Reductive Cleavage of Aryl Oxazolines to Benzaldehydes and Substituted Toluenes

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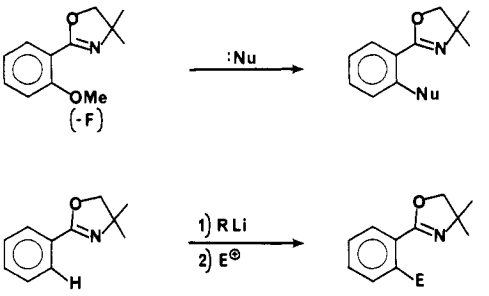
Aryl oxazolines have been converted to their corresponding benzaldehydes and toluenes by several routes by passing through the intermediate amino alcohols. The transformations proceeded under mild conditions and were shown to be generally applicable to a variety of substitutions on the aromatic nucleus.

Aryl oxazolines as a vehicle for the elaboration of suitably functionalized aromatic rings has been demonstrated by this group and others during the past 12 years.[1] As a functional protecting group for carboxylic acids, the oxazoline plays an important role in carbon–carbon bond forming reactions. The oxazoline can serve in an electrophilic sense to activate the aromatic ring toward nucleophilic aromatic substitution or in a nucleophilic sense via ortholithiation (Scheme I). Thus *o*-methoxy and *o*-fluoro oxazolines can be treated with a wide variety of nucleophiles to afford the corresponding ortho-substituted oxazolines whereas ortho lithiation of aryl oxazolines followed by treatment with electrophiles also provides the ortho-substituted derivative.

As an activator of aromatic rings toward substitution, the oxazoline also displays the requisite inertness to most reaction conditions. They are generally unreactive toward nucleophiles such as alkyl lithiums, Grignard reagents, alkoxides, amide bases, and most common laboratory reducing agents such as lithium aluminum hydride and sodium borohydride. They are also inert to mild acid hydrolysis conditions except in cases where a nucleophile is situated proximate to the oxazoline ring to assist in an internal ring opening.[2]

The most common means of oxazoline deprotection is strong acid hydrolysis to the corresponding benzoic acids.[3] This usually affords the acids in excellent yields except in the case of 2,6-disubstituted aryl oxazolines, which have proven difficult as hydrolysis proceeds only to the amide.[4] A base-induced hydrolysis has also been employed that involves conversion to the oxazolinium salt with methyl iodide followed by treatment with sodium hydroxide.[5] This method also fails with the hindered 2,6-disubstituted aryl oxazolines. Binaphthyl oxazolines have recently been converted to the corresponding binaphthyl alcohols in fair yields by acidic hydrolysis to the ester amine hydrochloride and direct reduction with lithium aluminum hydride.[6] Nordin[7] has reported the conversion of oxazolines to aldehydes via sodium borohydride reduction of the oxazolinium iodides. Although yields are generally good, preparation of the oxazolinium iodide is sometimes difficult and requires heating in nitromethane. Furthermore, reduction and hydrolysis with ortho substituents suffers from the same problem as acidic hydrolysis mentioned above. Most recently, Weinreb and Levin[8] have shown that oxazolines can be transformed to the corresponding carboxylic acids by treatment with sodium hypochlorite followed by basic hydrolysis of the intermediate ester.

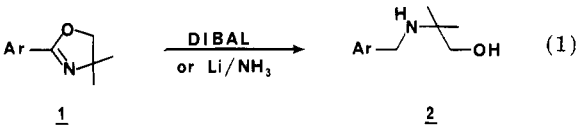
Scheme I



We now describe methods that result in the reductive cleavage of oxazolines to their corresponding benzaldehydes or toluenes. These reactions all proceed at room temperature and in good yields, thus extending the versatility and utility of oxazolines as activating and protecting groups.

Results and Discussion

We have observed that diisobutylaluminum hydride will reduce 2-aryl-4,4-dimethyl-2-oxazolines **1** and *trans*-(4*S*,5*S*)-2-aryl-4-(methoxymethyl)-5-phenyl-2-oxazolines **3** to the corresponding amino alcohols **2** and **4** in excellent yields (eq 1 and 2). The reaction is typically carried out



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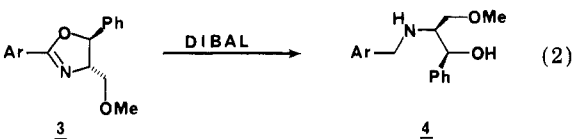

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using 3–5 equiv of DIBAL at room temperature in ether or hexane and is usually complete within a few hours. This complements the work of Pridgen[9] in which he demonstrates the use of diborane in refluxing THF to perform the same operation. As shown in Table I, the DIBAL reduction is compatible with various substituents and substitution patterns on the aromatic ring. In particular,

