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Stereoselective Synthesis of Polyfunctional Di- and Trisubstituted Cyclopentane Derivatives using a New Palladium Catalyzed Cyclization.

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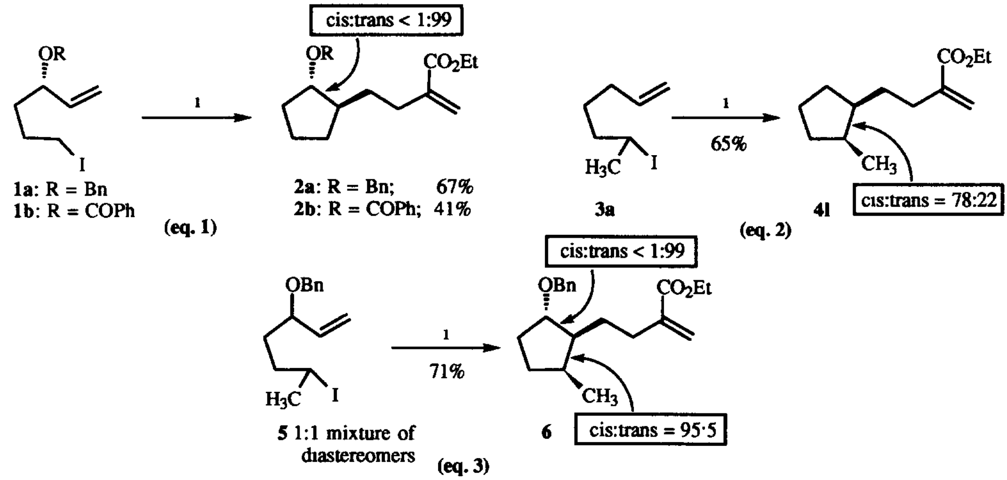
Abstract : Various functionalized 5-hexenyl iodides undergo a radical ring closure to give cyclopentylmethylzinc iodides when treated with Et_2Zn in the presence of $PdCl_2(dppf)$ (2 mol %). In the case of 4-substituted 5-hexenyl iodides *trans*-cyclopentanes are obtained (> 99 . 1) whereas 1-substituted-5-hexenyl iodides provide *cis*-cyclopentanes (ca. 80 : 20). The presence of a substituent at both positions considerably improves the *cis* stereoselectivity up to 95 : 5.



1a: R = Bn
1b: R = COPh
(eq. 1)

2a: R = Bn; 67%
2b: R = COPh; 41%

3a
(eq. 2)
4 1

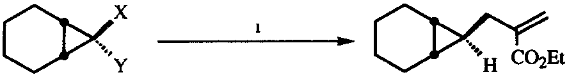
5 1:1 mixture of diastereomers
(eq. 3)
6

i : 1) Et_2Zn (2 equiv.), $PdCl_2(dppf)$ (2 mol%), 20 °C, 5-20h 2) CuCN•2LiCl 3) ethyl 2-(bromomethyl)acrylate

The stereoselective preparation of di- and trisubstituted cyclopentanes is an important synthetic goal since such ring units are present in numerous natural products of biological interest.[2] Recently, we have shown that primary alkyl iodides and Et_2Zn undergo an efficient iodine-zinc exchange reaction in the presence of catalytic amounts of Pd(II) or Ni(II) salts. 5-Hexenyl iodides are rapidly cyclized (25 °C, 2h) under these conditions providing cyclopentylmethylzinc iodides.[3] Although a wide range of both anionic[4] and radical[5] ring closures are known, the present method combines in a unique way, advantages of both cyclization modes. The ring closure, which we believe is of radical nature,[3] produces an organometallic species which can subsequently be trapped by a variety of electrophiles. Contrary to most anionic cyclizations, a large number of functionalities can be present in the unsaturated iodide. We wish now to report some remarkable stereochemical aspects of the ring closure involving secondary iodides as substrates and leading stereoselectively to functionalized di- and trisubstituted cyclopentane derivatives. We have found that 4-substituted-5-hexenyl iodides such as **1a-b** undergo a stereospecific ring closure (Et_2Zn(2 equiv.); $PdCl_2(dppf)$[6](1.5 mol %) leading, after a transmetalation with CuCN·2LiCl[7] and allylation with ethyl α-(bromomethyl)acrylate,[8] to *trans*-1,2-disubstituted cyclopentane derivatives **2a-b** in 41-67 % yield (*trans* : *cis* > 99 : 1; eq 1).[9] In strong contrast, *secondary* iodides[10] such as **3a-f** (substituent at position 1) afford preferentially, after transmetalation and quenching with an electrophile, the *cis*-1,2-disubstituted cyclopentanes **4a-4l** in 70 : 30 to 86 : 14 *cis* : *trans* ratios (eq. 2 and Table 1). The *cis*-selectivity of the ring closure increases when the size of the substituent R at position 1 decreases (compare entries 1-3 of Table I). The cyclized zinc reagent can be trapped after transmetalation with various electrophiles (3-iodo-2-cyclohexenone[11] (entries 1-3), ethyl α-(bromomethyl)acrylate[7] (entries 4, 6 and 8), 2-cyclohexenone (entry 5), *cis*-1-acetoxy-4-chloro-2-cyclohexene[12] (entry 7) and ethyl propiolate (entries 9 and 10) in satisfactory yields (52-87 %). This new cyclization has some remarkable features. The substrates **3** tolerate the presence of various functionalities (see **3d-3f**). Especially interesting is the ring closure of **3e** which bears a good leaving group in β-position (OPiv). If this iodide is converted during the cyclization process into an organozinc derivative, an immediate elimination which would lead to 1,6-heptadiene, is expected to occur. However, this ring closure proceeds very smoothly showing unambiguously that no organozinc species is formed prior to ring closure. The method allows the performance of tandem-cyclization reactions. Thus, the dienic iodide **3f** gives after transmetalation with CuCN·2LiCl and addition to ethyl propiolate, the bicyclic unsaturated ester **4k** (*cis*-ring junction, > 98 % E; *exo* : *endo* : 57 : 43) and the mono-cyclic *trans* dienic ester **4j** (the *trans* stereochemistry hampers the second ring closure); the ratio between **4k** and **4j** is 86 : 14.

