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Electrophilic amination of Cu(I) catalyzed phenylmagnesium bromide with N,O-bis(trimethylsilyl)hydroxylamine in THF:N-donor solvent. Control of C–N and C–O chemoselectivity

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ABSTRACT

Reaction of PhMgBr with $(Me_3Si)HNO(SiMe_3)$[TMSHA] in the presence of CuI or CuCN catalysis (10 –20 mol %) in THF:cosolvent (cosolvent = HMPA or TMEDA) at room temperature can provide an atom-economic and step-economic access for arylamine synthesis starting from aryl Grignard reagents. Chemoselectivity to yield C–N or C–O coupling can be controlled by changing reaction parameters. Cu(I) catalyzed reaction of PhMgBr in THF or in THF:HMPA (or TMEDA) affords both C–N and C–O coupling products, i.e. aniline and phenol (mol ratio ≥ 7:3), whereas uncatalyzed reaction of PhMgBr gives phenol. Mechanisms were proposed for the solvent dependence of chemoselectivity in the coupling of both uncatalyzed and Cu(I) catalyzed Grignard reagent with (TMS)HNO(TMS).

1. Introduction

Amines are of much importance due to the amino functionality in natural products and pharmaceutical compounds as well as building blocks in organic synthesis [1]. Modern methods are now available to form C–N bonds and using transition metal catalyzed amination of C-X bonds [2,3] or C–H bonds [4] provide important methodologies for the synthesis of arylamines and heteroarylamines. Electrophilic amination of organometallic compounds, that is coupling of carbanions with electrophilic aminating reagents, which are synthetic equivalents of $^{\oplus}NR_2$ synthons, is also an important and potentially valuable methodology for the synthesis of amines [5–7].

A number of electrophilic aminating reagents and methods have been developed for nonsymmetric and symmetric amination of ordinary carbanions [6a-f,h-l], and also for amination of enolates derived from carbonyl compounds [6g,h].

Electrophilic aminating reagents contain either sp^3N or sp^2N (Scheme 1). N-Chloramine **1** [8], O-substituted hydroxylamine **2**–**6** (O-organyl-, O-acyl-, O-silyl-, O-phosphinyl- and O-sulhydroxylamines) [6a, g, h, 7–9] and oxaziridines **7** [7,9] react with carbanions directly. O-Sulfonyloximes **8**, arenediazonium salts **9**, azides **10**, diazene dicarboxylates **11** and 1-chloro-1-nitrosocycloalkanes **12** form intermediates which require reductive work-up to produce amines [7,9].

Over the last twenty years, our research group has been involved in electrophilic amination of Grignard reagents, diorganocuprates, diorganozincs and triorganozincates with O-methylhydroxylamine **2** (Z = Me) [10e], with N,N-dimethyl O-(mesitylenesulfonyl)hydroxylamine **6** (R = Y = Me, R^1 = 2,4,6-$Me_3C_6H_2$) [10f, g] and with acetone O-(mesitylenesulfonyl)oxime **8** (R^1 = Me, R^2 = 2,4,6-$Me_3C_6H_2$) [10a-d,h].

However, to the best of our knowledge, N,O-bis(trimethylsilyl) hydroxylamine (TMSHA) **4a** [11a] and N-alkyl-O-(trimethylsilyl) hydroxylamines **4b** [11b] did not receive much attention. They have been used only for high yield amination of aryl and heteroaryl Lipshutz type cuprates, $R_2Cu(CN)Li_2$ by Ricci, Dembech, Seconi and coworkers (Scheme 2a) [11a]. Ferrocene carboxyaldehyde could be also aminated following α-lithiation and reaction of dilithium mixed cyanocuprate with **4a** (Scheme 2b) [11c]. In the amination of dialkylcyanocuprates and mixed (alkyl)(phenyl)cyanocuprates, both alkylamine and alkanol formation has been observed due to the above mentioned nitrenoid/oxenoid equilibrium of the reagent

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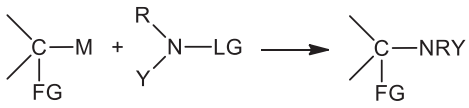
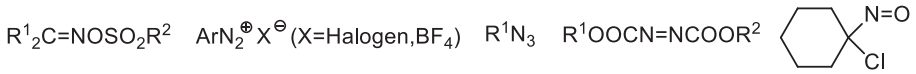


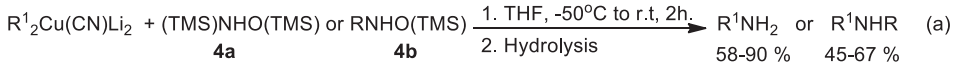
FG= H, R, COX (X= H, R, OH, OR, NR_2), CN
M= Li, Mg, Cu, Zn, B, Al, Si, Zr

R= H, Organyl
Y= H, R, SiR_3 in **4**, COOR

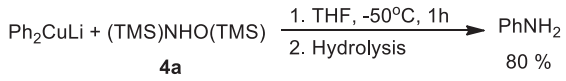


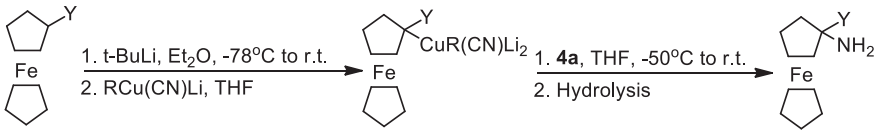
8 **9** **10** **11** **12**

Scheme 1. sp^3N and sp^2N type electrophilic aminating reagents.

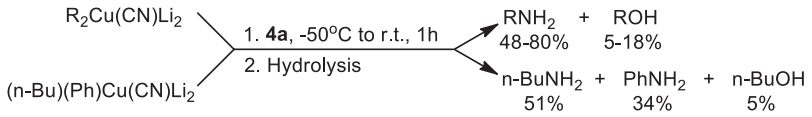


R^1= Aryl, heteroaryl
R= Me, i-Pr, t-Bu





Y= CHO acetal derivative



Scheme 2. **(a)** Amination of aryl and heteroaryl cyanocuprates with N,O-bis(trimethylsilyl)-hydroxylamine **4a** [11a] and with N-alkyl O-(trimethylsilyl)hydroxylamine **4b** [11b]. **(b)** Amination of 2-lithioferrocene carboxyaldehyde acetal derivative with **4a** [11c]. **(c)** Amination of dialkylcyanocuprates with **4a** [11a].

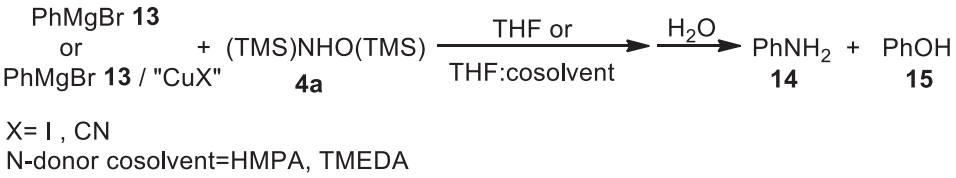
resulting in C–N and C–O coupling (Scheme 2c) [11c].