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(8) Levin, J. I.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 2347.
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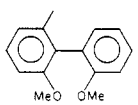
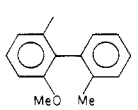
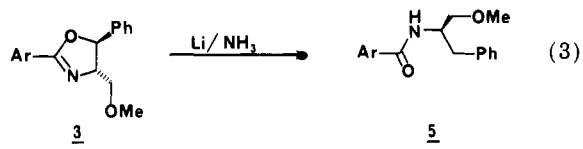
Table I. Reduction of Aryl Oxazolines 1 and 3 (eq 1 and 2)

oxazoline	aryl	reducing agent[c]	time, h	product (% yield)	mp, °C	^{1}H NMR ($CDCl_3$) of 2 and 4, δ
1a	C_6H_5	DIBAL Li/NH_3	2.5 0.5	2a (91) 2a (100)	55-57	1.12 (s, 6 H), 2.20-2.70 (br s, 2 H), 3.27 (s, 2 H), 3.60 (s, 2 H), 7.27 (s, 5 H)
1b	o-(n-Bu)C_6H_4	DIBAL	15	2b (95)	42.5-43.5	0.93 (br t, 3 H), 1.15 (s, 6 H), 1.20-2.00 (br m, 6 H), 2.63 (br t, 2 H), 3.30 (s, 2 H), 3.62 (s, 2 H), 6.97-7.28 (m, 4 H)
1c	o-(t-Bu)C_6H_4	Li/NH_3	2	2c (100)	61-62	1.15 (s, 6 H), 1.43 (s, 9 H), 1.70-1.90 (br s, 2 H), 3.29 (s, 2 H), 3.85 (s, 2 H), 7.10-7.40 (m, 4 H)
1d	p-$MeOC_6H_4$	DIBAL	3.5	2d (90)	57-58	1.30 (s, 6 H), 3.32 (br s, 2 H), 3.60 (br s, 2 H), 3.77 (s, 3 H), 6.73-7.37 (AB quartet, 4 H); NH and OH not detected
1e	m-ClC_6H_4	DIBAL	3.5	2e (100)	69-72	1.13 (s, 6 H), 3.33 (s, 2 H), 3.65 (s, 2 H), 7.15-7.37 (m, 4 H)
1f		DIBAL	3.5	2f (92)	98-100	1.12 (s, 6 H), 1.90-2.30 (br s, 2 H), 3.28 (s, 2 H), 3.55 (s, 2 H), 5.87 (s, 2 H), 6.65-6.85 (m, 3 H)
1g	o-(C_6H_5)C_6H_4	DIBAL	21	2g (90)	oil	0.97 (s, 6 H), 1.63 (br s, 2 H), 3.17 (s, 2 H), 3.57 (s, 2 H), 7.15-7.42 (m, 9 H)
1h		DIBAL	24	2h (70)[a]	72-72.5	1.10 (s, 6 H), 1.73-2.25 (m, 2 H), 2.40-2.80 (br s, 2 H), 2.73 (br t, 2 H), 3.30 (s, 2 H), 3.55 (s, 2 H), 4.03-4.27 (dd, 2 H), 6.53-7.10 (m, 3 H)
1i		DIBAL	12	2i (92)	105-106	1.15 (s, 6 H), 1.67-2.17 (br m, 2 H), 2.75 (br t, 2 H), 3.17-3.40 (m, 2 H), 3.32 (s, 2 H), 3.57 (s, 2 H), 6.33-6.93 (m, 3 H); NH and OH between 2.00 and 4.00
1j	1-naphthyl	DIBAL	24	2j (88)	oil	1.17 (s, 6 H), 2.10 (br s, 2 H), 3.28 (s, 2 H), 4.02 (s, 2 H), 7.13-8.17 (m, 7 H)
1k	2,6-$(Et)_2C_6H_3$	DIBAL Li/NH_3	18 0.33	2k (78) 2k (97)	40-41	1.17 (s, 6 H), 1.23 (t, J = 7 Hz, 6 H), 1.85 (br s, 2 H), 2.70 (q, J = 7 Hz, 4 H), 3.28 (s, 2 H), 3.63 (s, 2 H), 6.82-7.28 (m, 3 H)
1l	2,6-$(n\text{-}Pr)_2C_6H_3$	Li/NH_3	0.25	2l (91)	49-50	1.00 (t, 6 H), 1.18 (s, 6 H), 1.52-1.75 (m, 4 H), 2.57-2.73 (m, 4 H), 3.33 (s, 2 H), 3.68 (s, 2 H), 7.05-7.23 (m, 3 H), NH and OH not detected[b]
3a	o-BrC_6H_4	DIBAL	18	4a (95)	oil	2.58-2.87 (m, 1 H), 3.25 (s, 3 H), 2.97-3.52 (m, 4 H), 3.68, 3.88 (AB pattern, J_{AB} = 14 Hz, 2 H), 4.50 (d, J = 7 Hz, 1 H), 6.92-7 7.65 (m, 9 H)
3b	o-MeC_6H_4	DIBAL	12	4b (91)	oil	2.30 (s, 3 H), 3.27 (s, 3 H), 2.98-3.48 (m, 4 H), 3.60, 3.77 (AB pattern, J_{AB} = 12 Hz, 2 H), 4.47 (d, J = 7 Hz, 1 H), 7.02-7.45 (m, 9 H)
3c		DIBAL	5	4c (90)	oil	2.45-2.75 (m, 1 H), 2.85-3.80 (m, 6 H), 3.13 (s, 3 H), 3.67 (s, 6 H), 4.40 (d, J = 7 Hz, 1 H), 6.70-7.75 (m, 12 H)
3d		DIBAL	4	4d (90)	oil	1.97 (s, 3 H), 2.30-2.65 (m, 1 H), 2.81-3.47 (m, 6 H), 3.10 (s, 3 H), 3.63 (s, 3 H), 4.33 (d, J = 7 Hz, 1 H), 6.55-7.37 (m, 12 H)

