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Olefin Oxyamination with Unfunctionalized *N*-Alkylanilines

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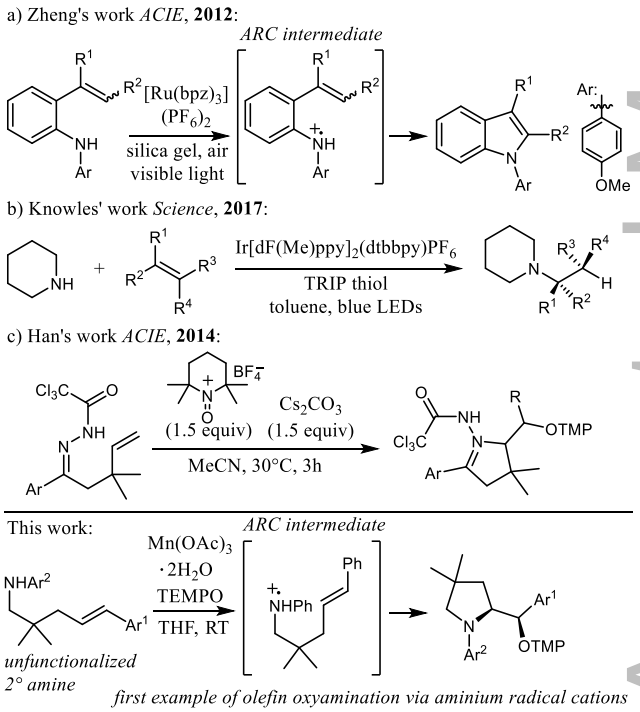
Abstract. *N*-Alkylanilines have rarely been used in oxyamination reactions, due to the normally necessary pre-functionalization of the N-atom. Also, the formation of aminium radical cations (ARCs) of anilines bearing alkyl substituents is plagued by the ARC's tendency to instantaneously convert to α-amino radicals or iminium ions. We present a readily available reagent combination that addresses both challenges, and thus allows for an oxyamination with *N*-alkylanilines via ARCs as the crucial reactive intermediates and excellent diastereoselectivity.

Keywords: N-centered radicals; aminium radical cations; olefin oxyamination; oxidation of secondary amines; C–N bond formation

As a highly valuable subclass of nitrogen-containing compounds, vicinal amino alcohols are widely found in natural products, bioactive molecules, chiral ligands and pharmaceutical agents.[1] Therefore, the development of synthetic routes accessing this structural motif is of great significance. Olefin oxyaminations[2] are a particularly powerful approach as both, the C–N and the C–O bond are formed simultaneously. Unfortunately, most of these reactions require specialized N–X reagents (N–O, N–S, N–N, N_3 and N-halogen)[3] for the introduction of the nitrogen atom, or the stabilization of an EWG at the N-radical intermediate.[3] This is not only unfavorable for the overall step-economy, but also limits the number and choice of substituents at the nitrogen in the amino alcohol.

To realize an oxyamination with *N*-alkylanilines without a pre-functionalization we envisioned a straightforward strategy via the generation of aminium radical cations (ARCs)[3a–h,4] as reactive intermediates. Even though the oxidation of amines is well established, the generation of secondary ARCs comes with a set of challenges, which has thus far severely limited their application in C–N bond formations. In most cases, even though being the first product of the oxidation, ARC intermediates are too fleeting to directly harvest their reactivity in the subsequent reaction pathway. They either immediately convert to α-amino radicals by a deprotonation of the α-carbon atom,[5] or the abstraction of hydrogen leads to the generation of iminium ions.[6] These processes become particularly predominant when the efficiency of the C–N bond formation is low. This is often the case, when the ARC is deprotonated to yield the N-radical. Thereby, the rate constant of the cyclization decreases by several orders of magnitude.[7] Also, reversibility of the C–N bond formation might become problematic if the interception of the cyclized radical is inefficient.[8]



Scheme 1. Olefin amination via ARCs (a,b), radical oxyamination (c), and oxyamination via ARCs.

