Synthesis of amido-spiro[2.2]pentanes *via* Simmons–Smith cyclopropanation of allenamides†

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A detailed account of 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 analyses, 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 members of the triangulane or oligo-spirocyclopropane family, represent a unique structural topology with both rigidity and orthogonality that has found application in a number of biological contexts.[2] In particular, simple α-spiropentyl acetic acid [Fig. 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 appearing 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 deoxy-ribonucleotide analogs[10] to exploring the chemistry and biology of spiro[2.2]pentane amino acid derivatives.[11,12]

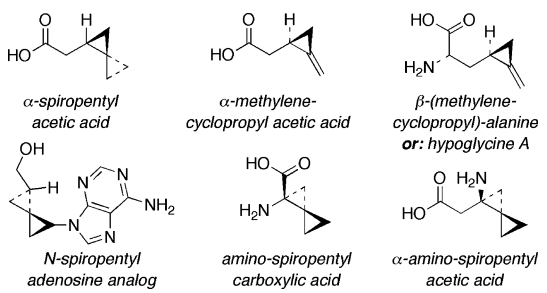
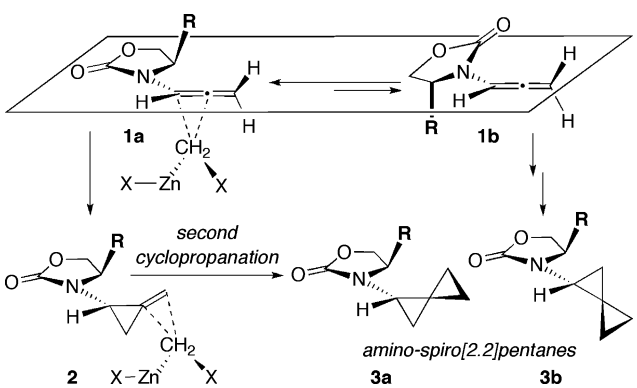


Fig. 1 Spiro[2.2]pentanes.

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 aminocyclopropanes[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 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 by the zinc carbenoid approaching 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.



Scheme 1 Simmons–Smith cyclopropanations of allenamides.

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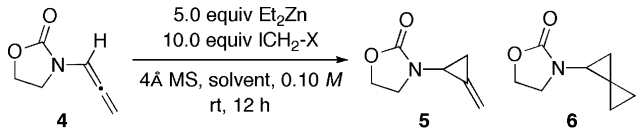
Results and discussions

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]



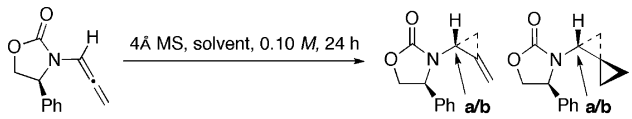
X	solvent		yield [%]
I	CH_2Cl_2	-	87
Cl	$[CH_2Cl]_2$	-	84

Scheme 2 Cyclopropanation of achiral allenamide **4**.

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 the 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 it was 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 Fig. 2. The ability to access both diastereomers of these structurally very interesting and novel amido-spiro[2.2]pentanes renders this non-stereoselective aspect of this reaction an opportunity and less of a limitation.

Table 1 Cyclopropanations of chiral allenamide **7**



Entry	cyclopropanat. agent	temp [°C]	solvent[a]	yield [%] [ratios][b] 8	9
1	$Zn(CH_2CI)_2$[c]	–20	DCE	–	–[d]
2	$Zn(CH_2Cl)_2$	25	DCE	–	67 [1.4:1]
3	$Zn(CH_2Cl)_2$	25	DCE[e]	22 [2.8:1]	45 [1.2:1]
4	$Zn(CH_2Cl)_2$	85	DCE	–	50 [1:1]
5	$Zn(CH_2Cl)_2$	25	DME	–	–[d]
6	$Zn(CH_2CI)_2$	25	THF	–	–[d]
7	$Zn(CH_2Cl)_2$	25	Tol	–	50 [1:1]
8	$Zn(CH_2I)_2$[f]	25	CH_2Cl_2	–	40 [1.5:1]
9	$Zn(CH_2I)_2$–DME[f]	25	DCE	10 [1.5:1]	–[d]
10	$CF_3CO_2ZnCH_2I$[g]	25	CH_2Cl_2	–	–[d]
11	$EtZnCH_2I$[h]	25	CH_2Cl_2	–	–[d]
12	$EtZnCH_2I$-DME[h]	25	CH_2Cl_2	–	–[d]
13	R_2AlCH_2I[i]	25	CH_2Cl_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_2Zn 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_2Zn 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

