Chemoselective C—H Bond Activation: Ligand and Solvent Free Iron-Catalyzed Oxidative C—C Cross-Coupling of Tertiary Amines with Terminal Alkynes. Reaction Scope and Mechanism

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ABSTRACT



 $FeCl_2$ catalyzes the oxidative C-C cross-coupling of tertiary amines with terminal alkynes into propargylamines using (*t*-BuO)₂ as oxidant. The reaction can be applied to aromatic and aliphatic amines and alkynes without solvent. High chemoselectivity for aminomethyl groups is due to a steric factor.

The direct C–H activation for C–C bond-forming reaction is of fundamental interest for preparative chemistry.¹ In 1932, de Paolini² reported the dealkylation of tertiary amines with benzoyl peroxide. In 1946, Horner et al.³ explained that benzoyl peroxide polymerization of styrene is accelerated by *N*,*N*-dimethylaniline. They later proposed the mechanism

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shown in Scheme 1 (X = Bz) for the amine dealkylation.⁴ Hydrogen transfer from the oxidant can occur in one step (direct hydrogen transfer, $1 \rightarrow 3$) or in two steps via the radical-cation intermediate 2 giving aminoalkyl radical intermediates 3. The latter induce polymerization of alkenes; they can be quenched by O₂.⁵ Collapse of 3 with BzO[•] generates the aminal derivatives 5 (X = Bz) or, by electron transfer, iminium salts of type 4. The latter react with H₂O to produce the secondary amines 6 and aldehydes R'CHO.

Oxidative dealkylations of tertiary amines with H₂O₂ catalyzed by horseradish peroxidase,⁶ lignin peroxidase,⁷ and other cytochrome P450 enzymes follow a similar mechanism in which

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Scheme 1. Oxidative Dealkylation of Tertiary Amines and Quenching of Iminium Ion Intermediates with Nucleophiles (Horner's Mechanism)

$$\begin{array}{rcl} R_{2}\dot{N}CH_{2}R'+(XO)_{2} & \rightleftharpoons & \left[R_{2}\dot{N}CH_{2}R'+XO'+XO & \rightleftharpoons & R_{2}\dot{N}CHR'+XO'+XOH\right]\\ 1 & 2 & 3\\ & \swarrow & \left[R_{2}\dot{N}=CHR'+XO'+XOH & \rightleftharpoons & R_{2}N-CHR'+XOH\right] \\ & 4 & OX_{5} \\ & & \left[\frac{NUH}{-2XOH} & \frac{R_{2}N-CHR'}{N_{U}}\right] \\ \end{array}$$

M=O species oxidize the amines as X-O^{.8} In 1988, Murahashi et al. found that ruthenium salts and complexes catalyze the oxidation of tertiary amines with t-BuOOH to give the corresponding α -aminoalkyl *tert*-butyl ethers (5, X = O-*t*-Bu) that are hydrolyzed into $6 + R'CHO.^9$ Nucleophiles other than H₂O can be reacted with the immonium intermediates 4, including carbon nucleophiles such as allylsilanes and HCN.^{10,11} Interestingly, with $RuCl_3$ catalyst the oxidant can be H_2O_2 or O_2 .¹⁰ In 1989, Miura and co-workers reported the O₂ oxidation of N,N-dimethylaniline (60 °C, MeCN) catalyzed by iron salts to give N-methylformanilide and several other products arising from the reactions of radical intermediates of type 3.¹² Using CuCl₂/O₂ and terminal alkynes, they managed to obtain (27-43% yield) the corresponding products of oxidative C-C cross-coupling, N-methyl-N-propargylanilines.¹³ This was an important discovery as propargyl amines are key synthetic intermediates in the preparation of a large variety of biologically active compounds.¹⁴ More recently, Li and co-workers, using t-BuOOH as oxidant and CuBr as catalyst, have realized better yielding oxidative coupling of tertiary amines with arylacetylenes,15 nitromethane,16 indoles,¹⁷ malonates, naphthols, and other carbon nucleophiles.¹⁸ An alternative method using NBS as oxidant and CuBr as catalyst has been proposed by Fu and co-workers.¹⁹ As these methods give only moderate yields of oxidative

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C–C coupling with aliphatic tertiary amines and/or with acetylenes that are not arylethynes, we have searched for a better method. Iron salts are inexpensive and benign to the environment, especially when they do not require coordination to expensive or/and toxic ligands; they are now the catalysts of choice.²⁰ We are pleased to report the FeCl₂ catalyzes the chemoselective oxidative C–C cross-coupling of a large variety of tertiary amines and terminal alkynes, using (*t*-BuO)₂ as oxidant and no solvent.

