Thieme Chemistry Journal Awardees – Where Are They Now? Aerobic Oxidative Coupling of Tertiary Amines with Silyl Enolates and Ketene Acetals

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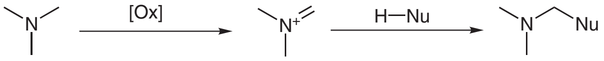
Abstract: Cyclic tertiary amines can be oxidatively coupled with a variety of silyl enol ethers or ketene acetals to furnish tertiary Mannich bases. The reactions are catalyzed by simple copper salts employing elemental oxygen as the oxidant.

Key words: amines, C–H bond functionalization, copper, oxidative cross-coupling, oxidations

Oxidative coupling allows the forging of new carbon–carbon (C–C) bonds by direct functionalisation of carbon–hydrogen (C–H) bonds.[1] Such reactions have the potential to significantly reduce the number of steps and waste products in a reaction sequence as no special leaving groups have to be introduced.

The oxidative coupling with amines has received special interest recently; in these reactions, the amines are generally believed to be oxidized to iminium ions which subsequently react with a nucleophile in a similar fashion as the classical Mannich reaction (Scheme 1).[2]



Scheme 1 Oxidative coupling reactions with amines

In most cases, metal catalysts are used together with organic peroxides as the terminal oxidant,[3] less commonly, environmentally benign oxidants like hydrogen peroxide or elemental oxygen are used.[4] The reactions with organic peroxides are known to proceed via α-oxygenated intermediates.[3a,4a,5]

Such oxidative Mannich-type reactions have been used to functionalise tertiary amines with good carbon nucleophiles such as malonates,[3b,c,4b] nitroalkanes,[3d] indoles,[3e] naphthols,[2c] or cyanide anion.[3f,g,4c–e] The activation of less nucleophilic carbonyl compounds has been achieved at elevated temperatures,[4f] by using amine organocatalysts to activate enones[2c] or simple ketones.[3h] Alternatively, preformed siloxyfurans have been used to introduce a butenolide moiety.[3a,4a] Other silyl enol ethers and organometallic reagents have also been used successfully in oxidative coupling reactions with cyclic ethers.[6]

Martin Klussmann studied chemistry at the universities of Mainz, Jena, and Darmstadt, Germany, and North Carolina in Chapel Hill. He obtained his PhD in 2004 with Prof. Michael Reggelin in Darmstadt on helically chiral polymeric ligands for transition-metal-catalysed asymmetric reactions. In 2004 he joined the group of Prof. Donna G. Blackmond at Imperial College London, UK, as a postdoctoral researcher to work on mechanistic studies of organocatalytic reactions. Since 2007 he is a junior research group leader at the Max Planck Institute für Kohlenforschung, working on his Habilitation with Prof. Benjamin List. His research group is interested in the development of new reactions and the study of their mechanisms, especially catalytic oxidative coupling reactions to form C–C bonds.

We became interested in the oxidative coupling of cyclic amines with carbonyl compounds. These reactions have the exciting potential to generate natural product-like structures in a single step.[3h] However, the known methodologies are still limited to activated carbonyl substrates or to a few simple ketones. In this communication, we report the use of various enol ethers and ketene acetals as nucleophiles in oxidative coupling reactions with tertiary amines, employing elemental oxygen as the oxidant.

We focused on elemental oxygen as a cheap and easy-to-use oxidant. We expected simple copper salts to be effective catalysts for the oxidation of amines whilst easily reoxidizable by oxygen, but we also screened some other metal compounds for comparison. As a test reaction, we chose the coupling of tetrahydroisoquinoline **1a**[3a,4b,c] with silyl enol ether **2** at room temperature in methanol (Table 1).

Among the metal salts, $FeCl_3$ and $RuCl_3$ proved to be active catalysts (entries 1–3) but less active than most of the copper salts tested (entries 4–8). Among these, $CuCl_2\cdot 2H_2O$ afforded the fastest conversions and the highest yields (entry 8). It is also the most convenient to handle, as it is neither prone to oxidation in air nor hygroscopic. Without a metal catalyst, the reaction did not oc-

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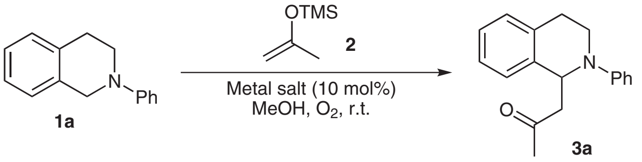
Table 1 Screening of Different Metal Salts as Oxidation Catalysts[a]



Entry	Catalyst	Time (h)	Yield (%)[b]
1	$FeCl_2 \cdot 2H_2O$	18	<5
2	$FeCl_3 \cdot 6H_2O$	18	25
3	$RuCl_3 \cdot xH_2O$	18	35
4	CuCl	18	69
5	CuBr	18	0
6	CuI	18	0
7	$CuCl_2$	5	81
8	$CuCl_2 \cdot 2H_2O$	5	92[c]
9	–	24	0

[a] Reaction conditions: **1** (0.12 mmol), **2** (0.6 mmol), metal salt (0.012 mmol), MeOH (1.0 mL), O_2 (1.02 bar).
[b] Isolated yield.
[c] Average of two experiments.