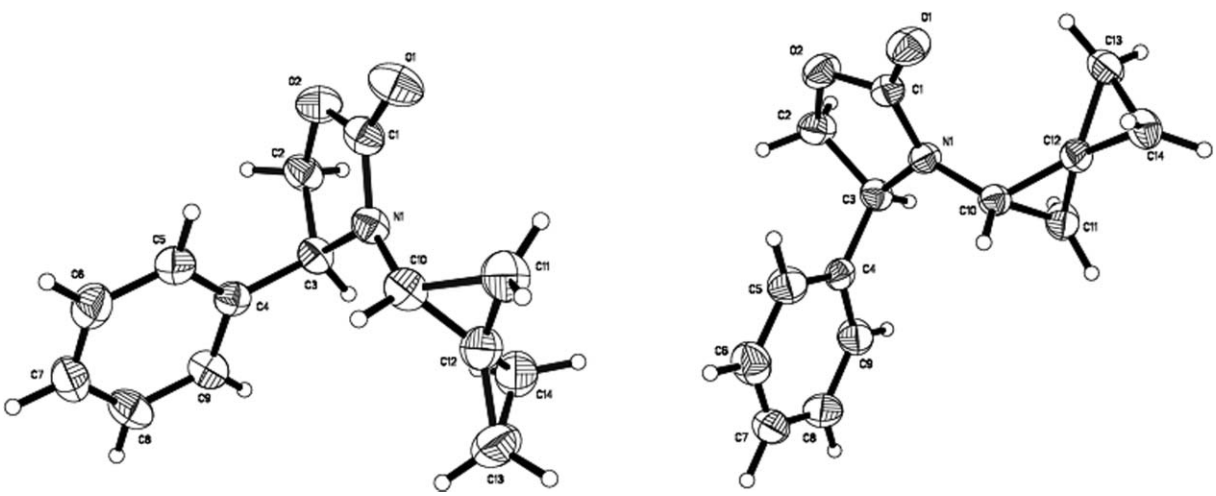
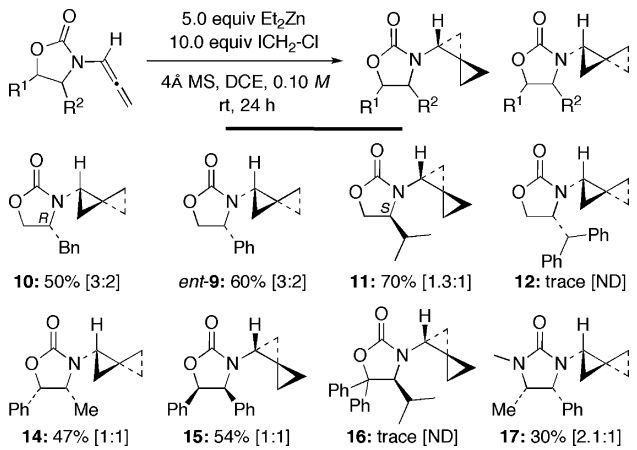


Fig. 2 X-Ray structures of **9a** [left] and **9b** [right].

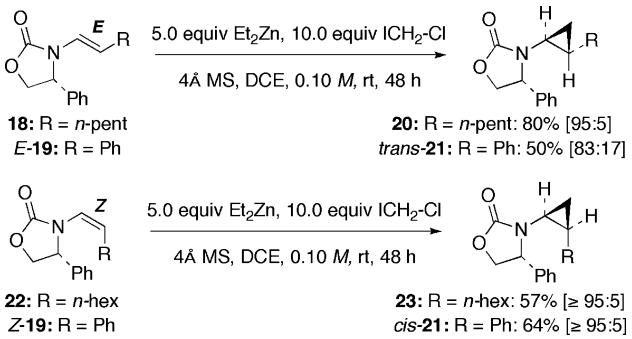
Subsequently, a number of chiral auxiliaries on the allenamide were probed in an attempt to improve the diastereoselectivity. As shown in Scheme 3, amido-spiro[2.2]pentanes such as **10**, **11**, **14**, and **15** could be attained in good yields through bis-cyclopropanations of their respective allenamides. 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 α to the amido-nitrogen atom [see **10–12**] and those with vicinal substitutions on the oxazolidinone ring [see **14–17**].



Scheme 3 Effect of chiral auxiliaries on stereoselectivity.

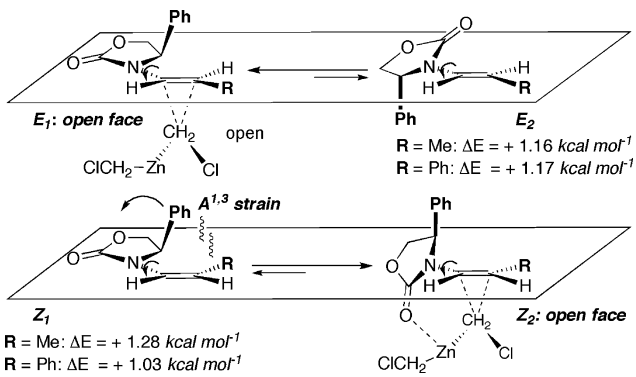
2. A comparison with chiral enamides

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.



