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Asymmetric Amine-Intercepted Nazarov Cyclization

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The Nazarov cyclization[1] is an efficient process for the construction of cyclopentenone rings from simple acyclic precursors. One of the variants[2] of the Nazarov reaction that we recently described is the cascade isomerization−cyclization−trapping process shown in Scheme 1. Addition of propargyllithium **1** to morpholino enamide **2** led to propargyl vinyl ketone **3**. Exposure of **3** to dry activated silica gel that had been thoroughly mixed with 1.2 equiv of cyclohexylamine gave α-aminocyclopentenone **4** in 65% yield. Amine-promoted isomerization of **3** led to an allenyl vinyl ketone that underwent cyclization in the presence of the weakly acidic silica gel. Trapping of the intermediate carbocation by the amine, followed by tautomerization and double bond migration, led to the observed product.

We hypothesized that the process of Scheme 1 could be carried out with the camphor-derived chiral auxiliary[3] that we developed in place of the propargylic methoxyl. Addition of propargyllithium **5** to morpholino enamide **2** led to ketone **6** (86% yield; Scheme 2) in a highly stereoselective reaction (ca. 50/1 in all cases).[4] Vigorous agitation of **6** for 45 min with dry activated Florisil (ca. 6 g/mmol ketone) that had been treated with 10 equiv of phenethylamine gave amino ketone **9** in 67% yield from **6** as a *single* diastereomer. The reaction also took place in the presence of silica gel, alumina (neutral, acidic, or basic) and in solution, but the yield was lower (40−53%). Thorough agitation of the reaction mixture was critical.

The interrupted Nazarov reaction has been developed primarily by West and co-workers as a cascade process for the formation of one or more carbon−carbon[5a−d] or carbon−heteroatom[5e,f] bonds subsequent to cyclization. To the best of our knowledge, the present work represents the first example of an *asymmetric* interrupted Nazarov cyclization process. Table 1 summarizes the results of a series of examples utilizing ketones **6**, **10**, and **11** and a series of primary, secondary, cyclic, and acyclic amines. Yields of aminocyclopentenones varied from 55 to 75%. In none of the reactions was any hydrolytic cleavage of the chiral auxiliary observed, testifying to the mildness of the reaction conditions. α-Phenylcinnamate-derived ketone **12** was not a suitable substrate for the reaction and led in all cases to complex mixtures of intensely colored decomposition products.

The absolute stereochemistry of the aminocyclopentenone products was determined in the case of **20** through X-ray crystallographic analysis of the derived picrate salt (Figure 1).[6] The absolute configuration of the ring carbon atoms was determined to be 4*R*,5*S*. The absolute stereochemistry of all other products was assigned by analogy to **20**.

The success of the bimolecular asymmetric interrupted Nazarov cyclizations prompted us to investigate an intramolecular reaction.

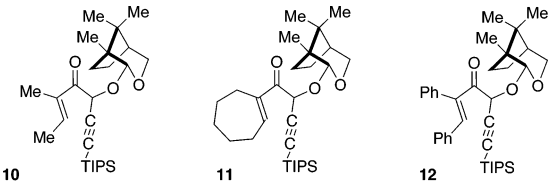
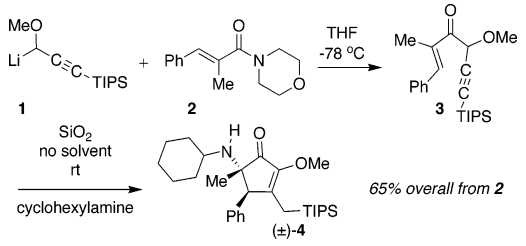
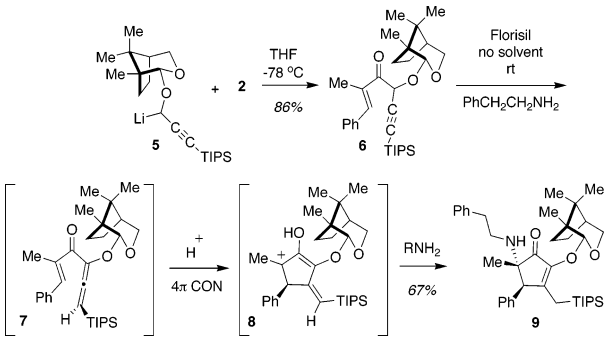


Figure 1. Propargyl vinyl ketones. Yields refer to the addition of **5** to the appropriate morpholino enamide.

