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Alkaloid-Catalyzed Enantioselective [3 + 2] Cycloaddition of Ketenes and Azomethine Imines

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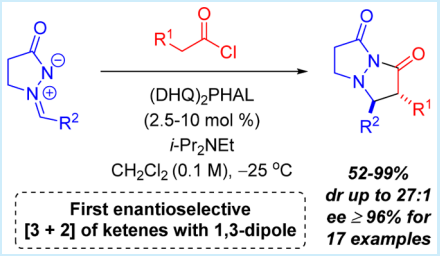
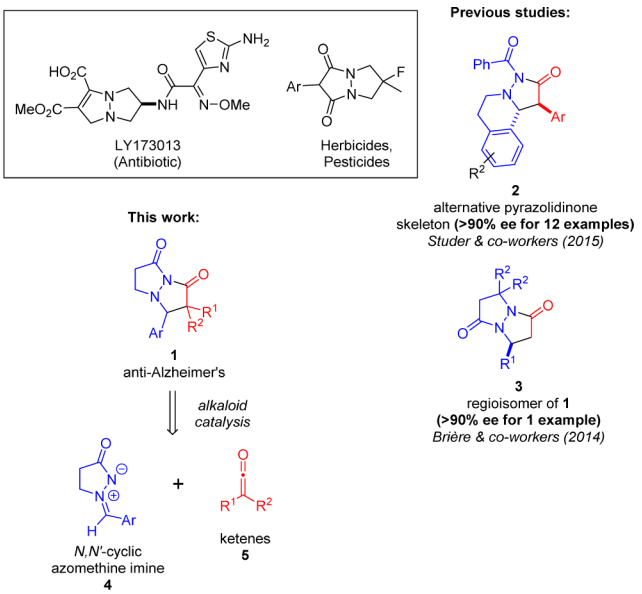
Supporting Information

ABSTRACT: A new asymmetric synthesis of bicyclic pyrazolidinones through an alkaloid-catalyzed formal [3 + 2] cycloaddition of in situ generated ketenes and azomethine imines is described. The products were formed in good to excellent yields (52−99% for 17 examples), with good to excellent diastereoselectivity (dr 5:1 to 27:1 for 11 examples), and with excellent enantioselectivity in all cases (≥96% ee). This method represents the first unambiguous example of an enantioselective reaction between ketenes and a 1,3-dipole.



The synthesis of bicyclic pyrazolidinones has recently attracted attention due to the presence of the pyrazolidinone structural motif in many biologically active complex molecules.[1] Some examples include anti-Alzheimer's disease molecule **1** and related bicyclic pyrazolidinone derivatives that exhibit herbicidal, pesticidal, and antibiotic activity (Scheme 1).[1] However, the catalytic asymmetric synthesis of pyrazolidinones of structure **1** has proven an elusive target.[2] Enantioselective access to pyrazolidinone motifs could be envisaged through a chiral catalyst-controlled 1,3-dipolar cycloaddition of an azomethine imine with a suitable dipolarophile reactant partner.[3] A number of research groups have followed that strategy.[4−8] In a seminal contribution, Fu's group reported a Cu(I)/chiral phosphaferrocene oxazoline-catalyzed asymmetric synthesis of the closely related bicyclic pyrazolines from azomethine imines and alkynes.[4] On the other hand Studer and co-workers showed that structurally novel pyrazolidinones **2** containing a tetrahydroisoquinoline moiety could be assembled through a chiral benzotetramisole-catalyzed 1,3-dipolar cycloaddition of azomethine imines with mixed anhydrides.[6] Although very high enantioselectivity could be obtained with this method, it is notably limited to the tetrahydroisoquinoline-containing imines, and as such is unable to provide access to the bicyclic pyrazolidinones represented by **1** or related fused bicyclic five-membered ring systems. It is also restricted to aryl substituents (from the anhydride) at the stereogenic center α to the imide carbonyl. This reaction is proposed to involve an ammonium enolate intermediate, most likely accessed through deprotonation of an acyl ammonium precursor. Ye and co-workers more recently reported the N-heterocyclic carbene-catalyzed reaction of α-chloroaldehydes with azomethine imines to give pyrazolidinones **2** with excellent enantioselectivity in most cases.[7] Brière and co-workers demonstrated that a related and unexpected regioisomer of a pyrazolidinone (**3**) could be prepared through the $(DHQ)_2PHAL$-catalyzed Knoevenagel−aza-Michael cyclocondensation reaction of Meldrum's acid with various azomethine imines, albeit with just one example formed in ≥90% ee.[8] A significant drawback of this method is its restriction to Meldrum's acid, and as a result the lack of a versatile diastereoselective variant, and moreover the lack of consistently high enantioselectivity across a range of examples. It should be noted that in all of these prior literature examples of organonucleophile-catalyzed enantioselective [3 + 2] cyclo-

Scheme 1. Plan for Synthesis of Bicyclic Pyrazolidinones



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additions, ketenes were not demonstrated to be involved as a reactant partner.