Scheme 4 Cyclopropanations of *E*- and *Z*-enamides.

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 Fig. 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 $\boldsymbol{E_1}$ [Scheme 5], which was what we had speculated earlier in some epoxidation work.[38,39] The other locally minimized conformation is $\boldsymbol{E_2}$ but it is less favored than $\boldsymbol{E_1}$ 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 cyclopropanations proceed through the major enamide [or allenamide] conformer with the awareness that the Curtin-Hamett principle could very well be in play here,



Scheme 5 A model for the enamide cyclopropanation.

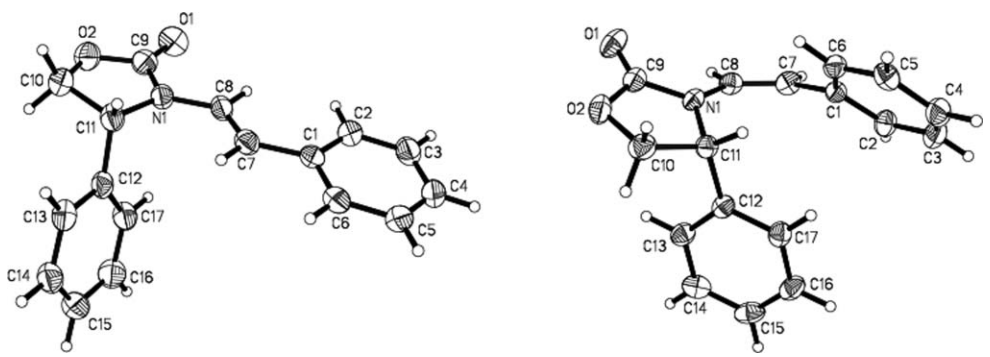


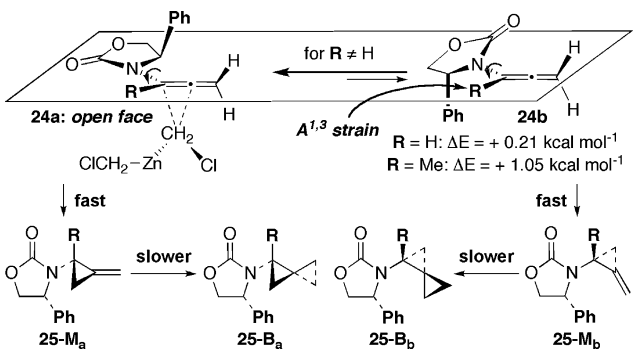
Fig. 3 X-Ray structures of enamides *E*-**19** [left] and *Z*-**19** [right].

and that we are only attempting to identify a model with some consistent rationale and predictive power at this juncture.

Based on this assumption, if the cyclopropanation proceeds through the more favored conformation $\boldsymbol{E}_1$, the necessary π-facial differentiation in $\boldsymbol{E}_1$ would provide the excellent stereochemical outcome with $\boldsymbol{E}_2$ being a possible source for the minor diastereomer. On the other hand, in both the X-ray structure [see *Z*-**19** in Fig. 3] and computation model of *Z*-enamides, there is a distinct shift from a coplanar motif in conformation $\boldsymbol{Z}_1$ to the more favored $\boldsymbol{Z}_2$ [ΔE = −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 such 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 $\boldsymbol{Z}_2$ 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 ΔE = −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$_b$**.

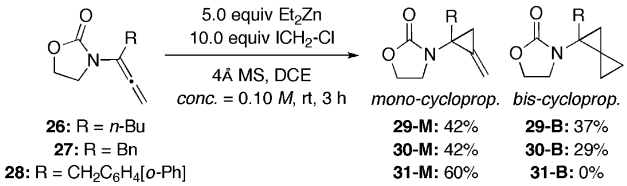


Scheme 6 A comparison with the enamide cyclopropanation.

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

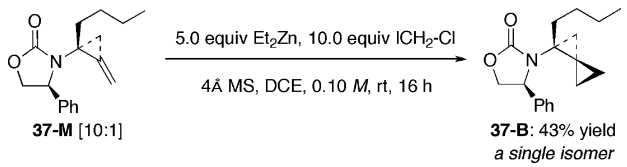
Based on the above conformational model, we prepared α-substituted achiral allenamides **26–28** [Scheme 7] through α-alkylation of the respective unsubstituted allenamides.[41] Cyclopropanations of allenamides **26–28** were not only feasible, but also led to the observation and isolation of a substantial 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 Fig. 4 through its single-crystal X-ray structure.