So, encouraged by these results and essentially in an effort to broaden the scope of electrophilic amination, we focused our interest on the investigation of utility of TMSHA **4a** for amination of aryl Grignard reagents in the presence of Cu(I) catalysts. We planned to develop a new method for arylamine synthesis using aryl Grignard reagent derived catalytic cuprates instead of prepared higher order diarylcyanocuprates $R_2Cu(CN)Li_2$. On the other hand, while we are optimizing the reaction parameters for high yield C–N coupling leading to arylamine synthesis, we observed that C–O coupling also takes place leading to phenol synthesis due to the nitrenoid/oxenoid equilibrium of the aminating reagent TMSHA **4a** (Scheme 4). These results prompted us to control the chemoselectivity in the reaction for allowing the formation of either arylamine and phenol.

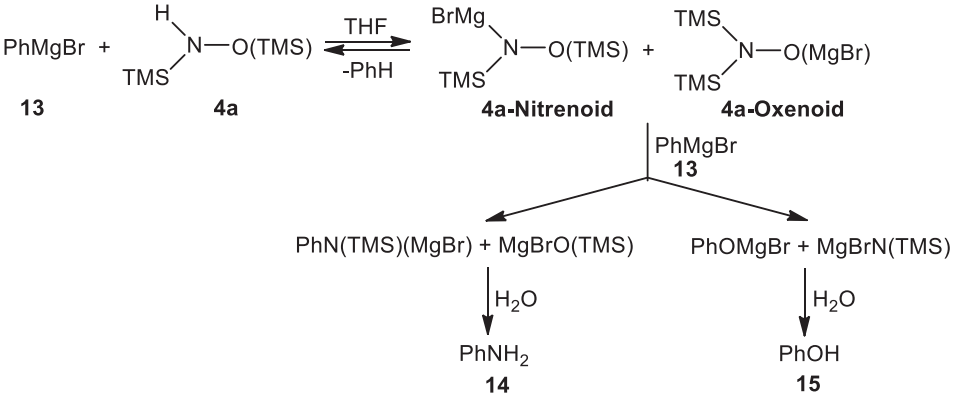
Herein, we report our successful findings for the development of a new method for one-pot C_{aryl}-N coupling using reaction of Cu(I) catalyzed aryl Grignard reagents with TMSHA **4a** and also for the applicability of the reaction of uncatalyzed reagents for C_{aryl}-O coupling. This method provides an atom-economic and step-economic access for arylamine synthesis using electrophilic amination.

2. Results and discussion

In the amination of Cu(I) catalyzed Grignard reagents with N,O-bis(trimethylsilyl)hydroxylamine (TMSHA) **4a**, we began our investigations by determining the background yields, i.e. the yields of uncatalyzed Grignard reagents. For these purpose, as model reactions, we selected reaction of phenylmagnesium bromide, PhMgBr **13** and reaction of Cu(I) catalyzed PhMgBr **13** with TMSHA **4a** in THF (Scheme 3). With the aim of both developing a new method for C–N coupling and also controlling N- or O- selectivity of the reactions, we planned to investigate the effect of reaction parameters, (i) firstly, on the reaction of PhMgBr **13** and (ii) secondly, on the reaction of Cu(I) catalyzed PhMgBr **13**. As reaction



Scheme 3. Reaction of TMSHA **4a** with uncatalyzed and Cu(I) catalyzed PhMgBr **13** in THF using a cosolvent.



Scheme 4. Reaction of PhMgBr **13** with protonated TMSHA **4a**, i.e. **4a-nitreneoid** and **4a-oxenoid** in THF.

parameters, we screened **13**:**4a** mol ratio, Cu(I) catalysts and N-donor solvents as organic catalysts. The reaction temperature and time were optimized to be 25 °C and 3.5 h, respectively.

The total yield was found very low with 1:1 mol ratio of **13**:**4a** and/or in the presence of 5 mol% Cu(I) catalysis. Aiming a successful atom-economic amination, we tried to carry out the reactions in 2:1 and 3:1 mol ratios of **13**:**4a** using CuI or CuCN catalyst lower than 50 mol%. As organic catalysts, N-donor TMEDA and HMPA were used as cosolvents in mostly 4:1 and 1:1 mol ratios of THF:cosolvent. The yield of coupled products $PhNH_2$ **14** and PhOH **15** were determined by finding their GC yields. The sum of the yields of **14** and **15** are given as total yield and the ratio of the yields of **14** and **15** are evaluated as chemoselectivity, i.e. C–N coupling:C–O coupling ($PhNH_2$:PhOH) ratio.

(iii) We also proposed mechanism to give brief convincing explanations for the solvent dependence of the total yield and the ratio of C–N and C–O coupling products in the reactions of uncatalyzed and catalyzed aryl Grignard reagents.

(i) The uncatalyzed reactions of PhMgBr **13** were carried out in THF and in THF:cosolvent with 2:1 and 3:1 mol ratios of **13**:**4a.** The total yield and C–N coupling:C–O coupling ratio were listed in Table 1. Following the deprotonation of **4a** with an equimolar amount of **13** to give nitrenoid/oxenoid equilibrium takes place (Scheme 4) [12]. So, both C–N and C–O coupling reactions might be expected to take place with **4a** in the presence of 2:1 and higher mol ratios of **13**:**4a** (Scheme 3).

Surprisingly, we observed only, PhOH **15** in THF with 56% and 35% yields in 2:1 and 3:1 mol ratios of **13**:**4a** (Table 1, entries 1 and 4, respectively). N-Donor solvents, monodendate HMPA and bidendate TMEDA were also tested as coordinating solvents in THF. As seen, C–N coupling did not take place and the yield decreased in

Table 1
Reaction of phenylmagnesium bromide **13** with TMSHA **4a** in THF at room temperature. Effect of **13**:**4a** ratio and N-donor cosolvent on the yield and chemoselectivity[a,b].

PhMgBr **13** + (TMS)NHO(TMS) **4a** $\xrightarrow[2.\text{Hydrolysis}]{1.\text{THF:cosolvent,25°C,3.5h}}$ $PhNH_2$ **14** + PhOH **15**

Entry	Solvent [c]	Coupling yield, % [d]	Chemoelectivity **14**:**15** [e]
13: **4a** mol ratio = 2:1			
1	THF	56	0:100
2	THF:HMPA(1:1)	45	0:100
3	THF:TMEDA(1:1)	30	0:100
13: **4a** mol ratio = 3:1			
4	THF	35	0:100
5	THF:HMPA(4:1)	28	0:100
6	THF:HMPA(1:1)	24	0:100
7	THF:TMEDA(4:1)	18	13:87
8	THF:TMEDA(1:1)	17	0:100

[a] All the data are the average of at least five experiments.
[b] The reactions were carried out on a 1 mmol scale.
[c] THF:cosolvent volume ratio.
[d] The sum of GC yields of **14** and **15**.
[e] The ratio of GC yields **14:15**.

the presence of coordinating solvents (Table 1, entries 2,3, and 5–8). Looking more closely at these results also showed an increase in the yield of PhOH in the presence of HMPA compared to that in TMEDA (Table 1, entries 2,3; 5.7 and 6,8).