[a] Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 70.99; H, 9.00. [b] 100-MHz NMR. [c] These reductions were run in ether except for 1b, hexane; 1i, toluene; 1k, xylene (at reflux temperature).

2,6-disubstituted aryl oxazolines (entries **1k** and **1l**) are readily reduced to the amino alcohols. In cases where the DIBAL reduction is sluggish, the use of lithium in ammonia offers advantages. The reaction of **1k** with DIBAL in hexane for several days or in xylene at reflux for 18 h affords a 78% yield of **2k** whereas reduction of **1k** with lithium in ammonia is rapid and provides a 97% yield of **2k**. The use of lithium in ammonia with chiral oxazolines **3a–d** affords only the amides **5a–d** as a result of benzyl ether cleavage (eq 3). Both reduction methods are less than satisfactory when the aromatic ring contains a methoxy group in the ortho position. When the reduction



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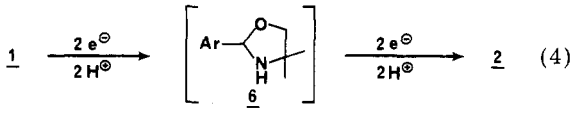
of *o*-methoxyphenyloxazoline is attempted with DIBAL, loss of the methyl group is a significant side reaction. Use of Li/NH_3 results in reductive cleavage of the methoxy group in addition to oxazoline reduction. In cases where the oxygen is part of a ring or other than ortho situated, this side reaction is absent with DIBAL reduction under our conditions.

The reduction of the oxazolines **1** to the amino alcohols **2** involves a four-electron transfer and thus requires 2 equiv of reducing agent (eq 4). Presumably the first stage in



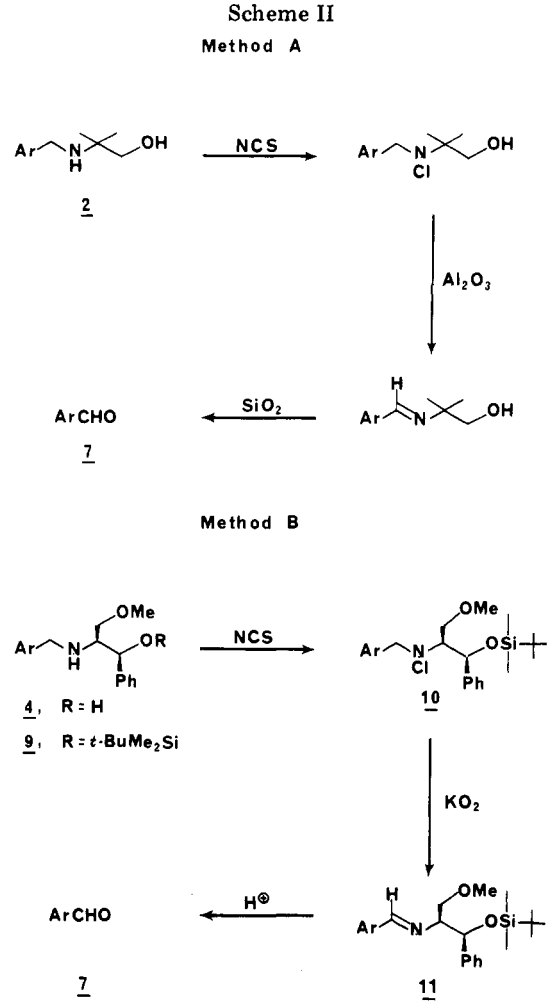
(4)

the reduction proceeds to the oxazolidine **6**, which is then reduced to the amino alcohol **2**. When the reduction of the oxazoline **1** was quenched prior to completion, only the oxazoline **1** and the amino alcohol **2** were observed (^1H NMR), indicating that the rate of reduction of oxazolidine **6** is faster than the rate of reduction of oxazoline **1** and that interrupting the reaction after the first reduction to **6** would not be practical.