As part of our interest in the development of new methodologies for the asymmetric synthesis of five-membered ring structures from ketenes, we proposed that the pyrazolidinone motif **1** could be straightforwardly assembled through a chiral nucleophile-catalyzed formal [3 + 2] cycloaddition of azomethine imines of type **4** with in situ generated ketenes **5**. Our results described herein represent the first unambiguous example of an enantioselective reaction between ketenes and a 1,3-dipole, and only the second example of an asymmetric [3 + 2] cycloaddition reaction involving ketenes (Scheme 1).[9,10]

We began our studies by investigating alkaloid and phosphine catalysts which we and others had previously found to be successful for promoting formal [2 + 2] cycloadditions of ketenes with various coupling partners.[10−13] In stark contrast to phosphines, alkaloid catalysts were found to be very successful promoters under the reaction conditions tested (in CH_2Cl_2, −25 °C, in situ ketene generation, acyl chloride added slowly). Slow addition of the acyl chloride over 10 h to the reaction solution (containing catalyst, azomethine imine, and Hünig's base) was found to be beneficial to the yield of bicyclic pyrazolidinone and limited both ketene homodimerization and aldehyde formation.[12,14]

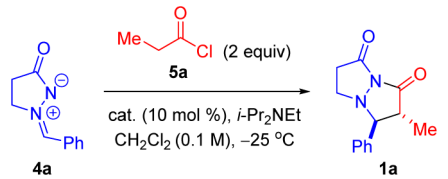
Initially Me-quinidine and TMS-quinine were found to be effective catalysts for providing high enantiocontrol, albeit accompanied by poor diastereoselectivity (Table 1, entries 1 and 2). A number of Lewis acid salt additives were investigated in an attempt to improve diastereoselectivity, but all attempts met with failure (see Supporting Information (SI)). Among the many other alkaloid catalysts investigated $(DHQ)_2PHAL$ was found to be optimal, providing the desired product in excellent yield, with excellent enantioselectivity, and, significantly, with improved diastereoselectivity (entry 6). A catalyst loading of as low as 2.5 mol % was found to be effective in terms of providing the desired product in good yield, dr, and ee (entry 7). Indeed, it was only when the reaction was run using a 1 mol % catalyst loading that a significant drop in yield (to *ca.* 45%) was observed, although with preservation of excellent enantioselectivity (94% ee).

We then went on to evaluate the substrate scope of the $(DHQ)_2PHAL$-catalyzed methodology using 10 mol % of the catalyst to ensure complete conversion and limit formation of aldehyde byproduct.[14] The method displayed excellent tolerance of substrate variation with respect to changes in the ketene substituent; methyl, ethyl, *n*-propyl, *n*-hexyl, and acetoxy substituents were all found to proceed with excellent enantioselectivity. In most cases, high yields were obtained (typically 70−99%), but it appears that AcO-substituted pyrazolidinones are somewhat acid-sensitive and that the slightly lower isolated yields (52−69%) are due to decomposition during purification on silica. The method was compatible with a variety of substituents on the aryl ring of the imines; both electron-donating and -withdrawing substituents were tolerated with excellent enantioselectivity obtained in all cases. Importantly, both enantiomers of bicyclic pyrazolidinone products can be accessed by employing the pseudoenantiomeric $(DHQ)_2PHAL$ **9** and $(DHQD)_2PHAL$ **10** (see entries 3−6 and 12−17). Remarkably, for all examples examined during the study of substrate scope, an enantioselectivity lower than 96% ee was never observed.

