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Catalytic, Enantioselective Alkylations of N,O- and N, N-Acetals and Hemiacetals

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Abstract: We report the first examples of catalytic, enantioselective alkylation of N,O-acetals to produce useful amino acid derivatives **5** in high yield (73-93%) and enantioselectivity (70-96%). We have extended the utility of our reaction to include a simple one-pot procedure from readily available starting materials. We also provide several different N-based protecting groups that greatly increase the flexibility of the reaction. In addition, we have elucidated novel mechanistic information including the discovery of unique transilylations that start off the catalytic reactions of enol silane nucleophiles with N,O-acetals. These details will guide us in further explorations of the reaction's scope and utility.

Keywords: Asymmetric Synthesis; Amino Acids; Acetals; Copper

Introduction. Asymmetric alkylation reactions of acetals represent a powerful and general method of C-C bond construction.[1] Methods employing either chiral acetals or promoters have been most extensively studied, whereas those utilizing a substoichiometric quantity of catalyst with either achiral or racemic acetals are much less studied,[2] and procedures employing N,O- or N,N-acetals remain unknown. We believed that the asymmetric alkylation of N,O-acetals could efficiently lead to chiral amines and amino acid derivatives if the RO-substituent were the leaving group (Path A, eq 1), and to chiral alcohols if NR_2 were the leaving group (Path B, eq 1). In order for an asymmetric variant to be successful, the catalyst must effectively serve a dual role, namely to dissociate RO^- and subsequently activate the putative intermediate imine towards an enantioselective addition. The alkylations of N,O-acetals could potentially play an important role especially when the corresponding imines are difficult or impossible to synthesize and store. When X is an electron-withdrawing group, we found that racemic hemiacetals **1a-1h** (R = H) possessing a flexible range of N-protecting groups become stable, convenient precursors to useful enantioenriched products. We wish to describe, with full experimental detail, the first high yielding (73-93%) asymmetric alkylations (ee's up to 96%) of conveniently prepared N,O-acetals using an effective chiral Cu(I)-based Lewis acid catalyst. We have used this catalyst in the catalytic, highly enantioselective alkylation of α-imino esters with

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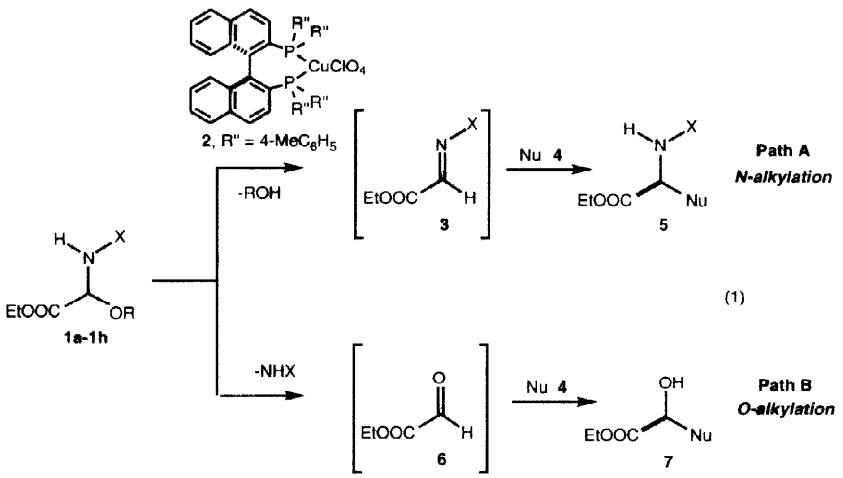
enol silanes and alkenes.[3] Our report also includes the use of N,N-acetals as useful alkylation substrates. In this report, we also summarize a method to synthesize several nonnatural amino acids[4] in high yield using readily available precursors via an in situ generation of N,O-acetals in a versatile one-pot procedure.[5] We documented that a novel transilylation reaction starts off the catalytic, enantioselective alkylation; other mechanistic investigations of our process reveal features that may lend general significance to alkylations of acetals by enol silanes.



Results and Discussion. When a solution of **1a** and catalyst **2** (5 mol%) was mixed at 0°C with 2 equiv of enol silane **4a** for 5 h, compound **5a** was produced in 93% yield and 95% ee (Table 1, entry 1). Although substrate **1a** (X = Ts, R = H) is a highly crystalline and stable starting material, removal of the tosyl group in a subsequent step requires long reaction times and highly acidic conditions.[6] We envisaged that other more easily removable sulfonamido protecting groups could be substituted for the tosyl group to provide complementary deprotection procedures. For example, acetal **1b** with a 2,6-dimethyl-4-methoxybenzenesulfonyl (Mds)[7] group reacts with enol silane **4a** in the presence of 5 mol% **2** to yield 87% of compound **5d** (94% ee, entry 4). It is noteworthy that the nature of the leaving group in substrate **1c** (OH vs OEt) does not significantly diminish the yield or selectivity of product **5d** (entry 5). Similarly, the 4-nitrophenylsulfonamido (Ns)[8] acetal **1d** affords product **5e** in 87% ee and 89% yield (entry 6). Excellent selectivity (up to 96% ee) can also be achieved by using the trimethylsilylethanesulfonamido (SES)[9] substituent on the N,O-acetal to form products **5g**, **5h**, and **5i** (entries 8-10). Minimal loss in selectivity is noted even when the steric bulk of the sulfonamido group is diminished, as shown in the alkylation of **1e** (X = Ms; 85% ee, entry 7). The decrease in selectivity is more pronounced in the alkylations of amide acetals **1g** and **1h** that yield 50% ee and a 42% ee of product **5j**, respectively, under the

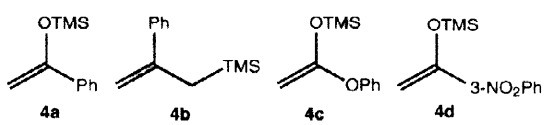
conditions specified above (entries 11 and 12). These results also confirm that the sulfonyl group is an important factor in determining enantioselectivity.

