from the cycloaddition of the alternative S-shaped *anti*-configured ylide **4b**; this *trans*-diastereoselectivity is consistent with previous reports[25] of both intra- and intermolecular cycloadditions with analogous AMYs derived from cyclic substrates (see the Supporting Information for further illustrations).[26]

To demonstrate the scalability of the current method, the known sulfonamide **13** was alkylated with commercially available 3,5-dinitrobenzyl chloride on a gram scale to provide aldehyde **9b** (79%), which underwent reaction with Bn-Gly-OH·HCl in 2 h to give 1.40 g of **12b** (68%), without any modifications to the standard conditions (Scheme 5). Notably,

Scheme 5. Larger-Scale Synthesis and Manipulations



both **9b** and **12b** were purified in this sequence by a single precipitation/trituration from methanol, without the need for an aqueous workup or recourse to conventional silica gel chromatography.

A series of standard transformations were carried out from **12b** to confirm the downstream utility of the nitro group (Scheme 5). Reduction with zinc powder produced aniline **14** in 99% yield, which provided a convenient divergence point to access a small set of derivatives **15**–**17** using conventional N-acetylation, iodination, and N-dimethylation methods. Finally, the tosyl group of **17** was reductively cleaved with $LiAlH_4$ to give the free *N*-H-benzoazepine **18** in 62% yield.

In conclusion, we have reported a strategic advance in AMY–arene cycloadditions: specifically, by tethering an electron-deficient dinitroarene to the site of ylide formation, we have established that intramolecular cycloaddition can occur in a highly productive manner with a wide scope, demonstrating that highly substituted, nonstabilized AMYs readily cycloadduct to the nitroarene and often with high diastereocontrol. This work further highlights the well-recognized yet still untapped potential of intramolecular, dearomatizing cycloadditions in the formation of complex heterocyclic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01580.

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

Accession Codes

CCDC 1911869–1911872 and 1911874–1911875 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chris_hyland@uow.edu.au.

ORCID

Steven M. Wales: 0000-0003-0637-4225
Michael G. Gardiner: 0000-0001-6373-4253
Christopher J. T. Hyland: 0000-0002-9963-5924

Author Contributions

⊥S.M.W. and D.J.R. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The CSIRO, The University of Wollongong, and ARC Discovery Project DP180101332 are acknowledged for generous funding of this research.

■ REFERENCES

(1) (a) Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent Advances in the Chemical Dearomatization of Nonactivated Arenes. *Chem. Soc. Rev.* **2018**, *47*, 7996–8017. (b) Remy, R.; Bochet, C. G. Arene–Alkene Cycloaddition. *Chem. Rev.* **2016**, *116*, 9816–9849. (c) Liebov, B. K.; Harman, W. D. Group 6 Dihapto-Coordinate Dearomatization Agents for Organic Synthesis. *Chem. Rev.* **2017**, *117*, 13721–13755. (d) Roche, S. P.; Porco, J. A., Jr. Dearomatization Strategies in the Synthesis of Complex Natural Products. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.

(2) Reisman, S. E.; Nani, R. R.; Levin, S. Buchner and Beyond: Arene Cyclopropanation as Applied to Natural Product Total Synthesis. *Synlett* **2011**, *2011*, 2437–2442.

(3) Trost, B. M.; Ehmke, V.; O'Keefe, B. M.; Bringley, D. A. Palladium-Catalyzed Dearomative Trimethylenemethane Cycloaddition Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 8213–8216.

(4) Ling, J.; Lam, S.; Low, K.-H.; Chiu, P. Dearomative Intramolecular (4 + 3) Cycloadditions of Arenes with Epoxy and Aziridinyl Enolsilanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 8879–8882.

(5) (a) Good, S. N.; Sharpe, R. J.; Johnson, J. S. Highly Functionalized Tricyclic Oxazinanones via Pairwise Oxidative Dearomatization and *N*-Hydroxycarbamate Dehydrogenation: Molecular Diversity Inspired by Tetrodotoxin. *J. Am. Chem. Soc.* **2017**, *139*, 12422–12425. (b) Schmidt, Y.; Lam, J. K.; Pham, H. V.; Houk, K. N.; Vanderwal, C. D. Studies on the Himbert Intramolecular Arene/Allene Diels–Alder Cycloaddition.

