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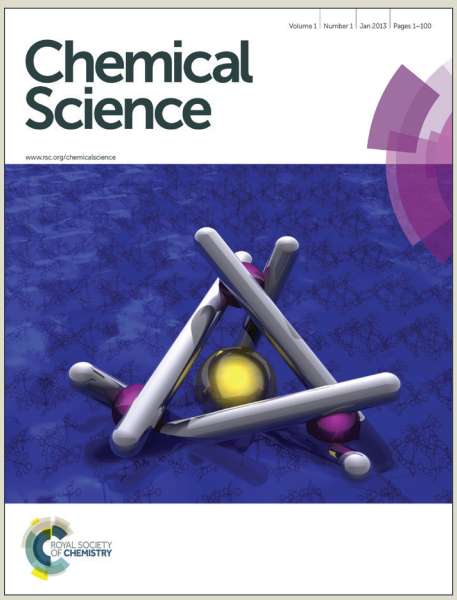

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EDGE ARTICLE

Asymmetric construction of quaternary stereocenters by magnesium catalysed direct amination of β-ketoesters using in situ generated nitrosocarbonyl compounds as nitrogen sources†

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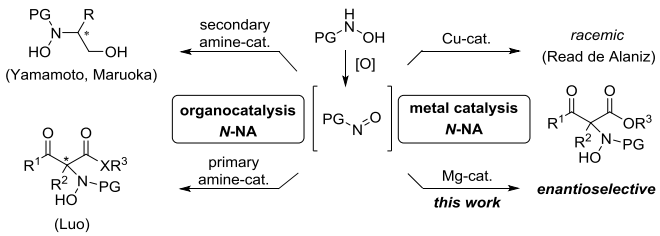
First example of Lewis acid catalysed asymmetric hydroxyamination of β-ketoesters with in situ generated nitrosocarbonyl compounds was accomplished. Combination of catalytic amount of $Mg(OTf)_2$ with chiral *N*,*N*'-dioxide ligand provides highly substituted quaternary β-keto amino acid derivatives in high yields (up to 97%) and enantioselectivities (up to 96%). Regioselectivities (*N*- vs. *O*-attack) are uniformly high for all substrates (> 20:1).

Introduction

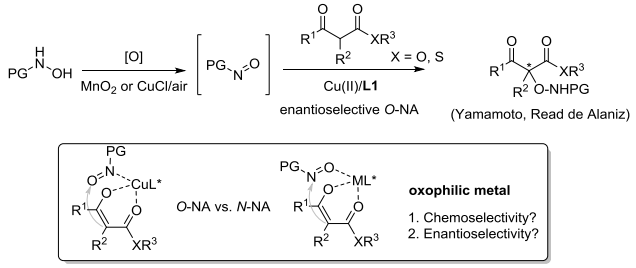
The development of catalytic and enantioselective reactions using unmodified reaction partners with simple experimental protocols has been a rapidly growing area in synthetic organic chemistry. In this regard, the construction of optically active nitrogen-containing molecules is of fundamental interest due to their diverse biological activities and applications in pharmaceutical industries.[1] In General, the construction of C–N bonds in asymmetric catalysis involves either the additions of nitrogen-based nucleophiles to electrophiles or nucleophilic additions to preformed C=N bonds.[2,3] An alternative to these strategies is the electrophilic amination using formal "NH_2^+" source.[4] Azodicarboxylates have most frequently been utilized in such reactions. However, the cleavage of N–N bonds to obtain desired α-aminocarbonyl compounds requires harsh conditions.[5] Nitrosoarenes have also been utilized as nitrogen source, but synthetic utility is unfortunately quite limited due to difficult removal of aromatic *N*-substituent.[6] In contrast, nitrosocarbonyl compounds with easily removable protecting groups (e.g. Boc or Cbz) are more versatile aminating reagents.[7] Unlike the stable arylnitroso compounds, nitrosocarbonyl compounds are transient species and usually generated by the oxidation of corresponding hydroxamic acid derivatives.[8] Mechanistically, this coupling of nucleophilic hydroxylamine with carbonyl compounds is a direct route to the α-aminocarbonyls with the challenge of compatibility of oxidation processes with catalytic cycle.[9]

In the seminal work, Read de Alaniz group has generated nitrosocarbonyl species through aerobic oxidation and utilized in Cu-catalysed *N*-nitroso aldol (*N*-NA, hydroxyamination) reactions of β-ketoesters in racemic fashion.[10] Recently, Luo et al. reported asymmetric version of this reaction using chiral primary amine as organocatalyst.[11] Our group and Maruoka group have also independently reported asymmetric *N*-NA reactions of nitrosocarbonyl species with aldehydes using chiral secondary amines as organocatalysts (Scheme 1).[12]



Scheme 1 *N*-nitroso aldol reactions of nitrosocarbonyl compounds. PG = protecting group.