An interesting result was obtained when the benzoyl N,O acetal **1i** was subjected a catalytic alkylation with nucleophile **4a** in the presence of **2**. Instead alkylating the intermediate imine (Path A), ethyl glyoxylate **6** formed and was subsequently alkylated (Path B) to give product **7a** in 83% yield without a trace of the expected benzoylated amino acid. In addition, alcohol **7a** was 70% enantiomerically enriched (entry 14).[10]

Table 1. Reactions of N,O-acetals and various nucleophiles catalyzed by complex **2**

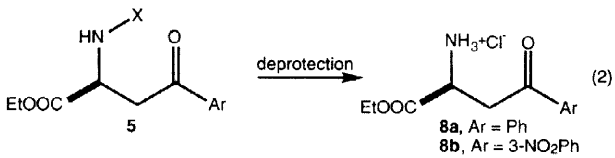
entry	Acetal	Nu	X	R	yield	ee%	prod
1	**1a**	**4a**	Ts	H	93	95	**5a**
2	**1a**	**4b**[a]	Ts	H	85	90	**5b**
3	**1a**	**4c**	Ts	H	81	76	**5c**
4	**1b**	**4a**[a]	Mds	H	87	94	**5d**
5	**1c**	**4a**[a]	Mds	Et	92	90	**5d**
6	**1d**	**4a**[a]	Ns	Et	89	87	**5e**
7	**1e**	**4a**	Ms	H	89	85	**5f**
8	**1f**	**4a**	SES	H	78	96	**5g**
9	**1f**	**4b**[a]	SES	H	73	89	**5h**
10	**1f**	**4c**	SES	H	75	70[b]	**5i**
11	**1g**	**4a**	Ac	H	86	50	**5j**
12	**1h**	**4a**	Ac	Ac	88	42	**5j**
13	**1d**	**4d**[c]	Ns	Et	85	87	**5k**
14	**1i**	**4a**	Bz	H	83	70	**7a**

Abbreviations: Ts = p-toluenesulfonyl, Mds = 2,6-dimethyl-4-methoxybenzenesulfonyl, Ns = p-nitrobenzenesulfonyl, Ms = methanesulfonyl, SES = trimethylsilylethanesulfonyl. Enantiomeric excesses were determined by CHIRALCEL OD chiral HPLC column unless otherwise noted. [a]Reaction carried out in refluxing CH_2Cl_2. [b]Enantiomeric excesses determined by ^1H NMR in the presence of $Pr(hfc)_3$ chiral shift reagent. [c]Reaction carried out in THF for increased solublity of reagents



To demonstrate the flexibility of the alkylation reaction, we tested a number of nucleophiles representing several classes. For example, allylsilane **4b**[11] reacts with both substrates **1a** and **1f** to afford products **5c** and **5h** in excellent yield and selectivity (entries 2 and 9). Ketene acetal **4c** also reacts well with these substrates to yield compounds **5c** and **5i** in 76% ee and 70% ee, respectively (entries 3 and 10). Once again, an array of sulfonamide groups such as SES,[9] Mds[7] and Ns[8] were highlighted. In the deprotection step, compounds **5d**, **5e**, and **5g** can be converted to amine hydrochloride **8a** in yields ranging from 75-87% with no detectable racemization (eq 2).[12] In fact, we used this

methodology for the multigram synthesis (2.0g) of (L)-3-nitrobenzoylalanine (**8b**, eq 2) in 48% overall yield from **1d** (entry 13) using only 1 mol% **2**. This compound is currently of interest as an inhibitor of enzymes that metabolize trypotophan such as kynurenine-3-hydroxylase and kynureninase.[13]



5d X = Mds, conditions = 9:1 TEA/MSA, PhSMe
5e X = Ns, conditions = PhSH, K_2CO_3
5g X = SES, conditions = CsF/DMF

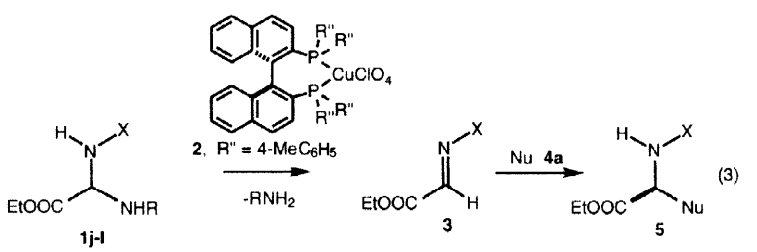
In an effort to further simplify the synthesis of protected amino acids **5a-5j**, an efficient one pot procedure was developed. The condensation of ethyl glyoxylate and *p*-toluenesulfonamide was done in CH_2Cl_2 over a 6 h period in the presence of catalyst **2** (5 mol%). The reaction mixture was then cooled to 0°C and 2 equiv of the nucleophile **4a** was added. *After 2h, the reaction was subjected to aqueous workup and the product was isolated in 89% yield and 95% ee.* A one-pot procedure was also implemented for the synthesis of compound **5g** (76% yield, 93% ee).

