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AN ASYMMETRIC SYNTHESIS OF CHIRAL PHTHALIDES VIA CHIRAL LITHIATED OXAZOLINES

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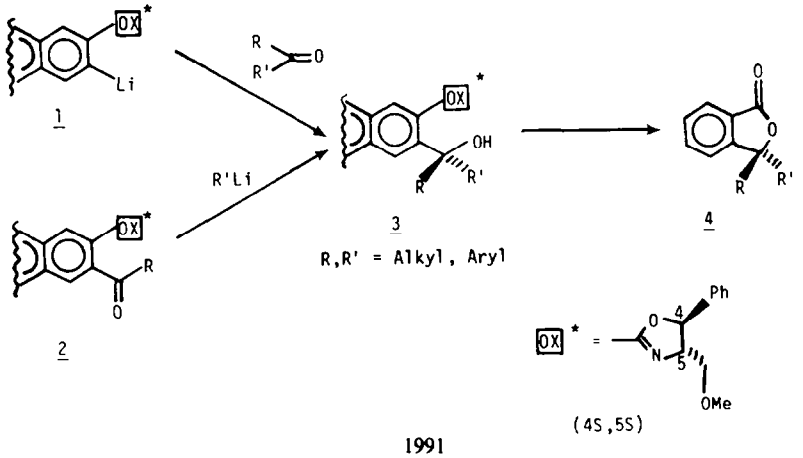
Abstract—Chiral aromatic oxazolines were prepared for utilization in asymmetric C–C bonding reactions. Lithiation of aryloxazolines could not be accomplished directly but were efficiently lithiated via halogen metal exchange of the *o*-bromo derivative (**16**). The resulting lithio compound (**9**) reacted smoothly with carbonyls to give adducts **19** but with poor stereoselectivity. Hydrolysis gave the phthalides **4** in poor ee's (20–25%). When the lithio-oxazolines **9** were transformed into **21**, they now served as chiral electrophiles. Addition of organometallics to **21** gave, particularly with Grignard reagents, useful levels of asymmetric induction which, after hydrolysis, gave phthalides **4** in 40–80% ee.

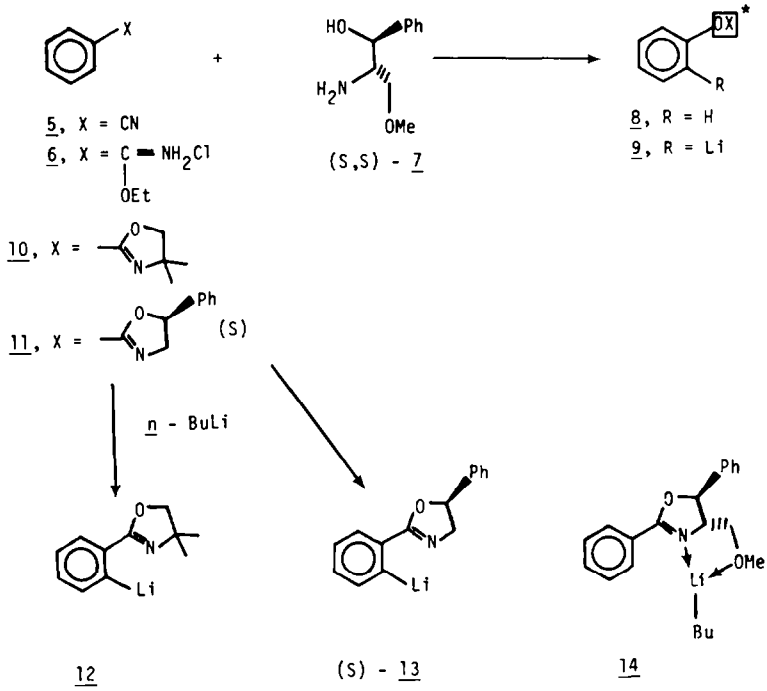
Previous studies from this laboratory have demonstrated the wide versatility of aromatic oxazolines toward the synthesis of various aromatic derivatives[3] via *o*-metallation and nucleophilic displacements. Furthermore, chiral oxazolines have been amply demonstrated as precursors to a variety of enantiomerically enriched compounds (acids, alcohols, lactones, binaphthyls) via asymmetric synthetic procedures.[4] In this report we wish to describe the combination of these two methods, namely aromatic substitution mediated by the chirality of an oxazoline substituent (**1** or **2**) to furnish chiral phthalides **4**. The latter are substances present in naturally occurring materials many of which possess biological activity.[5]

The scheme explored involves *o*-lithio aryloxazolines **1** or their corresponding *o*-acyl derivatives **2**, followed by addition to carbonyls or organometallics, respectively. Both routes, one via a chiral nucleophile **1** and the other via a chiral electrophile **2** provide the same gross structure, **3** containing a new chiral center. Satisfactory implementation of these synthetic modes would result, after hydrolytic removal of the oxazoline, in the transfer of chirality to the phthalides, **4**. There have only been a few reported instances of the asymmetric synthesis of phthalides,[6] the most noteworthy being that of Mukaiyama[7] who prepared **4** (R=H, R'=n-Bu) in 88% enantiomeric excess.

Chiral 2-aryloxazolines

Based on earlier work,[8] simple achiral aryloxazolines **10** are readily metalated with n-BuLi in THF at $-45°$ to give the *o*-lithio derivatives **12**. Assuming this was also feasible with chiral oxazolines **8**, the synthesis was carried out from benzonitrile **5** and conversion to its imidate salt **6**. As previously reported[4] reaction of the chiral methoxyamino alcohol **7** with various alkyl imidate salts also gave good yields of the oxazoline **8**. Repeated attempts to orthometalate **8** gave only starting materials after deuterium oxide or methyl iodide quench, thus indicating that the *o*-lithio derivative **9** was not formed.