While many asymmetric *N*-NA reactions of transient nitrosocarbonyl species have been established through organocatalysis, development of enantioselective *N*-NA reactions of these species using Lewis acid catalysis remains elusive. Recently, our group and Read de Alaniz group independently reported Cu-catalysed enantioselective *O*-nitrosoaldol (*O*-NA, aminooxylation) reactions of β-ketoesters with in situ generated nitrosocarbonyl species (Scheme 2).[13] We envisioned that the high *O*-selectivity of these reactions is possibly due to the high affinity of copper towards the nitrogen center of the ambident nitrosocarbonyl electrophile[14] and a judicial choice of oxophilic Lewis acid should switch the chemo-selectivity to *N*-NA (Scheme 2).[15] Herein, we report $Mg(OTf)_2$-catalysed enantioselective α-amination of β-ketoesters with *N*-protected hydroxyl amines as nitrogen source and MnO_2 as oxidant (Scheme 1).[16] This novel method allows asymmetric construction of quaternary stereocenters in high yields and enantioselectivities en route to diverse array of β-keto and β-hydroxy amino acid derivatives.

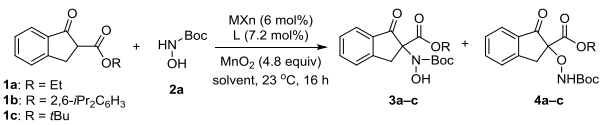


Scheme 2 *O*-nitrosoaldol reactions of nitrosocarbonyl compounds and tuning of regioselectivities by oxophilic metal centered Lewis acids. PG = protecting group. For **L1** see Table 1.

Results and discussions

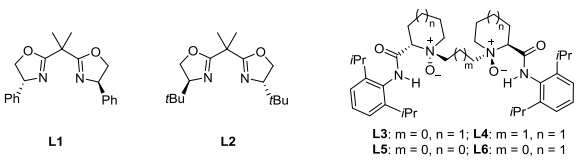
We commenced our investigation using β-ketoester **1a** as model substrate with oxophilic alkali metal salt $Mg(OTf)_2$ as catalyst in combination with commercially available bisoxazoline ligands (Table 1). To our delight, when a solution of readily available *N*-Boc-hydroxylamine **2a** was slowly injected into the mixture of 10 mol % of $Mg(OTf)_2$ and 12 mol % of PhBox ligand **L1** in the presence of substrate **1a** and oxidant MnO_2 in CH_2Cl_2 at room temperature, the aldol reaction proceeded with maintaining high regioselectivity (**3**/**4** = 15:1) and smoothly delivered desired product **3a** in 86% isolated yield. However, the asymmetric induction was very poor (entry 1). Replacement of ligand **L1** by **L2** did not improve the outcome. Implementation of chiral *N*,*N*'-dioxide ligand **L3** developed by Feng[17] exclusively delivered *N*-NA product **3a** in high yield (91%) and the enantioselectivity also increased to 68% (entry 3) with only 6 mol % catalyst loading. To further improve the asymmetric induction, we have modified the ester moiety of the β-ketoester **1**. Gratifyingly, asymmetric induction increases with the increase of steric bulk of R group in **1** (entries 3-5) and the best result was obtained for *t*Bu group producing **3c** in 91% yield and 95% ee, without compromising the regioselectivity (**3**/**4** > 20:1, entry 5). Thus, *t*Bu-β-ketoesters seems to be optimal for our purpose. Further screening of other *N*,*N*'-dioxide ligands **L4**-**L6** and Lewis acid catalysts (Ni-, Zn-, Ca-, Sr-, Sc-salts) with β-ketoesters**1c** was unsatisfactory in terms of both the reactivities and selectivities (entries 6-13). Altering the counter anions of Mg-catalysts and reaction solvents also showed inferior results (entries 14-16). Thus, $Mg(OTf)_2$ in combination with ligand **L3** was considered as a catalyst of choice. It should be noted that the β-ketoester **1b** exclusively delivered *O*-NA product **4b** in 68% yield and 88% ee when $Cu(OTf)_2$ was employed as catalyst in combination with the bisoxazoline ligand **L1** under identical condition.[13a]

Table 1 Optimization of reaction conditions.[a]



