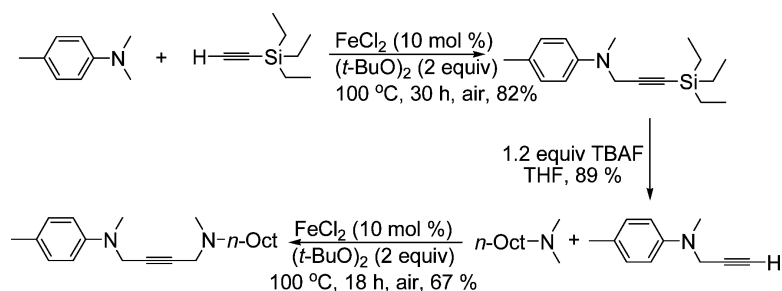


Chemoselective C#H Bond Activation: Ligand and Solvent Free Iron-Catalyzed Oxidative C#C Cross-Coupling of Tertiary Amines with Terminal Alkynes. Reaction Scope and Mechanism

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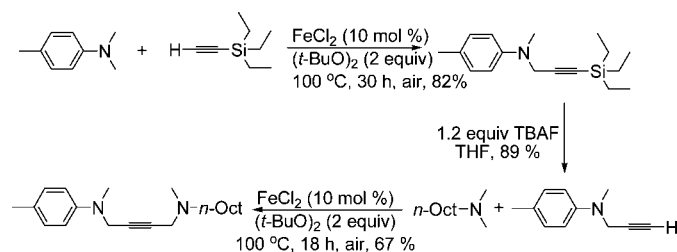
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ABSTRACT



FeCl₂ 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

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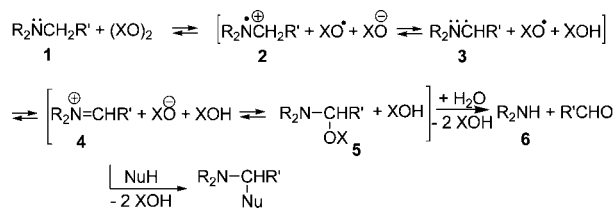
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Scheme 1. Oxidative Dealkylation of Tertiary Amines and Quenching of Iminium Ion Intermediates with Nucleophiles (Horner's Mechanism)



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 RuCl₃ catalyst the oxidant can be H₂O₂ or O₂.¹⁰ 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

C–C coupling with aliphatic tertiary amines and/or with acetylenes that are not arylethyne, 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*-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*-BuO₂-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 H₂O, 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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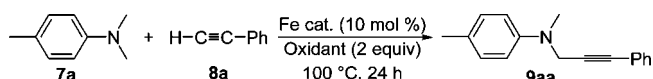
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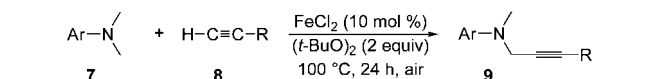
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Table 1. Iron-Catalyzed Coupling of 4,*N,N*-Trimethylaniline (**7a**) with Phenylacetylene (**8a**)^a


entry	Fe catalyst	oxidant (equiv)	atmosphere	yield (%) ^b
1	FeCl ₂	<i>t</i> -BuOOH (3)	Ar	tr
2	FeCl ₂	(<i>t</i> -BuO) ₂ (3)	Ar	42
3	FeCl ₂	(<i>t</i> -BuO) ₂ (2)	Ar	69
4	FeCl ₃	(<i>t</i> -BuO) ₂ (2)	Ar	56
5	Fe(acac) ₂	(<i>t</i> -BuO) ₂ (2)	Ar	12
6	Fe(acac) ₃	(<i>t</i> -BuO) ₂ (2)	Ar	0
7	Fe(OAc) ₂	(<i>t</i> -BuO) ₂ (2)	Ar	0
8	Fe(ClO ₄) ₂	(<i>t</i> -BuO) ₂ (2)	Ar	0
9	Fe ₂ (CO) ₉	(<i>t</i> -BuO) ₂ (2)	Ar	12
10	Fe(CO) ₅	(<i>t</i> -BuO) ₂ (2)	Ar	13
11	FeCl ₂	(<i>t</i> -BuO) ₂ (2)	Ar	7 ^c
12	FeCl ₂	H ₂ O ₂ (2)	Ar	
13	FeCl ₂	O ₂ (1 atm)		
14	FeCl₂	(<i>t</i>-BuO)₂ (2)	air	85
15	FeCl₂	(<i>t</i>-BuO)₂ (2)	air	88^d
16	FeCl ₂	(<i>t</i> -BuO) ₂ (2)	O ₂	65
17		(<i>t</i> -BuO) ₂ (2)	air	
18	FeCl ₂	(BzO) ₂ (2)	air	tr
19		(BzO) ₂ (2)	air	<i>e</i>
20	FeCl ₂	(<i>t</i> -BuO) ₂ (2)	air	tr ^f
21	FeCl ₂	(<i>t</i> -BuO) ₂ (2)	air	<i>g</i>