Scheme 7 Mono- versus bis-cyclopropanation of allenamides.

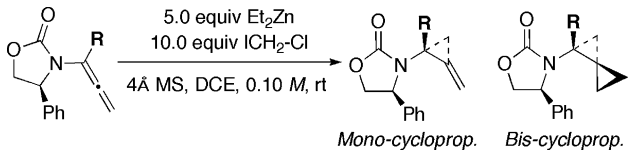
We proceeded to examine α-substituted chiral allenamides **32–35** as shown in Table 2. In all cases, we isolated both mono- [**36-M** through **39-M**] and bis-cyclopropanation products [**36-B** through **39-B**]. A longer reaction time usually resulted in more of the respective bis-cyclopropanation 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 [Fig. 4].

To ensure that major isomers of mono- and bis-cyclopropanation 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 bold] that correlates well overall with increasing size of



Scheme 8 Assignment of mono-cyclopropane **37-M**.

Table 2 Cyclopropanations of chiral α-substituted allenamides



entry	allenamide	R =	time [h]	yield [%] [ratios][a] Mono-cycloprop.	Bis-cycloprop.
1	**32**	Me	3	**36-M**: 38 [3.5:1] ***overall dr = 3.5:1***[b]	**36-B**: 26 [3.5:1]
2	**32**	Me	16	**36-M**: 19[c] [10.0:1] ***overall dr = 4.1:1***[b]	**36-B**: 36 [3.0:1]
3	**33**	*n*-Bu	3	**37-M**: 37[d] [5.0:1] ***overall dr = 7.9:1***[b]	**37-B**: 18 [≥20:1]
4	**33**	*n*-Bu	16	**37-M**: 30[d] [6.0:1] ***overall dr = 11.1:1***[b]	**37-B**: 22 [≥20:1]
5	**34**	Bn	16	**38-M**: 32 [7.0:1] ***overall dr =12.0:1***[b]	**38-B**: 20 [≥20:1]
6	**35**	$CH_2C_6H_4$[*o*-Ph]	3	**39-M**: 36 [5.0:1] ***overall dr = 8.8:1***[b]	**39-B**: 23 [≥20:1]

[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.

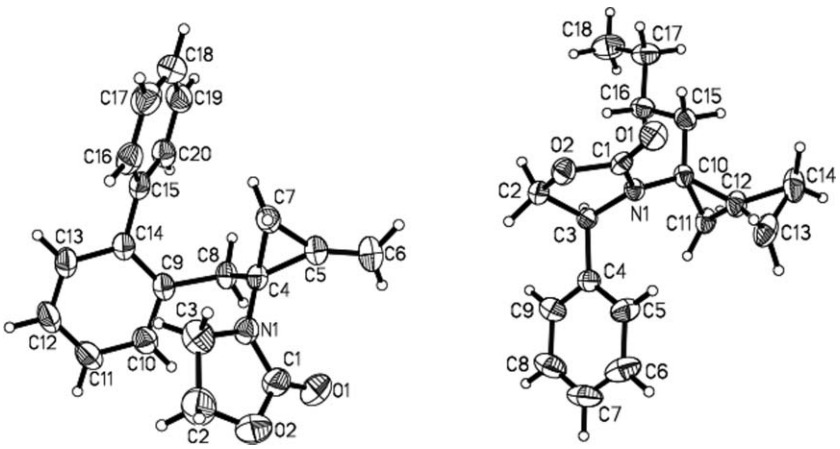
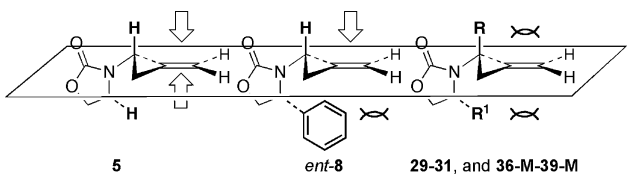


Fig. 4 X-Ray structures of **31-M** [left] and **37-B** [right].

the R group, and provides 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 π-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 π-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.



Scheme 9 Rate comparisons for the second cyclopropanation.

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 for constructing chemically and biologically intriguing amido-spiro[2.2]pentane systems.

