ORGANIC LETTERS

2005
Vol. 7, No. 17
3605−3607

Catalytic Asymmetric Ring Opening of 2,3-Substituted Norbornenes with Organometallic Reagents: A New Formal Aza Functionalization of Cyclopentadiene

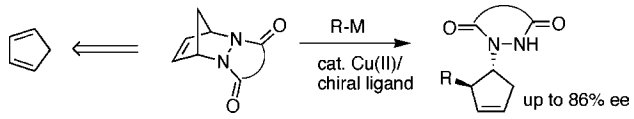
Mauro Pineschi,* Federica Del Moro, Paolo Crotti, and Franco Macchia

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

pineschi@farm.unipi.it

Received April 22, 2005

ABSTRACT



An unprecedented regioselective and anti stereoselective asymmetric ring opening of 1,3-cyclopentadiene-heterodienophile cycloadducts, including also 2,3-diazabicyclo[2.2.1]heptenes, with hard alkylmetals and copper–phosphoramidite catalysts, is reported. The induced ring opening, in conjunction with C–C bond formation, gives a catalytic and practical access to new heterofunctionalized cyclopentenes in an enantioenriched form (up to 86% ee).

Development of new methodologies for the preparation of nonracemic chiral compounds by means of asymmetric catalysis is of fundamental importance in synthetic organic chemistry. Catalytic asymmetric transformations are especially valuable when the starting materials are easily accessible and of low cost. For example, 3-aza-2-oxabicyclo-[2.2.1]hept-5-enes **1a**,**b** and 2,3-diazabicyclo[2.2.1]hept-5-enes **2a**−**c** (Figure 1) can be obtained in multigram amounts,

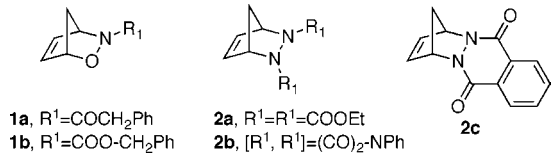


Figure 1. 2,3-Heteronorbornenes **1** and **2** used as starting material for asymmetric carbon−carbon bond formations.

in a very simple way, from the hetero Diels−Alder reaction between cyclopentadiene with transient acylnitroso species and azodicarboxylates, respectively.[1,2] Acylnitroso-derived Diels−Alder **1a**,**b** possess several potential electrophilic sites[3] but are most commonly elaborated through cleavage of the N−O bond to form 1,4-aminocyclopentenols.[4] A less common approach involves the cleavage of the C−O bond to give hydroxamic acid, which is an important functionality found in a variety of biologically active compounds.[5]

Symmetrical bi- and polycyclic hydrazines **2a**−**c** have been known for a long time,[2] though there are very few reports on their ring-opening reactions. Quite recently, a new anti stereoselective palladium-catalyzed hydrazido arylation of cyclic hydrazide to give novel hydrazino cyclopentenes, albeit in racemic form, has been reported by Kaufmann et al.[6] Although, palladium-catalyzed asymmetric hydroaryla-

(1) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford 1991; Vol. 5, pp 419−421.

(2) (a) Diels, O.; Blom, J. H.; Knoll, W. *Justus Liebigs Ann. Chem.* **1925**, *443*, 242−262. (b) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962**, *14*, 615−618.

(3) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348 and references therein.

(4) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181−3183.

(5) Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 2466−2469 and references therein.

10.1021/ol050895q CCC: $30.25
Published on Web 07/19/2005

tions of norbornene are well documented,[7] and huge efforts have been devoted to the development of highly efficient catalytic and enantioselective desymmetrization of 7-heteroatom-norbornene derivatives,[8] no enantioselective addition of carbon nucleophiles to norbornenes containing multiple heteroatoms such as **1** and **2** has been described.[9]

In our continuing interest in the development of new ring-opening reactions of heterocyclic rings to give synthetically useful enantiomerically enriched building blocks,[10] we have now found that readily available heteronorbornenes **1** and **2** can be opened with hard alkylmetals in the presence of catalytic amounts of copper−phosphoramidite ligands.[11]

In a preliminary experiment, the addition of Me_2Zn (2.0 equiv) to cycloadduct **1a** in the presence of a catalytic amount of $Cu(OTf)_2$ (1.5 mol %) and phosphoramidite (*R*,*R*,*R*)-**3a** (3.0 mol %) afforded the *trans*-1,2-hydroxamic acid **4b** cleanly with *complete regioselectivity and anti stereoselectivity* (Table 1, entry 1).

