Letter

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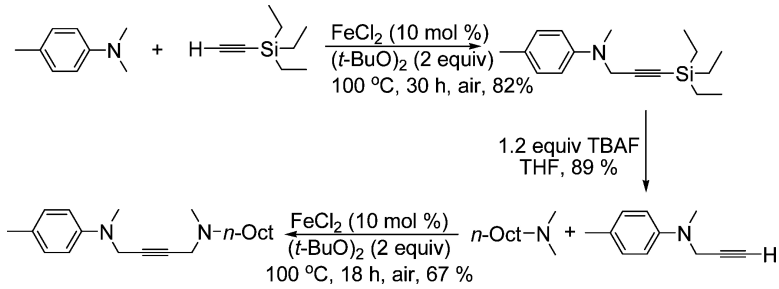

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Chemoselective C−H Bond Activation: Ligand and Solvent Free Iron-Catalyzed Oxidative C−C Cross-Coupling of Tertiary Amines with Terminal Alkynes. Reaction Scope and Mechanism

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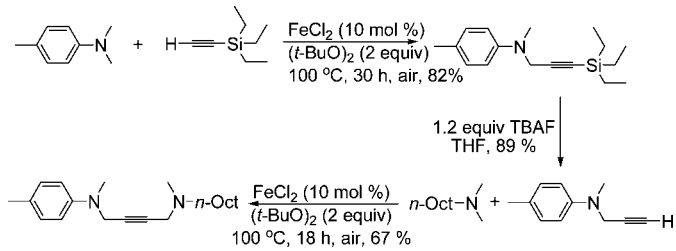
ABSTRACT



$FeCl_2$ 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 Paolini[2] 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 O_2.[5] Collapse of **3** with BzO$^\bullet$ generates the aminal derivatives **5** (X = Bz) or, by electron transfer, iminium salts of type **4**. The latter react with H_2O to produce the secondary amines **6** and aldehydes R′CHO.

Oxidative dealkylations of tertiary amines with H_2O_2 catalyzed by horseradish peroxidase,[6] lignin peroxidase,[7] and other cytochrome P450 enzymes follow a similar mechanism in which

(1) (a) Dyker, G. *Handbook of C-H Transformations*; Wiley-VCH: Weinheim, 2005. (b) Li, C. J.; Li, Z. P. *Pure Appl. Chem.* **2006**, *78*, 935–945. (c) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622. (d) Company, A.; Gómez, L.; Güell, M.; Ribas, X.; Luis, J. M.; Que, L., Jr.; Costas, M. *J. Am. Chem. Soc.* **2007**, *129*, 15766–15767. (e) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084. (f) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (g) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949–957. (h) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222–234. (i) Herrerias, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546–2562.

(2) de Paolini, I.; Ribet, G. *Gazz. Chim. Ital.* **1932**, *62*, 1041–1048.

(3) Horner, L.; Schwenk, E. *Ann. Chem. Justus Liebig* **1950**, *566*, 69–84.

(4) (a) Horner, L.; Junkermann, H. *Ann. Chem. Justus Liebig* **1955**, *591*, 53–68. (b) Horner, L.; Kirmse, W. *Ann. Chem. Justus Liebig* **1955**, *597*, 48–65.

(5) Lalevee, J.; Allonas, X.; Fouassier, J. P.; Ingold, K. U. *J. Org. Chem.* **2008**, *73*, 6489–6496.

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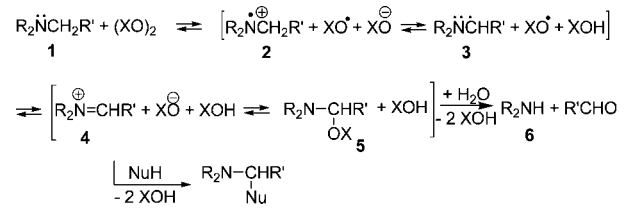
Scheme 1. Oxidative Dealkylation of Tertiary Amines and Quenching of Iminium Ion Intermediates with Nucleophiles (Horner's Mechanism)



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 H_2O 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 O_2 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 $CuCl_2/O_2$ 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 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 $FeCl_2$ catalyzes the chemoselective oxidative C−C cross-coupling of a large variety of tertiary amines and terminal alkynes, using $(t\text{-BuO})_2$ as oxidant and no solvent.

