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Synthesis of Heavily Substituted 1,2-Amino Alcohols in Enantiomerically Pure Form

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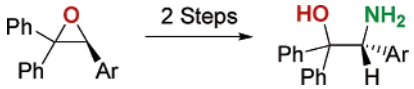


A simple and convenient methodology for the preparation of optically pure 2-amino-2-aryl-1,1-diphenylethanols is presented. Allylamine was found to produce the ring-opening of triaryloxiranes in a regioselective and a stereospecific fashion. Removal of the allyl protecting group provided the free 1,2-amino alcohols in enantiomerically pure form.

1,2-Amino alcohols are among the most valuable chiral building blocks for asymmetric synthesis and catalysis.[1] A large number of chiral auxiliaries and ligands hold 1,2-amino alcohols as stereogenic fragments (Figure 1). Oxazolidinone chiral auxiliaries (**1**), BOX ligands (**2**), and Salen-type ligands (**3**) exemplify the importance of these structures as building blocks.[2] Furthermore, β-amino alcohols are efficient catalysts for the ligand accelerated addition of dialkyzinc species to carbonyls.[3]

Our group has developed families of modular chiral amino alcohols for this and other transformations, starting from synthetic enantiopure epoxides.[4] Among these, the bulky 2-piperidino-1,1,2-triphenylethanol (**4**), containing a diphenylcarbynol moiety, is one of the most active catalysts for the asymmetric addition of dialkyl

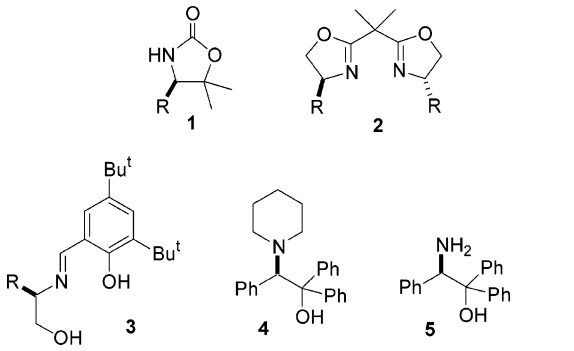
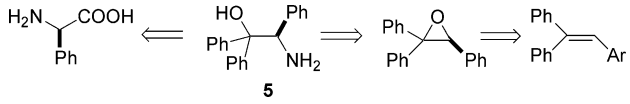


FIGURE 1.

SCHEME 1



and diarylzinc to aldehydes.[5] Our recent studies indicate that the bulky triaryl structure in **4** is responsible for this high catalytic activity.[6] To extend the use of congested 1,2-amino alcohols as a common building block for other applications, an efficient synthesis of 2-amino-1,1,2-triarylethanol structures is required.

Traditionally, the synthesis of highly substituted 1,2-amino alcohols is carried out from natural amino acids by nucleophilic attack of the carboxylic moiety with a Grignard or alkyllithium reagent[7] (Scheme 1). For example, the synthesis of 2-amino-1,1,2-triphenylethanol (**5**) has been reported from phenylglycine and 10 equiv of PhMgBr.[8] However, this approach has several drawbacks. It requires a large excess of Grignard reagent, and more significantly, the use of an optically pure amino acid as starting material limits the final structures that can be acceded to commercially available amino acids. Given that for many applications the nitrogen atom in the amino alcohol moiety acts as the metal chelating element it would be of great interest to modify at will the electronic and steric properties of the amino group. An alternative oxirane ring-opening approach should, in principle, allow for an efficient introduction of diversity in the 2 position, since different aryl groups can be introduced at that center at the olefin construction stage (Scheme 1). However, reliable procedures for the introduction of primary amino groups via ring-opening of sterically congested epoxides are not available. In this context, here we report the development of a simple and

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SCHEME 2

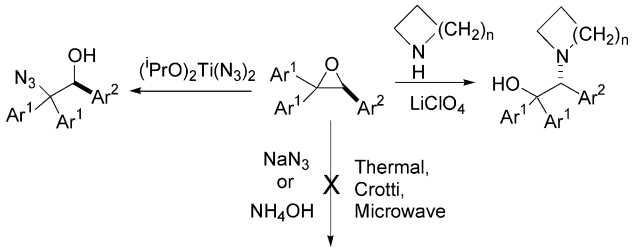
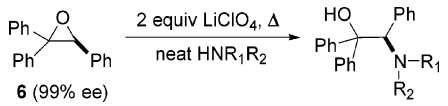


TABLE 1. Ring-Opening of (*S*)-Triphenylethylene Oxide with Various Ammonia Equivalents



6 (99% ee)

entry	R_1	R_2	*T* (°C)	time (h)	yield (%)[a]	product
1	Bn	H	140	24	70	**7**
2	PMB	H	140	24	72	**8**
3[b]	allyl	H	120	24	97	**9**
4	allyl	allyl	120	72	47	**10**

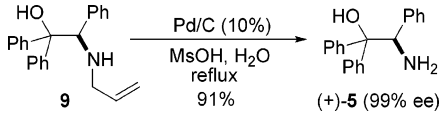
[a] Yields refer to compounds purified by flash chromatography. [b] Allylamine has a boiling point of 53−54 °C. Heating the reaction to 120 °C produces an overpressure of approx 1.5 bar. The reaction was regularly run in a glass pressure tube.

general synthesis of 2-amino-2-aryl-1,1-diphenylethanol structures from the corresponding optically pure oxiranes (Scheme 1).

