Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions of Nitroalkenes. A Versatile Asymmetric Synthesis of Highly Functionalized Aminocyclopentanes†

Scott E. Denmark* and Julie A. Dixon

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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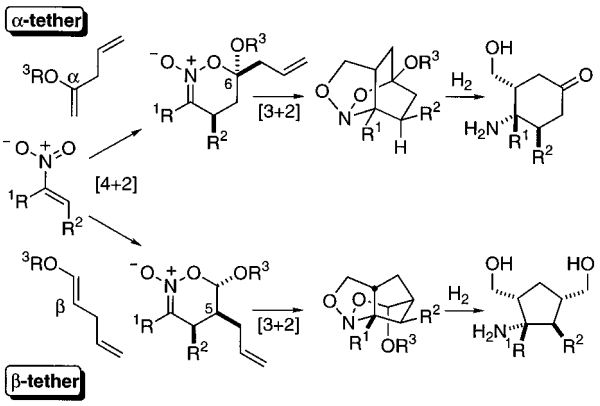
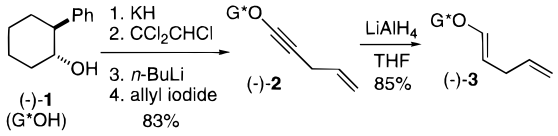
Tandem pericyclic reactions have become extremely useful for the rapid and efficient construction of highly functionalized compounds.[1] In these laboratories, the tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes and nitronates has been developed as a general approach for the synthesis of a diverse array of cyclic, nitrogen-containing structures.[2] Recently, we reported a novel subclass of the inter [4 + 2]/intra [3 + 2] cycloaddition sequence called the bridged-mode (α-tether).[3] This process involves the Lewis acid promoted [4 + 2] cycloaddition of nitro olefins with vinyl ethers bearing an α-tethered dipolarophile, Scheme 1. The resulting nitronates undergo thermal intramolecular [3 + 2] cycloaddition to afford bridged nitroso acetals which, upon reduction, provide aminocyclohexanemethanols. This success encouraged us to pursue a second variant of the bridged-mode tandem cycloaddition that would be applicable to the synthesis of aminocyclopentanes. If the dipolarophile were attached to the β-carbon of the vinyl ether, then the [4 + 2] cycloaddition would generate a cyclic nitronate now bearing a C(5)-tethered olefin, Scheme 1. Intramolecular [3 + 2] cycloaddition would subsequently provide a bridged tricyclic nitroso acetal that could be converted into a highly-functionalized aminocyclopentane.[4] In this communication, we report the successful realization of the bridged mode (β-tether) construction with an enantiomerically pure 1-alkoxy-1,4-diene. We also describe the remarkable effect of the Lewis acid on the diastereofacial selectivity of the [4 + 2] cycloaddition process.

Preparation of a chiral dienophile for use in the β-bridged-mode tandem process was accomplished in two steps from *trans*-(1*R*,2*S*)-phenylcyclohexanol ((−)-**1**). Thus, the potassium alkoxide of (−)-**1** (>99% ee) was combined sequentially with trichloroethylene and *n*-butyllithium, to afford, after quenching with allyl iodide, the acetylenic ether (−)-**2** in 83% yield, Scheme 2. Lithium aluminum hydride reduction of (−)-**2** provided exclusively the *trans*-vinyl ether (−)-**3** in 85% yield.[5]

