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Enamine-Iminium Ion Nazarov Cyclization of α-Ketoenones

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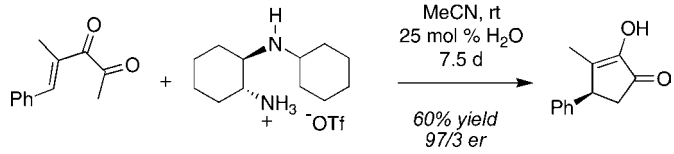
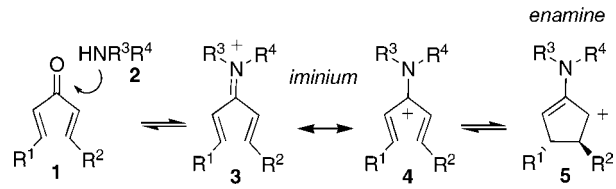
ABSTRACT



The *mono*-triflate salts of some chiral nonracemic 1,2-diamines react with α-ketoenones in a stoichiometric reaction to form products of the Nazarov cyclization in high enantiomeric ratios. The mechanism appears to involve rearrangement of an enamine−iminium ion.

Recent years have seen a resurgence of interest in the Nazarov cyclization.[1,2] An attractive approach to the asymmetric Nazarov cyclization is through iminium ion catalysis.[3] For example, treatment of divinyl ketone **1** (Scheme 1) with an asymmetric secondary amine **2** can be expected to lead to equilibrium with iminium ion **3**. Nazarov cyclization of the pentadienyl carbocation (cf. **4**) might lead to cyclic species **5** through a conrotatory process. Through appropriate choice of amine **2** and reaction conditions, asymmetric induction might be observed during this process. Although this general approach appears to be sound, in fact

Scheme 1



the pentadienyl cation (cf. **4**) is rendered more stable than the cyclic allylic cation **5** by conjugation with the nonbonding electron pair on the nitrogen atom.[4] This generally results in an equilibrium favoring the acyclic iminium ion. This

† Author to whom inquiries regarding the crystal structure of **51** should be directed.

(1) For reviews of the Nazarov reaction see: (a) Harmata, M. *Chemtracts* **2004**, *17*, 416–435. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (d) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206. (e) Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*, Vol. 45; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; pp 1−158.

(2) Recent examples of the Nazarov cyclization: (a) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560–7561. (b) Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504–7505. (c) Marx, V. M.; Burnell, D. J. *Org. Lett.* **2009**, *11*, 1229–1231. (d) Bitar, A. Y.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 49–52. (e) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073–4076. (f) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 300–308. (g) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022. (h) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792. (i) Gao, S.; Wang, Q.; Chen, C. *J. Am. Chem. Soc.* **2009**, *131*, 1410–1412. (j) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053–3056.

(3) Examples of the catalytic asymmetric Nazarov cyclization: (a) Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78–84. (b) Walz, I.; Togni, A. *J. Chem. Comm.* **2008**, 4315–4317. (c) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Ang. Chem. Int. Ed.* **2007**, *46*, 2097–2100. (d) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545. (e) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078. (f) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934. Examples of the use of chiral auxiliaries for the Nazarov: (g) Banaag, A. R.; Tius, M. A. *J. Org. Chem.* **2008**, *73*, 8133–8141. (h) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257. (i) de los Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579–2582. (j) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. *Synlett* **1999**, 1612–1614.

(4) Smith, D. A.; Ulmer, C. W., II *J. Org. Chem.* **1997**, *62*, 5110–5115.

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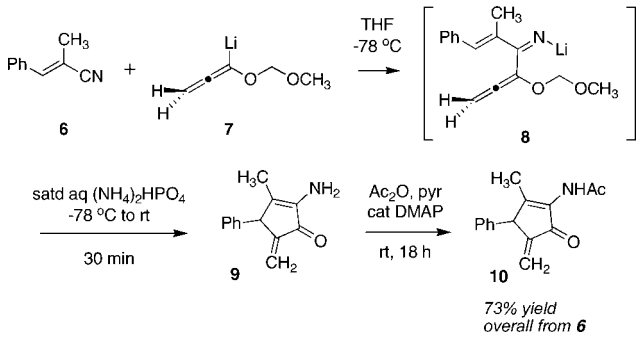
obstacle may be overcome by incorporating a structural feature into **1** that raises the energy of **3**/**4** compared to **5**.