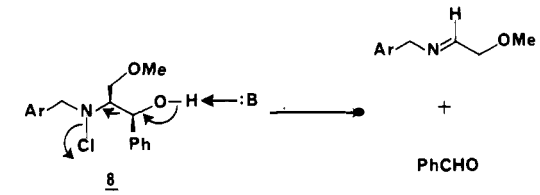
Conversion of benzylamines to benzaldehydes has been accomplished by several groups.[10] Transamination reactions involving prototropic rearrangement and equilibration of Schiff base intermediates utilizing pyridine-2-carboxaldehyde[11] and 4-formyl-1-methylpyridinium benzenesulfonate[12] have been employed but proceed only with primary amines. The use of sulfinamides has been demonstrated, but imine formation required use of refluxing xylene.[13] Bachmann[14] has shown that primary amines can be converted into carbonyl compounds by N-chlorination with *tert*-butyl hypochlorite, elimination with refluxing sodium ethoxide in ethanol, and hydrolysis of the resultant imine with refluxing 10% sulfuric acid solution.

Utilizing a modification of the Bachmann procedure, we have been able to transform the amino alcohols **2** to their benzaldehydes under very mild conditions. As depicted in Scheme II (method A), N-chlorination with *N*-chlorosuccinimide, elimination with basic alumina, and hydrolysis and purification by filtration through a small column of silica gel furnishes the desired aldehyde. The reactions are all carried out in one pot in methylene chloride at room temperature and afford generally good yields of the benzaldehydes **7**. From Table II, the method is seen to be applicable to a wide range of arylamino alcohols and results in an overall transformation of the oxazolines **1** to the benzaldehydes **7** in 56–84%. Unfortunately the chiral amino alcohols **4a–d** afforded only variable yields of benzaldehydes **7** due to a competing Grob fragmentation[15] of the *N*-chloramine **8**. The persistence of the Grob-type fragmentation in this series, not observed in the achiral amino alcohols, may be attributable to a transition state

Scheme II



that is reached late for this process in which substantial formation of the new carbon–oxygen double bond has taken place. This stabilization by the adjacent aromatic ring presumably lowers the activation energy for the fragmentation reaction (eq 5). In all cases the Grob-type



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fragmentation accounted for 15–20% of the reaction as evidenced by the presence of benzaldehyde in the ^1H NMR spectrum. Although several elimination conditions were employed, the fragmentation could not be completely suppressed and we were forced to slightly alter the route.

As shown in Scheme II (method B), a simple modification involving the amino alcohol led to an equally efficient route to aldehydes. The alcohol was protected as the *tert*-butyldimethylsilyl ether **9**, which eliminates any possibility of fragmentation. Although protection as the trimethylsilyl ether would have been desirable, it was found that this derivative did not survive subsequent reaction conditions. At this point, chlorination of **9** with *N*-chlorosuccinimide afforded the *N*-chloramine **10** without event; however, dehydrochlorination using basic alumina was unsuccessful. We also find that when the achiral amino alcohols **2** are protected as their *tert*-butyldimethylsilyl ethers, no elimination reaction occurs. This establishes the importance of the hydroxyl group in the

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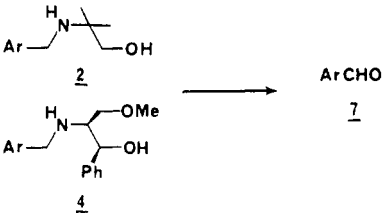
(15) Franck, R. W.; Rizzi, G. P.; Johnson, W. S. *Steroids* **1964**, *4*, 463. Masamune, T.; Takasugi, M.; Mori, Y. *Tetrahedron Lett.* **1965**, 489.

