$MgCl_2$-Catalyzed α-Amination of α-Alkyl-β-ketoesters via Oxidative *N*-Acylnitroso Aldol Reaction with Hydroxamic Acids

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Abstract: A practical method for α-amination of α-alkyl-β-ketoesters using hydroxamic acids is described. In this protocol, an oxidative *N*-acylnitroso aldol reaction is catalyzed by magnesium chloride in the presence of the oxidant *tert*-butyl hydroperoxide.

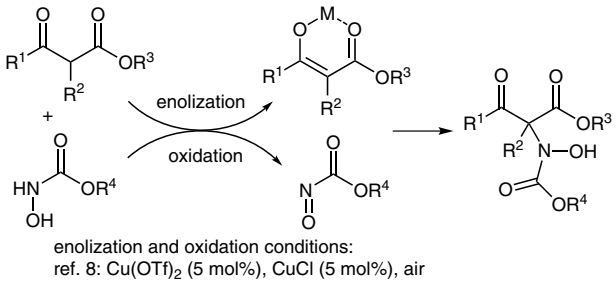
Key words: amination, α-alkyl-β-ketoesters, catalysis, magnesium chloride, acylnitroso

α-Amino-β-ketoesters are potential precursors of β-hydroxy-α-amino acids and of nitrogen-containing heterocyclic compounds that serve as important building blocks in many bioactive agents.[1–3] One pathway effective for constructing this useful scaffold is the direct electrophilic α-amination of β-ketoesters, and various aminating agents have been explored in this procedure.[4] In particular, aminating agents with nitrogen moieties that can react as aldol-type or Michael-type acceptors, such as azodicarboxylates, have been extensively investigated in the symmetric and asymmetric versions of this pathway.[5] However, few studies have examined acylnitroso species as aminating agents because they are highly reactive and usually need to be generated in situ via oxidation.[6,7]

Read de Alaniz and coworkers recently reported an N-selective acylnitroso aldol reaction that enables α-amination of α-alkyl-β-ketoesters; this procedure relies on acylnitroso intermediates as the electrophilic source of nitrogen. This one-pot transformation combines copper(II)-catalyzed enolization of β-ketoesters and copper(I)-catalyzed aerobic oxidation of hydroxamic acids (Scheme 1).[8] To ensure the success of this approach, the acylnitroso intermediates and enolates must be formed under compatible reaction conditions.[8,9] Here we describe a practical method in which compatible conditions can be ensured, using magnesium chloride to catalyze enolization and *tert*-butyl hydroperoxide (TBHP) for oxidation (Scheme 1).

During initial attempts to develop a new catalyst for the oxidative *N*-acylnitroso aldol reaction, we used the rhodium caprolactamate $[Rh_2(cap)_4]$/TBHP[11] catalytic protocol. Our previous studies on the oxidative acylnitroso hetero-Diels–Alder reaction[10] showed that $Rh_2(cap)_4$ accelerates the generation of acylnitroso compounds because it accelerates TBHP-mediated oxidation of hydroxamic acids. We carried out this approach in the present study using common bases such as Cs_2CO_3 or Et_3N, which promoted the enolization of β-ketoester **1a**, leading to the complete consumption of hydroxamic acid **2a**. However, no desired *N*-acylnitroso aldol product was observed (Table 1, entry 1). When we replaced the base with various Lewis acids, we found that catalytic amounts of magnesium chloride[12] facilitated the enolization of **1a** and generated α-amination product **3a** in 82% yield (Table 1, entry 2). Decreasing the catalyst loading of $Rh_2(cap)_4$ to 0.1 mol% did not affect the reaction, providing the desired product **3a** in 83% yield (Table 1, entry 3). In fact, comparably high yields were obtained in the absence of the precious rhodium catalyst: 83% at room temperature and 85% at 40 °C (Table 1, entries 4 and 5). Therefore we simplified our protocol for the acylnitroso aldol reaction to involve simply mixing starting materials with $MgCl_2$/TBHP in a suitable solvent.[13] Control experiments confirmed the necessity of each component in this simplified protocol: in the absence of TBHP,[14] no **2a** was consumed; in the absence of $MgCl_2$, the desired reaction did not occur, even though **2a** was oxidized by TBHP.

