

Catalytic Enantioselective Annulations via 1,4-Addition–Aldol Cyclization of Functionalized Organozinc Reagents

Robert Naasz, Leggy A. Arnold, Mauro Pineschi, Erik Keller, and Ben L. Feringa*

Department of Organic and Molecular Inorganic Chemistry
University of Groningen, Nijenborgh 4
9747 AG Groningen, The Netherlands

Received October 23, 1998

The construction of carbocyclic compounds by the Robinson annulation is one of the essential methodologies in organic synthesis.¹ The Hajos-Parrish asymmetric version has been applied in numerous syntheses of steroids, terpenes, and a variety of other natural products.² Typically the *l*-proline catalyzed Michael addition–intramolecular aldol reaction of 2-methyl-1,3-cyclohexadione and methylvinyl ketone results in the formation of Wieland–Miescher ketone (Scheme 1a) with 67% ee providing the enantiomerically pure decalone after crystallization.^{3,4} We envisioned that an alternative strategy could be developed based on a sequential enantioselective conjugate addition–aldol cyclization involving a C4-functionalized organometallic reagent (Scheme 1b).

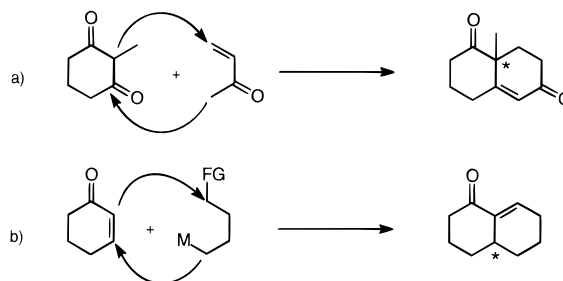
The essential differences between both methodologies are the following: (i) a reversal of the role of the cycloalkanone being the Michael donor in the first case and the Michael acceptor in the annulation methodology presented here and (ii) the asymmetric catalysis involves the aldol cyclization in the first method (Scheme 1a, step 2) whereas the stereocontrol is exerted during the catalytic 1,4-addition in the new procedure (step 1 in Scheme 1b).

In the pursuit of an enantioselective method for ring annulation according to Scheme 1b we took advantage of the ligand accelerated⁵ 1,4-addition using novel Cu(II)-phosphorus amidite catalysts recently developed in our laboratories.^{6,7}

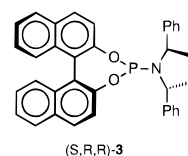
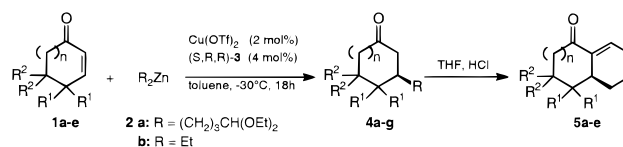
This paper describes highly enantioselective annulation methodology for cyclohexenones, cycloheptenones, and cyclooctenones with use of functionalized organozinc reagents. In addition we present catalytic enantioselective tandem reactions leading to the formation of 5,6- and 5,7-annulated systems.

For the annulation reactions, functionalized dialkylzinc reagent **2a**, with an acetal moiety at C(4), was employed. The (FG-R)₂-Zn reagent was readily prepared from the corresponding alkene⁸

Scheme 1



Scheme 2^a



^a See Table 1 for R¹, R², and n.

by hydroboration and subsequent zinc exchange in approximately 75% yield following the procedure of Knochel.⁹ When cyclohexenone **1a** was treated at $-30\text{ }^{\circ}\text{C}$ with **2a** in the presence of the catalyst in situ prepared from Cu(OTf)₂ (2 mol %) and phosphorus amidite **3** (4 mol %), derived from (*R,R*)-bis(1-phenylethyl)amine and (*S*)-2,2'-binaphthol, 4-substituted cyclohexanone **4a** was obtained in 91% yield and an ee of 98%. Addition of aqueous HCl to a solution of **4a** in THF and stirring at room temperature¹⁰ resulted in acetal hydrolysis and ring closure to afford decalone **5a** with 97% ee (Scheme 2).¹¹