Table II. Formation of Aldehydes 7



amino alcohol	oxidation method[a]	chlorination time, min	elimination time, h	product (% yield)	^{1}H NMR ($CDCl_3$) of 7, δ
2a	A	8	0.2	7a (83)[b]	7.40-7.90 (m, 5 H), 9.95 (s, 1 H)
2b	A	15	3	7b (76)[c]	0.65-1.90 (m, 7 H), 2.95 (br t, J = 7 Hz, 2 H), 7.05-7.95 (m, 4 H), 10.23 (s, 1 H)
2c	A	15	12	7c (84)[d]	1.50 (s, 9 H), 7.15-7.52 (m, 3 H), 7.76-8.00 (m, 1 H), 10.80 (s, 1 H)
2d	A	10	0.33	7d (78)[e]	3.83 (s, 3 H), 6.83-7.10 (d, 2 H), 7.67-7.93 (d, 2 H), 9.83 (s, 1 H)
2e	A	22	0.1	7e (68)[f]	7.15-7.88 (m, 4 H), 9.92 (s, 1 H)
2f	A	6	0.33	7f (67)[g]	5.98 (s, 2 H), 6.75-7.12 (m, 3 H), 9.68 (s, 1 H)
2g	A	43	2	7g (84)[h]	7.17-8.08 (m, 9 H), 9.74 (s, 1 H)
2k	A	10	8	7k (73)[i]	1.28 (t, J = 7 Hz, 6 H), 2.95 (q, J = 7 Hz, 4 H), 6.84-7.60 (m, 3 H), 10.57 (s, 1 H)
2l	A	39	24	7l (63)[j]	0.77-1.17 (br t, 6 H), 1.17-2.07 (m, 4 H), 2.70-3.07 (m, 4 H), 6.90-7.13 (m, 3 H), 10.50 (s, 1 H)
4a	B			7m (75)[k]	7.21-8.07 (m, 4 H), 10.27 (s, 1 H)
4b	B			7n (72)[l]	2.61 (s, 3 H), 7.05-7.85 (m, 4 H), 10.21 (s, 1 H)
4c	B			7o (70)[m]	3.67 (s, 3 H), 3.72 (s, 3 H), 6.71-7.67 (m, 7 H), 9.63 (s, 1 H)
4d	B			7p (70)[n]	2.07 (s, 3 H), 3.75 (s, 3 H), 7.00-7.74 (m, 7 H), 9.57 (s, 1 H)

[a] Method A: *N*-chlorosuccinimide; alumina; silica gel. Method B: *tert*-Butyldimethylsilyl chloride; *N*-chlorosuccinimide; potassium superoxide; oxalic acid. [b] Identical with authentic sample. [c] Semicarbazone mp 138-138.5 °C corrected (lit.[22] mp 139-140 °C). [d] Semicarbazone mp 185-186.5 °C corrected (lit.[23] mp 187 °C). [e] Identical with authentic sample. [f] Semicarbazone mp 226-227 °C corrected (lit.[24] mp 228 °C). [g] Semicarbazone mp 227.5-228.5 °C corrected (lit.[25] mp 230 °C). [h] Semicarbazone mp 206-207.5 °C corrected (lit.[26] mp 208-209 °C). [i] Semicarbazone mp 153-154 °C corrected. Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81. Found: C, 65.63; H, 8.15. [j] Semicarbazone mp 153-154 °C corrected. Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56. Found: C, 67.32; H, 8.27. Repeated attempts to reach acceptable limits were fruitless. [k] Silyl ether (94%): ^{1}H NMR ($CDCl_3$) δ -0.27 (s, 3 H), 0.00 (s, 3 H), 0.83 (s, 9 H), 2.65-3.55 (m, 4 H), 3.17 (s, 3 H), 3.77 (s, 2 H), 4.80 (d, J = 6 Hz, 1 H), 6.87-7.67 (m, 9 H); aldehyde was identical with authentic sample. [l] Silyl ether (98%): ^{1}H NMR ($CDCl_3$) δ -0.21 (s, 3 H), 0.02 (s, 3 H), 0.91 (s, 9 H), 2.25 (s, 3 H), 2.54-3.45 (m, 4 H), 3.19 (s, 3 H), 3.65 (s, 2 H), 4.75 (d, J = 6 Hz, 1 H), 6.83-7.64 (m, 9 H); aldehyde was identical with authentic sample. [m] Silyl ether (92%): ^{1}H NMR ($CDCl_3$) δ -0.23 (s, 3 H), 0.00 (s, 3 H). 0.87 (s, 9 H), 2.45-2.87 (m, 3 H), 3.10 (s, 3 H), 3.49 (s, 2 H), 3.65 (s, 6 H), 4.78 (d, J = 6 Hz, 1 H), 6.70-7.41 (m, 12 H). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.41; H, 5.93. [n] Silyl ether (80%): ^{1}H NMR ($CDCl_3$) δ -0.23 (s, 3 H), 0.00 (s, 3 H), 0.89 (s, 9 H), 1.95 (s, 3 H), 2.57-2.95 (m, 3 H), 3.10 (s, 3 H), 3.32 (s, 2 H), 3.65 (s, 3 H), 4.75 (d, J = 6 Hz, 1 H), 6.67-7.45 (m, 12 H). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.67; H, 6.19.

