2-Amino-1,3-butadienes as Chiral Building Blocks: Enantioselective Synthesis of 4-Piperidones, 4-Nitrocyclohexanones, and 1,3-Cycloheptadione Derivatives

José Barluenga,*,† Fernando Aznar,† Carlos Valdés,† Alfredo Martín,† Santiago García-Granda,‡ and Eduardo Martín‡

Departamentos de Química Organometálica y Química Física y Analítica, Universidad de Oviedo Julian Clavería s/n 33071-Oviedo, Spain

Received January 4, 1993

The preparation of functionalized 6-membered rings via enantioselective [4 + 2] cycloaddition processes is currently an area of very active research. The majority of the reported investigations on this topic have dealt with the use of chirally modified dienophiles,[1] although Lewis acids have also received increasing attention as chiral catalysts[2] for asymmetric cycloadditions. On the other hand, there have been only a few reports of [4 + 2] reactions in which the 4-π-electron component contains a chiral center.[3] Most of the examples in the literature involve C-1-substituted dienes whose allylic position is substituted with a heteroatom. The diastereofacial selectivity for [4 + 2] reactions of these C-1-substituted chiral dienes has been examined.[4] Enantioselective Diels–Alder reactions have also been reported for 1,3-dienes which have a chiral auxiliary appended to the C-1 position through a heteroatom linkage, such as an ester,[5] amide,[6] or carbohydrate.[7] Unfortunately, the enantioselectivities for these systems have not been very high. Furthermore, for the carbohydrate-containing dienes, the sugar moiety can prove to be a nuisance if it is merely intended to serve as a chiral auxiliary, since it cannot be easily removed or modified at a later stage in the synthesis.

The cycloaddition chemistry of 1,3-dienes which have a chiral group at C-2 has received surprisingly little attention thus far. The diastereofacial selectivity for reactions of 2-substituted dienes having heterosubstitution at the allylic center has been examined.[8] However, the diastereomeric excesses (de) have generally been low, and the chiral groups in these examples cannot really be considered as chiral auxiliaries.[9]

Recently, we have demonstrated that 2-amino-1,3-butadienes react with various electrophiles to give [4 + 2] adducts.[10] Thus, using simple nonactivated imines[11] or β-nitrostyrene,[12] the corresponding piperidones[13] or cyclohexanones can be prepared. We have also found that 2-amino-1,3-butadienes react with vinylchromium Fischer-type carbenes to afford highly functionalized 1,3-cycloheptadione derivatives with very high stereoselectivity.[14] We report herein the extension of this methodology toward the enantioselective synthesis of 6-membered and 7-membered rings (Scheme I), using chiral 2-amino-1,3-butadienes which have a pyrrolidine auxiliary at the C-2 position. These dienes are prepared easily in optically-pure form from commercially available enynes and (*S*)-2-(methoxymethyl)pyrrolidine.

We first examined the cycloaddition reactions of 2-aminobutadienes **1** with *N*-silylimines **2** (Scheme I). The additions take place at –80 °C to room temperature over a period of 10 h in the presence of 1 molar equiv of $ZnCl_2$ in THF. The cyclic enamines **5** produced in the reactions were not isolated due to their instability in the aqueous media required for removal of the catalyst. Consequently, the crude product mixture was hydrolyzed

† Departamento de Química Organometálica.

‡ Departamento de Química Física y Analítica (XR section).

(1) (a) For recent reviews, see: Helmchen, G.; Kargfe, R.; Weetmen, J. In *Modern Synthesis Methods*; Scheffold, R. Ed.; Springer Verlag: Berlin, 1986; Vol. 4, pp 261–306. Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Ressig, H.-U. *Organic Synthesis Highlights*; VCH Verlagsgesellschaft: Weinheim,1991; pp 54–60. (b) For some recent leading references on chiral dienophyles, see: Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. Evans, D.; Chapman, K. T.; Tan Hung, D.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184. Miyaji, K.; Ohara, Y.; Takahashi, Y.; Tsuruda, T.; Arai, K. *Tetrahedron Lett.* **1991**, *32*, 4557. Ståhle, W.; Kunz, H. *Synlett* **1991**, 260. Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299. Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, *75*, 109.

(2) (a) For some recent reviews, see: Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Ressig, H.-U. *Organic Synthesis Highlights*; VCH Verlagsgesellschaft: Weinheim, 1991, pp 61–63, 66–70. Kagan, B. H.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019. (b) For some leading references on asymmetric Diels–Alder catalysts, see: Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. Yamamoto. H.; Maruoka, M. *J. Am. Chem. Soc.* **1989**, *111*, 789. Kaufmann, D.; Gerhard, B. *Organomet. Chem.* **1990**, *390*, 1. Kagan, H. B.; Riant, O.; Rebiere, D. *Tetrahedron: Asymmetry* **1990**, *1*, 199. Helmchen, G.; Sartor, D.; Saffrich, J. *Synlett* **1990**, *4*, 197. Yamamoto, H.; Mayumi, T. *Synlett* **1990**, *4*, 194. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. Kaufmann, D.; Boese, R. *Angew. Chem.* **1990**, *102*, 568. Corey E.J.; Imwilnkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. Corey, E. J.; Teck-Peng, L. *J. Am. Chem. Soc.* **1991**, *113*, 8966. Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396. Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951. Corey, E. J.; Loh, T.-P; Roper, Th. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290.