We also examined the effect of using 4:1 mol ratio of **13**:**4a** for comparison with the results obtained using 2:1 and 3:1 mol ratio and we found 53% yield of PhOH in THF, not higher than the observed maximum yield.

(ii) Next, we turned our attention to the amination of PhMgBr **13** with TMSHA **4a** in the presence of CuI or CuCN as catalysts. Catalytic diorganocuprates "$Ph_2CuMgBr$" **16** and "PhCu(CN)MgBr" **17** and also PhMgBr **13** might deprotanate **4a** to form nitrenoid (Scheme 5). We carried out the experiments at 2:1 and 3:1 mol ratios of **13**:**4a** (Table 2, Table 3 and Table 4, respectively).

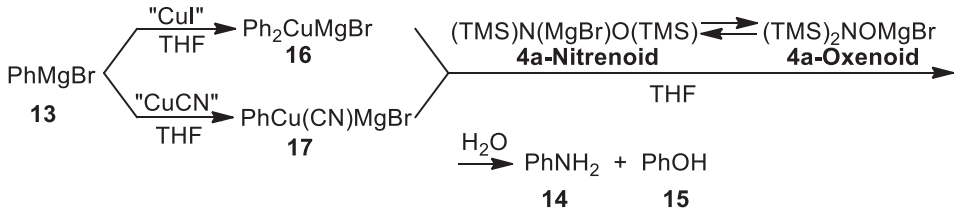
First, we used PhMgBr **13** with 10–40 mol % CuI or CuCN catalysis in the presence of 2:1 mol ratio of **13**:**4a** (Table 2). 10 mol% CuI catalysis in THF did not result in a higher yield and $PhNH_2$:PhOH ratio (Table 2, entry 1). Surprisingly, in THF:HMPA, the reaction gives $PhNH_2$ with a $PhNH_2$:PhOH ratio higher than 93:7 (Table 2, entries 2 and 3), however the total yield is pretty low (54% and 45%, respectively). Better results were obtained when using 20 mol% CuI both in THF (Table 2, entry 6) and also in THF:HMPA (Table 2, entries 7, 8). THF led to 75%yield ($PhNH_2$:PhOH ratio = 87:13) (Table 2, entry 6). We were delighted to find that the reaction in THF:HMPA (1:1) takes place with 83% yield and $PhNH_2$:PhOH ratio of 95:5 (Table 2, entry 8). These optimized conditions seemed us as an atom economic alternative to electrophilic amination of diarylcuprates with TMSHA. As a cosolvent, TMEDA gave quite low yields (Table 2, entries 9 and 10).

We next employed CuCN as a catalysts. In the presence of 10 mol % CuCN, 59% yield obtained with $PhNH_2$:PhOH ratio of 85:15 in THF (Table 2, entry 11). Using donor solvents resulted in diminished yields (Table 2, entries 12–15).

Next, we tried CuCN catalysis in 40 mol% (entries 16–18). In THF, a quite low yield was obtained again (entry 16). In THF, HMPA (or TMEDA) (THF:cosolvent = 4:1), the reaction was completed with a medium yield (57% and 60%), but with a high ratio of $PhNH_2$:PhOH (96:4 and 85:15), respectively (Table 2, entries 17 and 18).

It is also noteworthy that CuI catalyzed reactions lead to obtaining higher yield and higher $PhNH_2$:PhOH ratio in the presence of HMPA compared to that in the presence of TMEDA (entries 2,3 compared to 4,5; entries 7,8 compared to 9,10). In addition, increasing the cosolvent generally decreases the total yield (Table 2, entries 2,3; 4,5; 9,10 and 12, 13).

The effect of Cu(I) catalysis was also examined for the reaction carried out with 3:1 mol ratio of **13**:**4a** (Table 3). 10 mol% CuI catalysis gave 16–58% yields with quite high $PhNH_2$:PhOH ratios



Scheme 5. Reaction of catalytic $Ph_2CuMgBr$ **16** and PhCu(CN)MgBr **17** with **4a-nitrenoid** and **4a-oxenoid** in THF.

Table 2
Reaction of phenylmagnesium bromide **13** with TMSHA **4a** (**13**:**4a** mol ratio = 2:1) in THF at room temperature. Effect of Cu(I) catalyst and N-donor solvent on the yield and N-coupling:O-coupling ratio.[a,b]

PhMgBr **13** + (TMS)NHO(TMS) **4a** —CuX; 1.THF:cosolvent,25°C,3.5h; 2.Hydrolysis→ $PhNH_2$ **14** + PhOH **15** **13** : **4a** mol ratio = 2:1

Entry	CuX (mol%)	Solvent [c]	Coupling yield, % [d]	Chemoelectivity **14:15** [e]
1	CuI(10)	THF	62	45:55
2	CuI(10)	THF: HMPA (4:1)	54	96:4
3	CuI(10)	THF:HMPA(1:1)	45	93:7
4	CuI(10)	THF:TMEDA(4:1)	25	76:24
5	CuI(10)	THF:TMEDA(1:1)	6	33:67
6	CuI(20)	THF	75	87:13
7	CuI(20)	THF: HMPA (4:1)	61	89:11
8	CuI(20)	THF:HMPA(1:1)	83	95:5
9	CuI(20)	THF:TMEDA(4:1)	22	0:100
10	CuI(20)	THF:TMEDA(1:1)	7	43:57
11	CuCN(10)	THF	59	85:15
12	CuCN(10)	THF: HMPA (4:1)	23	91:9
13	CuCN(10)	THF:HMPA(1:1)	12	87:13
14	CuCN(10)	THF:TMEDA(4:1)	11	0:100
15	CuCN(10)	THF:TMEDA(1:1)	21	24:76
16	CuCN(40)	THF	39	77:23
17	CuCN(40)	THF: HMPA (4:1)	57	96:4
18	CuCN(40)	THF:TMEDA(4:1)	60	85:15

[a] All the data are the average of at least five experiments.
[b] The reactions were carried out on a 1 mmol scale.
[c] THF:cosolvent volume ratio.
[d] The sum of GC yields of **14** and **15**.
[e] The ratio of GC yields **14:15**.

(75:25–90:10) in THF and in THF:cosolvent (Table 3, entries 1-5). The use of 20 mol% CuI increased the total yield in THF and in THF:HMPA (Table 3, entries 6–8) generating $PhNH_2$ with 80% yield in THF:HMPA (1:1) (Table 3, entry 8). Meanwhile, 40 mol% CuI catalyzed reaction was completed with a quantitative yield and 73% and 76% yield of $PhNH_2$ in THF:HMPA (4:1) and THF:HMPA (1:1), respectively (Table 3, entries 12 and 13).