Table 1 summarizes the results of this new enantioselective synthesis of bicyclic enones. The introduction of a geminal dimethyl moiety adjacent to the enone as is present in **1b**, which results in annulated products with a prominent structural feature found in many natural products, also afforded the corresponding decalone (**5b**) in enantiomerically pure form (entry 2). The presence of two methyl substituents at C(5), as is the case with enone **1c**, led to a slight decrease of the stereoselectivity presumably due to 1,3-diaxial interactions (entry 3).

To establish if the scope of the annulation could be extended to 7- and 8-membered cyclic enones the catalytic 1,4-additions

(1) For reviews see: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 1–31. (b) Gawley, R. E. *Synthesis* **1976**, 777–794.

(2) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(3) Buchsacher, P.; Fürst, A. *Org. Synth.* **1984**, *63*, 37–43. For the [5,6]-bicyclo enedione 97% ee is obtained: Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412–417. Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1984**, *63*, 26–36.

(4) For reviews of other (asymmetric) annulation methodology, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 12. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. Annulation via the addition of allylsilanes: Schinzer, D. *Methods of Organic Chemistry*; Houben Weyl: Stuttgart, 1996; p 2087. Catalytic annulation via [3+2] cycloaddition: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1–20. Binger, F.; Fox, D.; *Methods of Organic Chemistry*; Houben Weyl: Stuttgart, 1996; Vol. E21, p 3055. Cyclopentannulation: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326–2335. Huart, C.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 634–636. Cycloisomerizations: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42. The enantioselective Diels–Alder reaction to (chiral) cycloalkenones to provide chiral decalones was extensively studied by Taticchi et al.: Minuti, L.; Radics, L.; Taticchi, A.; Venturini, L.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 4261–4265 and references cited therein. Until now no catalytic enantioselective version of this reaction was known. (Catalytic) asymmetric conjugate addition of organometallic reagents: Feringa, B. L.; De Vries, A. H. M. *Adv. Catal. Processes* 1995, *1*, 151. Bosshamer, S.; Gais, H.-J. *Synthesis* **1998**, 919–927.

(5) Berisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059–1070.

(6) (a) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374–2376. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.

(7) For a brief review: Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283–285.

(8) Hoaglin, R. I.; Kubler, D. G.; Montagna, A. E. *J. Am. Chem. Soc.* **1958**, *80*, 5460–5463.

(9) Langer, F.; Devasagayari, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410–412. Michael additions of functionalized organozinc reagents: Lipschutz, B. H.; Wood, M. R.; Tirado, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 6126–6127.

(10) (a) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–5050. (b) Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 44, 4217–4220. (c) Abbott, R. E.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 5398–5399. (d) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081–6091. (e) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352–7358. (f) Leone-Bay, A.; Paquette, L. A. *J. Org. Chem.* **1982**, *47*, 4173–4174.

(11) Typical experimental procedure: Under an Ar atmosphere in flame-dried glassware a mixture of 8.7 mg (0.024 mmol) of Cu(OTf)₂ and 26 mg (0.048 mmol) of (*S,R,R*)-**3** in 20 mL of toluene was stirred at room temperature for 1 h. The solution was cooled to $-30\text{ }^{\circ}\text{C}$ and 0.20 mL (2.1 mmol) of **1a** was added. After the solution was stirred for 10 min 2 mL of a 2 M solution of **2a** in toluene was added and the reaction mixture was stirred overnight at $-30\text{ }^{\circ}\text{C}$. Aqueous workup followed by column chromatography (silica, hexanes–ether: 3–1) yielded pure **4a** as a colorless oil (462 mg, 1.9 mmol, 91%). Cyclization to **5a** was performed according to a literature procedure: see ref 10b. Further details: see Supporting Information.