This was in direct contrast to the metallation of **10** to provide **12**. Furthermore, the aryloxazoline **11**, derived from the imidate **6** and (*S*)-2-phenyl-2-hydroxyethylamine, gave **13** in good yield when treated with n-BuLi. The resistance of **8** toward ortho-lithiation was then assumed to be due to the competitive chelation of n-BuLi with the OMe group, **14**, an effect seen earlier with related asymmetric syntheses.[9] The presence of the OMe in **14** probably aligns the base in a region too far from the proton to be abstracted. Confirmation of the chelation effect in **14** can be gathered by observing a downfield shift of 0.3–0.4 ppm for the methyl singlet of the OMe group in the presence of Li ions (LiCl, $LiClO_4$, BuLi). The Bu residue, therefore, must be a tight partner to the coordinated Li ion and unable to reach bonding distance to the ortho proton.

Failure to directly metalate **8** led to an alternative route to reach *o*-lithioaryloxazoline, **9**. The use of halogen–metal exchange was felt to be the viable choice to achieve this goal. In this vein the synthesis of *o*-bromophenyloxazoline **16** was attempted. Starting from *o*-method[10] of adding the acid (HCl or HBF_4) to an ethanolic solution of the nitrile. However, no imidates were formed and this was in agreement with earlier reports[11] that *o*-substituted benzonitriles are inert to these conditions. The imidate **17** was, however, readily prepared using the Meerwein technique[12] and treatment with the chiral amino alcohol **7** gave the desired bromophenyloxazoline **16** in 82% yield. The generality of this route to oxazolines from amides has been demonstrated.[13] With **16** in hand, treatment with n-BuLi (THF, −78°) smoothly gave the *o*-lithio derivative **9** which could be alkylated with a variety of electrophiles required for the asymmetric synthesis.

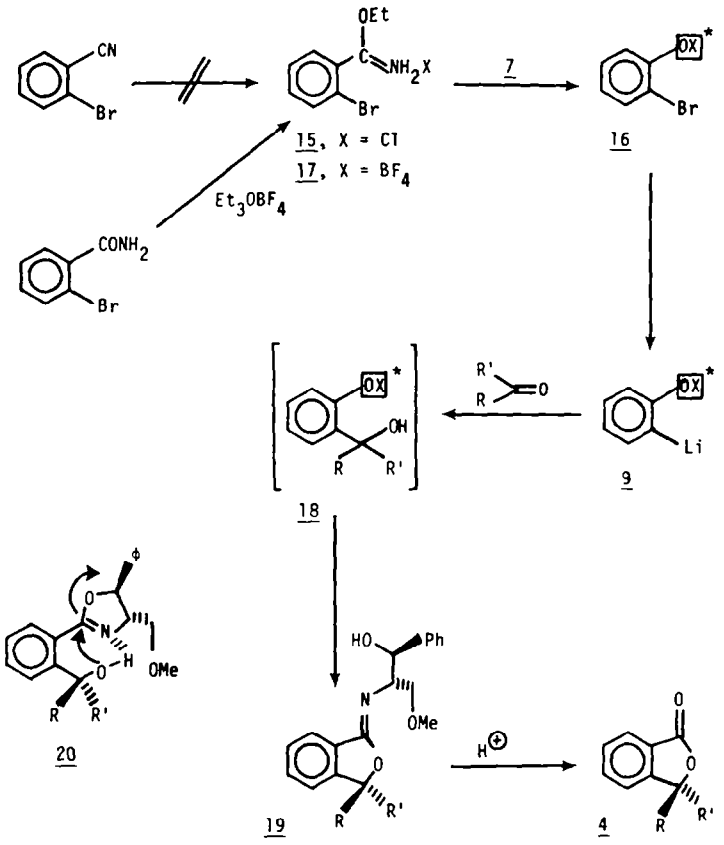
Additions to prochiral carbonyls

The lithiated aryloxazoline **9** was added to various carbonyl compounds affording adducts **18** in 60–70% yields. However, the final isolated products were found to be the rearranged imino lactones **19** presumably due to the facile tautomerism depicted by **20**. The rather poor stereoselectivity for this process using several carbonyl compounds is given in Table 1. The diastereomeric excess (de) was determined by ^{1}H-NMR which exhibited discreet baseline separated signals for each diastereomer (Table 3). Although the asymmetric addition of **9** to carbonyls was poor, the diastereomers, which spontaneously formed **19** (R=Me, R′=Ph), were separated by crystallization to provide pure material, each of which was hydrolyzed in THF–aqueous oxalic acid to virtually pure enantiomers of **4** (R, R′ = Me, Ph); (*R*)-**4** gave

Table 1. Addition of **9** to carbonyls at −78°

RCOR′	Solvent	% Yield 19	Diastereomer Ratios[b]
PhCOMe	THF	71	64:33
PhCOMe	Toluene[a]	60	53:47
P-BrC_6H_4COMe	THF	71	60:40
PhCHO	THF	73	57:43
o-$MeOC_6H_4$CHO	Toluene	63	59:41
n-BuCHO	THF	64	51:49

[a]MgBr salt used, triethylamine used to solubilize Grignard reagent of **16**.
[b]Determined by ^{1}H-NMR (see Table 3)



$[\alpha]_D$ − 66.3° whereas (*S*)-**4** gave $[\alpha]_D$ + 69.3°. Since no disubstituted chiral phthalides have been previously reported, the absolute configuration was determined on the pure diastereomer **19** (R′=Me, R=p-BrPh) obtained from hexane recrystallization. X-ray structural information (Fig. 1) gave the absolute configuration for the phthalides as *S*(+) and *R*(−). CD spectra for all the enantiomerically pure phthalides **4** showed their related sense of chirality (Fig. 2), confirming that the CD was a reliable measure of absolute configuration for 3,3-disubstituted derivatives. The synthetic scheme for phthalides was then altered so that organometallics were added to the *o*-acyl phenyloxazolines **2** in order to assess the value of this approach in reaching chiral phthalides.