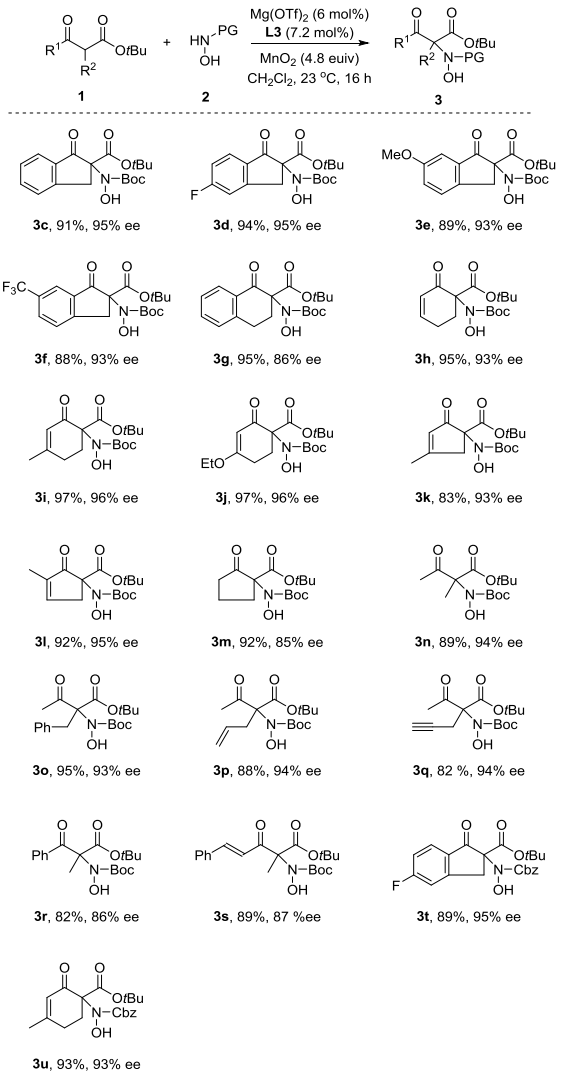
Entry	1	MX_n	L	Solvent	Yield of **3** (%)[b]	**3**/**4**[c]	ee of **3**(%)[d]
1[e]	**1a**	$Mg(OTf)_2$	**L1**	CH_2Cl_2	86	15/1	21
2[e]	**1a**	$Mg(OTf)_2$	**L2**	CH_2Cl_2	80	15/1	4
3	**1a**	$Mg(OTf)_2$	**L3**	CH_2Cl_2	91	>20/1	68
4	**1b**	$Mg(OTf)_2$	**L3**	CH_2Cl_2	68	>20/1	83
5	**1c**	**$Mg(OTf)_2$**	**L3**	**CH_2Cl_2**	**91**	**>20/1**	**95**
6	**1c**	$Mg(OTf)_2$	**L4**	CH_2Cl_2	74	>20/1	4
7	**1c**	$Mg(OTf)_2$	**L5**	CH_2Cl_2	74	>20/1	78
8	**1c**	$Mg(OTf)_2$	**L6**	CH_2Cl_2	94	>20/1	20
9[e]	**1c**	$Ni(OTf)_2$	**L3**	CH_2Cl_2	45	1/1	ND
10[e]	**1c**	$Zn(OTf)_2$	**L3**	CH_2Cl_2	60	2/1	ND
11[e]	**1c**	$Ca(OTf)_2$	**L3**	CH_2Cl_2	96	>20/1	31
12[e]	**1c**	$Sr(OTf)_2$	**L3**	CH_2Cl_2	88	15/1	43
13[e]	**1c**	$Sc(OTf)_3$	**L3**	CH_2Cl_2	85	13/1	–36
14	**1c**	$Mg(ClO_4)_2$	**L3**	CH_2Cl_2	94	>20/1	93
15	**1c**	$Mg(NTf)_2$	**L3**	CH_2Cl_2	82	15/1	95
16	**1c**	$Mg(OTf)_2$	**L3**	$(CH_2Cl)_2$	85	>20/1	93
17[f]	**1b**	$Cu(OTf)_2$	**L1**	CH_2Cl_2	68	<1/20	88

[a] Reaction of β-ketoester **1** (0.1 mmol) with hydroxamic acid **2** (0.12 mmol) was carried out in the presence of metal salt MX_n (0.006 mmol) and ligand **L**(0.0075 mmol) and MnO_2 (0.48 mmol). [b] Yield of isolated product. [c] Isolated product ratio. [d] Determined by HPLC on chiral stationary phase. [e] 0.01 mmol of MX_n and 0.012 mmol of **L** were used. [f] Ref. [13a]. ND = not determined.