Nevertheless, in a handful of recent reports the oxidation of *N*-alkylanilines and other secondary amines to ARCs was used to realize a C–N bond formation with an alkene, indicating for the feasibility of such a process. All are photocatalyzed reactions and

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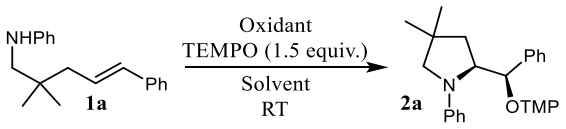
none gives a difunctionalized alkene (Scheme 1, a/b). In 2012, the Zheng group reported a C–N bond formation reaction of arylamines.[9] Proceeding via secondary ARCs, the seminal work of the Knowles group on photocatalyzed olefin hydroaminations[10] shows that N-atoms bearing aliphatic substituents can also be used despite the challenges mentioned above, and was elegantly extended to a first intermolecular process.[11]

Given the fact, that piperidine-*N*-oxoammonium tetrafluoroborate ($T^+BF_4^-$) has proven effective in both: 1.) oxidations of amines to iminium ions,[12] that proceed via the initial formation of an ARC as stated above, and 2.) the oxyamination of olefins with activated hydrazones (Scheme 1, c),[13] we started our investigation by treating our model substrate, *N*-alkylaniline **1a** with 2.0 equiv. $T^+BF_4^-$. But it was not before we changed the solvent to THF and added a base that we first observed the formation of the desired *anti*-oxyamination product **2a** in an encouraging 33% yield and excellent diastereoselectivity (Table 1, entry 2). As the oxidation is certainly crucial for an efficient reaction, we turned to an in-situ formation of $T^+BF_4^-$, from TEMPO and a co-oxidant. To our delight, a combination of 2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$ and 1.5 equiv. TEMPO in CH_3CN gave **2a** with an improved 40% yield (Table 1, entry 3). Other oxidants, such as $FeCl_3$, $AgNO_3$ and $K_2S_2O_8$, $Cu(OAc)_2$, TBHP, $Mn(acac)_3$ or DDQ lead to decomposition and only small amounts of **2a** were detected (Table 1, entries 4-8). A solvent screening identified THF as the best solvent, increasing the yield to 87% (Table 1, entry 9-13). Interestingly, when **1a** was treated with $T^+BF_4^-$ in the presence of 6.0 equiv. of $NaOAc_2$, the product was also obtained, albeit in a diminished 75% yield. (Table 1, entry 14). No reaction occurred with TEMPO alone (Table 1, entry 15).

With the optimized reaction conditions in hands, the substrate scope was examined. Both, electron rich and electron poor styrenes were readily oxyaminated (Table 2). Substitutions in the *ortho*, *meta* and *para* position are well tolerated. Different from previous work, in which the oxidation of anilines was found restricted to electron rich anilines,[9] the high efficiency of the reagent system also allowed for the conversion of moderately electron-poor anilines in excellent yields (Table 2, entry 8-9).

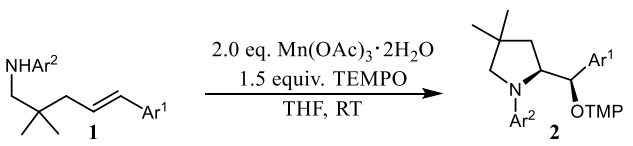
Table 1. Optimization of the reaction conditions.



Entry[a]	Oxidant	Solvent	Yield[b] (%)
1[c]	2.0 equiv. $T^+BF_4^-$	CH_3CN	-
2[c]	2.0 equiv. $T^+BF_4^-$ 3.0 eq. Cs_2CO_3	THF	33
3	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	CH_3CN	40
4	2.5 equiv. $FeCl_3$	CH_3CN	-
5	20 mol% $AgNO_3$ 2.0 equiv. $K_2S_2O_8$	DCM/H_2O 1:1	-
6	10 mol% $Cu(OAc)_2$ 2.0 equiv. TBHP	THF	26
7	2.0 equiv. $Mn(acac)_3$	THF	-
8	2.5 equiv. DDQ	toluene	-
9	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	THF	87
10	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	Dioxane	75
11	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	Et_2O	50
12	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	toluene	32
13	2.0 equiv. $Mn(OAc)_3{\cdot}2H_2O$	$CHCl_3$	14
14[c]	2.0 equiv. $T^+BF_4^-$ 6.0 equiv. NaOAc	THF	75
15	none	THF	-

[a] Reaction conditions: **1a** (0.2 mmol), TEMPO (0.3 mmol), oxidant, solvent (2 mL), RT, 7 h.
[b] Isolated yield.
[c] in the absence of TEMPO, 50 min.

Table 2. Substrate scope.

