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Zn-ProPhenol Catalyzed Enantioselective Mannich Reaction of 2*H*-Azirines with Alkynyl Ketones

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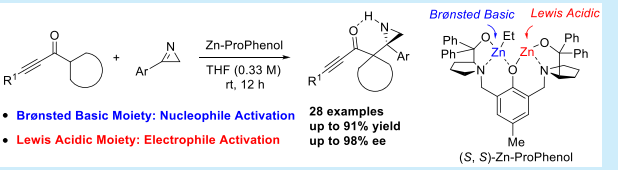
ABSTRACT: The enantioselective Mannich reaction of 2*H*-azirines with alkynyl ketones is achieved under Zn-ProPhenol catalysis, delivering various aziridines with vicinal tetrasubstituted stereocenters in high yields with excellent enantioselectivities. The bimetallic Zn-ProPhenol complexes activate both the nucleophile and the electrophile in the same chiral pocket. A unique intramolecular hydrogen bond is observed in the obtained Mannich adducts, which lowers the basicity of the product's aziridine nitrogen thus favoring enantioselective control and allowing catalyst turnover.



Owing to their intrinsic ring strain and medicinal priorities, incorporation of the chiral aziridines into potential medicines has impressive impacts that can substantially improve the bioactive properties of the parent molecules, especially for those bearing quaternary carbon centers (Figure 1).[1] Moreover, the aziridine motif is found in many natural

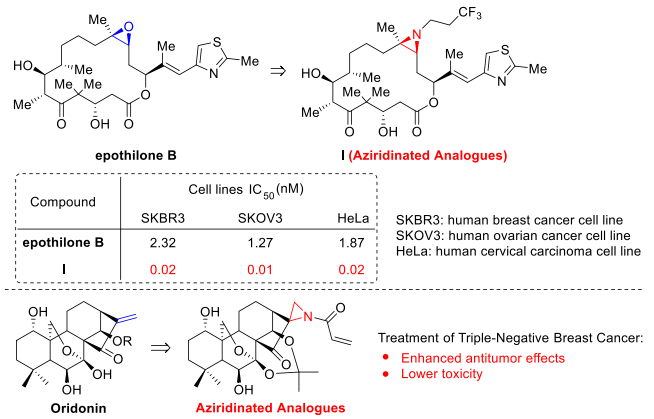
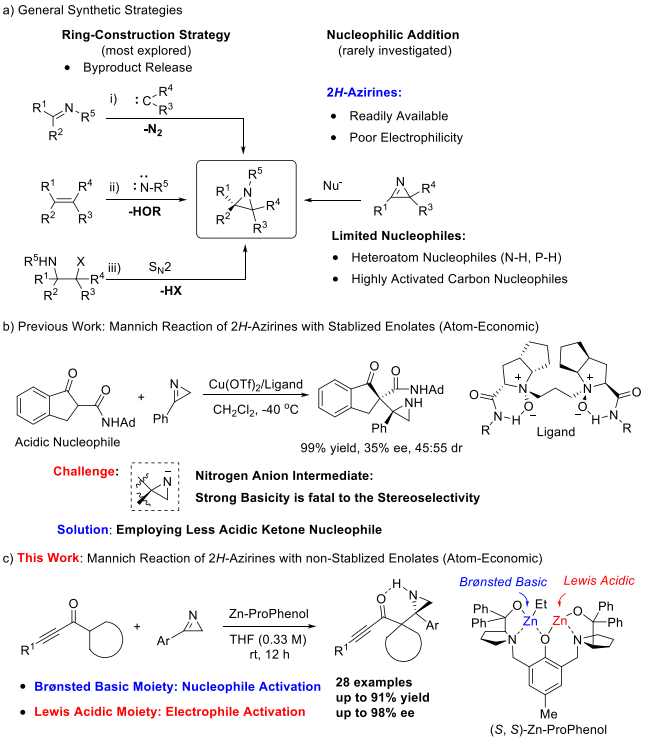