The *cis*-stereoselectivity can be dramatically improved by using an unsaturated iodide which bears a substituent at position 1 *and* at position 4. Thus the ring closure of **5** (used as a 1 : 1 mixture of diastereoisomers) produces after allylation the trisubstituted cyclopentane derivative **6** with high stereoselectivity (*trans* : *cis* between C-1 and C-2 (> 99 : 1); *trans* : *cis* between C-2 and C-3 (5 : 95); eq. 3).

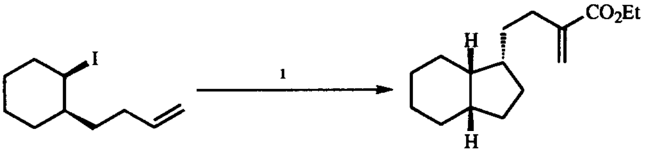
Further information about the mechanism of the reaction is obtained from the reaction of *exo* and *endo*-7-iodobicyclo [2.1.0] heptane **7** with Et_2Zn (ca. 2 equiv., 5 mol % $PdCl_2(dppf)$) in THF. Both of these iodides are converted to the same *exo*-organozinc reagent which, after the usual allylation reaction, provides in a stereoconvergent manner the *exo*-substituted bicyclic adduct **8** in 60 % yield (*endo* : *exo* 4 : 96; eq. 4).[13] This stereoconvergence indicates that the insertion of palladium proceeds through a radical mechanism.[14] Compared to conventional radical cyclizations, better regioselectivities and similar stereoselectivities are observed. Thus 1-(3-butenyl)-2-iodocyclohexane **9** provides, after allylation, the bicyclic esters **10** as the only products (*exo* : *endo* 20 : 80; 90 % yield). Similar or lower stereoselectivities are found in Bu_3SnH induced radical cyclizations; furthermore in such cases, the reaction is complicated by the presence of non-cyclized products resulting in significantly lower yields[15] (eq. 5).



(eq. 4)

exo-7 X= I; Y= H
endo-7: X=H; Y=I

8: exo:endo 96:4; 60%



(eq. 5)

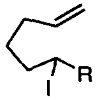
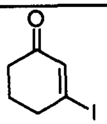
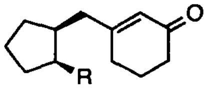
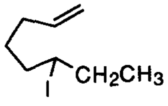
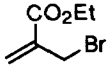
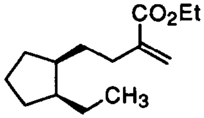
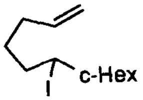
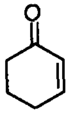
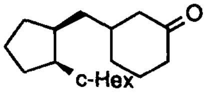
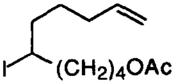
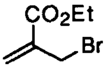
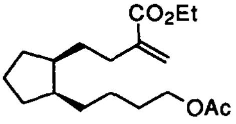
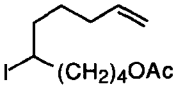
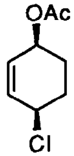
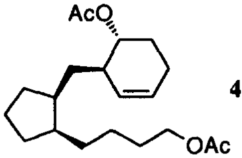
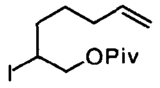
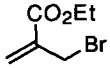
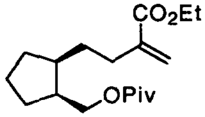
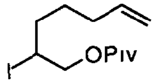
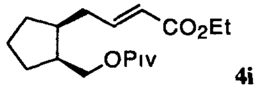
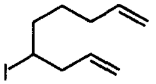
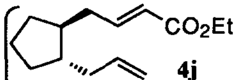
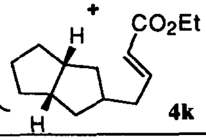
9