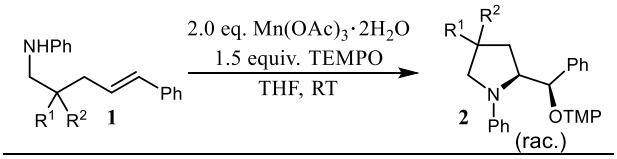


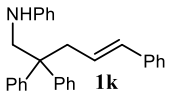
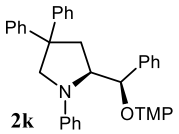
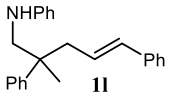
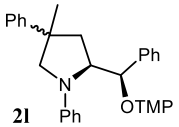
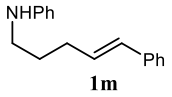
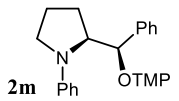
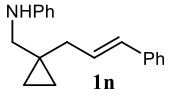
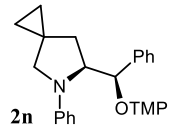
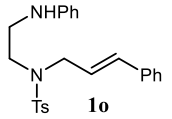
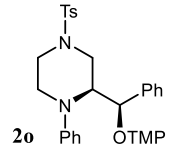
Entry[a]	Ar^1	Ar^2	1	Product	Yield[b] (%)
1	4-MeC_6H_4	C_6H_5	**1b**	**2b**	85
2	3-MeC_6H_4	C_6H_5	**1c**	**2c**	72
3	2-MeC_6H_4	C_6H_5	**1d**	**2d**	82
4	4-ClC_6H_4	C_6H_5	**1e**	**2e**	80
5	4-BrC_6H_4	C_6H_5	**1f**	**2f**	75
6	4-$CF_3C_6H_4$	C_6H_5	**1g**	**2g**	73
7	2-naphthyl	4-ClC_6H_4	**1h**	**2h**	80
8	C_6H_5	3-ClC_6H_4	**1i**	**2i**	73
9	C_6H_5	3-$MeOC_6H_4$	**1j**	**2j**	82

[a] Reaction conditions: **1** (0.2 mmol), TEMPO (0.3 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.4 mmol), THF (2 mL), RT, 7 h.
[b] Isolated yield.

Next, we turned our attention to the variation of the skeleton (Table 3). Symmetrically and unsymmetrically disubstituted substrates **1k** and **1l** readily reacted in the oxyamination reaction. In the absence of substituents on the skeleton, the conversion was slightly reduced and **2m** was obtained in 61% yield based on recovered starting material (brsm) (21% **1m** recovered). This is certainly due to the missing restriction of conformational freedom by the Thorpe-Ingold effect, that is promoting the cyclization in the presence of substituents. In accordance with the radical mechanism of the reaction, the cyclopropyl substituted backbone in **1n** gave rise to side reactions. Heteroatom substitution as in **1o**, as well as an increased chain length, giving the six-membered ring **2o**, were well tolerated. All oxyaminations proceed with excellent *anti*-selectivity as confirmed by a crystal structure of **2d** (see SI).[14]

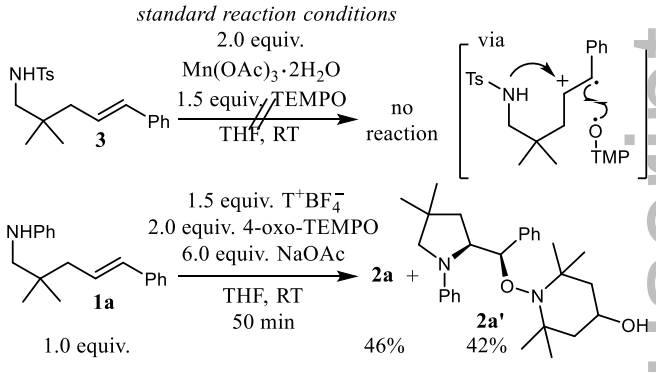
Table 3. Substrate scope.