Acknowledgements

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References

1 For the earliest example, see: (*a*) G. Gustavson, *J. Prakt. Chem.*, 1896, **54**, 97. For early accounts, see: (*b*) F. Rogowski, *Chem. Ber.*, 1939, **72B**, 2021; (*c*) M. J. Murray and E. H. Stevenson, *J. Am. Chem. Soc.*, 1944, **66**, 812; (*d*) J. Donohue, G. L. Humphrey and V. Schomaker, *J. Am. Chem. Soc.*, 1945, **67**, 332.
2 For a leading review see: A. de Meijere and S. I. Kozhushkov, *Chem. Rev.*, 2000, **100**, 93.
3 K. Y. Tserng, S.-J. Jin and C. L. Hoppel, *Biochemistry*, 1991, **30**, 10755.
4 D. Li, H.-Q. Zhou, S. Dakoji, I. Shin, E. Oh and H.-W. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 2008.
5 (*a*) H. Osmundsen and H. S. A. Sherratt, *FEBS Lett.*, 1975, **55**, 81; (*b*) E. A. Kean, *Biochem. Biophys. Acta*, 1976, **422**, 81; (*c*) R. H. Abeles, in *Enzyme Activated Irreversible Inhibitors*, ed. N. Seiler, M. J. Jung and J. Koch-Weser, Elsevier-North-Holland Press, Amsterdam, 1978, pp. 1–12; (*d*) S. Ghisla, A. Wenz and C. Thorpe, in *Enzyme Inhibitors*, ed. U. Brodbeck, Verlag Chim Press, Weinheim, Germany, 1980, pp. 43–60; (*e*) A. Wenz, C. Thorpe and S. Ghisla, *J. Biol. Chem.*, 1981, **256**, 9809; (*f*) S. Ghisla, K. Melde, H. D. Zeller and W. Boschert, in *Fatty Acid Oxidation; Clinical, Biochemical, and Molecular Aspects*, ed. K. Tanaka and P. M. Coates, Alan R. Liss, Inc. Press, New York, 1990, vol. 321, pp. 185–192.
6 (*a*) M.-T. Lai, D. Li, E. Oh and H.-W. Liu, *J. Am. Chem. Soc.*, 1993, **115**, 1619; (*b*) M.-T. Lai and H.-W. Liu, *J. Am. Chem. Soc.*, 1992, **114**, 3160; (*c*) M.-T. Lai and H.-W. Liu, *J. Am. Chem. Soc.*, 1991, **113**, 7388; (*d*) M.-T. Lai and H.-W. Liu, *J. Am. Chem. Soc.*, 1990, **112**, 4034; (*e*) N. D. Lenn, Y. Shih, M. T. Stankovich and H.-W. Liu, *J. Am. Chem. Soc.*, 1989, **111**, 3065.
7 (*a*) J. E. Baldwin, R. M. Adlington, D. Bebbinton and A. T. Riussell, *Tetrahedron*, 1994, **50**, 12015; (*b*) J. E. Baldwin and W. C. Widdison, *J. Am. Chem. Soc.*, 1992, **114**, 2245; (*c*) J. E. Baldwin, R. L. Ostrander, C. D. Simon and W. C. Widdison, *J. Am. Chem. Soc.*, 1990, **112**, 2021; (*d*) J. E. Baldwin and D. W. Parker, *J. Org. Chem.*, 1987, **52**, 1475.
8 (*a*) K. Tanaka, K. J. Isselbacher and V. Shih, *Science*, 1972, **175**, 69; (*b*) C. Holt, M. von Holt and H. Bohm, *Biochim. Biophys. Acta*, 1966, **125**, 11; (*c*) D. K. Black and S. R. Landor, *J. Chem. Soc. C*, 1968, 288.
9 (*a*) K. Tanaka, in *Handbook of Clinical Neurology*, *ed.* P. J. Vinken and G. W. Bruyn, Elsevier-North Holland Press, Amsterdam, 1979, vol. 37, pp 511–513; (*b*) K. L. Stuart, in *Hypoglycin ed.* E. A. Kean, Academic Press, New York, 1975, pp 31–38.
10 H.-P. Guan, M. B. Ksebati, Y.-C. Cheng, J. C. Drach, E. R. Kern and J. Zemlicka, *J. Org. Chem.*, 2000, **65**, 1280.
11 A. de Meijere, K. Ernst, B. Zuck, M. Brandl, S. I. Kozhushkov, M. Tamm, D. S. Yufit, J. A. K. Howard and T. Labahn, *Eur. J. Org. Chem.*, 1999, 3105.
12 R. Pellicciari, M. Marinozzi, E. Camaioni, M. del Carmen Nnez, G. Costantino, F. Gasparini, G. Giorgi, A. Macchiarulo and N. Subramanian, *J. Org. Chem.*, 2002, **67**, 5497.
13 For a leading review on cyclopropanations, see: (*a*) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev*, 2003, **103**, 977; For other reviews on cyclopropanations, see: (*b*) M. P. Doyle, *Chem. Rev.*, 1986, **86**, 919; (*c*) A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; (*d*) M. A. Calter, *Curr. Org. Chem.*, 1997, **1**, 37; (*e*) M. P. Doyle and D. C. Forbe, *Chem. Rev.*, 1998, **98**, 911; (*f*) H. M. L. Davies and E. Autoulinakis, *Org. React.*, 2003, **57**, 1; (*g*) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; (*h*) M. P. Doyle, *J. Org. Chem.*, 2006, **71**, 9253; (*i*) F. Brackmann and A. de Meijere, *Chem. Rev.*, 2007, **107**, 4493; (*j*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041.
14 For some examples, see: (*a*) A. B. Charette, E. Jolicoeur and G. A. S. Bydlinski, *Org. Lett.*, 2001, **3**, 3293; (*b*) M. Lautens and P. H. M. Delanghe, *J. Am. Chem. Soc.*, 1994, **116**, 8526; (*c*) M. Lautens and P. H. M. Delanghe, *Org. Chem.*, 1993, **58**, 5037; (*d*) J. A. Russo and W. A. Price, *J. Org. Chem.*, 1993, **58**, 3589; (*e*) N. S. Zefirov, S. I. Kozhushkov, T. S. Kuznetsova, K. A. Lukin and I. V. Kazimirchik, *Zh. Org. Khim.*, 1988, **24**, 673; For earlier work, see: (*f*) E. Ullman and W. J. Fanshave, *J. Am. Chem. Soc.*, 1961, **83**, 2379; (*g*) W. Rahman and H. G. Kuivila, *J. Org. Chem.*, 1966, **31**, 772; (*h*) R. Noyori, H. Takaya, Y. Nakanisi and H. Nozaki, *Can. J. Chem.*, 1969, **47**, 1242; (*i*) Also see reference 4.