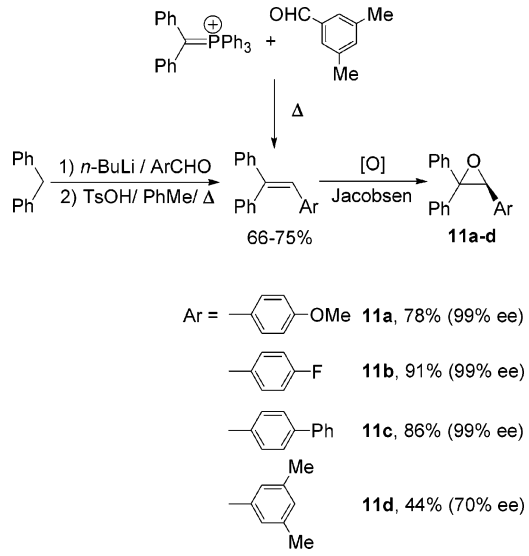
We have reported several examples of stereospecific ring-opening of triarylethylene oxides (Scheme 2). Whenever a cyclic, secondary amine is involved as the nucleophile in this process, the reaction occurs regioselectively, the less substituted carbon of the epoxide being exclusively[5a] or preferentially[4d] attacked. The reaction failed, however, for ammonia and other standard ammonia equivalents. The use of sodium azide under thermal conditions, Crotti conditions,[9] or microwave activation led to no detectable levels of reaction on triphenylethylene oxide. Much in the same way, aqueous ammonia under thermal or microwave activation (pressure tube in both cases) was also ineffective.[10] In contrast, reaction with diisopropoxytitanium diazide provided stereospecifically an azide ring-opening product with opposite regiochemistry (Scheme 2).[4c]

To overcome this limitation, and in search for a large-scale, safe process leading to **5**, a series of benzylic and allylic ammonia equivalents were studied for the ring-opening of **6** (Table 1). Initial experiments under the original Crotti conditions ($LiClO_4$, 70 °C, acetonitrile) failed to yield any of the ring-opening products. In contrast, good yields of the corresponding amino alcohols were obtained when the reaction was run at higher temperatures (120−140 °C) using the nucleophilic amine as a solvent (Table 1). Primary benzylic and allylic amines gave better results and provided in good yield the reaction products resulting from ring-opening at the less

SCHEME 3



SCHEME 4



substituted carbon. Among these reagents, allylamine afforded amine **9** in an excellent 97% yield (Table 1, entry 3). Secondary amines such as diallylamine gave, in general, lower yields even when reaction times were extended (Table 1, entry 4).

Removal of the amino-protecting group from **7**, **8**, and **9** was next examined. While benzylic-protecting groups for **7** and **8** yielded complex reaction mixtures under hydrogenolytic (H_2, Pd/C) and oxidative conditions (DDQ, CAN), for **9**, double bond isomerization and imine hydrolysis in water provided **5** in 91% yield (Scheme 3). Most rewardingly, chiral HPLC analysis of the amino alcohol product confirmed that no racemization had taken place either in the initial epoxide ring-opening step with allylamine or in the deprotection of the allyl group with Pd/C in the presence of methansulfonic acid in refluxing water.[11]

To determine the scope of the present sequence for the synthesis of 2-amino-2-aryl-1,1-diphenylethanols, several triarylethylene oxides were prepared from the corresponding olefins by Jacobsen epoxidation (Scheme 4).[12] Metalation of diphenylmethane with *n*-BuLi and reaction with the appropriate aromatic aldehyde provided an intermediate secondary alcohol that, upon dehydration (TsOH in toluene at reflux), afforded the corresponding alkene precursors in good overall yields. Alternatively, the synthesis of 1-(3,5-dimethylphenyl)-2,2-diphenylethene was performed under Wittig olefination conditions. Asymmetric salen-manganese-catalyzed epoxidation of the resulting olefins provided the oxirane substrates in moderate to excellent yields (44−91%) and enantiomeric

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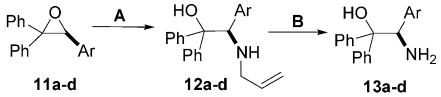
TABLE 2. Synthesis of 2-Amino-2-aryl-1,1-diphenylethanols[a]



11a-d 12a-d 13a-d

Entry	Epoxide	Yield (%)[b] step A	Yield (%)[b] Step B	Product	Rotation
1	**11a**	99	61	**13a**	(+)
2	**11b**	95	74	**13b**	(+)
3	**11c**	75	64	**13c**	(+)
4	**11d**	90	66	**13d**	(+)

[a] Conditions A: Allylamine (10 equiv), $LiClO_4$ (2 equiv), 120 °C in a pressure tube, 24 h. Conditions B: 5 mol % Pd/C, MsOH (2 equiv), H_2O, reflux. [b] Yields refer to isolated crystalline compounds of >95%. Purity as determined by elemental analysis.

excess between 70 and 91% ee. In most cases, a single crystallization sufficed to afford enantiomerically pure (99% ee) products.