To the best of our knowledge, the Nazarov cyclization of an iminium ion has been reported only twice. The first example is summarized in Scheme 2.[5] Addition of

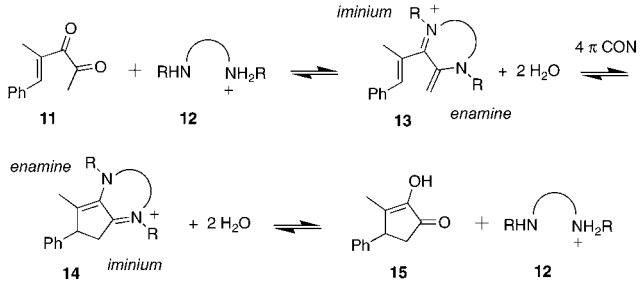
Scheme 2



lithioallenyl ether **7** to *E*-α-methyl cinnamonitrile **6** leads to *N*-lithio imine **8**. Workup with mild aqueous acid protonates the imine that then undergoes Nazarov cyclization to **9**. *N*-Acetylation in a separate step gave acetamide **10** in 73% overall yield from **6**. The success of this reaction is probably due to release of allene strain (10.76 kcal/mol)[3g] as well as the irreversible loss of methoxymethyl cation during the cyclization. In the second example of an imino Nazarov cyclization, the stability of the iminium ion was attenuated by *N*-tosylation.[6]

We first screened a small set of monoamines to determine whether they would catalyze the asymmetric conversion of **11** to **15** (Scheme 3). Stoichiometric L-proline, (*S*)-α-

Scheme 3



methylbenzylamine or (1*R*,2*S*)-(−)-ephedrine in the presence of a Brønsted acid led to small amounts (<10%) of racemic **15** in a very slow reaction. These negative results suggested a solution to the problem through a cooperative mechanism (vide infra).

We conceived of an alternative approach to the ones described above that would allow us to use iminium ion catalysis for a Nazarov cyclization. Scheme 3 summarizes the approach. Exposure of an α-ketoenone such as **11** to a diamine salt **12** is expected to generate enamine−iminium ion **13** under Brønsted acid catalysis. The carbonyl group of the methyl ketone is likely to be the more reactive of the two and will form an enamine. Subsequent reaction of the free amino group with the enone carbonyl group leads to enamine−iminium ion **13**. Intermediate **13** should be an excellent substrate for the Nazarov reaction since the enamine is polarized so as to favor cyclization.[7] Critically, this Nazarov cyclization converts enamine−iminium ion **13** to enamine−iminium ion **14**. Consequently, *both* **13** and **14** are stabilized by a nonbonding electron pair on a nitrogen atom therefore there is no reason to expect the equilibrium to favor **13**. Hydrolysis of **14** would regenerate diamine salt **12**, liberating the α-hydroxyenone product **15**. We thought that this approach had some merit since we knew from our earlier work that efficient cyclization of **11** to **15** can be accomplished under a variety of reaction conditions.

We subsequently screened the series of diamines that are listed in Figure 1, all based on the (1*R*,2*R*)-(−)-1,2-

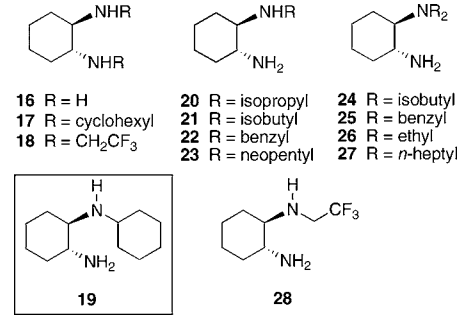


Figure 1. Diamines screened.

diaminocyclohexane motif that has been widely used in asymmetric catalysis.[8] All diamines were evaluated as their *mono*-triflate salts in the stoichiometric reaction with **11**. We were surprised that neither primary−primary diamine **16**, nor secondary−secondary diamines **17** and **18** led to cyclic product **15** under a variety of conditions. Primary−tertiary diamines **24**−**27** were also ineffective. On the other hand, primary−secondary diamines **19**−**23** were all effective in converting **11** to **15** with varying degrees of asymmetric induction in a 4 M solution in

(5) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419–2422.

(6) Suarez-Pantiga, S.; Rubio, E.; Alvarez-Rua, C.; Gonzalez, J. M. *Org. Lett.* **2009**, *11*, 13–16.

(7) (a) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871–885. (b) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.

(8) (a) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775–1778. (b) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409–1412. (c) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228–9229. (d) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867. (e) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286–287.

DMSO at room temperature. Diamines **19** and **20** led to **15** in 85/15 and 86/14 er's, respectively, whereas diamines **21** and **22** gave enantiomeric ratios of 79/21 and 77.5/22.5, respectively. Diamine **23** led to nearly racemic product (er 53/47). Under optimized conditions of solvent and concentration (0.1 M in MeCN containing 25 mol % water), the *mono*-triflate salt of **19** led to **15** in 60% yield and 97/3 er after 7.5 d at room temperature (Figure 2).