We then examined the substrate scope of this optimized protocol for $MgCl_2$-catalyzed α-amination of α-alkyl-β-ketoesters.[15] We tested a wide range of substituted β-ketoesters and *N*-hydroxycarbamates, obtaining high or excellent yields in most cases (Table 2). Various α-methyl-acetoacetates with different ester moieties, such as ethyl, benzyl, and *tert*-butyl, reacted smoothly to give high yields (**3a**–**c**). β-Ketoesters with alkyl substituents (linear or branched) or aryl substituents (electron-rich or elec-



Scheme 1 α-Amination of α-alkyl-β-ketoesters using hydroxamic acids

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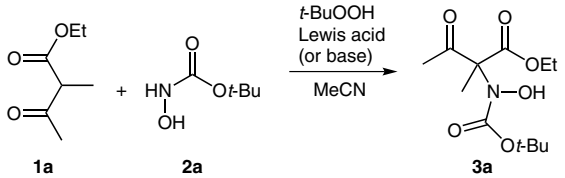
Table 1 $MgCl_2$-Mediated α-Amination of α-Alkyl-β-ketoesters[a]



1a 2a 3a

Entry	Catalytic protocol	Yield (%)[b]
1	$Rh_2(cap)_4$ (1.0 mol%), base (1.0 equiv)[c]	0
2	$Rh_2(cap)_4$ (1.0 mol%), $MgCl_2$ (10 mol%)	82
3	$Rh_2(cap)_4$ (0.1 mol%), $MgCl_2$ (10 mol%)	83
4	$MgCl_2$ (10 mol%)	83
5[d]	$MgCl_2$ (10 mol%)	85 (81)[e]

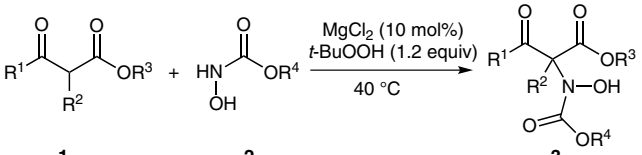
[a] Reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv), and *t*-BuOOH in nonane (1.2 equiv) at r.t., unless otherwise noted.
[b] Isolated yield of **3a** after purification by silica gel chromatography. The reaction was allowed to continue until **2a** was completely consumed based on TLC analysis.
[c] Base: Cs_2CO_3 or Et_3N; solvent: CH_2Cl_2.
[d] Reaction was performed at 40 °C.
[e] Preparation of **3a** on a 1-gram scale.

tron-deficient) at R^1 were effective nucleophilic partners, generating functionalized *N*-carbamate hydroxylamines **3a**–**l** in yields of 75–99%. Varying the substituents at the α-position of the β-ketoesters led to structurally diverse α-quaternary α-amino-β-ketoesters (**3m** and **3n**), as well as their cyclic counterparts (**3o**–**q**). Even hydroxylamines protected with the frequently used nitrogen-protecting groups Cbz, Troc, and Fmoc worked in our reaction, giving moderate to high yields of the desired products (**3r**–**t**). It is worth noting that we occasionally observed byproducts derived from the O-selective acylnitroso aldol reaction: **3a**, with a ratio of *N*-aldol product to *O*-aldol product of 13:1; **3d**, 18:1; **3r**, 13:1; and **3s**, 16:1.[9b]

The reaction was sluggish and low-yielding (<20%) with β-ketoesters containing hindered substituents at R^1 such as *tert*-butyl or bulky substituents at R^2 such as isopropyl. When the unsubstituted β-ketoester ethyl acetoacetate was used, the reaction produced an uncharacterized mixture. This result may reflect electrophilic transformations of an α-imino β-ketoester intermediate. Read de Alaniz and coworkers postulated that such an intermediate forms during the *N*-aldol reaction when ethyl acetoacetate and the acylnitroso intermediate couple together, and the β-hydroxyl group is eliminated.[8]

We then tried to extend this catalytic process to asymmetric catalysis, but our efforts proved fruitless. When we used MgI_2 as catalyst together with a chiral pybox ligand[16] in the reaction of **1a** and **2a**, we obtained α-amination product **3a** as a racemic mixture (Scheme 2, conditions 1 and 2).[17] In addition to TBHP, we tested the mild oxidant MnO_2,[9a] which gave **3a** in moderate yield without asymmetric induction (conditions 3).

