Synthesis of Amido-Spiro[2.2]Pentanes via Simmons-Smith Cyclopropanation of Allenamides.[†]

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Abstract

A detailed account on Simmons-Smith cyclopropanations of allenamides *en route* to amido-spiro [2.2]pentanes is described here. While the diastereoselectivity was low when using unsubstituted allenamides, the reaction is overall efficient and general, representing the most direct synthesis of both chemically and biologically interesting amido-spiro[2.2]pentane systems. With α-substituted allenamides, while the diastereoselectivity could be improved significantly based on a series of conformational analysis, both mono- and bis-cyclopropanation products were observed. Consequently, several structurally intriguing amido-methylene cyclopropanes could also be prepared.

Introduction

Spiro[2.2]pentanes,[1] the smallest member of the triangulane or oligo-spirocyclopropane family, represent a unique structural topology with both rigidity and orthogonality that have found applications in a number of biological contexts.[2] In particular, simple α-spiropentyl acetic acid [Figure 1] has been shown to mimic α-(methylenecyclopropyl) acetic acid, a well-known inhibitor against acyl-CoA dehydrogenase that is critical in the fatty acid oxidation pathway. In addition, α-(methylenecyclopropyl) acetic acid itself has also been identified as a toxic metabolite of the natural amino acid hypoglycine A found in the fruits of Jamaican ackee trees.[3−7] Consequently, it is a key cause of vomiting sickness when ingesting the Jamaican ackee fruit due to the resulting deficiency it causes in the acyl-CoA dehydrogenase activity. [8,9] Moreover, amino-spiro[2.2]pentanes have received much attention recently for an array of other purposes ranging from constructing deoxyribonucleotide analogs[10] to exploring the chemistry and biology of spiro[2.2]pentane amino acid derivatives.[11,12]

Despite these biological interests, and despite a number of elegant approaches toward spiro [2.2]pentanes in literature, the overall synthetic effort toward amino-spiro[2.2]pentanes has been limited.[2,13] Few involve direct bis-cyclopropanations of allenes[14] with many adopting mono-cyclopropanations of methylene cyclopropanes prepared through other means.[15] To the best of our knowledge, preparation of amino-spiro[2.2]pentanes directly through bis-cyclopropanations of 1-amino-allenes is not known.[2,10−13,16] Our recent interest[17,18] in cyclopropanations of enamides[13,19,20] *en route* to optically enriched amino-cyclopropanes[21,22] coupled with our decade long efforts in developing the chemistry of allenamides[23−26] allowed us to envision the possibility of developing a direct construction of

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[†]Experimental Electronic supplementary information (ESI) available: experimental procedures, ^{1}H NMR spectra, characterizations for all new compounds, and X-ray structural data.

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amido-spiro[2.2]pentanes via Simmons-Smith cyclopropanation of allenamides **1** [Scheme 1]. Based on our previous work on a number of different stereoselective cycloaddition manifolds employing allenamides,[27] we anticipated that this cyclopropanation could proceed stereoselectively in which the zinc carbenoid can approach the bottom π-face of the more favored conformer **1a** [Scheme 1]. This would lead to methylene cyclopropane **2**, and while **2** is useful in its own right,[28] an ensuing second cyclopropanation would provide **3a** as the major amino-spiro[2.2]pentane isomer with **3b** being derived from cyclopropanation of the minor conformer **1b**. We report here details of these investigations.

Results and Discussions

1. Cyclopropanations of α-Unsubstituted Allenamides

The feasibility for Simmons-Smith cyclopropanations of allenamides was quickly established as shown in Scheme 2. By using 5.0 equiv Et_2Zn and 10.0 equiv ICH_2-X, cyclopropanation of achiral allenamide **4** proceeded in excellent yields to give amido-spiro[2.2]pentane **6**[29] with no difference between using ICH_2-I and ICH_2-Cl respectively in CH_2Cl_2 and $ClCH_2CH_2Cl$ [DCE]. We did not observe any mono-cyclopropanation product **5** after 12 h, suggesting that the second cyclopropanation via **5** took place rapidly in these reactions with $Zn(CH_2X)_2$ serving as the highly reactive cyclopropanating species.[30]

We turned our attention to chiral allenamides using specifically **7** [Table 1], and while the cyclopropanation was equally effective in providing *de novo* amido-spiro[2.2]pentane **9**, the diastereomeric ratio was not desirable. We explored a range of conditions[13a] including different temperatures [entries 1–4] and solvents [entries 5–7], while featuring $Zn(CH_2Cl)_2$ as the cyclopropanating species. In addition, we examined the nature of cyclopropanating species such as $Zn(CH_2I)_2$ either without [entry 8] or with the addition of a chelating solvent such as DME [rendering the zinc cyclopropanating reagent more nucleophilic] [entry 9]. Finally, we explored Furukawa type reagents [entries 10–12][31,32] as well as Yamamoto's $AlMe_3$ activation of ICH_2-I [entry 13].[33]

We did not continue to pursue other cyclopropanating species such as Molander's Sm-Hg activation of ICH_2-Cl,[34] as we recognized that we were not going to improve the diastereomeric ratio of amido-spiro[2.2]pentane **9** via bis-cyclopropanation of **7** by only using different cyclopropanating species. It is noteworthy that this effort allowed us to observe by ^{1}H NMR the mono-cyclopropanation product **8**, although not isolated [entries 3 and 9]. This implies that the 2nd cyclopropanation is slower for chiral allenamides. Stereochemically, both the major and minor diastereomers of **9** were unambiguously assigned using single-crystal X-ray structures as shown in Figure 2. The ability to access both diastereomers of these structurally very interesting and novel amido-spiro[2.2]pentanes renders this none-stereoselective aspect of this reaction an opportunity and less of a limitation.

Subsequently, a number of chiral auxiliaries on the allenamide were probed in an attempt to improve the diastereoselectivity. As shown in Scheme 3, amido-spiro[2.2]pentanes such as **10**, **11**, **14**, and **15** could be attained in good yields through bis-cyclopropanations of their respective allenamides. However, the diastereomeric ratio remained low, and when employing the more bulky Sibi's auxiliary[35] or Seebach's auxiliary,[36] the reaction appeared to be shut down, as only trace amounts of amido-spiro[2.2]pentanes **12** and **16** could be found. Close's auxiliary[37] gave the best ratio in **17** but with a lower yield. There is essentially no difference in the level of stereoselectivity between using auxiliaries containing just the mono-substitution alpha to the amido-nitrogen atom [see **10**–**12**] and those with vicinal substitutions on the oxazolidinone ring [see **14**–**17**].

2. A Comparison with Chiral Enamides

While the lack of diastereoselectivity was frustrating, it intrigued us mechanistically. We had previously examined Simmons-Smith cyclopropanations of chiral enamides and achieved a much greater success in stereochemical control.[17] As shown in Scheme 4, chiral *E*-enamides such as **18** and *E*-**19** gave amido-cyclopropanes **20** and *trans*-**21** with diastereomeric ratios of 95:5 and 83:17, respectively, while chiral *Z*-enamides such as **22** and *Z*-**19** led to even higher diastereomeric ratios of ≥95:5 in each case. These results are in direct contrast to our current cyclopropanation work

To rationalize the above stereochemical outcome, we examined conformations of these enamides through both X-ray structures [see structures of *E*-**19** and *Z*-**19** in Figure 3] and PM3 calculations via Spartan Model.™ Both the X-ray structure [see *E*-**19**] and computation model revealed that *E*-enamides [R = alkyl or aryl] assume the more favorable conformation E_1 [Scheme 5], which was what we had speculated earlier in some epoxidation work.[38,39] The other locally minimized conformation is E_2 but it is less favored than E_1 by 1.17 kcal mol^{-1}. In both conformers, the olefin is approaching co-planarity with the oxazolidinone ring, allowing delocalization of the nitrogen lone pair into the olefin. Being devoid of actual transition state calculations, we will make an assumption here that these cyclopropnations proceed through the major enamide [or allenamide] conformer with the awareness that Curtin-Hamette could very well be in play here, and that we are only attempting to identif a model with some consistent rationale and predictative power at this juncture.

Based on this assumption, if the cyclopropanation proceeds through the more favored conformation E_1, the necessary π-facial differentiation in E_1 would provide the excellent stereochemical outcome with E_2 being a possible source for the minor diastereomer. On the other hand, in both the X-ray structure [see *Z*-**19** in Figure 3] and computation model of *Z*-enamides, there is a distinct shift from a coplanar motif in conformation Z_1 to the more favored Z_2 [$\Delta E = -1.03$ to -1.28 kcal mol^{-1}]. This is likely due to the oxazolidinone ring rotating along the C-N bond toward the direction so that the Ph substituent could be shifted away from the R group to alleviate the allylic strain. Despite such conformational change relative to *E*-enamides, the bottom π-face in the more favored conformation Z_2 remains sterically more accessible, thereby providing the same sense of facial selectivity in the cyclopropanation as for the *E*-enamide.

Although we have not examined this in detail, the greater diastereoselectivity attained for *Z*-enamides relative to those of *E*-enamides could be a result of a greater shielding of the top face by the phenyl ring, and/or a possible chelation of the oxazolidinone carbonyl oxygen with the zinc reagent in a directed cyclopropanation manner.

