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Ag-Catalyzed Asymmetric Mannich Reactions of Enol Ethers with Aryl, Alkyl, Alkenyl, and Alkynyl Imines

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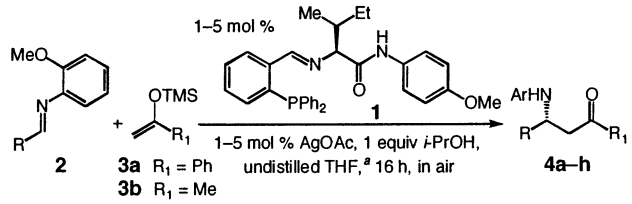
β-Amino carbonyls represent a class of compounds that can be used in the synthesis of biologically active molecules. The design and development of catalytic asymmetric methods for the preparation of these building blocks is thus a critical objective in chemical synthesis.[1] Several laboratories have disclosed significant advances regarding catalytic asymmetric additions of silyl ketene acetals to imines (mostly aryl imines).[2] Notable progress involving reactions of the less nucleophilic enol ethers to afford β-amino ketones has also been made; nonetheless, numerous challenges have not yet been effectively addressed. Two protocols are in connection with additions of ketones with non-metal-based catalysts;[3] however, typically high loadings (20−35 mol %)[3a,b] are required, and, in certain cases, reactions proceed with low enantioselectivities (<90% ee).[3a] Some of the more efficient enantioselective metal-catalyzed processes are particular to enol ethers and activated imines, such as those derived from glyoxylates.[4] One method has been designed for the synthesis of α-hydroxyl,β-amino carbonyls and is limited to reactions of enol ethers with an α-heteroatom (only aryl imines).[5] Another approach deals with transformations of ketones that contain an activating acyl substituent as well as a hydroxyl group adjacent to the carbonyl (predominantly aryl imines).[6]

Herein, we report a general Ag-catalyzed asymmetric method for additions of silyl enol ethers to aryl, alkyl, alkenyl, and alkynyl imines. β-Amino ketones are obtained efficiently and in high optical purity (up to >98% ee) in the presence of 1−5 mol % of AgOAc and the readily available iso-Leu-derived phosphine **1**. All catalytic transformations can be effected with undistilled solvents and in air. Amides or amines can be accessed by efficient removal of the *o*-anisyl activating group. The utility of the method is demonstrated by a concise enantioselective synthesis of alkaloid sedamine.

We first investigated the ability of chiral phosphine **1** and AgOAc in promoting catalytic Mannich-type reactions, based on recent results in connection with related cycloadditions.[7] Our studies focused on transformations involving TMS enol ethers **3a** and **3b** with imines derived from aromatic and heterocyclic aldehydes. Reactions of **3a** and **3b** are promoted efficiently (>98% conv) by 1−5 mol % **1** and AgOAc in undistilled THF without the need for an inert atmosphere (Table 1). As was the case with the related cycloadditions,[7] 1 equiv of *i*-PrOH is required for high conversion. Unsubstituted (**2a**), as well as *para*- and *meta*-substituted phenyl groups bearing electron-rich or electron-deficient aryl imines (entries 3−12, Table 1), undergo Ag-catalyzed reactions to afford the desired β-amino ketones in 86−98% ee. Electron-poor imines are more reactive such that their transformations can be effected at lower temperatures, giving rise to improved optical purities. Reactions of the electron-rich substrates (entries 3 and 4) are more selective when carried out in toluene (e.g., **4b** is obtained in 82% ee in THF). Catalytic asymmetric reactions of the more sterically demanding imines that bear an *ortho* substituent (entries 13 and 14) proceed efficiently but with lower asymmetric induction (74−80% ee). Heterocyclic imines also participate in facile and enantioselective additions (entries 15 and 16).

Table 1. Ag-Catalyzed Enantioselective Mannich Reactions of Silyl Ethers with Aryl Imines



entry	R		R_1		**1**, AgOAc (mol %)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	Ph	**3a**	3	−10	54	94
2	Ph	**2a**	Me	**3b**	5	−10	65	92
3	*p*-$OMeC_6H_4$	**2b**	Ph	**3a**	5	22	61	96
4	*p*-$OMeC_6H_4$	**2b**	Me	**3b**	5	22	71	90
5	*p*-$NO_2C_6H_4$	**2c**	Ph	**3a**	3	−5	88	92
6	*p*-$NO_2C_6H_4$	**2c**	Me	**3b**	5	−10	91	92
7	*p*-ClC_6H_4	**2d**	Ph	**3a**	1	4	84	96
8	*p*-ClC_6H_4	**2d**	Me	**3b**	5	−10	79	90
9	*m*-$NO_2C_6H_4$	**2e**	Ph	**3a**	3	−10	97	86
10	*m*-$NO_2C_6H_4$	**2e**	Me	**3b**	3	−5	96	86
11	2-naphth	**2f**	Ph	**3a**	3	−5	88	98
12	2-naphth	**2f**	Me	**3b**	3	−5	94	92
13	*o*-BrC_6H_4	**2g**	Ph	**3a**	5	4	70	80
14	*o*-BrC_6H_4	**2g**	Me	**3b**	5	4	46	76
15	2-furyl	**2h**	Ph	**3a**	3	4	84	86
16	2-furyl	**2h**	Me	**3b**	3	4	78	90

[a] Reactions in THF except entries 3 and 4 which were run in toluene. [b] Isolated yields. [c] By chiral HPLC.

