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Direct alkenylation of arylamines at the *ortho*-position

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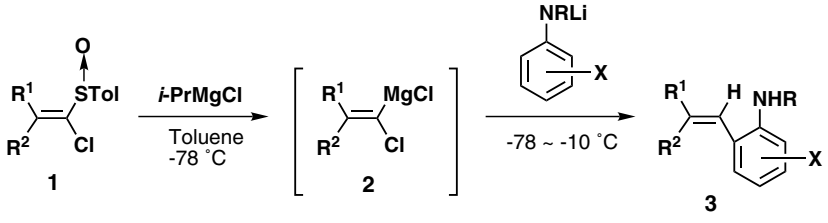
Abstract—Treatment of magnesium alkylidene carbenoids, which were generated from 1-chlorovinyl *p*-tolyl sulfoxides with isopropylmagnesium chloride at −78 °C in toluene, with *N*-lithio arylamines gave *ortho*-alkenylated arylamines in moderate to good yields. The reaction was found to proceed in a highly stereospecific manner at the carbenoid carbon. This reaction offers a quite novel and direct alkenylation of arylamines at the *ortho*-position of the aromatic ring.

Arylamines are obviously one of the most important and fundamental compounds in organic chemistry because arylamines have been widely used as the material for medicine, dyes, and other chemical products. In view of this importance of arylamines, innumerable studies have been carried out concerning their chemistry and synthesis.[1]

The alkylation of the aromatic ring of arylamines is quite important chemistry for the synthesis of derivatives of arylamines; however, this is not a so easily accessible process. An even more difficult process is the direct alkenylation of the arylamines. To the best of our knowledge, only one report concerning the direct alkenylation of arylamines on the aromatic ring has been published by Sartori and co-workers.[2] The authors synthesized 1,1-diarylethylenes directly from substituted anilines and phenylacetylene in the presence of montmorillonite KSF.

We recently reported a new method for the generation of magnesium alkylidene carbenoids **2** from 1-chlorovinyl *p*-tolyl sulfoxides **1** with a Grignard reagent[3] via sulfoxide–magnesium exchange reaction.[4] From the generated magnesium alkylidene carbenoids, a new method for the synthesis of *tetra*-substituted olefins[5] and allenes[6] was realized. In continuation of our interest in the development of new synthetic methods by utilizing the generated magnesium alkylidene carbenoids **2** in organic synthesis, we investigated the reaction of **2** with *N*-lithio amides and found that the reaction with *N*-lithio arylamines gave *ortho*-alkenylated arylamines **3** in moderate to good yields (Scheme 1).

1-Chlorovinyl *p*-tolyl sulfoxide **4**[5] in dry toluene was treated with *t*-BuMgCl (0.12 equiv) at −78 °C to remove a trace of moisture in the reaction mixture. After 10 min, *i*-PrMgCl (2.8 equiv) was added to the reaction mixture. The sulfoxide–magnesium exchange reaction took place



Scheme 1.

Keywords: Sulfoxide; Sulfoxide–magnesium exchange reaction; Magnesium alkylidene carbenoid; Alkenylation; *ortho*-Alkenylated arylamine.
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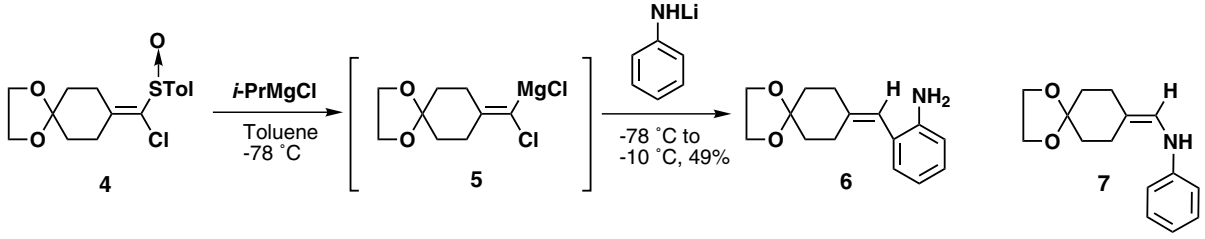
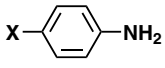
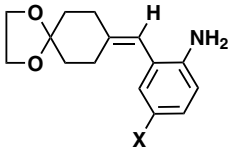
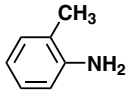
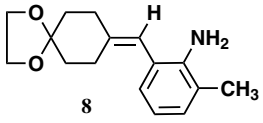
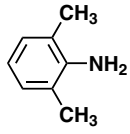
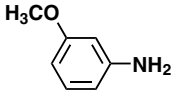
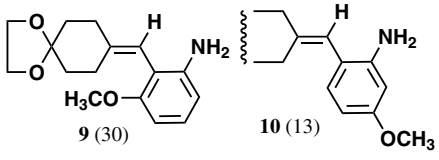
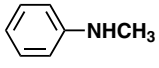
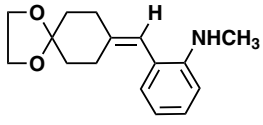
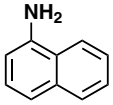
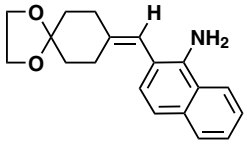
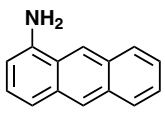
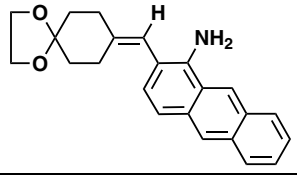