Organometallic addition to chiral o-acyl phenyloxazolines

Reaction of the *o*-lithiophenyloxazoline **9** with various acylating derivatives led to the acylated products **21**. Esters and anhydrides served best as acylating agents whereas acid chlorides, amides and nitriles gave very poor yields of **21**. Additions to **21** by various organolithium reagents (PhLi, MeLi, n-BuLi) under various conditions gave excellent chemical yields of **19** (via spontaneous rearrangement of **18**) but diastereomeric ratios were poor (9–20%). However, addition of Grignard reagents at −45° gave useful ratios of **19** as seen from Table 2. These ratios were readily derived by inspection of the chemical shifts of substituents at the 3-position and in some cases, the OMe group in **19** (Table 3). In all cases, the *S*-configuration was found to appear at

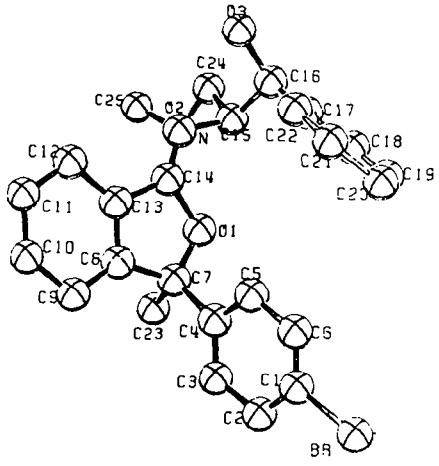


Fig. 1. ORTEP diagram of **19** (R′=Me, R=*p*-BrC_6H_4) showing *S*-configuration at C-7.

lower field than the *R*-configuration. This coupled with the X-ray structure of **19** (R=*p*-BrC_6H_4, R′=Me) shown to be *S* and the CD curves obtained put the assignments for the other derivatives of **19** on relatively firm ground. In order to rationalize the predominant diastereomer in **19** after addition of Grignard reagents to **21**, one may invoke Cram's cyclic model[14] as applied to the oxazolines (**22**). Entry of the Grignard reagent may be assumed to come from the *re*-face as shown in **22** and this results in the absolute configurations observed in Table 2. Topside entry in **22** is probably precluded by the presence of the phenyl group which inhibits approach of the

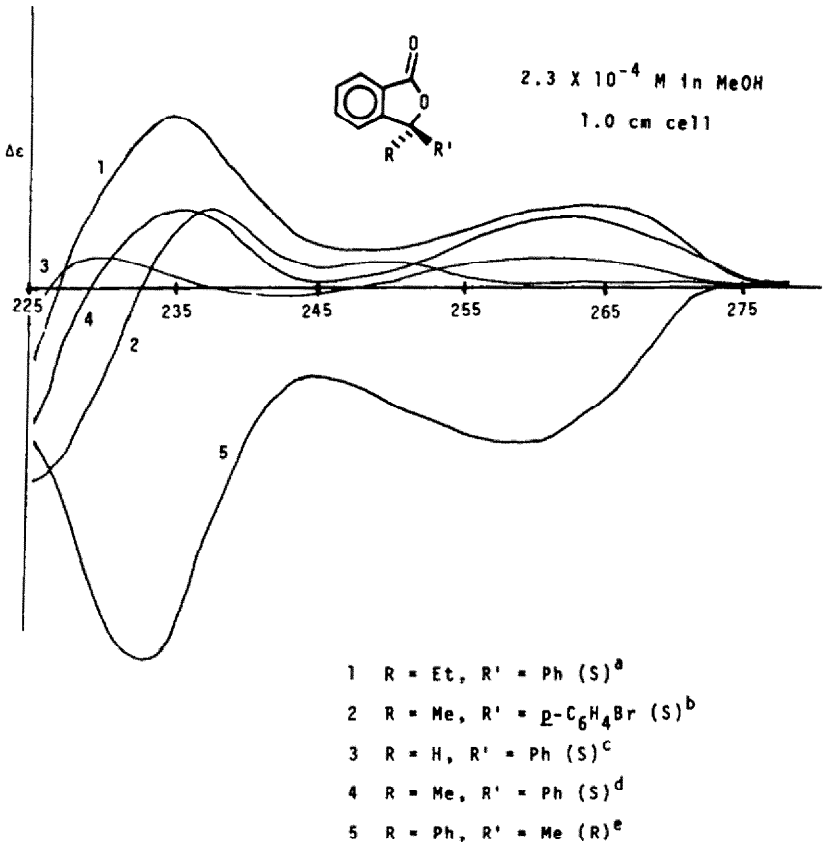


Fig. 2. CD spectra of phthalides, **4**.

Table 2. Addition of RMgX to **21**, formation of **19** and **4**

Exp.	R (in 21)	R'MgX[a]	Yield 19	Diastereomer Ratios[b]	Yield 4	ee[c]
1	Me	EtMgBr	96	73:27	48	46(S)
2	Me	BuMgBr	92	73:27	--	--(S)
3	Me	t-BuMgBr	90	83:17	25	66(R)
4	Me	PhMgBr	97	90:10	67	80(S)
5	Ph	MeMgCl	99	88:12	93	76(S)
6	Ph	EtMgBr	99	83:17	30	66(S)
7	Et	MeMgCl	93	82:18	82	64(R)
8	t-Bu	MeMgCl	66	52:48	--	--
9	p-BrC_6H_4	MeMgCl	95	87:13	87	74(S)
10	n-Bu	MeMgCl	89	84:16		(R)

[a] 2.2 equiv added to oxazoline (0.07 m in THF) at -45°.

