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Advanced Nitroso Aldol Reaction: Metal-Free Cross-Coupling of Anilines with Silyl Enol Ethers en Route to α-Amino Ketones

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Supporting Information

ABSTRACT: A practical and step-economical nitroso aldol reaction has been developed based on metal-free direct cross-coupling of ready-stock anilines with silyl enol ethers at room temperature affording α-amino ketones in high yields (up to 82%). The protocol features a one-pot cascade of nitroso compound generation, selective C−N bond formation, and N−O bond cleavage using solely inexpensive and user-friendly Oxone and displays remarkable functional group tolerance. The method was further extended to prepare densely functionalized indoles that are otherwise difficult to synthesize.

Heteroatom-substituted carbonyls, particularly α-amino ketones, represent a pivotal structural motif that is frequently found in naturally occurring compounds and bioactive molecules (Figure 1).[1] These high-value synthons

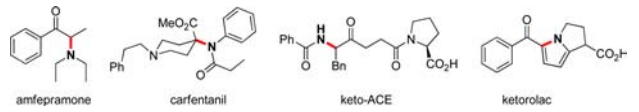
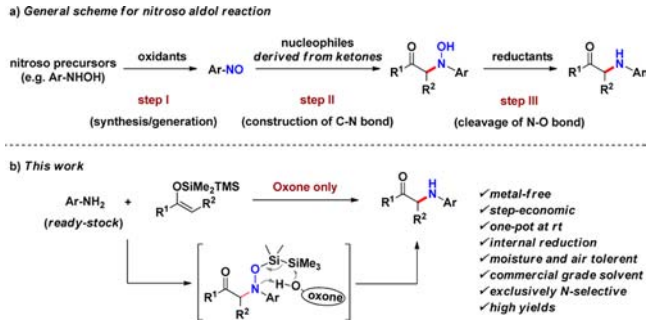


Figure 1. Examples of bioactive α-amino carbonyls.

are also extensively used as building blocks in the synthesis of myriad heterocycles.[2] Thus, the pursuit of novel synthetic approaches for the preparation of α-amino ketones has remained a topic of general interest.[3]

One important route is the nitroso aldol reaction pioneered by Yamamoto, Miller, Read de Alaniz, Studer, and other groups.[4−6] Despite the great advancements made in terms of reactivity, selectivity, and substrate scope, the nitroso aldol reaction is underdeveloped from a green chemistry perspective.[7] A central limitation of the α-amination of ketones via nitroso aldol reaction is that the overall transformation currently requires three discrete steps: synthesis/generation of nitroso compound, construction of the C−N bond, and cleavage of the N−O bond (Scheme 1a). Typically, nitrosoarenes must be prepared ex situ from the appropriate precursors, requiring an additional oxidation step. Many of these nitroso compounds are toxic, unstable, and require special precautions during isolation/purification, limiting their commercial availability. Furthermore, after the completion of the nitroso aldol reaction, the N−O bond must be cleaved to provide the α-amino ketone, leading to additional steps and reagents. Common methods for N−O bond cleavage include hydrogenolysis and stoichiometric metal reductions, which are often toxic and have compromised functional group compatibility.[5,6] Therefore, development of efficient, step-economical,

Scheme 1. α-Amination of Ketones through Nitroso Aldol Reaction



and environmentally benign nitroso aldol reactions en route to α-amino ketones is highly desirable.

An extremely rewarding scenario that will dramatically improve the synthetic portfolio of nitroso aldol reactions would be the execution of the aforementioned steps in a one-pot fashion and with a single catalyst/mediator. Toward this end, Srivastava and co-workers reported an intriguing iron-catalyzed direct C−H amination with arylhydroxylamines.[8] However, the reaction is most effective with activated 1,3-dicarbonyl substrates and is not amenable with simple ketones. Moreover, a higher reaction temperature is also necessary to achieve good yields. Recently, Read de Alaniz and co-workers also reported α-amination of esters and amides by reacting the corresponding α-bromocarbonyls with arylhydroxylamines in the presence of catalytic copper chloride and excess (1.8 equiv) bulky tridentate ligand PMDTA.[9] Though the reaction proceeds at ambient temperature in high yields, an excess amount of SmI_2 was employed for N−O bond cleavage at the

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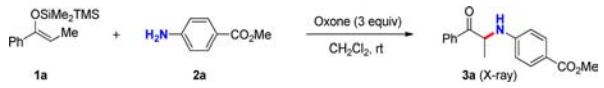
later stage. Currently, step-economic nitroso aldol reactions under metal-free conditions are scarce.