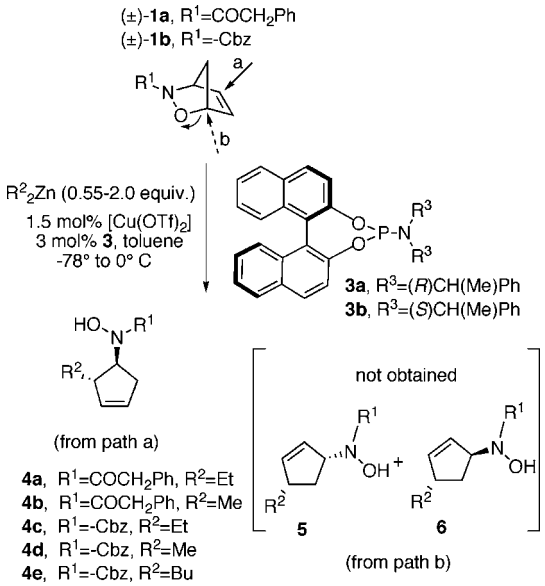
Table 1. Regio- and Stereoselective Addition of Dialkylzinc Reagents to (±)-3-Aza-2-oxabicyclo[2.2.1]hept-5-enes **1a**,**b**[a]

entry	substrate	R^2 (equiv)	time (conversion (%))[b]	ee (%)[c]
1	**1a**	Me (2.0)	3 h (>96)	
2	**1a**	Et (0.55)	8 h (45)	44
3	**1a**	Me (0.60)	3 h (52)	56
4[d]	**1a**	Et (0.55)	5 h (20)	8
5	**1b**	Me (0.60)	2 h (46)	58
6	**1b**	Et (0.60)	3 h (48)	53
7[d]	**1b**	Et (0.60)	3 h (42)	30
8	**1b**	Bu (0.60)	4 h (49)	37

[a] Reactions carried out with chiral ligand (*R*,*R*,*R*)-**3a**. For the typical procedure, see Supporting Information. [b] Determined by ^1H NMR of the crude product. [c] Determined on adducts **4** by HPLC on a Daicel Chiralcel OD-H column. For the determination of the absolute configuration of the major enantiomer, see Supporting Information. [d] Reaction carried out with diastereoisomeric ligand (*R*,*S*,*S*)-**3b**.

The copper−phosphoramidite catalyst efficiently promotes the addition of the organometallic reagent on the double bond, with cleavage of the C−O bond accompanied by allylic rearrangement (path a, Scheme 1).[12] When the reaction was performed with Et_2Zn (0.55 equiv) in accordance with a kinetic resolution protocol, it was possible to obtain **4a** with a 44% ee at 45% conversion (Table 1, entry 2). A slighty

Scheme 1. Regio- and Stereoselective Addition of Dialkylzinc Reagents to 3-Aza-2-oxabicyclo[2.2.1]hept-5-enes



better enantioselectivity (56% ee at 52% conversion) was obtained with the use of Me_2Zn (entry 3). When the kinetic resolution reaction was carried out with diastereoisomeric ligand (*R*,*S*,*S*)-**3b**,[11a] a very low enantioselectivity was obtained (Table 1, entry 4). Similar results were obtained with compound **1b** containing an easily removable carbobenzyloxy (Cbz) protecting group on the nitrogen (Table 1, entries 5−8).

On the basis of the encouraging results obtained with racemic acyl nitrosoderived cycloadduct **1a**,**b**, initial experiments devoted to a challenging desymmetrization reaction of symmetrical bicyclic hydrazines **2** were focused on the use of dialkylzincs as the organometallic reagent. Unfortunately, the copper phosphoramidite-catalyzed reaction of dicarboxyethyl bicyclic hydrazine **2a** with dialkylzinc reagents proved to be unsuccessful.