(3) For a recent review on chiral dienes, see: Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Ressig, H.-U. *Organic Synthesis Highlights*; VCH Verlagsgesellschaft: Weinheim, 1991; pp 60–61, and references cited therein.

(4) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257. Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625. Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, *167*. Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2274. Kaila, N; Franck, R. W.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 4206. Hamada,T.; Sato, H.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 6405. Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472. Burnouf, C.; Cristobal-Lopez, J.; Calvo-Flores, F. G.; de los Angeles Laborde, M.; Olesker, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1990**, *823*. Barluenga, J.; Gonzalez, F. J.; Fustero, S.; García-Granda, S.; Perez-Carreño, E. *J. Org. Chem.* **1991**, *56*, 4459. Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. *Tetrahedron Lett.* **1991**, *32*, 1649.

(5) Tripathy, R.; Carrol, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630. Siegel, C.; Thornton, E. R. *Tetrahedron: Asymmetry* **1991**, *2*, 1413. Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225. Jung, M. E.; Jung, Y. H.; Miyazawa, Y. *Tetrahedron Lett.* **1990**, *31*, 6983.

(6) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295.

(7) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455. Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908. Gupta, R. C.; Slavin, A. M.; Stoodley, R. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 668. Lubineau, A.; Queneau, Y. *Tetrahedron* **1989**, *45*, 6697. Larsen, D. S.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1339.

(8) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Lawrence, N. J.; Selim, M. R. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1893. Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 953. Bloch, R.; Chaptal-Gradoz, N. *Tetrahedron Lett.* **1992**, *33*, 6147.

(9) While this paper was in the refereeing process, an example of an enantioselective [4 + 2] cycloaddition of a chiral 2-aminobutadiene to nitroalkenes was reported: Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242.

(10) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M.-P. *J. Org. Chem.* **1991**, *56*, 6168.

(11) Barluenga, J.; Aznar, F.; Cabal, M.-P.; Hernandez-Cano, F.; Foces-Foces, M. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1247. Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M.-P., submitted for publication.

(12) Barluenga, J.; Aznar, F.; Cabal, M.-P.; Valdés, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 633.

(13) 4-Piperidones are important synthetic intermediates, particularly in the preparation of alkaloids and medicinal drugs. (a) For some recent monographs on piperidone chemistry, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine. Structure, Preparation, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (b) Bosch, J.; Domingo, A.; López, F.; Rubiralta, M. *J. Heterocycl. Chem.* **1980**, *17*, 241. (c) Bosch, J.; Rubiralta, M.; Monserrat, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595 and references cited therein. (d) For some leading references, see: Janssens, F.; Torremans, J.; Janssens, P. A. J. *J. Med. Chem.* **1986**, *29*, 2290. (e) Bagley, J. R.; Wynn, R. L.; Rudo, F. G.; Doorley, B. M.; Spencer, H. K.; Spaulding, T. *J. Med. Chem.* **1989**, *32*, 663. (f) Kuzma, L. V.; Severnak, S. A.; Bevenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C. *J. Med. Chem.* **1989**, *32*, 2534.

(14) Barluenga J.; Aznar, F. Martín, A.; García-Granda, S.; Salvadó, M. A.; Pertierra, P. *J. Chem. Soc., Chem. Commun.* **1993**, 319.

