ORGANIC LETTERS

2003
Vol. 5, No. 25
4771−4774

Stereoselective Ring Opening of *meso* Bicyclic Hydrazines: A Straightforward Approach to Hydrazino Cyclopentenic Cores

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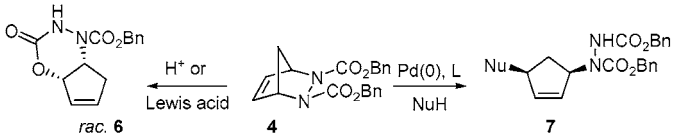
Received September 10, 2003

ABSTRACT



The diastereoselective synthesis of hydrazinocyclopentenes 6 or 7 can be achieved in a straightforward manner from Diels–Alder adduct 4 using an acid-catalyzed rearrangement or a palladium-catalyzed allylic substitution reaction. In the latter case, enantioenriched compounds with ee values up to 58% can be obtained when an appropriate chiral ligand is used.

Disubstituted cyclopentenes are key intermediates in the preparation of numerous natural or synthetic biologically active compounds, including glycosidase inhibitors,[1] antiviral and antitumor carbonucleosides,[2] or kinase inhibitors (Figure 1).[3] Various racemic or enantioselective strategies, based on stoichiometric or catalytic stereoselective transformations, have been devised for the preparation of such intermediates.[4]

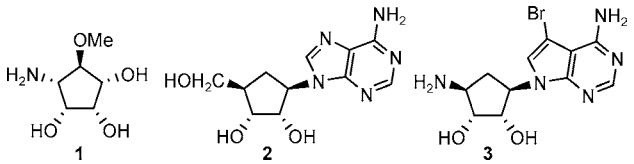


Figure 1. Examples of bioactive aminocyclopentanic derivatives.

Among them, one of the most powerful and elegant is the well-known Trost approach based on the desymmetrization of *meso* 3,5-dihydroxy-1-cyclopentene by asymmetric allylic substitution. It provides useful synthetic intermediates in excellent stereo- and enantioselectivities.[5] Another route has been developed by Miller and co-workers, using isoxazolidines as starting material.[6] However, in both strategies, the use of π-allyl palladium chemistry for the introduction of

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10.1021/ol0357393 CCC: $25.00
Published on Web 11/12/2003

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heterocyclic substituents has found some limitations mainly due to regioselectivity and solubility problems.[7]

We have recently described the desymmetrization of *meso* hydrazines **4**, based on a rhodium- or iridium-catalyzed hydroboration, as a simple way to provide enantioenriched cyclopentanic diamino alcohol **5** in 66% overall yield from cyclopentadiene (Figure 2).[8] At the same time, Kaufmann

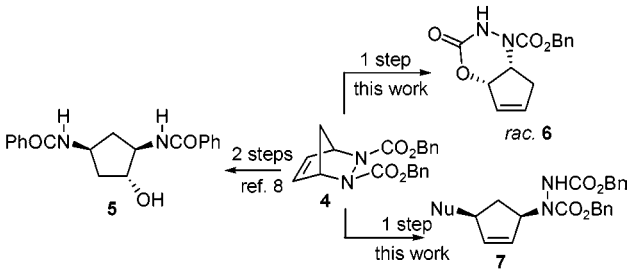


Figure 2. Desymmetrization of *meso*-hydrazines.

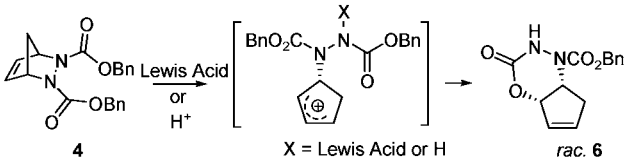
and co-workers reported a diastereoselective palladium-catalyzed ring opening of similar intermediates during hydroarylation reactions, providing racemic trans-3,4-disubstituted hydrazino-cyclopentene derivatives in up to 69% overall yield from cyclopentadiene.[9] We wish to report herein our results concerning the ring opening of *meso* hydrazine **4** using acid-catalyzed rearrangement or palladium-catalyzed allylic substitutions, leading to bicyclic carbazate **6** or *cis*-hydrazinocyclopentenes **7**.

Such derivatives could be useful intermediates in the modulation of heterocyclic substituents by multicomponent hydrazine-based chemistry.[10]

Ring opening of *N*,*N*-acyloxy-2,3-diazabicyclo[2.2.1]-heptenes by cleavage of the C−N bond has only been reported for a limited number of particular substrates[11] and has not been exploited for synthetic purposes. To evaluate the fragmentation ability of hydrazine **4**, we first investigated its acid-catalyzed rearrangement to carbazate **6** (Table 1).

