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A Chiral Ag-Based Catalyst for Practical, Efficient, and Highly Enantioselective Additions of Enolsilanes to α-Ketoesters

Laura C. Akullian, Marc L. Snapper,* and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received February 17, 2006; E-mail: amir.hoveyda@bc.edu

Research in these laboratories has led to the discovery of chiral amino acid-based metal complexes that catalyze C−C bond formation by addition of carbon nucleophiles to imines,[1] ketones,[2] and olefins.[3] An objective of these programs is the development of efficient and practical methods for enantioselective formation of sterically hindered carbon centers, such as all-carbon quaternary stereogenic centers[4] and tertiary alcohols.[2] Accordingly, we have initiated a program toward development of effective catalysts for asymmetric aldol reactions of ketones.

Through enantioselective Mukaiyama aldol reactions,[5] α-ketoesters can be converted to synthetically versatile optically enriched tertiary alcohols. A limited number of related catalytic protocols have been disclosed. Evans has outlined the use of chiral C_2-symmetric bis(oxazolinyl)Cu(II) complexes in catalytic enantioselective additions of *tert*-butyl thioketene acetals to alkyl-substituted α-ketoesters (36% ee with *i*-Pr-substituted ketone).[6] Pagenkopf has used modified bis(oxazoline) ligands in Cu(II)-catalyzed reactions of dienolsilanes to aryl- and alkyl-substituted α-ketoesters.[7] Bolm has shown that C_1-symmetric chiral sulfoximines are effective in Cu(II)-catalyzed aldol reactions of acetophenone-derived trimethylsilylenol ether and *n*-alkyl-substituted α-ketoesters.[8] Nonetheless, noteworthy shortcomings persist. Substrate generality, particularly in reactions of enolsilanes with α-ketoesters that bear sterically demanding substituents, remains a challenge. There are pressing issues of practicality: Cu(II)-catalyzed processes require rigorous exclusion of air and moisture (drybox techniques).

Herein we report a new Ag-based chiral catalyst that promotes enantioselective additions of ketone-derived enolsilanes to α-ketoesters that contain alkyl, alkenyl, and aromatic substituents.[9] Reactions proceed to >98% conversion with 1−10 mol % of AgF_2 and an amino acid-based ligand that bears a pyridyl Schiff base—a metal/ligand combination identified as optimal for the first time. Desired products are typically isolated in >90% yield and in up to 96% ee. Highest enantioselectivities are observed with sterically demanding alkyl-substituted α-ketoesters. The method is operationally simple: *reactions can be easily carried out with commercially available Ag salts (without purification), in air and with undistilled solvent.*

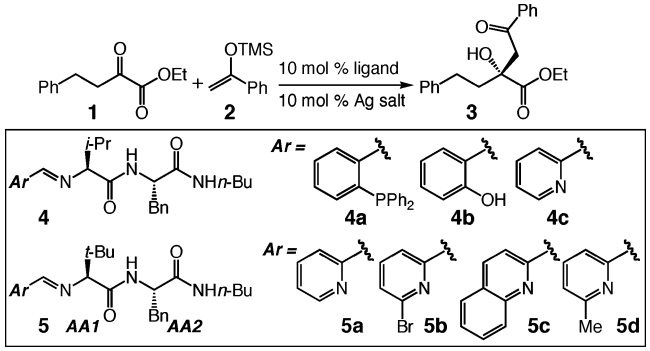
Catalyst optimization strategies developed in these laboratories[10] were utilized to probe the efficiency of an assortment of amino acid-based ligands in combination with a range of transition metal salts (e.g., Cu(I), Cu(II), Ag(I), Al(III), Zn(II), Sc(III), and Yb(III) salts) to promote enantioselective Mukaiyama aldol addition of α-ketoester **1** and enolsilane **2**. With L- or D-Val and Phe serving as the initial representative amino acid moieties (AA1 and AA2; see Table 1), small peptides including those bearing a phosphine (e.g., **4a**), a phenol (e.g., **4b**), or a pyridyl (e.g., **4c**) N-terminus moiety were investigated; ligands bearing a single amino acid, as well as those with amine and amide linkages at their N-termini (vs Schiff bases, such as **4a**−**c**) were scrutinized.