CuCN catalysis also resulted in high yields and high $PhNH_2$:PhOH ratios in THF:cosolvent. The yields of anilines were found to be 71% with 10 mol% CuCN, in THF:HMPA (4:1) (Table 3, entry 17), 69% with 20 mol% CuCN in THF:TMEDA (4:1) (Table 3, entry 24) and 80% with 40 mol% CuCN in THF:HMPA (4:1) (Table 3, entry 27) and 84% in THF:TMEDA (4:1) (Table 3, entry 28).

These results obtained using 3:1 mol ratio of **13**:**4a** with CuI or CuCN catalysis in THF:HMPA and also in THF:TMEDA gratifyingly bring us a complement for CuI catalyzed reactions in THF:HMPA carried out in 2:1 mol ratio of **13**:**4a**.

As we noted for the reactions carried out with 2:1 mol ratio of **13**:**4a**, we observed higher $PhNH_2$:PhOH ratio in THF:HMPA compared to that in THF:TMEDA also in the reactions carried out with 3:1 mol ratio of **13**:**4a** (Table 3, entries 12, 13 compared to 14, 15; entries 22, 23 compared to 24, 25).

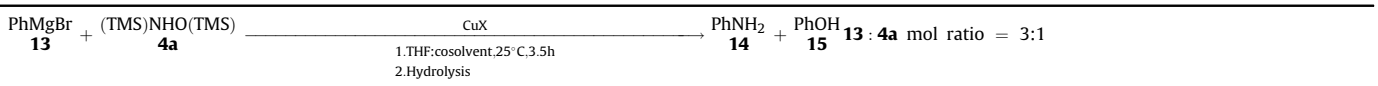
This one-pot procedure for amination of catalytic diarylcuprates and (aryl)(cyano)cuprates was also carried out with 4:1 mol ratio of PhMgBr: **4a** in order to see a probable comparative change in the outcome of the reactions. Focusing to the atom-economic synthesis of $PhNH_2$, the total yields and chemoselectivities of the reactions with 2:1–4:1 mol ratio resulting more than 68% yield are listed in Table 4.

Under the optimized conditions, we observed that the results are consistent. In the reactions carried out with 4:1 mol ratio of **13:4a**, 20 mol% CuI catalysis in THF:HMPA (4:1) led to 68% yield of aniline (Table 4, entry 9). In THF:HMPA (4:1 or 1:1), 40 mol% CuI catalyzed reactions afforded 72% and 75% yield of aniline, respectively (Table 4, entries 10 and 11). In the presence of 10 mol% and 40 mol% CuCN catalysis, the reaction in THF:TMEDA (4:1) gave 72% and 77% aniline, respectively (Table 4, entries 12 and 13). We also used a Lewis base additive, Ph_3P in reactions of PhMgBr **13** reagents with TMSHA **4a**. The reaction at 2:1 mol ratio of **13**:**4a**, the use of 10 mol % Ph_3P with 10 mol % and 20 mol % CuI and 10 mol % CuCN catalysis generated 67%, 65% and 96% yield with $PhNH_2$:PhOH ratio of 46:54, 82:18 and 89:11, respectively. At 3:1 mol ratio of **13**:**4a**, we found that, 10 mol % Ph_3P with 10 mol %CuI, 20 mol % CuI and 10 mol % CuCN afforded 100%, 75% and 100% yield with $PhNH_2$:PhOH ratio of 50:50, 81:19 and 86:14, respectively. However, it seems that the use of Ph_3P as a Lewis base catalyst does not give better results on the yield and $PhNH_2$:PhOH ratio compared to those taken from the reactions obtained in the presence of donor solvents.

These results obtained on the uncatalyzed and Cu(I) catalyzed reactions of PhMgBr **13** with (TMS)NHO(TMS) **4a** (Scheme 3) using 2:1, 3:1 and 4:1 mol ratios of **13**:**4a** in THF and in THF:N-donor solvents are summarized below:

(i) The reaction of uncatalyzed PhMgBr in 2:1 mol ratio of **13**:**4a** in THF yields only C–O coupling product, i.e. PhOH with a maximum yield of 56% (Table 1, entry 1).

Table 3
Reaction of phenylmagnesium bromide **13** with TMSHA **4a** (**13**:**4a** mol ratio = 3:1) in THF at room temperature. Effect of Cu(I) catalyst and N-donor solvent on the yield and N-coupling[a,b].



Entry	CuX (mol%)	Solvent [c]	Coupling yield, % [d]	Chemoelectivity **14:15** [e]
1	CuI(10)	THF	58	90:10
2	CuI(10)	THF: HMPA (4:1)	41	90:10
3	CuI(10)	THF:HMPA(1:1)	16	75:25
4	CuI(10)	THF:TMEDA(4:1)	48	83:17
5	CuI(10)	THF:TMEDA(1:1)	35	77:23
6	CuI(20)	THF	77	71:29
7	CuI(20)	THF: HMPA (4:1)	72	89:11
8	CuI(20)	THF:HMPA(1:1)	88	91:9
9	CuI(20)	THF:TMEDA(4:1)	75	83:17
10	CuI(20)	THF:TMEDA(1:1)	23	26:74
11	CuI(40)	THF	51	67:33
12	CuI(40)	THF: HMPA (4:1)	100	73:27
13	CuI(40)	THF:HMPA(1:1)	100	76:24
14	CuI(40)	THF:TMEDA(4:1)	48	67:33
15	CuI(40)	THF:TMEDA(1:1)	57	51:49
16	CuCN(10)	THF	78	71:29
17	CuCN(10)	THF: HMPA (4:1)	87	82:18
18	CuCN(10)	THF:HMPA(1:1)	65	82:18
19	CuCN(10)	THF:TMEDA(4:1)	29	50:50
20	CuCN(10)	THF:TMEDA(1:1)	34	0:100
21	CuCN(20)	THF	66	91:9
22	CuCN(20)	THF: HMPA (4:1)	72	83:17
23	CuCN(20)	THF:HMPA(1:1)	65	82:18
24	CuCN(20)	THF:TMEDA(4:1)	98	70:30
25	CuCN(20)	THF:TMEDA(1:1)	63	74:26
26	CuCN(40)	THF	54	85:15
27	CuCN(40)	THF: HMPA (4:1)	100	80:20
28	CuCN(40)	THF:TMEDA(4:1)	99	84:16

[a] All the data are the average of at least five experiments.
[b] The reactions were carried out on a 1 mmol scale.
[c] THF:cosolvent volume ratio.
[d] The sum of GC yields of **14** and **15**.
[e] The ratio of GC yields **14:15**.

Table 4
Optimized conditions for obtaining $PhNH_2$ **14** with medium to high yields (≥68%) in the CuX catalyzed reaction of PhMgBr **13** with **4a** in THF or in THF:cosolvent.