elimination, which may assist in an internal deprotonation or may chemically bond to the alumina surface resulting in a lowering of the entropy of activation for the elimination.[16] This problem was circumvented by utilizing the method of Scully[17] for chloramine elimination using potassium superoxide in ether. At room temperature the elimination is usually complete within 2–3 h. This affords the imine 11, which is not isolated but immediately hydrolyzed to the benzaldehydes 7 by using saturated oxalic acid. Although an extra step was now involved, method B results in the transformation of oxazolines 3 to the benzaldehydes 7 in an overall yield of 63–71%. This technique appears to have the potential to be useful for both chiral and achiral 2-alkyl oxazolines which have been successfully employed in asymmetric syntheses.[6,18]

As benzylamines, the amino alcohols 2 and 4 should be reducible in catalytic hydrogenation.[19] Debenzylation of amino alcohols 2 was accomplished by using hydrogen with a palladium catalyst and furnished the toluenes 12 (eq 6)

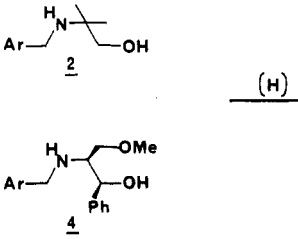


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Table III. Conversion of Amino Alcohols 2 and 4 to Toluenes 12 (eq 6)

amino alcohol	reduction method[a]	time, h	product (% yield)	^{1}H NMR ($CDCl_3$) of 12, δ
2b	A	19	12b (29)[c]	0.70-1.10 (m, 3 H), 1.20-1.80 (m, 4 H), 2.27 (s, 3 H), 2.55 (br t, 2 H), 7.07 (s, 4 H)
2d	A	12	12d (81)[d]	2.25 (s, 3H), 3.67 (s, 3 H), 6.62-7.22 (m, (m, 4 H)
2e	A	0.25	b	
2f	A	6	12f (91)[e]	2.25 (s, 3 H), 5.82 (m, 2 H), 6.42-6.78 (m, 3 H)
2g	A	21	12g (87)[f]	2.30 (s, 3 H), 7.25 (s, 4 H), 7.35 (s, 5 H)
2i	A	12	12i (78)[g]	1.70-2.17 (m, 2 H), 2.07 (s, 3 H), 2.77 (br t, 2 H), 3.33 (br t, 2 H), 6.33-7.06 (m, 3 H)
2j	A	8	12j (88)[h]	2.67 (s, 3 H), 7.17-8.13 (m, 7 H)
2k	A	12	i	
4c	B	96	12l (71)[j]	1.93 (s, 3 H), 3.63 (s, 3 H), 3.70 (s, 3 H), 6.65-7.40 (m, 7 H)
4d	B	120	12m (75)[k]	1.93 (s, 3 H), 2.00 (s, 3 H), 3.67 (s, 3 H), 6.67-7.45 (m, 7 H)

[a] Method A: Pd-H_2 reduction. Method B: Pd-formic acid-methanol. [b] Toluene (4%) and amino alcohol **2a** (75%) were the only products recovered. [c] n^{20}_D 1.496 (5) (lit.[27] n^{20}_D 1.4958). [d] n^{19}_D 1.5122 (lit.[28] n^{20}_D 1.5124). [e] bp 82 °C (7 mm) (lit.[29] bp 81-83 °C (11 mm)); n^{16}_D 1.5324 (lit.[29] n^{16}_D 1.53165). [f] *o*-Phenyltoluene obtained was oxidized to the acid: mp 108-109 °C (lit.[30] mp 110 °C). [g] The benzoyl derivative was prepared: mp 105-106.5 °C (lit.[31] mp 108 °C). [h] Identical with an authentic sample. [i] Amino alcohol **2k** was resistant to debenzylation by method A or B and was recovered unchanged. [j] Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.62; H, 7.26. [k] Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.77; H, 7.71.

(Table III). As seen from the table, this conversion is limited to substrates that are not heavily substituted. Nevertheless, with most substrates, the reaction proceeds smoothly to afford the toluenes **12** in 72–82% from the oxazolines **1**. Again, the chiral amino alcohols **4**, with their increased substitution, proved to be substantially different in reactivity and showed little or no debenzylation under these conditions. However, catalytic transfer hydrogenation using formic acid in methanol[20] proved to be effective, and chiral oxazolines **3** were converted to their toluenes **12** in overall yield of 63–68%.

In summary, we have shown that aryl oxazolines can be reductively cleaved via their amino alcohols to either the corresponding benzaldehydes or toluenes. The procedures are extremely facile and are carried out under mild conditions.