Figure 1. Chiral aziridines bearing quaternary centers in bioactive compounds.

products and pharmaceuticals and also serves as versatile synthetic intermediates for the construction of complex nitrogen containing molecules.[2] Thus, the synthesis and application of chiral aziridines becomes more significant in drug library design and drug discovery.[3] As depicted in Scheme 1a, three general methods have been reported to access chiral aziridines bearing quaternary carbon centers: (i) enantioselective reaction of carbene with imines; (ii) asymmetric nitrogen transfer to a Michael acceptor; (iii) stereoselective intramolecular S_N2 reactions of α-halo-β-amines.[4] These well-established ring-construction strategies usually release stoi-

Scheme 1. Background and Reaction Design



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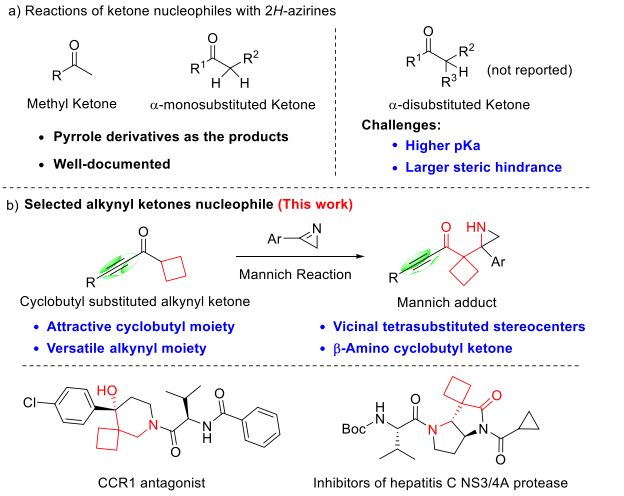
chiometric amounts of byproducts. On the other hand, the catalytic enantioselective addition of nucleophilies to readily available cyclic 2*H*-azirines could also become a straightforward strategy for the construction of chiral aziridines.[5−8] However, the lower reactivity of the poorly electrophilic 2*H*-azirines has led to much fewer developments in this area and limited these nucleophiles to heteroatom nucleophiles[6] or highly activated carbon nucleophiles such as organolithium reagents,[7] Breslow intermediates,[8] and decarboxylative carboxylic acids.[9]

Enolates are among the most important and powerful carbon nucleophiles for enantioselective carbon−carbon bond formation,[10] especially for those directly derived from unmodified carbonyl donors.[10d,11] Therefore, the direct enantioselective Mannich reaction of enolates with 2*H*-azirines would become an atom-economic strategy for the synthesis of chiral aziridines. To the best of our knowledge, the only enolate example was reported by Feng et al., which employed very easily enolizable 1,3-dicarbonyl compounds as the nucleophiles (Scheme 1b).[12] Expectedly, addition of the enolizable 1,3-dicarbonyl compound to the 2*H*-azirine would generate an aziridine nitrogen anion intermediate. However, the strong basicity of the product's aziridine nitrogen anion could directly deprotonate the enolizable 1,3-dicarbonyl compound without the presence of the catalyst, which is fatal to the stereoselectivity of the products. Although Feng and co-workers used the additional free acidic amide N−H bond of the nucleophile to reduce the influence of the strong basicity of the aziridine nitrogen anion, however, the Mannich adduct was still obtained in 35% enantiomeric excess (ee) and 45:55 diastereoisomer ratio (dr). On the other hand, less acidic nucleophiles, such as prochiral nonstabilized ketone enolates, may be preferable, making the enantiodeterminating step the attack of the enolate on the imine. However, this useful but challenging enantioselective Mannich reaction of poorly electrophilic 2*H*-azirines with nonstabilized enolates has not been reported and remains a challenge. Presumably such a process, if possible, requires a powerful catalytic system that activates both the electrophile and the nucleophile.