Diastereoselectivity favoring formation of the *trans* (*anti*)-diastereomer was moderate to good (dr up to 6.5:1) in most cases when an alkyl substituent was present on the ketene (Table 2, entries 1−11). The major diastereomer of the products was determined to be the *trans*-isomer by X-ray crystallographic analysis of the major isomer of **1f** (see SI). The major enantiomer from the $(DHQD)_2PHAL$ **10**-catalyzed formation of **1f** was determined to be the (2*S*,3*R*)-enantiomer by X-ray crystallography. By analogy, the products of all **10**-catalyzed reactions were assigned the (2*S*,3*R*)-configuration, while products of all the **9**-catalyzed reactions were assigned the (2*R*,3*S*)-configuration. The absolute stereochemical outcome is consistent with models previously proposed by the Calter and Lectka groups for related alkaloid-catalyzed reactions.[10a,15] Examples obtained with moderate diastereoselectivity could be enriched to high diastereopurity through simple recrystallization; For example, **1f** (dr 3:1) was recrystallized from CH_2Cl_2/pentane to provide **1f** in good yield (67%) and with excellent diastereomeric purity (dr 37:1). Interestingly, when an OAc substituent was present on the ketene, excellent levels of diastereoselectivity were obtained (entries 12−17). The origin of this increase in diastereoselectivity is currently under investigation.

Our proposed mechanism for the $(DHQ)_2PHAL$-catalyzed formation of bicyclic pyrazolidinones involves addition of the alkaloid catalyst to the less sterically hindered side of the monosubstituted ketene to afford an ammonium enolate I in stereoselective fashion (in accord with previous mechanistic proposals) (Scheme 2).[10,11] Addition of the ammonium enolate

Table 1. Optimization of Alkaloid-Catalyzed [3 + 2] Cycloaddition of Ketenes with Azomethine Imines



4a 1a

entry	cat.	temp (°C)	% yield[a]	dr[b]	% ee[c]
1	**6**	−25	80	1:1	98
2	**7**	−25	63	1.5:1	98
3	**6**	−78	(70)	1:1	
4	**7**	−25	(40)	1.5:1	
5	**8**	−25	(25)	2:1	
6	**9**	**−25**	**90**	**3:1**	**99**
7[d]	**9**	−25	85	3:1	99

[a]Isolated yield for both diastereomers. Conversion as determined by GC-MS in parentheses. [b]dr determined by ^{1}H NMR or HPLC analysis of crudes. (*R*,*S*)-isomer = major in most cases. [c]ee determined by chiral HPLC or chiral GC analysis for major diastereomer. [d]2.5 mol % of catalyst used.

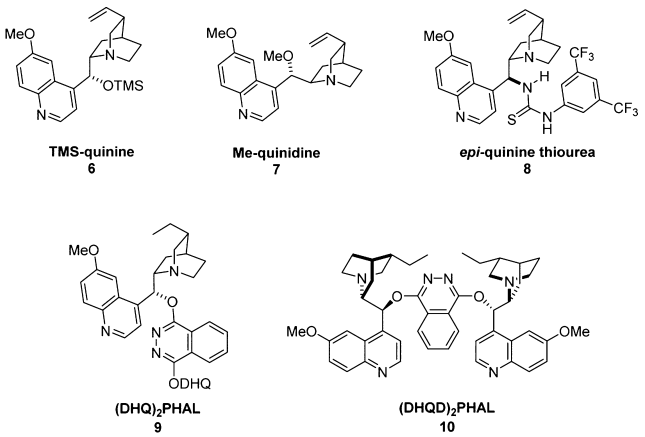


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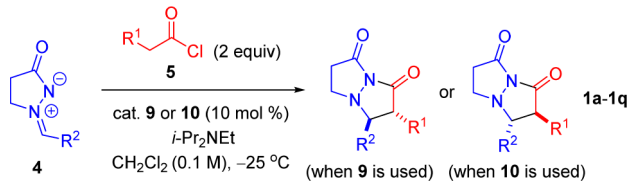
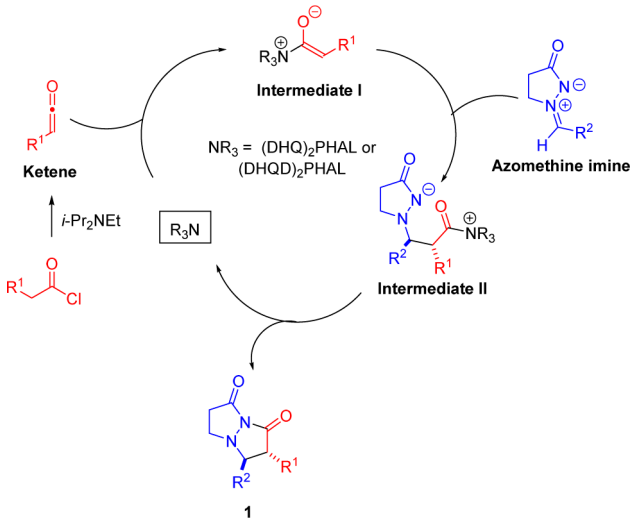
Table 2. Scope of Alkaloid-Catalyzed [3 + 2] Cycloaddition of Ketenes with Azomethine Imines