Experimental Section

General Methods. DIBAL was used as a 1 M solution in hexane obtained from Aldrich Chemical Co., or in some cases the solution was prepared from pure DIBAL obtained from Alfa Products, Ventron Corporation. Alumina used in the eliminations is Baker Alumina, Brockmann Activity 1 (pH 9.5–10.5), and the silica gel used in the hydrolysis is Woelm silica gel 60 for medium-pressure chromatography. The oxazolines employed in this study were all prepared as previously described.[1,4,6,21] All NMR spectra are 60 MHz unless stated otherwise.

Reduction of Oxazolines 1a–l and 3a–d with DIBAL. General Procedure. To 1 mmol of oxazoline in 5 mL of ether (unless otherwise specified) at 0 °C under an inert atmosphere was added DIBAL (3 mmol for **1a–l** and 5 mmol for **3a–d**). The reaction was allowed to stir at room temperature and monitored for the disappearance of the oxazoline by thin-layer chromatography on silica gel. The solution was cooled to 0 °C and slowly quenched with 1 M HCl to destroy excess DIBAL and solubilize the aluminum salts. The layers were separated, and the aqueous layer was made alkaline with 5 M NaOH, extracted with ether, washed with brine, and dried with K_2CO_3 to give, after concentration, the amino alcohols **2a–l** and **4a–d**. The amino alcohols obtained in this manner required no further purification and were taken on to the aldehydes **7** and the aryl methyls **12**. Reductions to the amino alcohols were run on a 0.5–10.0-mmol scale with reagents scaled proportionately.

Reduction of Oxazolines 1a,k,l with Lithium in Ammonia. General Procedure. To 1.0 mmol of oxazoline in 5 mL of THF was condensed ca. 20 mL of liquid ammonia. Then 5.0 mmol of lithium wire were added in small pieces. After 20 min the reaction was quenched with ethanol or water and the ammonia allowed to evaporate. The residue was extracted with ether, washed with brine, dried (K_2CO_3), and concentrated to give the amino alcohol **2a,k,l**. The amino alcohols **2a,k** thus obtained were found to be identical with those obtained from the DIBAL reduction. Reductions were run on a 1.0–5.0-mmol scale with reagents scaled proportionately.

Preparation of Aldehydes 7a–l from Amino Alcohols 2a–l. General Procedure (Method A). To 0.5 mmol of amino alcohol in 2 mL of methylene chloride at room temperature was added 0.5 mmol of *N*-chlorosuccinimide (NCS). The reaction was stirred and monitored for the disappearance of the amino alcohol by silica gel TLC. Then 2 g of alumina was added with stirring and the reaction again monitored for the disappearance of the *N*-chloramine by silica gel TLC. The mixture was then filtered through a column of ca. 3 cm of silica gel and the filtrate concentrated to give pure aldehydes **7a–l**. Conversion of the amino alcohols to the aldehydes was run on a 0.2–1.2-mmol scale with reagents scaled proportionately.

Preparation of Aldehydes 7m–p from Amino Alcohols 4a–d. General Procedure (Method B). To 1.0 mmol of the amino alcohol in 5 mL of THF was added 2.1 mmol of *tert*-bu-

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tyldimethylsilyl chloride and 2.2 mmol of imidazole. The reaction was stirred for 12 h at room temperature under a nitrogen atmosphere. The mixture was then diluted with ether, washed with saturated sodium bicarbonate and brine, and dried over magnesium sulfate. Purification by silica gel column chromatography (25% EtOAc–hexane) afforded silyl ethers **9a–d**.

To 1.0 mmol of silyl ether **9** in 2 mL of methylene chloride was added 1.0 mmol of NCS and the reaction stirred for 15 min. Filtration through a small plug of silica gel and concentration afforded chloramine **10**. This product was dissolved in 5 mL of ether; then 2.2 mmol of potassium superoxide and 5 mg of 18-crown-6 were added and the reaction was stirred at room temperature for 3–6 h. Filtration and concentration afforded the imine **11**, which was directly hydrolyzed to the aldehyde **7** by stirring in 1:1 saturated oxalic acid–pentane at room temperature for 12 h. The organic layer was separated, washed with sodium bicarbonate, dried ($MgSO_4$), and concentrated to afford the aldehyde **7**, which was purified by silica gel thin-layer chromatography (25% Et_2O–hexane). Conversion of the amino alcohols to the aldehydes was run on a 0.4–1.0-mmol scale with reagents scaled proportionately.

Catalytic Hydrogenation of Amino Alcohols 2a–l. General Procedure. To 5.0 mmol of the amino alcohol and 25 mL of absolute ethanol with 2.5 mL of pH 7 buffer in a Fisher–Porter hydrogenation bottle was added 200 mg of 5% palladium on charcoal. The bottle was pressurized with hydrogen to 50 psi and stirred at room temperature while monitoring for the disappearance of the amino alcohol by silica gel TLC. The flask was then depressurized, and the contents were filtered and taken up in methylene chloride, washed with water, 1 M HCl, and brine, dried ($MgSO_4$), and concentrated to give the toluene **12**. These reactions were run on a 3.3–5.0-mmol scale with the exception of **2i**, which was run on a 0.2-mmol scale with all reagents scaled proportionately.

