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The Highly Diastereoselective Palladium-Catalyzed Cyclizations. Stereoselective Syntheses of *cis* and *trans*-Disubstituted Hydroxycyclopentanes

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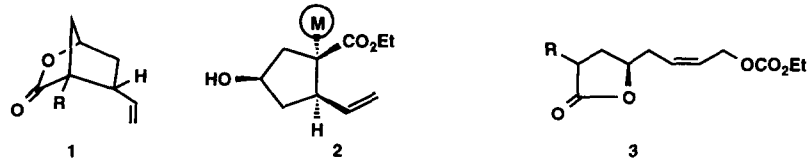
Abstract: A new variant of palladium-catalyzed stereoselective cyclization has been developed. This process provides an excellent 1,2-diastereocontrol of two new stereogenic centers as well as 1,3-asymmetric induction. In addition, desulfonylation of the cyclization product with retention of the initial stereochemistry and conversion of the desulfonylation product to the advanced carbaprostacyclin intermediate is described. © 1997 Elsevier Science Ltd.

Palladium catalyzed cyclization has proven to be one of the most powerful synthetic tools for carbocycle construction in terms of high chemo-, regio- and diastereoselectivities.[1] The recent interests of organic chemists have also included palladium-catalyzed asymmetric cyclization of allylic precursors.[1,2] However, stereocontrol of the nucleophilic carbon possessing two anion stabilizing groups has been less explored[3] due to the difficulty of stereocontrol at this center as well as the ultimate loss of the stereochemistry upon removal of the anion stabilizing auxiliary.

Accordingly, 1,2-diastereocontrol of the new two stereogenic centers in palladium-catalyzed cyclizations of allylic precursors as well as retention of the established stereochemistries remain as formidable tasks in spite of their significant synthetic utilities especially for the preparation of thermodynamically less favorable *cis*-disubstituted carbocyclic products.[4]

In this communication, we report a new variant of palladium-catalyzed stereoselective cyclization which provides both 1,2-diastereocontrol of two new stereogenic centers and 1,3-asymmetric induction. Moreover, desulfonylation with retention of the stereochemistry of the initial cyclization product affords an additional 1,3'-asymmetric induction as shown in Figure 1. The transformational diversities of the heteroatom substituent in our system also intensify the versatility of this cyclization sequence.



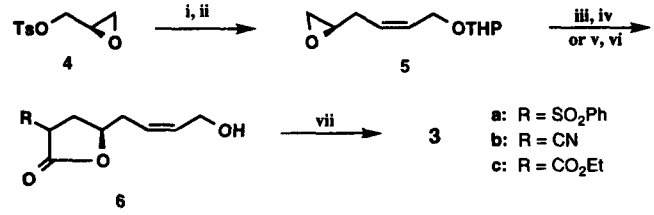
1 2 3

a: R = SO_2Ph **b**: R = CN **c**: R = CO_2Et M: metals

Figure 1

For our unique strategy, we examined the stereoselective synthesis of the bicyclic lactone **1** since the bicyclic lactone such as **1a** can serve as an excellent equivalent of the optically active anion **2** by virtue of geometric advantage for the preparation of thermodynamically disfavorable *cis*-trisubstituted carbocyclic products. It should be also noted that this type of product possesses the adequate functionalities for further

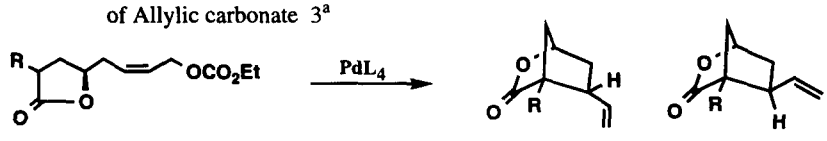
ring formations.[5] The requisite cyclization precursors **3a**, **3b** and **3c** were straightforwardly prepared from the tosylated *S*-(-)-glycidol **4** by the five step sequence as illustrated in scheme 1. This reaction sequence is quite convenient and can be carried out in 10 to 20 gram scale.