With $(t\text{-BuO})_2$ as oxidant we found that $Fe(acac)_2$, $FeCl_3$, $Fe_2(CO)_9$, $Fe(CO)_5$, and $FeCl_2$ (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). $Fe(OAc)_2$, $Fe(ClO_4)_2$, and $Fe(acac)_3$ did not catalyze the reaction. Interestingly, we found that the yield of the $FeCl_2/(t\text{-BuO})_2$-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 O_2, decrease of yield (65%) was observed, probably because of the known[4,5] O_2 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-C_6H_4N(Me)CH_2O-*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

(6) (a) Galliani, G.; Rindone, B.; Marchesini, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 456–460. (b) Galliani, G.; Rindone, B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1–3.

(7) (a) Guengerich, F. P.; MacDonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9–16. (b) Baciocchi, E.; Gerini, M. F.; Lapi, A. *Chem. Commun.* **2002**, 946–947. (c) Baciocchi, E.; Gerini, M. F.; Lanzalunga, O.; Lapi, A.; Lo Piparo, M. G.; Mancinelli, S. *Eur. J. Org. Chem.* **2001**, *230*, 5–2310.

(8) (a) *Cytochrome P-450*, 2nd ed.; Plenum: New York, 1995; (b) Cuppoletti, A.; Galli, C.; Gentili, P.; Petride, H. *J. Phys. Org. Chem.* **2002**, *15*, 672–675. (c) Urlacher, V. B.; Bell, S. G.; Wong, L. L. *Mod. Biooxid.* **2007**, 99–122. (d) Chiavarino, B.; Cipollini, R.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lapi, A. *J. Am. Chem. Soc.* **2008**, *130*, 3208–3217.

(9) Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256–8258.

(10) Murahashi, S. I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005–11012, and references therein.

(11) For other metal-catalyzed α-C-H activation of tertiary amines, see: (a) Wilson, R. B., Jr.; Laine, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 361–369. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941. (c) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557. (d) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221. (e) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649.

(12) (a) Murata, S.; Miura, M.; Nomura, M. *J. Org. Chem.* **1989**, *54*, 4700–4702. (b) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116–118.

(13) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *J. Chem. Res., Synop.* **1993**, 434.

(14) See e. g.: (a) Likhar, P. R.; Subhas, M. S.; Roy, S.; Kantam, M. L.; Sridhar, B.; Seth, R. K.; Biswas, S. *Org. Biomol. Chem.* **2009**, *7*, 85–93. (b) Zhou, Y.; Beeler, A. B.; Cho, S.; Wang, Y.; Franzblau, S. G.; Snyder, J. K. *J. Comb. Chem.* **2008**, *10*, 534–540. (c) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X. M.; Paterson, I. A.; Yu, P. H. *Drug Dev. Res.* **1997**, *42*, 150–156. (d) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999–5004.

(15) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.

(16) (a) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673. See also the $CuBr/O_2$-promoted oxidative α-(nitroalkylation) of tertiary amines: (b) Baslé, O.; Li, C. J. *Green Chem.* **2007**, *9*, 1047–1050.

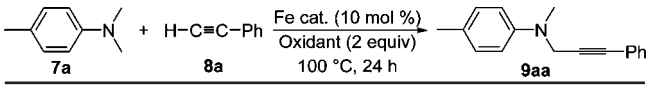
(17) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969.

(18) Li, Z. P.; Bohle, D. S.; Li, C. J. *Proc. Nat. Acad. Sci. U.S.A.* **2006**, *103*, 8928–8933.