In contrast, while chiral allenamides assume a similar set of conformations[40] as shown in Scheme 6, calculations [PM3 calculations via Spartan Model™] suggest that the energetic difference between conformers **24a** and **24b** [see $\Delta E = -0.21$ kcal mol^{-1} for R = H] appears to be relatively much smaller than those from enamides. In addition, we also find that the first cyclopropanation is very facile relative to the cyclopropanation of enamides. In general, the starting allenamides are consumed within 1–2 h at 0 °C [or rt] based on monitoring by NMR, leading to **25-M$_a$** and **25-M$_b$**, whereas cyclopropanation of enamides in most cases required 24–72 h.[17] A mixture of mono- and bis-cyclopropanation products with a ratio of 1:1.5 was usually seen after 3 h at 0 °C, and the long reaction time is associated with the second cyclopropanation, leading to **25-B$_a$** and **25-B$_b$**.

Consequently, again, based on the assumption that these cyclopropnations also proceed through the major allenamide conformer, the lack of diastereoselectivity observed in Simmons-Smith cyclopropanations of allenamides could be due to a facile cyclopropanation through an almost

equal distribution of unsubstituted allenamide conformers **24a** and **24b** [for R = H]. While this proposed model is based on ground state energetic difference, if valid, α-substituted allenamides [for R ≠ H] would then lead to an improved selectivity because **24a** is now favored by 1.05 kcal mol^{-1} [for R = Me] over **24b** due to its the enhanced allylic strain.

3. Cyclopropanations of α-Substituted Allenamides

Based on the above conformational model, we prepared α-substituted achiral allenamides **26–28** [Scheme 7] through α-alkylation of the respective unsubstituted allenamides.[41] Cyclopropanations of allenamides **26–28** were not only feasible, but also led to the observation and isolation of a substantial amount of mono-cyclopropanation products **29-M** through **31-M**. In the case of allenamide **28**, we isolated 60% of mono-cyclopropane **31-M**. These results suggest that α-substituted allenamides further impede the second cyclopropanation compared to unsubstituted chiral allenamides. The unique structural motif of the amido-methylene cyclopropane **31-M** is displayed in Figure 4 through its single-crystal X-ray structure.

We proceeded to examine α-substituted chiral allenamides **32–35** as shown in Table 2. In all cases, we isolated both mono-[**36-M** through **39-M**] and bis-cyclopropanation products [**36-B** through **39-B**]. A longer reaction time usually resulted in more of the respective bis-cyclopropanation product. In accord with our conformational analysis, the diastereomeric ratio was indeed improved with a dependence on the size of the R groups. The stereochemistry of **37-B** was unambiguously assigned using X-ray structural analysis [Figure 4].

To ensure that major isomers of mono- and bis-scyclopropanation product **37-M** and **37-B** in fact possess the same stereochemistry at the carbon bearing the amido group, amido-methylene cyclopropane **37-M** was subjected to the same cyclopropanation conditions [Scheme 8]. While the reaction was slow and incomplete, we found a 43% yield of **37-B** [as a single isomer], thereby confirming that the major isomer of bis-cyclopropanation products indeed comes from a second cyclopropanation of the major isomer of the respective mono-cyclopropanation products. This assessment would then translate the individual ratios of mono- and bis-cyclopropanation into an excellent overall or combined diastereoselectivity for the first cyclopropanation [see numbers in red] that correlates well overall with increasing in the size of the R group, and provide a solid support for the conformational model proposed above.

Lastly, the rate of the second cyclopropanation appears to be directly correlated with the degree of steric crowding of either π-face of the methylene cyclopropane intermediate. As shown in Scheme 9, in the case of unsubstituted allenamides, both p-faces of the olefin in achiral amido-methylene cyclopropane **5** are open for the second cyclopropanation, whereas chiral amido-methylene cyclopropane *ent*-**8** is blocked on the bottom p-face with the top still available. Thus, we did not observe amido-methylene cyclopropane **5** but saw *ent*-**8** in 12 h under the same reaction conditions. For α-substituted allenamides, both π-faces of amido-methylene cyclopropanes such as **29–31** and **36-M** through **39-M** are now sterically more encumbered. Consequently, the second cyclopropanation of **29–31** and **36-M** through **39-M** should be slower relative to those of **5** and *ent*-**8**, leading to the observation and/or isolation of methylene cyclopropanes for α-substituted allenamides.

Conclusion

We have described here Simmons-Smith cyclopropanations of allenamides in the synthesis of amido-spiro[2.2]pentanes. While the diastereoselectivity was low when using unsubstituted allenamides, the reaction is overall efficient and general, leading to an array of amido-spiro [2.2]pentanes. With α-substituted allenamides, while the diastereoselectivity could be improved significantly based on a conformational analysis, both mono- and bis-cyclopropanations were observed in these cases. Consequently, several structurally intriguing

amido-methylene cyclopropanes could also be prepared. With allenamides being readily accessible, these efforts have yielded the most straightforward protocol in constructing chemically and biologically intriguing amido-spiro[2.2]pentane systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. For the earliest example, see: (a) Gustavson G. J. Prakt. Chem 1896;54:97. For early accounts, see: (b) Rogowski F. Chem. Ber 1939;72B:2021. (c) Murray MJ, Stevenson EH. J. Am. Chem. Soc 1944;66:812. (d) Donohue J, Humphrey GL, Schomaker V. J. Am. Chem. Soc 1945;67:332.

2. For a leading review see: de Meijere A, Kozhushkov SI. Chem. Rev 2000;100:93. [PubMed: 11749235]

3. Tserng KY, Jin S-J, Hoppel CL. Biochemistry 1991;30:10755. [PubMed: 1931995]

4. Li D, Zhou H-Q, Dakoji S, Shin I, Oh E, Liu H-W. J. Am. Chem. Soc 1998;120:2008.

5. (a) Osmundsen H, Sherratt HSA. FEBS Lett 1975;55:81. [PubMed: 1140430] (b) Kean EA. Biochem. Biophys. Acta 1976;422:81.(c) Abeles, RH. Enzyme Activated Irreversible Inhibitors. Seiler, N.; Jung, MJ.; Koch-Weser, J., editors. Amsterdam: Elsevier-North-Holland Press; 1978. p. 1(d) Ghisla, S.; Wenz, A.; Thorpe, C. Enzyme Inhibitors. Brodbeck, U., editor. Weinheim, Germany: Verlag Chim Press; 1980. p. 43 (e) Wenz A, Thorpe C, Ghisla S. J. Biol. Chem 1981;256:9809. [PubMed: 7275979] (f) Ghisla, S.; Melde, K.; Zeller, HD.; Boschert, W. Fatty Acid Oxidation; Clinical, Biochemical, and Molecular Aspects. Tanaka, K.; Coates, PM.; Alan, R., editors. New York: Liss, Inc. Press; 1990. p. 185

6. (a) Lai M-T, Li D, Oh E, Liu H-W. J. Am. Chem. Soc 1993;115:1619. (b) Lai M-T, Liu H-W. J. Am. Chem. Soc 1992;114:3160. (c) Lai M-T, Liu H-W. J. Am. Chem. Soc 1991;113:7388. (d) Lai M-T, Liu H-W. J. Am. Chem. Soc 1990;112:4034. (e) Lenn ND, Shih Y, Stankovich MT, Liu H-W. J. Am. Chem. Soc 1989;111:3065.

7. (a) Baldwin JE, Adlington RM, Bebbinton D, Riussell AT. Tetrahedron 1994;50:12015. (b) Baldwin JE, Widdison WC. J. Am. Chem. Soc 1992;114:2245. (c) Baldwin JE, Ostrander RL, Simon CD, Widdison WC. J. Am. Chem. Soc 1990;112:2021. (d) Baldwin JE, Parker DW. J. Org. Chem 1987;52:1475.

8. (a) Tanaka K, Isselbacher KJ, Shih V. Science 1972;175:69. [PubMed: 5008580] (b) Holt C, von Holt M, Bohm H. Biochim. Biophys. Acta 1966;125:11. [PubMed: 5968584] (c) Black DK, Landor SR. J. Chem. Soc. C 1968:288.

9. (a) Tanaka, K. Handbook of Clinical Neurology. Vinken, PJ.; Bruyn, GW., editors. Vol. Vol. 37. Amsterdam: Elsevier-North Holland Press; 1979. p. 511-513.(b) Stuart, KL. Hypoglycin. Kean, EA., editor. New York: Academic Press; 1975. p. 39

10. Guan H-P, Ksebati MB, Cheng Y-C, Drach JC, Kern ER, Zemlicka J. J. Org Chem 2000;65:1280. [PubMed: 10814087]

11. de Meijere A, Ernst K, Zuck B, Brandl M, Kozhushkov SI, Tamm M, Yufit DS, Howard JAK, Labahn T. Eur. J. Org. Chem 1999:3105.

12. Pellicciari R, Marinozzi M, Camaioni E, del Carmen Nnez M, Costantino G, Gasparini F, Giorgi G, Macchiarulo A, Subramanian N. J. Org. Chem 2002;67:5497. [PubMed: 12153247]

13. For a leading review on cyclopropanations, see: (a) Lebel H, Marcoux J-F, Molinaro C, Charette AB. Chem. Rev 2003;103:977. [PubMed: 12683775] For other reviews on cyclopropanations, see: (b) Doyle MP. Chem. Rev 1986;86:919. (c) Padwa A, Krumpe KE. Tetrahedron 1992;48:5385. (d) Calter MA. Curr. Org. Chem 1997;1:37. (e) Doyle MP, Forbe DC. Chem. Rev 1998;98:911. [PubMed: 11848918] (f) Davies HML, Autoulinakis E. Org. React 2003;57:1. (g) Maas G. Chem. Soc. Rev 2004;33:183. [PubMed: 15026823] (h) Doyle MP. J. Org. Chem 2006;71:9253. [PubMed: 17137350]

(i) Brackmann F, de Meijere A. Chem. Rev 2007;107:4493. [PubMed: 17944521] (j) Pellissier H. Tetrahedron 2008;64:7041.