PhMgBr **13** + (TMS)NHO(TMS) **4a** —CuI or CuCN, THF:cosolvent, 25°C, 3h→ $PhNH_2$ **14** + PhOH **15**

Entry	**13:4a** mol ratio	CuX, (mol%)	Solvent	Coupling yield, %	Chemoelectivity **14:15**	Yield of $PhNH_2$ **14**, %
1	2:1	CuI (20)	THF:HMPA(4:1)	83	95:5	79
2	3:1	CuI (20)	THF:HMPA(1:1)	88	91:9	80
3	3:1	CuI (40)	THF:HMPA(4:1)	100	73.27	73
4	3:1	CuI (40)	THF:HMPA(1:1)	100	76:24	76
5	3:1	CuCN (10)	THF:HMPA(4:1)	87	82:18	71
6	3:1	CuCN (20)	THF:TMEDA(4:1)	98	70:30	69
7	3:1	CuCN (40)	THF:HMPA(4:1)	100	80:20	80
8	3:1	CuCN (40)	THF:TMEDA(4:1)	99	84:16	84
9	4:1	CuI (20)	THF:TMEDA(4:1)	76	90:10	68
10	4:1	CuI (40)	THF:HMPA(4:1)	100	80.20	72
11	4:1	CuI (40)	THF:HMPA(1:1)	99	76.24	75
12	4:1	CuCN (10)	THF:TMEDA(4:1)	100	72:28	72
13	4:1	CuCN (20)	THF:TMEDA(1:1)	100	77:23	77

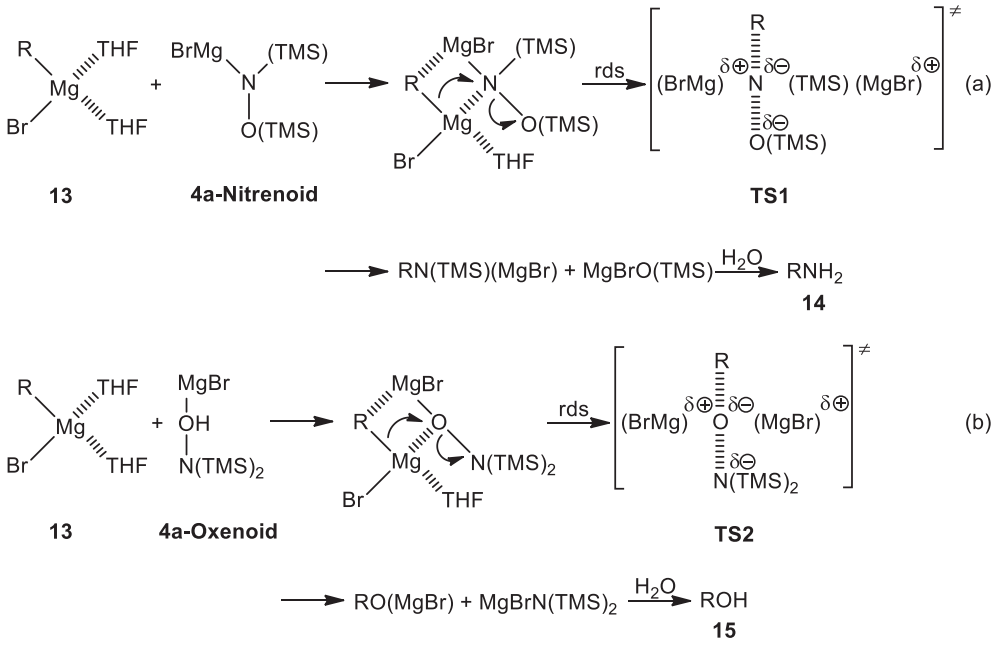
(ii) The reaction of CuI or CuCN catalyzed reaction of PhMgBr allows formation C–N coupling product, $PhNH_2$ generally much more than PhOH. However, chemoselectivity depends on catalyst and its amount as well as on N-donor solvent and its amount.

As seen, for an atom-economic amination, reactions carried out with 4:1 mol ratio of **13**:**4a** do not lead to higher yields compared to the reactions carried out with 2:1 and 3:1 mol ratio of **13**:**4a**. Amination using 2:1 or 3:1 mol ratio of **13**:**4a** in THF:HMPA (4:1 or 1:1) in the presence of 20 mol% CuI provide aniline with 79% and 80% yield, respectively (Table 4, entry 1 and 2). The use of less expensive CuCN (40 mol%) in THF:HMPA (or TMEDA) (4:1) also gives about the same yields of aniline, i.e. 80% in THF:HMPA (4:1) (Table 4, entry 7) and 84% in THF:TMEDA (4:1) (Table 4, entry 8). So, successful amination of PhMgBr **13** with **4a** (**13**:**4a** mol ratio = 2:1 or 3:1) in THF:HMPA (4:1 or 1:1) with 20 mol% CuI seems as an alternative atom-economic and step-economic method to offer for synthesis of arylamines from Grignard reagents.

(iii) With these results in hand, we afforded explanations for the effect of N-donor solvents on the outcome of both uncatalyzed and CuI or CuCN catalyzed reaction of PhMgBr **13** with **4a** in THF leading to C–N coupling and/or C–O coupling.

For the reaction of PhMgBr **13** with aminating reagent **4a**, we offered the mechanism given in Scheme 6 written on the attack of RMgBr to metallated nitrenoid and also attack of PhMgBr to metallated oxeneoid. Similar mechanisms were already proposed by Beak's group for amination reaction of organolithium reagents with O-substituted hydroxylamines **2**–**6** [7,13–15]; by Schverdina and Kotscheshkov for the reaction of alkyl Grignard reagents with $MeONH_2$ **2** [16] and by Boche and coworkers for the reaction of aryl Grignard reagents with O-(dipenylphosphyl)hydroxylamine **5** [17].

In this mechanism, carbanion of $RMgBr(THF)_2$ **13** attacks electrophilic N of N(MgBr)(TMS)OTMS **4a-nitrenoid**, leading to an S_N2-like transition state to give the product which offers the amine after hydrolysis (Scheme 6a). Similarly, attack of $RMgBr(THF)_2$ **13** to electrophilic O of $N(TMS)_2O(MgBr)$ **4a-oxeneoid**, might form



Scheme 6. Proposed mechanism for the reaction of RMgBr **13** with (a) N(MgBr)(TMS)O(TMS) **4a-Nitrenoid** and (b) with $N(TMS)_2O(MgBr)$ **4a-Oxenoid** in THF.

another S_N2-like transition state to give the product which offers the phenol after hydrolysis (Scheme 6b). Reaction of PhMgBr **13** with **4a** in THF and in THF:cosolvent generated only PhOH as product. In order to bring an explanation for the observation of the observed lower yields of PhOH in the presence of coordinating solvents, i.e. HMPA and TMEDA, we first thought that in the four-center intermediate [18,19] coordination of Mg to O occurs by replacement of donor THF (Scheme 6b). Nucleophilic solvation of Mg can lead to polarization of the C–Mg bond and an increase both in the nucleophilicity of carbanion and in electrophilicity of O appear. Then, replacement of donor THF by a coordinating solvent causes to give a less reactive complex leading to lower reaction yields, as observed. We can also think that in the coordination with bidendate TMEDA, RMgBr may have no vacant coordination to react, i.e. less favorable complex formation takes place compared with monodendate HMPA and as a cosolvent TMEDA leads to lower yields compared to HMPA, as expected.