The treatment of ProPhenol with Et_2Zn could generate dinuclear main group metal salts that have proven to be effective metal catalysts for the addition of nonstabilized enolates with activated imines.[13,14] Activation of the imine with a strong electron-withdrawing group on the nitrogen proved critical also to allow turnover. Indeed, if the product lacked such electron-withdrawing groups on the nitrogen, the resulting product would be a basic amine which would have killed the use of the ProPhenol zinc complexes as catalysts. On the other hand, these chiral bimetallic complexes have a Brønsted basic and a Lewis acidic moiety and are capable of simultaneous activation of both the nucleophile and the electrophile in the same chiral pocket. Given our recent success of Zn-ProPhenol catalyzed enantioselective Mannich reactions of acyclic imines activated with electron-withdrawing groups with nonstabilized enolates,[14] we herein report the Zn-ProPhenol catalyzed enantioselective Mannich reaction of cyclic 2*H*-azirines with alkynyl ketones, delivering various chiral aziridines with vicinal tetrasubstituted stereocenters in high yields with excellent enantioselectivities (Scheme 1c).

As presented in Scheme 2a, the reactions of methyl ketones and α-monosubstituted ketones with 2*H*-azirines usually gave pyrrole derivatives as the products, because the newly formed aziridine nitrogen anions, by addition of ketone enolates to

Scheme 2. Reaction Development



2*H*-azirines, would attack the carbonyl moiety of these ketone nucleophiles which was followed by a dehydrative ring-opening process to give the pyrrole rings.[5] Thus, α-disubstituted ketones become the choice regarding nucleophiles, which could prohibit the dehydrative ring-opening process. However, the higher pK_a of the C−H bond in α-disubstituted ketones and the larger steric hindrance become hurdles that need to be conquered in their asymmetric Mannich reaction with 2*H*-azirines. We settled on cyclobutyl substituted alkynyl ketone as the nucleophile and investigated its Mannich reaction with 2*H*-azirines for several advantages (Scheme 2b). First, due to their high ring strain and structural rigidity, cyclobutanes are also highly valuable building blocks in numerous bioactive small molecules and chemical sciences and have also found prominence as synthetic intermediates.[15] Direct modification of cyclobutyl substituted ketones is a straightforward and promising strategy to construct cyclobutyl contained complex molecules.[16] Second, the higher s character of the attached alkyne could activate the carbonyl moiety which should increase the acidity of its α-C(sp^3)−H bond and facilitate its enolization process. Importantly, the high unsaturation of alkynes compared to alkenes and alkanes allows a broad scope of reactivities, providing a useful platform for structural diversification.[17] Most importantly, the obtained Mannich adduct features a β-amino cyclobutyl ketone skeleton, which has been found in many bioactive compounds, such as the CCR1 antagonist and the inhibitors of hepatitis C NS3/4A protease.[18]

After settling on the cyclobutyl substituted alkynyl ketone **1a** as the nucleophile, we performed its reaction with 2*H*-azirine **2a** in the presence of our standard Zn-ProPhenol catalyst **L1**. Remarkably, Mannich adduct **3a** was obtained in 83% isolated yield (Table 1, entry 1). However, the intramolecular hydrogen bond between the N−H bond of the aziridine moiety and the carbonyl moiety might result in a chiral center at the nitrogen atom; thus, compound **3a** had a very complex ^{1}H NMR spectrum[19] and was found to be difficult for HPLC analysis. Therefore, a sequential quantitative N−H bond acetylation of **3a** was conducted to give product **4a** in 82% overall isolated yield with 95% ee. We believe that this unique intramolecular hydrogen bond has a positive influence toward the excellent enantioselectivity of the product. Next, various types of ProPhenol ligands (**L2**−**L6**) with different electronic proper-