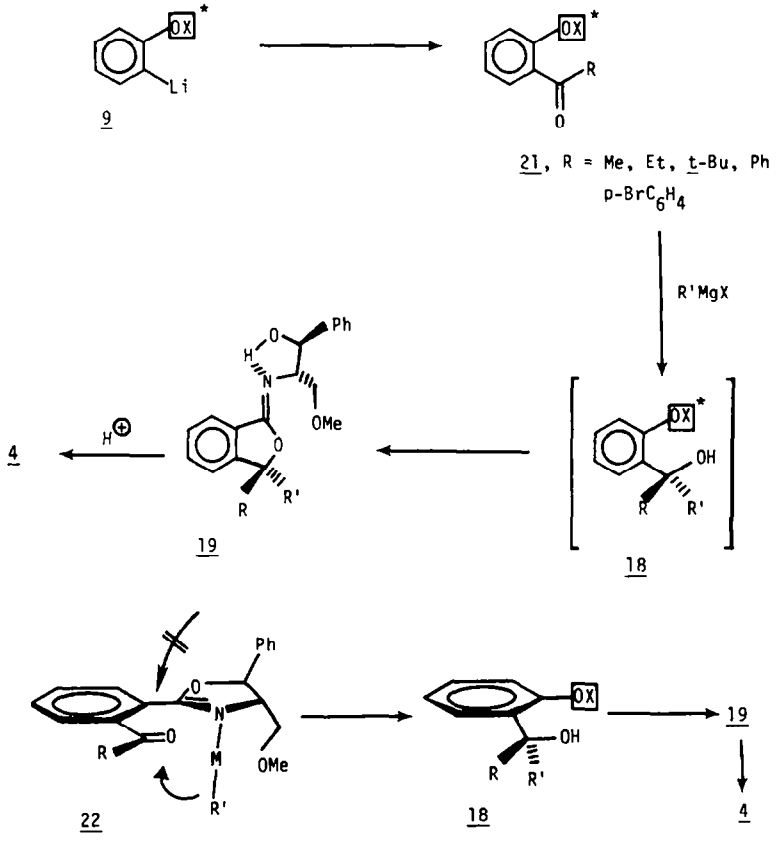
[b] Determined by ^{1}H-nmr spectrum.

[c] Configurations based on x-ray data and comparison of CD curves.

Table 3. Diastereomeric shifts at 60 MHz for **19**

R	19 R'	Config'n at C-3	Chemical Shifts, δ[a] R	R'	OMe
Me	Et	S	1.47(s)[b]	0.32(t)	
		R	1.28(s)	0.62(t)	
Me	n-Bu	S	1.52(s)		
		R	1.38(s)		
Me	t-Bu	S	1.49(s)	0.73(s)	
		R	1.38(s)	0.94(s)	
Me	Ph	S	1.90(s)		3.38(s)
		R	1.72(s)		3.31(s)
Me	p-BrC_6H_4	S[c]	1.89(s)		
		R	1.69(s)		
Et	Ph	S	0.70(t)		
		R	0.49(t)		

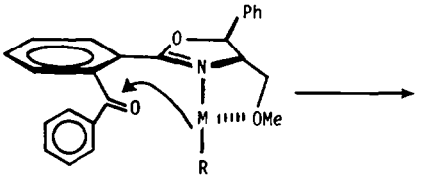
[a] All spectra taken in $CDCl_3$ except where noted.
[b] CCl_4 used as solvent.
[c] Absolute configuration taken from x-ray analysis.



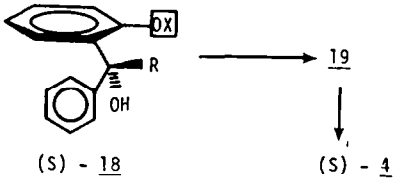
Grignard reagent. A closer examination of space filling models reveals that **22** as drawn is somewhat encumbered by virtue of the aryl ketone and the oxazoline lying in the same plane. Maximum overlap and minimum repulsions are best achieved if the acyl group in **22** is rotated 10–30° out of the plane of the aryl and oxazoline. This also allows the carbanion of the Grignard reagent to approach the C of the CO group at a more desirable angle (~ 110°).[15] Using this model as an approach to the transition state the absolute configurations given in Table 2 may be understood. Reversing the order of the alkyl introduction also reverses the absolute configurations (Exp. 1 and 7). The introduction of t-Bu via its Grignard (Exp. 3) gave unexpectedly the *R*-configuration in **19** and this may be due to the fact that t-BuMgCl has been shown to react with carbonyls via election transfer.[16]

Another interesting aspect seen in Table 2 is the lack of absolute configuration change for either

phenyl or methyl Grignard (Exp. 4, 5). Although phenyl Grignard added according to the model **22** to give the *S*-phthalide **4**, reversal of this sequence still gave the *S*-phthalide. This is undoubtedly due to a change in conformation in **21** to accommodate the large benzoyl substituent. In fact, it is known that 2-substituted benzophenones containing an electron withdrawing substituent (as in **21**, R=Aryl) prefer the CO to be coplanar with the unsubstituted ring[17] **23**. This would then account for the *S*-configuration observed in all the benzophenone systems (Exp. 5, 6, 9) since alkyl entry would be from the si-face in **23**. In an effort to assess the value of the methoxymethylene group in **22** and **23**, similar reactions were carried out using the aryloxazoline (*S*)-**11**. By use of the lithio salt **13**, the benzoyl derivative **24** was prepared in an analogous manner to **21**. Addition of 2.2 equiv. MeMgCl followed by hydrolysis gave the

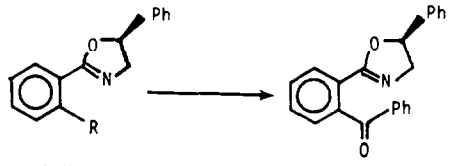


23



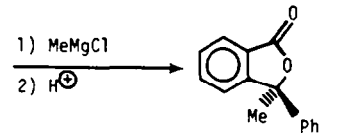
(S) - 18 (S) - 4

S-phthalide **4** in 40–42% ee as compared to 76% ee using **21**. The absolute configuration, however, remained the same suggesting that the Me Grignard still appears to enter as shown in **23**. Perhaps chelation of the Grignard with the ring N- and O-atoms in **24** is responsible for imparting some rigidity to the transition state.