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX–XXX

Mechanistic Studies and Expansion of Scope to All-Carbon Tethers. *J. Am. Chem. Soc.* **2013**, *135*, 7339−7348.
(6) (a) Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. Dearomative Dihydroxylation with Arenophiles. *Nat. Chem.* **2016**, *8*, 922−928. (b) Okumura, M.; Sarlah, D. Arenophile-Mediated Dearomative Functionalization Strategies. *Synlett* **2018**, *29*, 845−855.
(7) General reviews on cycloadditions of AMYs: (a) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. *Acc. Chem. Res.* **2014**, *47*, 1296−1310. (b) Adrio, J.; Carretero, J. C. Novel Dipolarophiles and Dipoles in the Metal-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides. *Chem. Commun.* **2011**, *47*, 6784−6794. (c) Meyer, A. G.; Ryan, J. H. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides with Carbonyl Dipolarophiles Yielding Oxazolidine Derivatives. *Molecules* **2016**, *21*, 935. (d) Pandey, G.; Dey, D.; Tiwari, S. K. Synthesis of Biologically Active Natural Products by [3 + 2] Cycloaddition of Non-Stabilized Azomethine Ylides (AMY): Concepts and Realizations. *Tetrahedron Lett.* **2017**, *58*, 699−705.
(8) Ryan, J. H. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides with Aromatic Dipolarophiles. *Arkivoc* **2015**, *i*, 160−183.
(9) Huisgen, R.; Scheer, W. Dipolarophilic Activity of Aromatic Bonds Towards an Azomethine Ylide. *Tetrahedron Lett.* **1971**, *12*, 481−484.
(10) (a) Starosotnikov, A. M.; Bastrakov, M. A.; Pechenkin, S. Y.; Leontieva, M. A.; Kachala, V. V.; Shevelev, S. A. 1,3-Dipolar Cycloaddition of Unstabilized *N*-Methyl Azomethine Ylide to Nitrobenzene Annelated with Azoles. *J. Heterocycl. Chem.* **2011**, *48*, 824−828. (b) Bastrakov, M. A.; Starosotnikov, A. M.; Kachala, V. V.; Fedyanin, I. V.; Shevelev, S. A. Facile Dearomatization of Nitroquinolines through [3 + 2] and [4 + 2] Cycloaddition Reactions. *Asian J. Org. Chem.* **2015**, *4*, 146−153. (c) Gerten, A. L.; Stanley, L. M. Enantioselective Dearomative [3 + 2] Cycloadditions of Indoles with Azomethine Ylides Derived from Alanine Imino Esters. *Org. Chem. Front.* **2016**, *3*, 339−343. (d) Awata, A.; Arai, T. PyBidine/Copper Catalyst: Asymmetric *exo*′-Selective [3 + 2] Cycloaddition using Imino Ester and Electrophilic Indole. *Angew. Chem., Int. Ed.* **2014**, *53*, 10462−10465. (e) Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. 1,3-Dipolar Cycloaddition of 2- and 3-Nitroindoles with Azomethine Ylides. A New Approach to Pyrrolo[3,4-*b*]indoles. *Tetrahedron Lett.* **2007**, *48*, 1313−1316.
(11) (a) Lee, S.; Chataigner, I.; Piettre, S. R. Facile Dearomatization of Nitrobenzene Derivatives and Other Nitroarenes with *N*-Benzyl Azomethine Ylide. *Angew. Chem., Int. Ed.* **2011**, *50*, 472−476. (b) Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I.; Piettre, S. R. Aromatic C = C Bonds as Dipolarophiles: Facile Reactions of Uncomplexed Electron-Deficient Benzene Derivatives and Other Aromatic Rings with a Non-Stabilized Azomethine Ylide. *Chem. - Eur. J.* **2013**, *19*, 7181−7192.
(12) Starosotnikov, A. M.; Bastrakov, M. A.; Kachala, V. V.; Belyakov, P. A.; Fedyanin, I. V.; Shevelev, S. A. One-Step Method for the Synthesis of Nitroisoindoles via 1,3-Dipolar Cycloaddition of Azomethine Ylides to Polynitrobenzenes. *Synlett* **2012**, *23*, 2400−2404.
(13) General review: Coldham, I.; Hufton, R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005**, *105*, 2765−2809.
(14) For rare examples of intramolecular (3 + 2) AMY−(hetero)arene cycloadditions with stabilized AMYs, see: (a) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. Intramolecular 1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides to Unactivated Dipolarophiles. *J. Org. Chem.* **1992**, *57*, 7056−7066. (b) Tsuge, O.; Ueno, K.; Kanemasa, S. Intramolecular 1,3-Dipolar Cycloadditions to a Furan Ring. *Chem. Lett.* **1984**, *13*, 285−288. (c) Tsuge, O.; Ueno, K.; Kanemasa, S. Reactions of Nitrones Bearing an Olefinic Dipolarophile with Dimethylacetylene Dicarboxylate. Inter- and Intramolecular Double 1,3-Dipolar Cycloadditions. *Chem. Lett.* **1984**, *13*, 797−800.