15 For some examples, see: (*a*) J. J. Gajewski and L. T. Burka, *J. Org. Chem.*, 1970, **35**, 2190; (*b*) B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1973, **95**, 5307; (*c*) N. S. Zefirov, S. I. Kozhushkov, B. I. Ugrak, K. A. Lukin, O. V. Kokoreva, D. S. Yufit, Y. T. Struchkov, S. Zoellner, R. Boese and A. Demeijere, *J. Org. Chem.*, 1992, **57**, 701; (*d*) M. Weber and A. de Meijere, *Chem. Ber.*, 1986, **118**, 2450; (*e*) I. V. Akhachinskauya, N. A. Donskaya, I. V. Kalykina, Y. F. Oprunenko and Y. S. Shabarov, *Zh. Org. Khim.*, 1989, **25**, 1645; (*f*) C. Cheng, T. Shimo, K. Somekawa and M. Kawaminami, *Tetrahedron Lett*, 1997, **52**, 9005; (*g*) O. Muehling and P. Wessig, *Photochemical & Photobiological Sciences*, 2006, **5**, 1000; (*h*) Also see reference 4.
16 For some other examples of amino-spiro[2.2]pentane synthesis, see: (*a*) N. V. Yashin, E. B. Averina, Y. K. Grishin, T. S. Kuznetsova and N. S. Zefirov, *Synthesis*, 2006, 279; (*b*) D. E. Applequist, M. R. Johnston and F. Fisher, *J. Am. Chem. Soc.*, 1970, **92**, 4614; (*c*) L. M. Konzelma and R. T. Conley, *J. Org. Chem.*, 1968, **33**, 3828.
17 Z. Song, T. Lu, R. P. Hsung, Z. F. Al-Rashid, C. Ko and Y. Tang, *Angew. Chem., Int. Ed.*, 2007, **46**, 4069.
18 T. Lu, Z. Song and R. P. Hsung, *Org. Lett.*, 2008, **10**, 541.
19 For some examples of cyclopropanations of enamides, see: (*a*) T. Melby, E. Hughes and T. Hansen, *Synlett*, 2007, 2277; (*b*) V. K. Aggarwal, J. Vicente and R. V. Bonnert, *Org. Lett.*, 2001, **3**, 2785; (*c*) J. Voigt, M. Noltemeyer and O. Reiser, *Synlett*, 1997, 202; (*d*) J. Jiménez, J. Rifé and R. M. Ortuño, *Tetrahedron Asym.*, 1996, **7**, 537; (*e*) L. Arenare, P. De Carprariis, M. Marinozzi, B. Natalini and R. Pellicciari, *Tetrahedron Lett.*, 1994, **35**, 1425; (*f*) T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa and S. Terashima, *Tetrahedron*, 1994, **50**, 3905; (*g*) K. Paulini and H.-U. Reissig, *Liebigs Ann. Chem.*, 1991, 455; (*h*) H. M. L. Davies, E. Saikali and W. B. Young, *J. Org. Chem.*, 1991, **56**, 5696; (*i*) D. Seebach, G. Stucky and E. Pfammatter, *Chem. Ber.*, 1989, **122**, 2377; (*j*) D. Seebach and G. Stucky, *Angew. Chem., Int. Ed.*, 1988, **27**, 1351; (*k*) E. Wenkert and T. Hudlicky, *J. Org. Chem.*, 1988, **53**, 1953.
20 For reviews of chemistry of enamides, see: (*a*) Z. Rappoport, *The Chemistry of Enamines in The Chemistry of Functional Groups*, John Wiley and Sons Press, New York, 1994; (*b*) J. K. Whitesell and M. A. Whitesell, *Synthesis*, 1983, 517; (*c*) P. W. Hickmott, *Tetrahedron*, 1982, **38**, 1975 and 3363; (*d*) For a review on the synthesis of enamides, see: M. R. Tracey, R. P. Hsung, J. E. Antoline, K. C. M. Kurtz, L. Shen, B. W. Slafer and Y. Zhang, in *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*, ed. Steve M. Weinreb, Georg Thieme Verlag KG Press, 2005, Chapter 21.4.
21 For leading reviews on amino-cyclopropanes, see: (*a*) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603; (*b*) D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; (*c*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; (*d*) K. Burgess, K. K. Ho and D. Moyesherman, *Synlett*, 1994, 575; (*e*) A. Alami, M. Calmes, J. Daunis and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1993, **130**, 5.
22 For recent examples, see: (*a*) C. A. Faler and M. M. Joullié, *Org. Lett.*, 2007, **9**, 1987; (*b*) X. Z. Zeng, X. D. Wei, V. Farina, E. Napolitano, Y. B. Xu, L. Zhang, N. Haddad, N. K. Yee, N. Grinberg, S. Shen and C. H. Senanayake, *J. Org. Chem.*, 2006, **71**, 8864; (*c*) G. Begis, T. D. Sheppard, D. E. Cladingboel, W. B. Motherwell and D. A. Tocher, *Synthesis*, 2005, 3186.
23 For a leading review on allenamides, see: R. P. Hsung, L.-L. Wei and H. Xiong, *Acc. Chem. Res.*, 2003, **36**, 773.
24 For a compendium on the chemistry of allenes, see: (*a*) N. Krause and A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA Press, Weinheim, 2004, vol. 1 and 2; For general reviews on the chemistry of allenes, see: (*b*) K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263; (*c*) S. Ma, *Chem. Rev.*, 2005, **105**, 2829.