(S)-11, R = H
(S)-13, R = Li

24

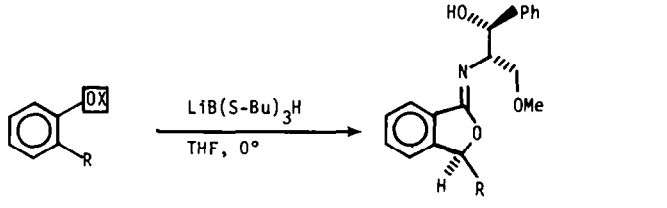


(S)-4 (40% ee)

Hydride reductions of o*-acyl aryloxazolines*

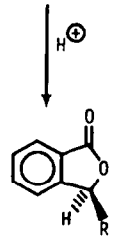
The prochiral *o*-acyl aryloxazolines **21** were also made the subject of hydride reductions in an attempt to assess whether chiral 3-monosubstituted phthalides could be efficiently reached. Optimum conditions were evaluated using the 2-benzoyl derivative of **21** (R=PhCO). LAH (ether, 0°) gave a 54:46 mixture of diastereomers of **25** (R=Ph) with the *R*-configuration at C-3 predominating. $NaBH_4$ gave, in ethanol at 0°, a 65:35 ratio of **25** with the *S*-configuration at C-3 as the major epimer. The best ratios were reached using lithium *tri* sec-butyl borohydride (L-selectride)® in THF at 0° providing the *S*-epimer of **25**, as the major diastereomer. Hydrolysis gave the 3-substituted phthalides **26** in ee's comparable to the diastereomeric ratios shown for **25**. The use of potassium *tri* sec-butyl borohydride (K-selectride)® in these reductions led to lower diastereoselectivity (1.5–2.5 to 1) due perhaps, to less effective chelation by the K ion. The predominance of the *S*-enantiomer in **26** is consistent with the approach shown in **22** (R'=H) wherein the hydride is delivered from the reface of the CO group.

In summary, aryloxazolines containing an *o*-acyl group are alkylated or reduced with reasonable stereoselectivity affording the chiral 3,3- or 3-substituted



21, R = PhCO, MeCO, t-BuCO

(S) - 25, R = Ph (85:15)
R = Me (72:28)
R = t-Bu (74:26)



(S) - 26

phthalides through a mechanism assumed to involve chelation of the metal by the oxazoline N and the OMe group. A number of optically pure phthalides are now accessible by simple recrystallization of the diastereomeric imino lactones, **19**.

EXPERIMENTAL[18]

(4S,5S)-2-Phenyl-4-methoxymethyl-5-phenyl-2-oxazoline, **8**

To a suspension of ethyl benzimidate hydrochloride[19] (4.0 g, 21.6 mmol) in 25 ml 1,2-dichloroethane was added 4.3 g (23.7 mmol) of 7.[20] The mixture was heated at reflux for 18 hr. After cooling, the mixture was poured into 5% $NaHCO_3$, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Distillation (145°, 0.05 mm) gave 5.0 g (87%) of **8**, as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 3.30–3.90 (m, 5), 4.05–4.50 (m, 1), 5.40 (d, J = 6 Hz, 1), 7.10–7.60 (m, 8), 7.60–8.25 (m, 2); ^{13}C NMR ($CDCl_3$) δ 59.2 (q), 74.2 (t), 74.8 (d), 83.5 (d), 125.2, 127.3, 127.9, 128.1, 128.2, 128.4, 131.2, 140.6 (s), 163.7 (s); IR (film) 1650 (C=N), 1452 cm^{-1}. (Found: C, 76.75; H, 6.31. Calc for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41%.)

(5S)-2,5-Diphenyl-2-oxazoline, **11**

The procedure above was followed using 0.67 g (3.6 mmol) of ethyl benzimidate hydrochloride, 0.55 g (4.0 mmol) of *S*-(+)-2-amino-1-phenylethanol[21] and 20 ml 1,2-dichloroethane. Preparative TLC (silica gel, 50% ether–hexane) gave 0.64 g (79%) of **11**, as an oil, which crystallized on standing: ^{1}H NMR ($CDCl_3$) δ 3.72–4.72 (m, 2), 5.46–5.82 (m, 1), 7.12–8.18 (m, 10); ^{13}C NMR ($CDCl_3$) δ 63.0 (t), 80.9 (d), 125.4, 127.4, 128.5, 131.1, 140.7 (s), 163.7 (s); IR (film) 1645, 1490, 1448, 1332, 1252, 691 cm^{-1}; m.p. 38–40°; $[\alpha]_D$ = + 162.3° (c 4.7 in $CHCl_3$). (Found: C, 80.52; H, 5.84. Calc for $C_{15}H_{13}NO$: C, 80.69; H, 5.87%.)