14. For some examples, see: (a) Charette AB, Jolicoeur E, Bydlinski GAS. Org. Lett 2001;3:3293. [PubMed: 11594817] (b) Lautens M, Delanghe PHM. J. Am. Chem. Soc 1994;116:8526. (c) Lautens M, Delanghe PHM. Org. Chem 1993;58:5037. (d) Russo JA, Price WA. J. Org. Chem 1993;58:3589. (e) Zefirov NS, Kozhushkov SI, Kuznetsova TS, Lukin KA, Kazimirchik IV. Zh. Org. Khim 1988;24:673. For earlier work, see: (f) Ullman E, Fanshave WJ. J. Am. Chem. Soc 1961;83:2379. (g) Rahman W, Kuivila HG. J. Org. Chem 1966;31:772. (h) Noyori R, Takaya H, Nakanisi Y, Nozaki H. Can. J. Chem 1969;47:1242. (i) Also see reference [4].

15. For some examples, see: (a) Gajewski JJ, Burka LT. J. Org. Chem 1970;35:2190. (b) Trost BM, Bogdanowicz MJ. J. Am. Chem. Soc 1973;95:5307. (c) Zefirov NS, Kozhushkov SI, Ugrak BI, Lukin KA, Kokoreva OV, Yufit DS, Struchkov YT, Zoellner S, Boese R, Demeijere A. J. Org. Chem 1992;57:701. (d) Weber M, de Meijere A. Chem. Ber 1986;118:2450. (e) Akhachinskauya IV, Donskaya NA, Kalykina IV, Oprunenko YF, Shabarov YS. Zh. Org. Khim 1989;25:1645. (f) Cheng C, Shimo T, Somekawa K, Kawaminami M. Tetrahedron Lett 1997;52:9005. (g) Muehling O, Wessig P. Photochemical & Photobiological Sciences 2006;5:1000. [PubMed: 17077895] (*h*) Also see reference [4].

16. For some other examples of amino-spiro[2.2]pentane synthesis, see: (a) Yashin NV, Averina EB, Grishin YK, Kuznetsova TS, Zefirov NS. Synthesis 2006:279. (b) Applequist DE, Johnston MR, Fisher F. J. Am. Chem. Soc 1970;92:4614. (c) Konzelma LM, Conley RT. J. Org. Chem 1968;33:3828.

17. Song Z, Lu T, Hsung RP, Al-Rashid ZF, Ko C, Tang Y. Angew. Chem. Int. Ed 2007;46:4069.

18. Lu T, Song Z, Hsung RP. Org. Lett 2008;10:541. [PubMed: 18205371]

19. For some examples of cyclopropanations of enamides, see: (a) Melby T, Hughes E, Hansen T. Synlett 2007:2277. (b) Aggarwal VK, Vicente J, Bonnert RV. Org. Lett 2001;3:2785. [PubMed: 11506634] (c) Voigt J, Noltemeyer M, Reiser O. Synlett 1997;202 (d) Jiménez J, Rifé J, Ortuño RM. Tetrahedron Asym 1996;7:537. (e) Arenare L, De Carprariis P, Marinozzi M, Natalini B, Pellicciari R. Tetrahedron Lett 1994;35:1425. (f) Akiba T, Tamura O, Hashimoto M, Kobayashi Y, Katoh T, Nakatani K, Kamada M, Hayakawa I, Terashima S. Tetrahedron 1994;50:3905. (g) Paulini K, Reissig H-U. Liebigs Ann. Chem 1991:455. (h) Davies HML, Saikali E, Young WB. J. Org. Chem 1991;56:5696. (i) Seebach D, Stucky G, Pfammatter E. Chem. Ber 1989;122:2377. (j) Seebach D, Stucky G. Angew. Chem. Int. Ed 1988;27:1351. (k) Wenkert E, Hudlicky T. J. Org. Chem 1988;53:1953.

20. For reviews of chemistry of enamides, see: (a) Rappoport, Z. The Chemistry of Enamines in The Chemistry of Functional Groups. New York: John Wiley and Sons Press; 1994. (b) Whitesell JK, Whitesell MA. Synthesis 1983;517 (c) Hickmott PW. Tetrahedron 1982;38:1975–3363. (*d*) For a review on the synthesis of enamides, see: Tracey, MR.; Hsung, RP.; Antoline, JE.; Kurtz, KCM.; Shen, L.; Slafer, BW.; Zhang, Y. Science of Synthesis, Houben-Weyl Methods of Molecular Transformations. Steve, M., editor. Weinreb, Georg Thieme Verlag KG Press; 2005. Chapter 21.4.

21. For leading reviews on amino-cyclopropanes, see: (a) Gnad F, Reiser O. Chem. Rev 2003;103:1603. [PubMed: 12683791] (b) Seebach D, Matthews JL. Chem. Commun 1997:2015. (c) Gellman SH. Acc. Chem. Res 1998;31:173. (d) Burgess K, Ho KK, Moyesherman D. Synlett 1994:575. (e) Alami A, Calmes M, Daunis J, Jacquier R. Bull. Soc. Chim. Fr 1993;130:5.

22. For recent examples, see: (a) Faler CA, Joullié MM. Org. Lett 2007;9:1987. [PubMed: 17447776] (b) Zeng XZ, Wei XD, Farina V, Napolitano E, Xu YB, Zhang L, Haddad N, Yee NK, Grinberg N, Shen S, Senanayake CH. J. Org. Chem 2006;71:8864. [PubMed: 17081017] (c) Begis G, Sheppard TD, Cladingboel DE, Motherwell WB, Tocher DA. Synthesis 2005:3186.

23. For a leading review on allenamides, see: Hsung RP, Wei L-L, Xiong H. Acc. Chem. Res 2003;36:773. [PubMed: 14567711]

24. For a compendium on the chemistry of allenes, see: (a) Krause, N.; Hashmi, ASK. Modern Allene Chemistry. Vol. vol. 1 and 2. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA Press; 2004. For general reviews on the chemistry of allenes, see: (b) Brummond KM, Kent JL. Tetrahedron 2000;56:3263. (c) Ma S. Chem. Rev 2005;105:2829. [PubMed: 16011326]

25. For recent reports on allenamide chemistry, see: (a) Skucas E, Zbieg JR, Krische MJ. J. Am. Chem. Soc 2009;131:5054. [PubMed: 19317402] (b) Armstrong A, Emmerson DPG. Org. Lett

2009;11:1547. [PubMed: 19254002] (c) Beccalli EM, Broggini G, Clerici F, Galli S, Kammerer C, Rigamonti M, Sottocornola S. Org. Lett 2009;11:1563. [PubMed: 19260702] (d) Broggini G, Galli S, Rigamonti M, Sottocornola S, Zecchi G. Tetrahedron Lett 2009;50:1447. (e) Brummond KM, Yan B. Synlett 2008:2303. (f) Fuwa H, Tako T, Ebine M, Sasaki M. Chem. Lett 2008;37:904. (g) González-Gómez Á, Añorbe L, Poblador A, Domínguez G, Pérez-Castells J. Eur. J. Org. Chem 2008:1370. (h) Navarro-Vázquez A, Rodríguez D, Martínez-Esperón MF, García A, Saá C, Domínguez D. Tetrahedron Lett 2007;48:2741. (i) Fuwa H, Sasaki M. Org. Biomol. Chem 2007;5:2214. [PubMed: 17609751] (j) Watanabe T, Oishi S, Fuji N, Ohno H. Org. Lett 2007;9:4821. [PubMed: 17924641] (k) Hyland CJT, Hegedus LS. J. Org. Chem 2006;71:8658. [PubMed: 17064053] (l) Parthasarathy K, Jeganmohan M, Cheng C-H. Org. Lett 2006;8:621. [PubMed: 16468726] (m) Fenández I, Monterde MI, Plumet J. Tetrahedron Lett 2005;46:6029. (n) Alouane N, Bernaud F, Marrot J, Vrancken E, Mangeney P. Org. Lett 2005;7:5797. [PubMed: 16354069] (o) de los Rios C, Hegedus LS. J. Org. Chem 2005;70:6541. [PubMed: 16050728] (p) Hyland CJT, Hegedus LS. J. Org. Chem 2005;70:8628. [PubMed: 16209626] (q) Trost BM, Dylan ST. Org. Lett 2005;7:2117. [PubMed: 15901148]

26. For our recent efforts, see: (a) Song Z, Hsung RP, Lu T, Lohse AG. J. Org. Chem 2007;72:9722. [PubMed: 17979293] (b) Song Z, Hsung RP. Org. Lett 2007;9:2199. [PubMed: 17480091] (c) Huang J, Ianni JC, Antoline JE, Hsung RP, Kozlowski MC. Org. Lett 2006;8:1565. [PubMed: 16597111] (d) Shen L, Hsung RP. Org. Lett 2005;7:775. [PubMed: 15727438] (e) Berry CR, Hsung RP, Antoline JE, Petersen ME, Rameshkumar C, Nielson JA. J. Org. Chem 2005;70:4038. [PubMed: 15876094] (f) Shen L, Hsung RP, Zhang Y, Antoline JE, Zhang X. Org. Lett 2005;7:3081. [PubMed: 15987210] (g) Huang J, Hsung RP. J. Am. Chem. Soc 2005;127:50. [PubMed: 15631443]

