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Electronic effect on the regioselectivity in the ring opening of *para*-substituted phenyloxiranes by acetylides

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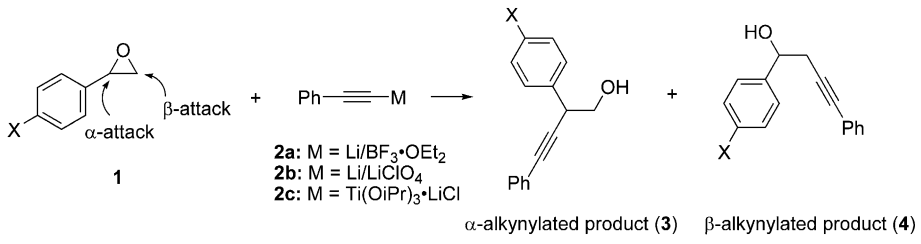
Abstract—The electronic effect on the regioselectivity in the alkynylation of phenyloxiranes was investigated using three kinds of metal acetylides. BF_3 mediated lithium acetylide provided either the α- or β-alkynylated products by controlling the effect of the *para*-substituents of the phenyloxiranes. $LiClO_4$ mediated lithium acetylide and titanium acetylide, on the other hand, afforded predominantly the β- and α-products, respectively.

The alkynylation of oxiranes via ring opening with metal acetylides is an important carbon–carbon forming reaction.[1] However, this useful reaction suffers from some intrinsic limitations, including low yields and regioselectivity. Recently, several new methods have been suggested in order to solve these issues. Lithium acetylides in the presence of $BF_3{\cdot}OEt_2$ by Yamaguchi and Hirao,[2] titanium acetylides by Krause and Seebach,[3] trimethylgallium catalyzed lithium acetylides by Matsubara and co-workers,[4] and lithium acetylides in the presence of $LiClO_4$ by Crotti and co-workers[5] all afford better yields than the classical methods. While simple alkyloxiranes are usually attacked at the less hindered position, the regioselectivity of aryloxiranes depends on a balance between the steric and resonance effects at the benzylic carbon. The procedures described above differ in their regiochemical control: whereas the ring opening of phenyloxirane by BF_3 or Me_3Ga mediated lithium acetylides provides mixtures of the α- and β-alkynylated products, the use of titanium acetylides leads only to the α-alkynylated products, and $LiClO_4$ assisted ring opening by lithium acetylides predominantly affords β-alkynylated products. The regioselectivity also seems to depend on a balance between the nucleophilicity of the acetylides and the Lewis acidity of the metal. Although the metal effect of acetylides has been extensively studied, systematic studies on the sensitivity of the regioselectivity to the influence of the substituents on the aromatic ring of the aryloxiranes have not been reported as far as we know.[6] We report herein the electronic effect on the regioselectivity in the alkynylation of *para*-substituted phenyloxiranes.

The above mentioned lithium acetylide with $BF_3{\cdot}OEt_2$ (**2a**), lithium acetylide with $LiClO_4$ (**2b**) and titanium acetylides (**2c**) were used as metal acetylides (Scheme 1). Table 1 shows the results of the alkynylation of *para*-substituted phenyloxiranes with **2a**.[7] The ratios of



Scheme 1.

Keywords: Oxirane; Alkynylation; Regioselectivity; Electronic effect; Lewis acid.
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Table 1. Alkynylation of *p*-X-phenyloxiranes **1** by lithium acetylide in the presence of $BF_3{\cdot}OEt_2$ (**2a**)[a]

Entry	X	Time	**3**:**4**	Yield[b] (%)
1	NO_2	5 h	1:>99	85
2	CO_2Me	3 h	28:72	79
3	Cl	1 h	58:42	90
4	H	10 min	68:32	81
5	Me	10 min	93:7	85
6	OMe	10 min	>99:1	49

[a] All reactions were carried out with **1**:lithium acetylide:$BF_3{\cdot}OEt_2$ (1:3:3) at −78 °C in THF.
[b] Isolated yields.

the α- and β-alkynylated products **4**/**3** in the reactions of the phenyloxiranes with electron withdrawing groups are higher than that of the unsubstituted one (entries 1–4). When a nitro group was the substituent, the β-alkynylated product **4** was produced exclusively in 5 h (entry 1). On the other hand, substrates with an electron donating group afforded mainly the α-alkynylated products **3** within 10 min (entries 5 and 6), clearly demonstrating that the electron withdrawing substituents retard the reaction. Plots of $\Delta\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{\beta} - \Delta G^{\ddagger}_{\alpha}$ (kJ/mol)) versus the σ^+ values from the Hammett equation[8] gave a straight line, indicating the dramatic electronic effect (Fig. 1).