The Ag-catalyzed method can be applied to alkenyl (**2i**−**k**, Table 2) and alkynyl imines (**2l**)[8] as well. As the data in Table 2 demonstrate, a range of unsaturated β-amino ketones **4i**−**l** have been prepared in synthetically useful yields and high enantioselectivities. The corresponding reactions involving aliphatic imines **2m**−**o**,[9] summarized in Table 3, can be carried out through a three-component process that affords the desired amines **5m**−**o** in 92−94% ee; the relatively low isolated yields are likely due to the instability of the aliphatic imine substrates. It should be noted that the equivalent of water released through in situ formation of the aliphatic imines obviates the need for the use of *i*-PrOH (cf., Tables 1 and 2).

The optically enriched Mannich products obtained through the Ag-catalyzed method can be converted to amines or Boc amide derivatives in >70% isolated yield through a simple oxidative procedure.[9] Two representative examples, involving an aryl (**6**) and an alkynyl β-amino ketone (**7**), are shown in eq 1. The unmasking operation is carried out in a single vessel at ambient temperature,

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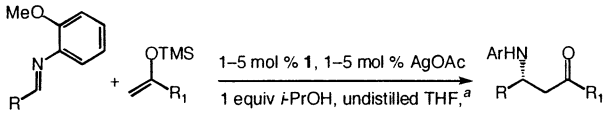
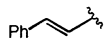
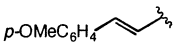
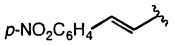
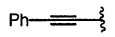
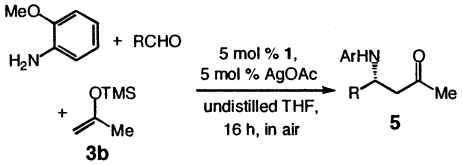
Table 2. Ag-Catalyzed Enantioselective Mannich Reactions of Silyl Enol Ethers with Unsaturated Imines



entry	R		R_1		1, AgOAc (mol %)	T (°C)	yield (%) [b]	ee (%) [c]
1		i	Ph	**3a**	1	4	51	90
2		i	Me	**3b**	1	4	77	89
3		j	Ph	**3a**	3	22	74	96
4		j	Me	**3b**	5	22	47	90
5		k	Ph	**3a**	3	–5	>98	92
6		k	Me	**3b**	3	–5	74	90
7		l	Ph	**3a**	1	4	93	92
8		l	Me	**3b**	3	–5	91	88

[a] Reactions in THF except entries 3 and 4. [b] Isolated yields. [c] By chiral HPLC.

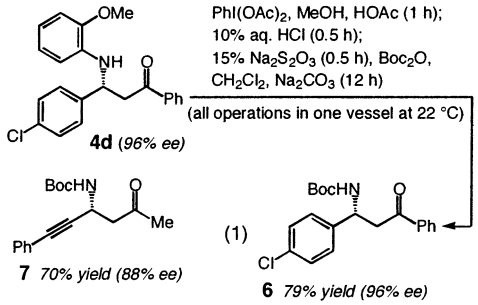
Table 3. Three-Component Ag-Catalyzed Asymmetric Mannich Reactions Involving Aliphatic Imines



entry	R		1, AgOAc (mol %)	*T* (°C)	yield (%)[a]	ee (%)[b]
1	n-$C_{10}H_{21}$	**m**	5	4	60	92
2	Cy	**n**	5	4	53	94
3	*i*-Bu	**o**	5	4	41	94

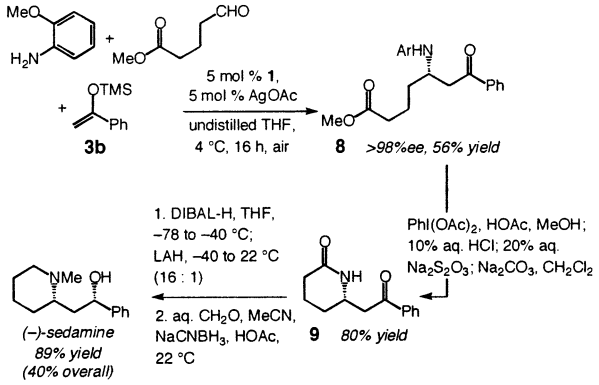
[a] Isolated yields. [b] By chiral HPLC.

and optically pure material can be obtained after simple recrystallization from hexanes.



Because of the range of imines and silyl enol ethers that can be effectively employed and the ubiquity of β-amino carbonyls, the Ag-catalyzed protocol should find utility in the synthesis of biologically active molecules.[10] One such application is depicted in Scheme 1 in the context of a brief total synthesis of optically pure (−)-sedamine.[11] The Ag-catalyzed three-component enantioselective reaction shown in Scheme 1 proceeds smoothly in the presence of an ester group, giving rise to **8** in >98% ee and 56% isolated yield. Oxidative removal of the *o*-anisyl group gives cyclic amide **9**. Diastereoselective reduction of the carbonyl group (16:1) (DIBAL-H)[12] and subsequent addition of LAH (to ensure complete

Scheme 1. Enantioselective Synthesis of Sedamine



conversion to the cyclic amine), followed by reductive amination in the presence of formaldehyde and $NaCNBH_3$,[13] affords the natural product in 89% yield.

Development of additional catalytic asymmetric Mannich reactions and related mechanistic studies are in progress.

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

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