Entry[a]	1	Product	Yield[b] (%)
1			95
2			87% d.r. (3:1)
3			61 (brsm)[c]
4			30
5			65

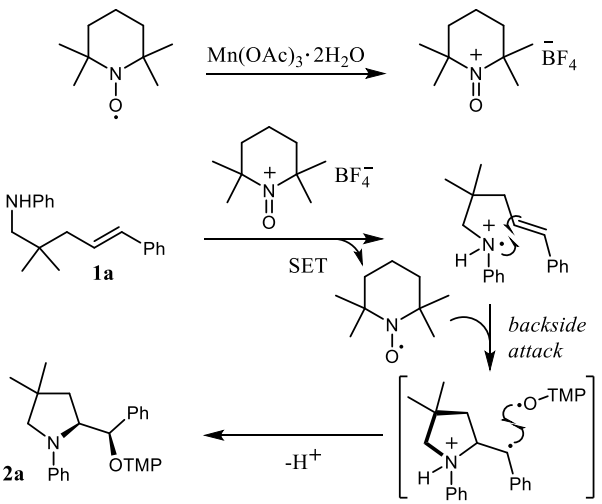
[a] Reaction conditions: **1** (0.2 mmol), TEMPO (0.3 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (0.4 mmol), THF (2 mL), RT, 7 h.
[b] Isolated yield.
[c] Yield based on recovered starting material (brsm) (starting material **1m** recovered: 21%).

To confirm ARCs as the reactive intermediates and to gain further insight into the mechanism, control experiments were conducted (Scheme 2). As a mechanistic probe for the exclusion of an alternative reaction pathway, proceeding via the oxidation of the styrene moiety to a radical cation followed by nucleophilic addition of the amine and trapping of the remaining benzyl radical,[15] *N*-tosyl substituted amine **3** was subjected to the standard reaction conditions. No conversion of the starting material was observed, ruling out an oxidation of the styrene moiety. As no reaction occurred in the presence of TEMPO alone (Table 1, entry 15), an initiation by this reagent is also unlikely. A competition experiment with $T^+BF_4^-$ in the presence of a second radical scavenger, 4-oxo-TEMPO, gave a 1:1 mixture of both trapping products **2a** and **2a'**.[16] This further confirms the radical pathway, as a two-step ARC addition–radical trapping process. A concerted reaction is improbable.[17]



Scheme 2. Control experiments.

According to the control experiments and the results of the optimization process, a mechanism for the oxyamination is proposed in Scheme 3. TEMPO is oxidized in-situ to $T^+BF_4^-$ by $Mn(OAc)_3 \cdot 2H_2O$. Then a SET from the aniline to $T^+BF_4^-$ generates the ARC along with the release of a TEMPO radical. The ARC adds to the tethered C–C double bond and the resulting carbon radical is trapped by TEMPO. The high *anti* selectivity of the reaction is governed by the efficient shielding of the front side by the aniline's arene moiety, forcing TEMPO to attack from the back side .



Scheme 3. Proposed mechanism.

In summary, we have developed a rare olefin oxyamination reaction with *N*-alkylanilines with readily available reagents, that yields vicinal amino alcohols with excellent diastereoselectivity. Therefore, ARCs were engaged as the crucial intermediates, which in turn were generated via a new method for the oxidation of simple alkyl substituted anilines.

Experimental Section

The alkene tethered aniline **1** (0.2 mmol, 1.0 equiv.), TEMPO (0.3 mmol, 1.5 equiv.) and $Mn(OAc)_3{\cdot}2H_2O$ (0.4 mmol, 2.0 equiv.) are dissolved in 2.0 mL THF at room temperature and stirred for 7 h until the conversion of the starting material is complete (monitored by TLC). For the isolation of the product, 5 mL sat. $NaHCO_3$-solution are added, the aqueous phase is extracted with dichloromethane, the combined organic phases are dried over Na_2SO_4, and concentrated *in vacuo*. The crude product is purified by column chromatography (pentane/ethyl acetate = 100:1).

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[14] CCDC 1869702 contains the supplementary crystallographic data for 2d. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Olefin Oxyamination with Unfunctionalized *N*-Alkylanilines

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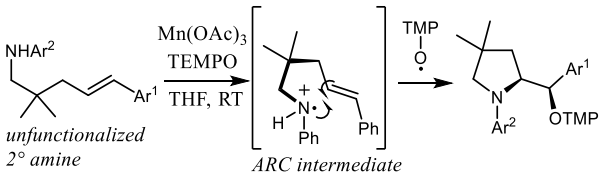

- step and atom-economical: direct conversion of unfunctionalized *N*-alkyl anilines
- rare example of olefin oxyamination via aminium radical cations (ARCs)
- excellent diasteroselectivity: only *anti*-oxyamination observed
- new method for ARC generation with readily available reagents