Table 2. Reactions of N,N-Acetals and nucleophile **4a** catalyzed by complex **2**

entry	Acetal	Nu	X	R	yield	ee%	prod
1	**1j**	**4a**[a]	Ts	Ts	90	95	**5a**
2	**1k**	**4a**[a]	Ns	Ns	87	85	**5e**
3	**1l**	**4a**	Ms	Ms	86	82	**5f**

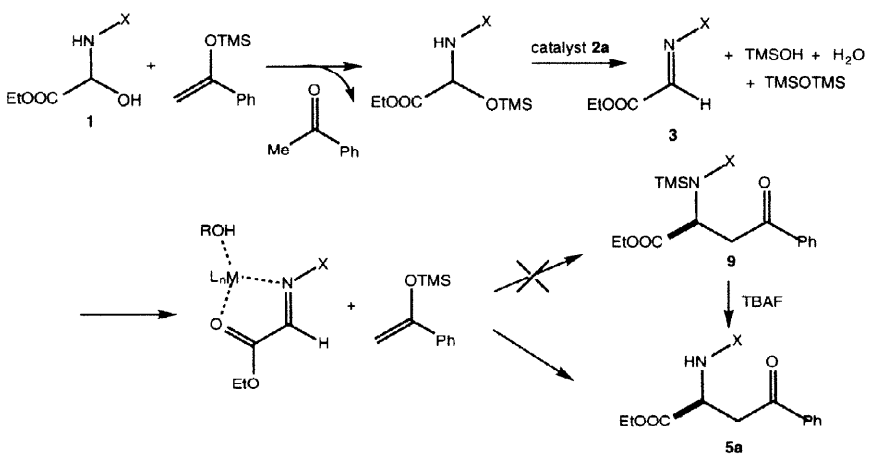
Abbreviations: Ts = p-toluenesulfonyl, Ns = p-nitrobenzenesulfonyl, Ms = methanesulfonyl. Enantiomeric excesses were determined by CHIRALCEL OD chiral HPLC column unless otherwise noted. [a]Reaction carried out in refluxing THF for increased solubility.

The alkylation of N,N-acetals can also be accomplished under these conditions. Acetals **1j-l** were synthesized in high yield and purity by mixing two equivalents of the requisite sulfonamide with ethyl glyoxylate in toluene with azeotropic removal of water. The reaction of enol silane **4a** with N,N-Acetals **1j-l** in the presence of 5 mol % **2** produced products **5a**, **5e** and **5f** in high yield (86-90%) and ee (82-95%) (eq 3).



Mechanism. To our surprise, the use of one equiv enol silane **4a** with N,O-acetal **1a** did not lead to product **5a** with 5 mol% **2**; however, when two equiv were used, product **5a** was formed in good yield. Although silyl ketene acetals can be quenched through silyl transfer reactions with alcohols, enol silanes are not precedented to act as silylating reagents.[14] This anomaly prompted us to determine mechanistic details of the enol silane reaction through ^{1}H NMR experiments. For example, when acetal **1a** was dissolved in CD_2Cl_2 along with 1 equiv of enol silane **4a**, an immediate change in the ^{1}H NMR spectrum occurred. The enol silane resonances disappeared and those characteristic of acetophenone developed. In addition, the alcohol proton disappeared, indicating O-silylation (Scheme 1). A second equiv of enol silane **4a** was then added to the mixture and the reaction was monitored; no product formation was noted even after extended periods of time. After addition of the catalyst **2** however, resonances due to product began to appear. Interestingly, peaks due to the putative intermediate imine **3**[15] were not observed, nor were those for the N-trimethylsilylated product **9** (Scheme 1). In our previous work, imine **3** (X = Ts) reacts with enol silane **4a** in the presence of catalyst **2**, to produce **9** exclusively (Scheme 1)[3] that retains its silyl group through aqueous workup. In fact, product **9** will only partially desilylate in the presence of 1:1 THF:H_2O even after several hours, but can be desilylated immediately upon treatment with fluoride or standard column chromatography on silica gel. In the reaction of N,O-acetal **1a** with enol silane **4a** *no silylated product* **9** *is observed by* ^{1}*H NMR or TLC.* This finding leads us to suggest that adventitious water, silanol or an L_nCu•ROH species is protonating the product immediately after alkylation,[16] as shown in a possible mechanism (Scheme 1). Not surprisingly, only 1 equiv of enol silane **4a** is needed to alkylate N,O-acetals **1c** and **1d** in which O-silylation can not take place. Further studies on the scope and mechanism of the asymmetric reactions of N,O-acetals are underway and will be reported in due course.

Scheme 1. Proposed mechanism of N,O-alkylation



Conclusion. In summary, we have developed the first practical method for catalytic, enantioselective alkylation of N,O- and N, N-acetals. Stable, readily available acetals **1a-l** can be alkylated with a variety of nucleophiles in up to 96% ee with as little as 1 mol % of catalyst **2**. This research has many practical applications including the large scale synthesis of γ-oxo-α-amino acids. In addition, the mechanistic work in this manuscript provides new insight into the alkylation of acetals.

Experimental

General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. Formation of ligand-metal complex **2** was done in a glove box under N_2. All solvents were dried and distilled by standard procedures. The ^1H and ^{13}C NMR spectra were acquired on a Varian Unity 400 MHz Spectrometer. The ^1H (400 MHz) and ^{13}C chemical shifts (101 MHz) are given in parts per million (δ) with respect to internal TMS standards or residual solvent peaks. FTIR spectra were recorded on a Bruker IFS-55 spectrometer and optical rotations were recorded on a Perkin Elmer 120 polarimeter at room temperature. When possible, enantiomeric ratios were obtained using a Chiralcel OD chiral HPLC column. The ethyl glyoxylate was synthesized and purified by a known procedure.[17] The $Cu(I)ClO_4•(CH_3CN)_4$ was made according to the Kubas procedure.[18] Trimethylsilylethanesulfonamide[19] and 4-Methoxy-2,6-dimethylbenzenesulfonamide,[20] and nucleophiles **4a-4d**[11,21] were prepared according to published procedures. All other starting materials were purchased from Aldrich Chemical Company, except for (*R*)-Tol-BINAP which were purchased from Strem Chemical. N, O-acetals **1g** and **1h**,[22] and products **5a**, **5b**,[3] and **7a**[23] are known so characterization data is excluded.