Table 2 Substrate Scope for α-Amination of α-Alkyl-β-ketoesters Using Hydroxamic Acids[a–c]



1 2 3

R^1, R^2 = Alk, Ar
R^3 = Et, Bn, *t*-Bu, Me
R^4 = *t*-Bu, Bn, CCl_3CH_2, 9-fluorenylmethyl

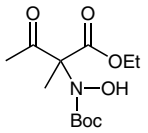
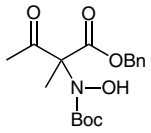
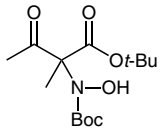
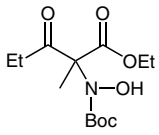
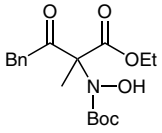
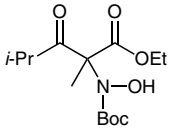
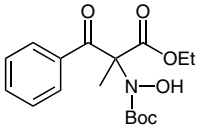
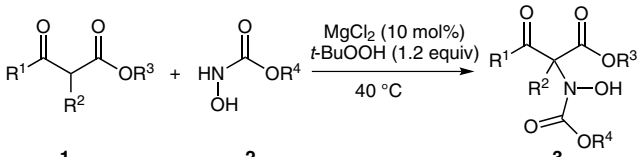
Entry	Product	Time (h)	Yield (%)
1	 **3a** N/O ratio[d] = 13:1	34	85
2	 **3b**	22	83
3	 **3c**	65	82
4	 **3d** N/O ratio[d] = 18:1	20	80
5	 **3e**	25	84
6	 **3f**	40	80
7	 **3g**	49	96

Table 2 Substrate Scope for α-Amination of α-Alkyl-β-ketoesters Using Hydroxamic Acids[a–c] (continued)



1 **2** **3**

R^1, R^2 = Alk, Ar
R^3 = Et, Bn, *t*-Bu, Me
R^4 = *t*-Bu, Bn, CCl_3CH_2, 9-fluorenylmethyl

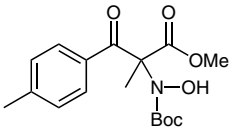
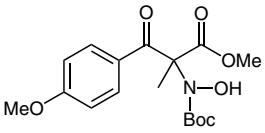
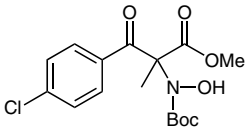
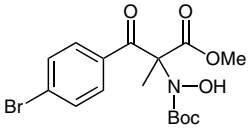
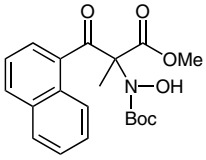
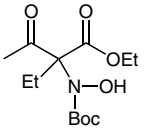
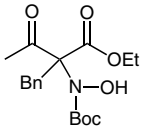
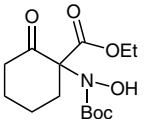
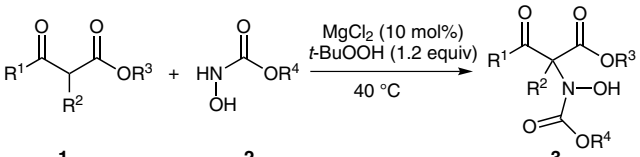
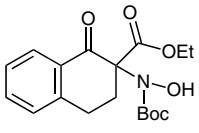
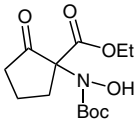
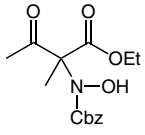
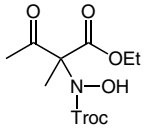
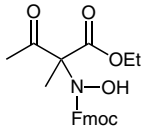
Entry	Product	Time (h)	Yield (%)
8	 **3h**	46	91
9	 **3i**	26	75
10	 **3j**	46	97
11	 **3k**	51	99
12	 **3l**	41	97
13	 **3m**	60	80
14	 **3n**	47	92
15	 **3o**	70	80

Table 2 Substrate Scope for α-Amination of α-Alkyl-β-ketoesters Using Hydroxamic Acids[a–c] (continued)



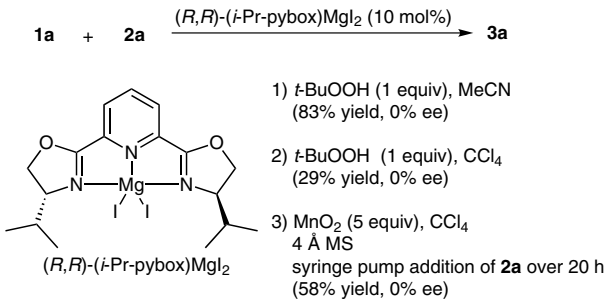
1 **2** **3**

R^1, R^2 = Alk, Ar
R^3 = Et, Bn, *t*-Bu, Me
R^4 = *t*-Bu, Bn, CCl_3CH_2, 9-fluorenylmethyl