Scheme 2.

rapidly to give the magnesium alkylidene carbenoid **5**.[6b] First, reaction of **5** with *N*-lithio piperidine and *N*-lithio *n*-hexylamine was investigated; however, only a rather complex mixture was obtained with these *N*-lithio *alkylamines*.

Next, the reaction was investigated with *N*-litho *arylamines*. *N*-Litho aniline (3 equiv) was added to the solution of the magnesium alkylidene carbenoid **5** at −78 °C and the temperature of the reaction mixture was gradually allowed to warm to −10 °C. We obtained a colorless crystalline product in 49% yield. The product showed $C_{15}H_{19}NO_2$ as the molecular formula and N–H absorption on its IR spectrum. At this stage two products, alkenyl aniline **6** and enamine **7**, were expected to be produced. ^{1}H NMR showed two NH protons and only four aromatic protons (δ 6.69 (1H, d), 6.73 (1H, t), 6.98 (1H, d), 7.06 (1H, t)). From the coupling pattern of these aromatic protons and ^{13}C NMR, the structure of the product was unambiguously determined to be the *ortho*-alkenylated aniline **6** (Scheme 2).

Table 1. Synthesis of *ortho*-alkenylated arylamines by the reaction of the magnesium alkylidene carbenoid **5** and *N*-lithio arylamines

Entry	Arylamine[a]	*ortho*-Alkenylated arylamine	(Yield/%)
1		 X=OCH_3	(44)
2		X=Cl	(28)
3		 **8**	(32)
4		—[b]	
5		 **9** (30) **10** (13)	
6			(38)
7			(66)
8			(60)

[a] Three equivalents of *N*-lithio arylamines were reacted with **5**.
[b] No *para*-alkenylated product was obtained.

We were somewhat surprised and pleased by this result because no report has been published on the reaction of anilines with alkylidene carbenes (or carbenoids).[7] In addition, this reaction is a quite novel and direct alkenylation of arylamines on the aromatic ring. We investigated the generality of this reaction of **5** with other *N*-lithio arylamines and the results are summarized in Table 1.

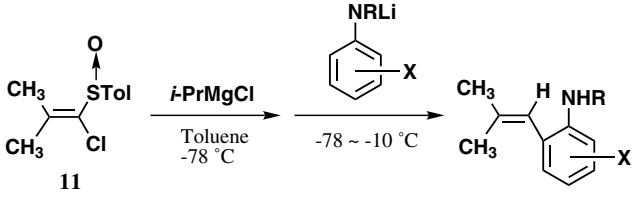
The reaction with the aniline having an electron-donating group (OCH_3) at the 4-position gave a similar yield (entry 1); however, the aniline having an electron withdrawing group (Cl) gave a markedly diminished yield (entry 2). The reaction with *o*-toluidine gave the *o*-alkenylated aniline **8** (entry 3). Interestingly, 2,6-dimethylaniline gave no *p*-alkenylated aniline. This result indicated that this reaction only gives *o*-alkenylated products.