General Synthesis of N,O Acetals 1a-h. The requisite amide or sulfonamide (5.0 g, 29.2 mmol) was mixed with ethyl glyoxylate (3.0 g, 29.2 mmol) in $CHCl_3$ and refluxed for several hours depending on the amide or sulfonamide. The reactions were monitored by ^1H NMR assays and glyoxylate was added when necessary to drive the reaction to completion. The reactions were worked up by removal of the solvent and any excess glyoxylate *in vacuo*. The crystalline residue was recrystallized from EtOAc/Hexanes, Et_2O/Hexanes or chromatographed on Florisil to yield analytically pure material.

***N-p*-Toluenesulfonylhydroxyglycine ethyl ester (1a).** White crystalline solid recrystallized from EtOAc/Hexanes; mp = 178-180 °C, Yield = 87%. ^1H NMR ($CDCl_3$) δ 7.78 (d, 2H), 7.28 (d, 2H), 5.92 (d, 1H), 5.28 (d, 1H), 4.20 (m, 2H), 3.78 (bs, 1H), 2.41 (s, 3H), 1.23 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.8, 143.9, 137.7, 129.6, 127.0, 75.4, 62.9,

21.5, 13.8 ppm; IR (CH_2Cl_2): 3459, 3278, 2955, 1736, 1338, 1161, 1096; Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.54; N, 5.13. Found C, 48.24; H, 5.55; N, 5.16.

***N*-2,6 Dimethyl-4-methoxybenzenesulfonylhydroxyglycine ethyl ester (1b).** White crystalline solid recrystallized from Et_2O; mp = 98-100 °C, Yield = 85%. ^1H NMR ($CDCl_3$) δ 6.60 (s, 2H), 5.68 (d, 1H), 5.18 (d, 1H), 4.19 (m, 2H), 3.80 (s, 3H), 3.50 (d, 1H), 2.64 (s, 6H), 1.25 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 161.4, 141.7, 129.0, 116.1, 94.3, 75.2, 62.8, 55.3, 23.3, 13.8 ppm; IR (CH_2Cl_2): 3267, 2921, 1736, 1596, 1461, 1309, 1212, 1153, 1088; Anal. Calcd for $C_{13}H_{19}NO_6S$: C, 49.20; H, 6.04; N, 4.42. Found C, 48.29; H, 6.08; N, 4.42.

***N*-2,6 Dimethyl-4-methoxybenzenesulfonylethoxyglycine ethyl ester (1c).** The general procedure was followed except that the reaction was carried out in EtOAc and heated for several days to get the ether **1c** (45% yield) as the major product upon workup and column chromatography on silica gel (EtOAc/Hexanes). White crystalline solid mp = 89-91 °C; ^1H NMR ($CDCl_3$) δ 6.60 (s, 2H), 5.82 (d, 1H), 4.97 (d, 1H), 4.11 (q, 2H), 3.78 (s, 3H), 3.42 (m, 2H), 2.60 (s, 6H), 1.19 (t, 3H), 0.98 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 161.2, 141.3, 129.6, 116.0, 94.3, 81.1, 63.6, 62.3, 55.2, 23.3, 14.5, 13.8 ppm; IR (CH_2Cl_2): 3288, 2996, 2932, 1736, 1590, 1477, 1440, 1336, 1309, 1153, 1088; Anal. Calcd for $C_{15}H_{23}NO_6S$: C, 52.16; H, 6.72; N, 4.06. Found C, 52.27; H, 6.63; N, 3.97.

***N*-Methanesulfonylhydroxyglycine ethyl ester (1d).** White crystalline solid recrystallized from Et_2O/hexane, mp = 76-78 °C, yield = 83%; ^1H NMR ($CDCl_3$) δ 6.21 (d, 1H), 5.28 (d, 1H), 4.22 (q, 2H), 3.70 (bs, 1H), 3.08 (s, 3H), 1.28 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.2, 75.5, 63.0, 43.2, 13.9 ppm; IR (CH_2Cl_2): 3285, 2927, 1744, 1334, 1159, 1094; Anal. Calcd for $C_5H_{11}NO_5S$: C, 30.45; H, 5.63; N, 7.11. Found C, 30.54; H, 5.59; N, 7.14.

***N*-*p*-Nitrobenzenesulfonylethoxyglycine ethyl ester (1e).** The 4-nitrobenzenesulfonamide (2.0 g, 10 mmol) was refluxed in EtOAc (5 mL) with ethyl diethoxy acetate (1.76 g, 10 mmol) and a catalytic amount of p-toluenesulfonic acid for several days to get the ether **1e** (2.5 g, 75% yield) upon workup and column chromatography on silica gel (EtOAc/Hexanes). Yellow crystalline solid mp = 94-96 °C, ^1H NMR ($CDCl_3$) δ 8.31 (d, 2H), 8.04 (d, 2H), 6.26 (d, 1H), 5.14 (d, 1H), 4.18 (q, 2H), 3.54 (m, 2H), 1.25 (t, 3H), 1.04 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.9, 150.0, 146.7, 128.2, 124.1, 81.3, 64.1, 62.7, 14.5, 13.9 ppm; IR (CH_2Cl_2): 3279, 2983, 1746, 1533, 1351, 1172; Anal. Calcd for $C_{12}H_{16}N_2O_7S$: C, 43.36; H, 4.86; N, 8.43. Found C, 43.56; H, 4.79; N, 8.46.