25 For recent reports on allenamide chemistry, see: (*a*) E. Skucas, J. R. Zbieg and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 5054; (*b*) A. Armstrong and D. P. G. Emmerson, *Org. Lett.*, 2009, **11**, 1547; (*c*) E. M. Beccalli, G. Broggini, F. Clerici, S. Galli, C. Kammerer, M. Rigamonti and S. Sottocornola, *Org. Lett.*, 2009, **11**, 1563; (*d*) G. Broggini, S. Galli, M. Rigamonti, S. Sottocornola and G. Zecchi, *Tetrahedron Lett.*, 2009, **50**, 1447; (*e*) K. M. Brummond and B. Yan, *Synlett*, 2008, 2303; (*f*) H. Fuwa, T. Tako, M. Ebine and M. Sasaki, *Chem. Lett.*, 2008, **37**, 904; (*g*) Á. González-Gómez, L. Añorbe, A. Poblador, G. Domínguez and J. Pérez-Castells, *Eur. J. Org. Chem.*, 2008, 1370; (*h*) A. Navarro-Vázquez, D. Rodríguez, M. F. Martínez-Esperón, A. García, C. Saá and D. Domínguez, *Tetrahedron Lett.*, 2007, **48**, 2741; (*i*) H. Fuwa and M. Sasaki, *Org. Biomol. Chem.*, 2007, **5**, 2214; (*j*) T. Watanabe, S. Oishi, N. Fuji and H. Ohno, *Org. Lett.*, 2007, **9**, 4821; (*k*) C. J. T. Hyland and L. S. Hegedus, *J. Org. Chem.*, 2006, **71**, 8658; (*l*) K. Parthasarathy, M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, 2006, **8**, 621; (*m*) I. Fenández, M. I. Monterde and J. Plumet, *Tetrahedron Lett.*, 2005, **46**, 6029; (*n*) N. Alouane, F. Bernaud, J. Marrot, E. Vrancken and P. Mangeney, *Org. Lett.*, 2005, **7**, 5797; (*o*) C. de los Rios and L. S. Hegedus, *J. Org. Chem.*, 2005, **70**, 6541; (*p*) C. J. T. Hyland and L. S. Hegedus, *J. Org. Chem.*, 2005, **70**, 8628; (*q*) B. M. Trost and S. T. Dylan, *Org. Lett.*, 2005, **7**, 2117.

