Umpolung of Vinyloxiranes: Regio- and Stereoselectivity of the In/Pd-Mediated Allylation of Carbonyl Compounds

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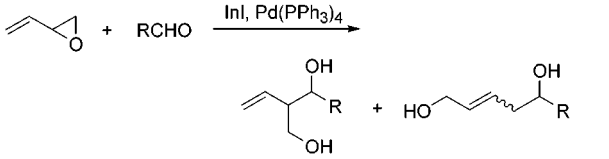
The use of vinyloxiranes as nucleophilic allylating reagents is a synthetically important method. However, this umpolung has hitherto been realized with a limited number of low-valent metals such as chromium,[1] tin,[2] and samarium.[3] Recently, we demonstrated that a variety of allylic substrates, including 2-phenyl-3-vinyloxirane, can be converted to allylic indium(III) reagents via a reductive transmetalation of a π-allylpalladium(II) complex with indium(I) salts.[4] Here we disclose the full scope of the reactions of allylic indium reagents derived from vinyloxiranes with carbonyl compounds, which exert marked differences in the regio- and stereoselectivity depending on the reaction temperature, solvents, carbonyl compounds, and substitution pattern of vinyloxiranes.

The In/Pd-mediated reaction of 2-vinyloxirane with aldehydes was first examined under various reaction conditions. The results are summarized in Table 1. In polar organic solvents such as 1,3-dimethyl-2-imidazolidinone (DMI) and THF, both the 1,3- and 1,5-diols were formed in modest selectivities from the aromatic and aliphatic aldehydes. By lowering the reaction temperature, we observed a slight preference for the *anti*-1,3-diol. In less polar organic solvents such as CH_2Cl_2 and hexane, no coupling products were obtained. Interestingly, the same reaction in aqueous media showed high selectivity for the 1,3-diol, and negligible amounts of the 1,5-diol were formed in these solvents (entries 6 and 7).

Table 2 summarizes the reactions of a series of vinyloxiranes with a methyl group in different positions. It is evident that the regioselectivity of the coupling is highly dependent on the position of the methyl group; i.e., 2-methyl-2-vinyloxirane (entries 3 and 4) gave the 1,3-diol exclusively, whereas 2-(1-propenyl)oxirane (entries 7 and 8) gave only the corresponding 1,5-diol. The latter oxirane gave no 1,3-diol even in an aqueous solvent. No significant effect of the methyl substituent was observed in the cases of 2-methyl-3-vinyloxirane (entries 1 and 2) and 2-(1-methylvinyl)oxirane (entries 5 and 6).

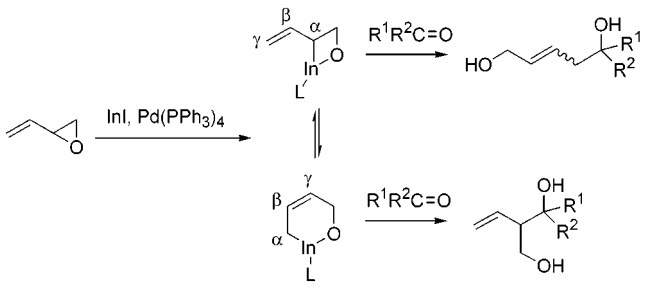
Table 1. Reaction of 2-Vinyloxirane with Aldehydes[a]



entry	R	conditions	% yield: 1,3-diol (syn:anti)[b]	% yield: 1,5-diol (E:Z)[c]
1	Ph	DMI, room temp, 5 h	62 (22:78)	33 (29:71)
2	n-C_5H_{11}	DMI, room temp, 20 h	59 (37:63)	31 (28:72)
3	Ph	THF, −20 °C, 24 h	53 (19:81)	11 (36:64)
4	Ph	THF, room temp, 15 h	54 (24:76)	36 (32:68)
5	Ph	THF, 50 °C, 15 h	23 (36:64)	38 (43:57)
6	Ph	H_2O, room temp, 15 h	79 (23:77)	trace
7	Ph	1:1 THF/H_2O, room temp, 15 h	86 (18:82)	trace

[a] Reactions were carried out with 2:2:1 InI/oxirane/RCHO and $Pd(PPh_3)_4$ (5 mol %). [b] Determined by ^1H NMR. [c] Determined by ^{13}C NMR.