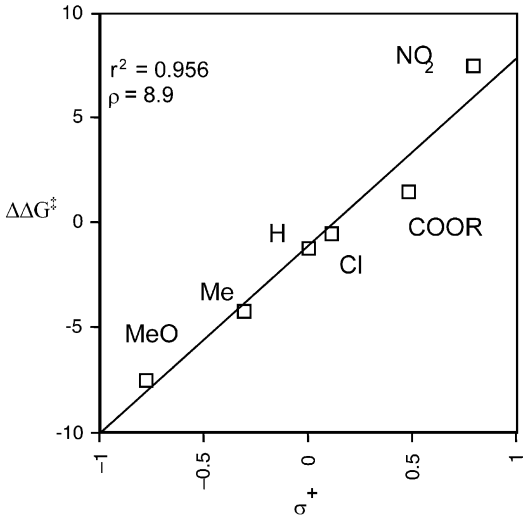
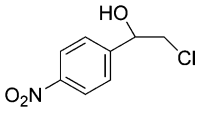


Figure 1. Plots of σ^+ value versus $\Delta\Delta G^{\ddagger}$ for alkynylation of *para*-substituted phenyloxiranes with **2a**.

It is noteworthy that the reaction of the optically active *p*-methoxyphenyloxirane **1** (X = OMe, 93% ee)[9] with lithium trimethylsilylacetylide/$BF_3{\cdot}OEt_2$ gave the almost racemic α-alkynylated product **6** (6% ee), while the reaction of the unsubstituted phenyloxirane **1** (X = H, 90% ee)[9] furnished the α-alkynylated product **7**[10] without any loss of optical purity, along with the β-alkynylated one **8** (Scheme 2).

In contrast, the $LiClO_4$ mediated lithium acetylide **2b**, which is much less reactive than **2a**, furnished mainly the β-alkynylated products **4** (Table 2, entries 1–3),[11] even in the reaction of *p*-methoxyphenyloxirane (**1**, X = OMe), along with 27% of the side product **11**, which would be formed by the Meinwald rearrangement,[12] followed by addition of the acetylide to the resulting aldehyde **10**. However *p*-nitrophenyloxirane provided exclusively **4** in moderate yield along with 12% of **11** (Scheme 3). The titanium acetylide **2c** afforded only the α-alkynylated products **3** (entries 5 and 6),[13] although *p*-nitrophenyloxirane did not give the alkynylated products, but rather 2-chloro-1-(4-nitrophenyl)ethanol (**9**) was obtained in 30% yield (entry 4).



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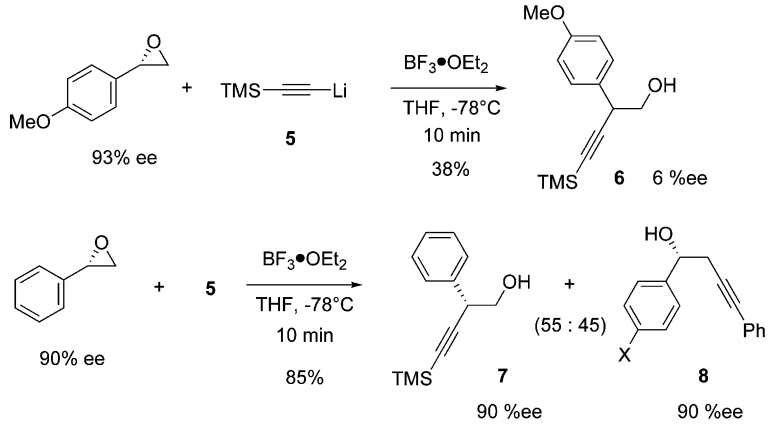
From these results, among the acetylide species, the BF_3 mediated lithium acetylide **2a** was found to be the most sensitive to the influence of the electronic effect of the *para*-substituents in terms of the α/β selectivity. This species can afford either the α- or β-alkynylated products by simply changing the *para*-substituent of phenyloxirane, while the $LiClO_4$–lithium acetylides and titanium acetylides provide the β- and α-alkynylated products, respectively.