As a part of our ongoing program on nitroso aldol chemistry, we have observed that pentamethyldisilane-protected hydroxylamines undergo rapid cleavage of the N−O bond in the presence of Brønsted acids owing to higher energy of the Si−O (110 kcal mol^{-1}) bond compared to that of N−O (55 kcal mol^{-1}) and Si−Si (52 kcal mol^{-1}) bonds.[10,11] Based on these findings, we envisioned that an appropriate oxidant could serve the dual role of oxidizing a nitroso precursor in situ and cleave the N−O bond of the nitroso aldol product. Considering both scenarios concurrently, we conjectured that the reaction of silyl enol ethers bearing the pentamethyldisilane group with aromatic primary amines in the presence of Oxone (pK_a ~ 2)[12d] could directly provide the desired α-amino ketones. Thus, a step-economic nitroso aldol reaction could be realized under metal-free conditions. Additionally, Oxone is an attractive oxidant as it is practical, nontoxic, and easy to handle.[12]

Our study began with evaluation of the reaction of propiophenone-derived silyl enol ether **1a** with commercially available aniline **2a** (Table 1). Gratifyingly, when **1a** was slowly

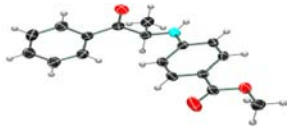
Table 1. Optimization of Metal-Free Cross-Coupling Reaction of Aromatic Amine and Silyl Enol Ether[a]



entry	deviation from standard conditions	yield[b] (%)
1	**none**	**78**
2	CH_3CN instead of CH_2Cl_2	35
3	$ClCH_2CH_2Cl$ instead of CH_2Cl_2	28
4	THF instead of CH_2Cl_2	trace
5	K_2CO_3 or $NaHCO_3$ (2 equiv) as additives	NR[c]
6	PhSeSePh (5 mol %)/H_2O_2 (2 equiv) instead of Oxone	*d*
7	$NaWO_4$ (5 mol %)/H_2O_2 (2 equiv) instead of Oxone	*d*
8	2.0 equiv of Oxone	64
9	4.0 equiv of Oxone	50

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.20 mmol), Oxone (3 equiv), CH_2Cl_2 (4 mL), 18 h. [b]Yield of isolated product. [c]NR: No reaction. TLC showed the presence of starting materials **1a** and **2a**. [d]Desilylation was observed with the recovery of propiophenone.

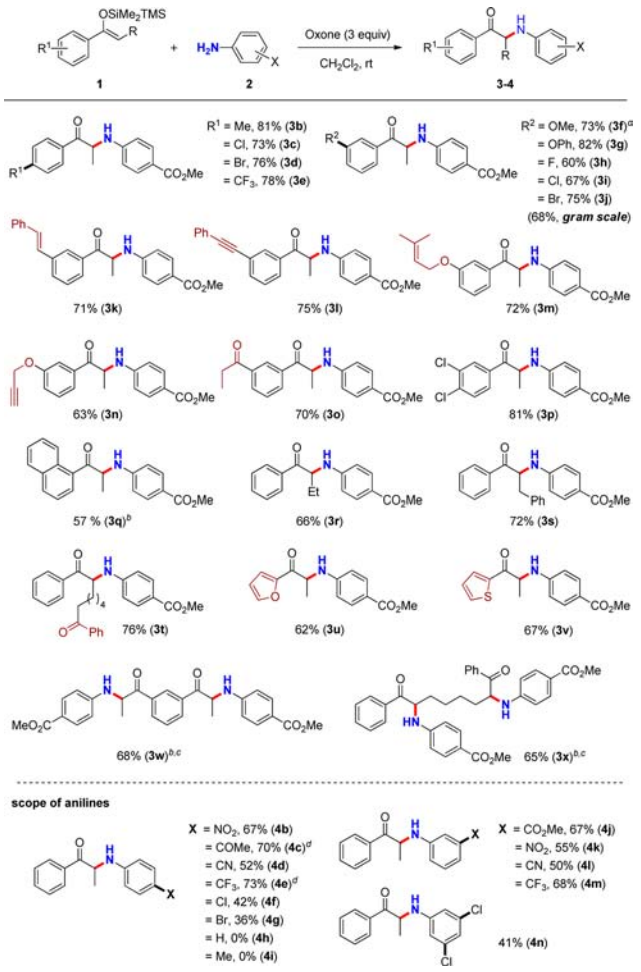
Crystal structure of **3a**:



injected into the mixture of **2a** and Oxone in commercial grade CH_2Cl_2 at room temperature, cross-nucleophile coupling via nitroso aldol reaction proceeded smoothly with concomitant construction of a C−N bond and cleavage of the N−O bond, delivering α-amino ketone **3a** in 78% isolated yield, the structure of which was confirmed through X-ray analysis (Table 1, entry 1).[13] Interestingly, the reaction proceeded with complete selectivity for the *N*-nitrosoaldol product, as the *O*-nitrosoaldol product was not observed. Changing of the reaction solvent from CH_2Cl_2 to acetonitrile, dichloroethane, or THF resulted in inferior results (entries 2−4). The reaction completely shut down in the presence of inorganic bases (entry 5). When Oxone was replaced with other oxidants, hydrolysis of silyl enol ether was observed with recovery of propiophenone (entries 6 and 7). The amount of Oxone also has significant influence on the reaction outcome; while the presence of 2 equiv of Oxone delivered the expected product **3a** in moderated yield (64%), marked deterioration in yield was observed when higher equivalents of Oxone were employed (entries 8 and 9).

With the optimized reaction conditions in hand, we turned our attention to exploring the scope of this metal-free step-economic nitroso aldol reaction. As shown in Scheme 2, a series

Scheme 2. Scope of the Metal-Free Cross-Coupling Reaction[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.20 mmol), Oxone (3 equiv), CH_2Cl_2 (4 mL), 18 h. Yields of isolated products are given. [b]Reaction time was 36 h. [c]Oxone (6 equiv) and **2a** (2.6 equiv) were used. [d]These reactions were also performed on a 1.0 mmol scale, and products **3f**, **4c**, and **4e** were isolated in 77%, 72%, and 72% yields, respectively.

of silyl enol ethers possessing both the electron-rich and electron-deficient groups are effective, delivering the α-amino ketones in uniformly high yields (**3b−q**, up to 82% yield).

Silyl enol ethers having longer and bulky alkyl chains produced higher homologues of α-amino ketones **3r−t** in good yields (66−76%). The functional group compatibility of this reaction is very broad: halogens (**3c-e,h−j,p**), phenoxy (**3g**), alkenes (**3k**), alkynes (**3l**), ketones (**3o,t**), and ester groups are well-tolerated. Compounds bearing sensitive prenyl (**3m**) and propargyl (**3n**) frameworks were also undisturbed. The silyl enol ethers derived from heterocyclic ketones are also suitable

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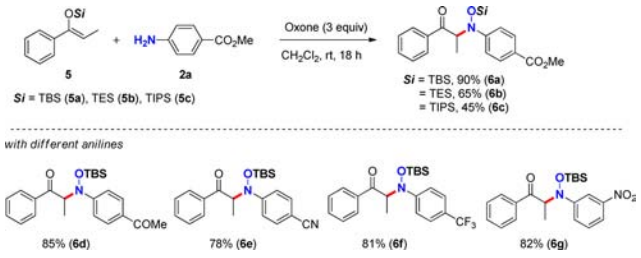
for this reaction, offering compounds **3u,v** in 62% and 67% isolated yields, respectively. Notably, double-nitroso aldol reaction was fruitful, furnishing synthetically important 1,7- and 1,6-diamines **3w,x** in good yields. Furthermore, the reaction can be executed on a gram scale, and the efficiency is comparable to that of a small-scale reaction, delivering **3j** in 68% yield.