(4S,5S)-2-(2-Bromophenyl)-4-methoxymethyl-5-phenyl-2-oxazine, **16**

To a soln of 3.0 mmol of *o*-bromobenzamide in 25 ml 1,2-dichloroethane was added 3.0 mmol of Et_3OBF_4.[22] The soln was stirred overnight at room temp and 3.3 mmol of 7[20] added. After heating at reflux overnight, the soln was cooled, poured into 5% $NaHCO_3$ aq, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to afford the oxazoline, as an oil. Purification was accomplished using preparative TLC (silica gel, acetone–hexane) to give **16** in 82% yield; $[\alpha]_D$ + 19.3° (*c* 25.0, $CHCl_3$); IR (film) 1642, 1582, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.20–3.90 (m, 5), 4.10–4.60 (m, 1), 5.40 (d, J = 7 Hz, 1), 7.00–7.80 (m, 9). (Found: C, 59.26; H, 4.64. Calc for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66%.)

Addition of **9** *to carbonyls*

General procedure for Table 1. To a soln of 3.0 mmol of **16** in 20 ml THF or toluene at − 78° was added 3.1 mmol of n-BuLi. After 30 min, 3.3 mmol of the appropriate aldehyde or ketone was added (Table 1) and the soln stirred at − 78° for 2 hr. The mixture was allowed to warm to 25°, poured into water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration gave the oxazoline and/or the iminolactone, as an oil, which was not purified. After establishing the diastereomeric ratio (Table 3), the oil was hydrolyzed to the phthalides **4** (*vide supra*).

Addition of **9** *to electrophiles*

Preparation of **21**—*General procedure*. To a soln of 2.9 mmol of **16** in 25 ml THF at − 78° was added 3.1 mmol of n-BuLi. After 15 min, 3.7 mmol of the electrophile (Aldrich) was added and the soln allowed to warm to 25°. The mixture was poured into water, extracted with CH_2Cl_2, dried (K_2CO_3), and concentrated to provide the oxazolines as oils. Purification was accomplished by TLC (20% acetone–hexane) and/or medium pressure liquid chromatography using the same solvent pair. Following are specifics for each compound prepared in this manner.

Compound **21** (R=Me). Ac_2O used as electrophile. Excess anhydride was decomposed prior to purification by stirring the CH_2Cl_2 soln with 10% NaOH for 30 min. Yield 50%, $[\alpha]_D^{25}$ + 37.5° (*c*, 5.3, $CHCl_3$); IR (film) 1700, 1655, 1248, 1142 cm^{-1}; ^{1}H-NMR (CCl_4) δ, 2.45 (s, 3), 3.23–3.83 (m, 5), 4.01–4.93 (m, 1), 5.40 (d, J = 7 Hz, 1), 7.10–7.60 (m, 8), 7.71–8.02 (m, 1). (Found: C, 73.56, H, 6.11. Calc for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19%.)

Compound **21** (R=Et). Propionic anhydride used as electrophile, yield 40%, $[\alpha]_D^{25}$ + 33.9° (*c*, 8.3, $CHCl_3$); IR (film) 1700, 1650, 1218, 1130 cm^{-1}; ^{1}H-NMR (CCl_4)δ, 1.09 (t, J = 7 Hz, 3), 2.69 (q, J = 7 Hz, 2), 3.29–3.78 (m, 5), 3.99–4.32 (m, 1), 5.38 (d, J = 7 Hz, 1), 7.01–7.49 (m, 8), 7.70–7.99 (m, 1). (Found: C, 73.99; H, 6.67. Calc for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55%.)

Compound **21** (R=t-Bu). Methyl pivalate used as electrophile, yield, 50%, $[\alpha]_D^{25}$ + 55.7° (*c*, 10.3, $CHCl_3$); IR (film) 1693, 1655, 1480, 1192, 1131 cm^{-1}; ^{1}H-NMR (CCl_4)δ, 1.22 (s, 9), 3.31–3.76 (m, 5), 4.11–4.50 (m, 1), 5.46 (d, J = 7 Hz, 1), 7.04–7.69 (m, 8), 7.90–8.19 (m, 1). (Found: C, 75.29; H, 7.17. Calc for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17%.)

Compound **21** (R=Ph). Ethyl benzoate used as electrophile, yield 70%, $[\alpha]_D^{25}$ + 50.7° (*c*, 5.3, $CHCl_3$); IR (film) 1680, 165, 1452 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ, 2.89–3.68 (m, 5), 3.88–4.30 (m, 1), 5.05 (d, J = 7 Hz, 1), 6.98–8.20 (m, 14). (Found: C, 76.43; H, 5.70. Calc for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70%.)

Compound **21** (R=*p*-BrC_6H_4). Ethyl *p*-bromobenzoate used as electrophile, yield 47%, $[\alpha]_D^{25}$ + 22.3 (*c*, 6.2, $CHCl_3$); IR (film) 1670, 1648, 1580 cm^{-1}; ^{1}H-NMR (CCl_4)δ, 2.70–3.51 (m, 5), 3.88–4.19 (m, 1), 5.10 (d, J = 7 Hz, 1), 6.89–7.68 (m, 12), 7.79–8.10 (m, 1). (Found: C, 63.80; H, 4.63. Calc for $C_{24}H_{20}BrNO_3$: C, 64.01; H, 4.48%.)

Addition of Grignard reagents to **21** (Table 2)

Formation of **19**—*General procedure*. The Grignard reagent (5.3 mmol) in ether or THF was added to 2.3 mmol of **21** in 30 ml of THF at − 45°. After 2 hr at − 45° and 1 hr at 25°, the mixture was quenched in sat NH_4Cl aq, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration gave **18** and/or **19** as an oil which was not purified. After establishing the diastereomeric ratio the oil was hydrolyzed to **4** (*vide supra*).

