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Chirons in the 1,3-dioxane series: stereospecific cross-coupling reactions and chirality transfers

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Abstract

Palladium catalyzed cross-coupling reactions are described for enantiopure axially chiral vinylic bromides with arylzinc reagents leading to new compounds with axial chirality. In addition, transfers of axial to central chirality are described. Both reactions exhibit full retention of enantiomeric purity. © 1998 Elsevier Science Ltd. All rights reserved.

In previous studies we have described the highly enantioselective access to brominated chirons **1** in the 1,3-dioxane series *via* a dehydrobromination reaction carried out under the influence of chiral alkoxides; the latter reagents, which were able to select one enantiotopic proton of a prochiral methylene moiety, were used either in excess[1] or in a substoichiometric amount.[2] As part of our program for the use of these chirons in the synthesis of various chiral targets, we wish to disclose here our success in carrying out cross-coupling reactions starting from compounds **1**, as well as chirality transfers from axial to central stereogenic units. Both of these transformations can be performed without any loss of enantiomeric purity (Scheme 1).

Our first attempts of cross-coupling reactions were based on the use of aryllithium reagents, according to Murahashi's method,[3] which has been previously designed to avoid isomerization when applied to configurationally defined vinylic halides. For this reason, we expected this procedure to retain the configuration of the chiral substrates.[4]

Regarding aryllithium reagents (Table 1), enantiomeric excesses of the coupled products **2** were as high as those of the starting materials **1**, demonstrating that no racemization occurred during the cross-coupling reaction. Nevertheless, yields were disappointing (between 29 and 77%) and in the best cases the use of a large amount of Pd^0 catalyst was needed. In order to improve the reaction and to minimize

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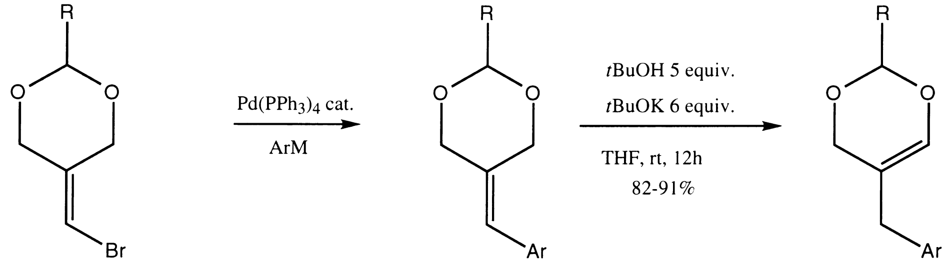


(*R*) **1**, ee>98%

R=*t*Bu, $pPhC_6H_4$

(*R*) **2**, ee>98%

Ar=Ph, $pMeOC_6H_4$, $pBrC_6H_4$

3, ee>98%

Scheme 1.

Table 1

Cross-coupling reactions starting from substrate (*R*)-**1**[5]

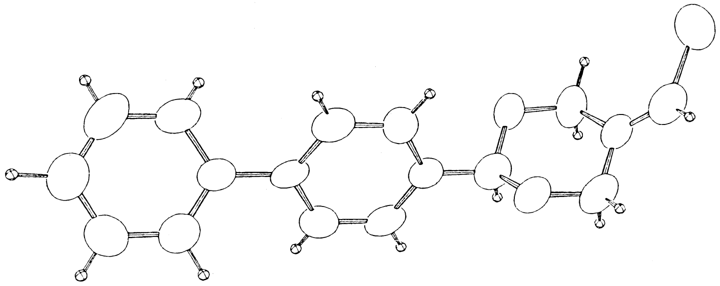
R	ArM[a]	Catalyst, % mol	Yield % **2**[b]	ee (%)[c]
t-Bu	PhLi[d]	$Pd(PPh_3)_4$, 5%	29	>98
t-Bu	PhLi[d]	$Pd(PPh_3)_4$, 50%	66	>98
t-Bu	PhLi[d]	$Pd(PPh_3)_4$, 100%	56	>98
t-Bu	$pMeOC_6H_4Li$[e]	$Pd(PPh_3)_4$, 50%	60	>98
$pPhC_6H_4$	PhLi[d]	$Pd(PPh_3)_4$, 10%	47	>98
$pPhC_6H_4$	PhLi[d]	$Pd(PPh_3)_4$, 60%	77	>98
$pPhC_6H_4$	$pMeOC_6H_4Li$[e]	$Pd(PPh_3)_4$, 50%	46	>98
t-Bu	PhMgBr	$FeCl_3$, 5%	93	48[f]
t-Bu	PhZnBr	$Pd(PPh_3)_4$, 5%	93	>98
t-Bu	$pMeOC_6H_4ZnBr$	$Pd(PPh_3)_4$, 5%	89	>98
$pPhC_6H_4$	PhZnBr	$Pd(PPh_3)_4$, 5%	90	>98
$pPhC_6H_4$	$pMeOC_6H_4ZnBr$	$Pd(PPh_3)_4$, 5%	83	>98
$pPhC_6H_4$	$pBrC_6H_4ZnBr$	$Pd(PPh_3)_4$, 5%	80	>98

(a) Titrated according to [6] for aryllithiums; (b) Chromatographied material; main impurity (10-30%) is the homocoupled derivative; (c) (*R*) configuration, ee>98% as determined by GLC or HPLC and polarimetry; (d) 2M, cyclohexane/Et_2O (70/30); (e) Prepared from $pMeOC_6H_5$ and *n*-BuLi according to [7]; (f) (*S*) configuration.