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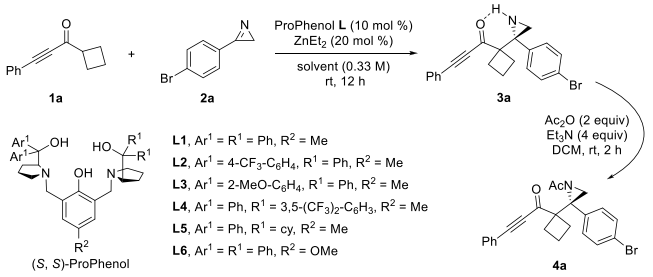
Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	yield (%)[b]	ee[c]
1	**L1**	THF	83 (84)	95
2	**L2**	THF	73 (74)	82
3	**L3**	THF	79 (80)	91
4	**L4**	THF	70 (72)	96
5	**L5**	THF	36 (39)	20
6	**L6**	THF	82 (83)	95
7	**L1**	Et_2O	53 (55)	81
8	**L1**	toluene	72 (73)	56
9	**L1**	dioxane	37 (40)	33

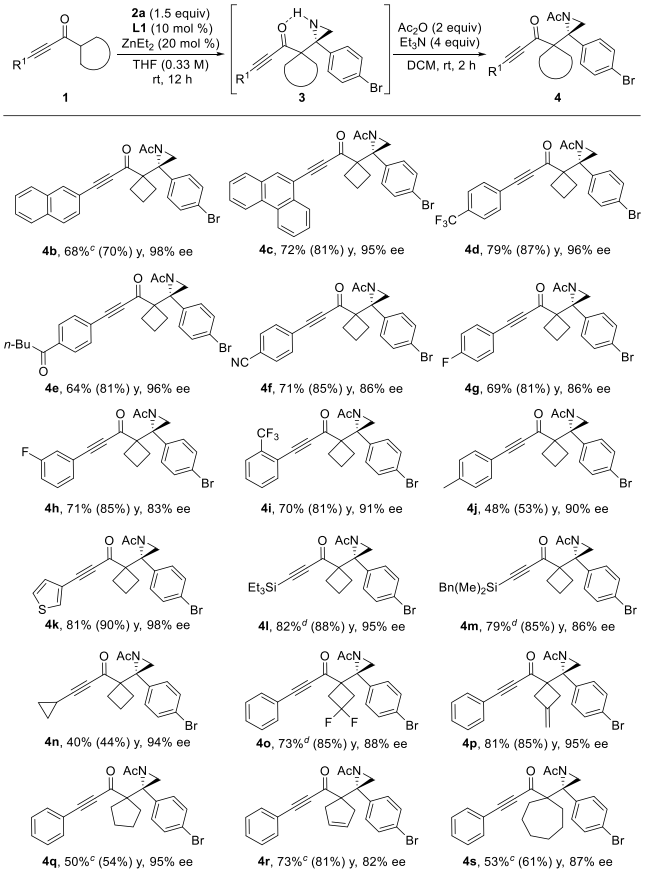
[a]All reactions were carried out with **1a** (0.1 mmol), **2a** (1.5 equiv), $ZnEt_2$ (20 mol %), and ligand (10 mol %) at rt in solvent (0.33 M) for 12 h under Ar. [b]Isolated yield of **4a**. The number in the parentheses was isolated yield of **3a**. [c]Ee of **4a** was determined by chiral HPLC.

ties and structural diversities and solvents were investigated, but no superior results were obtained (entries 2−9).