***N*-(Trimethylsilyl)ethanesulfonylhydroxyglycine ethyl ester (1f).** Colorless oil, yield = 93%; ^1H NMR ($CDCl_3$) δ 5.92 (d, 1H), 5.27 (d, 1H), 4.25 (q, 2H), 3.65 (bs, 1H), 3.04 (m, 2H), 1.30 (t, 3H), 1.03 (m, 2H) 0.02 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.3,

75.4, 62.9, 51.6, 13.9, 10.2, -2.05 ppm; IR (CH_2Cl_2): 3273, 2956, 1743, 1266, 1147; Anal. Calcd for $C_9H_{21}NO_5SSi$: C, 38.15; H, 7.48; N, 4.95. Found C, 38.26; H, 7.49; N, 4.97.

Synthesis of Trimethyl(2-phenyl-2-propenyl)silane (4b). This material was generated by a modification of a known route to the corresponding stannane.[24] A flask was loaded with potassium *tert*-butoxide (4.52 g, 40.27 mmol) and α-methyl styrene (4.73 g, 40.00 mmol). The reagents were dissolved in THF (120 mL) and the resultant pale yellow solution cooled to -78 °C. To this solution was added a 1.29 M solution of butyllithium in hexanes (31 mL, 40.00 mmol) over 5 min causing color change to dark red. The solution was warmed and allowed to stir for 5 h at -50 °C. This solution was then added to rapidly stirring -78 °C solution of chlorotrimethylsilane (11 mL, 86.67 mmol) in THF (30 mL). During the addition, the solution of silane becomes very thick and cloudy. The solution is then allowed to warm and stir at rt overnight. The THF was removed and the residue taken up in n-pentane. The solution was filtered through celite, the solvent removed and the residue purified by column chromatography on florisil (5x13cm Pet Ether to 1% Et_20/Pet Ether) to give 79% yield of a clear colorless oil (6.06g 31.77 mmol) identical to that reported previously in the literature.[11]

Representative Alkylation Procedure. The catalyst **2** was made by dissolving (*R*)Tol-BINAP (15 mg, 0.022 mmol) and $CuClO_4•(CH_3CN)_2$ (7 mg, 0.021 mmol) in CH_2Cl_2. To the tosyl acetal **1a** (100 mg, 0.37 mmol), in CH_2Cl_2 (2 mL) was added the solution of catalyst **2**. This reaction mixture was cooled to 0 °C and the enol silane **4a** (142 mg, 0.74 mmol) was added to the reaction mixture over a period of 30 minutes. The reaction was stirred at room temperature or heated to reflux until completion as shown by TLC (30% EtOAc/Hexanes). The reaction was partitioned with water (3 mL) and CH_2Cl_2 (3 mL). The organic layer was dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude residue (200 mg) was subject to column chromatography on silica gel to yield 128 mg of the final product (93% yield, 95% ee).

(*S*)-Ethyl-3-(phenylcarboxy)-2-(tosylamino)propanoate (5c). White crystalline solid. mp = 88-90 °C; $[\alpha]_D$ = +16.6 (c = 0.03, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.78 (d, 2H), 7.30 (m, 5H), 7.00 (d, 2H), 5.61 (d, 1H), 4.22 (m, 1H), 4.03 (m, 2H), 3.16 (m, 2H), 2.40 (s, 3H), 1.07 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 169.6, 168.8, 150.1, 143.8, 136.5, 129.7, 129.4, 127.2, 126.1, 121.3, 62.4, 52.2, 38.2, 21.5, 13.8; IR (CH_2Cl_2): 3283, 2926, 1743, 1493, 1342, 1267, 1164; HPLC (10% iPrOH/Hexane, 0.7 mL/min) (*R*) = 42.5, (*S*) = 48.2 min. Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.3; H, 5.41; N, 3.58. Found C, 58.50; H, 5.44; N, 3.62.

(*S*)-Ethyl-3-Benzoyl-2-(4-methoxy-2,6-dimethylbenzenesulfonylamino)-propanoate (5d). Colorless oil; $[\alpha]_D$ = +35.6 (c = 0.042, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.81 (d, 2H), 7.57 (t, 1H), 7.42 (t, 2H), 6.58 (s, 2H), 4.20 (m, 1H), 4.09 (m, 2H), 3.78 (s, 3H), 3.59 (d, 2H), 2.62 (s, 6H), 1.12 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 196.8, 170.6, 161.1, 141.6, 135.8, 133.7, 128.8, 128.6, 128.0, 116.0, 62.0, 55.1, 51.5, 41.5, 23.3, 13.8 ppm; IR

(CH_2Cl_2): 3300, 2978, 2936, 1738, 1682, 1594, 1449, 1312, 1155, 1088; HPLC (12% EtOH/Hexane, 1.4 mL/min) (*R*) = 17.62, (*S*) = 20.95 min. Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.12; H, 6.01; N, 3.34. Found C, 60.34; H, 6.07; N, 3.37.

(*S*)-Ethyl-3-Benzoyl-2-(4-nitrobenzenesulfonylamino)propanoate (5e). White crystalline solid mp = 152-154 °C; $[\alpha]_D$ = +46.2 (c = 0.19, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.29 (d, 2H), 8.04 (d, 2H), 7.82 (d, 2H), 7.57 (t, 1H), 7.41 (t, 2H), 6.05 (d, 1H), 4.35 (m, 1H), 4.03 (q, 2H), 3.74 (m, 1H), 3.58 (m, 1H), 1.08 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 196.8, 169.8, 146.0, 135.5, 134.0, 128.7, 128.4, 128.0, 124.1, 62.2, 52.0, 41.9, 13.8 ppm; IR (CH_2Cl_2): 3305, 3054, 1742, 1533, 1422, 1350, 1265, 1167; HPLC (12% EtOH/Hexane, 1.0 mL/min) (*R*) = 25.8, (*S*) = 30.9 min. Anal. Calcd for $C_{18}H_{18}N_2O_7S$: C, 53.19; H, 4.47; N, 6.90. Found C, 53.34; H, 4.54; N, 6.67.