Interestingly, behavior similar to Lewis acid-catalyzed rearrangement of *N*-acyl aziridines was observed.[12] Oxophilic Lewis acids (entries 1, 2) did not promote the rearrangement,

Table 1. Acid-Catalyzed Stereoselective Rearrangement of Hydrazine **4**



entry[a]	acid (equiv)	time (h)	yield (%)[b]
1	Et_2AlCl (1.75)	12	0
2	$TiCl_4$ (0.25)	5	0
3	$SnCl_4$ (0.5)	2	73
4	$Zn(OTf)_2$ (1.0)	24	82
5	BPh_3 (0.25)	5	0
6	$BF_3.Et_2O$ (1.0)	1	43
7	CH_3COOH[c]	24	0
8	CF_3COOH[c]	1	55

[a] All reactions were performed in CH_2Cl_2, at room temperature. [b] Yield of analytically pure compound. [c] Used as a solvent.

whereas more azaphilic catalysts (entries 3, 4) led to the bicyclic cyclopentene **6** in 73−82% yield.[13] BF_3·Et_2O (entry 6) and protic conditions (entry 8) also catalyzed the rearrangement. These results suggest that fragmentation probably occurs through nitrogen activation. Mechanisms involving both a [3,3]-sigmatropic rearrangement[14] or the stepwise trapping of an intermediate allylic cation have been proposed for similar transformations.[15] In our case, the detection by MS of dimeric structures coming from the collapse of two ionic species indicates that a dissociative pathway takes place.

Although neutral nitrogen leaving groups are not commonly used in palladium-catalyzed allylic substitutions,[16] several examples of such a reactivity have been described on strained substrates.[17]

The encouraging results in acid-catalyzed fragmentations led us to envision the use of palladium for generating and trapping this allylic reactive species (Table 2).

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(10) Although an impressive number of carbocyclic nucleosides syntheses have been described, reports on the preparation of such derivatives bearing pyrazoles or fused heterocyclic pyrazoles are scarce; see ref 7 and: Bhagwat, S.; Cowart, M. D. WO 96/4068. For examples of the usefulness of hydrazinocyclopentanes in the synthesis of bioactive compounds, see: Kuang, R.; Ganguly, A. K.; Chan, T.-M.; Pramanik, B. N.; Blythin, D. J.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2000**, *41*, 9575 and references therein.

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(13) **Experimental Procedure.** Compound **4** (91 mg, 0.25 mmol) was introduced in a round-bottom flask, dissolved in freshly distilled methylene chloride (2.5 mL), and placed under argon. $SnCl_4$ (1 M in CH_2Cl_2, 125 μL, 0.125 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (2 mL) was added next, and the organic layer was separated and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate = 70/30) afforded *rac*-**6** as a colorless oil (50 mg, 73%).

(14) Mackay, D.; Campbell, J. A.; Jennison, C. P. R. *Can. J. Chem.* **1970**, *48*, 81.

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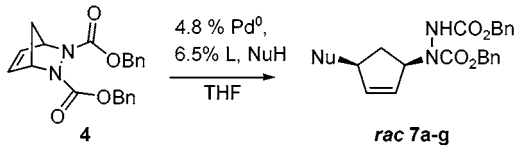
Table 2. Palladium-Catalyzed Diastereoselective Ring Opening of Compound **4**



4 *rac* **7a-g**

entry	NuH	conditions	compd	yield (%)[a]
1[b,d]	PhOH	$Pd_2(dba)_3$; PPh_3	**7a**	75
2	PhOH	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7a**	83
3	3-BrPhOH	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7b**	83
4	AcONa	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7c**	0
5[b]	phthalimide	$Pd_2(dba)_3$; DPPF	**7d**	84
6[c]	CH_3NO_2	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7e**	75
7[b]	$CH_2(COOEt)_2$	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7f**	76
8	$CH_2(COOtBu)_2$	$[Pd(allyl)Cl]_2$; NaH; DPPF	**7g**	75

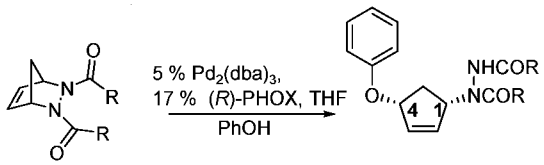
[a] Yield of analytically pure compound. [b] Performed under reflux. [c] Performed at 0 °C. [d] Performed with 10% $Pd_2(dba)_3$ and 40% PPh_3 .

Thus, treatment of hydrazine **4** in the presence of phenol and a large amount of catalyst in refluxing tetrahydrofuran led to the desired compound **7a** in 75% yield. No reaction could be observed in the absence of palladium or phosphine, ensuring that the ring opening occurred via a true catalytic process. Better results were obtained using dppf[18] as ligand and $[Pd(allyl)Cl]_2$ as a precatalyst, enabling the substitution to occur at room temperature with a lower amount of catalyst. Addition of a small amount of sodium hydride (5%) was necessary to generate the Pd(0) reactive species. This set of conditions proved to be suitable for phenolic nucleophiles (entries 1−3) or nitromethane (entry 6). However, no reaction occurred with phthalimide, and the π-allyl intermediate had to be generated with $Pd_2(dba)_3$. Malonates (entries 7, 8) were first deprotonated with 1 equiv of sodium hydride before reacting. Disubstituted hydrazinocyclopentenes **7a**−**g** bearing oxygen, nitrogen, or carbon substituents could be prepared in a completely regio- and stereoselective manner in 69−84% yield.[19]

The starting material being *meso*, we then envisioned using chiral ligands in order to perform an enantioselective transformation (Table 3).