27. For [4 + 3] cycloadditions, see: (a) Antoline JE, Hsung RP. Synlett 2008:739. (b) Antoline JE, Hsung RP, Huang J, Song Z, Li G. Org. Lett 2007;9:1275. [PubMed: 17335226] (c) Xiong H, Hsung RP, Berry CR, Rameshkumar C. J. Am. Chem. Soc 2001;123:7174. [PubMed: 11459504] (d) Huang J, Hsung RP. J. Am. Chem. Soc 2005;127:50. [PubMed: 15631443] (e) Rameshkumar C, Hsung RP. Angew. Chem. Int. Ed 2004;43:615. (f) Xiong H, Huang J, Ghosh S, Hsung RP. J. Am. Chem. Soc 2003;125:12694. [PubMed: 14558802] For hetero-[4 + 2] cycloadditions, see: (g) Berry CR, Hsung RP. Tetrahedron 2004;60:7629. (h) Wei L-L, Hsung RP, Xiong H, Mulder JA, Nkansah NT. Org. Lett 1999;1:2145. For epoxidations, see: (i) Rameshkumar C, Xiong H, Tracey M, Berry CR, Yao LJ, Hsung RP. J. Org. Chem 2002;67:1339. [PubMed: 11846684]

28. Without citing specific examples, for leading reviews, see: (a) Rubin M, Rubina M, Gevorgyan V. Chem. Rev 2007;107:3117. [PubMed: 17622181] (b) Brandi A, Cicchi S, Cordero FM, Goti A. Chem. Rev 2003;103:1213. [PubMed: 12683782]

29. See Supporting Information.Crystallographic data for **9a**: $C_{14}H_{15}NO_2$, M = 229.27, triclinic, $P1$, a = 6.2295(4), b = 11.8164(7), c = 12.8744(8) Å, α = 84.5470(10), β = 86.5820(10), γ = 76.4120(10)°, V = 916.30(10) Å^3, T = 173(2) K, Z = 3, μ = 0.083 mm^{-1}, 3730(R_{int}=0.0242), final R indices[$I >$ 2$\sigma(I)$], R_1 = 0.0320, wR_2 = 0.0732, R indeces (all data) R_1 = 0.0424, wR_2 = 0.0793.Crystallographic data for **9b**: $C_{14}H_{15}NO_2$, M = 229.27, orthorhombic, $P2_12_12_1$, a = 6.4331(18), b = 11.657(3), c = 15.860(4) Å, α = 90, β = 90, γ = 90 °, V = 1189.4(6) Å^3, T = 173(2) K, Z = 4, μ = 0.086 mm^{-1}, 1265 (R_{int}=0.0431), final R indices[$I > 2\sigma$ (I)], R_1 = 0.0329, wR_2 = 0.0756, R indeces (all data) R_1 = 0.0416, wR_2 = 0.0815.Crystallographic data for E-**19**: $C_{17}H_{15}NO_2$, M = 265.30, orthorhombic, $P2_12_12_1$, a = 6.0167(5), b = 10.2379(9), c = 22.355(2) Å, α = 90, β = 90, γ = 90 °, V = 1377.0(2) Å^3, T = 173(2) K, Z = 4, μ = 0.084 mm^{-1}, 1790(R_{int}=0.0439), final R indices[$I > 2\sigma(I)$], R_1 = 0.0329, wR_2 = 0.0761, R indeces (all data) R_1 = 0.0460, wR_2 = 0.0803.Crystallographic data for Z-**19**: $C_{17}H_{15}NO_2$, M = 265.30, monoclinic, $C2$, a = 30.294(8), b = 6.4077(17), c = 7.0525(19) Å, α = 90, β = 100.238(4), γ = 90 °, V = 1347.2(6) Å^3, T = 173(2) K, Z = 4, μ = 0.086 mm^{-1}, 1492(R_{int}=0.0503), final R indices[$I > 2\sigma(I)$], R_1 = 0.0394, wR_2 = 0.0868, R indeces (all data) R_1 = 0.0553, wR_2 = 0.0922.Crystallographic data for **31M**: $C_{20}H_{19}NO_2$, M = 305.36, monoclinic, $P2_1/n$, a = 10.3033 (13), b = 10.2448(13), c = 15.332(19) Å, α = 90, β = 95.088(2), γ = 90 °, V = 1612.0(4) Å^3, T = 173 (2) K, Z = 4, μ = 0.081 mm^{-1}, 3678(R_{int}=0.0269), final R indices[$I > 2\sigma(I)$], R_1 = 0.0415, wR_2 = 0.1043, R indeces (all data) R_1 = 0.0584, wR_2 = 0.1178.Crystallographic data for **37B**: $C_{18}H_{23}NO_2$, M = 285.37, monoclinic, $P2_1/n$, a = 6.2307(11), b = 16.094(3), c = 8.0544(15) Å, α = 90, β = 96.906(2), γ = 90 °, V = 801.8(3) Å^3, T = 173(2) K, Z = 2, μ = 0.076 mm^{-1}, 1704(R_{int}=0.0328), final R indices[$I > 2\sigma(I)$], R_1 = 0.0342, wR_2 = 0.0811, R indeces (all data) R_1 = 0.0425, wR_2 = 0.0861

30. Denmark SE, Edwards JP. J. Org. Chem 1991;56:6974.

31. (a) Furukawa J, Kawabata N, Nishimura J. Tetrahedron Lett 1966;7:3353. (b) Furukawa J, Kawabata N, Nishimura J. Tetrahedron 1968;24:53.

32. Yang Z, Lorenz JC, Shi Y. Tetrahedron Lett 1998;39:8621.

33. Maruoka K, Fukutani Y, Yamamoto H. J. Org. Chem 1985;50:4412.

34. (a) Molander GA, Harring LS. J. Org. Chem 1989;54:3525. (b) Molander GA, Etter JB. J. Org. Chem 1987;52:3942. Also see: (c) Lautens M, Ren Y. J. Org. Chem 1996;61:2210.

35. (a) Sibi MP, Deshpande PK, Ji JG. Tetrahedron Lett 1995;36:8965. (b) Sibi MP, Ji JG. Angew. Chem., Int. Ed. Engl 1996;35:190. (c) Sibi MP, Porter NA. Acc. Chem. Res 1999;32:163.

36. For a leading reference, see: Hintermann T, Seebach D. Helv. Chim. Acta 1998;81:2093.

37. Close WJ. J. Org. Chem 1950;15:1131.

38. Xiong H, Hsung RP, Shen L, Hahn JM. Tetrahedron Lett 2002;43:4449.

39. Adam independently reported their work thereafter, see: (a) Adam W, Bosio SG, Wolff BT. Org. Lett 2003;5:819. [PubMed: 12633080] For subsequent work with Turro, see: (b) Sivaguru J, Saito H, Poon T, Omonuwa T, Franz R, Jockusch S, Hooper C, Inoue Y, Adam W, Turro NJ. Org. Lett 2005;7:2089. [PubMed: 15901141] and references cited therein.

40. Tracey MR, Grebe TP, Brennessel WW, Hsung RP. Acta Cryst 2004;C60:o830.

41. Xiong H, Hsung RP, Wei L-L, Berry CR, Mulder JA, Stockwell B. Org. Lett 2000;2:2869. [PubMed: 10964386]

42. An unexpected oxidative product **i** [see below] was found in the reaction mixture. Compound **i** was also seen during the purification of chiral allenamide **33**, but we are not certain of its origin at this point.
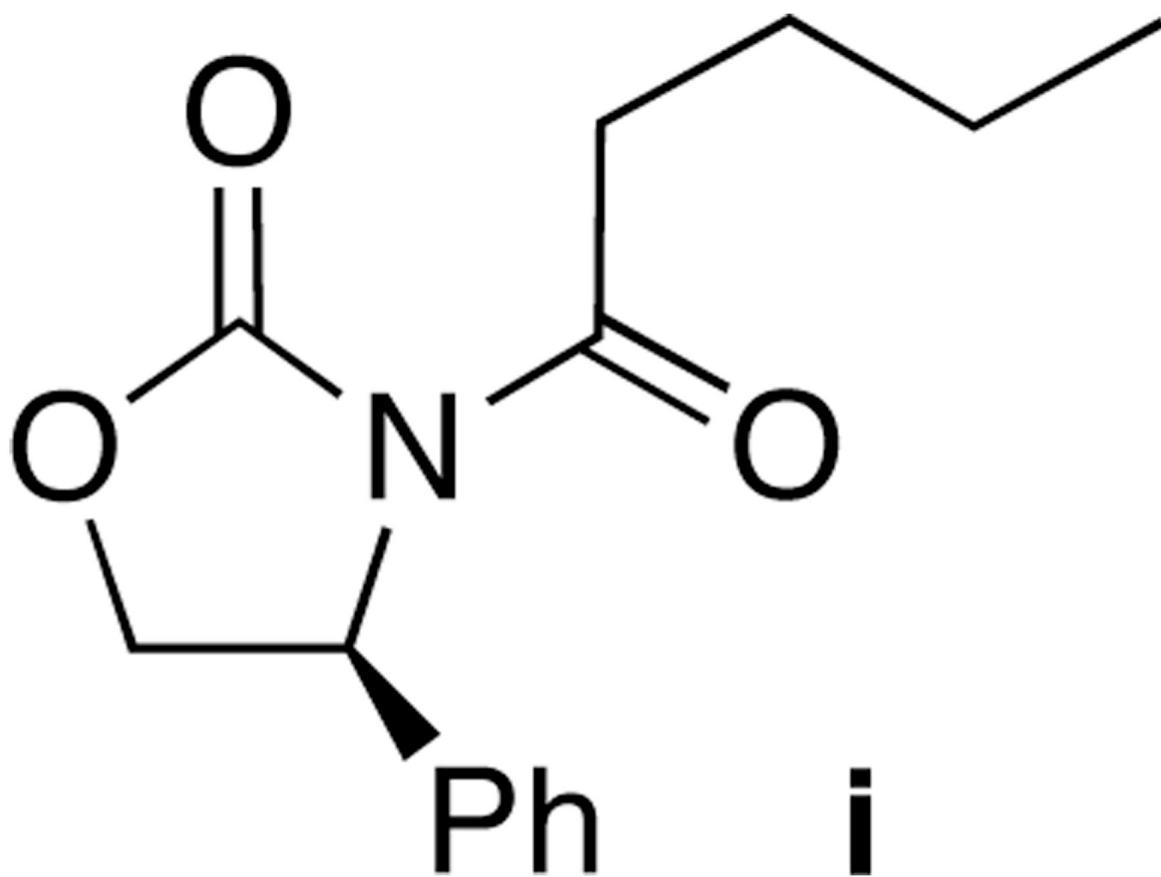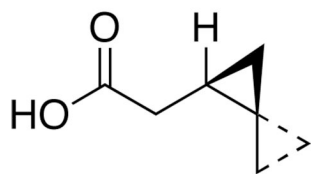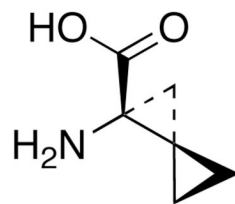
α-spiropentyl
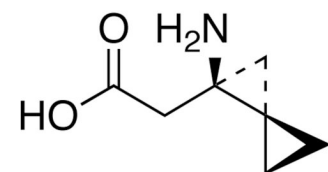acetic acid
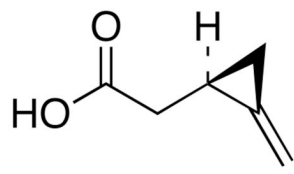
α-methylene-
cyclopropyl acetic acid
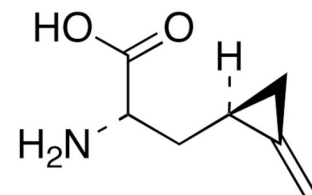
β-(methylene-
cyclopropyl)-alanine
or: hypoglycine A
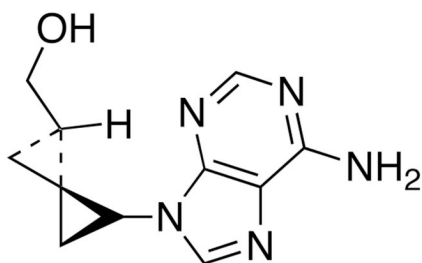
N-spiropentyl
adenosine analog