i) $CH{\equiv}CCH_2OTHP$, *n*-BuLi, BF_3OEt_2, -78°C then K_2CO_3, MeOH, 81% ii) Pd/$BaSO_4$, quinoline, MeOH, 99% iii) $EtO_2CCH_2SO_2Ph$ or $EtO_2CCH_2CO_2Et$, EtONa, EtOH, reflux iv) TsOH, MeOH, 78% for **6a** and 80% for **6c** from **5** v) EtO_2CCH_2CN, NaH, DMF,100 °C vi) PPTS, EtOH, 55 °C, 43% for **6b** from **5** vii) $ClCO_2Et$, pyridine, benzene, 96% for **3a**, 98% for **3b** and 98% for **3c**

Scheme 1

Table 1. Effects of Anion Stabilizing group, Ligand and Solvent on Cyclization of Allylic carbonate 3[a]



Entry	Allylic carbonate(R)	Ligand(mol %)	Solvent	Yield(%)[b]	Ratio(**7** : **8**)[c]
1	**3a** (SO_2Ph)	dppe(5)[d]	DMSO	79	5.8 : 1
2		dppe(5)	THF	80	12.0 : 1
3		dppe(20)	THF	78	8.0 : 1
4		dppe(10)	Benzene	63	3.4 : 1
5		dppe(10)	Toluene	59	5.9 : 1
6		dppe(10)	CH_3CN	77	2.2 : 1
7		dppe(5)	CH_2Cl_2	80	20.5 : 1
8		Ph_3P(5)	DMSO	63	1.8 : 1
9		Ph_3P(5)	THF	27	1.0 : 2.6
10		dba(5)[e]	THF	no reaction	
11	**3b** (CN)	dppe(5)	THF	85	2.0 : 1
12		dppe(5)	CH_2Cl_2	89	2.2 : 1
13		Ph_3P(5)	DMSO	81	1.2 : 1
14	**3c** (CO_2Et)	dppe(5)	CH_2Cl_2	85	1.3 : 1

a. Reactions were performed at 0.1 to 0.05M concentration for 30min to 2h under reflux or 80 °C b. Isolated yields. c. The ratio was determined by intergrating the resonance of the angular hydrogen in 400MHz ^{1}H-NMR spectrum of the diastereomeric mixture. d. 1,2-diphenylphosphinoethane e. dibenzylideneacetone

Conditions for the cyclization of the lactone precursor **3** were intensively explored by examination of the effects of anion stabilizing groups, ligands and solvents as summarized in Table 1. Pd(dppe)2 and

dichloromethane turned out to be the best combination for both the highest 1,3-asymmetric induction and the highest conversion yield. Especially, cyclization of **3a** in the presence of 5 mol% of $Pd(dppe)_2$ in dichloromethane (entry 7) proceeded smoothly to afford a 20.5 : 1 diastereomeric mixture of **7a** and **8a** in favor of **7a** as the desired isomer[6] while the cyano precursor **3b** and the ester precursor **3c** gave the diastereomeric ratios of 2.2 : 1 (entry 12) and 1.3 : 1 (entry 14), respectively under the same cyclization conditions. As we expected, the high stereoselectivities in cyclization of **3a** presumably arise due to the differences of steric interactions between the bulky benzenesulfonyl group and allylic hydrogen or methylene in the transition states of the favored *syn*-π-allyl palladium complex. This significant steric interactions are obviously induced by the geometry enforced by the preexistent butyrolactone moiety. Consequently, cyclization proceeds through the more favorable transition state A as shown in Figure 2. Our rationale is partly supported by the relatively low stereoselectivities in cyclization of the less bulky precursors **3b** and **3c**.