entry/1	cat.	R^1	R^2	% yield[a]	dr[b]	% ee[c]
1/**1a**	**9**	Me	Ph	90	3:1	99
2/**1b**	**9**	Me	4-MeC_6H_4	94	5:1	98
3/**1c**	**9**	Me	2-MeC_6H_4	85	5:1	99
4/**1d**	**10**	Me	2-MeC_6H_4	80	4:1	99
5/**1e**	**9**	Me	4-$MeOC_6H_4$	99	6.5:1	99
6/**1f**	**10**	Me	4-$MeOC_6H_4$	97	3:1	99
7/**1g**	**9**	Me	4-FC_6H_4	95	4:1	98
8/**1h**	**10**	Me	4-FC_6H_4	93	3:1	99
9/**1i**	**9**	Et	4-$MeOC_6H_4$	74	4:1	98
10/**1j**	**9**	*n*-Pr	4-$MeOC_6H_4$	81	5:1	99
11/**1k**	**9**	*n*-Hex	4-$MeOC_6H_4$	84	6:1	99
12/**1l**	**9**	OAc	4-$MeOC_6H_4$	58	27:1	99
13/**1m**	**10**	OAc	4-$MeOC_6H_4$	55	18:1	96
14/**1n**	**9**	OAc	4-MeC_6H_4	64	22:1	99
15/**1o**	**10**	OAc	4-MeC_6H_4	52	19:1	99
16/**1p**	**9**	OAc	Ph	69	16:1	99
17/**1q**	**10**	OAc	Ph	64	12:1	96

[a]Isolated yield for both diastereomers. [b]dr determined by ^{1}H NMR or HPLC analysis of crudes. [c]ee determined by chiral HPLC or chiral GC analysis for major diastereomer. (*R*,*S*)-isomer is the major isomer from the **9**-catalyzed reaction. (*S*,*R*)-isomer is the major isomer from the **10**-catalyzed reaction.

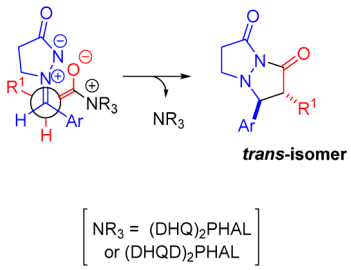
Scheme 2. Proposed Mechanism for Catalytic Asymmetric Synthesis of Bicyclic Pyrazolidinones



to the azomethine imine provides access to zwitterionic species II, which subsequently undergoes 5-exo-trig cyclization to afford pyrazolidinone **1**, along with simultaneous regeneration of the alkaloid catalyst. The participation of a ketene rather than an acyl chloride in reaction with the alkaloid catalyst was supported by the following experimental observations: The use of pregenerated methylketene (rather than propionyl chloride) led to the formation of bicyclic pyrazolidinone **1e** in virtually the same enantiomeric excess (98% ee) and diastereoselectivity (7:1) as when propionyl chloride and *i*-Pr_2NEt were used. Significantly the major isomer was formed with the same sense of enantio- and diastereoselectivity as was observed for the in situ generated ketene case. Other mechanistic observations included the following: (1) Reaction of azomethine imine with propionyl chloride was examined under typical reaction conditions (−25 °C, in CH_2Cl_2, but with no catalyst) and resulted in no product formation, thus suggesting that formation of azomethine imide followed by enolization is an unlikely mechanistic pathway. (2) In an experiment where $(DHQ)_2$PHAL and azomethine imine were dissolved in CD_2Cl_2, no evidence for interaction of $(DHQ)_2$PHAL with azomethine imine was observed by ^{1}H NMR spectroscopy. (3) In the absence of the alkaloid catalyst, a complex mixture of products resulted.

