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Asymmetric Synthesis of Tertiary Benzylic Alcohols

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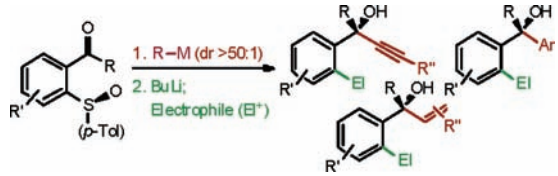
ABSTRACT



Vinyl, aryl, and alkynyl organometallics add to ketones containing a stereogenic sulfoxide. Tertiary alcohols are generated in diastereomerically and enantiomerically pure form. Reductive lithiation converts the sulfoxide into a variety of useful functional groups.

Efficient organic synthesis requires control over absolute and relative stereochemistry. Among the many chemical transformations that form stereogenic centers, additions to ketones and aldehydes are especially important.[1] Their value to organic synthesis arises from several characteristics: many types of nucleophiles will react with ketones and aldehydes; addition reactions display high atom economy and represent convergent fragment couplings; the products, secondary and tertiary alcohols, are ubiquitous in natural products, pharmaceutical agents, and other biologically active materials; and the secondary and tertiary alcohol products are substrates for a rich diversity of subsequent synthetic transformations.

Owing to the utility of secondary alcohols, significant attention has focused on the asymmetric addition of hard nucleophiles to aldehydes.[2−5] In contrast, asymmetric additions of alkynyl, vinyl, and aryl groups to *ketones* have proven more elusive.[6,7] For example, amino alcohols and phosphorylated diamines promote the addition of Ph_2Zn to ketones.[8] Bis-sulfonamide ligands promote the same reaction in the presence of stoichiometric $Ti(O^iPr)_4$,[9] and aryl aluminum reagents effect arylation in the presence of 10−20 mol % BINOL and excess $Ti(O^iPr)_4$.[10] These approaches generally require expensive arylating agents, often in large excess, stoichiometric quantities of an additional metal salt, and/or structurally complex ligands. With regard to alkenylation, a bis-sulfonamide ligand enables the asymmetric addition of terminal vinyl zinc reagents to ketones with high selectivity.[11] Finally, asymmetric catalytic additions of alkynyl zinc reagents have been reported,[12−15] but high catalyst loadings, long reaction times, and large excesses of reagent are generally required.[6,16]

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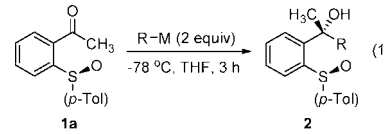
We considered the use of chiral auxiliaries to effect the stereoselective addition of hard nucleophiles to ketones. Most applications of chiral auxiliaries incorporate the stereodirecting group onto the nucleophilic component of the reaction.[17] The sulfoxide group represents a rare example of a chiral auxiliary which usually resides on the electrophilic reaction partner.[18] The Ellman group has popularized the use of *tert*-butyl sulfinamide for the synthesis of optically active amines.[19] Likewise, the groups of Colobert and Toru have demonstrated the utility of sulfoxide chiral auxiliaries in asymmetric additions to aldehydes.[20] These applications, in turn, built on a rich literature describing the use of sulfoxides in asymmetric reductions, conjugate additions, and Diels−Alder cycloadditions pioneered by the group of García Ruano among others.[18] Here we show that the toluene sulfinyl group effectively controls the asymmetric addition of simple alkynyl, aryl and vinyl organometallic reagents to aryl ketones (eq 1). In contrast to most previous studies, the methodology utilizes readily available Grignard reagents and lithium acetylides. Furthermore, we demonstrate the reductive lithiation of the sulfoxide and its conversion to other useful functionality.

Toluene sulfinyl groups can be introduced onto an aromatic nucleus through the stereospecific reaction of menthol sulfinate with an aryl lithium reagent.[20a,21] The requisite sulfinate is commercially available but can also be prepared conveniently in large scale from the reductive coupling of toluene sulfonyl chloride with menthol.[22] With these considerations in mind, we prepared methyl ketone **1a**[23] and examined its reactivity toward a variety of organometallic reagents, initially focusing on the synthesis of propargylic alcohols. The lithium anion of phenyl acetylene provided tertiary alcohol **2a** with good diastereoselectivity, but in unsatisfactory yield (Table 1, entry 1). Alkynyl Grignard reagents were even more selective but did not fully consume the sulfoxide. A less basic organocerium reagent[24] completely consumed the ketone and provided the tertiary alcohol as a ca. 50:1 mixture of diastereomers (entry 4). Using less than 2 equiv of the nucleophile resulted in incomplete consumption of **1a** (entry 3).

