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Metal-assisted amination with oxime derivatives*

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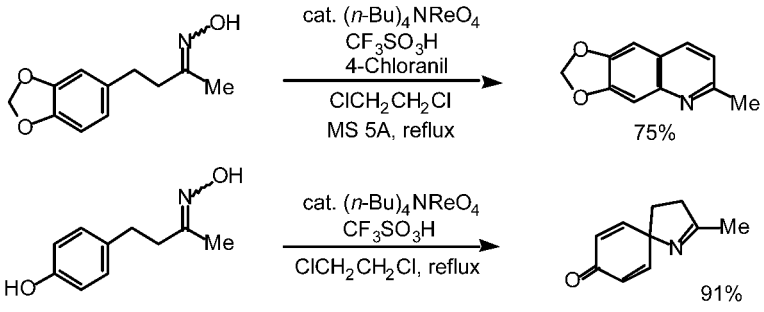
Abstract: Electrophilic amination of Grignard reagents is accomplished by using *O*-sulfonyloximes of benzophenone derivatives. In the presence of a catalytic amount of CuCN, *O*-sulfonyloxime of 4,4′-bis(trifluoromethyl)benzophenone reacts with alkyl Grignard reagents in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA), yielding primary alkylamines by successive hydrolysis of the resulting *N*-alkylimines. Arylamines are also prepared as well as alkylamines by treating *O*-sulfonyloxime of 3,3′,5,5′-tetrakis(trifluoromethyl)-benzophenone in toluene-ether with Grignard reagents.

Various cyclic imines are synthesized by palladium-catalyzed cyclization of olefinic oxime derivatives. That is, the reaction of *O*-pentafluorobenzoyloximes of olefinic ketones with a catalytic amount of $Pd(PPh_3)_4$ and triethylamine in dimethylformamide (DMF) affords nitrogen-containing heterocycles, such as pyrroles, pyridines, isoquinolines, spiroimines, and aza-azulenes. This reaction proceeds via the initial formation of alkylideneaminopalladium species generated by oxidative addition of oximes to Pd(0), and the successive intramolecular Heck-type amination occurs on the olefinic moiety.

INTRODUCTION

During the course of study on the catalytic Beckmann rearrangement of oximes with tetrabutyl ammonium perrhenate and *p*-toluenesulfonic acid [1], it was found that phenethyl ketone oximes cyclized on the oxime nitrogen atom with phenyl group. As shown in the following equations, phenethylketone oximes are converted to quinolines and aza-spiro compounds by treatment with a catalytic amount of tetrabutylammonium perrhenate and trifluoromethanesulfonic acid [2].



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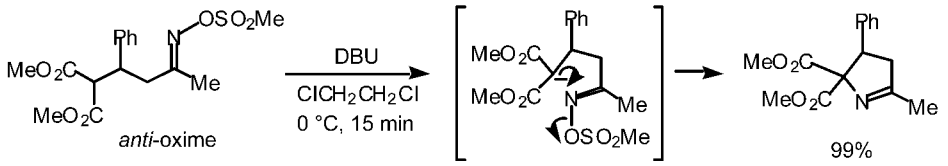
This reaction was revealed to proceed by intramolecular SN2-type reaction on the sp^2 nitrogen of oximes [3] and was further applied to the cyclization reaction of *O*-sulfonyloxime having γ or δ-active methine group. The reaction is stereospecific, and the *anti*-oximes cyclize to 5- and 6-membered cyclic imines, while the *syn*-isomers do not give any such cyclization products [4].

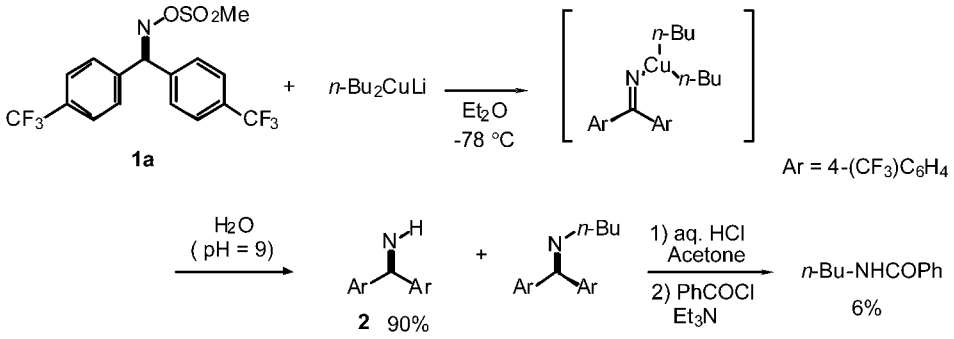


Based on these results, oxime derivatives were considered to be utilized as good electrophilic amination reagents. It was, therefore, expected that other nucleophiles such as organometallics would react with oxime derivatives.