10: exo:endo 20:80, 90%

i 1) Et_2Zn (2 equiv.), $PdCl_2(dppf)$ (2 mol%), 20 °C, 5-20h 2) CuCN•2LiCl 3) ethyl 2-(bromomethyl)acrylate

In summary,[17] we have shown that various unsaturated secondary iodides undergo a unique radical cyclization in the presence of Et_2Zn and a catalytic amount of Pd(II) or Ni(II) salts providing an organometallic species which can be trapped by various electrophiles. In most cases ca. 80 : 20 *cis* : *trans* ratios are obtained. We have demonstrated that this *cis* selectivity can be considerably improved by introducing another substituent at position 4 allowing a highly stereoselective synthesis of polyfunctional

Table I. Polyfunctional Cyclopentanes Obtained by the Pd Catalyzed Cyclization.[16]

Entry	Iodide of Type 3	Electrophile	Product of Type 4	cis:trans	Yield[a] (%)
1	 **3a**: R = Me		 **4a**: R = Me	78:22	62
2	**3b**: R = Et		**4b**: R = Et	75:25	81
3	**3c**: R = c-Hex		**4c**: R = c-Hex	70:30	65
4	 **3b**		 **4d**	75:25	87
5	 **3c**		 **4e**	70:30[b]	52
6	 **3d**		 **4f**	77:23	67
7	 **3d**		 **4g**	77:23[b]	52
8	 **3e**		 **4h**	78:22	87
9	 **3e**	HC≡C-CO$_2$Et	 **4i**	78:22[c]	80
10	 **3f**	HC≡C-CO$_2$Et	 **4j** +  **4k**	86:14[c,d]	82

[a] All yields refer to analytically pure products; [b] Mixture of diastereoisomers; [c] >98% E isomer; [d] **4k** is obtained as a 43:57 mixture of *endo exo* isomers;

trisubstituted cyclopentane derivatives (eq. 3). Extensions of this method and applications to the preparation of more complex polycyclic molecules are currently underway in our laboratories.

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6. Dichloro (1,1'-bis-(diphenylphosphino)ferrocene)palladium(II) (PdCl$_2$(dppf) has been prepared according to: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J Am. Chem Soc* , **1984**, *106*, 158: Other Pd or Ni complexes such as PdCl$_2$(CH$_3$CN)$_2$, Ni(acac)$_2$ can also be used.

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9 This high *trans*-selectivity is in strong contrast with the *uncatalyzed* carbozincation of 3-alkoxy-1-iodo-5-hexene derivatives which gives in most cases 2 : 3 mixtures of *cis* and *trans* 1,2-disubstituted cyclopentanes (see ref. 4l).

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13. This reaction constitutes an excellent preparation of cyclopropylzinc derivatives, since the direct insertion of zinc proceeds only very sluggishly.

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16 The relative stereochemistry of the *cis* - cyclopentane derivatives has been assigned by NOESY- NMR- experiments on several products (**2a**, **4f**). The exo- endo ratios of **8** and **10** have been determined respectively by iodolysis of the zinc intermediates and by comparison with the ^{13}C NMR spectra of related compounds. Thus the minor diastereoisomer of **10** shows a down-field shift for most signals (ref. 15c).

17 Typical Procedure: Preparation of (E)-1-(3-carboethoxy-2-propen-1-yl)-2-pivaloyloxymethylcyclopentane **4j**: A 3-necked flask equipped with a magnetic stirring bar, a thermometer and a gas inlet and charged with PdCl$_2$(dppf) (0.07 g, 2 mol %) in THF (5 mL) was cooled to -78 °C. 2-Iodo-6-heptenyl 2,2-dimethylpropanoate **3e** (1.62 g, 5 mmol) and Et$_2$Zn (1.0 mL, 1.23 g, 10 mmol) were added. After warming to 25 °C and stirring for 2 h, the solvent and excess Et$_2$Zn were removed (0.1 mm Hg, 25 °C, 1 h). After adding THF (5 mL) and cooling to -40 °C, CuCN·2LiCl (5 mmol) in THF (5 mL) was added, and the reaction mixture was warmed to 0 °C (5 min) and cooled to -78 °C. Ethyl propiolate (0.39 g, 4.0 mmol) in THF (3 mL) was added and the reaction mixture was slowly warmed to -10 °C and stirred for 5 h. After the usual workup the residual oil was purified by flash column chromatography (ether : hexanes 1 : 9) to yield **4j** as a clear oil (1.18 g, 80 %).

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