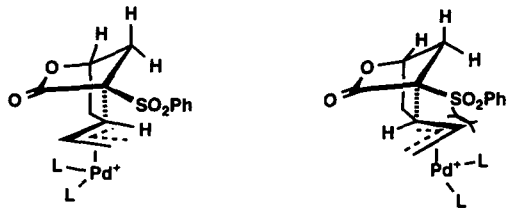
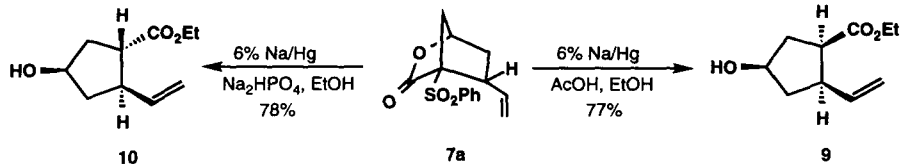


Figure 2

The bicyclic lactone **7a** could be selectively converted to the *cis*-1,2-substituted hydroxycyclopentane **9** or the *trans*-1,2-substituted hydroxycyclopentane **10** of highly versatile synthetic intermediates[7] by variation of the desulfonylation conditions.[8] Particularly, this two step sequence of the stereoselective cyclization followed by desulfonylation with retention of the initially established stereochemistry provides the thermodynamically less favorable and synthetically useful *cis*-isomer **9**. The synthetic utility of the *cis*-isomer **9** has been demonstrated by the efficient conversion to the key intermediate for carbaprostacyclin and its analogues[9] which have been attracting synthetic and biological attention.

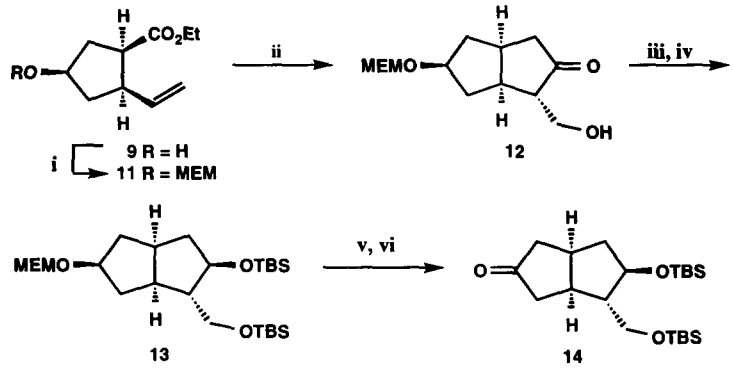


Scheme 2

As outlined in scheme 3, the *cis*-1,2-substituted hydroxycyclopentane **9** was protected with methoxyethyl chloride then straightforwardly transformed into the hydroxy ketone **12** in 60% overall yield by the procedure established in our laboratory.[5] Stereoselective reduction of the hydroxy ketone **12** with $NaBH_4$[10] followed by protection of the resulting diol with TBSCl gives *bis*silyl ether **13**. Finally, conversion of *bis*silyl ether **13** into the optically active carbaprostacyclin intermediate **14** was achieved by selective deprotection of MEM ether with bromocatecholborane[11] followed by PDC oxidation of the free alcohol. The final product **14** was identical in all aspects with the known carbaprostacyclin intermediate **14**.[9b,12]

In conclusion, we have developed a new variant of the palladium-catalyzed diastereoselective cyclization involving 1,3-asymmetric induction as well as 1,2-diastereocontrol of two new stereogenic centers. Also an excellent desulfonylation of the cyclization product with retention of stereochemistry provides the additional 1,3'-asymmetric induction. The synthetic utility of the optically active *cis*-trisubstituted hydroxycyclopentane obtained by this sequence has been demonstrated by an application to the stereoselective synthesis of the highly advanced carbaprostacyclin intermediate. Further studies on the scope

of this cyclization as well as synthetic applications to natural products and bioactive molecules will be forthcoming.



i) MEMCl, iPr$_2$NEt, CH_2Cl_2, 93% ii) reference 5, 60% from **11** iii) $NaBH_4$, EtOH, -78°C, 92% iv) TBSCl, imidazole, DMF, 91% v) *B*-bromocatecholborane, CH_2Cl_2, -78°C, 76% vi) PDC, CH_2Cl_2, 85%

Scheme 3

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