PREPARATION OF PRIMARY AMINES FROM *O*-SULFONYLOXIMES AND GRIGNARD REAGENTS [5]

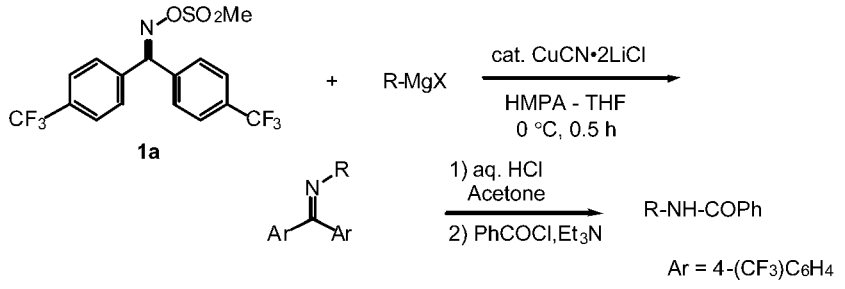
In general, primary amines are prepared by the reduction of the corresponding nitrogen functional compounds such as nitroalkanes and azides or the Gabriel-type nucleophilic amination reactions. Though electrophilic amination provides another method to prepare primary amines, this method has rarely been employed in organic synthesis [6]. Oxime derivatives were found to act as electrophilic amination reagents, as mentioned in the above introduction; the reaction of oxime derivatives and organometallic reagents was examined. Concerning the reaction of oxime derivatives with organometallics, there have been reported two examples. Hagopian prepared primary arylamines by the reaction of tetraphenylcyclopentadienone *O*-sulfonyloxime with large excess amounts of aryl magnesium and lithium compounds, whereas dialkylation occurred with alkyl metals [7]. Erik reported the reaction of acetone *O*-sulfonyloxime with Grignard reagents, which gave primary amines in moderate to low yield [8].

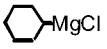
For amination with oxime, we chose *O*-sulfonyloximes **1a** of a benzophenone derivative such as 4,4′-bis(trifluoromethyl)benzophenone, which have no acidic hydrogen and have electron-withdrawing groups to suppress the Beckmann rearrangement. Firstly, the reaction of **1a** with lithium dibutylcuprate was found to give mainly benzophenone imine **2**, giving the desired *N*-buthyl benzophenone imine only in 6% yield.



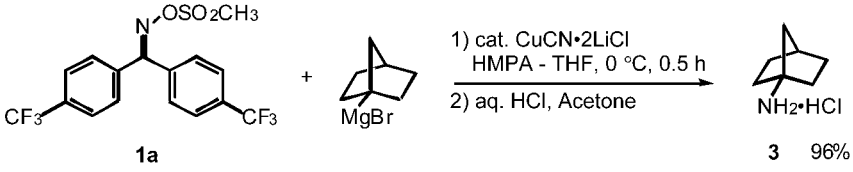
Because the imine **2** was supposed to be produced by the hydrolysis of alkylideneaminocopper intermediate, the reaction was tried by the combination of a catalytic CuCN and butylmagnesium chloride to facilitate the reductive elimination of the *N*-alkyl imine. In a mixed solvent of THF and HMPA,

1a reacted with butyl Grignard reagent at 0 °C in the presence of a catalytic amount of CuCN•2LiCl, and *N*-butylbenzamide was obtained in 96% yield, after acid treatment of the resulting reaction mixture and successive benzoylation. Primary-, secondary-, and tertiary-alkyl primary amines are synthesized in good yield by this electrophilic amination reaction.