With the optimized conditions (Table 1, entry 1) in hand, we set out to evaluate the scope of alkynyl ketones that would participate in this reaction (Scheme 3). Electron-neutral naphthalene and phenanthrene substituted alkynyl ketones were well suitable substrates for this Zn-ProPhenol catalytic system (**4b** and **4c**). Alkynyl ketones with diverse valuable electron-withdrawing groups, such as the trifluoromethyl, carbonyl, cyano, and fluoro substituent on the *para*-, *meta*-, and *ortho*-position of the phenyl ring, all gave the desired products **4d−i** in high yield with high to excellent ee values. Especially, our Zn-ProPhenol catalytic system could efficiently distinguish two different carbonyl moieties in the same substrate, and adduct **4e** was isolated in 64% yield with 96% ee. An alkynyl ketone which has an electron-donating methyl group on the phenyl ring could also deliver adduct **4j** in reasonable yield with 90% ee. A heteroaromatic thienyl substituted alkynyl ketone afforded **4k** in 81% yield with 98% ee. The triethylsily group in **4l** can potentially be removed to deliver the terminal alkyne, and the benzyldimethylsily group in **4m** might be suitable for cross-coupling functionalization. Notably, an aliphatic cyclopropyl substituted alkynyl ketone also delivered product **4n** in acceptable yield with 94% ee. Furthermore, substrates bearing 3,3-difluorocyclobutyl and 3-methylenecyclobutyl moieties afforded products **4o** and **4p** in high yields with good ee values. It is worth noting that this cyclobutyl substituent in alkynyl ketones could be extended to the cyclopentyl, cyclopent-3-en-1-yl, and cycloheptyl group. The corresponding products **4q−s** were isolated in good to high yields with high enantioselectivities. Additionally, alkynyl ketones bearing both terminal and internal alkene moieties could be well tolerated in this catalytic system (**4p** and **4r**).

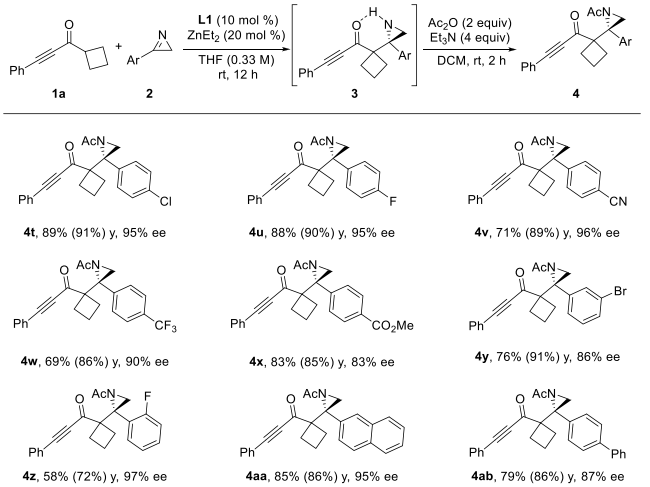
Next, various 2*H*-azirine electrophiles were examined with cyclobutyl substituted alkynyl ketone **1a** as the reaction partner. The results are summarized in Scheme 4. 2*H*-Azirines

Scheme 3. Scope of Alkynyl Ketone Nucleophiles[a,b]



[a]Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2a** (1.5 equiv), $ZnEt_2$ (20 mol %), and ligand **L1** (10 mol %) at rt in THF (0.33 M) for 12 h under Ar. [b]Isolated yields of **4**; the numbers in the parentheses were the isolated yield of **3**; ee was determined by chiral HPLC. [c]**L4** was used instead of **L1**. [d]AcCl was used instead of Ac_2O.

Scheme 4. Scope of 2*H*-Azirine Electrophiles[a,b]



[a]All reactions were carried out with **1a** (0.1 mmol), **2** (1.5 equiv), $ZnEt_2$ (20 mol %), and ligand **L1** (10 mol %) at rt in THF (0.33 M) for 12 h under Ar. [b]Isolated yields of **4**; the numbers in the parentheses were the isolated yield of **3**; ee was determined by chiral HPLC.