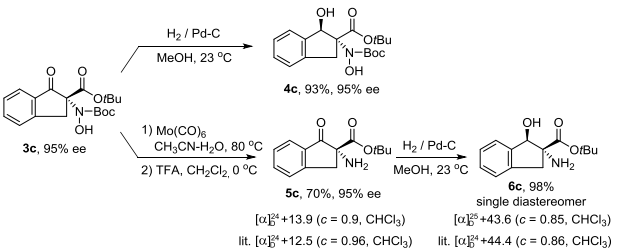
With the optimal reaction conditions in hand, the substrates scope of this Lewis acid catalysed asymmetric *N*-NA reaction for the construction of C–N bond was explored and the results are summarised in Scheme 3. The reaction is quite general. A broad spectrum of β-ketoesters, cyclic as well as acyclic, could be employed to afford quaternary *N*-NA products **3** in high yields and enantioselectivities. Worthy of note that the undesired *O*-NA products **4** were not detected in all cases. The cyclic β-ketoesters having substituted 1-indanone subunits (**3c**-**f**) gave uniformly high yields (88-95%) and enantioselectivities (92-95%). The β-ketoesters with 1-tetralone subunit **1g** worked equally well with slight erosion in enantioselectivity (95% yield, 86% ee). The cyclic β-ketoesters possessing sensitive cyclohexene and cyclopentene subunits are also good substrates for this reaction delivering *N*-NA products **3h-l** in high yields (83-96%) and selectivities (93-96%). Substitutions at R^1 and R^2 for acyclic β-ketoesters have minimal effects in the outcome of the reaction. Reactions of tertiarybutyl acetoacetates with a range of substituents (methyl, benzyl, allyl, propergyl) at R^2 position are very efficient yielding **3n-q** with high asymmetric induction (94, 93, 94, 94 % ee, respectively). The products **3p** and **3q** are particularly very interesting, where hydroxyamination proceeded without affecting labile functionalities such as allyl and propargyl, demonstrating the mildness of our oxidation/catalytic

cycle. Substrates with phenyl and cinnamyl substitution at R^1 are also efficient and desired products **3r** and**3s** were isolated with 86% and 87% ee, respectively. It is important to mention that while asymmetric hydroxyamination reaction via organocatalysis developed by Luo group have unfortunately failed for the β-ketoesters substrates containing aromatic substituents at R^1 position,[11] high asymmetric induction have been achieved with our protocol for this class of substrates (**1r** and **1c**-**g**), which appreciates the efficiency of this catalytic protocol. The reaction is also compatible with other hydroxamic acid derivatives, for instance *N*-Cbz-hydroxylamine**2b**, and the desired products (**3t**,**u**) were obtained in high yields (89, 93%, respectively) with high asymmetric induction (95, 93 % ee, respectively).



Scheme 3 Scope of enantioselective *N*-nitroso aldol reaction. Reaction condition: β-ketoester **1** (0.1 mmol), hydroxamic acid (0.12 mmol), $Mg(OTf)_2$ (0.006 mmol), **L3** (0.0075 mmol), MnO_2 (0.48 mmol). Yield of isolated products are given. The *ee* value was determined by HPLC on chiral stationary phase. PG = protecting group.

In order to highlight synthetic utility of the hydroxyamination products, functionalization of *N*-NA product (**3c**) has been performed (Scheme 4). Under the hydrogenation conditions using Pd/C keto-carbonyl group was smoothly reduced offering β-hydroxy amino acid derivative **4c** in 93% yield. Treatment of $Mo(CO)_6$ cleanly cleaved N–O bond[18] affording β-keto amino acid derivative **5c** after Boc-deprotection with TFA (70% yield). The enantioselectivity of **3c** was also reserved in the products **4c** and **5c**. Finally **5c** can easily be reduced to corresponding β-hydroxy amino acid derivative **6c** under hydrogenation condition (single diastereomer, 98% yield). The absolute configuration of β-keto amino acid derivative **5c** (and hence **3c**) was assigned to be *R* by comparing optical rotation of **4c** with the previously reported literature data.[19]



Scheme 4 Transformation of hydroxyamination product: Synthesis of β-keto and β-hydroxy amio acid derivatives.

Conclusions

In conclusion, we have developed Lewis acid catalysed asymmetric hydroxyamination of β-ketoesters with in situ generated nitroso compounds using readily available Mg-catalyst in combination with *N*,*N*'-dioxide ligand. This protocol is very mild with broad substrates scope offering easy access to enantioenriched quaternary β-keto amino acid derivatives in high yields while maintaining high level of chemoselectivities. Further investigations are underway to clarify the detailed mechanism of this transformation and to explore the scope of nitrosocarbonyl chemistry in asymmetric synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Complete experimental procedures and full compound characterization, including HPLC traces and NMR spectra (PDF). See DOI: 10.1039/b000000x/

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