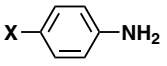
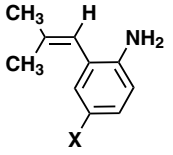
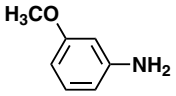
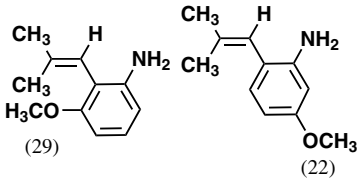
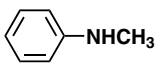
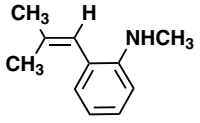
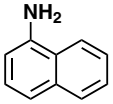
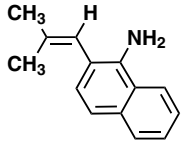
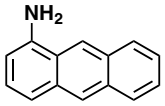
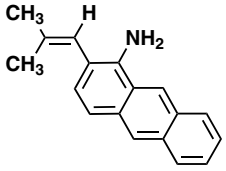
The result shown in entry 5 is quite interesting. The reaction with *m*-anisidine gave two *o*-alkenylated products **9** and **10**. The main product **9** was found to have the alkenyl group at a more hindered position. The reason and the mechanism of this reaction will be discussed later. *N*-Methylaniline gave an *o*-alkenylated product (entry 6). Interestingly, the reaction with 1-aminonaphthalene and 1-aminoanthracene gave much better yields (entries 7 and 8).

We further studied this reaction using 1-chlorovinyl *p*-tolyl sulfoxide **11** derived from acetone and the results are summarized in Table 2. Entries 1 and 2 show that quite similar yields were obtained with aniline and *p*-anisidine. The reaction with *m*-anisidine again gave two products and the main product was found to be a more sterically hindered compound (entry 3). *N*-Methylaniline gave much better yield compared with the result in Table 1. Again, much better yields were obtained from the reaction of **11** with 1-aminonaphthalene and 1-aminoanthracene (entries 5 and 6).

Next, we investigated the stereochemistry of these reactions. The stereoisomers **12*E*** and **12*Z*** were synthesized from 2-cyclohexenone[8] and the reaction was carried out with 1-aminonaphthalene and 1-aminoanthracene. The results are summarized in Table 3.

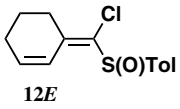
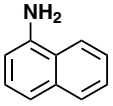
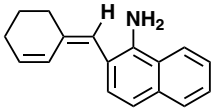
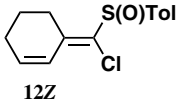
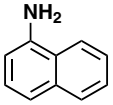
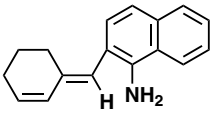
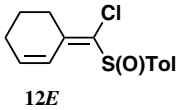
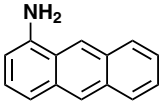
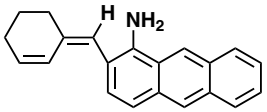
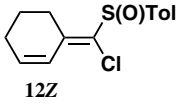
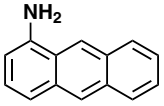
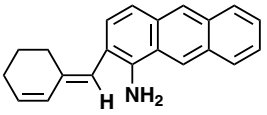
Table 2. Synthesis of *ortho*-alkenylated arylamines by the reaction of the magnesium alkylidene carbenoid derived from **11** and *N*-lithio arylamines