(19) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961–3963.

(20) (a) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787, and references therein. (b) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511. (c) Plietker, B. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, 2008. (d) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341–1369. (e) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (f) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321. (g) Carril, M.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 4862–4865. (h) Volla, C. M. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307. (i) Loska, R.; Volla, C. M. R. *Adv. Synth. Catal* **2008**, *350*, 2859–2864. (j) Reymond, S.; Ferrié, L.; Guerinot, A.; Capdevielle, P.; Cossy, J. *Pure Appl. Chem.* **2008**, *80*, 1683–1691. (k) Volla, C. M. R.; Vogel, P. *Tetrahedron Lett.* **2008**, *49*, 5961–5964.

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



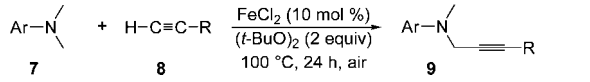
7a 8a 9aa

entry	Fe catalyst	oxidant (equiv)	atmosphere	yield (%)[b]
1	$FeCl_2$	*t*-BuOOH (3)	Ar	tr
2	$FeCl_2$	$(t\text{-BuO})_2$ (3)	Ar	42
3	$FeCl_2$	$(t\text{-BuO})_2$ (2)	Ar	69
4	$FeCl_3$	$(t\text{-BuO})_2$ (2)	Ar	56
5	$Fe(acac)_2$	$(t\text{-BuO})_2$ (2)	Ar	12
6	$Fe(acac)_3$	$(t\text{-BuO})_2$ (2)	Ar	0
7	$Fe(OAc)_2$	$(t\text{-BuO})_2$ (2)	Ar	0
8	$Fe(ClO_4)_2$	$(t\text{-BuO})_2$ (2)	Ar	0
9	$Fe_2(CO)_9$	$(t\text{-BuO})_2$ (2)	Ar	12
10	$Fe(CO)_5$	$(t\text{-BuO})_2$ (2)	Ar	13
11	$FeCl_2$	$(t\text{-BuO})_2$ (2)	Ar	7[c]
12	$FeCl_2$	H_2O_2 (2)	Ar	
13	$FeCl_2$	O_2 (1 atm)		
14	**$FeCl_2$**	**$(t\text{-BuO})_2$ (2)**	**air**	**85**
15	**$FeCl_2$**	**$(t\text{-BuO})_2$ (2)**	**air**	**88**[d]
16	$FeCl_2$	$(t\text{-BuO})_2$ (2)	O_2	65
17		$(t\text{-BuO})_2$ (2)	air	
18	$FeCl_2$	$(BzO)_2$ (2)	air	tr
19		$(BzO)_2$ (2)	air	*e*
20	$FeCl_2$	$(t\text{-BuO})_2$ (2)	air	tr[f]
21	$FeCl_2$	$(t\text{-BuO})_2$ (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 H_2O was added. [g] 20 equiv of H_2O 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]