The more rigid, tri- or tetracyclic Diels−Alder adducts **2b** and **2c** of 1,3-cyclopentadiene with the cis-configured dienophiles derived from 4-phenyl-1,2,4-triazolin-3,5-dione and 2,3-phthalazine-1,4-dione, respectively, proved to be more reactive (Scheme 2). With these substrates, the reaction of Et_2Zn in the presence of the copper−phosphoramidite catalyst **3a** afforded the corresponding trans-3,4-disubstituted hydrazino cyclopentene derivatives **7a** and **7c**, albeit with low yields and in almost racemic form (Table 2, entries 1 and 2). A low enantioselectivity (18%) was also obtained with Bu_2Zn (Table 2, entry 3).

(6) Yao, M.-L.; Adiwidjaja, G.; Kaufmann, D. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 3375−3378.

(7) (a) Brunner, H.; Kramler, K. *Synthesis* **1991**, 1121−1124. (b) Namyslo, J. C.; Kaufmann, D. E. *Eur. J. Org. Chem.* **1998**, 1997−2001. (c) Brunel, J. M.; Hirlemann, M.-H.; Heumann, A.; Buono, G. *Chem. Commun.* **2000**, 1869−1870.

(8) For a review, see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(9) For the unique example we know of a palladium-catalyzed asymmetric ring-opening of diazabicycloheptenes with O-nucleophiles, proceeding with a different regiochemistry and moderate enantioselectivity (up to 58% ee), see: Luna, A. P. L.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771−4774.

(10) For a recent review, see: Pineschi, M. *New. J. Chem.* **2004**, *28*, 657−665 and references therein.

(11) For overviews of phosphoramidites in catalytic asymmetric conjugate additions, see: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236.

(12) Corresponding blank reactions performed without the use of phosphoramidite ligands gave a mixture of products and a lower conversion. Miller et al. have recently reported a ring opening of 3-aza-2-oxabicyclo-[2.2.1]hept-5-enes of type **1** with Grignard reagents in combination with catalytic amounts of $CuCl_2$. However, the reaction is not completely regio- and stereoselective, and the main product, racemic *anti*-1,2-hydroxamic acids of type **4** (through path a, Scheme 2), were invariably obtained in a mixture of ring-opened products of types **5** and **6** in which the attack of the organometallic reagent had occurred at the bridgehead carbon atom (path b, Scheme 2). See: Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4115−4121.

Scheme 2. Enantioselective Desymmetrization of Polycyclic Hydrazines **2b**,**c** with Organometallic Reagents

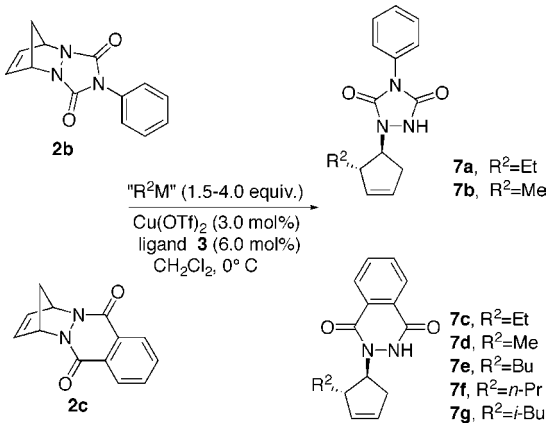


Table 2. Desymmetrization of Polycyclic Hydrazines **2b**,**c** with Organometallic Reagents (R^2-M)[a]

no.	substrate	R^2-M	time (h)	conversion (%)[b]	ee (%)[c]
1	**2b**	Et_2Zn	24	38	3
2	**2c**	Et_2Zn	6	22	0
3	**2c**	Bu_2Zn	6	34	18
4	**2b**	Et_3Al	4	>98	66(+)
5	**2b**	Me_3Al	1	>98	80(+)
6	**2c**	Et_3Al	4	94	78(+)
7	**2c**	Me_3Al	4	>98	86(+)
8[d]	**2c**	Me_3Al	4	>98	64(−)
9[e]	**2c**	$(n\text{-Pr})_3Al$	20	>98	54(+)
10[e]	**2c**	$(i\text{-Bu})_3Al$	20	95	14(−)

[a] Reactions entirely carried out at 0 °C with chiral ligand (*R*,*R*,*R*)-**3a**.[20] For the general procedure, see Supporting Information. [b] Determined by ^1H NMR of the crude mixture. [c] Determined by HPLC on a Daicel Chiralpack AD-H. Sign of optical rotation reported in parantheses. [d] Reaction carried out with diastereoisomeric ligand (*R*,*S*,*S*)-**3b**. [e] Reaction carried out at up to room temperature.