Preliminary studies led us to determine that AgOAc or AgF, in combination with certain dipeptide ligands, generate appreciable reactivity and enantioselectivity (Table 1). Phosphines, such as **4a**, optimal for Mannich-type reactions,[1c,11] promote nonselective additions (entries 1−2, Table 1). Salicyl-based systems, such as **4b**, are ineffective (entry 3). However, pyridyl-based **4c** in combination with AgF delivers **3** in 73% conversion and 23% ee (24 h, 0 °C). Further screening indicated that higher asymmetric induction can be attained with L-*t*-Leu as AA1 and L-Phe as AA2: **3** is isolated in 56% ee with **5a** and AgF (entry 6). Examination of modified pyridyl termini, represented by **5b**−**d** (entries 7−9), pointed to Me-substituted **5d** as the preferred ligand (63% ee, >98% conv). Lowering of temperature[12] leads to enhancement of enantioselectivity (84% ee) but reduced reactivity (60% conv). To improve catalyst activity, we turned to AgF_2, an oxidant that can serve as a source of AgF.[13] Under optimized conditions (entry 11, Table 1), the reaction proceeds to >98% conversion to afford **3** in 84% ee (86% ee and 92% yield at −40 °C; entry 1, Table 2).

As the findings summarized in Table 2 illustrate, the combination of AgF_2 and **5d** can be used to catalyze enantioselective aldol reactions of enolsilanes and a variety of α-ketoesters in high yield and in up to 96% ee.

Several points regarding data in Table 2 are noteworthy. (1) Reactions of *n*-alkyl-substituted substrates deliver products in 86−92% ee (entries 1−3). Addition to methyl pyruvate affords the desired product in 60% ee and 62% yield (>98% conv, −30 °C, 24 h). However, Ag-catalyzed processes are particularly effective

Table 1. Initial Screening of Chiral Ligands. Selected Data[a]



entry	ligand	Ag salt	temp (°C)	conv (%)[b]	ee (%)[c]
1	**4a**	AgOAc	0	55	<2
2	**4a**	AgF	0	40	<2
3	**4b**	AgOAc or AgF	0	<2	
4	**4c**	AgOAc	0	54	13
5	**4c**	AgF	0	73	23
6	**5a**	AgF	0	>98	56
7	**5b**	AgF	0	>98	29
8	**5c**	AgF	0	>98	18
9	**5d**	AgF	0	>98	63
10	**5d**	AgF	−30	60	84
11	**5d**	AgF_2	−30	>98	84

[a] Reactions in CH_2Cl_2 (entries 1−9) or THF (entries 10−11), under N_2 atm, 24 h. [b] Determined by 400 MHz ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis (see Supporting Information for details).

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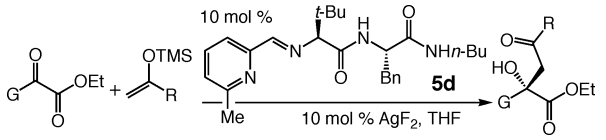
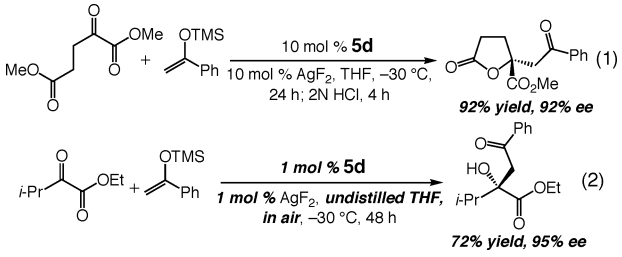
Table 2. Ag-Catalyzed Enantioselective Aldol Additions to α-Ketoesters