Encouraging preliminary results could be obtained using PHOX ligand, leading to compound **7a** in good yield and

Table 3. Palladium-Catalyzed Enantioselective Ring Opening of Compounds **4** and **8**−**10**



4, 8-10 **7a, 11-13**

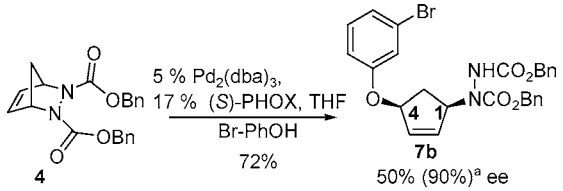
entry	R, R	compd	*t* (h)	yield (%)[a]	ee (%)[b]
1	OBn, OBn	**7a**	2	82	50
2[c]	OBn, OBn	**7a**	2	80	58
3[d]	OBn, OBn	**7a**	2	68	55
4	O*i*Pr, O*i*Pr	**11**	4	88	40
5	O*t*Bu, O*t*Bu	**12**	15	75	36
6	−NPh−	**13**	15	<5	

[a] Yield of analytically pure compound. [b] Determined by chiral HPLC. [c] Performed in toluene. [d] Performed in toluene with $[Pd(allyl)Cl]_2$ as a precatalyst.

50% ee.[20] Hydrazine protective groups proved to have an influence on the conversion rate as well as the enantioselectivity (entries 1, 4, 5), and almost no reaction occurred starting from a tricyclic urazole (entry 6). A slight increase in ee was observed when toluene was used as the solvent (entry 2). It is worth noting that with a P,N ligand, $Pd_2(dba)_3$ could be used as a precatalyst, suggesting that electron-donating ligands enhance the system's reactivity and make it unnecessary to add sodium hydride. Moreover, the choice of precatalyst had little influence on enantioselectivity (entry 3). Since the enantioselective determining step in this transformation is probably an irreversible ionization step, the enantioselectivity should be weakly dependent on the nucleophile used.[21]

The use of *m*-bromophenol as a nucleophile in such a transformation led to compound **7b** in 50% ee (Scheme 1).

Scheme 1



4 **7b**
50% (90%)[a] ee

[a] After one recrystallization

This compound could be enriched up to 90% ee by a single crystallization, and its absolute configuration was determined by X-ray crystallography.[20]

(18) dppf: 1,1′-bis-(diphenylphosphino)ferrocene.

(19) **General Procedure for Allylic Substitution.** Racemic allylic substitution of **4** with phenol is representative: $[Pd(allyl)Cl]_2$ (2.3 mg, 0.0063 mmol) and 1,1′-bis-(diphenylphosphino)-ferrocene (9.5 mg, 0.017 mmol) were placed in a Schlenk tube, dried under vacuum (0.1 mmHg) for 1 h, and then placed under argon. Freshly distilled THF (3 mL) was degassed and then added to the mixture at room temperature. The yellow solution was stirred for 30 min. **4** (96 mg, 0.26 mmol) and phenol (127.5 mg, 1.35 mmol) dissolved in THF (1 mL) were added. Next, NaH (60% dispersion in mineral oil, 8.1 mg, 0.2 mmol) was added and the solution was stirred at room temperature until TLC analysis indicated full conversion. After dilution with diethyl ether (5 mL), the mixture was washed with sodium hydroxide (1 M, 2 × 5 mL) and brine (5 mL) and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate = gradient) afforded **8a** as a slowly crystallizing white solid (100 mg, 83%).

(20) See Supporting Information. PHOX: 2-[2(diphenylphosphino)-phenyl]-4-phenyl-4,5-dihydrooxazole. No conversion was obtained when using the classical Trost ligand 1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenyl-phosphinobenzoyl).

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In conclusion, we have shown that bicyclic hydrazines can rearrange under acidic conditions or be desymmetrized by an unusual allylic substitution reaction in a totally regio- and diastereoselective manner. Considering the ease of the preparation of bicyclic hydrazine **4** and the overall good chemical yields of these transformations, these routes provide a new valuable entry to the diastereoselective synthesis from cyclopentadiene of polysubstituted amino-cyclopentenes as well as their hydrazino counterparts. Furthermore, preliminary results using chiral ligands open the road to enantioselective transformations, leading to valuable intermediates for the development of compounds of biological interest. The use of compound **6** in the synthesis of glycosidase inhibitors as well as hydrazines **7** in the search for kinase inhibitors is under investigation in our laboratory and will be reported in a due course.

Acknowledgment. We thank the CNRS for financial support and Prof. H.-P. Husson for fruitful discussions and encouragement.

Supporting Information Available: Experimental procedure for enantioselective allylic substitution reaction and characterizations of compounds **6**, **7a**, **7d**−**g**, **11**, and **12** and determination of absolute configuration of **7b** by X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0357393