(15) (a) Bastrakov, M. A.; Fedorenko, A. K.; Starosotnikov, A. M.; Kachala, V. V.; Shevelev, S. A. Dearomative (3 + 2) Cycloaddition of 2-Substituted 3,5-Dinitropyridines and *N*-Methyl Azomethine Ylide. *Chem. Heterocycl. Compd.* **2019**, *55*, 72−77. (b) Bastrakov, M. A.; Starosotnikov, A. M.; Pechenkin, S. Y.; Kachala, V. V.; Glukhov, I. V.; Shevelev, S. A. Double 1,3-Dipolar Cycloaddition of *N*-Methyl Azomethine Ylide to *Meta*-Dinitrobenzene Annelated with Nitrogen Aromatic Heterocycles. *J. Heterocycl. Chem.* **2010**, *47*, 893−896. (c) Konstantinova, L. S.; Bastrakov, M. A.; Starosotnikov, A. M.; Glukhov, I. V.; Lysov, K. A.; Rakitin, O. A.; Shevelev, S. A. 4,6-Dinitrobenzo[*c*]isothiazole: Synthesis and 1,3-Dipolar Cycloaddition to Azomethine Ylide. *Mendeleev Commun.* **2010**, *20*, 353−354.
(16) Examples of intramolecular (3 + 2) AMY−alkene cycloadditions that occur with concomitant formation of a seven-membered ring system: (a) Zhang, B.; White, J. M.; Jones, D. J.; Wong, W. W. H. Regioselective Synthesis of Fullerene Multiadducts via Tether-Directed 1,3-Dipolar Cycloaddition. *Org. Biomol. Chem.* **2015**, *13*, 10505−10510. (b) Saravanan, N.; Arthanareeswari, M.; Kamaraj, P.; Sivakumar, B. Efficient Synthesis of Quinolo-Oxepanes through [3 + 2] Cycloaddition Reaction of α,β-Unsaturated Ester with Unstabilized Azomethine Ylides. *Asian J. Chem.* **2015**, *27*, 3667−3670. (c) Nayak, M.; Rastogi, N.; Batra, S. Synthesis of Pyrazole-Fused Polycyclic Systems via Intramolecular 1,3-Dipolar Cycloaddition Reactions. *Tetrahedron* **2013**, *69*, 5029−5043. (d) Habermann, J.; Capitò, E.; Ferreira, M. d. R. R.; Koch, U.; Narjes, F. Discovery of Pentacyclic Compounds as Potent Inhibitors of Hepatitis C Virus NS5B RNA Polymerase. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 633−638. (e) Armstrong, P.; Grigg, R.; Jordan, M. W.; Malone, J. F. X = Y−ZH Systems as Potential 1,3-Dipoles−5. Intramolecular Cycloadditions of Imines of α-Amino Acid Esters. *Tetrahedron* **1985**, *41*, 3547−3558.
(17) Di Fabio, R.; Micheli, F.; Baraldi, D.; Bertani, B.; Conti, N.; Dal Forno, G.; Feriani, A.; Donati, D.; Marchioro, C.; Messeri, T.; Missio, A.; Pasquarello, A.; Pentassuglia, G.; Pizzi, D. A.; Provera, S.; Quaglia, A. M.; Sabbatini, F. M. Benzoazepine Derivative as Potent Antagonists of the Glycine Binding Site Associated to the NMDA Receptor. *Farmaco* **2003**, *58*, 723−738.
(18) Kondo, K.; Kan, K.; Tanada, Y.; Bando, M.; Shinohara, T.; Kurimura, M.; Ogawa, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Kido, M.; Mori, T.; Tominaga, M. Characterization of Orally Active Nonpeptide Vasopressin V2 Receptor Agonist. Synthesis and Biological Evaluation of both the (5*R*)- and (5*S*)-Enantioisomers of 2-[1-(2-Chloro-4-pyrrolidin-1-yl-benzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]-*N*-isopropylacetamide. *J. Med. Chem.* **2002**, *45*, 3805−3808.
(19) (a) Bhatia, R. K. Isoindole Derivatives: Propitious Anticancer Structural Motifs. *Curr. Top. Med. Chem.* **2016**, *17*, 189−207. (b) Speck, K.; Magauer, T. The Chemistry of Isoindole Natural Products. *Beilstein J. Org. Chem.* **2013**, *9*, 2048−2078.
(20) Mantelingu, K.; Lin, Y.; Seidel, D. Intramolecular [3 + 2]-Cycloadditions of Azomethine Ylides Derived from Secondary Amines via Redox-Neutral C−H Functionalization. *Org. Lett.* **2014**, *16*, 5910−5913.
(21) (a) The O-linked substrate, 2-((3,5-bis(trifluoromethyl)benzyl)oxy)benzaldehyde was also investigated but under the same conditions gave recovered starting material. (b) The ratios of the isoindoline/isoindole (**12**/**12**′) in all crude samples directly after workup were quantified by ^{1}H NMR spectroscopy and are listed in the Supporting Information. In one case, an isoindole side product (**12j**′) was isolated in 12% yield and fully characterized.
(22) Attempts to optimize the yield of **12m** by solvent screening (THF, MeCN, DCE; each at 80 °C) or using other bases (DBU, pyridine, DABCO) were unsuccessful. Two additional O-tethered products were prepared in 23 and 15% yield from the reaction of sarcosine and 2-((3,5-dinitrobenzyl)oxy)-5-methylbenzaldehyde or 5-bromo-2-((3,5-dinitrobenzyl)oxy)benzaldehyde; see the Supporting Information.
(23) Formation of **12m** was monitored by reverse-phase LC-MS at 120 and 80 °C to attempt detection of the dearomatized cycloadduct **5m.** Along with clear peaks for the aromatized cycloadduct and starting material, a small peak with mass corresponding to **5m** could be observed, lending tentative support to the proposed mechanism in Scheme 2 and the short lifetime of intermediate **5** (this species could not be isolated by chromatography). It should be noted that the azomethine ylide **4m** has the same mass as **5m**; however, this