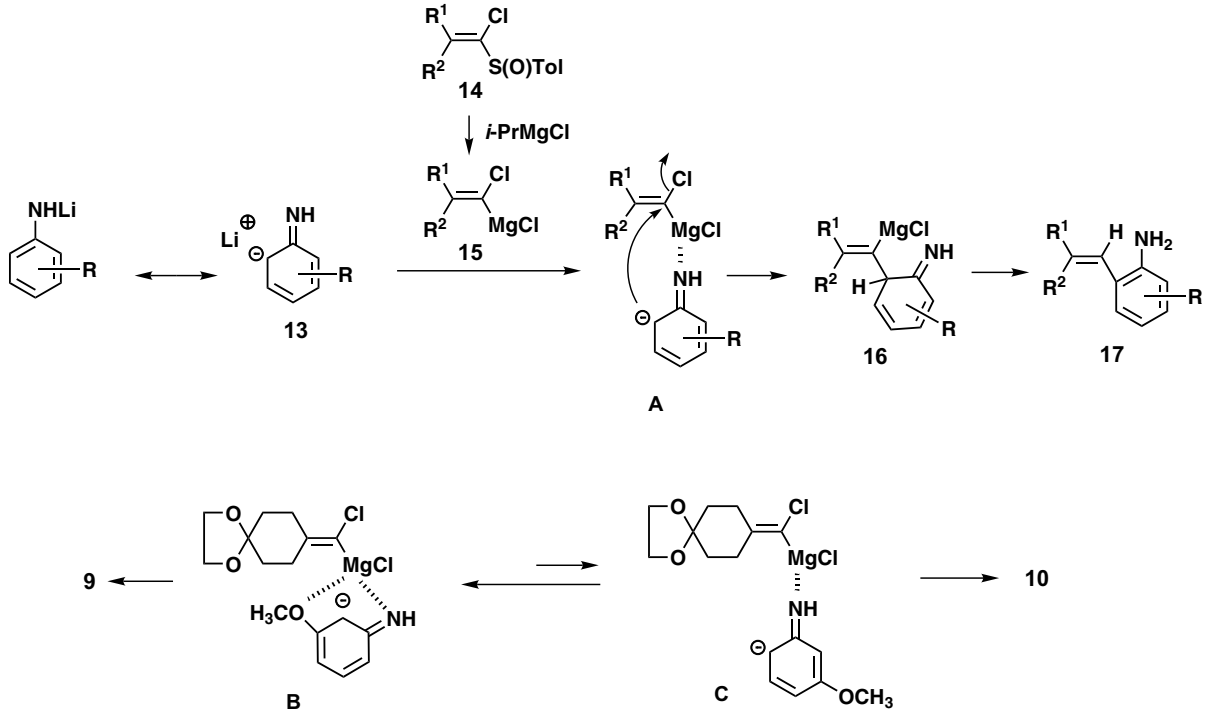
Entry	Arylamine[a]	*ortho*-Alkenylated arylamine		(Yield/%)
1			X=H	(43)
2			X=OCH_3	(43)
3		 (29) (22)		
4				(46)
5				(81)
6				(79)

[a] Three equivalents of *N*-lithio arylamines were reacted with the carbenoid derived from **11**.

Table 3. The reaction of the magnesium alkylidene carbenoids derived from *E*- and *Z*-1-chlorovinyl *p*-tolyl sulfoxides (**12*E*** and **12*Z***) with *N*-lithio 1-aminonaphthalene and *N*-lithio 1-aminoanthracene

Entry	Arylamine[a]	Product		
			E/*Z*[b]	(Yield/%)
1	 **12*E***			3:97	(65)
2	 **12*Z***			95:5	(71)
3	 **12*E***			22:78	(69)
4	 **12*Z***			84:16	(66)

[a] Three equivalents of *N*-lithio 1-aminonaphthalene and *N*-lithio 1-aminoanthracene were reacted with **12*E*** and **12*Z***.
[b] The ratio of *E*/*Z* was determined from their ^{1}H NMR.



Scheme 3.

Quite interestingly, the reaction of the carbenoids derived from **12*E*** and **12*Z*** with 1-aminonaphthalene gave *Z*-*o*-alkenylated 1-aminonaphthalene and *E*-*o*-alkenylated 1-aminonaphthalene, respectively, with high stereospecificity (entries 1 and 2). The reaction of **12*E*** and **12*Z*** with 1-aminoanthracene gave also the *o*-alkenylated 1-aminoanthracenes, though the stereospecificity was somewhat lower (entries 3 and 4).

Finally, based on the stereochemical aspects of the results shown in Tables 1–3, the mechanism and the stereochemistry of this reaction are proposed as follows (Scheme 3). The *N*-lithio arylamine is present in the resonance form, lithium α-imino carbanion **13**. On the other hand, the magnesium alkylidene carbenoid **15** was generated stereospecifically from 1-chlorovinyl *p*-tolyl sulfoxide **14** with *i*-PrMgCl at −78 °C. The reaction of **13**

with **15** takes place via the intermediate **A** with inversion of the configuration at the carbenoid carbon to give **16**. The product **17** is derived from **16** with proton transfer from carbon or nitrogen. The inversion of the configuration in the reaction of lithium alkylidene carbenoids with alkyllithium has been reported by Walborsky and co-workers,[9] and Oku and co-workers.[10]

The result shown in Table 1, entry 5, can be explained from the intermediates **B** and **C** in Scheme 3. Two lithium α-imino carbanions were expected to generate from *N*-lithio *m*-anisidine. These carbanions react with the magnesium alkylidene carbenoid **5** via chelated intermediates **B** and **C**. As the intermediate **B** has chelation between magnesium and nitrogen and oxygen, the intermediate **B** is more likely to be present in the reaction. From the intermediate **B** the main product **9** would be produced.

In conclusion, we have found a quite novel and direct alkenylation of arylamines at the *ortho*-position of the aromatic ring. We are continuing to study the scope and limitation of this chemistry.

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