The α-amination protocol was further examined with substituted aromatic primary amines (Scheme 2). In general, electron-deficient aromatic primary amines efficiently participated in the reaction. For instance, anilines having nitro (**2b,k**), keto (**2c**), cyano (**2d,l**), ester (**2j**), and trifluoromethyl (**2e,m**) substitutions at the *para*- and *meta*-positions rendered the desired products in good to high yields (50−73%). In the case of halogen-substituted anilines (**2f,g** and **2n**), moderate yields (36−42%) were observed. However, the reaction was sluggish for electron-rich anilines (**2h,i**), and α-amination was not observed under the current conditions.

To investigate the role of the silyl group on the reaction, we examined enol silanes **5a−c** bearing other silyl groups under otherwise identical reaction conditions (Scheme 3). Interestingly, siloxy nitroso aldol products **6a−c** were obtained, indicating the N−O bond cleavage reaction had been interrupted. Similar consequences were also observed for other substituted anilines (**6d−g**). These findings highlight the unique ability of the pentamethyldisilyl group to serve as an internal reductant to cleave the N−O bond and exquisitely support our conjecture.

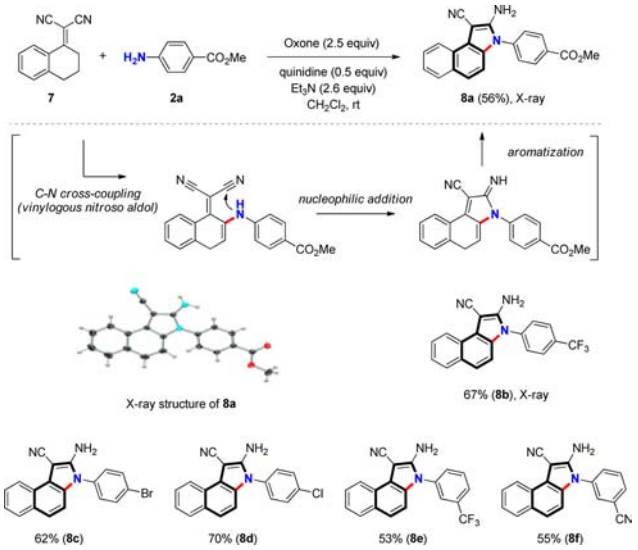
Scheme 3. α-Amination with Different Silyl Enol Ethers



To extend the applicability of our metal-free cross-coupling methodology, we set out to search for other coupling partners and conceived a challenging vinylogous reaction with vinyl malononitrile **7** (Scheme 4).[14] Treatment of a mixture of amine **2a** and vinyl malonitrile **7a** with Oxone in the presence of quinidine and triethylamine bases produced a white crystalline solid, and the X-ray analysis demonstrated the formation of densely functionalized indole **8a** (see the Supporting Information for details).[13] The presence of both bases is crucial, which possibly maintains the requisite buffer conditions for this reaction. The formation of indole product can be rationalized on the basis of C−N cross-coupling via a vinylogous nitroso aldol reaction followed by nucleophilic addition of amine to the nitrile group followed by an aromatization process.[15] This serendipitous indole synthesis is quite general, delivering indoles **8b−f** in good yields (Scheme 4). It is worth noting that our protocol for the synthesis of indole is complementary to the reductive cyclization of the *o*-nitrosostyrene route developed by Zhu, Kurti, and other groups.[16]

In conclusion, we have developed an advanced nitroso aldol reaction based on direct cross-coupling of readily available anilines and silyl enol ethers under metal-free conditions at room temperature. The protocol is operationally simple, scalable, tolerates diverse functional groups, and requires Oxone as a sole reagent to produce α-amino ketones in high yields. The concept was further utilized for vinylogous reaction to access highly functionalized indoles. We anticipate that this reaction will find application in the synthesis of important pharmaceuticals. Further investigation is currently ongoing in our laboratory.

Scheme 4. Synthesis of Densely Functionalized Indoles via Nitroso Aldol Cascade[a]



[a]Reaction conditions: **7** (0.15 mmol), **2** (0.20 mmol), Oxone (2.6 equiv), quinidine (0.5 equiv), NEt_3 (2.5 equiv), CH_2Cl_2 (4 mL), 20 h. Yields of isolated products are given.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03686.

Complete experimental details and characterization data for the prepared compounds (PDF)
Crystallographic data for compound **3a** (CIF)
Crystallographic data for compound **8a** (CIF)
Crystallographic data for compound **8b** (CIF)

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Notes

The authors declare no competing financial interest.

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