Catalytic Hydrogenation of Amino Alcohols 4a–d. General Procedure. To 0.4 mmol of the amino alcohol was added 5 mL of 4.4% formic acid in methanol followed by 150 mg of 10% palladium on charcoal. The reaction was stirred at room temperature under a nitrogen atmosphere. Filtration, concentration, and purification by preparative layer chromatography using 15% ether–hexane afforded the toluene **12**.

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Registry No. **1a**, 19312-06-2; **1b**, 57629-47-7; **1c**, 87306-63-6; **1d**, 53416-46-9; **1e**, 80762-49-8; **1f**, 85588-72-3; **1g**, 57598-40-0; **1h**, 75948-75-3; **1i**, 75934-10-0; **1j**, 87306-64-7; **1k**, 66464-27-5; **1l**, 87306-65-8; **2a**, 10250-27-8; **2b**, 87306-66-9; **2c**, 87306-67-0; **2d**, 25452-29-3; **2e**, 87306-68-1; **2f**, 87306-69-2; **2g**, 87306-70-5; **2h**, 87306-71-6; **2i**, 87306-72-7; **2j**, 87306-73-8; **2k**, 87306-74-9; **2l**, 87306-75-0; **3a**, 77250-60-3; **3b**, 87306-76-1; **3c**, 87306-76-1; **3d**, 87306-77-2; **4a**, 87306-78-3; **4b**, 87306-79-4; **4c**, 87306-80-7; **4d**, 87306-81-8; **7a**, 100-52-7; **7b**, 59059-42-6; **7b** semicarbazone, 69621-96-1; **7c**, 16358-79-5; **7c** semicarbazone, 16678-37-8; **7d**, 123-11-5; **7e**, 587-04-2; **7e** semicarbazone, 16678-40-3; **7f**, 120-57-0; **7f** semicarbazone, 16742-62-4; **7g**, 1203-68-5; **7g** semicarbazone, 2928-48-5; **7k**, 87306-82-9; **7k** semicarbazone, 87306-86-3; **7l**, 87306-83-0; **7l** semicarbazone, 87306-87-4; **7m**, 6630-33-7; **7n**, 529-20-4; **7o**, 87306-84-1; **7p**, 87306-85-2; **9a**, 87306-88-5; **9b**, 87306-89-6; **9c**, 87306-90-9; **9d**, 87306-91-0; **10a**, 87306-92-1; **10b**, 87306-93-2; **10c**, 87306-94-3; **10d**, 87306-95-4; **11a**, 87306-96-5; **11b**, 87306-97-6; **11c**, 87306-98-7; **11d**, 87306-99-8; **12b**, 1595-11-5; **12d**, 104-93-8; **12f**, 7145-99-5; **12g**, 643-58-3; **12i**, 52601-70-4; **12j**, 90-12-0; **12l**, 87307-00-4; **12m**, 38324-52-6; *o*-phenylbenzoic acid, 947-84-2; 1-benzoyl-8-methyl-1,2,3,4-tetrahydroquinone, 87307-01-5.

Palladium-Catalyzed Carbonylation. A New Synthesis of α-Methylene γ-, δ-, and ε-Lactams and -Lactones Including Bicyclic Lactams of Pyrrolizidine and Indolizidine Skeletons

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The insertion of carbon monoxide into vinyl halides bearing the secondary amine or alcohol with a catalytic amount of $Pd(OAc)_2$ and PPh_3 was realized to give five-, six-, and seven-membered lactams and lactones carrying α-methylene groups in fairly good yields. Bicyclic heterocycles, pyrrolizidine and indolizidine derivatives, were also synthesized from pyrrolidine and piperidine derivatives possessing vinyl halide groups in the side chain at the 2-position of the ring by means of palladium-catalyzed carbonylation.

Many biologically active substances possessing α-methylene carbonyl groups are found in natural sources,[1] and a number of synthetic methods for these compounds have been reported.[2] We now describe details of an efficient synthesis of α-methylene γ-, δ-, and ε-lactams and -lactones by utilization of palladium-catalyzed carbonylation, which was already successfully applied to the synthesis of α-methylene β-lactams, important precursors of 3-amino-nocardicinic acid (3-ANA),[3a] as an extension of syntheses of heterocycles with organometallic compounds developed in this laboratory.[3] The method proved to be potentially available for the synthesis of bicyclic lactams of pyrrolizidine and indolizidine skeletons also. In the meantime, several other groups have independently reported

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