26 For our recent efforts, see: (*a*) Z. Song, R. P. Hsung, T. Lu and A. G. Lohse, *J. Org. Chem.*, 2007, **72**, 9722; (*b*) Z. Song and R. P. Hsung, *Org. Lett.*, 2007, **9**, 2199; (*c*) J. Huang, J. C. Ianni, J. E. Antoline, R. P. Hsung and M. C. Kozlowski, *Org. Lett.*, 2006, **8**, 1565; (*d*) L. Shen and R. P. Hsung, *Org. Lett.*, 2005, **7**, 775; (*e*) C. R. Berry, R. P. Hsung, J. E. Antoline, M. E. Petersen, C. Rameshkumar and J. A. Nielson, *J. Org. Chem.*, 2005, **70**, 4038; (*f*) L. Shen, R. P. Hsung, Y. Zhang, J. E. Antoline and X. Zhang, *Org. Lett.*, 2005, **7**, 3081; (*g*) J. Huang and R. P. Hsung, *J. Am. Chem. Soc.*, 2005, **127**, 50.

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

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

29 See ESI.† 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, $\alpha = 84.5470(10)$, $\beta = 86.5820(10)$, $\gamma = 76.4120(10)°$, $V = 916.30(10)$ Å^3, $T = 173(2)$ K, $Z = 3$, $\mu = 0.083$ mm^{-1}, 3730(R_{int}= 0.0242), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0320$, $wR_2 = 0.0732$, R indices (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, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1189.4(6)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\mu = 0.086$ mm^{-1}, 1265(R_{int}= 0.0431), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0329$, $wR_2 = 0.0756$, R indices (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, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1377.0(2)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\mu = 0.084$ mm^{-1}, 1790(R_{int}= 0.0439), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0329$, $wR_2 = 0.0761$, R indices (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, $\alpha = 90$, $\beta = 100.238(4)$, $\gamma = 90°$, $V = 1347.2(6)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\mu = 0.086$ mm^{-1}, 1492(R_{int} = 0.0503), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0394$, $wR_2 = 0.0868$, R indices (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, $\alpha = 90$, $\beta = 95.088(2)$, $\gamma = 90°$, $V = 1612.0(4)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\mu = 0.081$ mm^{-1}, 3678($R_{int} = 0.0269$), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0415$, $wR_2 = 0.1043$, R indices (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, $\alpha = 90$, $\beta = 96.906(2)$, $\gamma = 90°$, $V = 801.8(3)$ Å^3, $T = 173(2)$ K, $Z = 2$, $\mu = 0.076$ mm^{-1}, 1704(R_{int}= 0.0328), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0342$, $wR_2 = 0.0811$, R indices (all data) $R_1 = 0.0425$, $wR_2 = 0.0861$.

30 S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974.

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

32 Z. Yang, J. C. Lorenz and Y. Shi, *Tetrahedron Lett.*, 1998, **39**, 8621.

33 K. Maruoka, Y. Fukutani and H. Yamamoto, *J. Org. Chem.*, 1985, **50**, 4412.

34 (*a*) G. A. Molander and L. S. Harring, *J. Org. Chem.*, 1989, **54**, 3525; (*b*) G. A. Molander and J. B. Etter, *J. Org. Chem.*, 1987, **52**, 3942; Also see: (*c*) M. Lautens and Y. Ren, *J. Org. Chem.*, 1996, **61**, 2210.

35 (*a*) M. P. Sibi, P. K. Deshpande and J. G. Ji, *Tetrahedron Lett.*, 1995, **36**, 8965; (*b*) M. P. Sibi and J. G. Ji, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 190; (*c*) M. P. Sibi and N. A. Porter, *Acc. Chem. Res.*, 1999, **32**, 163.

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

37 W. J. Close, *J. Org. Chem.*, 1950, **15**, 1131.

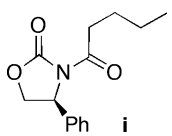
38 H. Xiong, R. P. Hsung, L. Shen and J. M. Hahn, *Tetrahedron Lett.*, 2002, **43**, 4449.

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

40 M. R. Tracey, T. P. Grebe, W. W. Brennessel and R. P. Hsung, *Acta Cryst.*, 2004, **C60**, o830.

41 H. Xiong, R. P. Hsung, L.-L. Wei, C. R. Berry, J. A. Mulder and B. Stockwell, *Org. Lett*, 2000, **2**, 2869.

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.



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