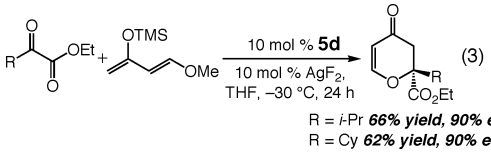
entry	G	R	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	$(CH_2)_2Ph$	Ph	−40	48	92	86
2[c]	$(CH_2)_2CO_2Me$	Ph	−30	24	95	92
3	CH_2 *i*-Pr	Ph	−30	24	95	87
4	*i*-Pr	Ph	−30	24	93	95
5	*i*-Pr	*t*-Bu	−15	48	61	92
6	*i*-Pr	Me	−40	48	>98	88
7	Cy	Ph	−30	24	98	95
8	Cy	Me	−30	24	97	90
9	cyclopropyl	Ph	−40	48	90	96
10	H_2C═CH(Me)	Ph	−40	48	98	90
11	Ph	Ph	−30	24	93	60
12	2-thienyl	Ph	−30	48	95	72

[a] With 1.2 equiv of enolsilane; >98% conversion; isolated yields. [b] Determined by chiral GLC or HPLC analysis (see the Supporting Information for details). [c] The corresponding α-ketomethylester was used.

with sterically hindered substrates (entries 4−10; 88−96% ee with those bearing α-branched alkyl and alkenyl groups). Reactions of aryl-substituted α-ketoesters proceed efficiently but with lower selectivity (entries 11−12); however, these are the best selectivities reported to date. (2) Enolsilanes derived from 3,3-dimethyl-2-butanone (entry 5) and acetone (entries 6 and 8) can be used; sterically hindered enolsilanes require elevated temperature (−15 °C) to proceed to >98% conversion. (3) Higher enantioselectivities can be obtained at −40 °C (vs −30 °C), although longer reaction times are needed (48 vs 24 h). For example, the process in entry 10 (Table 2) affords the desired tertiary alcohol in 91% ee (85% yield) at −30 °C (24 h). (4) There is <2% conjugate addition product formed with the α,β-unsaturated substrate in entry 10.[14] (5) Optically enriched products bearing a suitably positioned carboxylic ester (cf. entry 2, Table 2) can be converted to the derived lactone simply by the use of acidic workup conditions; the example in eq 1 is illustrative. (6) Ag-catalyzed reactions were set up in air on a benchtop; the solution was purged with N_2 and the vessel sealed. Reactions can be carried out exposed to air and in commercial grade undistilled THF (eq 2). (7) Although transformations in Table 2 were run with 10 mol % catalyst, enantioselective additions proceed to >98% conversion, in high yield and enantioselectivity with 1 mol % catalyst loading (even when the solution is exposed to air); the example in eq 2 is illustrative.[15]



The catalytic process can be carried out with Danishefsky's diene (eq 3).[11] Reactions proceed with α-ketoesters that bear sterically hindered alkyl substituents with significantly higher enantioselectivity than that previously reported.[16] In contrast to Cu(II)-catalyzed methods,[17] the Ag-catalyzed reactions are run under operationally simple conditions.



We have thus identified a chiral amino acid-based ligand that in combination with AgF_2 promotes efficient and enantioselective Mukaiyama aldol additions to α-ketoesters. The catalytic process is effective with a range of substrates, particularly, those that bear sterically hindered alkyl substituents; the method is complementary, in terms of substrate range, to related catalytic enantioselective procedures.[6−8] Investigations directed toward outlining the mechanistic details[13] of the catalytic protocol are in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) At lower temperatures, increased reactivity is observed with THF as solvent (e.g., 42% conv in CH_2Cl_2 for entry 10).

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(15) When reactions are performed at >50 mg scale, addition of 1 equiv of MeOH is required for complete conversion. For example, the reaction in eq 2, with 250 mg of α-ketoester, proceeds to 33% conversion (10 mol % of **5d**, −30 °C, 24 h) but to >98% conversion in the presence of 1 equiv of MeOH. Presumably, on small scale, there is sufficient moisture present to ensure high conversion. Mechanistic details regarding the importance of a proton source are under investigation and will be reported in due course.

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