(*S*)-Ethyl-3-Benzoyl-2-(methanesulfonylamino)propanoate (5f). Colorless oil; $[\alpha]_D$ = +16.4 (c = 0.02, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.90 (d, 2H), 7.61 (t, 1H), 7.47 (t, 2H), 5.58 (d, 1H), 4.47 (m, 1H), 4.21 (m, 2H), 3.80 (m, 1H), 3.57 (m, 1H), 3.07 (s, 3H), 1.20 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 135.6, 133.9, 128.8, 128.1, 62.2, 52.2, 42.4, 41.5, 14.0 ppm; IR (CH_2Cl_2): 3056, 2975, 2936, 1736, 1681, 1338, 1261, 1152, 906; HPLC (10% EtOH/Hexane, 1.0 mL/min) (*R*) = 42.44, (*S*) = 50.54 min. Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.73; N, 4.68. Found C, 51.98; H, 5.79; N, 4.72.

(*S*)-Ethyl-3-Benzoyl-2-((trimethylsilyl)ethanesulfonylamino)-propanoate (5g). Colorless oil; $[\alpha]_D$ = +17.3 (c = 0.026, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.91 (d, 2H), 7.58 (t, 1H), 7.45 (t, 2H), 5.44 (d, 1H), 4.44 (m, 1H), 4.20 (m, 2H), 3.78 (m, 1H), 3.56 (m, 1H), 3.03 (m, 2H), 1.23 (t, 3H), 1.03 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 197.3, 171.0, 135.7, 133.9, 128.7, 128.1, 62.0, 52.2, 50.0, 42.6, 14.0, 10.3, -2.02 ppm; IR (CH_2Cl_2): 3206, 2912, 1740, 1676, 1325, 1220, 1152, 1116, 1029; HPLC (10% EtOH/Hexane, 1.0 mL/min) (*R*) = 42.44, (*S*) = 50.54 min. Anal. Calcd for $C_{17}H_{27}NO_5SSi$: C, 52.97; H, 7.07; N, 3.64. Found C, 52.72; H, 7.18; N, 3.71.

(2*S*)-4-Phenyl-2-(toluene-4-(trimethylsilyl)ethanesulfonyl)-pent-4-enoic acid ethyl ester (5h). Colorless oil; $[\alpha]_D$ = +5.3 (c = 0.004); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H), 5.38 (s, 1H), 5.18 (s, 1H), 4.77 (d, 1H), 4.12 (m, 1H), 4.00 (m, 2H), 3.01 (m, 1H), 2.92 (m, 1H), 2.76 (m, 2H), 1.20 (t, 3H), 0.90 (m, 2H), -0.03 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.8, 142.9, 139.2, 128.5, 128.0, 126.3, 117.1, 61.7, 54.7, 49.9, 39.4, 14.0, 10.1, -2.07 ppm; IR (CH_2Cl_2): 3209, 1736, 1339, 1145, 910; HPLC (10% iPrOH/Hexane, 1.0 mL/min) (*R*) = 8.25, (*S*) = 9.15 min. Anal. Calcd for $C_{18}H_{29}NO_4SSi$: C, 56.37; H, 7.63; N, 3.65. Found C, 56.57; H, 7.60; N, 3.55.

(*S*)-Ethyl-3-(phenylcarboxy)-2-(trimethylsilylethanesulfonylamino)-propanoate (5i). Colorless oil; $[\alpha]_D$ = + 5.7 (c = 0.012, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.37 (t, 2H), 7.22 (t, 1H), 7.05 (d, 2H), 5.38 (d, 1H), 4.42 (m, 1H), 4.22 (m, 2H), 3.24 (m, 1H), 3.10 (m, 1H), 3.00 (m, 2H), 1.26 (t, 3H), 1.08 (m, 2H), 0.02 (s, 9H) ppm; ^{13}C NMR

($CDCl_3$) δ 170.3, 169.3, 150.1, 129.5, 126.2, 121.2, 62.4, 52.6, 50.1, 38.4, 14.1, 10.3, -2.05 ppm; IR (CH_2Cl_2): 3296, 2955, 1751, 1593, 1332, 1251, 1194, 1145; Anal. Calcd for $C_{17}H_{27}NO_6SSi$: C, 50.86; H, 6.78; N, 3.49. Found C, 50.67; H, 6.85; N, 3.52.[25]

(*S*)-Ethyl-3-(benzoyl)-2-(acetamino)propanoate (5j). Colorless oil; $[\alpha]_D$ = +31.3 (c = 0.064, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.89 (d, 2H), 7.56 (t, 1H), 7.41 (t, 2H), 6.72 (d, 1H), 4.93 (m, 1H), 4.19 (q, 2H), 3.73 (m, 1H), 3.57 (m, 1H), 2.00 (s, 3H), 1.22 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 197.8, 171.1, 169.9, 135.8, 133.7, 128.7, 128.0, 61.7, 48.2, 40.4, 23.0, 13.9 ppm; IR (CH_2Cl_2): 3437, 3055, 1741, 1680, 1503, 1265, 1219; HPLC (10% iPrOH/Hexane, 0.4 mL/min) (*R*) = 41.1, (*S*) = 43.4 min. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found C, 63.74; H, 6.45; N, 5.26.

