Catalytic, Enantioselective Alkylations of *N,O*-Acetals

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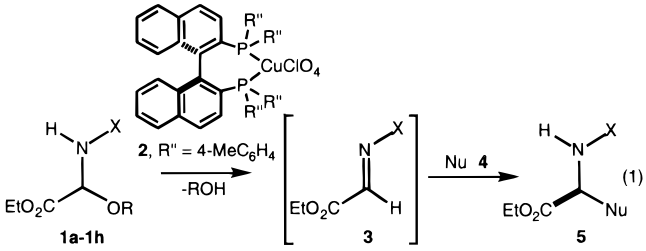
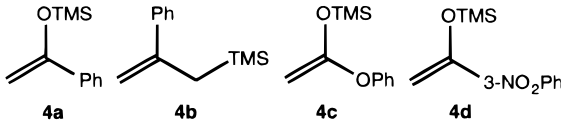
Over the past few years, asymmetric alkylation reactions of acetals have attained a prominent position in organic synthesis.[1] Methods employing either chiral acetals or promoters are well-known; however, those utilizing a substoichiometric quantity of catalyst on either achiral or racemic acetals are few,[2] and procedures employing *N,O*-acetals remain unknown. We anticipated that the asymmetric alkylation of *N,O*-acetals could efficiently lead to useful chiral amines and amino acid derivatives, especially in cases where the corresponding imines are less easily accessed (eq 1). However, in order for an asymmetric variant



to be successful, the Lewis acid catalyst must effectively serve a dual role, namely to dissociate RO^- and subsequently to activate the intermediate imine toward enantioselective addition. When X is an electron-withdrawing group, we have found that racemic hemiacetals **1a**−**1h** possessing a flexible range of N-protecting groups become stable, convenient precursors to useful enantioenriched products.[3] We describe the first high-yielding (73−93%) asymmetric alkylations (ee's up to 96%) of conveniently prepared *N,O*-acetals using our versatile chiral Cu(I)-based Lewis acid catalyst **2**. We also summarize a process to synthesize several non-natural amino acids[4] in high yield using readily available precursors via an in situ generation of *N,O*-acetals in a one-pot procedure.[5] We discovered that a unique transilylation reaction starts off the catalytic, enantioselective alkylation; other mechanistic investigations of our process reveal novel features that may lend general significance to alkylations of acetals by enol silanes.

Table 1. Reactions of *N,O*-Acetals and Various Nucleophiles Catalyzed by Complex 2



4a **4b** **4c** **4d**

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

[a] 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. [b] Reaction carried out in refluxing CH_2Cl_2. [c] Enantiomeric excesses determined by ^1H NMR in the presence of $Pr(hfc)_3$ chiral shift reagent.

When a solution of **1a** and catalyst **2** (6 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).[6] 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.[7] 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**, containing a 2,6-dimethyl-4-methoxybenzenesulfonyl (Mds)[8] group, reacts with enol silane **4a** in the presence of 6 mol % **2** to yield **5d** (87% yield, 94% ee, entry 4). It is noteworthy that the nature of the leaving group in substrate **1c** (OH vs OEt) does not significantly lower the yield or selectivity of product **5d** (entry 5). Similarly, the 4-nitrophenylsulfonamido (Ns)[9] acetal **1d** affords product **5e** in 87% ee and 89% yield (entry 6). Excellent selectivity (up to 96% ee) can also be achieved

(1) For reviews, see: Alexakis, A.; Mangeney, P. *Tetrahedron*: *Asymmetry* **1990**, *1*, 477−511. (b) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043−1054. For mechanistic work on alkylation of acetals: (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916. (d) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999.

(2) Hoveyda et al. have developed a Ni-catalyzed alkylation reaction of allylic acetals as formal equivalents for conjugate addition reactions: (a) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650. For reviews of achiral α-amidoalkylation reactions, see: (b) Zaugg, H. E. *Synthesis* **1984**, 85−110. (c) Zaugg, H. E. *Synthesis* **1984**, 181−212. For amido alkylation using stoichiometric quantities of Lewis acid, see: (d) Mooiweer, H. H.; Ettema, K. W. A.; Hiemstra, H.; Spekamp, W. N. *Tetrahedron* **1990**, *46*, 2991−2998. (e) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843−844. (f) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172−1175.

(3) Our recent work has focused on the use of chiral, transition metal−phosphine complexes **2** to catalyze the addition of carbon-based nucleophiles **4** to imino esters **3** (X = Ts) with high diastereo- and enantioselectivity to yield protected amino acids **5**: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090−6091. (c) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006−11007. The drawbacks of this synthetic methodology are the purification and hydrolytic lability of the imine **3** as well as the deprotection of the tosyl group after alkylation.