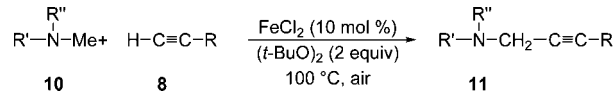


7 8 9

entry	Ar	R	time (h)	yield (%)[b]
1	4-MeC_6H_4 (**7a**)	Ph (**8a**)	24	88 (**9aa**)
2	4-MeC_6H_4 (**7a**)	4-MeC_6H_4 (**8b**)	24	76 (**9ab**)
3	4-MeC_6H_4 (**7a**)	4-$MeOC_6H_4$ (**8c**)	24	57 (**9ac**)
4	4-MeC_6H_4 (**7a**)	2-pyridyl (**8d**)	24	79 (**9ad**)
5	4-MeC_6H_4 (**7a**)	3-pyridyl (**8e**)	24	93 (**9ae**)
6	4-MeC_6H_4 (**7a**)	*n*-hexyl (**8f**)	30	66 (**9af**)
7	4-MeC_6H_4 (**7a**)	Et_3Si (**8g**)	30	82 (**9ag**)
8	4-MeC_6H_4 (**7a**)	1-cyclohexenyl (**8h**)	24	47 (**9ah**)
9	4-MeC_6H_4 (**7a**)	COOEt (**8i**)	24	61 (**9ai**)
10	4-MeC_6H_4 (**7a**)	$ClCH_2CH_2CH_2$ (**8j**)	30	69 (**9aj**)
11	4-MeC_6H_4 (**7a**)	$PhOCH_2$ (**8k**)	24	71 (**9ak**)
12	2-MeC_6H_4 (**7b**)	Ph (**8a**)	24	71 (**9ba**)
13	Ph (**7c**)	Ph (**8a**)	24	24 (**9ca**)[c]
14	Ph (**7c**)	4-MeC_6H_4 (**8b**)	24	32 (**9cb**)[d]
15	2-MeC_6H_4 (**7b**)	4-MeC_6H_4 (**8b**)	24	79 (**9bb**)
16	4-BrC_6H_4 (**7d**)	Ph (**8a**)	24	54 (**9da**)

[a] Reaction conditions: 1 equiv (2 mmol) of **8**, 1.5 equiv (3 mmol) of **7**, $FeCl_2$ (0.2 mmol), $(t\text{-BuO})_2$ (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 $FeCl_2$-Catalyzed Oxidative Couplings



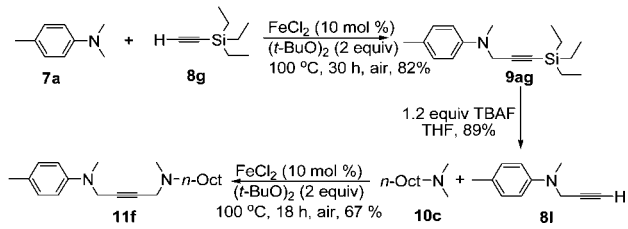
10 8 11

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′ = *n*-octyl, R″ = Me (**10c**)	Ph (**8a**)	24	74 (**11c**)
4	R′ = *c*-hexyl, R″ = Me (**10d**)	Ph (**8a**)	18	89 (**11d**)
5	R′ = *n*-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 $FeCl_2$-Catalyzed Oxidative Couplings with Two Different *tert*-Amines



7a 8g 9ag 11f 10c 8l

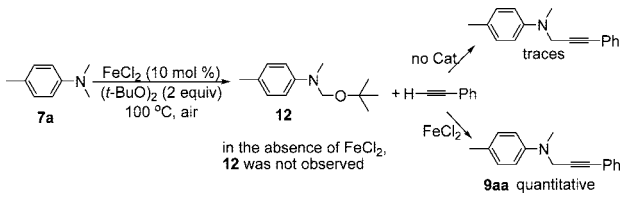
The product resulting from the oxidation of the benzylic C−H of **10a** could not be detected, thus showing the high chemoselectivity of our oxidative C−C coupling reaction, the least sterically hindered α-C-H bonds of the amine being oxidized preferentially. This can be explained by the known chemoselectivity of hydrogen transfer from tertiary amines to *t*-BuO• radical, which is faster for $PhNMe_2$ and Et_3N than for $(allyl)_3N$ and $PhN(CH_2Ph)_2$.[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

(21) See e. g.: (a) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, 59–72. (b) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440–1449. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (e) Buchwald, S. L.; Martin, R. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (f) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486–1499.