The formation of the major diastereomer of the product with *trans*-relative stereochemistry may be rationalized through a transition state in which the attacking ammonium enolate is oriented gauche to the C═N of the iminium electrophile (Scheme 3). This arrangement is presumably stabilized relative

Scheme 3. Model for Diastereoselection



to competing antiperiplanar arrangements, due to Coulombic attraction between the negatively charged oxygen of the enolate and the positively charged nitrogen of the imine.[16] When an OAc substituent was present on the ketene (R^1 = OAc in Scheme 3), very good to excellent levels of diastereoselectivity were obtained (Table 2, entries 12−17). We speculate that a favorable interaction between lone pairs on the carbonyl oxygen of the OAc group and the positively charged imine further stabilizes the putative gauche arrangement in the transition state (Scheme 3) leading to a greater preference for formation of the *trans*-isomer.

In summary, we have developed an alkaloid-catalyzed asymmetric synthesis of bicyclic pyrazolidinones, which represents the first unambiguous enantioselective [3 + 2] of ketenes with a 1,3-dipole. Pyrazolidinones were formed from in situ generated ketenes and azomethine imines, with excellent enantioselectivity in all cases (17 examples). Future work will involve applications of the reported methodology and the development of other new nucleophile-catalyzed enantioselective [3 + 2] cycloaddition reactions of ketenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02038.

Experimental procedures (PDF)
spectroscopic data, chromatograms for all new compounds (PDF)
Crystallographic data for **1f** (CIF)
Crystallographic data for **1p** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (b) Fischer, R.; Bretschneider, T.; Gesing, E. R. F.; Feucht, D.; Kuck, K.-H.; Loesel, P.; Malsam, O.; Arnold, C.; Auler, T.; Hills, M. J.; Kehne, H. PCT Int. Appl. WO 2005016873 [Chem. Abstr. 2005, *142*, 261530]. (c) Kosower, E. M.; Radkowsky, A. E.; Fairlamb, A. H.; Croft, S. L.; Neal, R. A. *Eur. J. Med. Chem.* **1995**, *30*, 659−671. (d) Kosower, E. M.; Hershkowitz, E. Isr. Patent, ISXXAQ IL 94658 [Chem. Abstr. 1994, *122*, 214077].

(2) For a diastereoselective approach: Winterton, S. E.; Ready, J. M. *Org. Lett.* **2016**, *18*, 2608−2611.

(3) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366−5412.

(4) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778−10779.

(5) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337−13348.

(6) Hesping, L.; Biswas, A.; Daniliuc, C. G.; Mück-Lichtenfeld, C.; Studer, A. *Chem. Sci.* **2015**, *6*, 1252.

(7) Gao, Z.-H.; Chen, X.-Y.; Cheng, J.-T.; Liao, W.-L.; Ye, S. *Chem. Commun.* **2015**, *51*, 9328−9331.

(8) Pair, E.; Berini, C.; Noël, R.; Sanselme, M.; Levacher, V.; Brière, J.-F. *Chem. Commun.* **2014**, *50*, 10218−10221.

(9) Shao, P.-L.; Chen, X.-Y.; Ye, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8412−8416.

(10) (a) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565. (b) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771−6803. (c) Chen, S.; Salo, E. C.; Kerrigan, N. J. In *Lewis Base and Acid Catalysts*; Science of Synthesis Reference Library, Asymmetric Organocatalysis, Vol. *1*; List, B., Ed.; Thieme: Stuttgart: 2012; Chapter 1.1.10, pp 455−496.

(11) Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. *J. Am. Chem. Soc.* **2012**, *134*, 2942−2945.

(12) Calter, M. A.; Orr, R. K. *Org. Lett.* **2003**, *5*, 4745−4748.

(13) (a) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784−1787. (b) Chen, S.; Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *J. Org. Chem.* **2014**, *79*, 4920−4929. (c) Mondal, M.; Chen, S.; Othman, N.; Wheeler, K. A.; Kerrigan, N. J. *J. Org. Chem.* **2015**, *80*, 5789−5794.

(14) Background decomposition of azomethine imine to aldehyde was found to occur during shorter acyl chloride addition times. Formation of aldehyde also occurs in the absence of catalyst and with low catalyst loadings.

(15) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.

(16) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747−5756.

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Org. Lett. XXXX, XXX, XXX−XXX