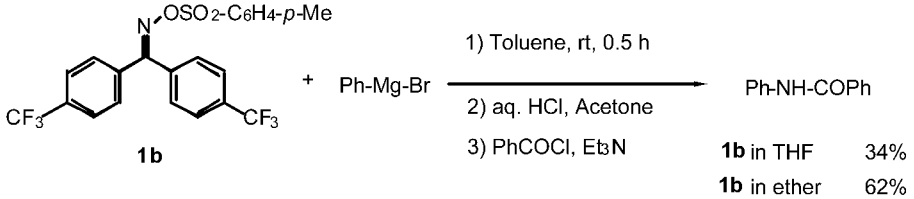


R-MgX	Yield / %
n-BuMgCl	96
i-PrMgBr	93
	80
t-BuMgCl	61

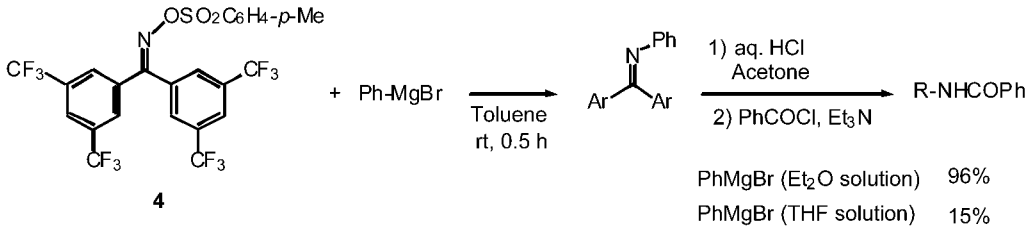
A typical characteristic of this amination can be seen in the synthesis of 1-norbornylamine **3**, which is hard to be prepared from 1-norbornyl halides by conventional nucleophilic amination methods.



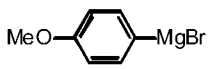
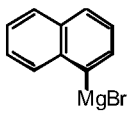
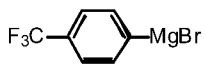
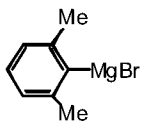
Thus, the present catalytic procedure was widely applied for the preparation of primary alkylamines, while aniline derivatives could not be prepared successfully. The reaction of **1a** with phenylmagnesium bromide in the presence of CuCN•2LiCl gave benzanilide only in 7% yield but mainly biphenyl in 74% yield. In the absence of the copper catalyst, *O*-*p*-tolylsulfonyloxime **1b** reacted with phenyl Grignard reagent, where a marked solvent effect was observed. Treatment of **1b** in toluene with phenylmagnesium bromide prepared in THF afforded benzanilide in 34% yield with the recovery of the starting material. The same reaction with the Grignard reagent prepared in ether provided benzanilide in better yield, but the Beckmann product was also obtained in 6% yield.



In order to suppress the Beckmann rearrangement, a more electron-deficient benzophenone derivative, 3,3′,5,5′-tetrakis(trifluoromethyl)benzophenone *O*-*p*-tolylsulfonyloxime (**4**) was employed for the amination of aryl Griganrd reagents. As expected, benzanilide was obtained in 96% yield without the Beckmann product. Even a sterically hindered Grignard reagent such as 2,6-dimethylphenylmagnesium bromide reacted smoothly with **4** to yield 2,6-dimethylanilide in 98%. In addition to aniline derivative formation, this method found the application to prepare primary-alkyl and secondary-alkyl primary amines, whereas not to tertiary-alkyl ones.