(*S*)-Ethyl-3-(phenylcarboxy)-2-(amino)propanoate hydrochloride (8a).[9] Potassium carbonate (45 mg, 0.33 mmol) was added to a solution of optically pure (*S*)-**5e** (40 mg, 0.10 mmol) and thiophenol (13 mg, 0.11 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at room temperature overnight. The volatiles were removed *in vacuo* and the residue was taken up in Et_2O and extracted with 1 N HCl. The acid layer was basified with solid potassium carbonate and extracted with EtOAc (3 mL) to afford 28 mg of the crude amine. The crude compound was dissolved in Et_2O and gaseous HCl was bubbled through the solution to precipitate the hydrochloride salt **6a** (22 mg, 88% yield): $[\alpha]_D$ = + 5.5 (c = 0.010, D_2O); ^1H NMR (D_2O) δ 8.00 (d, 2H), 7.72 (t, 1H), 7.58 (t, 2H), 4.58 (m, 1H), 4.28 (m, 2H), 3.94 (q, 2H), 1.22 (t, 3H) ppm; ^{13}C NMR (D_2O, dioxane reference) δ 199.7, 170.3, 135.5, 135.4, 129.6, 128.9, 64.3, 49.5, 38.7, 13.7 ppm; IR (NaCl): 3305, 3054, 1740, 1350, 1265, 1167; HPLC (amine) (20% EtOH/Hexane, 1.4 mL/min) (*R*) = 8.15, (*S*) = 9.54 min. Anal. Calcd for $C_{12}H_{16}ClNO_3$: C, 65.13; H, 6.84; N, 6.33. Found C, 65.33; H, 6.85; N, 6.26. Acidic hydrolysis of **6** in 6 M HCl yielded (L)-benzoylalanine hydrochloride (96%) which was identical in all respects ([α], ^1H NMR, ^{13}C NMR and IR) to the literature compound.[12]

Deprotection of 5d.[20] Compound **5d** (50 mg, 0.12 mmol) was taken up into a solution of (trifluoroacetic acid:thioanisole; 9:1; 1 mL) followed by the addition of methylsulfonic acid (0.2 mL). The mixture was stirred for 12 h at rt and the volatiles removed under high vacuum. The resulting oil was diluted with 1 N HCl (2 mL) and washed repeatedly with Et_2O, the aqueous layer was basified with K_2CO_3, and extraction with EtOAc. The EtOAc layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a yellow oil. The crude compound was dissolved in Et_2O and gaseous HCl was bubbled through the solution to precipitate the hydrochloride salt **6** (24 mg, 77% yield). Acidification of amine **6** as stated above produced (L)-benzoylalanine in similar yield.

Deprotection of 5g.[26] A solution of compound **5g** (65 mg, 0.17 mmol) and Cesium fluoride (82 mg, 0.54 mmol) were heated together in DMF (1 mL) for 24 h. The reaction mixture was concentrated and the resulting crude residue was partitioned between Et_2O

and 1 M HCl. Basification of the acid layer followed by extraction with EtOAc (3 mL) afforded the crude amine which was transformed to the hydrochloride salt as above (36 mg, 90% yield). The amine was refluxed for 4 h in 6M HCl and concentrated to afford 34 mg (87% overall yield) of (L)-benzoylalanine hydrochloride.

One pot Synthesis of 5a. A solution of toluenesulfonamide (150 mg, 0.88 mmol) and freshly distilled ethyl glyoxylate (90 mg, 0.88 mmol) were mixed together in CH_2Cl_2 (3 mL). After 1 h, a solution of catalyst **2** was added and the reaction mixture was stirred at rt for 24 h. The enol silane **4a** was then added to the mixture at 0 °C over a 30 min period. After 2 h, the reaction was quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (3 mL). The aqueous layer was reextracted with CH_2Cl_2 and the combined organics were dried with $MgSO_4$ and concentrated. The crude reaction mixture was triturated with hexanes and the resulting crystals were recrystallized from Et_2O to yield 294 mg (89%) of compound **5a**. Chiral HPLC analysis revealed that the product was 95% enantiomerically enriched.

Synthesis of [L]-*m*-Nitrobenzoylalanine. To solution of N, O acetal **1d** (2.18 g, 6.5 mmol) in THF (20 mL) was added 1-(*m*-Nitrophenyl)-1-(trimethylsilyloxy)ethylene[27] (1.7 g, 7.0 mmol) and a solution of catalyst **2** (100 mg, 0.1 mmol) at rt. The reaction was refluxed for 24 hours and quenched with water (15 mL). The product was extracted from the THF:H_2O mixture with CH_2Cl_2 (2 x 20 mL). The combined organics were dried, concentrated and chromatographed on silica gel (1:5:5 EtOAc:Hexanes:CH_2Cl_2) to afford 2.45 g (85% yield, 94 %ee) of a yellow crystalline solid. Recrystallization of **5k** from EtOAc/Hexanes provided 1.8 g of 99% enantiomerically enriched material. mp = 130-131°C $[\alpha]_D$ = +21.9 (c = 0.05, EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1H), 8.43 (d, 2H), 8.33 (d, 2H), 8.22 (d, 1H), 8.04 (d, 2H), 7.68 (t, 1H), 6.00 (d, 1H), 4.37 (m, 1H), 4.03 (m, 2H), 3.79 (m, 1H), 3.66 (m, 1H), 1.04 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 194.9, 169.5, 150.1, 148.4, 145.6, 136.7, 133.5, 130.2, 128.5, 128.2, 124.2, 123.0, 62.6, 51.8, 42.5, 13.9 ppm; IR (CH_2Cl_2): 3355, 3075, 2942, 1742, 1692, 1613, 1535, 1352, 1313, 1221, 1169; HPLC (15% EtOH/Hexane, 1.0 mL/min) (*R*) = 41.1, (*S*) = 43.1 min. Anal. Calcd for $C_{18}H_{17}N_3O_9S$: C, 47.89; H, 3.80; N, 9.31. Found C, 47.75; H, 3.84; N, 9.28. Deprotection of the nitrosulfonyl group was done analagously to compound (*S*)-**5e** stated above. The ethyl ester was cleaved by heating in 6M HCl (10 mL) to yield 0.703 g (77% overall) of the enantiomerically pure [L]-*m*-Nitrobenzoylalanine.[13b]

General Synthesis of N,N-Acetals. The requisite amide or sulfonamide (5.0 g, 29.2 mmol) was mixed with ethyl glyoxylate (1.5 g, 14.6 mmol) and refluxed for several hours in toluene with a Dean-Stark trap to remove water. The reactions were monitored by ^{1}H NMR assays. The reactions were worked up by removal of the solvent and recrystallization of the crude material in EtOAc or Et_2O.