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX−XXX

azomethine ylide might not be expected to be stable under aqueous HPLC conditions.

(24) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. The Decarboxylative Route to Azomethine Ylides. Mechanism of 1,3-Dipole Formation. *J. Chem. Soc., Chem. Commun.* **1987**, 49−51.

(25) (a) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. The Decarboxylative Route to Azomethine Ylides. Stereochemistry of 1,3-Dipole Formation. *J. Chem. Soc., Chem. Commun.* **1987**, *0*, 47−49. (b) Hong, B.-C.; Liu, K.-L.; Tsai, C.-W.; Liao, J.-H. Proline-Mediated Dimerization of Cinnamaldehydes via 1,3-Dipolar Cycloaddition Reaction with Azomethine Ylides. A Rapid Access to Highly Functionalized Hexahydro-1*H*-Pyrrolizine. *Tetrahedron Lett.* **2008**, *49*, 5480−5483. (c) Bakthadoss, M.; Kannan, D.; Srinivasan, J.; Vinayagam, V. Highly Regio- and Diastereo-Selective Synthesis of Novel Tri- and Tetra-Cyclic Perhydroquinoline Architectures via an Intramolecular [3 + 2] Cycloaddition Reaction. *Org. Biomol. Chem.* **2015**, *13*, 2870−2874. (d) Ghandi, M.; Kia, M. A.; Sadeghzadegh, M.; Bozcheloei, A. H.; Kubicki, M. Diastereoselective Synthesis of Novel Pyrrolidine or Pyrrolizine-Fused Benzo-*δ*-Sultams via 1,3-Dipolar Cycloadditions. *J. Heterocycl. Chem.* **2015**, *52*, 1646−1653. (e) Sarrafi, Y.; Sadatshahabi, M.; Hamzehloueian, M.; Alimohammadi, K.; Tajbakhsh, M. Synthesis of Functionalized Pyrrolizidines/Pyrrolidines Incorporating a Spirooxindole Motif through [3 + 2] Cycloaddition. *Synthesis* **2013**, *45*, 2294−2304.

(26) For each of the W- or S-shaped ylides shown, the moderately flexible tether is likely capable of adopting the necessary conformation to deliver the pendant arene for cycloaddition, but the precise orientation of approach (*exo* or *endo*) need not be considered here, as subsequent elimination of HNO_2 takes place to restore aromaticity (see Scheme 2).

DOI: 10.1021/acs.orglett.9b01580
Org. Lett. XXXX, XXX, XXX−XXX