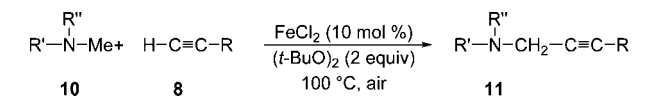
^a Reaction conditions: 1 equiv of phenylacetylene (2 mmol) and 2 equiv of 4,*N,N*-trimethylaniline (4 mmol) with iron catalyst (0.2 mmol) and oxidant. ^b Yield of isolated product after column flash chromatography on silica gel. ^c Reaction was done at room temperature. ^d 1.5 equiv of 4,*N,N*-trimethylaniline 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**) Giving Propargylamines (**9**)^a


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 ₆ H ₄ (8b)	24	76 (9ab)
3	4-MeC ₆ H ₄ (7a)	4-MeOC ₆ 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)	<i>n</i> -hexyl (8f)	30	66 (9af)
7	4-MeC ₆ H ₄ (7a)	Et ₃ Si (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 ₂ CH ₂ CH 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 ₆ H ₄ (7d)	Ph (8a)	24	54 (9da)

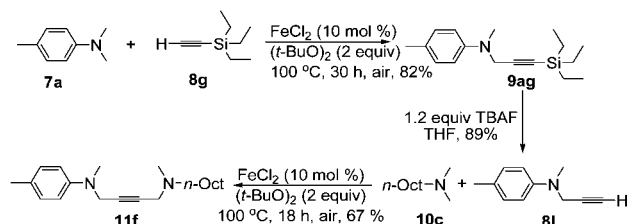
^a Reaction conditions: 1 equiv (2 mmol) of **8**, 1.5 equiv (3 mmol) of **7**, FeCl₂ (0.2 mmol), (*t*-BuO)₂ (4 mmol). ^b Yield of isolated product after column flash chromatography on silica gel, not optimized. ^c 48% of recovered **8a**. ^d 39% of recovered **8b**.

Table 3. Chemoselective FeCl₂-Catalyzed Oxidative Couplings


entry	amine	R	time (h)	yield (%)
1	R' = Bn, R'' = Me (10a)	Ph (8a)	24	42 (11a)
2	R' = Bn, R'' = Ph (10b)	Ph (8a)	24	13 (11b)
3	R' = <i>n</i> -octyl, R'' = Me (10c)	Ph (8a)	24	74 (11c)
4	R' = <i>c</i> -hexyl, R'' = Me (10d)	Ph (8a)	18	89 (11d)
5	R' = <i>n</i> -octyl, R'' = Me (10c)	3-pyridyl (8e)	18	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** → **11a** is somewhat slower than reaction **8a** + **7a** → **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).

Scheme 2. Chemoselective FeCl₂-Catalyzed Oxidative Couplings with Two Different *tert*-Amines

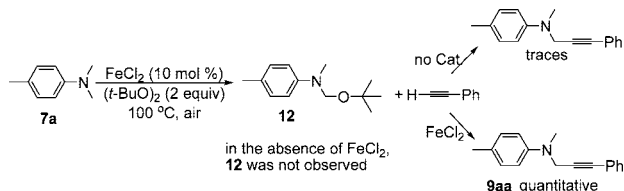
The product resulting from the oxidation of the benzylic C–H of **10a** could not be detected, thus showing the high chemoselectivity of our oxidative C–C coupling reaction, the least sterically hindered α-C–H bonds of the amine being oxidized preferentially. This can be explained by the known chemoselectivity 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** → **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 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,

Scheme 3. Formation of *tert*-Butyl Aminomethyl Ether and Subsequent Coupling with Phenylacetylene

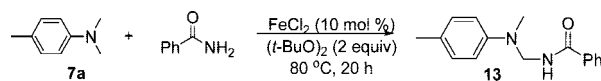


(*t*-BuO)₂ + **7a** did not react to produce **12** (12 h, 100 °C). This demonstrates that FeCl₂ catalyzes the formation of **12**, even though it was reported that dialkyl peroxides are unreactive with FeCl₂.²⁶ Reaction **1** + (*t*-BuO)₂/FeCl₂ → **5** might not involve homolysis, (*t*-BuO)₂ → 2 *t*-BuO•. 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 electron-poor (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 + FeCl₂ 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

Scheme 4. Iron-Catalyzed Oxidative Coupling of 4,*N,N*-Trimethylaniline with Benzamide



In summary, the first iron-catalyzed oxidative C–C cross-coupling 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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