Table 2 Further Optimisation of Reaction Conditions[a]

$$\mathbf{1a} + \mathbf{2} \xrightarrow[O_2,\ r.t.]{CuCl_2 \cdot 2H_2O} \mathbf{3a}$$

Entry	Cu (mol%)	Solvent	**2** (equiv)	Time	Yield (%)[b]
1	10	CH_2Cl_2	5	4.5 d	72
2	10	$CHCl_3$	5	4.5 d	76
3	10	toluene	5	5 d[c]	38
4	10	DMF	5	7 h	82
5	10	MeOH	5	7 h	92[d]
6	10	acetone	5	2.5 h	93[d]
7	**10**	**acetone**	**2.5**	**1 h**	**96[d]**
8	10	acetone	2.0	1 h	95
9	10	acetone	1.5	1 h	92
10	20	acetone	2.5	1 h	94
11	5	acetone	2.5	6 h	94

[a] Reaction conditions: **1** (0.12 mmol), solvent (1.0 mL), O_2 (1.02 bar).
[b] Isolated yield.
[c] Compound **1a** not fully converted.
[d] Average of two experiments.

cur (entry 9). Next, we further optimized other reaction parameters (Table 2).

Among the solvents examined, only acetone proved to be better than methanol, resulting in essentially the same yields but faster conversions (entries 1–6). In later reactions with acetone as the solvent (vide infra), we encountered more difficulties, especially in the case of methoxy-substituted amine substrates. Accordingly, the reactions were generally run in acetone as the solvent, while methanol was used in selected cases for amines other than **1a**.

Reduction of the relative amount of TMS enol ether **2** from 5 equivalents to 2.5 equivalents was possible with keeping the reaction time short and even a slight increase of product yield (entry 7). Further reducing the amount to 2.0 equivalents or 1.5 equivalents only slightly decreased the yields (entries 8 and 9). When reducing it even further to 1.2 equivalents, the reaction no longer reaches full conversion (not shown). In later studies with different nucleophiles, we found that reducing the amount did in fact lead to a more significant drop in the product yield, probably in case of more sensitive reagents that decomposed during the reaction. Therefore, we kept the concentration of the nucleophile at 2.5 equivalents for all other screenings, but this parameter could in principle be lowered and optimized for each individual reaction.

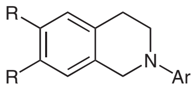
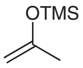
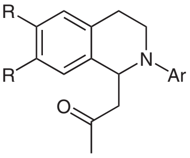
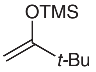
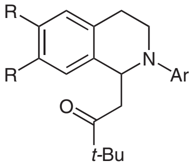
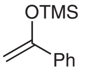
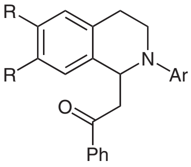
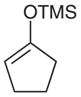
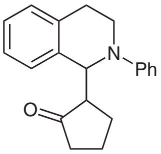
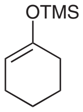
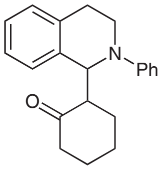
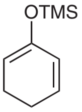
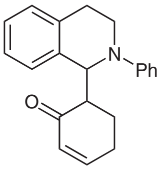
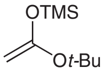
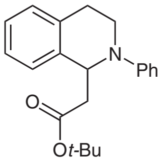
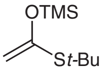
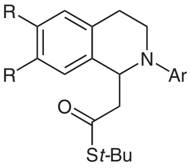
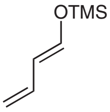
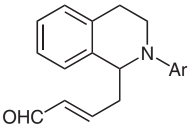
A further increase of the catalyst loading to 20 mol% did not lead to any improvement (entry 10), while reducing it to 5 mol% led to significantly prolonged reaction times (entry 11). Upon further reduction of the catalyst loading, full conversion of the amine substrate was no longer achieved, even after one day. Because of the low cost of $CuCl_2$, we kept the amount at 10 mol% for all further reactions.

With high-yielding conditions in hand, we explored the substrate scope with respect to the silyl nucleophile and also with a few other substituted tetrahydroisoquinolines (Table 3).[7]

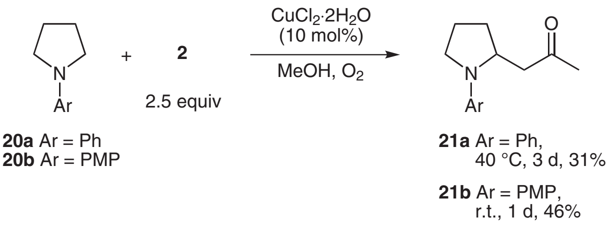
A broad range of nucleophiles can be coupled with the amines, allowing the introduction of open-chain and cyclic ketone and enone functionalities (entries 1–13) as well as esters and thioesters (entries 14–17). The yields are generally high, only the introduction of a *tert*-butyl acetate fragment could not be achieved with more than 26% (entry 14). With cyclic enolates, the reactions proceeded without significant diastereoselectivities, giving the isomers of products **14**–**16** in nearly equal amounts (entries 11–13). In the case of **16**, the product diastereomers could be separated by column chromatography. In the case of dienolate **11**, a 1,4-addition took place to yield the unsaturated aldehydes **19a** and **19b** (entries 18 and 19). Other cyclic amines than the tetrahydroisoquinolines were found to be less suitable substrates. With N-substituted piperidines, the desired products could not be detected. Nevertheless, we could obtain the coupling products with *N*-aryl pyrrolidines in moderate yields (Scheme 2).