Table 1. Addition of Organometallic Reagents to Aryl Ketones[a]



1a 2

entry	R-M	conv (%)[b]	dr[b]
1	Ph—≡—Li	60	17:1
2	Ph—≡—MgBr	50	>50:1
3[c]	Ph—≡—Li/$CeCl_3$	63	~50:1
4	Ph—≡—Li/$CeCl_3$	**100 (95)**[d]	**~50:1**
5	PhMgBr/$CeCl_3$	50	>50:1
6	PhMgBr	**94 (83)**[d]	**>50:1**
7	PhLi	70	>50:1

[a] Reactions carried out on a 20 mg scale at 0.07−0.08 M. [b] Conversion (Conv) and diastereomeric ratio (dr) determined by ^{1}H NMR analysis of the crude reaction mixture. [c] 1.2 equiv of acetylide was used. [d] Isolated yield shown in parentheses.

We extended our study to include the addition of aryl nucleophiles. Using either the arylcerium reagent (entry 5) or the aryl Grignard (entry 6), we obtained excellent diastereoselectivity, as only one diastereomer was observed in the crude reaction mixture. In contrast to the reactivity profile observed with acetylides, however, the inclusion of $CeCl_3$ in the reaction mixture actually decreased conversion when aryl nucleophiles were used. Nonetheless, simple Grignard reagents generated the desired product in high yield. Phenyl lithium proved equally selective, but conversion was incomplete using this reagent (entry 7). Finally, alkyl and allyl Grignard reagents displayed poor diastereoselectivity (ca. 4:1) and yielded complex mixtures of products.

Using the optimal reaction conditions for the addition of acetylides (Table 1, entry 4) and aryl Grignards (Table 1, entry 6), we explored the generality of the methodology. As shown in Table 2, a wide range of optically active, tertiary benzylic alcohols were prepared in high yield. Alkyl-, aryl-, and silyl-substituted alkynes added to methyl (entries 1−5, 24, 26), ethyl (entries 11−13), and aryl (entry 21) ketones with crude diastereoselectivities > 10:1. Likewise, electron-rich, -poor, and -neutral aryl Grignards added to several ketones with at least 50:1 diastereoselectivities. Importantly, the addition could accommodate alkenyl Grignard reagents as well: vinyl (entry 9), 2-propenyl (entries 10, 18, 23) and 2-methyl-1-propenyl (entry 22) magnesium bromide yielded benzylic, allylic alcohols in at least 20:1 dr. Additional substitution was tolerated on the aryl sulfoxide fragment as well, including halogens (entries 15−19, 24−25) and tri-

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(23) Full experimental details are provided in the Supporting Information.

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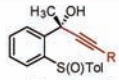
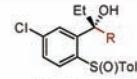
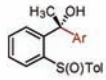
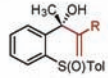
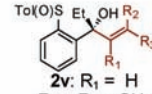
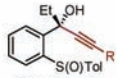
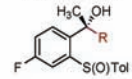
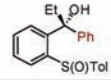
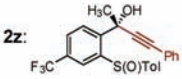
Table 2. Asymmetric Synthesis of Tertiary Benzylic Alcohols[a]

entry	product	M[b]	yield (%)[c]	dr[d]	entry	product	M[b]	yield (%)[c]	dr[d]
									
1	**2a**: R = Ph	[Ce]	95	>50:1 (~50:1)	15	**2o**: R = CCPh	[Ce]	78	>50:1 (~50:1)
2	**2c**: R = 2-CH_3-Ph	[Ce]	88	>50:1 (~50:1)	16	**2p**: R = CC-(2-Th)	[Ce]	82	>50:1 (33:1)
3	**2d**: R = 6-CH_3O-2-Np	[Ce]	81	>50:1 (20:1)	17	**2q**: R = 4-CH_3O-Ph	MgBr	79	>50:1 (>50:1)
4	**2e**: R = Si(^{i}Pr)$_3$	[Ce]	87	>50:1 (>50:1)	18	**2r**: R = 2-Propenyl	MgBr	72	>50:1 (25:1)
5	**2f**: R = CH_2OTBS	[Ce]	65	33:1 (12:1)					
									
6	**2b**: Ar = Ph	MgBr	83	>50:1 (~50:1)	19	**2s**: R = 4-CH_3O-Ph	MgBr	75	>50:1 (~50:1)
7	**2g**: Ar = 3,5-$(CF_3)_2$-Ph	MgBr	82	>50:1 (>50:1)	20	**2t**: R = 6-CH_3O-2-Np	MgBr	79	>50:1 (>50:1)
8	**2h**: Ar =4-CH_3O-Ph	MgBr	87	>50:1 (>50:1)	21	**2u**: R = CCPh	[Ce]	77	>50:1 (~50:1)
									
9	**2i**: R = H	MgBr	74	>50:1 (>50:1)	22	**2v**: R_1 = H, R_2 = R_3 = CH_3	MgBr	80)	>50:1 (25:1)
10	**2j**: R = CH_3	MgBr	90	>50:1 (33:1)	23	**2u**: R_1 = CH_3, R_2 = R_3 = H	MgBr	86	>50:1 (20:1)
									