A similar explanation can be given for the reaction of PhMgBr **13** with **4a** to produce $PhNH_2$ (Scheme 6a). As another explanation for the C–O coupling instead of C–N coupling in the reaction of PhMgBr **13** with **4a**, we think to offer the stability of nitrenoid as N-magnesium complex, **4a-nitrenoid**, which might prevent or at least slow down the C–N coupling of PhMgBr. Then, oxeneoid as O-magnesium complex, **4a-oxenoid** will react with PhMgBr leading C–O coupling (Scheme 6b).

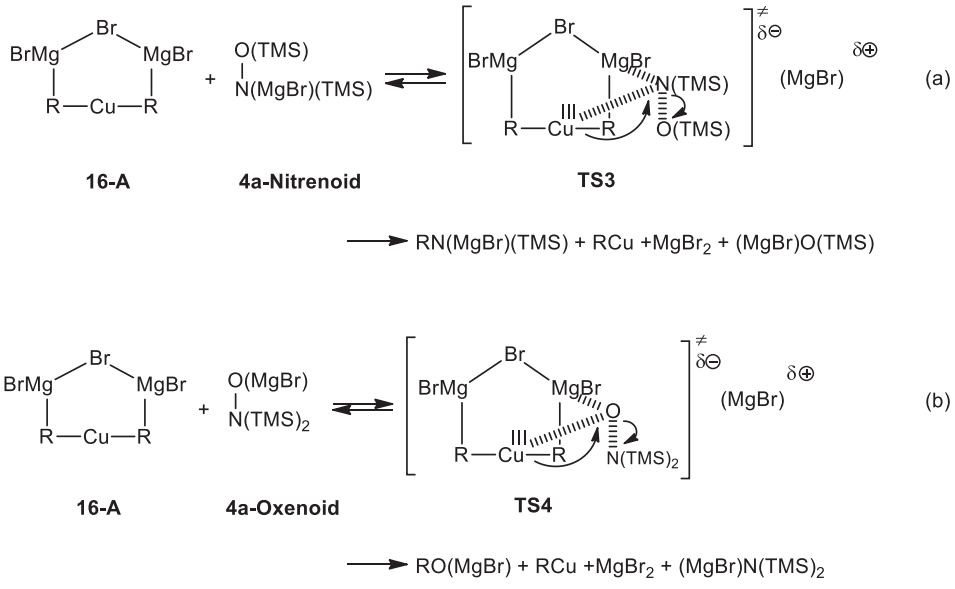
We also supported this mechanism with our work based on the kinetics and Hammett substituted constants of the reaction of substituted PhMgBr reagents with $MeONH_2$, **2** [10e].

We also found that catalytic diphenylcuprates $Ph_2CuMgBr$ **16** and phenylcyanocuprates PhCu(CN)MgBr **17** derived from PhMgBr, **13** are succesful in C–N coupling resulting in high yield of $PhNH_2$. Before offering mechanism for C–N and C–O coupling of catalytic diphenylcuprates, $R_2CuMgBr$ **16** and RCu(CN)MgBr **17**, we first preferred proposing transition states. We assumed a contact ion pair (CIP) structure as an heteroaggregate **A** which is in equilibrium with a solvent separated ion pair (SSIP) **B** for $R_2CuMgBr$ **16** and homo dimer structure **C** for RCu(CN)MgBr **17** (Scheme 7) [18–25].

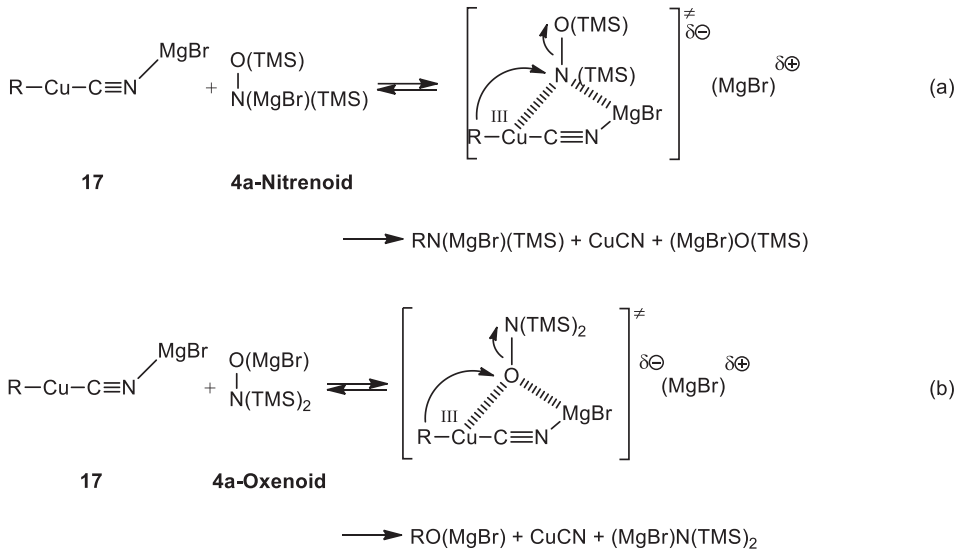
Taking these structures and mechanisms suggested for the reactions of cuprates by Nakamura and coworkers [24] and Bertz and coworkers [25] into consideration, we offered reaction pathways [10e] for the reaction $R_2CuMgBr$ **16** and RCu(CN)MgBr **17** with **4a** (Scheme 8 and Scheme 9, respectively). For the sake of clarity, we used monomer structure for RCu(CN)MgBr instead of **C**.

We will propose that in the reaction of $R_2CuMgBr$ **16-A** with **4a**, oxidative addition takes place either to electrophilic N or electrophilic O (Scheme 8 a and b, respectively) forming the transition states **TS3** or **TS4**, respectively. In **TS3**, N–MgBr bonding and Cu–N coordination take place and in **TS4**, O–MgBr bonding and Cu–O coordination take place. Reductive elimination gives the C–N coupling (Scheme 8a) or C–O coupling product (Scheme 8b). The mechanism for the reaction of RCu(CN)MgBr with **4a** leading to C–N coupling or C–O coupling is analogous to that offered for the reaction of $R_2CuMgBr$ (Scheme 9 a and b, respectively). As diorganocuprates are more reactive than Grignard reagents, **16** and **17** give mostly C–N coupling product with the stable N-magnesium complex of nitrenoid **4a**, as expected. In order to bring an explanation for the higher yield and higher $PhNH_2$:PhOH ratio in THF:HMPA compared to THF:TMEDA, we think the equilibrium between CIP and SSIP structures (Scheme 7) [21,24c,26]. Generally CIP is dominant in weakly solvating solvents and SSIP in solvents

Scheme 7. Structures for $R_2CuMgBr$, **A**, **B** and RCu(CN)MgBr, **C**.



Scheme 8. Proposed mechanism for the reaction of $R_2CuMgBr$ **16-A** with (a) N(MgBr)(TMS)O(TMS) **4a-Nitrenoid** (b) with $N(TMS)_2O(MgBr)$ **4a-Oxenoid** in THF.