amino-spiropentyl
carboxylic acid

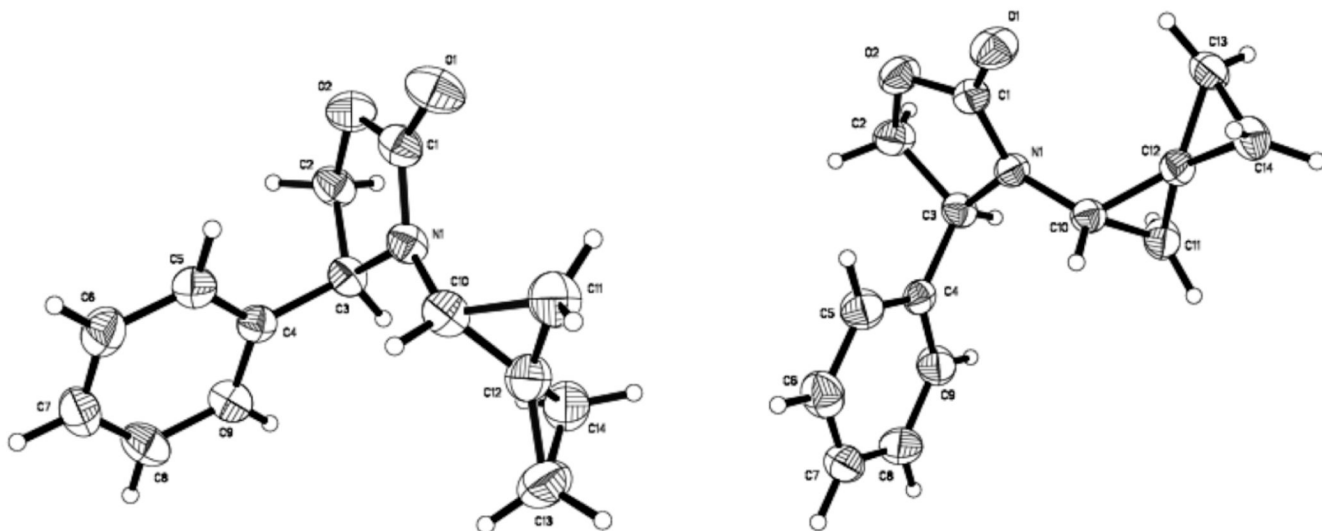*α*-amino-spiropentyl
acetic acid

Figure 1.
Spiro[2.2]Pentanes.

Figure 2.
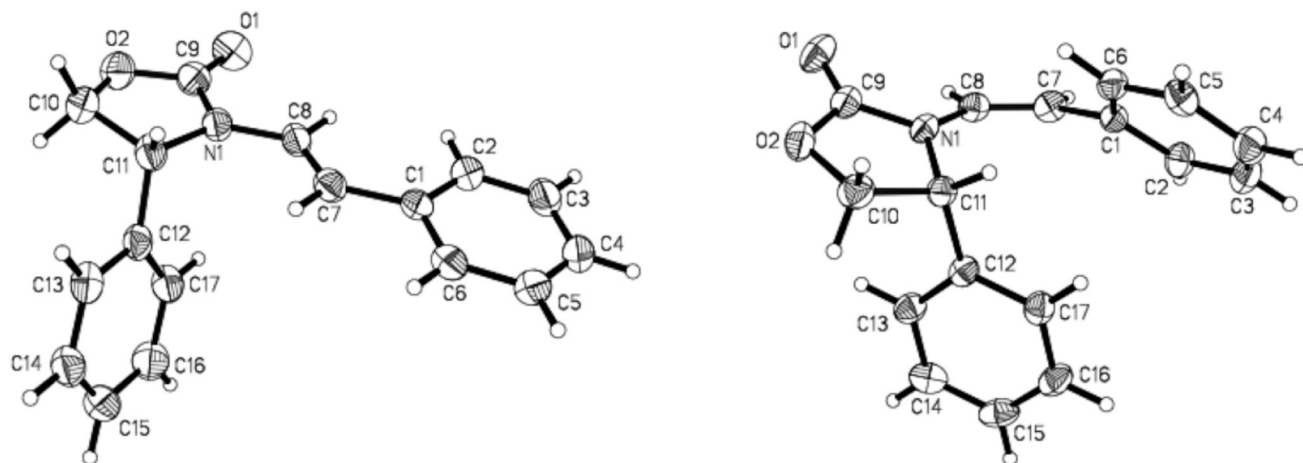X-Ray Structures of **9a** [left] and **9b** [Right].