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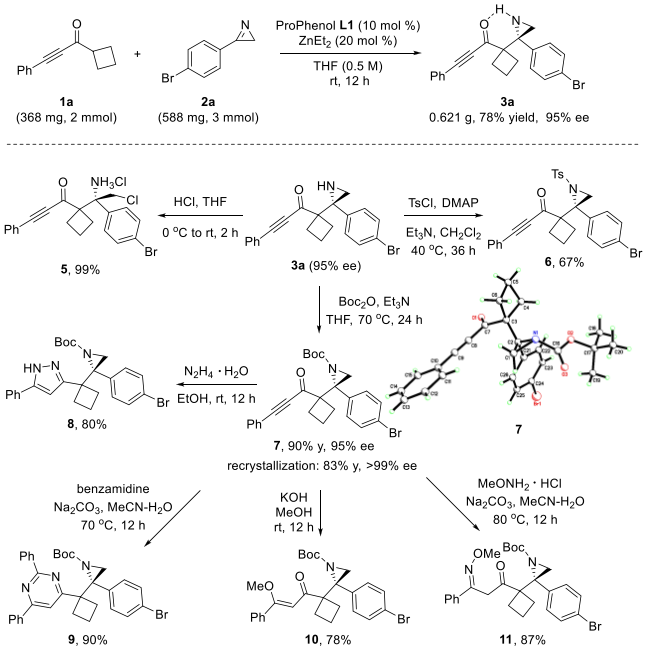
with electron-withdrawing chloro, fluoro, cyano, trifluoromethyl, and ester groups at different positions of the phenyl ring could all afford the desired products **4t−z** in high yields and high to excellent enantioselectivities. Electron-neutral 2-naphthyl and [1,1′-biphenyl]-4-yl substituted 2*H*-azirines are also good substrates as good results were obtained (**4aa** and **4ab**).

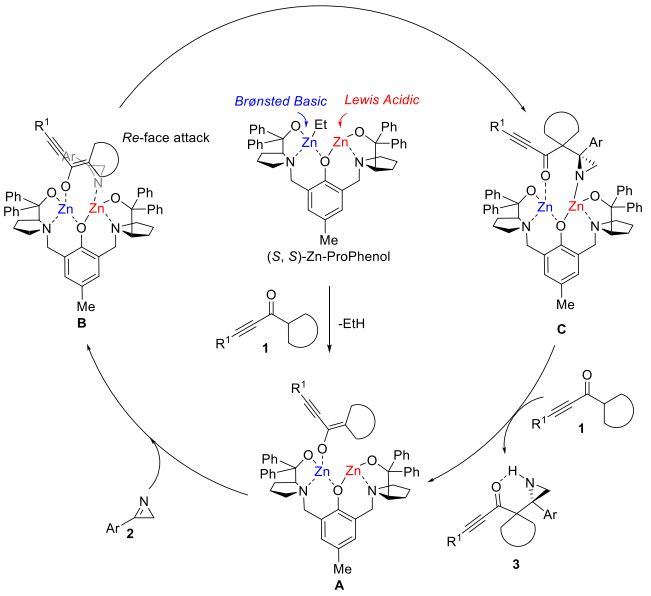
To further explore this unique protocol, a 2 mmol scale Mannich reaction of 2*H*-azirine **2a** and alkynyl ketone **1a** was carried out to afford **3a** in 78% yield with 95% ee (Scheme 5, above). Furthermore, the synthetic applications of these aziridines were explored with **3a** as a model substrate (Scheme 5, below). Ring opening of **3a** with hydrogen chloride gave the tertiary amine hydrogen chloride salt **5** in 99% yield. Given the broad applications of tosylated aziridines,[20] compound **6** was synthesized in 67% yield. Importantly, boc-protected aziridine **7** proved to be crystalline, and its structure, including its absolute configuration (*R*), was then determined by means of X-ray crystallographic analysis. Condensation of **7** with hydrazine monohydrate afforded pyrazole **8** smoothly, whereas treating **7** with benzamidine furnished pyrimidine **9** in 90% yield. Conjugate addition of **7** with methoxide delivered **10** in 78% yield. Finally, the hydration and selective dehydrative condensation of **7** with H_2O and *O*-methoxyamine hydrochloride gave ketone product **11** in 87% yield as a single regioisomer.