With $(t\text{-BuO})_2$ as oxidant we found that Fe(acac)₂, FeCl₃, Fe₂(CO)₉, Fe(CO)₅, and FeCl₂ (10 mol%) catalyze the coupling reaction (24 h, 100 °C, Ar atm) giving **9aa** in 12%, 56%, 12%, 13%, and 69% yield, respectively (4 mmol of **7a**, 2 mmol of **8a**, no solvent) (Table 1). Fe(OAc)₂, Fe(ClO₄)₂, and Fe(acac)₃ did not catalyze the reaction. Interestingly, we found that the yield of the FeCl₂/(*t*-BuO)₂-induced coupling reaction was higher under air atmosphere (88%) than under Ar atmosphere (69%). We cannot explain yet this observation. Under 1 atm of pure O₂, decrease of yield (65%) was observed, probably because of the known^{4,5} O₂ quenching of short-lived α -aminoalkyl radical of type **3** (Scheme 1).

In the presence of 1 equiv of H_2O , the reaction was slower and α -aminoether 4-Me-C₆H₄N(Me)CH₂O-*t*-Bu (12, this product could not be isolated; see below) was present in the crude reaction mixture after 24 h at 100 °C. More water inhibited the reaction completely, thus demonstrating that anhydrous conditions must be chosen for success. The reaction occurs already at 20 °C but in much lower yield (7%, 24 h, no solvent).

We then explored the scope of our reaction conditions (Table 2) and found that various aryl substituted N,N-dimethylanilines (7) can be coupled with arylacetylenes (**8a,b,c**), heteroarylacetylenes (**8d,e**), and nonaromatic terminal alkynes (**8f**-**k**) including a conjugated enyne (**8h**), a silylethyne (**8g**), ethyl propynoate (**8i**), 5-chloropent-1-yne (**8j**), and phenyl propargyl ether (**8k**). Oxidative coupling of bromoaniline **7d** is particularly interesting as

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Table 1. Iron-Catalyzed Coupling of 4, N, N-Trimethylaniline (**7a**) with Phenylacetylene (**8a**)^{*a*}

-	≻−N + H−C=	C-Ph Fe cat. (10 mo Oxidant (2 eq	uiv)	-NPh
/a	8	a 100 °C, 24	n g	aa
entry	Fe catalyst	oxidant (equiv)	atmosphere	yield $(\%)^b$
1	$FeCl_2$	t-BuOOH (3)	Ar	tr
2	$FeCl_2$	$(t-BuO)_2(3)$	Ar	42
3	$FeCl_2$	$(t-BuO)_2(2)$	Ar	69
4	$FeCl_3$	$(t-BuO)_2(2)$	Ar	56
5	$Fe(acac)_2$	$(t-BuO)_2(2)$	Ar	12
6	$Fe(acac)_3$	$(t-BuO)_2(2)$	Ar	0
7	$Fe(OAc)_2$	$(t-BuO)_2(2)$	Ar	0
8	$Fe(ClO_4)_2$	$(t-BuO)_2(2)$	Ar	0
9	$Fe_2(CO)_9$	$(t-BuO)_2(2)$	Ar	12
10	Fe(CO) ₅	$(t-BuO)_2$ (2)	Ar	13
11	$FeCl_2$	$(t-BuO)_2(2)$	Ar	7^c
12	$FeCl_2$	$H_2O_2(2)$	Ar	
13	$FeCl_2$	O_2 (1 atm)		
14	$\overline{FeCl_2}$	$(t-BuO)_2$ (2)	air	85
15	$\overline{FeCl_2}$	$(t-BuO)_{2}(2)$	air	88^d
16	$FeCl_2$	$(t-BuO)_2(2)$	O_2	65
17	-	$(t-BuO)_2$ (2)	air	
18	$FeCl_2$	$(BzO)_2(2)$	air	tr
19	-	$(BzO)_2(2)$	air	е
20	$FeCl_2$	$(t-BuO)_2(2)$	air	tr^{ℓ}
21	$\overline{\text{FeCl}_2}$	$(t-BuO)_2(2)$	air	g

^{*a*} Reaction conditions: 1 equiv of phenylacetylene (2 mmol) and 2 equiv of 4,*N*,*N*-trimethylaniline (4 mmol) with iron catalyst (0.2 mmol) and oxidant. ^{*b*} Yield of isolated product after column flash chromatography on silica gel. ^{*c*} Reaction was done at room temperature. ^{*d*} 1.5 equiv of 4,*N*,*N*-trimethylaniline was used. ^{*e*} Decomposition of *tert*-amine was observed. ^{*f*} 1 equiv of H₂O was added. ^{*g*} 20 equiv of H₂O was added.

it generates propargyl amine **9da** that can, in principle, undergo further transition-metal-catalyzed C-C or C-hetero coupling reactions.²¹