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 $FeCl_2$ is to catalyze the formation formation of intermediates of type **5**.[23] In the absence of alkyne the reaction **7a** + (t-BuO)$_2$/$FeCl_2$ produces the α-aminoether 4-MeC_6H_4N(Me)CH_2-O-t-Bu (**12**).[24] The later does not react with phenylacetylene (**8a**) in the absence of $FeCl_2$, showing that $FeCl_2$, 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 $FeCl_2$,

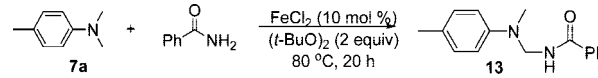
Scheme 3. Formation of *tert*-Butyl Aminomethyl Ether and Subsequent Coupling with Phenylacetylene



(t-BuO)$_2$ + **7a** did not react to produce **12** (12 h, 100 °C). This demonstrates that $FeCl_2$ catalyzes the formation of **12**, even though it was reported that dialkyl peroxides are unreactive with $FeCl_2$.[26] Reaction **1** + (t-BuO)$_2$/$FeCl_2$ → **5** might not involve homolysis, (t-BuO)$_2$ → 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-C_2-D and n-$C_6H_{13}C_2$-H was heated to 100 °C for 12 h in the presence of 2 equiv of Et_3N, a 0.5:0.5:0.5:0.5 mixture of Ph-C_2-H, Ph-C_2-D, n-hex-C_2-D, and n-hex-C_2-H was formed. The same experiment run with 10% $FeCl_2$ and the absence of Et_3N 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 $FeCl_2$ and Et_3N 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 $FeCl_2$ itself can generate iron acetylide intermediates, but more slowly than deprotonation by Et_3N.

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-MeOC_6H_4, 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)$_2$ + $FeCl_2$ 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 $PhCONH_2$, **7a** reacted to give the corresponding product of oxidative coupling 4-MeC_6H_4N(Me)CH_2NHCOPh (**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 chemistry[28] 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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(22) Tanko, J. M.; Friedline, R.; Suleman, N. K.; Castagnoli, N., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 5808–5809.

(23) (a) Kern, W.; Schulz, R. *Makromol. Chem.* **1954**, *13*, 210–222. (b) Li, Z. P.; Cao, L.; Li, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505–6507. (c) Zhang, Y.; Li, C. J. *Eur. J. Org. Chem.* **2007**, 4654–4657.

(24) Characterized by its ^{1}H NMR spectrum, which is analogous to that *N*-ethyloxymethyl-*N*-methylaniline Raap, J.; Nieuwenhuis, S.; Creemers, A.; Hexpoor, S.; Kragle, U.; Lugtenburg, J. *Eur. J. Org. Chem.* **1999**, 2609–2621.

(25) Deng, G.; Li, C. J. *Tetrahedron Lett.* **2008**, *49*, 5601–5604.

(26) Sawyer, D. T.; Sobkowiak, A.; Matsushita, T. *Acc. Chem. Res.* **1996**, *29*, 409–416.

(27) After submission of this manuscript, Li and co-workers reported the $FeCl_3$ catalyzes conversion of terminal alkynes, aldehydes, and secondary amines into aminoalkynes, reactions that probably imply iminium ion intermediates reacting with acetylide intermediates: Li, P.; Zhang, Y.; Wang, L. *Chem. Eur. J.* **2009**, *15*, 2045–2049.

(28) For aminoalkynes as potential drugs, see: (a) Pisano, C.; Battistuzzi, G.; Di Marzo, M.; Giannini, G.; Marzi, M.; Vesci, L.; Zunino, F.; Pezzi, R. *PCT Int. Appl. 2006*; *Chem. Abstr.* **2006**, *146*, 62468. (b) Fournet, G.; Quash, G. A.; Gore, J. *PCT Int. Appl. 2001*; *Chem. Abstr.* **2001**, *136*, 5727. (c) Moon, M. W.; Heier, R. F. *PCT Int. Appl. 1990*; *Chem. Abstr.* **1990**, *113*, 115301. (d) Adams, T. C.; Dupont, A. C.; Carter, J. P.; Kachur, J. F.; Guzewska, M. E.; Rzeszotarski, W. J.; Farmer, S. G.; Noronha-Blob, L.; Kaiser, C. *J. Med. Chem.* **1991**, *34*, 1585–1593.