Sample for X-ray analysis, **19** (R'=Me, R=*p*-BrC_6H_4)

Following the general procedure 4.70 ml (13.1 mmol) of MeMgCl was added to 2.69 g (6.0 mmol) of **21** (R=*p*-BrC_6H_4) in 95 ml THF at − 45°. Workup afforded 2.87 g (102%) of **19** (*S*:*R*, 87:12, ^{1}H-NMR) as a viscous oil. Crystallization from hexane followed by recrystallization from hexane and then cyclohexane gave crystalline material: ^{1}H-NMR ($CDCl_3$) 1.82 (s, 3), 3.10–3.82 (m, 5), 4.02 (broad s, 1), 4.33–4.68 (m, 1), 5.02 (dJ = 3 Hz, 1), 6.70–8.00 (m, 13); ^{13}C-NMR ($CDCl_3$)δ, 26.7 (q), 58.7 (q), 61.8 (d), 72.8 (d), 73.2 (t), 88.3 (d), 120.7, 121.4, 123.5, 125.9, 126.5, 127.6, 128.3, 131.3, 131.5, 141.2 (s), 143.2 (s), 150.2 (s), 159.4 (s); IR (KBr) 3420 (sharp OH), 1685 (C=N); m.p. 82.5–84°; $[\alpha]_D^{25}$ = + 285.7° (*c*, 6.4 in $CHCl_3$). (Found: C, 64.63; H, 5.34. Calc for $C_{25}H_{24}BrNO_3$: C, 64.38; H, 5.19%.)

A white plate-like single crystal with no dimension exceeding 0.25 mm was used in the X-ray diffraction study. It crystallizes in the monoclinic system (C_2) with 8 molecules in a unit cell of dimensions: α = 15.692(3) Å; b = 10.933(3) Å; c = 28.748(3) Å; and β = 95.15(1) Å. Data was taken to a 2θ limit of 120°, resulting in 1681 independent and statistically significant pieces of data. The unit cell contains two crystallographically unique molecules (60 non-hydrogen atoms) which have been shown to be structurally identical. The structure was solved by heavy-atom methods utilizing the phases resulting from locating the bromine atom on each of the unique molecules. At the present stage

of refinement, the usual reliability index has a value of $R = 0.11$.[23]

The compound has three asymmetric carbons, two of which have known *S* configurations. This structure study proves that this compound (Fig. 1) has the configuration *SSS* of the possible diastereomers.

Phthalides **4**

General procedure for hydrolysis. A soln of crude **18** and/or **19** (2.3 mmol) in 40 ml saturated aqueous oxalic acid and 10 ml of THF was heated at reflux for 12–18 hr. After cooling, the soln was extracted with CH_2Cl_2, washed with 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated. The lactones were purified by preparative TLC or bulb-to-bulb distillation. Table 4 provides physical data for **4**.

Resolution of 3-methyl-3-phenyl phthalide **4**

A 66:34 mixture of **19**, obtained from **9** and acetophenone, (10.1 g, 26.1 mmol) was dissolved in EtOAc and placed in the freezer overnight. The ppt was collected by filtration and recrystallized twice from EtOAc to give 1.35 g (13%) of **19** (R=Me, R'=Ph) as a white solid: ^{1}H-NMR ($CDCl_3/D_2O$)δ, 1.72 (s, 3), 3.33 (s, 3), 3.40–3.70 (m, 2), 4.38–4.65 (m, 1), 4.99 (d, J = 5 Hz, 1), 7.03–7.63 (m, 13), 7.80–8.04 (m, 1); ^{13}C-NMR ($CDCl_3$)δ, 26.9 (q), 58.8 (q), 61.7 (d), 73.3 (t), 73.3 (d), 89.2 (s), 121.1, 123.5, 124.7, 126.3, 126.7, 127.6, 128.2, 128.9, 131.5, 142.0 (s), 142.7 (s), 150.7 (s), 160.0 (s); IR (KBr) 3100–3600 (broad OH), 1700 (C=N), 1300, 1125, 938 cm^{-1}; m.p. 145–146°, $[\alpha]_D = -110°$ (*c*, 5.8 in $CHCl_3$). (Found: C, 77.70; H, 6.53. Calc for $C_{25}H_{25}NO_3$: C, 77.50; H, 6.50%.)

The mother liquor was concentrated to provide a viscous yellow oil. Crystallization from hexane gave an off-white solid. Recrystallization (twice) from cyclohexane gave 0.98 g (10%) of **19** (R=Ph, R'=Me) as white needles: ^{1}H-NMR ($CDCl_3/D_2O$)δ, 1.91 (s, 3), 3.40 (s, 3), 3.49–3.82 (t, J = 6 Hz, 2), 4.36–4.69 (m, 1), 5.00 (d, J = 5 Hz, 1), 6.80–7.63 (m, 13), 7.89–8.06 (m, 1); ^{13}C-NMR ($CDCl_3$)δ, 27.0 (q), 58.8 (q), 61.7 (d), 72.8 (d), 73.2 (t), 89.0 (s), 121.0, 123.4, 124.2, 126.1, 126.6, 127.3, 127.7, 128.3, 128.6, 131.5, 142.1 (s), 143.2 (s), 150.9 (s), 159.9 (s); IR (KBr) 3480 (sharp OH), 1700, 1300, 1022 cm^{-1}; m.p. 95–96°; $[\alpha]_D = +298°$ (*c*, 6.5 in $CHCl_3$).

Compound R-(−)-**4**(R=Me, R'=Ph). Following the general procedure for acid hydrolysis 0.60 g (1.5 mmol) of **19**, 25 ml (34.7 mmol) of saturated aqueous oxalic acid, and 10 ml THF gave 0.33 g (96%) of *R*-(−)-**4** as a crystalline solid: ^{1}H-NMR ($CDCl_3$)δ, 1.90 (s, 3), 7.00–7.90 (m, 9); $[\alpha]_D = -66.3°$ (*c*, 1.0 in $CHCl_3$).