Scheme 9. Proposed mechanism for the reaction of RCu(CN)MgBr **17** with (a) N(MgBr)(TMS)O(TMS) **4a-Nitrenoid** and (b) with $N(TMS)_2O(MgBr)$ **4a-Oxenoid** in THF.

with strong coordination ability [15,19,24b,27]. It is also known that essentially only CIP structure of a cuprate reacts and reactions can proceed with a small equilibrium concentration in solution and SSIP is the much less or even unreactive structure [15,21,24,28,29]. As expected, in the reactions of $R_2CuMgBr$ and RCu(CN)MgBr, $PhNH_2$:PhOH ratio in THF:HMPA was generally observed higher than that in THF. However, in THF:TMEDA, the reactions gave mostly lower $PhNH_2$:PhOH ratio than that in THF and in THF:HMPA. We think that TMEDA can strongly complex with two $(MgBr)^{\oplus}$ ions as a bridging bidentate ligand [21]. In this case, the equilibrium lying mostly in favor of SSIP structure can much decrease CIP structure in small equilibrium concentration to react, as in accordance with the observed results.

3. Conclusions

With the aim of developing a new method for synthesis of arylamines using electrophilic amination of Grignard reagents with (TMS)HNO(TMS);

(i) We have demonstrated that reaction of PhMgBr (2 or 3 equiv) with (TMS)HNO(TMS) (1 equiv) in the presence of 10–20 mol% CuI or CuCN catalysis in THF:cosolvent (cosolvent = HMPA or TMEDA) at room temperature gives medium to high yields of aniline. This one-pot procedure can provide an atom-economic and step-economic access for arylamine synthesis starting from aryl Grignard reagents.

(ii) Chemoselectivity in the reaction of PhMgBr with (TMS)HNO(TMS) to give C–N or C–O coupling can be controlled by changing reaction parameters. Cu(I) catalyzed reaction of PhMgBr in THF:HMPA (or TMEDA) affords both C–N and C–O coupling (aniline:phenol≥7:3) whereas uncatalyzed PhMgBr gives C–O coupling yielding phenol. It is obvious that (TMS)HNO(TMS) is a workable substrate for amination of catalytic diarylcuprates and arylcyanocuprates.

(iii) Mechanisms were proposed for the solvent dependence of chemoselectivity in the coupling of both uncatalyzed and Cu(I) catalyzed Grignard reagent with (TMS)HNO(TMS).

(iv) Application of remarkable ability of Cu(I) catalyzed PhMgBr for C–N coupling with (TMS)HNO(TMS) to other aryl Grignard reagents are in progress.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen atmosphere in oven dried glassware using standard syring-septum cap techniques [30]. Quantitative GC analysis were performed on a Thermo Focus gas chromatograph equipped with a ZB-1 capillary column packed with phenylpolydimethylsiloxane using the internal standard technique. THF was distilled from sodium benzophenone dianion. Grignard reagent was prepared in THF by standard method and its concentration was found by titration prior to use [31]. (TMS)HNO(TMS) was distilled and kept under nitrogen. HMPA and TMEDA were distilled and kept under nitrogen. CuI [32] and CuCN [33] were purified according to the published procedures.

4.2. Typical procedure for CuI catalyzed reaction of PhMgBr with (TMS)HNO(TMS) in THF:HMPA

PhMgBr (2 mmol) was added to CuI (0.0762 g, 0.4 mmol) at room temperature in THF:HMPA (4:1) mixture (5 ml), and after stirring for 2–3 min (TMS)HNO(TMS) (0,1774 g, 1 mmol) was added. The reaction mixture was stirred for 3.5 h. For hydrolytic work-up and separation of phenol and aniline, aqueous HCl was used. The aqueous phase was washed with Et_2O, made basic with aqueous NaOH and free amine was extracted with Et_2O. Internal standards were added to organic phases containing phenol extract, aniline extract and aliquots were analyzed by GC.

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References

[1] (a) A. Ricci (Ed.), Modern Amination Methods, Wiley-VCH, Weinheim, 2000;
(b) S.A. Lawrence, Amines, Synthesis, Properties and Applications, Cambridge Unıversty Press, Cambridge, 2004;
(c) A. Ricci (Ed.), Amino Group Chemistry: From Synthesis to the Life Sciences, Wiley- VCH, Weinheim, 2008.
[2] (a) J.F. Hartwig, Acc. Chem. Res. 31 (1998) 852;
(b) J.P. Wolfe, S. Wagow, J.F. Marcoux, S.L. Buchwald, Acc. Chem. Res. 31