In analogy to related reactions,[2c,3a,4a] we assume a mechanism involving iminium ions as key intermediates, as depicted in Scheme 1. Alternatively, one could envision the oxidation of the amines to radicals which would then attack the double bond of the enolates or ketene acetals.[8]

Table 3 Oxidative Coupling of Tetrahydroisoquinolines with TMS Enolates and Ketene Acetals[a]

Entry	Amine		Nucleophile		Product		Solvent	Time (h)	Yield (%)[b]
1		**1a**		**2**		**3a**, R = H, Ar = Ph	acetone	1	96
2		**1b**				**3b**, R = H, Ar = PMP	MeOH	1.5	81
3		**1c**				**3c**, R = OMe, Ar = Ph	acetone	48	91
4		**1d**				**3d**, R = H, Ar = DMP	MeOH	1	97
5		**1a**		**4**		**12a**, R = H, Ar = Ph	acetone	15	87
6		**1b**				**12b**, R = H, Ar = PMP	acetone	4	79
7		**1c**				**12c**, R = OMe, Ar = Ph	acetone	48	90
8		**1a**		**5**		**13a**, R = H, Ar = Ph	acetone	6	84
9		**1b**				**13b**, R = H, Ar = PMP	MeOH	1.5	78
10		**1d**				**13d**, R = H, Ar = DMP	MeOH	1.5	75
11		**1a**		**6**		**14**, dr = 1.4:1	acetone	6	86
12		**1a**		**7**		**15**, dr = 1.5:1	acetone	5	87
13[c]		**1a**		**8**		**16**, dr = 1:1	acetone	8	68
14		**1a**		**9**		**17**	acetone	24	26
15		**1a**		**10**		**18a**, R = H, Ar = Ph	acetone	12	74
16		**1b**				**18b**, R = H, Ar = PMP	MeOH	3	95
17		**1c**				**18c**, R = OMe, Ar = Ph	MeOH	48	75
18		**1a**		**11**		**19a**, R = H, Ar = Ph	acetone	5	60
19		**1b**				**19b**, R = H, Ar = PMP	MeOH	3	61

[a] General reaction conditions: amine (0.12 mmol), nucleophile (0.30 mmol), $CuCl_2\cdot 2H_2O$ (0.012 mmol), solvent (1.0 mL), O_2 (1.02 bar), r.t.
[b] Isolated yield.
[c] Nucleophile (5 equiv) added in aliquots over 2.5 h.



Scheme 2 Oxidative coupling with *N*-aryl pyrrolidines. *Reagents and conditions*: amine (0.50 mmol), **2** (1.25 mmol), CuCl$_2$·2H$_2$O (0.05 mmol), MeOH (3 mL), O$_2$ (1.02 bar).

Depending on the catalytic system being used, radical species have been either ruled out or suggested to be intermediates in the formation of iminium ions by single-electron transfer.[3h,4a] As a probe for the possible occurrence of such radicals, we performed the reaction with **1a** using the stable radical 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) instead of a nucleophile. Coupling products between the amine **1a** and TEMPO would indicate radical formation of **1a**.[9] No conversion of the substrates occurred for three days, supporting a mechanism without the involvement of free radicals. Additionally, the coupling of **1a** with **2** could be performed in the presence of the radical inhibitor 2,4,6-tri-*tert*-butylphenol, again supporting the absence of free radicals.

In summary, we have developed a high-yielding method to functionalise C–H bonds in tertiary amines by oxidation with elemental oxygen using a simple copper salt as catalyst. The reactions are easily performed without the need of extra purification or drying of the reagents. A variety of preformed silyl enolate or silyl ketene acetal nucleophiles can be coupled with cyclic amines, resulting in amino ketones, aldehydes, esters, and thioesters.

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

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(7) **General Procedure for the Oxidative Coupling of Amines**
To a solution of the appropriate amine (0.12 mmol, 1.0 equiv) in acetone or MeOH (1.0 mL), the TMS enol ether or silyl ketene acetal (0.30 mmol, 2.5 equiv) and CuCl$_2$·2H$_2$O (2 mg, 10 mol%) were added, and the mixture was stirred under an atmosphere of oxygen (1 atm) at r.t. After full conversion was achieved, H$_2$O and CH$_2$Cl$_2$ were added and the mixture was extracted with additional CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$ and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (5–10% EtOAc–pentane), giving the product as a solid or oil.

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