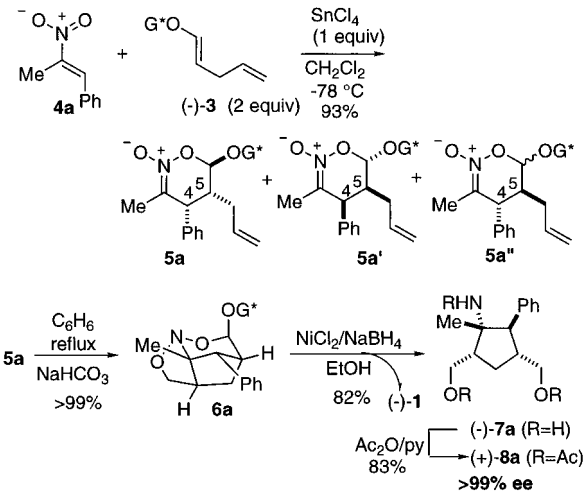
Scheme 1



Scheme 2



Scheme 3



For the initial investigations of the tandem process, we chose (*E*)-2-methyl-2-nitrostyrene (**4a**) as the test substrate. The [4 + 2] cycloaddition of nitroalkene **4a** with (−)-**3** was efficiently promoted by $SnCl_4$ to afford a mixture of diastereomeric nitronates **5a**, **5a'**, and **5a"** (32/2/1) in 93% yield, Scheme 3. Diastereomers **5a** and **5a'** possess a cis relationship between the phenyl and allyl substituents and retain the trans relationship in the vinyl ether. Thus, they must arise from an exo(alkoxy)-mode cycloaddition while trans (C(4)/C(5)) nitronate **5a"** results from an endo(alkoxy)-mode reaction.[6] The nitronic ester subunits of **5a** and **5a'** are enantiomorphic and arise from exo-mode cycloadditions with the diastereotopic faces of the chiral vinyl ether. Therefore, the overall exo/endo selectivity of the cycloaddition is >30/1 (**5a**+**5a'**/**5a"**), while the diastereofacial selectivity in the exo series is 15/1 (**5a**/**5a'**). Intramolecular [3 + 2] cycloaddition of pure **5a** in refluxing benzene provided the tricyclic nitroso acetal **6a** as a crystalline solid in quantitative yield. The full stereostructure of **6a** was secured through single

† This paper is dedicated to Professor Dieter Seebach with admiration and best wishes on the occasion of his 60th birthday.

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(6) The stereostructural assignment of the endo(alkoxy)-derived product **5a"** was established by X-ray crystal structure analysis.

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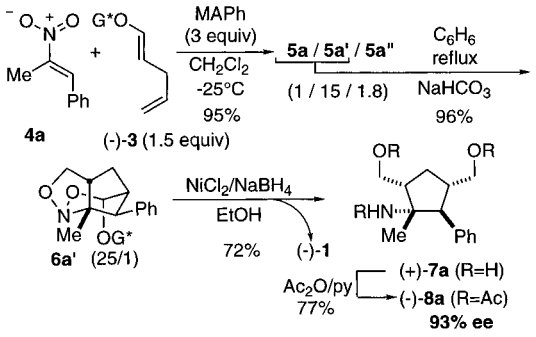
Scheme 4

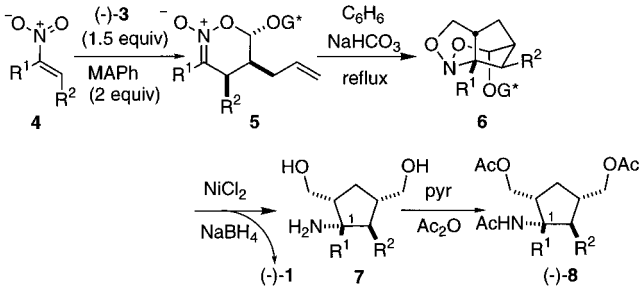


crystal X-ray analysis of (±)-**6a** that was obtained from a $SnCl_4$-promoted tandem cycloaddition of nitroalkene **4** with enol ether (±)-**3**.[7] Nickel boride[8] reduction of the nitroso acetal afforded an amino diol (−)-**7a** in 82% yield along with 94% of the recovered alcohol (−)-**1**. To facilitate purification and determine the extent of enantiomeric enrichment, the amino diol was peracylated to provide the triacetate (+)-**8a** in 83% yield and >99% ee.[9]

In view of our previous observations on the influence of Lewis acids on the stereochemical course of the [4 + 2] cycloaddition,[2c] we next examined the reaction of **4a** with (−)-**3** promoted by MAPh.[10] The same three diastereomeric nitronates (**5a**, **5a'**, and **5a"**) were formed in excellent yield (95%), however, this time in a ratio of 1/15/1.8 (Scheme 4). Thus, the reaction was again highly exo-selective (exo/endo, >8.8/1 (**5a**+**5a'**/**5a"**), but remarkably, the major diastereomer from the MAPh-promoted cycloaddition corresponded to the minor exo diastereomer obtained in the $SnCl_4$-promoted cycloaddition. The 15/1 mixture of nitronates **5a'** and **5a** was heated in benzene to afford a 25/1 mixture of nitroso acetals **6a'** and **6a** in 96% yield. Unmasking of the nitroso acetals with nickel boride provided a single amino diol (+)-**7a** in 72% yield (94% of (−)-**1** was recovered). The triacetate (−)-**8a**, obtained by acetylation of (+)-**7a**, was found to be of 93% ee[9] but was levorotatory and thus belonged to the opposite enantiomeric series as the triacetate derived from the $SnCl_4$-promoted tandem process. *Therefore, from a single, chiral, nonracemic auxiliary, either enantiomer of the final amino diol can be obtained by appropriate selection of the Lewis acid in the tandem sequence.* A number of Lewis acid dependent switches in enantioselectivity have been observed.[11] However, in these cases the change is presumably due to different coordination modes of the Lewis acid. In our system, both products derive from exo transition structures, so the change in stereochemical course is not likely due to different modes of coordination, but rather, due to a remarkable change in the reactive conformation of the vinyl ether (s-cis with $SnCl_4$ and s-trans with MAPh).