(1998) 805;
(c) J.F. Hartwig, in: E.İ. Negishi (Ed.), Handbook of Palladium Chemistry for Organic Synthesis, vol. 1, Wiley - VCH, Weinheim, 2002, p. 1051;
(d) A.R. Muci, S.L. Buchwald, Top. Curr. Chem. 219 (2002) 131;
(e) S.L. Buchwald, C. Mauger, G. Mignani, U. Scholz, Adv. Synth. Catal. 348 (2006) 23;
(f) J.L. Kinkanberg, J.F. Hartwig, Angew. Chem. Int. Ed. 50 (2011) 86;
(g) D.S. Surry, S.L. Buchwald, Chem. Sci. 2 (2011) 27.
[3] (a) S.V. Ley, A.W. Thomas, Angew. Chem. Int. Ed. 42 (2003) 5400;
(b) K. Kunz, U. Scholz, D. Ganzer, Synlett. (2003) 2428;
(c) I.P. Beletzkaya, A.V. Chaprakov, Coord. Chem. Rev. 248 (2004) 2337;
(d) D. Ma, Q. Cai, Acc. Chem. Res. 41 (2008) 1450;
(e) F. Mannier, M. Taillefer, Angew. Chem. Int. Ed. 48 (2009) 6954;
(f) I.P. Beletzkaya, A.V. Chaprakov, Organometallics 318 (2012) 7753;
(g) A.M. Thomas, A. Sujatha, G. Anilkumar, Mini-Reviews in Org. Chem. 12 (2015) 3.
[4] (a) A. Armstrong, J.C. Collins, Angew. Chem. Int. Ed. 49 (2010) 2282;
(b) D.N. Zaletan, J. Dubois, Top. Curr. Chem. 292 (2010) 347;
(c) F. Collet, C. Lescot, P. Dauben, Chem. Soc. Rev. 40 (2011) 1926;
(d) T.A. Ramirez, B. Zhao, Y. Shi, Chem. Soc. Rev. 41 (2012) 931;
(e) , in: J.-Q. Yu (Ed.), Science of Synthesis. Catalytic Transformations via C-H Activation, vol. 2, Thieme, 2016.
[5] M. Kienle, S.R. Dubbaka, K. Brade, P. Knochel, Eur. J. Org. Chem. (2007) 4166.
[6] (a) E. Erdik, M. Ay, Chem. Rev. 89 (1989) 1947;
(b) R. Askani, D.F. Taber, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, vol. 7, Pergamon Press, Oxford, 1996, p. 1881;
(c) J.P. Genet, C. Greck, Synlett. (1997) 741;
(d) P. Dembech, G. Seconi, A. Ricci, Chem. Eur. J. 6 (2000) 1281;
(e) T. Daşkapan, ARKIVOC 5 (2011) 230;
(f) C. Greck, B. Drouillot, C. Thomassiany, Eur. J. Org. Chem. 10 (2004) 1377;
(g) E. Erdik, Tetrahedron 60 (2004) 8747;
(h) E. Ciganek, Org. React. (2008) 72;
(i) D.E. Olson, Mini-Reviews Org. Chem. 8 (2011) 341;
(j) A.M.R. Smith, K.K. Hill, Chem. Rev. 111 (2011) 1637;
(k) M. Carpet, C. Gosmini, Synthesis 46 (2014) 2258;
(l) X. Tan, X. Yang, C. Xi, Catal. Sci. Technol. 4 (2014) 4169.
[7] P. Starkov, T.F. Jamison, I. Merek, Chem. Eur J. 21 (2015) 5278.
[8] (a) T.J. Barker, E.R. Jarvo, Synthesis 111 (2011) 1637;
(b) T.J. Barker, E.R. Jarvo, J. Am. Chem. Soc. 131 (2009) 15598;
(c) T. Hatekayama, Y. Yashimoto, S.K. Ghorai, M. Nakamura, Org. Lett. 12 (2010) 1516.
[9] (a) Z. Rappoport, J. Libman, in: E. Erdik (Ed.), Patai's The Chemistry of Hydroxyamines,Oximes and Hydroxamic acids, Wiley-VCH, Chichester, 2009, p. 303, part 1, Chap. 8;
(b) A.M. Berman, J.S. Johnson, J. Org. Chem. 71 (2006) 219;
(c) M.J. Campbell, J.S. Johnson, Org. Lett. 9 (2007) 1521 (and references cited therein);
(d) S. Bhadra, S. Ahammed, B.C. Ranu, Curr. Org. Chem. 16 (2012) 1453;
(e) H. Yaon, Y. Lee, J. Org. Chem. 80 (2015) 10244.
[10] (a) E. Erdik, M. Ay, Synth. React. Inorg. Metal-Org. Nano-Metal Chem. 19 (1989) 663;
(b) E. Erdik, T. Daşkapan, J. Chem. Soc. Perkin Trans I(J. Org. Biomolecular Chem.) (1999) 3139;
(c) E. Erdik, T. Daşkapan, Tetrahedron Lett. 43 (2002) 6237;
(d) E. Erdik, Ö. Ömür Pekel, Appl. Organomet. Chem. 19 (2005) 887;
(e) E. Erdik, F. Eroğlu, D. Kahya, J. Phys. Org. Chem. 18 (2005) 950;
(f) E. Erdik, S. Ateş, Synth. Commun. 36 (2006) 2183;
(g) E. Erdik, S.A. Ülkü, J. Phys. Org. Chem. 20 (2007) 671;
(h) E. Erdik, Ö.Ö. Pekel, M. Kalkan, Appl. Organomet. Chem. 23 (2009) 245.
[11] (a) A. Casarini, P. Dembech, D. Lazzari, E. Marini, G. Reginato, A. Ricci, G. Seconi, J. Org. Chem. 58 (1993) 5620;
(b) P. Bernardi, P. Dembech, G. Fabbri, A. Ricci, G. Seconi, J. Org. Chem. 64 (1999) 641;
(c) O. Riant, O. Samuel, T. Flessner, S. Taudien, H.B. Kagan, J. Org. Chem. 62 (1997) 6733.
[12] (a) R. West, P. Boudjouk, J. Am. Chem. Soc. 95 (1973) 3987;
(b) A. Venugopal, A. Willner, N.W. Mitzel, Z. Naturforschung B 63b (2008) 339.
[13] (a) P. Beak, A. Bosha, B. Rokko, D.K. Loo, J. Am. Chem. Soc. 108 (1986) 6016;
(b) P. Beak, G.W. Selling, J. Org. Chem. 54 (1989) 5574;
(c) P. Beak, B.J. Kokko, J. Org. Chem. 47 (1982) 2822.
[14] N. Krause (Ed.), Modern Organocopper Chemistry, Wiley-VCH, Weinheim, 1996.
[15] Z. Rappoport, I. Marck (Eds.), Patai's the Chemistry of Organocopper Compounds, Wiley, Chichester, 2009.
[16] N.I. Schverdina, Z. Kotscheschkow, Z. Chem. Zentrabl. 1 (1942) 1872.
[17] G. Boche, M. Bernheim, W. Schrott, Tetrahedron Lett. 23 (1982) 5399.
[18] R. Davies, Coord. Chem. Rev. 255 (2011) 1226.
[19] N. Yashiaki, E. Nakamura, Chem. Rev. 112 (2012) 2339.
[20] R. Bamporola, R.P. Davies, S. Lal, A.J.P. White, Organometallics 31 (2012) 7877.
[21] R. Bamporola, R.P. Davies, S. Hornaver, A.J.P. White, Angew. Chem. Int. Ed. 47 (2008) 5812.
[22] T. Gartner, R.M. Henze, J. Gschwind, J. Am. Chem. Soc. 129 (2007), 11362.
[23] E. Erdik, E.Z. Serdar, J. Organomet. Chem. 703 (2012) 1.
[24] (a) S. Mori, E. Nakamura, K. Morakuma, J. Am. Chem. Soc. 122 (2000) 7294;
(b) E. Nakamura, S. Mori, Angew. Chem. Int. Ed. 39 (2000) 3750;
(c) E. Nakamura, N. Yoshikai, Bull. Chem. Soc. Jpn. 77 (2004) 1.
[25] (a) S.H. Bertz, S. Cope, D. Donna, M.D. Murpy, C.A. Ogle, Angew. Chem. Int. Ed. 46 (2007) 7082;
(b) S.H. Bertz, R.A. Hardin, M.D. Murpy, C.A. Ogle, J.D. Richter, E.A. Thomas, Angew. Chem. Int. Ed. 51 (2012) 2681.
[26] M. John, C. Auel, C. Behrens, M. Marsch, R. Harris, F. Bosold, R.M. Gschwind, P.R. Rajamohanan, G. Boche, Chem. Eur J. 6 (2000) 3060.
[27] R.M. Gschwind, Chem. Rev. 108 (2008) 3029.
[28] D.R. Amstrong, C. Dougan, D.V. graham, E. Hevia, A.R. Kennedy, Organometallics 27 (2008) 6063.
[29] S. Mori, A. Hirai, M. Makamura, Tetrahedron 56 (2000) 2805.
[30] J. Leonard, B. Lygo, G. Practer, Advanced Practical Organic Chemistry, Blackie, London, 1995.
[31] C.H. Watson, J.F. Eastham, J. Organomet. Chem. 9 (1967) 165.
[32] R.N. Keller, H.D. Wycoff, Inorg. Synth. 2 (1946) 1.
[33] H.J. Barber, J. Chem. Soc. 1 (1943) 79.