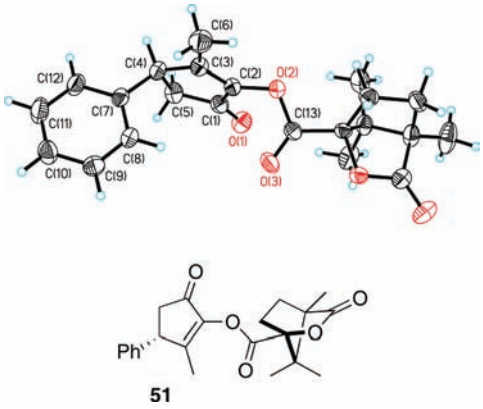
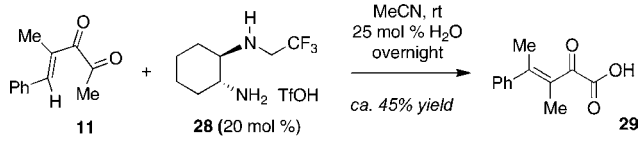


Figure 2. ORTEP diagram of **51**, the ester derivative of **15** with (−)-camphanic acid chloride. Ellipsoids are shown at the 50% level. Selected bond lengths (Å): C(1)−C(2) 1.472(2), C(2)−C(3) 1.329(2), O(1)−C(1) 1.2139(19). Selected bond angles (deg): C(3)−C(2)−C(1) 113.11(14), C(2)−C(3)−C(4) 110.42(14), C(3)−C(4)−C(5) 104.28(12), C(1)−C(5)−C(4) 105.46(13).

We were unable to find conditions that would allow **19** to function catalytically, either through inclusion of additives[9] or by varying the reaction conditions. Acid-catalyzed liberation of the diamine from its bound form is required, suggesting that product inhibition takes place.

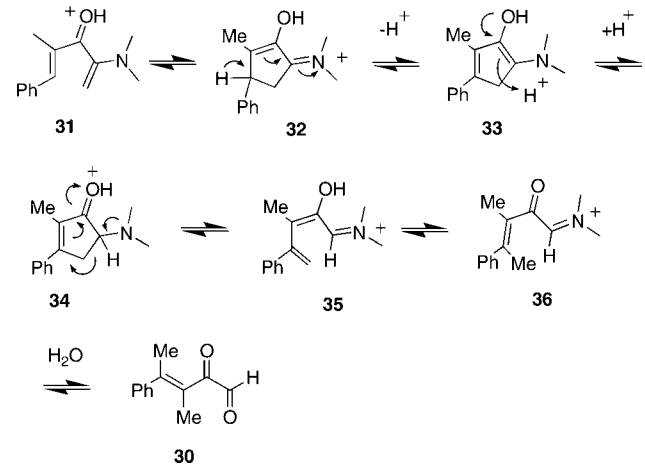
A catalytic process was observed with diamine **28**; however, this led to an unexpected product (Scheme 4).

Scheme 4



Exposure of **11** to 20 mol % of the *mono*-triflate salt of **28** in MeCN at room temperature overnight led to α-ketoacid **29** in ca. 45% yield (unoptimized) along with another unidentified dimeric product. α-Ketoacid **29** was formed in variable yields along with α-ketoaldehyde **30** from the reaction of **11** with some secondary amines, suggesting that aldehyde **30** was the primary product and that air oxidation to **29** had taken place during the reaction. The β-vinylic methyl group in **29** must have its origin as the acetyl methyl group in **11**. It is difficult to imagine a means of forming the carbon−carbon bond between the β-vinyl carbon atom and the acetyl methyl group of **11** unless the two are first joined in a ring. Scheme 5

Scheme 5



summarizes our postulated mechanism. Alternative mechanisms involving the initial formation of an enamine−iminium species similar to **13** that rationalize the formation of **30** can also be imagined. Protonated keto enamine **31** can undergo Nazarov cyclization to **32**. A series of proton transfer steps converts **32** to **34**. The cleavage step that converts **34** to **35** can be thought of as a retro-Nazarov reaction.[10] Enol−keto conversion leads from **35** to **36**. Hydrolysis of **36** gives **30** and regenerates the catalyst **28**. The origins of the differences in reactivity between **28** and **19** are difficult to rationalize.