The generality of the new, bridged-mode tandem [4 + 2]/[3 + 2] reaction was demonstrated by applying

Table 1. The Tandem [4 + 2]/[3 + 2] Cycloaddition and Reduction Sequence



series (R^1, R^2)	**5** yield,[a] %	**6** yield, % (ratio of)	**7** yield, %	(−)-**8** yield, % (ee, %)[d]
b (Me, c-Hex)	90	91 (6.7/1)	96	73 (>95)
c (H, Ph)	92	87 (25/1)	82[b]	59[b] (95)
d (H, OBz)	68	− (nd)	61[c]	68 (>98)

[a] Isolated as a mixture of diastereomers. [b] Isolated as 3/1 mixture of epimeric amino diols at C(1). [c] Yield over two steps. [d] Determined by chiral HPLC.

the reaction sequence to a variety of substrates which incorporated branched alkyl, aromatic, and heteroatom substituents. Thus, nitroalkenes **4b**−**d** underwent MAPh promoted [4 + 2] cycloaddition with (−)-**3** to afford nitronates **5b**−**d** in good to excellent yields (68−92%), Table 1. In all cases, the major diastereomer is believed to have arisen from an exo(alkoxy)-mode cycloaddition. Unfortunately, the exact diastereomeric ratios could not be determined at this stage due to the propensity of the nitronates to slowly undergo [3 + 2] cycloaddition at ambient temperature. Consequently, intramolecular [3 + 2] cycloadditions of **5b** and **5c** proceeded smoothly in refluxing benzene to provide the tricyclic nitroso acetals **6b** (6.7/1 ratio of facial diastereomers) and **6c** (25/1 ratio of facial diastereomers) in 87 and 91% yield, respectively. Nickel boride reduction of a diastereomerically enriched sample of **6b** (>25/1 mixture) afforded amino diol **7b** in 96% yield along with recovered (−)-**1** (98%). Acetylation of **7b** provided the corresponding triacetate (−)-**8b** in 73% yield and >95% ee.[9] The reduction of nitroso acetal **6c** afforded the desired amino diol **7c** as a 3/1 mixture of epimers at C(1) in 82% yield.[12] After acylation, the ee of **8c** was established to be 95%.[9] Intramolecular [3 + 2] cycloaddition of nitronate **5d** and subsequent reduction of the unstable nitroso acetal **6d**[13] with nickel boride provided the amino diol **7d** in 61% over two steps. Acetylation of **7d** afforded the triacetate **8d** in 68% yield and >98% ee.[9]

In summary, we have developed a novel variant of the tandem cycloaddition of nitroalkenes which is useful for the asymmetric synthesis of highly substituted aminocyclopentanes. Moreover, by changing the Lewis acid from $SnCl_4$ to MAPh in the tandem sequence, enantiomeric amino diols can be obtained using a single enantiomer of the chiral vinyl ether. Further studies on the application of this process to the synthesis of aminocyclopentanoid natural products are in progress.

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Supporting Information Available: General and experimental procedures along with complete spectroscopic and analytical data for all characterized compounds (35 pages).

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(9) Determined by chiral stationary phase HPLC, see Supporting Information for details.

(10) Methylaluminum bis(2,6-diphenylphenoxide). Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001.

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(12) Epimeric ratios ranging from 3−20/1 have been obtained for this reaction. The epimerization of C(1) in **7c** may proceed via an enamine from a dehydrogenation/reduction sequence due to the benzylic nature of the hydrogen at the C(9) position of the nitroso acetal.

(13) Nitroso acetal **6d** was unstable to alumina and silica gel chromatography and was used in the subsequent reaction without purification.