Representative Alkylation Procedure of N,N-Acetals. The catalyst was made by dissolving (*R*)Tol-BINAP (15 mg, 0.022 mmol) and $CuClO_4$•$(CH_3CN)_2$ (7 mg, 0.021 mmol) in THF. To the 4-Nitrobenzenesulfonyl N,N-acetal (150 mg, 0.30 mmol), in THF (2 mL) was added the solution of catalyst **2**. To this reaction mixture was added the enol silane of acetophenone (114 mg, 0.60 mmol) at room temperature. The reaction was stirred at room temperature or heated to reflux until completion as shown by TLC (30% EtOAc/Hexanes). The reaction was partitioned with water (3 mL) and CH_2Cl_2 (3 mL). The organic layer was dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was subject to column chromatography on silica gel to yield the final product (85% yield, 87% ee).

***N,N*-di-*p*-Toluenesulfonylglycine ethyl ester (1j).** White crystalline solid recrystallized from EtOAc; mp = 178-180 °C, Yield = 89%. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 4H), 7.40 (d, 2H), 7.38 (d, 4H), 5.40 (t, 1H), 3.87 (q, 2H), 2.41 (s, 3H), 1.03 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.5, 143.8, 139.5, 130.0, 127.6, 64.6, 62.6, 29.0, 13.7 ppm; IR (NaCl): 3279, 2917, 1746, 1531, 1436, 1348; Anal. Calcd for $C_{18}H_{22}N_2O_6S_2$: C, 50.69; H, 5.20; N, 6.57. Found C, 50.75; H, 5.23; N, 6.59.

***N,N*-di-*p*-nitrobenzenesulfonylglycine ethyl ester (1k).** Yellow crystalline solid recrystallized from CH_3CN; mp = 190-192 °C, Yield = 83%. ^{1}H NMR (CD_3CN) δ 8.28 (d, 4H), 7.97 (d, 4H), 7.00 (d, 2H), 5.41 (t, 1H), 3.95 (q, 2H), 1.02 (t, 3H) ppm; ^{13}C NMR (CD_3CN) δ 167.0, 151.1, 147.3, 129.2, 125.2, 64.6, 63.8, 14.0 ppm; IR (NaCl): 3281, 3108, 1749, 1607, 1531, 1444, 1351, 1311; Anal. Calcd for $C_{16}H_{16}N_4O_{10}S_2$: C, 39.34; H, 3.30; N, 11.48. Found C, 39.50; H, 3.34; N, 11.41.

***N,N*-dimethanesulfonylglycine ethyl ester (1l).** White crystalline solid recrystallized from EtOAc; mp = 152-154 °C, Yield = 86%. ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 1H), 5.43 (t, 1H), 4.28 (q, 2H), 3.11 (s, 3H), 1.09 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.5, 64.9, 63.3, 42.5, 14.3 ppm; IR (CH_2Cl_2): 3284, 1747, 1442, 1319; Anal. Calcd for $C_6H_{14}N_2O_6S_2$: C, 26.27; H, 5.15; N, 10.22. Found C, 26.41; H, 5.17; N, 10.26.

O-Silylation NMR Experiment: The following 0.5 mL CD_2Cl_2 solutions were made up A) N-p-Toluenesulfonylhydroxyglycine ethyl ester **1a** (25 mg, 0.091 mmol) B) Cu(I)ClO_4•$(CH_3CN)_4$ (30 mg, 0.091 mmol) and (*R*)-Tol-BINAP (62 mg, 0.091 mmol) C) 1-phenyl-1-(trimethylsilyloxy)ethylene **4a** [35 mg, 0.181 mmol, ^{1}H NMR: δ 7.65 (d, 2H), 7.38 (m, 3H), 5.00 (s, 1H), 4.51 (s, 1H), 0.38 (s, 9H) ppm]. Solutions A and B were mixed together. No detectable peak shifts were observed. A solution of C (0.125 mL) is added to the solution of A/B. The spectra contained peaks corresponding to both the enol silane (see above) and acetophenone [^{1}H NMR: δ 8.01 (d, 2H), 7.58 (t, 1H), 7.50 (t, 2H), 2.62 (s, 3H) ppm]. The amide peak of **1a** (δ 5.95 ppm) maintained its relative integration. The relative integration of the alcohol proton of **1a**, however, (δ 3.78 ppm) decreased and the presence of a new silyl group (δ 0.18 ppm) emerged. Another 0.130 mL of C is added to A/B and

the spectra taken at 5 min and 1 hr after the addition. After 1 hr all new peaks can be attributed to the product **5a**. The rest of C is added to A/B and the proton spectra collected at 5 min, 1 hr, 2 hr, 4 hr and 18 hr. During this period the smooth conversion to product is observed. As indicated in the text: 1) peaks corresponding to the silylated product **9** are not observed during the reaction. 2) peaks corresponding to the imine **3** are not observed. In a separate experiment, *N*-*p*-Toluenesulfonylhydroxyglycine ethyl ester **1a** (25 mg, 0.091 mmol) and 1-phenyl-1-(trimethylsilyloxy)ethylene **4a** (70 mg, 0.364 mmol) were dissolved in CD_2Cl_2 (0.75 mL) and a ^1H spectra was obtained. There is no evidence for any product formation under these conditions even after 18 hr.

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