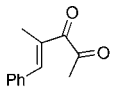
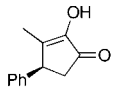
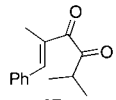
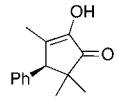
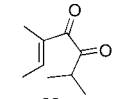
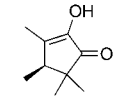
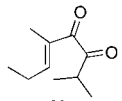
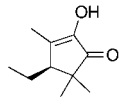
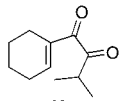
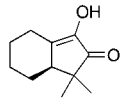
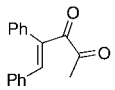
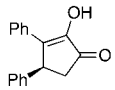
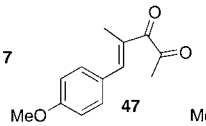
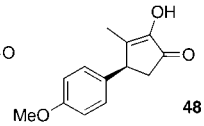
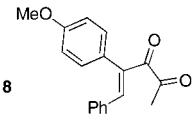
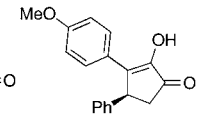
Table 1 summarizes the results of the stoichiometric reaction between the *mono*-triflate salt of **19** and a series of diketones. The reactions are in all cases slow, requiring approximately one week for completion. In the case of products bearing α *gem*-dimethyl substitution (**38**, **40**, **42**, and **44**) the minor enantiomer was undetectable by chiral HPLC. The cyclization is, however, delicately balanced as indicated by the results with substrates **45**, **47**, and **49** that led to cyclic products of lower er in poor yield. These reactions also led to the generation of numerous byproducts, rendering the purification of the cyclopentenones difficult.

The absolute stereochemistry of **15** was determined crystallographically from the (1*S*)-(−)-camphanic acid chloride derivative **51** (Figure 2). Ester **51** crystallizes in

(9) The following additives were evaluated: silica gel, alumina (neutral, basic, acidic), $CuCl_2$, LiCl, $LiClO_4$, aq NH_4OH.

(10) (a) Harmata, M.; Lee, D. R.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1881–1883. (b) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 10954–10957. (c) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328–14329.

Table 1. α-Hydroxycyclopentenones from the Nazarov Reaction (All Reactions Were Performed in Acetonitrile at 0.1 M with 25 mol % Water and 1.05 equiv of the *Mono*-triflate Salt of **19**)

entry	diketone	cyclopentenone	yield	er[a]	rxn time
1	 **11**	 **15**	60(63)%[b]	97/3	7.5 d
2	 **37**	 **38**	66(73)%	>99/1	7.5 d
3	 **39**	 **40**	49%[c]	>99/1	6.5 d
4	 **41**	 **42**	65%	>99/1	7.5 d
5	 **43**	 **44**	62%	>99/1[d]	7.5 d
6	 **45**	 **46**	11%	90/10	5.5 d
7	 **47**	 **48**	20%	91/9	6 d
8	 **49**	 **50**	24%	81/19[d]	5 d

[a] Enantiomer ratios were determined by chiral HPLC with a Chiralcel AD-H column. [b] Yields in parentheses are based on recovered diketone. [c] Volatile solid. [d] Sequence of elution of major and minor enantiomers was inverted.

space group $P2_1$, which is compatible with chiral crystal structures.[11] The absolute stereochemistry of the other α-hydroxycyclopentenones shown in Table 1 has been assigned by analogy with **15**. The inversion in chromatographic mobility that was observed for the enantiomers of **44** and **50** may indicate an inversion of the stereochemical preference in these cases, or it may be due to a unique interaction of these two cyclopentenones with the chiral stationary phase.[12]

In summary, we have described an iminium ion mediated asymmetric Nazarov cyclization of α-diketones through a mechanism requiring the formation of an enamine-iminium ion.[13] To the best of our knowledge this represents only the third example of an imino Nazarov cyclization. Although the process is not catalytic at its present level of development, the results suggest a number of ways to overcome the problem of product inhibition. The excellent enantioselectivities provide an impetus to do so.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support. We thank Mr. Paolo Larini (Università degli Studi di Torino) for his contribution to this work.

Supporting Information Available: Experimental procedures for **15** and **19**; ^{1}H and ^{13}C NMR, HRMS, and IR data for **19**, **40**, **42**, **48**, and **50**; HPLC and optical rotations for **15**, **19**, **38**, **42**, **44**, **46**, **48**, **50**; reproductions of ^{1}H and ^{13}C NMR spectra for **15**, **19**, **38**, **40**, **42**, **44**, **46**, **48**, and **50**. Crystallographic data for **51** and for the (−)-camphanic acid derivative of **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Flack, H. D. *Helv. Chim. Acta* **2003**, *86*, 905–921.

(12) Crystallographic data for the (−)-camphanic acid derivative of **38** show that the absolute stereochemistry of **38** is the same as **15**. See Supporting Information.

(13) A referee has suggested that the mechanism that we have proposed may in fact be better described as an "intramolecular enamine-Michael addition to enone". We think that this is unlikely for two reasons. First, such a process would correspond to a 5-*endo*-*trig* reaction that is disfavored by Baldwin's Rules. Second, if the reasonable assumption is made that the rate-limiting step is the ring-forming step, then one would have expected a very large difference in rate for the cyclizations leading to **15** and to **38**. Since the enamine derived from **37** is β,β-disubstituted it is a much poorer Michael donor than the unsubstituted enamine derived from **11** and would be expected to react at a significantly slower rate. No difference in reaction rate was evident for the cyclizations of **11** and **37**.