Figure 3.
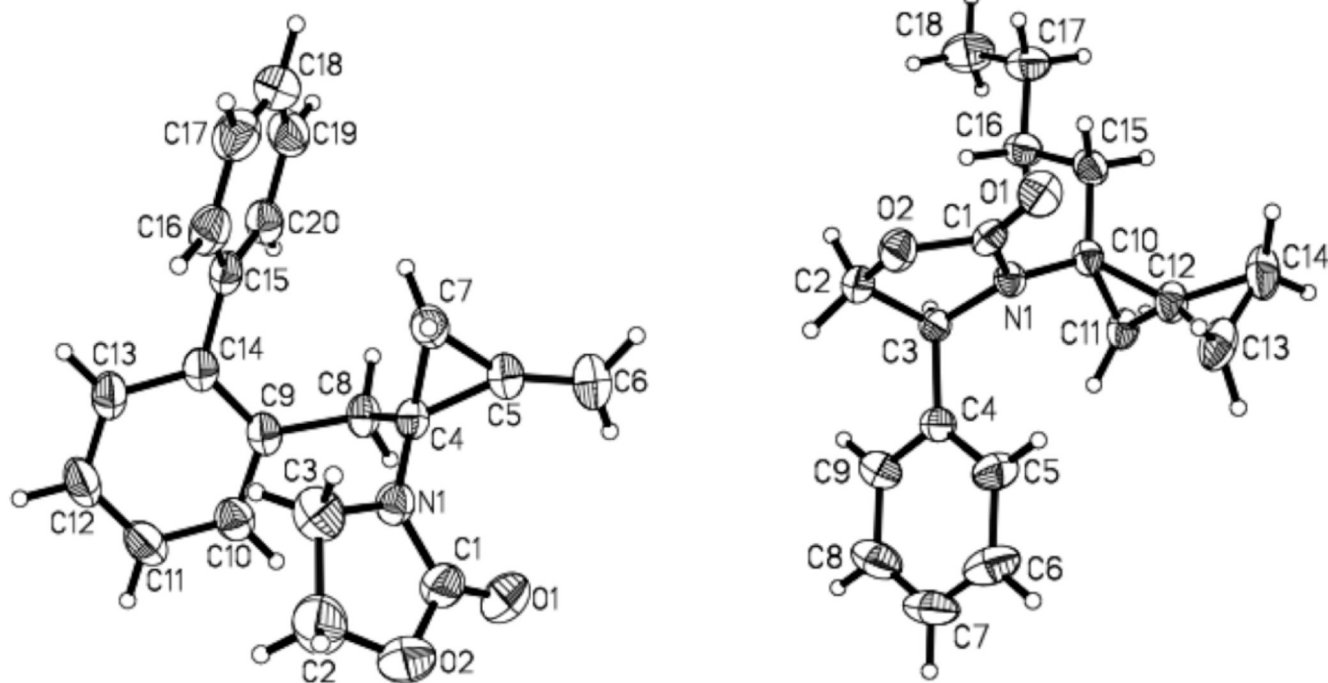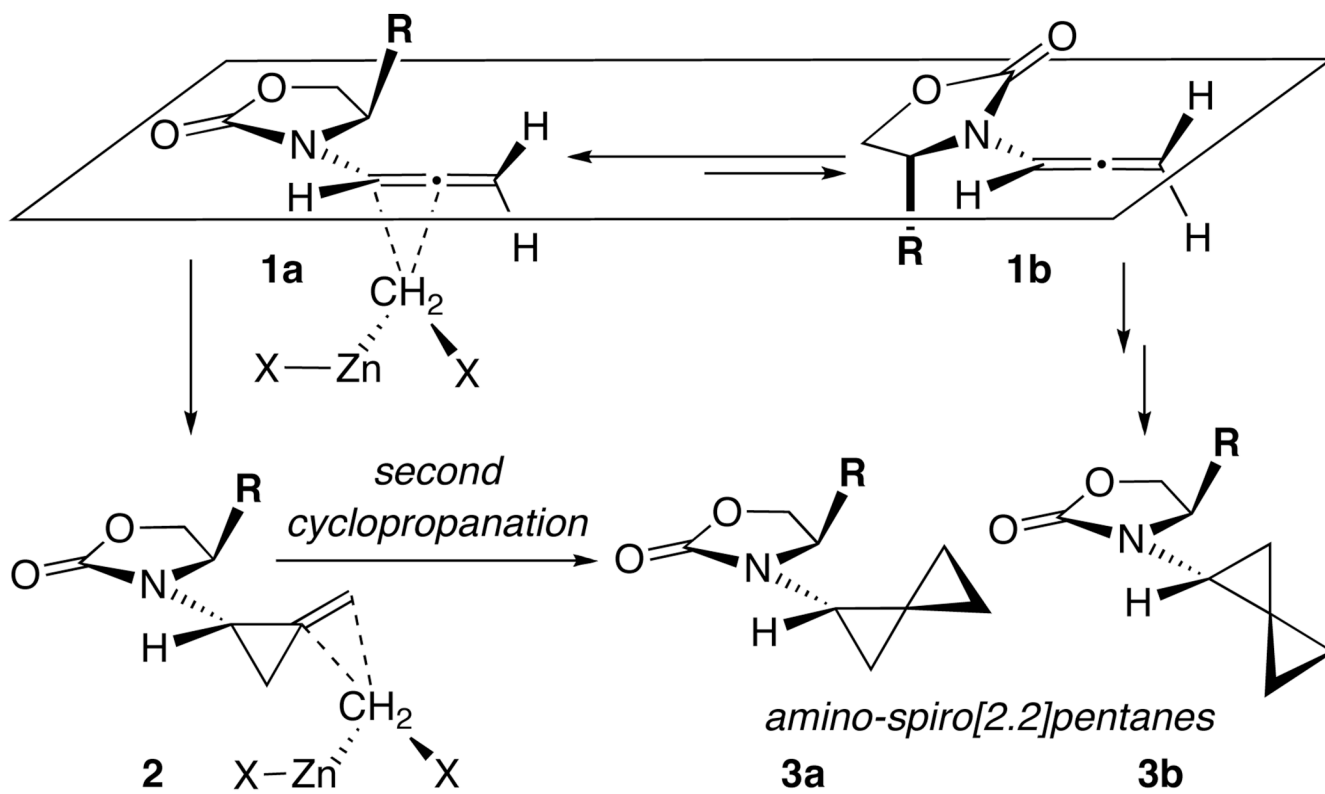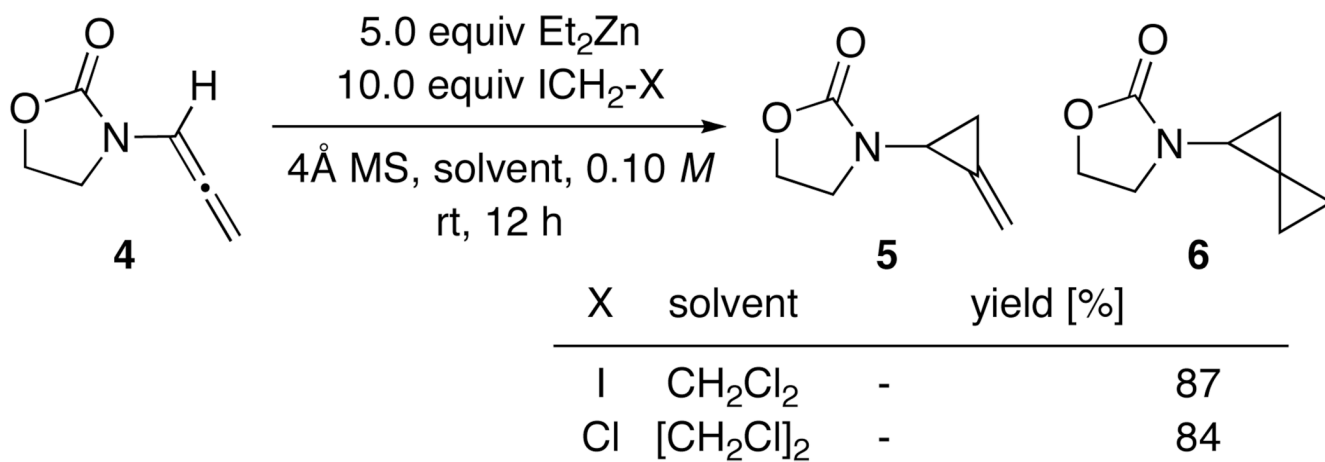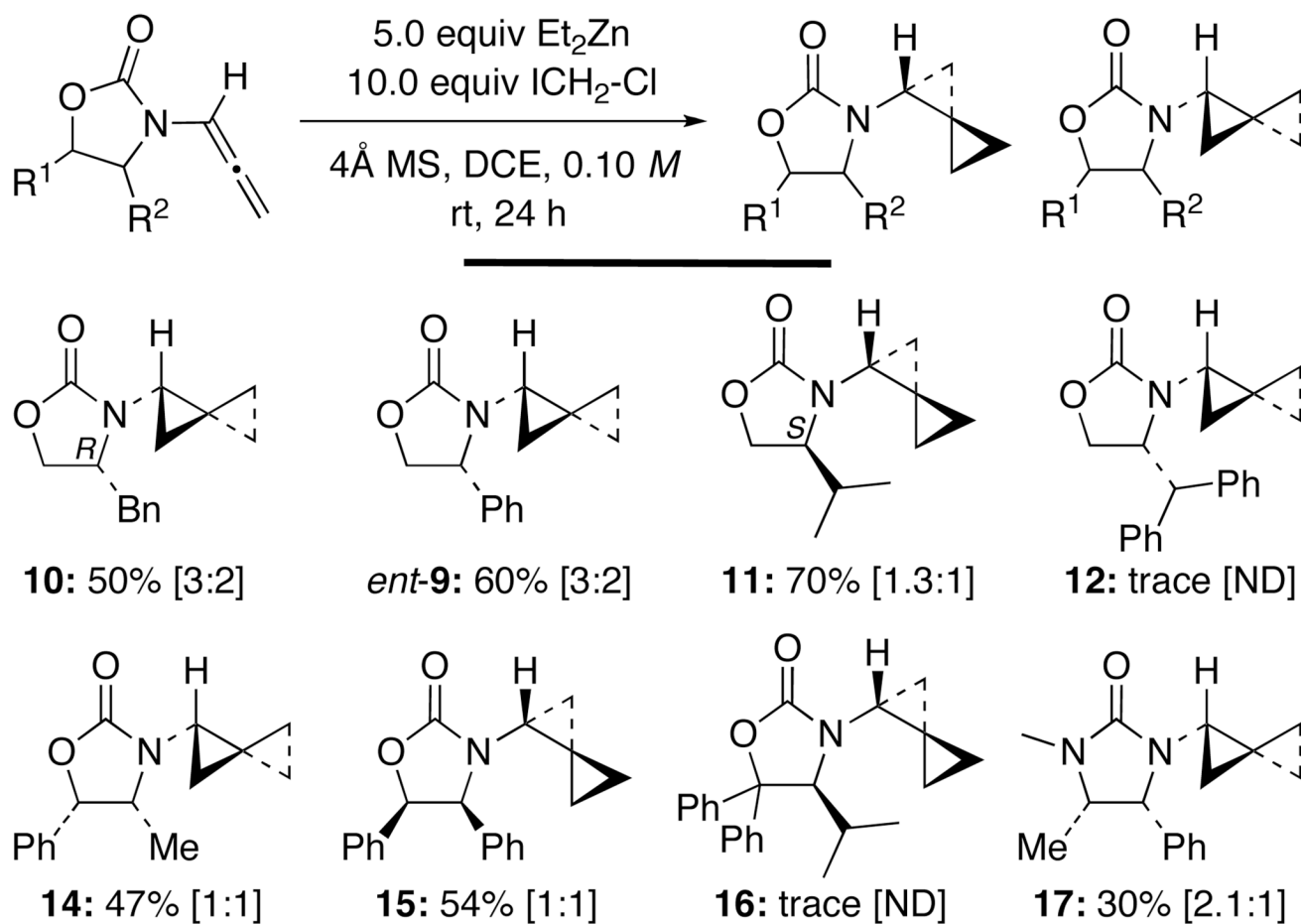X-Ray Structures of Enamides *E*-**19** [Left] and *Z*-**19** [Right].