Entry	Product	Time (h)	Yield (%)
16	 **3p**	78	90
17	 **3q**	65	57
18	 **3r** N/O ratio[d] = 13:1	8	87
19	 **3s** N/O ratio[d] = 16:1	17	89
20	 **3t**	90	41

[a] Reactions were performed using **1** (1.2 equiv), **3** (1.0 equiv), catalyst (10 mol%), and oxidant (1.2 equiv) in MeCN at 40 °C. Boc = *tert*-butoxycarbonyl; Cbz = benzyloxycarbonyl; Troc = (2,2,2-trichloroethoxy)carbonyl; Fmoc = [(9-fluorenylmethyl)oxy]carbonyl.
[b] Hydroxamic acid was completely consumed after the indicated time.
[c] Isolated yield of **3** after silica gel chromatography.
[d] The ratio of *N*-aldol product to *O*-aldol product (N/O ratio) was determined by ^{1}H NMR analysis of the crude reaction mixture.

In summary, we have developed a practical and efficient catalytic protocol for the α-amination of α-alkyl-β-ketoesters that relies on an oxidative *N*-acylnitroso aldol reaction with hydroxamic acids. In this process, the combination of $MgCl_2$ catalyst and TBHP oxidant simultaneously achieves the catalytic enolization of β-ketoester and oxidation of hydroxamic acid.



Scheme 2 Attempts to extend our protocol to asymmetric catalysis

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) For O-selective acylnitroso aldol reactions, see: (a) Cu(II)-catalyzed enolization–MnO_2 oxidation with syringe pump addition of hydroxamic acids: Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566. (b) Cu(II)-catalyzed enolization–Cu(I)-catalyzed aerobic oxidation: Frazier, C. P.; Sandoval, D.; Palmer, L. I.; Read de Alaniz, J. *Chem. Sci.* **2013**, *4*, 3857.

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(11) For $Rh_2(cap)_4$-catalyzed oxidation of tertiary amines to initiate the Mannich reaction or [3+2] cycloaddition reaction, see: (a) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (b) Wang, H.-T.; Lu, C.-D. *Tetrahedron Lett.* **2013**, *54*, 3015. For cascade transformations initiated by catalytic oxidation of tertiary amines using $CuBr_2$ and TBHP, see: (c) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. *Chem. Commun.* **2011**, 1036.

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(14) Less expensive T-HYDRO® (70 wt% *tert*-butylhydroperoxide in water) can also be used as terminal oxidant in this reaction; it provides comparable yields to those reported in the text.

(15) **General Experimental Procedure for the $MgCl_2$-Catalyzed α-Amination of α-Alkyl-β-ketoesters**
TBHP (5–6 M in decane, 0.48 mmol) was added dropwise to a mixture of β-ketoesters **1** (0.48 mmol), hydroxamic acids **2** (0.40 mmol), and $MgCl_2$ (3.8 mg, 0.040 mmol) in MeCN (2 mL). The reaction was stirred at 40 °C for the indicated time; reaction completion was confirmed based on the disappearance of hydroxamic acids (Table 2). Then the reaction mixture was cooled to r.t., quenched with aq $NaHSO_3$ solution and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford amination product **3**. This General Experimental Procedure was carried out using **1a** (69.2 mg, 0.48 mmol) and **2a** (53.2 mg, 0.40 mmol). The reaction mixture was stirred for 34 h at 40 °C and purified by silica gel chromatography using PE–CH_2Cl_2–EtOAc (4:1:0.75) as eluent to give product **3a** (94.3 mg, 85%) as a colorless oil. The structure of **3a** was identified by comparison of its ^{1}H NMR and ^{13}C NMR spectra with the reported data in ref. 8. See the Supporting Information for experimental details and characterization data for all new compounds.

(16) For selected examples of the use of (pybox)MgI_2 catalysts in asymmetric catalysis involving β-dicarbonyl compounds, see: (a) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (b) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.

(17) Chiral HPLC analysis conditions for **3a**: Chiralcel AD-H column (0.46 cm × 25 cm), hexanes–*i*-PrOH (97:3), flow rate = 1.0 mL/min, λ = 210 nm, t_R 1 = 16.4 min, t_R 2 = 19.8 min.