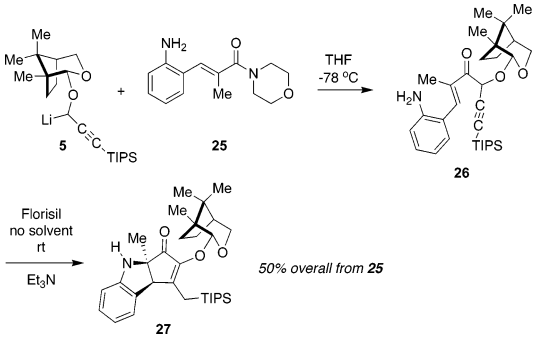
Scheme 1



Scheme 2



Scheme 3



The amine nucleophile could be located at either the α or the β enone carbon atom through a suitable tether. For our first example, we opted to prepare aniline **25** (Scheme 3).

Amide **25** was prepared in three steps according to known procedures.[7] Nucleophilic addition of **5** to **25** led cleanly to **26**.

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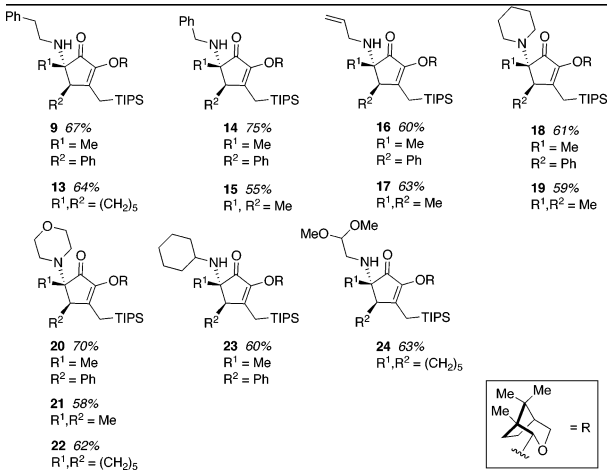
Table 1. Aminocyclopentenones[a]



[a] Enones were stirred with activated Florisil (ca. 6 g/mmol ketone) and 10 equiv of amine for 45 min. Yields are for cyclization of the propargyl vinyl ketones.

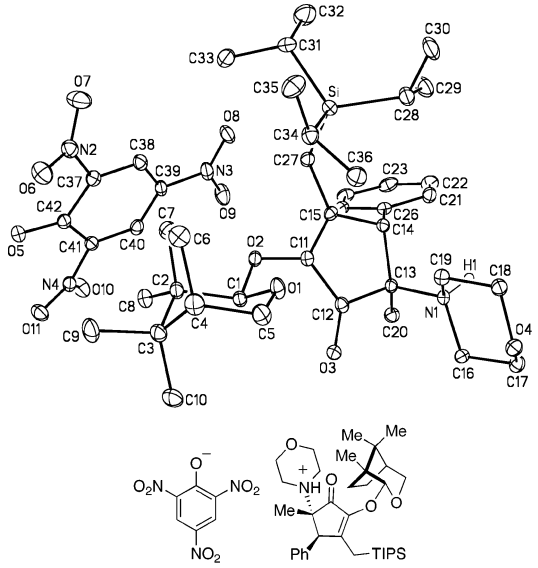


Figure 2. Molecular diagram of the picrate salt of **20** with thermal ellipsoids shown at 30% probability. Quaternary amine hydrogen atom H1 depicted with arbitrary radius. All other hydrogen atoms are omitted for clarity. Orthorhombic; $P2_12_12_1$; a = 12.583(4), b = 16.903(6), c = 19.953(7) Å; wR = 4.95%; CCDC 639752.

Exposure of this sensitive aminoketone to activated Florisil (ca. 6 g/mmol ketone) and 10 equiv of triethylamine in the absence of solvent and with vigorous agitation gave indoline **27** in 50% overall yield from **25**. The stereochemistry that is shown[8] reflects the preferred sense of conrotatory ring closure followed by intramolecular trapping of the intermediate carbocation (cf. **8**, Scheme 2). It is interesting to note that, due to the constraints of the intramolecular attack, the α carbon atom in **27** has the opposite stereochemistry as for products in which the carbocation is trapped in a bimolecular process.

In conclusion, we have demonstrated the first asymmetric version of the amine-interrupted Nazarov cyclization process. This reaction furnishes diastereomerically pure products. The success of the whole process relies on the ease with which allenyl vinyl ketones undergo the Nazarov cyclization in the presence of even the weakest acid catalysts,[4,9] the tolerance of the system to acid-labile functional groups, and the isomerization of the propargyl vinyl ketones which may result in formation of single axial isomers of the intermediate allenyl ketones. This tandem process is likely to have utility in total synthesis.[10]

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Supporting Information Available: Complete experimental procedures for the preparation of **6**, **20**, and **27**−**29**, analytical data, and ^{1}H and ^{13}C NMR for **6**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The TIPS group and chiral auxiliary are easily cleaved from the products. Exposure of **23** to tetra-*n*-butylammonium fluoride in THF led to rapid cleavage of the TIPS group (**28**, 92% yield). Subsequent exposure of the product to chlorotrimethylsilane in methanol at 0 °C led to cleavage of the chiral auxiliary (**29**, 93% yield). See the Supporting Information for details.

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