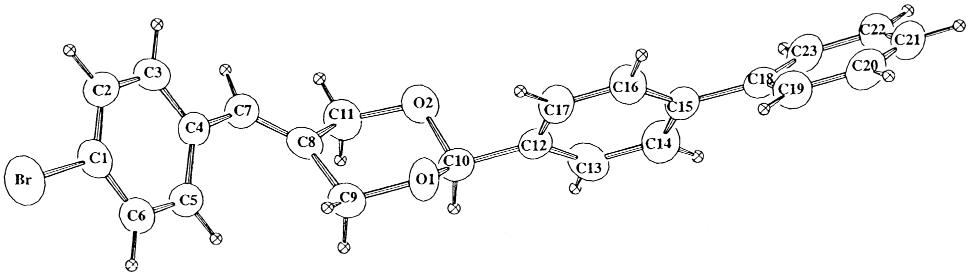
these drawbacks, we then considered less basic organometallic derivatives. Phenylmagnesium bromide (in the presence of 5% $FeCl_3$)[8] was then selected. While the chemical yield was excellent, this cross-coupling reaction gave unsatisfactory results in terms of enantiomeric excess. Not only was a drop in enantiomeric purity observed but also an inversion of the absolute configuration of the obtained material occurred, as shown by the sign of the optical rotation. In contrast, organozinc compounds appeared to be the reagents of choice since they gave successful transformations without any loss of enantiomeric purity. Moreover, good turnovers of the palladium catalyst were observed,[9] and side reactions were minimized. The retention of configuration from **1** to **2** was assigned by means of X-ray analyses. Single crystals were obtained from **1** (R=*p*PhC_6H_4) and from one example of compounds **2** (R=*p*PhC_6H_4 and Ar=*p*BrC_6H_4). Both products were found to have (*R*) configuration (Fig. 1).[10]

Finally, we examined the exo to endo isomerization starting from compounds **2**. This transformation has special interest in our next study since it represents the key step of an axial to central transfer of chirality. We realized this isomerization without loss of stereochemical information when using a *t*BuOK/*t*BuOH system (Scheme 1).[11]

This last reaction opens up the access to a new family of chirons in the 1,3-dioxane series, which is complementary to the parent set of axially dissymmetric compounds **2**.



ORTEP representation of **1** (R = pPhC$_6$H$_4$)^{10} as determined by X-ray crystallography



ORTEP representation of **2** (R = pPhC$_6$H$_4$, Ar = pBrC$_6$H$_4$)^{10} as determined by X-ray crystallography

Fig. 1.

In conclusion, we wish to emphazise that both the cross-coupling reactions and the isomerization processes were performed keeping the enantiomeric purities unchanged. Synthesis of various chiral targets is under investigation, taking advantage of the reactivity of the enol ether function of chirons **3**.

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5. In a typical experiment, a 1 N solution of the required arylmagnesium bromide in THF (1.3 mmol, 1.3 mL) was added dropwise under argon and at 0°C to dry zinc bromide (1.5 mmol, 338 mg) in THF (3 mL). The mixture was stirred for 2 h at room temperature whereupon the magnesium bromide precipitated. Then a solution of 2-alkyl or 2-aryl-5-bromomethylene-1,3-dioxane (*R*)-**1** (1 mmol) and tetrakis(triphenylphosphine) palladium (0.05 mmol, 58 mg) in THF (2 mL) was added dropwise. The reaction was stirred at room temperature for 3 h and then was diluted with diethyl ether (20 mL). The organic layer was washed with water and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with saturated sodium chloride then dried over anhydrous magnesium sulfate. The solution was filtered, concentrated and the residue was purified by flash chromatography (petroleum ether:diethyl ether=99:1) to give compounds (*R*)-**2**.
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9. Organozinc reagents have already exhibited high efficiency in such reactions. For reviews, see: (a) J. Tsuji *Palladium Reagents and Catalysts. Innovation in Organic Synthesis*; John Wiley & Sons: New York, 1995; (b) E. Erdik *Tetrahedron* **1992**, 44, 9577–9648; (c) P. Knochel and R. D. Singer *Chem. Rev*. **1993**, 93, 2117–2188.
10. The full details of the X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.
11. In a typical experiment, a solution of the compound (*R*)-**2** (0.25 mmol) in THF (0.5 mL) was added at room temperature to a solution of potassium *tert*-butoxide (1.5 mmol, 170 mg) and *tert*-butanol (1.1 mmol, 0.1 mL) in THF (9 mL). The reaction was stirred at room temperature for 12 h and was then neutralized with saturated sodium hydrogencarbonate. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the residue by flash chromatography (petroleum ether:diethyl ether=90:10) gave the pure **3** derivative.