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THE PALLADIUM-CATALYZED ARYLATION OF 4*H*-1,3-DIOXIN

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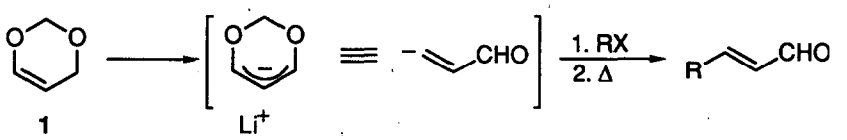
Abstract: 4*H*-1,3-Dioxin was firstly arylated by using Heck reaction, and the reaction in the presence of (*R*)-BINAP gave enantiomerically enriched 4-phenyldioxin which was converted into optically active 1-phenyl-1,3-propanediol.

4*H*-1,3-Dioxin (1,3-diox-4-ene) (**1**)[1] has been used as a synthon to introduce β-formylvinyl group by lithiation, alkylation, and subsequent bis-hetero retro-Diels-Alder reaction.[2] No procedure, however, has been reported for the arylation of 4*H*-1,3-dioxin in spite of its great synthetic potential, because the method mentioned above is limited to the preparation of alkyl derivatives.

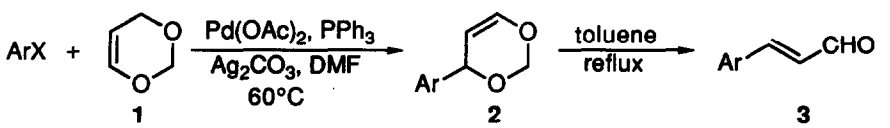


Scheme 1

Heck reaction[3] is one of the most fruitful synthetic means for the carbon-carbon bond formation in these two decades, and not only terminal olefins but also cyclic olefins can be arylated with aryl halides by the catalytic action of a palladium complex[4]. The Heck reaction of cyclic olefins, including heterocyclic olefins such as 2,3-dihydrofuran, has been well studied by Larock and co-workers[5], and convenient three procedures (A, B, C) were suggested.

Here, we report the Heck reaction of 4*H*-1,3-dioxin (**1**) as the convenient method for the arylation of **1** together with the asymmetric induction using a chiral ligand.

As shown in Table I, use of silver carbonate[6] as a base (Larock's procedure B) gave excellent results and both electron-donating and electron-withdrawing groups as *para*-substituent were examined not to affect essentially on the reaction. The arylated dioxins (**2**) were transformed into α,β-unsaturated aldehydes (**3**) on heating in boiling toluene in high yields.



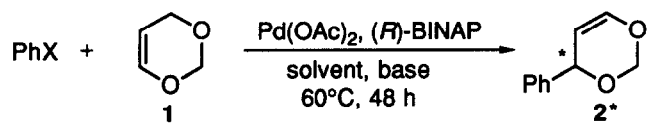
Scheme 2

Table I. Arylation of 4*H*-1,3-Dioxin and Retro-Diels-Alder Reaction

ArX	Reaction time (h)	Yield (%) 2	Reaction time (h)	Yield (%) 3
PhI	48	85	5	90
PhOTf	24	56		
p-$MeOC_6H_4I$	24	72	4	86
p-$EtOOCC_6H_4I$	72	56	16	88
p-$O_2NC_6H_4I$	72	47	17	82

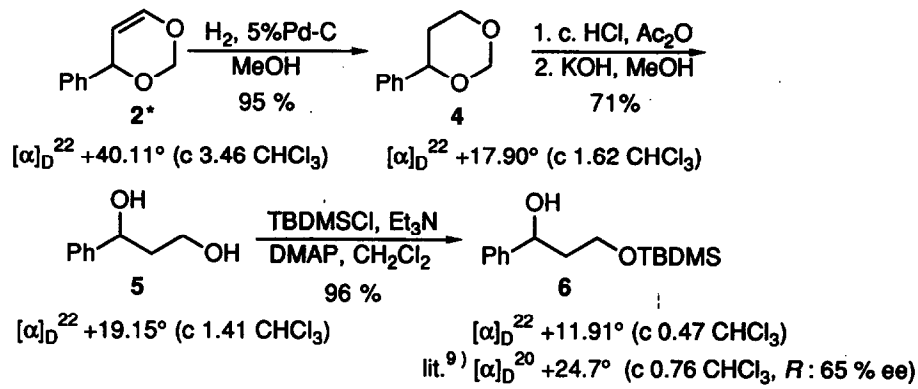
The asymmetric Heck reaction[7] is an ideal method for asymmetric syntheses, because the creation of a chiral center can be performed at the same time with a carbon-carbon bond formation using catalytic amounts of a chiral source. Hayashi reported a highly enantioselective arylation of 2,3-dihydrofuran[7e], and the asymmetric Heck arylation is expected to be applicable on 4*H*-1,3-dioxin ring. Although the Heck reaction of phenyl triflate with **1** under Hayashi's best conditions did not give any products, the use of DMF as a solvent and slightly higher temperature facilitated the reaction. The reaction of not only phenyl triflate but also iodobenzene showed enantioselectivity when silver carbonate was employed as a base as shown in Table II.