With these oxirane substrates in hand, the ring-opening with allylamine and subsequent deprotection sequence was assayed (Table 2). Reaction with allylamine was monitored by TLC for the disappearance of the starting material (approximately 24 h) and afforded the corresponding secondary allylamines as crystalline solids in high yields (70−99%). Allyl deprotection was effected in refluxing water, the propanal produced being continuously removed from the reaction medium with the aid of a small stream of inert gas. The resulting 1,2-amino alcohols were obtained as crystalline solids in high optical purity.[13]

In summary, we demonstrated here that allylamine is an effective synthetic equivalent of ammonia for the transformation of epoxides into 1,2-amino alcohols. For encumbered oxirane rings in which azide fails to provide ring-opening products, allylamine produces a smooth stereospecific reaction. The present methodology is a simple and convenient technique for the preparation of bulky 2-amino-2-aryl-1,1-diphenylethanols and is the only method currently available when the corresponding arylglycines are not accessible in enantiomerically pure form.

Experimental Section

(*R*)-2-(Allylamino)-1,1,2-triphenylethanol (9). A glass pressure tube equipped with a stirring bar was charged with (*S*)-2,2,3-triphenyloxirane **5** (0.500 g, 1.84 mmol), $LiClO_4$ (0.391 g, 3.67 mmol), and allylamine (1.4 mL, 18.40 mmol). The suspension was then stirred at 120 °C overnight. The resulting solution solidified when cooled to room temperature. The crude was then disolved in dichloromethane, and the organic layer was washed successively with brine. The organics were dried ($MgSO_4$) and removed together with the excess amine (bp 53 °C) under vaccum. The pure product was obtained as a white solid in 97% yield (0.590 g, 1.8 mmol); 99% ee. mp = 110−112 °C; $[\alpha]_D$ +168.9 (*c* 0.945, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7 Hz, 2H), 7.40 (t, J = 8 Hz, 2H), 7.28 (m, 1H), 7.15−6.95 (m,-10H), 5.80 (m, 1H), 5.00 (m, 2H), 4.70 (s, 1H), 4.30 (broad s, 1H), 3.10 (dd, J = 14 Hz, J' = 5 Hz, 1H), 2.98 (dd, J = 14 Hz, J' = 7 Hz, 1H), 1.60 (broad s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8 (C), 143.5 (C), 137.5 (C), 136.2 (CH), 129.5 (CH), 128.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 127.2 (CH), 126.6 (CH), 126.2 (CH), 126.1 (CH), 116.4 (CH_2), 79.9 (C), 68.1 (CH), 49.4 (CH2) ppm; IR (KBr) ν_{max} 3400, 3100, 2850, 1489 cm^{-1}; MS (CI−NH_3) *m/z*: 329 [(M)$^+$, 100%]; HRMS (CI−CH_4): calcd for $C_{23}H_{23}NO$ (M + H$^+$) 330.1858, found 330.1863; HPLC Daicel CHIRALCEL-ODH. Hexane/*i*-PrOH 95:5, 0.5 mL/min, λ = 254 nm, t_R (*R*) = 8.7 min, t_R (*S*) = 10.1 min.

(*R*)-2-Amino-1,1,2-triphenylethanol (5). (*R*)-2-(Allylamino)-1,1,2-triphenylethanol (**9**) (114 mg, 0.35 mmol), methanesulfonic acid (45 μL, 0.69 mmol), 10% Pd/C (47 mg), and water (5 mL) were added to a two-necked round-bottom flask. The mixture was heated under reflux overnight. A slow flow of argon passed through the solution to aid removal of propionaldehyde. The solution was then basified with NaOH to pH 10, and a white solid appeared. To remove the catalyst the suspension was filtered through Celite, and the residue was washed with dichloromethane. The organic layer was washed with brine, dried (MgSO4), and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **5** (91 mg, 0.31 mmol) as white solid in 91% yield and 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8 Hz, 2H), 7.40 (t, J = 7 Hz, 2H), 7.30−7.00 (m, 11H), 5.00 (s, 1H), 1.62 (broad s, 2H); HPLC Daicel CHIRALCEL-ODH. Hexane/*i*-PrOH 80:20, 0.5 mL/min, λ = 254 nm, t_R (*R*) = 19.7 min, t_R (*S*) = 21.1 min.

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Supporting Information Available: General experimental information, complete experimental details, and characterization data for compounds **11a**−**d**, **12a**−**d**, and **13a**−**d**. Copy of ^{1}H and ^{13}C NMR spectra for compounds **9**, **11d**, **12d**, **13b**, and **13d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) By analogy with **5**, the resulting 1,2-amino alcohols we assumed to preserve the optical purity of the starting epoxides.