Table 1. $[n+4]$ Annulation According to Scheme 2

entry	enone	R ¹	R ²	<i>n</i>	R ₂ Zn	product	yield (%)	ee (%)	product	yield ^a (%)	ee ^b (%)
1	1a	H	H	1	2a	4a	91 ^a	98 ^c	5a	62	97
2	1b	Me	H	1	2a	4b	49 ^a	n.d.	5b	55	>98
3	1c	H	Me	1	2a	4c	57 ^a	n.d.	5c	56	84
4	1d	H	H	2	2a	4d	61 ^a	n.d.	5d	50	96
5	1e	H	H	3	2a	4e	61 ^{a,d}	n.d.	5e	42	>98
6	1d	H	H	2	2b	4f	>95	>98 ^b			
7	1e	H	H	3	2b	4g	>95	97 ^b			

^a Isolated yield. ^b ee's determined by chiral GC (see Supporting Information). ^c Determined by ¹³C NMR after derivatization with (*1R,2R*)-(+)–1,2-diphenylethylenediamine. See: Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* 1993, 4, 2431. ^d Isolated as a mixture of aldehyde and acetal due to partial hydrolysis during column chromatography.

Table 2. $[n+3]$ Annulation According to Scheme 3

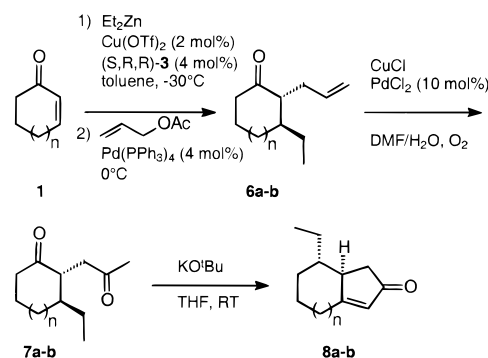
entry	enone	product	<i>n</i>	yield ^d (%)	ee ^b (%)	trans/cis	product	yield (%)	ee (%)	trans/cis	product	yield (%)	ee (%)	trans/cis
1	1a	6a	1	88	96	9/1	7a	65	96	35/1	8a	56 ^c	96	13/1
2	1d	6b	2	86	n.d.	<i>d</i>	7b	78	97	<i>d</i>	8b	82	96	<i>d</i>

^a Isolated yield. ^b ee determined by chiral GC (see Supporting Information). ^c Yield not optimized. ^d Cis could not be detected by GC.

of diethylzinc to cycloheptenone (**1d**) and cyclooctenone (**1e**) were examined next. Much to our delight in the presence of Cu(OTf)₂ (1.2 mol %) and ligand **3** (2.4 mol %) both **4f** and **4g** were obtained in quantitative yield as single enantiomers (entries 6, 7).¹² By employing the acetal functionalized dialkylzinc reagent **2a** in the 1,4-addition–aldol cyclization protocol to cycloheptenone (**1d**) and cyclooctenone (**1e**) again excellent enantioselectivities were achieved in the annulation of a six-membered ring (entries 4, 5). To the best of our knowledge this represents the first catalytic annulation protocol that affords 6,6- (including the 4,4-dimethyl substituted derivative), 6,7-, and 6,8-annulated ring systems with enantiomeric excesses in all cases exceeding 96%. It is noteworthy that a single catalyst with a monodentate chiral ligand tolerates dialkyl- and acetal-functionalized dialkylzinc reagents, substituted enones as well as six, seven, and eight membered enones with nearly complete stereocontrol.