Scheme 1



The regioselectivity of this coupling also depends on the electrophiles; ketones show a strong preference for 1,5-diols (Table 3). 2-Vinyloxirane gave the exclusive formation of the 1,5-diols in good to moderate yields, except for the reaction with cyclohexanone, which gave a small amount (7% yield) of the 1,3-diol together with the major 1,5-diol (41% yield) (entry 4). The reactions of the methyl-substituted vinyloxiranes with acetophenone were sluggish (entries 5−8), and only 2-(1-methylvinyl)-oxirane yielded the corresponding 1,5-diol in a moderate yield with complete Z-selectivity.

The present allylation reaction has been considered to proceed via a reductive transmetalation of an intermediate π-allylpalladium(II) to allylindium(III) reagents.[4] The allylic indium compounds derived from vinyloxiranes can be considered to exist as two forms: four- and six-membered cyclic alkoxyindiums (Scheme 1). As the coupling of allylic indium reagents with carbonyl compounds generally takes place at the γ-carbon,[5] it is reasonable to postulate that the 1,5- and 1,3-diols are formed from the four- and six-membered cyclic alkoxyindiums, respectively. The high 1,3-diol selectivity of 2-methyl-2-vinyloxirane (Table 2, entries 3 and 4) can be ascribed to the destabilization of the four-membered ring intermediate, where the methyl group on the indium-bearing α-carbon makes the intermediate unfavorable both sterically and electronically. In turn, the methyl

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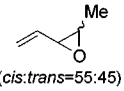
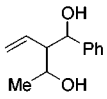
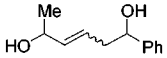
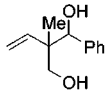
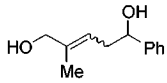
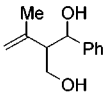
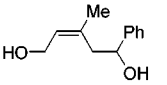
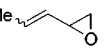
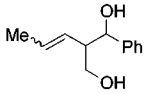
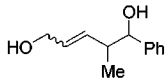
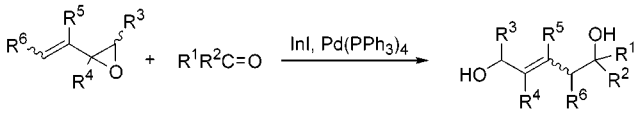
Table 2. Reaction of Substituted Vinyloxiranes with Benzaldehyde[a]

entry	vinyloxirane	conditions[b]	1,3-diol	yield (%)	diastereomeric ratio[c]	1,5-diol	yield (%)	diastereomeric ratio[d]
1		A		51	67:29:4		39	27:73[e]
2	(*cis*:*trans*=55:45)	B		52	73:27		5	-
3		A		83	8:92[f]		0	
4		B		91	25:75[f]		0	
5		A		63	52:48		29	0:100[e]
6		B		71	51:49		6	0:100[e]
7		A		0			77	43:42:15[g]
8	(*E*:*Z*=96:4)	B		0			trace	-

[a] All reactions were carried out in a Barbier-type manner with 2:2:1 InI/oxirane/PhCHO and $Pd(PPh_3)_4$ (5 mol %). [b] A: DMI, 5−7 h. B: 1:1 THF/H_2O, 15 h. [c] Determined by ^1H NMR. [d] Determined by ^{13}C NMR. [e] E:Z ratio. [f] Ratio of syn:anti. [g] Determined by GC.

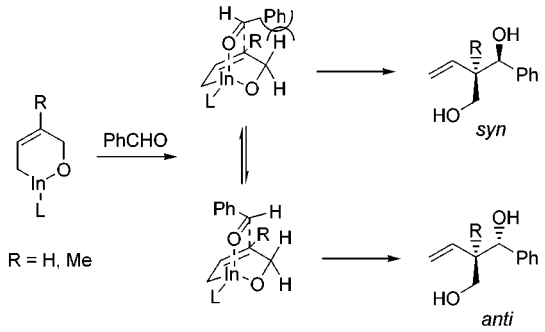
Table 3. Reaction of Vinyloxiranes with Ketones[a]