Table 2. Oxidative Iron-Catalyzed C-C Cross-Coupling of	
N,N-Dimethyl Anilines (7) with Terminal Alkynes (8) Givir	ıg
Propargylamines $(9)^{a}$	

	Ar—N +	H−C≡C 8	-R <u>(<i>t</i>-BuO)₂ (2 equiv)</u> 100 °C, 24 h, air	Ar—N	≕ −R
entry	Ar	•	R	time (h)	yield $(\%)^b$
1	4-MeC ₆	H ₄ (7a)	Ph (8a)	24	88 (9aa)
2	$4 - MeC_6$	H ₄ (7a)	$4 - MeC_6H_4$ (8b)	24	76 (9ab)
3	$4 - MeC_6$	H ₄ (7a)	$4\text{-MeOC}_{6}\text{H}_{4}$ (8c)	24	57 (9ac)
4	$4 - MeC_6$	H ₄ (7a)	2-pyridyl (8d)	24	79 (9ad)
5	$4 - MeC_6$	H ₄ (7a)	3-pyridyl (8e)	24	93 (9ae)
6	$4 - MeC_6$	H ₄ (7a)	n-hexyl (8f)	30	66 (9af)
7	$4-MeC_6$	H ₄ (7a)	$Et_3Si(8g)$	30	82 (9ag)
8	$4 - MeC_6$	H_4 (7a)	1-cyclohexenyl (8h)	24	47 (9ah)
9	$4 - MeC_6$	H_4 (7a)	COOEt (8i)	24	61 (9ai)
10	$4 - MeC_6$	H_4 (7a)	$ClCH_2CH_2CH_2$ (8j)	30	69 (9aj)
11	$4 - MeC_6$	H_4 (7a)	$PhOCH_2$ (8k)	24	71 (9ak)
12	$2 - MeC_6$	H_4 (7b)	Ph (8a)	24	71 (9ba)
13	Ph (7c)		Ph (8a)	24	$24 \ (9ca)^c$
14	Ph (7c)		$4-MeC_{6}H_{4}$ (8b)	24	$32 \ (9cb)^d$
15	$2 - MeC_6$	H_4 (7b)	$4-MeC_{6}H_{4}$ (8b)	24	79 (9bb)
16	$4-BrC_6H$	\mathbf{I}_4 (7d)	Ph (8a)	24	54 (9da)

^{*a*} Reaction conditions: 1 equiv (2 mmol) of **8**, 1.5 equiv (3 mmol) of **7**, FeCl₂ (0.2 mmol), (*t*-BuO)₂ (4 mmol). ^{*b*} Yield of isolated product after column flash chromatography on silica gel, not optimized. ^{*c*} 48% of recovered **8a**. ^{*d*} 39% of recovered **8b**.

R'—	R" N-Me+ 10	H−C≡C−R 8	FeCl ₂ (10 (<i>t</i> -BuO) ₂ (100 °C) mol %) (2 equiv) ≻ R' C, air	R" '−N−CH₂− 11	C≡C−R
entry		amine		R	time (h)	yield (%)
$ \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} $	R' = R' = R' = R' = R' =	Bn, $\mathbf{R}'' = \mathbf{Me}$ Bn, $\mathbf{R}'' = \mathbf{Ph}$ <i>n</i> -octyl, $\mathbf{R}'' =$ <i>c</i> -hexyl, $\mathbf{R}'' =$ <i>n</i> -octyl, $\mathbf{R}'' =$	(10a) (10b) Me (10c) Me (10d) Me (10c)	Ph (8a) Ph (8a) Ph (8a) Ph (8a) 3-pyridyl (8)	24 24 24 18 (e) 18	42 (11a) 13 (11b) 74 (11c) 89 (11d) 65 (11e)

We have found also that tertiary amines that are not anilines can be coupled with terminal alkynes under our conditions (Table 3). Interestingly, *N*,*N*-dimethylbenzylamine (**10a**) gave a major product **11a** resulting from the chemoselective coupling with the methyl group rather than with its benzyl group. The moderate yield (42%) after 24 h can be improved to 75% if the reaction is run over 3 days. Reaction **8a** + **10a** \rightarrow **11a** is somewhat slower than reaction **8a** + **7a** \rightarrow **9aa**.

Desilylation of propargyl amine **9ag** provides terminal alkyne **8l** that can be coupled with N,N-dimethyloctylamine under the same conditions to give **11f** in 67% yield (Scheme 2).