0002-7863/93/1515-4403$04.00/0

Scheme I

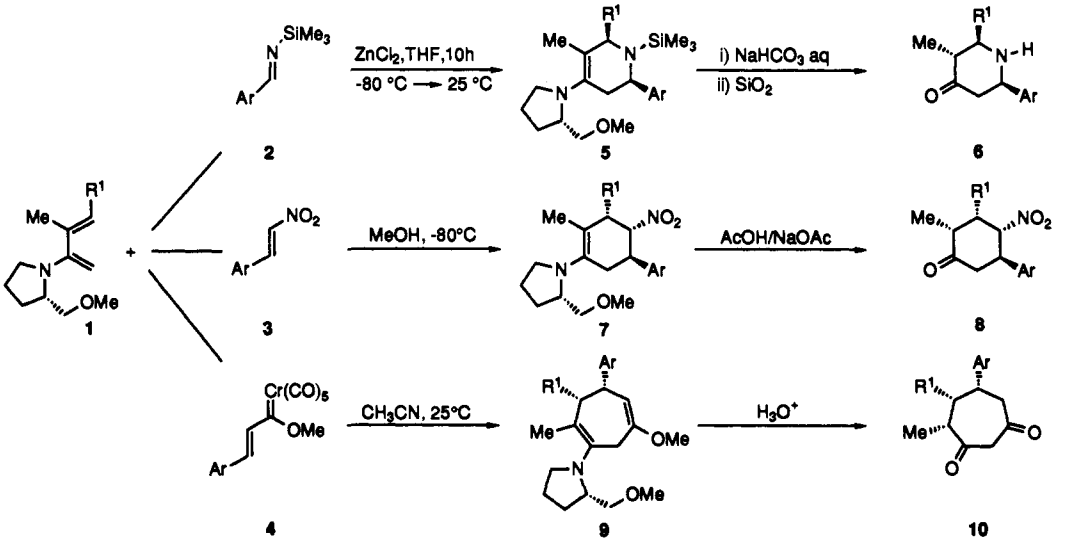

Table I. Preparation of Compounds 6, 8, and 10

compd	R^1	Ar	yield (%)	ee (%)
6a	CH_2OH	phenyl	65	95
6b	CH_2OCH_3	2-bromophenyl	63	86
8a	CH_2OCH_3	phenyl	70	82
8b	CH_2OCH_3	2-chlorophenyl	76	90
10a	CH_2OCH_2Ph	phenyl	55	72
10b	CH_2OCH_3	2-furyl	45	86
10c	CH_2OCH_2Ph	2-furyl	52	81

with aqueous $NaHCO_3$ and purified by silica gel flash chromatography (dichloromethane:ethyl acetate 3:1) to afford piperidones **6** in good yields (Table I).

In a similar manner, 2-amino-1,3-butadienes **1** reacted with nitroolefins **3** in methanol at −80 °C over an 8-h period to give cyclic enamines **7** (Scheme I). Evaporation of the solvent and ^{1}H-NMR analysis of the crude reaction mixture revealed the presence of a major diastereoisomer, which unfortunately decomposed during attempted purification by column chromatography. Therefore, the crude enamine was hydrolyzed in NaOAc/HOAc buffer solution (pH = 4.6) to provide 4-nitrocyclohexanones **8** in good yields after flash chromatography (Table I).

We next turned our attention to reaction of chiral dienes **1** with vinylchromium carbene complexes **4**. Vinylcarbenoids[15] and Fischer-type carbene complexes[16] have previously been shown to react with dienes to give 7-membered ring compounds via a tandem cyclopropanation/Cope rearrangement process. However, the direct preparation of 7-membered rings in an enantioselective manner has remained a problem yet to be solved.[17] The prospect of accomplishing this via an enantioselective [4 + 3] cycloaddition between chiral dienes **1** and vinylchromium carbene complexes **4** was therefore intriguing.

To test this strategy, a 0.12 M solution of **4** was treated with an equimolar amount of **1** at room temperature for 48 h. To our delight, aminocycloheptadienes **9** were produced in the reactions, along with minor amounts of the [4 + 2] cycloadducts (Scheme I).[14] Hydrolysis of the crude reaction mixture with 3 N HCl for 3 h (longer times result in epimerization at the methyl center) afforded cycloheptadienes **10** in 45-55% yield after SiO_2 flash chromatography (ethyl acetate:hexane 1:3). The results are summarized in Table I.

To summarize, we have demonstrated that chiral 2-amino-1,3-butadienes serve as excellent starting materials for the enantioselective synthesis of highly functionalized six-membered and seven-membered rings. Features which make this methodology most attractive for asymmetric synthesis are the ease in which the chiral diene can be prepared and the facile conversion of the enamine cyclic adduct to a ketone using mild hydrolytic conditions. We are currently exploring additional aspects and some synthetic applications of this chemistry.

Acknowledgment. We thank Dr. Jesús T. Vazquez of the La Laguna University (Spain) for CD measurements. This research was supported by Dirección General de Investigación Científica y Tecnológica (DGICYT) PB 89-0538. C.V. and A.M. are grateful to M.E.C. for a Fellowship.

Supplementary Material Available: Synthetic procedures and characterization data for **6a,b**, **8a,b**, **10a–c**; crystal data, tables of structural parameters, and structural diagrams of **8a** and **8b** (29 pages); lising of observed and calculated structure factors for **8a** and **8b** (33 pages). Ordering information is given on any current masthead page.

(15) Davies, H. M. L.; Smith H. D. Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853. Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817. Davies, H. M. L.; Clark, T. J.; Kimmer, G. F. *J. Org. Chem.* **1991**, *56*, 6440.

(16) Wulff, W. D.; Yang, C.; Murray, C. K. *J. Am. Chem. Soc.* **1988**, *110*, 2653.

(17) Enantioselective synthetic processes to seven-membered carbocycles are valuable because these rings are present in several important classes of natural products. For general reviews in this field, see: Heathcock, C. H.; Grahm, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; Simon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 333–384. Rigby, J. H. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1988; Vol. 1, pp 545–576. Vandewalle, M.; De Clerq, P. *Tetrahedron* **1985**, *41*, 1767.