Table II. The Asymmetric Heck Reaction of 4*H*-1,3-Dioxin (1)



X	Base	Solvent	Yield(%) 2*	$[\alpha]_D^{22}$ ($CHCl_3$)
OTf	i-Pr_2NEt	C_6H_6	0	—
OTf	i-Pr_2NEt	DMF	37	+ 32.76° (c 2.73)
I	i-Pr_2NEt	DMF	46	+ 0.77° (c 1.45)
I	Ag_2CO_3	DMF	62	+ 40.11° (c 3.46)
I	AgOAc	DMF	58	+ 0.78° (c 1.51)
I	Ag_2CO_3	C_6H_6	43	+ 1.10° (c 1.22)
I	Ag_2CO_3	MeCN	53	+ 0.78° (c 1.34)

The optically active 4-phenyldioxin (**2***) was converted to phenyl-1,3-propanediol (**5**) by the acid catalyzed ring opening reaction[8] followed by methanolysis. The enantiomer excess (ee) was estimated as 31% ee by transforming the diol into the TBDMS derivative and comparing the $[\alpha]_D$ value with the reported one[9]. Furthermore, to determine the ee value unambiguously, the TBDMS derivative was converted to the (*S*)-(+)-α-methoxyphenylacetate[10] and the value was determined as 43% ee by analyzing the ^1H NMR spectrum.



Scheme 3

Since optically active phenyl-1,3-propanediol (**5**) has been used as an important intermediate for the preparation of well-known antidepressant (*R*)-fluoxetine,[11] the present study has potential for providing a facile method to synthesize such kinds of biological active compounds. Further investigation to obtain better enantioselectivity is under progress.[12]

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(12) Relating to the present results, the reaction of 2,3-dihydrofuran with iodobenzene in the presence of (*R*)-BINAP using our reaction conditions was examined. Interestingly, (*S*)-2-phenyl-2,3-dihydrofuran (17% ee) was obtained. See references 7e,g.

(13) **4-Phenyl-4*H*-1,3-dioxin**: A mixture of iodobenzene (0.41 g, 2 mmol) or phenyl triflate (0.45 g,2 mmol), 4*H*-1,3-dioxin (0.86 g, 10 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), PPh_3 (32 mg, 0.12 mmol), Ag_2CO_3 (2 mmol), and DMF (1 mL) was stirred at 60°C for 48 h. After reaction, the mixture was diluted with Et_2O (20 mL), filtered, and washed with H_2O (10 mL). The aqueous layer was extracted with additional Et_2O (10 mL x 2). The combined organicphases were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residual material was subjected to SiO_2 column chromatography using n-hexane/AcOEt (9/1) as an eluent to give a viscous oil (276 mg, 85%). ^1H NMR ($CDCl_3$) δ 7.44-7.31 (m, 5H), 6.71 (dd, *J*=6.1, 1.8 Hz, 1H), 5.36-5.34 (m, 1H), 5.14 (d, *J*=6.1 Hz, 1H), 5.08 (dd, *J*=6.1, 2.4 Hz, 1H), 5.07 (d, *J*=6.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 143.73, 140.12, 128.36, 128.15, 127.47, 105.12,88.25, 73.88. MS, *m/e* 162 (M^+). HRMS calcd for $C_{10}H_{10}O_2$ 162.0680, found 162.0658.

(14) **Cinnamaldehyde** : 4-Phenyl-4*H*-1,3-dioxin (1 mmol) was dissolved in PhMe (10 mL), and the mixture was refluxed for 5 h. After reaction, the solvent was removed in vacuo, and the residue was subjected to SiO_2 column chromatography using n-hexane/AcOEt (2/1) as an eluent. The crude material was purified by distillation to give colorless liquid (119 mg, 90%). ^1H NMR ($CDCl_3$) δ: 9.72 (d, *J*=7.3 Hz, 1H), 7.59-7.57 (m, 2H), 7.49 (d, *J*=15.9 Hz, 1H), 7.46-7.43 (m, 3H), 6.33 (dd, *J*=15.9, 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): 193.80, 152.88, 134.07,131.35, 129.18, 128.67, 128.57. IR ($CHCl_3$) ν: 1675 cm^{-1}.

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