The product resulting from the oxidation of the benzylic C–H of **10a** could not be detected, thus showing the high chemoselectivity of our oxidative C–C coupling reaction, the least sterically hindered α -C-H bonds of the amine being oxidized preferentially. This can be explained by the known chemoselectivity of hydrogen transfer from tertiary amines to *t*-BuO[•] radical, which is faster for PhNMe₂ and Et₃N than for (allyl)₃N and PhN(CH₂Ph)₂.²² Although the hydrogen transfer from a benzylic C–H bond to *t*-BuO[•] is more exothermic (by ca. 12 kcal/mol) than the hydrogen transfer from a methyl group, entropy effects (due to steric requirements) make this reaction chemoselective in favor of the least sterically hindered α -C-H bond. According to Horner's mechanism (Scheme 1), proton transfer from **2** could be responsible for the chemoselectivity. The low yield of

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reaction $8a + 10b \rightarrow 11b$ (13%, 24 h) is the manifestation of a retardation of the hydrogen atom or proton transfer because of the bulk introduced by the phenyl and benzyl groups.²² The importance of this steric factor is evidenced also with the reaction of aliphatic tertiary amines **10c,d**. They require only 18 h (instead of 24 h) to give good yields of propargyl amines under our conditions.

Horner's mechanism (Scheme 1) interprets all of our observations. The role of FeCl₂ is to catalyze the formation formation of intermediates of type **5**.²³ In the absence of alkyne the reaction **7a** + (*t*-BuO)₂/FeCl₂ produces the α -aminoether 4-MeC₆H₄N(Me)CH₂-O-*t*-Bu (**12**).²⁴ The later does not react with phenylacetylene (**8a**) in the absence of FeCl₂, showing that FeCl₂, which acts as Lewis acid promoter, induces the S_N1 cleavage of the α -aminoethers of type **5** into iminium ion intermediates of type **4** (Scheme 3).²⁵ In the absence of FeCl₂,



 $(t-BuO)_2 + 7a$ did not react to produce 12 (12 h, 100 °C). This demonstrates that FeCl₂ catalyzes the formation of **12**, even though it was reported that dialkyl peroxides are unreactive with FeCl_2 .²⁶ Reaction $1 + (t-\text{BuO})_2/\text{FeCl}_2 \rightarrow 5$ might not involve homolysis, $(t-BuO)_2 \rightarrow 2 t-BuO^{\bullet}$. The C-C bond-forming step involves reaction of iminium ions of type 4 with acetylide anions. When 1:1 mixture of Ph-C₂-D and *n*-C₆H₁₃C₂-H was heated to 100 °C for 12 h in the presence of 2 equiv of Et₃N, a 0.5:0.5:0.5:0.5 mixture of Ph-C2-H, Ph-C2-D, n-hex-C2-D, and *n*-hex-C₂-H was formed. The same experiment run with 10%FeCl₂ and the absence of Et₃N also led to H/D exchange between the two terminal acetylenes, but the reaction was not complete after 12 h at 100 °C. When using FeCl₂ and Et₃N the exchange was complete at 100 °C after 12 h. These experiments showed not only that tertiary amines are able to deprotonate the alkynes but that FeCl₂ itself can generate iron acetylide intermediates, but more slowly than deprotonation by Et₃N.

Any mechanism involving addition of iminium ion intermediates to the alkynes in the rate-determining step (with formation of alkenyl cation intermediates) can be ruled out because one does not observe significant differences in the initial reaction rates as a function of the nature of the alkyne (electron-rich (R = 4-MeOC₆H₄, alkyl, silyl) or electronpoor (R = COOEt)). If the reaction should involve aminoalkyl radical addition to the alkynes in the rate-determining step (with formation of alkenyl radical intermediates), significant differences in rates should be observed for the various alkynes studied, which is not the case. For instance, when a 1:1:1 mixture of 8a, 8f, and 8i was reacted with 7a and $(t-BuO)_2 + FeCl_2$ for 5 h at 100 °C (ca. 30% conversion), a 1:0.6:1.5 mixture of 9aa, 9af, and 9ai was formed (similar rate constant for phenyl-, hexyl-, and ester-substituted ethyne; see Supporting Information for detailed scheme). Using PhCONH₂, 7a reacted to give the corresponding product of oxidative coupling 4-MeC₆H₄N(Me)CH₂NHCOPh (13, Scheme 4), in agreement with Horner's mechanism (Scheme 1).²⁷



In summary, the first iron-catalyzed oxidative C–C crosscoupling of tertiary amines with terminal alkynes to give propargylamines is presented. The conditions can be applied to aromatic and nonaromatic amines and alkynes. The reaction is chemoselective: for steric reasons the methylamino group reacts faster than other alkylamino groups. Our discovery should find applications in medicinal chemistry²⁸ and material sciences.

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Supporting Information Available: Experimental procedures, characterization of compounds and further references. This material is available free of charge via the Internet at http://pubs.acs.org.

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