The formation of carbobicyclic structures incorporating a five- as well as a six-membered ring (bicyclo[4.3.0]nonenone skeleton) would represent an important extension of this new asymmetric annulation methodology.^{4,13} Despite the excellent enantiocontrol exerted by the copper catalyst based on chiral ligand **3** for the larger rings, surprisingly hardly any selectivity (ee = 10%) is found for cyclopentenone. By employing a TADDOL-based phosphorus amidite we recently could enhance the enantioselectivity (e.e. = 70%) in the conjugate addition of dialkylzinc reagents to cyclopentenone but the levels of enantioselectivity are still insufficient for a synthetically useful annulation procedure for cyclopentenones.^{14,15} It was anticipated that a reverse sequence, i.e. annulation of a five-membered ring to a cyclic enone, might be achieved if the in situ prepared zinc enolate, resulting from the 1,4-addition, is prone to palladium-catalyzed allylation¹⁶ as is depicted in Scheme 3.

The regio- and enantioselective three-component coupling was indeed achieved when the enolate formed from **1a** and diethylzinc in the presence of Cu(OTf)₂ (2.0 mol %) and ligand **3** (4.0 mol %) was treated with allyl acetate and a catalytic amount of Pd(PPh₃)₄ (4 mol %) at 0 °C. A mixture of *trans*- and *cis*-2-allyl-3-ethylcyclohexanone **6a** (9:1 ratio) was obtained in excellent yield and an ee of 96%. Subsequent Pd-catalyzed Wacker oxidation of the allyl moiety to the corresponding methyl ketone¹⁷ fol-

Scheme 3

lowed by aldol cyclization employing KO^tBu in THF at room temperature¹⁸ afforded the 5,6-annulated product **8a** (trans:cis ratio = 13:1) with 96% ee for the major isomer.^{19,20} Starting from cycloheptenone **1d** the tandem 1,4-addition, Pd-catalyzed oxidation, aldol sequence afforded the 5,7-carbocyclic product **8b** in excellent yield exclusively as the *trans* isomer with 96% ee (Scheme 3).

On the basis of the high selectivities observed with a variety of R₂Zn reagents in the 1,4-addition⁶ it is to be expected that several of these zinc reagents can be applied in the tandem-annulation procedure presented here. Current methodology to accomplish catalytic ring-annulation commonly provides high enantioselectivity only for specific ring sizes. The catalytic transformations described here result in uniform high enantioselectivity in the construction of a variety of bicyclic structures which makes it a powerful extension to our annulation repertoire.

Acknowledgment. Financial support from The Netherlands Foundation for Scientific Research and from the European Community (EU Contract No. ERBFMBICT 961635) is gratefully acknowledged.

Supporting Information Available: Typical experimental procedures for $[n+4]$ and $[n+3]$ annulation (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA983693G

(12) For 3-ethylcycloheptanone the ee was incorrectly reported to be 53% (see ref 6b).

(13) The bicyclo[4.3.0]nonenone skeleton can be found in many natural products: Porter, L. A. *Chem. Rev.* 1967, 67, 441–464.

(14) Keller, E.; Maurer, J.; Naasz, R.; Schrader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* 1998, 9, 2409–2413. Arnold, L. A.; Feringa, B. L. unpublished results.

(15) Pfaltz *et al.* recently reported up to 72% ee in the 1,4-addition to cyclopentenone: Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* 1997, 1429–1431.

(16) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* 1996, 37, 5141–5144.

(17) (a) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* 1976, 17, 2975–2976. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (c) Feringa, B. L. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

(18) Procedures for related ring closures with KOH in water or ethanol at reflux yielded a mixture of three products: (a) Welch, S. C.; Asserq, J.-M.; Loh, J.-P. *Tetrahedron Lett.* 1986, 27, 1115–1118. (b) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* 1952, 4086–4087.

(19) A trans:cis ratio of 35:1 was found after the Wacker oxidation which is due to slow conversion of the *cis*-isomer of **6a**.

(20) For a recent enantioselective synthesis of a bicyclo[4.3.0]nonenone skeleton, see: Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M. *Tetrahedron Lett.* 1998, 39, 7909–7912.