Scheme 5. Further Derivatizations of the Mannich Products



Based on the configuration of the obtained Mannich adduct, we propose the mechanism as outlined in Scheme 6 initiated by the generation of the dinuclear Zn-ProPhenl complex. Coordination and deprotonation of the alkynyl ketone by the Brønsted basic site of the catalyst gives zinc enolate **A**. Then the 2*H*-azirine coordinates to the Lewis acidic site of **A** to deliver the complex **B**, which directs the *re* face attack of alkynyl ketone to the 2*H*-azirine and affords complex **C**. Subsequently, the protonation and decomplexation of **C** with a second equivalent of alkynyl ketone provides the Mannich aziridine adduct and regenerates the zinc enolate **A**. The success of this unactivated imine derives from the strain and hybridization of the azirine. Importantly, the low basicity of the product's aziridine nitrogen decreases its coordination to zinc thus allowing catalyst turnover.

Scheme 6. Proposed Mechanism



In summary, our Zn-ProPhenol system efficiently achieves the direct Mannich reaction of a variety of alkynyl ketones to various 2*H*-azirines, delivering chiral aziridines with vicinal tetrasubstituted stereocenters in high yields (up to 91% yield) and excellent enantioselectivities (up to 98% ee). The key to the success of this reaction is that the dual roles (Brønsted base and Lewis acid) of the bimetallic Zn-ProPhenol complexes are capable of simultaneous activation of both the nucleophile and the electrophile in the same chiral pocket, which overcomes the hurdles associated with using nonstabilized enolates and poorly electrophilic cyclic 2*H*-azirines as the reactants. A unique intramolecular hydrogen bond is observed in the obtained Mannich adducts. These obtained Mannich adducts are densely functionalized and can be further elaborated into various potentially attractive molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03737.

Typical experimental procedures and characterization for all products (PDF)

Accession Codes

CCDC 2027241 (**7**) contains 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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nicolaou, K. C.; Rhoades, D.; Wang, Y.; Bai, R.; Hamel, E.; Aujay, M.; Sandoval, J.; Gavrilyuk, J. *J. Am. Chem. Soc.* **2017**, *139*, 7318−7334. (b) Nicolaou, K. C.; Shelke, Y. G.; Dherange, B. D.; Kempema, A.; Lin, B.; Gu, C.; Sandoval, J.; Hammond, M.; Aujay, M.; Gavrilyuk, J. *J. Org. Chem.* **2020**, *85*, 2865−2917. (c) Ding, Y.; Li, D.; Ding, C.; Wang, P.; Liu, Z.; Wold, E. A.; Ye, N.; Chen, H.; White, M. A.; Shen, Q.; Zhou, J. *J. Med. Chem.* **2018**, *61*, 2737−2752.

(2) (a) Lowden, P. A. S. Aziridine Natural Products-Discovery, Biological Activity and Biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 11, pp 399−442. (b) Menjo, Y.; Hamajima, A.; Sasaki, N.; Hamada, Y. *Org. Lett.* **2011**, *13*, 5744−5747.

(3) (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *2000*, 1347−1365. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082−2084. (d) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643−665. (e) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. O. *Chem. Rev.* **2014**, *114*, 8199−8256. (f) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954−8015. (g) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029−1040.

(4) (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2920. (c) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194−206. (d) Sweeney, J. *Eur. J. Org. Chem.* **2009**, *2009*, 4911−4919. (e) Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5538−5540. (f) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899−1935. (g) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881−7929.

(5) (a) Khlebnikov, A. F.; Novikov, M. S.; Rostovskii, N. V. *Tetrahedron* **2019**, *75*, 2555−2624. (b) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363−3401.

(6) (a) Hu, H.; Liu, Y.; Lin, L.; Zhang, Y.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 10098−10101. (b) An, D.; Guan, X.; Guan, R.; Jin, L.; Zhang, G.; Zhang, S. *Chem. Commun.* **2016**, *52*, 11211−11214. (c) Nakamura, S.; Hayama, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 8785−8789.