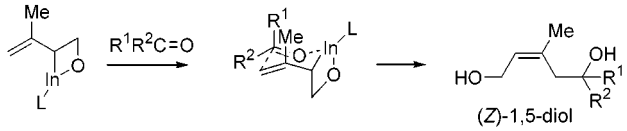
	vinyloxirane				ketone		
entry	R^3	R^4	R^5	R^6	R^1	R^2	% yield (E:Z)[b]
1	H	H	H	H	Ph	Me	78 (33:67)
2	H	H	H	H	Et	Me	39 (21:79)
3	H	H	H	H	*n*-C_6H_{13}	Me	52 (42:58)
4[c]	H	H	H	H	$(CH_2)_5$		41 (37:63)
5	Me	H	H	H	Ph	Me	10 (cis:trans = 55:45)
6	H	Me	H	H	Ph	Me	0
7	H	H	Me	H	Ph	Me	54 (0:100)
8	H	H	H	Me	Ph	Me	0 (E:Z = 96:4)

[a] Reactions were carried out with 2:2:1 InI/oxirane/ketone and $Pd(PPh_3)_4$ (5 mol %) in DMI at room temperature for 5−24 h. [b] Determined by ^{13}C NMR. [c] A small amount (7% yield) of the 1,3-diol was also formed.

Scheme 2



Scheme 3



substituent destabilizes the corresponding six-membered ring intermediate from 2-(1-propenyl)oxirane, and hence no 1,3-diol is formed from this oxirane (Table 2, entry 7). The preference for the 1,5-diols in the reactions of the ketones can be rationalized by a steric reason: the ketones tend to couple with the less-hindered γ-carbon of the four-membered ring allylindium rather than that of the six-membered ring intermediate. The enhanced 1,3-selectivity in aqueous media indicates that the rate of addition to the six-membered ring intermediate is enhanced compared to that to the four-membered one in the presence of water; however, the reason is unknown.

The stereoselection of the present carbonyl allylation with vinyloxiranes is generally not very high; nevertheless, good anti-selectivity and Z-preference are observed in some cases for the 1,3- and 1,5-diol products, respectively. The anti-selectivity in the reactions of benzaldehyde with 2-vinyloxirane (Table 1) and 2-methyl-2-vinyloxirane (Table 2, entries 3 and 4) can be explained by the transition state in Scheme 2: in the transition state leading to the syn isomers, there should be steric crowding between the phenyl group of benzaldehyde and the pseudoaxial hydrogen of the six-membered ring allylic indium reagents. Hence, the anti-diastereomers are formed dominantly.[6] No anti-selectivity is observed in the reaction with 2-(1-methylvinyl)oxirane (Table 2, entries 5 and 6), where the methyl substituent diminishes the energy difference between the two transition states. The observed high Z-selectivity in the 1,5-diol products from 2-(1-methylvinyl)oxirane (Table 2, entries 5 and 6; Table 3, entry 7) is worth noting, probably occurring via the bicyclic transition state depicted in Scheme 3.[7]

In summary, an efficient and convenient method for umpolung of vinyloxiranes has been demonstrated by converting them to nucleophilic allylic indium reagents. The regio- and stereoselectivities of the coupling with carbonyl compounds have been found to depend on the reaction temperature, solvents, carbonyl compounds, and substitution pattern of vinyloxiranes.

(6) The anti-diastereoselectivity of the chromium-induced coupling reaction of vinyloxiranes and carbonyl compounds is explained by a similar boat-formed transition state.[1]

(7) A transition state akin to the present bicyclic one is postulated in the reaction of intramolecularly chelated 1-benzyloxymethyl-2-methyl-2-propenylindium with aldehydes, which also shows high Z-selectivity: Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Muller, D.; Thormann, M.; Hofmann, H. J. *Tetrahedron* **2000**, *56*, 1081−1095.

Experimental Section

Typical Experimental Procedure. To a mixture of indium(I) iodide (0.24 g, 1.0 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in dry DMI (2 mL) were added 2-ethenyloxirane (80 μL, 1.0 mmol) and benzaldehyde (51 μL, 0.50 mmol). The reaction mixture was stirred under argon for 5 h at room temperature. Diluted hydrochloric acid (1 M) was added, and the products were extracted with ether. The extracts were washed with saturated aqueous sodium hydrogencarbonate and brine and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was chromatographed on silica gel (2:1 hexane/AcOEt) to give 2-ethenyl-1-phenyl-1,3-propanediol (56 mg, 62%, syn:anti = 22:78) and 5-phenyl-2-pentene-1,5-diol (30 mg, 33%, E:Z = 29:71).

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Supporting Information Available: Spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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