Figure 4.
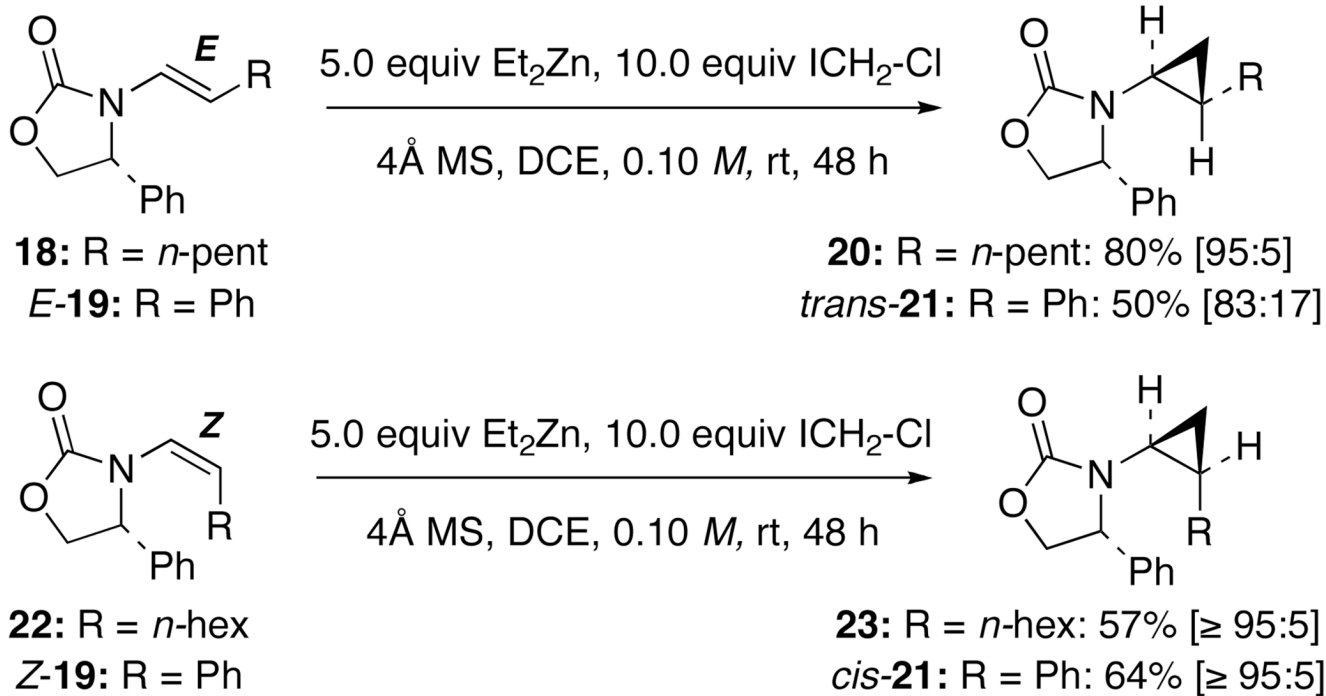X-Ray Structures of **31-M** [Left] and **37-B** [Right].

Scheme 1.
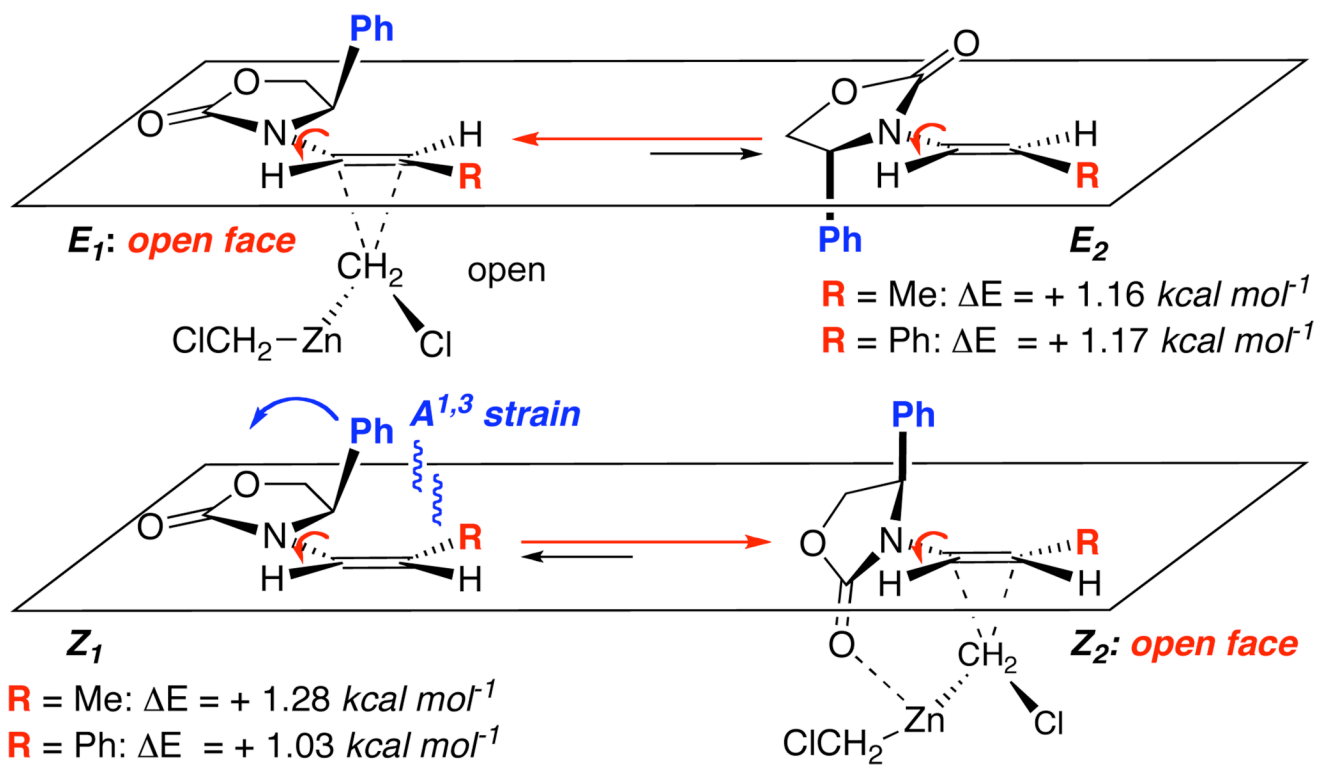Simmons-Smith Cyclopropanations of Allenamides.

Scheme 2.
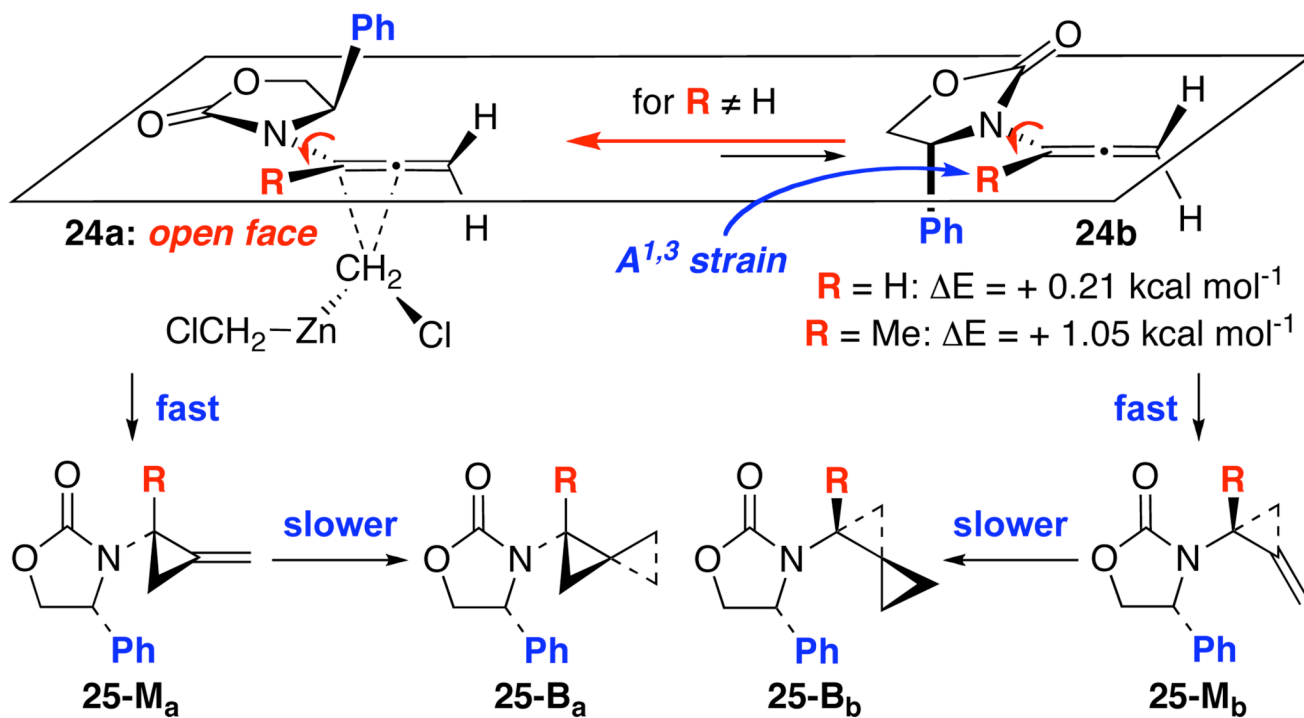Cyclopropanation of Achiral Allenamide **4**.