Compound S-(+)-**4**(R'=Me, R=Ph). In the above manner, 0.57 g of **19** (1.5 mmol) gave 0.34 g (100%) of *S*-(+)-**4**, as a solid, which was purified by bulb-to-bulb distillation (150°, 0.5 mm): ^{1}H-NMR ($CDCl_3$)δ, 1.90 (s, 3), 7.00–7.90 (m, 9); IR (KBr) 1768 (C=O) 1470, 1450, 1382, 937 cm^{-1}; m.p. 108°; $[\alpha]_D = +69.0°$ (*c*, 1.2 in $CHCl_3$). (Found: C, 80.58; H, 5.53. Calc for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39%.)

(5S)-2-(*Benzoyl*)*phenyl*-5-*phenyl*-2-*oxazoline* (**24**)

To a soln of 0.24 g (1.1 mmol) of **11** and 20 ml THF at −45° was added 0.61 ml (1.1 mmol) of n-BuLi. After 3.5 hr, 0.17 ml of ethyl benzoate was added to the dark red soln. The mixture was allowed to warm to 25°, poured into water, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Preparative TLC (silica gel, 20% acetone–hexane R_f 0.27) gave 0.07 g (20%) of **24** as a yellow oil: ^{1}H-NMR ($CDCl_3$)δ, 3.38–4.40 (m, 2), 5.20 (t, 1), 6.80–8.24 (m, 14); ^{13}C-NMR ($CDCl_3$)δ, 62.8 (t), 81.5 (d), 125.3, 125.5, 126.0, 126.2, 127.7, 127.9, 128.1, 128.4, 128.9, 129.1, 129.6, 130.9, 131.6, 132.5, 137.5, 139.8, 140.2, 162.4 (s), 196.6 (s).

Addition of methylmagnesium chloride to **24**

Preparation of (S)-**4** (R=Ph, R'=Me). To a soln of 0.07 g (0.20 mmol) of **24** and 5 ml THF at 45° was added 0.19 ml (0.46 mmol) of MeMgCl. After 2 hr at −45° was added 0.19 ml (0.46 mmol) of MeMgCl. After 2 hr at −45° and 1 hr at 25°, the soln was poured into sat NH_4Cl aq, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration gave 0.05 g (75%) of the imino lactone as an orange oil which was not purified. The diastereomeric ratio (73:27) was determined by expanding (2 ppm) and integrating the diastereomeric Me signals at 1.85 and 1.90 ppm. Following the general hydrolysis procedure, 52.2 mg of the iminolactone gave 30.5 mg of crude *S*-**4**. Preparative TLC (silica gel, CH_2Cl_2, R_f 0.37) produced 23.3 mg (68%) of phthalide whose $[\alpha]_D^{25} = 28.8°$ (*c*, 2.3, $CHCl_3$) which represented 40% ee, based on 69° for pure **4** obtained by resolution above.

Reduction of ketones **21** *with* K- *or* L-*Selectride to* **25**

General procedure. To a soln of 1.8 mmol of **21** in 15 ml of THF at −78° was added 4.0 mmol of *K*- or *L*-Selectride.® After 1 hr, 1 ml of MeOH was carefully added and the mixture allowed to warm to 25°. The solvent was removed *in vacuo* and the residue dissolved in 10 ml hexane. After cooling the solution to 0°, 3 ml 30% H_2O_2 and 2 ml 10% NaOH aq were added. The mixture was stirred overnight at 25°, poured into water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration provided **25** as a cloudy oil which was not purified. The diastereomeric ratio and absolute configuration were established by ^{1}H-NMR using the chemical shifts of the newly created asymmetric center. For **25** (R=t-Bu) the t-Bu signals appeared at δ 0.74 and 0.95 ($CDCl_3$). For **25** (R=Ph), the proton at the chiral center appeared as singlets at δ 6.29 and 6.15, the OMe group also showed two singlets at δ 3.38 and 3.23 ($CDCl_3$). For **25** (R=Me) the diastereomers could not be discerned by ^{1}H-NMR. The absolute configurations were determined by CD (for R=Ph) and comparison with known *S*-(−)-3-methylphthalide.[24] Hydrolysis of **25** was performed using oxalic acid as described in the general procedure to give *S*-**26** [R=Ph, $[\alpha]_D + 37.9°$ (*c*, 4.3, $CHCl_3$)]. The latter, as an 85:15 ratio (70% de) in **25** indicates that enantiomerically pure 3-phenyl phthalide should show an $[\alpha]_D$ of 54.1°. For

Table 4. Physical data for phthalides **4**[a]

R	R'	Mp, °C	Analysis Calculated C	Calculated H	Found C	Found H
H	Ph	113[b]	79.98	4.79	79.75	4.85
Me	p-BrC_6H_4	98-99°	59.43	3.66	59.51	3.40
Me	Et	Oil	74.98	6.86	74.68	6.63
Me	Ph	108[c]	80.34	5.39	80.15	5.19
Et	Ph	Oil	80.65	5.92	80.50	6.06

[a] IR spectra (KBr or film) showed carbonyl stretch at 1750-1760 cm^{-1}.

[b] W. H. Puterbaugh and C. R. Hauser, J. Org. Chem. 29, 853 (1964) report mp 115°.

[c] ibid; Report 77-78° for racemate, the above mp (108°) is for 99+%ee obtained by resolution below.

25 (R=Me) hydrolysis gave **26** (R=Me), $[\alpha]_D = -13.2°$ (*c*, 4.8, MeOH) 44% ee based on $-30°$ reported.[24] For **25** (R=t-Bu) the hydrolysis to **26** was not attempted.

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