Therefore, we decided to change the primary organometallic reagent from the poorly reactive dialkylzinc reagents to the more reactive organoaluminum reagents.

The copper-catalyzed conjugate addition of organoaluminum reagents to α,β-unsaturated carbonyl compounds is a well-established, simple procedure for the transfer of hydrocarbon substituents.[13] However, only a few examples of enantioselective additions using trialkylaluminum reagents have been reported, and bicyclic hydrazines have never been considered as substrates for this reaction.[14] To our delight, with the use of trialkylaluminum, the corresponding opening products **7** were obtained with high yields and good enantioselectivities (Table 2, entries 4−7).[15] In most cases, it was possible to obtain adducts **7a**−**g** in a pure state after a simple washing of the crude mixtures with hexanes to get rid of the chiral ligand. This reaction can be considered a new asymmetric formal hydrazido alkylation of cyclopentadiene.[16]

Very interestingly, in the desymmetrization reaction of diazabicyclic compounds **2b** and **2c**, the sense of chirality of the amine part of the phosphoramidite proved to exhibit a major influence on the stereochemical outcome of the reaction. In fact, diastereoisomeric phosphoramidite ligand (*R*,*S*,*S*)-**3b** afforded the opposite enantiomer of adduct **7d** (64% ee, entry 8) with respect to ligand (*R*,*R*,*R*)-**3a**.[17] It should be noted that this is an important exception to the normal trend in which it is the binaphthol unit of the chiral phosphoramidite ligand that imposes the absolute stereochemistry of the conjugate adduct.[11,14a]

The nice results obtained with diazabicycloheptenes **2b**,**c** seem to indicate an evident dependence of the enantioselectivity on the nature of the aluminum organyl.[18] The best enantioselectivities were obtained with Me_3Al, and by the use of the more sterically demanding $(i\text{-Bu})_3Al$, a reversal of the facial selectivity was even observed (Table 2, entry 10). These facts support the notion that the structure of the active catalyst incorporates an AlR_3-dependent substrate *binding pocket*.[19]

The present findings represent an unprecedented asymmetric ring opening of norbornenes containing multiple heteroatoms with hard alkylmetals. The induced ring opening, in conjunction with C−C bond formation, gives for the first time a catalytic and practical access to hetero-functionalized alkyl cyclopentenes in an enantioenriched form.

Acknowledgment. This work was supported by Ministero dell'Istruzione, dell'Università e della Ricerca (M.I.U.R. Rome, P.R.I.N. 2004) and by the University of Pisa. The authors thank Prof. Rita Menicagli for useful discussion about organoaluminum reagents.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050895Q

(13) Westermann, J.; Nickisch, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1368−1370.

(14) For the use of trialkyl aluminums with α,β-unsaturated carbonyl compounds, see: (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378. (b) Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244−1245. (c) Su, L.; Li, X.; Chan, W. L.; Jia, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 1865−1869. (d) Bennett, S. M.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767−1770. (e) Dieguez, M.; Deerenberg, S.; Pamies, O.; Claver, C.; van Leeuwen, P. W. N. M.; Kamer, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3161−3166. With vinyl epoxides, see: (f) Equey, O.; Alexakis, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1531−1536. With oxabicyclic alkenes, see: (g) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902−3909.

(15) On the other hand, trialkylaluminums gave a complex mixture of products when used with oxabicyclic compounds **1a**,**b** and with bicyclic hydrazine **2a**.

(16) For a recent report on hydrohydrazination of simple alkenes, see: Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *32*, 4099−4102.

(17) Some other phosphoramidite ligands that were employed gave lower enantioselectivities (see Supporting Information).

(18) Substituted vinylic alane, readily available by hydroalumination of 1-hexyne, and freshly prepared $AlPh_3$ proved to be only scarcely reactive in our reaction conditions (<10% conversion after 18 h at 0 °C, data not reported in Table 2).

(19) Fraser, P. K.; Woodward, S. *Chem. Eur. J.* **2003**, *9*, 776−782.

(20) Reactions reported in Table 2 can be performed at −25 °C for 10−18 h with only marginal variation of ee values.