Scheme 3.
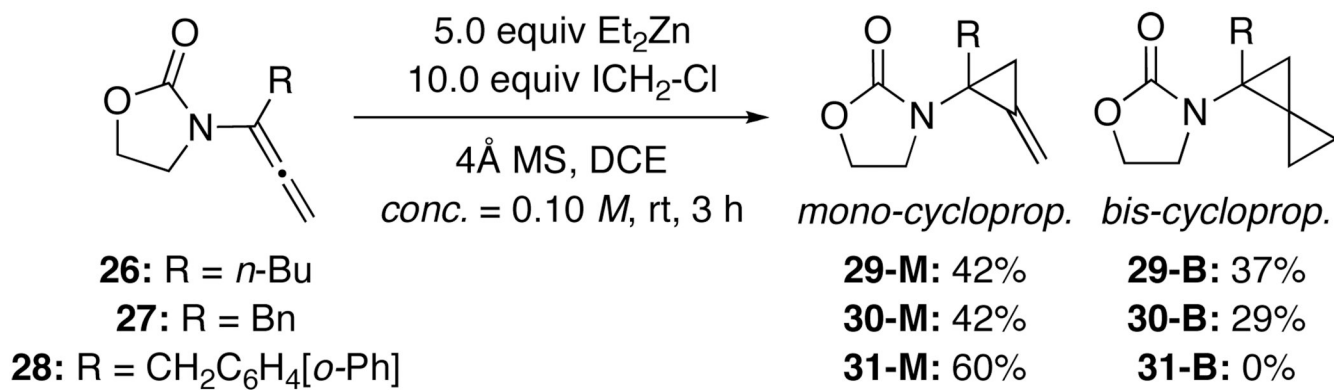Effect of Chiral Auxiliaries on Stereoselectivity.
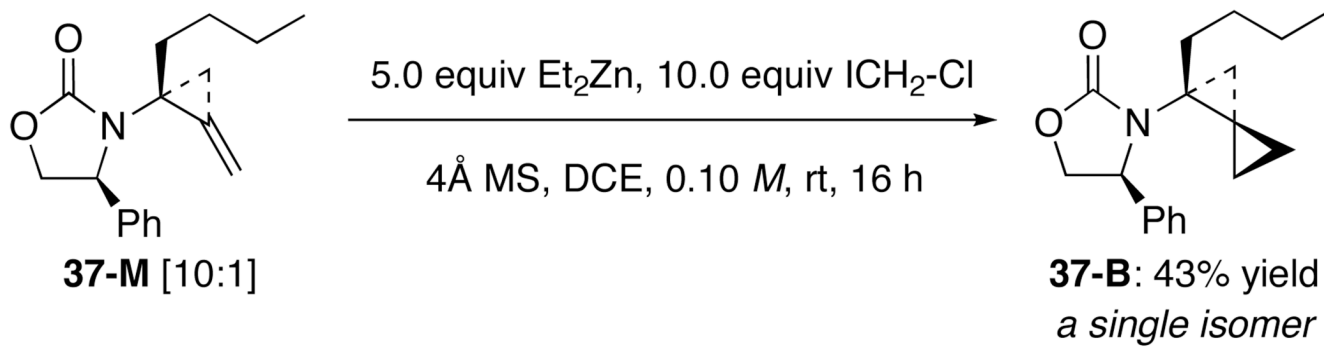
Scheme 4.
Cyclopropanations of *E*- and *Z*-Enamides.

Scheme 5.
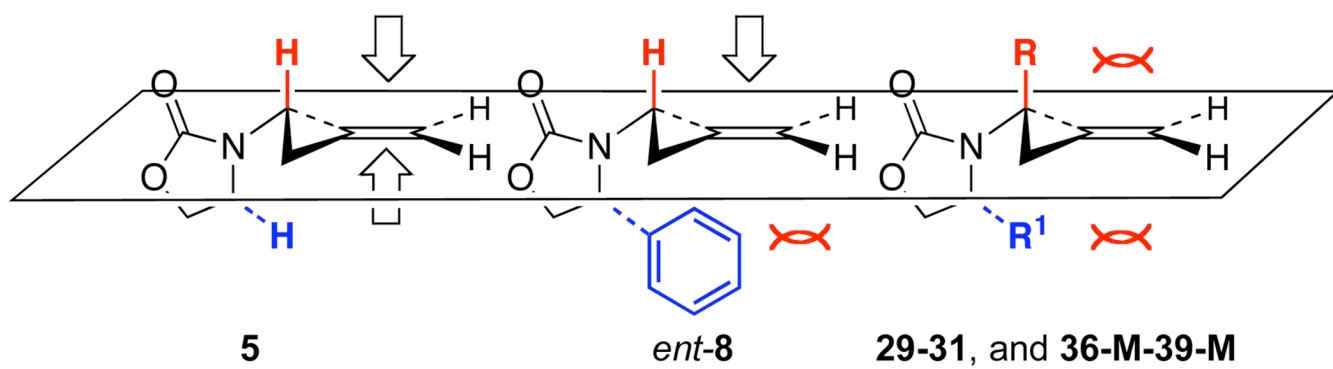A Model for the Enamide Cyclopropanation.

Scheme 6.
A Comparison with the Enamide Cyclopropanation.

Scheme 7.
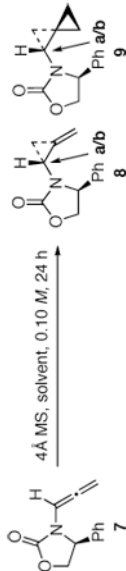Mono- Versus Bis-Cyclopropanation of Allenamides.

Scheme 8.
Assignment of Mono-Cyclopropane **37-M**.

5　　　　*ent*-**8**　　　**29-31**, and **36-M-39-M**

Scheme 9.
Rate Comparisons for the Second Cyclopropanation.

Table 1

Cyclopropanations of Chiral Allenamide **7**.

entry	cyclopropanat. agent	temp [°C]	solvent[a]	yield [%] [ratios][b]	
1	Zn(CH$_2$Cl)$_2$[c]	− 20	DCE	-	_d
2	Zn(CH$_2$Cl)$_2$	25	DCE	-	67 [1.4:1]
3	Zn(CH$_2$Cl)$_2$	25	DCE[e]	22 [2.8:1]	45 [1.2:1]
4	Zn(CH$_2$Cl)$_2$	85	DCE	-	50 [1:1]
5	Zn(CH$_2$Cl)$_2$	25	DME	-	_d
6	Zn(CH$_2$Cl)$_2$	25	THF	-	_d
7	Zn(CH$_2$Cl)$_2$	25	Tol	-	50 [1:1]
8	Zn(CH$_2$I)$_2$[f]	25	CH$_2$Cl$_2$	-	40 [1.5:1]
9	Zn(CH$_2$I)$_2$-DME[f]	25	DCE	10 [1.5:1]	_d
10	CF$_3$CO$_2$ZnCH$_2$I[g]	25	CH$_2$Cl$_2$	-	-
11	EtZnCH$_2$I[h]	25	CH$_2$Cl$_2$	-	_d
12	EtZnCH$_2$I-DME[h]	25	CH$_2$Cl$_2$	-	_d
13	R$_2$AlCH$_2$I[i]	25	CH$_2$Cl$_2$	-	_d

[a]DCE: 1,2-Dichloroethane. DME: 1,2-Dimethoxyethane.

[b]NMR yields for **8** and Isolated yields for **9**. The ratio in brackets denotes **a:b** with **a** being the major isomer as shown in the scheme, and was assigned via NMR.

[c]Employing 5.0 equiv Et$_2$Zn and 10.0 equiv ICH$_2$-Cl.

[d]Recovering 20–65% of the starting allenamide **7**.

[e]conc. = 0.05 M.

[f]Employing 5.0 equiv Et$_2$Zn and 10.0 equiv ICH$_2$-I. For entry 9, 5.0 equiv of DME was added.

(g)Employing 5.0 equiv each of Et_2Zn, ICH_2-I, and CF_3CO_2H.

(h)Employing 5.0 equiv Et_2Zn and 5.0 equiv ICH_2-I. For entry 12, 5.0 equiv of DME was added.

(i)Employing 5.0 equiv Me_3Al and 5.0 equiv ICH_2-I.

Table 2

Cyclopropanations of Chiral α-Substituted Allenamides.

Mono-cycloprop.   Bis-cycloprop.
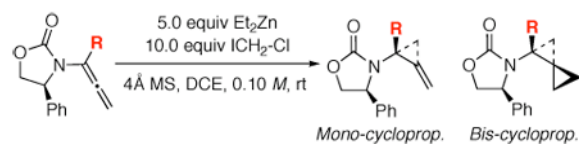
entry	allenamide	R =	time [h]	yield [%] [ratios][a]
1	**32**	Me	3	**36-M:** 38 [3.5:1] **36-B:** 26 [3.5:1]
				overall dr = 3.5:1[b]
2	**32**	Me	16	**36-M:** 19[c] [10.0:1] **36-B:** 36 [3.0:1]
				overall dr = 4.1:1[b]
3	**33**	*n*-Bu	3	**37-M:** 37[d] [5.0:1] **37-B:** 18 [≥20:1]
				overall dr = 7.9:1[b]
4	**33**	*n*-Bu	16	**37-M:** 30[d] [6.0:1] **37-B:** 22 [≥20:1]
				overall dr = 11.1:1[b]
5	**34**	Bn	16	**38-M:** 32 [7.0:1] **38-B:** 20 [≥20:1]
				overall dr = 12.0:1[b]
6	**35**	CH$_2$C$_6$H$_4$[*o*-Ph]	3	**39-M:** 36 [5.0:1] **39-B:** 23 [≥20:1]
				overall dr = 8.8:1[b]

[a] Isolated yields. *Dr* ratios are in the bracket with the respective major diastereomer being shown in the scheme and all ratios were assigned using crude ^{1}H NMR.

[b] Overall *dr* ratios represent the combined *dr* for the first cyclopropanation.

[c] NMR yield.

[d] See reference [42].