The mechanism of the regioselectivity depends on a balance between the nucleophilicity and the Lewis acidity. Since the lithium acetylide would not be converted into the boron acetylide at −78 °C,[14] BF_3, it would function as a relatively strong Lewis acid, and, thus, efficiently activate both the C_α–O and the C_β–O bonds of the oxiranes (Fig. 2, **14**). Since electron donating *para*-substituents stabilize the α-carbocation via resonance, the C_α–O

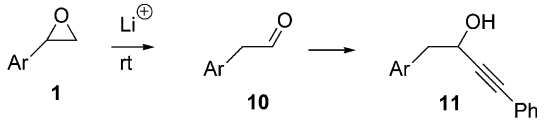
Table 2. Alkynylation of *p*-X-phenyloxiranes **1** by lithium acetylide in the presence of $LiClO_4$ (**2b**) and by titanium acetylide (**2c**)

X	**2b**[a]				**2c**[b]			
	Entry	Time (h)	**3**:**4**	Yield[c] (%)	Entry	Time (h)	**3**:**4**	Yield[c] (%)
NO_2	1	10	1:>99	44[d]	4	48	—	0[f]
H	2	36	3:97	85	5	10	>99:1	78
OMe	3	20	25:75	35[e]	6	1	>99:1	82

[a] Reactions were carried out with **1**:lithium acetylide:$LiClO_4$ = 1:3:2 at room temperature in THF.
[b] Reactions were carried out with **1**:titanium acetylide = 1:2 at −50 °C then warmed to room temperature over 2 h and stirred for indicated hours.
[c] Isolated yield.
[d] The byproduct **11** was isolated in 12% yield.
[e] The byproduct **11** was isolated in 27% yield.
[f] The chlorinated product **9** was formed in ca. 30% yield.



Scheme 2.



Scheme 3.

bond would be more activated and elongated than the C_β–O bond, and the nucleophile would selectively attack the α-site (**15**) via the S_N1 like mechanism. However, since electron withdrawing substituents deactivate the α-site, β-attack via S_N2 is relatively favored, although the reaction is retarded (**13**). The linear relationship between σ^+ and the regioselectivity indicates that increasing carbocation character of the α-site tends to increase α-attack. $LiClO_4$ is a much weaker Lewis acid than BF_3, and thus, the oxiranes are only slightly activated (**12**).[15] However, since this species still has nucleophilicity as high as *lithium acetylide*, only the β-alkynylated products were obtained due to the steric effect, and the resonance effect does not contribute to the selectivity. Since the reaction was carried out at room temperature, the Meinwald rearrangement competed with the α-alkynylation.

In contrast, the triisopropoxy titanium acetylide would have moderate Lewis acidity and very poor nucleophilicity. The generation of the benzylic carbocation by coordination of the oxirane to titanium is crucial for the reaction of titanium acetylide, and thus *p*-nitrophenyloxirane did not provide alkynylated products, but gave the chlorinated product (**9**) instead.[16]

In conclusion, we have demonstrated the electronic effect on the alkynylation of aryloxiranes by metal acetylides. The BF_3 mediated lithium acetylide is very sensitive to the effect, and the selectivity is controlled by the *para*-substituents. $LiClO_4$ mediated lithium acetylide and titanium acetylides are much less sensitive to the effect in terms of the regioselectivity, and afford the β- and α-alkynylated products, respectively. This is the first systematic study on the electronic effect in alkynylation, which should be useful for organic chemists, since the products are synthetically very important.