(7) Risberg, E.; Somfai, P. *Tetrahedron: Asymmetry* **2002**, *13*, 1957−1959.

(8) Peng, Q.; Guo, D.; Bie, J.; Wang, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 3767−3771.

(9) Zhang, H.-J.; Xie, Y.-C.; Yin, L. *Nat. Commun.* **2019**, *10*, 1699−1707.

(10) (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580−591. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569. (c) Macmillan, D. W. C. *Nature* **2008**, *455*, 304−308. (d) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117−1127. (e) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600−1632. (f) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348. (g) Zou, Y.-Q.; Hörmann, F. M.; Bach, T. *Chem. Soc. Rev.* **2018**, *47*, 278−290. (h) Trost, B. M.; Tracy, J. S. *Acc. Chem. Res.* **2020**, *53*, 1568−1579.

(11) (a) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600−1632. (b) Meyer, C. C.; Ortiz, E.; Krische, M. J. *Chem. Rev.* **2020**, *120*, 3721−3748.

(12) Hu, H.; Xu, J.; Liu, W.; Dong, S.; Lin, L.; Feng, X. *Org. Lett.* **2018**, *20*, 5601−5605.

(13) (a) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688−701. (b) Trost, B. M.; Hung, C. I. J.; Mata, G. *Angew. Chem., Int. Ed.* **2020**, *59*, 4240−4261.

(14) (a) Trost, B. M.; Saget, T.; Lerchen, A.; Hung, C. I. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 781−784. (b) Trost, B. M.; Saget, T.; Hung, C. I. J. *J. Am. Chem. Soc.* **2016**, *138*, 3659−3662. (c) Trost, B. M.; Gnanamani, E.; Tracy, J. S.; Kalnmals, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 18198−18201. (d) Trost, B. M.; Saget, T.; Hung, C. I. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 2440−2444. (e) Trost, B. M.; Hung, C. I. J.; Scharf, M. I. *Angew. Chem., Int. Ed.* **2018**, *57*, 11408−11412. (f) Trost, B. M.; Hung, C. I. J.; Saget, T.; Gnanamani, E. *Nat. Catal.* **2018**, *1*, 523−530. (g) Trost, B. M.; Hung, C. I. J.; Gnanamani, E. *ACS Catal.* **2019**, *9*, 1549−1557. (h) Trost, B. M.; Tracy, J. S.; Yusoontorn, T.; Hung, C. I. J. *Angew. Chem., Int. Ed.* **2020**, *59*, 2370−2374.

(15) (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485−1538. (b) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740−7752. (c) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272−286. (d) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257−8322.

(16) Chan, J. Z.; Yao, W. Z.; Hastings, B. T.; Lok, C. K.; Wasa, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 13877−13881.

(17) *Modern alkyne chemistry. Catalytic and atom-economic transformations*; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, 2015.

(18) (a) Gardner, D. S.; Santella, J. B.; Duncia, J. V.; Carter, P. H.; Dhar, T. G. M.; Wu, H.; Guo, W.; Cavallaro, C.; van Kirk, K.; Yarde, M.; Briceno, S. W.; Grafstrom, R. R.; Liu, R.; Patel, S. R.; Tebben, A. J.; Camac, D.; Khan, J.; Watson, A.; Yang, G.; Rose, A.; Foster, W. R.; Cvijic, M. E.; Davies, P.; Hynes, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3833−3840. (b) Andrews, D. M.; Carey, S. J.; Chaignot, H.; Coomber, B. A.; Gray, N. M.; Hind, S. L.; Jones, P. S.; Mills, G.; Robinson, J. E.; Slater, M. J. *Org. Lett.* **2002**, *4*, 4475−4478.

(19) Different solvents such as $CDCl_3$, d_6-DMSO, d_3-MeOD, and d_6-Benzene at different analysis temperatures were tested.

(20) Takeda, Y.; Sameera, W. M. C.; Minakata, S. *Acc. Chem. Res.* **2020**, *53*, 1686−1702.