11	**2k**: R = Ph	[Ce]	72	>50:1 (11:1)	24	**2x**: R = CCPh	[Ce]	77	>50:1 (14:1)
12	**2l**:R = 3,5-$(CF_3)_2$-Ph	[Ce]	81	>50:1 (14:1)	25	**2y**: R = Ph	MgBr	85	>50:1 (~50:1)
13	**2m**: R = $CH_2N(CH_3)_2$	[Ce]	71	>50:1 (~50:1)					
14	**2n**: 	MgBr	84	>50:1 (>50:1)	26	**2z**: 	[Ce]	79)	>50:1 (10:1)

[a] Reaction conditions same as those in Table 1, entry 4 (M = [Ce]) or 6 (M = MgBr) on a 0.4 mmol scale. The (*S*)-sulfoxides were used. [b] [Ce] = reagent derived from alkynyl Li and $CeCl_3$. [c] Yield of isolated single diastereomer except entry 5 (33:1 dr). The numbers in parentheses represent conversion of **1** as determined by ^{1}H NMR analysis of crude reaction mixture. [d] dr determined by ^{1}H NMR analysis of purified material. The numbers in parentheses represent dr of crude reaction products. TBS = *tert*-butyldimethyl silyl; Tol = *p*-tolyl; Np = naphthyl; Th = thienyl.

fluoromethyl groups (entry 26). Illustrating the value of the chiral auxiliary, a single diastereomer was isolated after either column chromatography or trituration in all but one case (entry 5, dr = 33:1). X-ray crystallography established the absolute and relative stereochemistry of representative products derived from the addition of alkynyl (entries 1, 2, 11) and aryl (entry 7) organometallic reagents. Other products in Table 2 were assigned by analogy.

The sulfoxide chiral auxiliary can be reductively removed in high yield.[18b] As shown in Table 3, several diversely substituted sulfoxides were treated with *n*-butyl lithium, and the corresponding tertiary alcohols (**3**) were obtained in high ee. Optically pure materials could be prepared by simply recrystallizing the sulfoxide prior to reductive cleavage.

Exposure of sulfoxides **2** to butyl lithium generates an aryl lithium which can be trapped with various electrophiles.[25] Thus alcohol **2a** was deprotonated with methyl lithium, then lithiated with *tert*-butyl lithium, and trapped with diiodoethane, CO_2, or O_2 to provide the iodide **4**, lactone **5**, or phenol **6** in good yields (Scheme 1). The lactone could have emerged from either condensation or S_N1 substitution with the carboxylate, which could occur with racemization. Gratifyingly, the isolated lactone **5** was found to be optically pure.

Propargylic alcohols are valuable as precursors to other functional groups including allenes. For example, S_N2' substitution of propargylic alcohols and their derivatives with organometallic reagents yields allenes, but occasionally these transformations are imperfectly stereospecific or are accompanied by racemization.[26] In this context, the presence of a chiral auxiliary could benefit both the synthesis of the propargylic alcohol and its conversion to an allene. To explore this possibility, alcohol **2z** was acylated and con-

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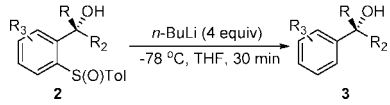
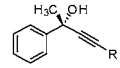
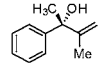
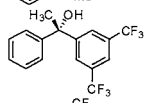
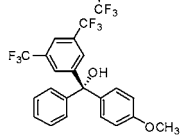
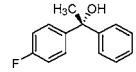
Table 3. Reductive Removal of Sulfinyl Moiety



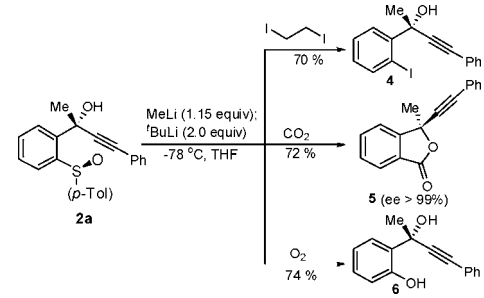
entry	product	yield (%)[a]	ee (%)[b]
			
1	R = Ph	97 (97)	96 (99)
2	R = Si(^{i}Pr)$_3$	92	96
3	R = 6-CH$_3$O-2-naph	94	>99
4		93	99
5		96	>99
6		99 (99)	92 (>99)
7		95	>99

[a] Yield of isolated product. [b] Values in parentheses represent yield and ee obtained using recrystallized **2**.

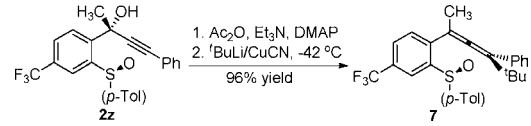
verted to allene **7** which was isolated in 96% yield as a single diastereomer (Scheme 2).

Tertiary alcohols are important functional groups in organic synthesis, although their preparation in optically active form has traditionally proven challenging. Here we describe a general, high yielding, and selective approach to their synthesis. Furthermore, the chiral auxiliary, a tolyl sulfoxide, can be converted into other useful functionality via reductive lithiation. Overall, this process should represent a valuable component of the synthetic arsenal.

Scheme 1. Synthetic Manipulations of Sulfoxide **2a**



Scheme 2. Asymmetric Synthesis of Allenes



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Supporting Information Available: Experimental details and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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