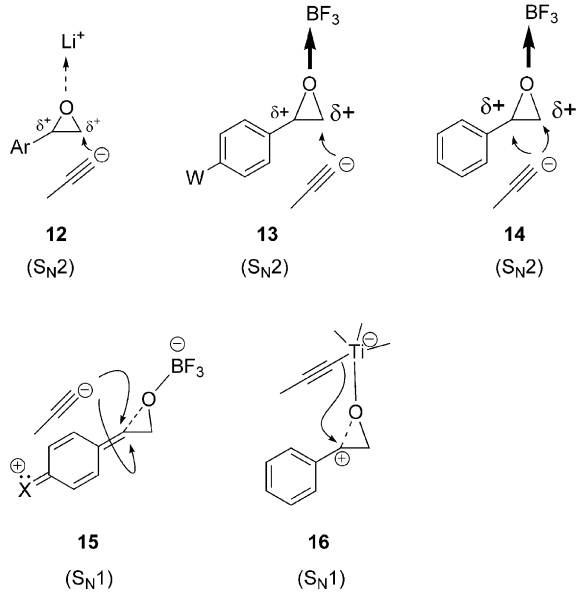


Figure 2. Activation of oxiranes by Lewis acids.

Acknowledgements

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7. A typical procedure: to a solution of phenylacetylene (306 mg, 3.0 mmol) in THF (3 mL) was added a solution of butyllithium (3.0 mmol, 1.58 M in hexane) at −78 °C under argon, and the mixture was stirred for 1 h. $BF_3{\cdot}OEt_2$ (0.43 mmol, 3 mmol) was added, and after 10 min, a solution of 4-nitrophenyloxirane (165 mmol, 1.0 mmol) in THF (1 mL) was added. After the reaction was stirred for 5 h at −78 °C, it was quenched with satd aq $NaHCO_3$. The mixture was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a crude mixture, which was purified by preparative HPLC (LiChrosorb® Si, ethyl acetate/hexane) to afford 227 mg (85%) of **4** (X = NO_2).
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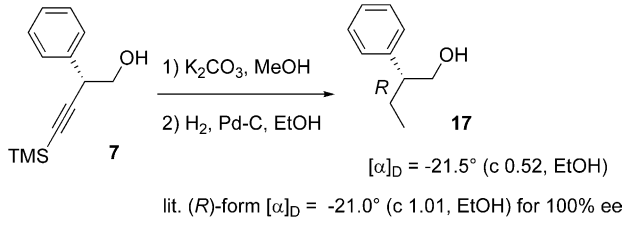

11. A typical procedure: to a solution of phenylacetylene (306 mg, 3.0 mmol) in THF (5 mL) was added a solution of butyllithium (3.0 mmol, 1.58 M in hexane) at 0 °C under argon, and the mixture was stirred for 10 min. A solution of phenyloxirane (120 mg, 1.0 mmol) and $LiClO_4$ (212 mg, 2.0 mmol) in THF (1 mL) was added. The reaction was stirred for 36 h at room temperature, then diluted with H_2O. The mixture was extracted with ether, and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a crude mixture, which was purified by preparative HPLC (LiChrosorb® Si, ethyl acetate/hexane) to afford 188 mg (85%) of **4** (X = H).
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13. A typical procedure: to a solution of phenylacetylene (204 mg, 2.0 mmol) in THF (3.5 mL) was added a solution of butyllithium (2.0 mmol, 1.58 M in hexane) at 0 °C under argon, and the mixture was stirred for 10 min. The solvents were removed in vacuo, and 4.5 mL of THF was added. A solution of triisopropyloxytitanium chloride (2.0 mmol, 1 M in hexane) was added at −50 °C. After 10 min, a solution of *p*-methoxyphenyloxirane (150 mg, 1.0 mmol) in THF (1.5 mL) was added to the solution at −50 °C, and the mixture was allowed to stand at room temperature over 2 h. The reaction was stirred for 1 h, and 1 M HCl was added. The mixture was extracted with ether, and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a crude mixture, which was purified with preparative HPLC (LiChrosorb® Si, ethyl acetate/hexane) to afford 206 mg (82%) of **3** (X = OMe).
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15. Without Lewis acids, the alkynylation does not proceed. See Ref. 5.
16. According to Ref. 3, when optically pure phenyloxirane is used, the product is partially racemized. This supports the S_N1 like reaction involving a carbocation intermediate.