(4) Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Pergamon: New York, 1989.

(5) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *51*, 5773−5776.

(6) General procedure for conduction of alkylation reactions: 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 min. 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 subjected to column chromatography on silica gel to yield 128 mg of the final product (93% yield, 95% ee).

(7) Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649−651.

(8) Fujino, M.; Wakimasu, M.; Kitada, C. *Chem. Pharm. Bull.* **1981**, *10*, 2825−2831.

(9) Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787−15798.

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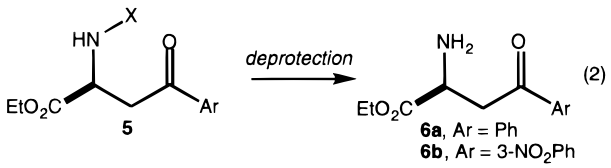
by using the trimethylsilylethanesulfonamido (SES)[10] substituent on the *N*,*O*-acetal to form products **5g**, **5h**, and **5i** (entries 8−10). A slight loss in selectivity is noted when the steric bulk of the sulfonamido group is diminished, as shown in the alkylation of **1e** (X = Ms; 85% ee, entry 7). However, the decrease in selectivity is more pronounced in the alkylations of amide acetals **1g** and **1h**, affording product **5j** in modest ee (entries 11 and 12). These results confirm that the sulfonyl group is an important factor in determining enantioselectivity.

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 **5b** 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% and 70% ee, respectively (entries 3 and 10). Once again, an array of sulfonamido groups including SES,[10] Mds,[8] and Ns[9] were highlighted. In the deprotection step, compounds **5d**, **5e**, and **5g** can be converted to amine hydrochloride **6a** in yields ranging from 75 to 87% with no detectable racemization (eq 2).[12] In fact, we used this

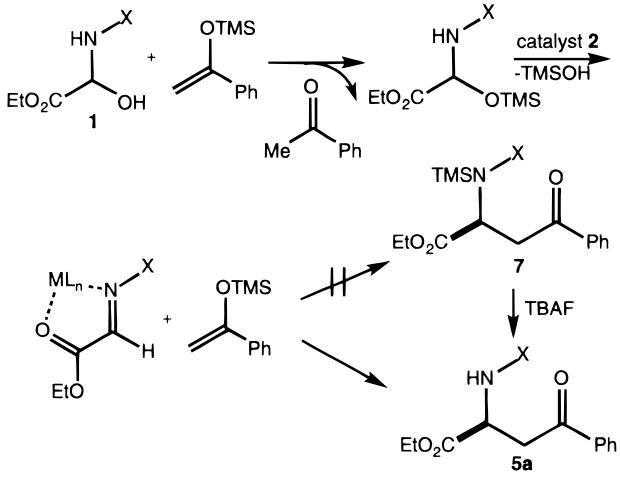


5d X = Mds, conditions = 9:1 TEA/MSA, PhSMe
5e X = Ns, conditions = PhSH, K_2CO_3
5g X = SES, conditions = CsF/DMF

methodology for the multigram synthesis of L-3-nitrobenzoylalanine (**6b**, 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, including kynurenine-3-hydroxylase and kynureninase.[13] 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** (6 mol %). The reaction mixture was then cooled to 0 °C, and 2 equiv of nucleophile **4a** was added. After 2 h, 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).

To our surprise, the use of 1 equiv of enol silane **4a** with *N*,*O*-acetal **1a** did not lead to product **5a** with 6 mol % **2**; however, when 2 equiv was used, product **5a** was formed in good yield. Although silyl ketene acetals can be quenched through silyl transfer reactions with alcohols, enol silanes

Scheme 1. Proposed Mechanism of N,O-Alkylation



are not well-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. 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.[15] Interestingly, peaks due to the intermediate imine **3**[16] were not observed, nor were those for the N-trimethylsilylated product **7** (Scheme 1). In our previous work, imine **3** (X = Ts) reacts with enol silane **4a** in the presence of catalyst **2** to produce **7** exclusively (Scheme 1)[3] that retains its silyl group through aqueous workup. In fact, product **7** 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 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,[17] 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 cannot 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.

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Supporting Information Available: General procedures for the conduct of catalytic reactions, spectroscopic details for all new compounds, and proof of absolute configuration.

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(12) All deprotection products **6a** were converted to L-benzoylalanine upon acidic hydrolysis. The hydrolysis products were identical in every way to the literature compound; see: Gulobev, A. S.; Sewald, N.; Burger, K. *Tetrahedron* **1996**, *52*, 14757−14776. See Supporting Information for details.

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(15) See the Supporting Information for details.

(16) Imine **3** has been fully characterized by Wienreb et al.: Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058−5064.

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