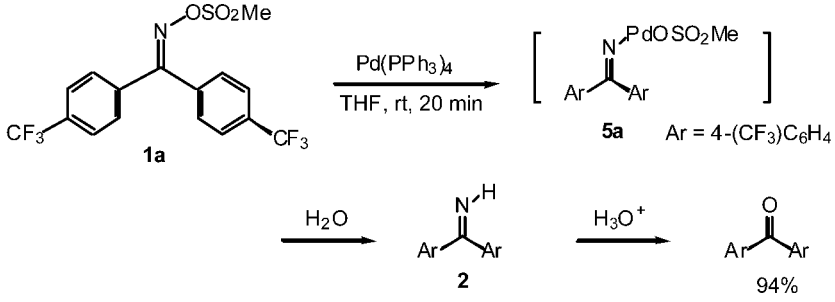


Amination of Grignard Reagents with **4**

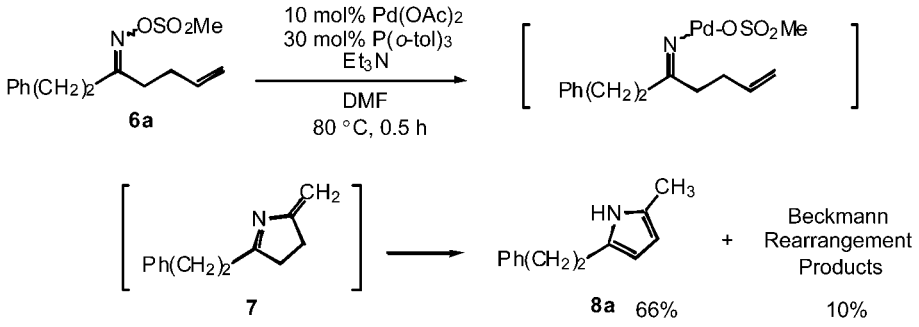
R-MgX	Yield/%	**R**-MgX	Yield/%
	98		96
	71	Et-MgBr	87
	98	cyclo-C_6H_{11}-MgCl	87
		t-Bu-MgCl	35

PREPARATION OF NITROGEN-CONTAINING HETEROCYCLES BY PALLADIUM-CATALYZED CYCLIZATION OF OXIME DERIVATIVES OF OLEFINIC KETONES [9]

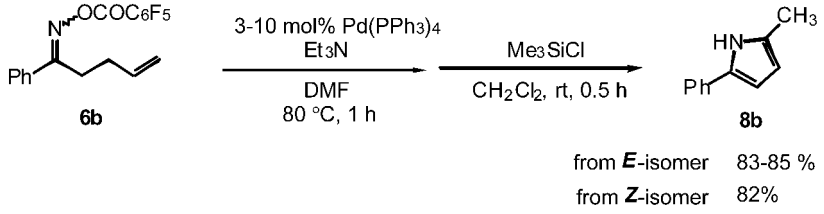
Due to the electron-donating property of lower-valent transition-metal compounds, Pd(0) complexes were expected to react with oxime derivatives to generate oxidative addition products. In fact, when 4,4′-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1a**) was treated with an equimolar amount of $Pd(PPh_3)_4$ in THF, benzophenone was isolated quantitatively after hydrolysis.



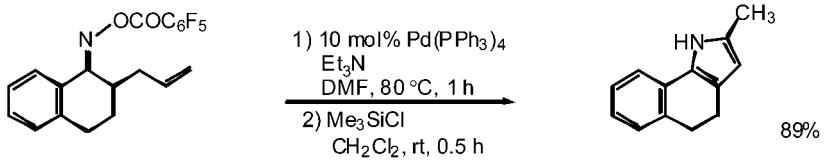
This result suggested that *O*-sulfonyloxime readily undergoes oxidative addition to palladium(0) to generate alkylideneaminopalladium(II) species **5a**, which is then hydrolyzed to the imine **2**. Although it has not been successful to isolate this oxidative addition species, the generation of such an intermediate is reliable, because a similar oxidative addition of oxime to Re(I) complex was reported recently [10]. To utilize this aminopalladium species for organic synthesis, intramolecular Heck-type reaction was investigated starting from γ,δ-unsaturated ketone *O*-sulfonyloxime **6a**. 2-Methyl-5-phenethylpyrrole (**8a**), which is an isomerization product of the initially formed 2-methylene-5-phenethyl-3,4-dihydro-2*H*-pyrrole **7**, was obtained in 66% yield by a catalytic use of $Pd(OAc)_2$-$P(o\text{-}Tol)_3$ and triethylamine, whereas the Beckmann rearrangement was also observed.



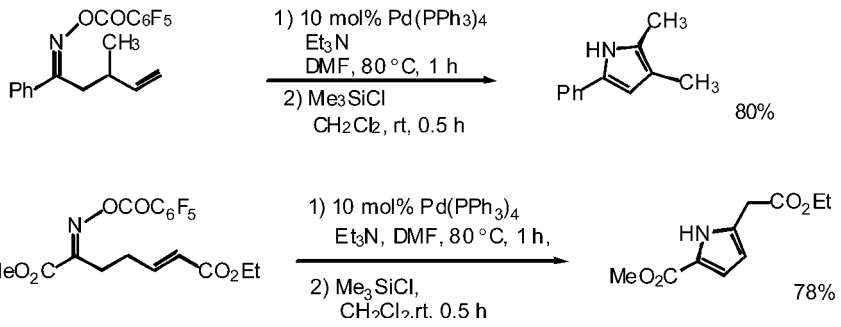
To avoid the rearrangement, some other *O*-acyloximes were employed in the palladium-catalyzed reaction, and *O*-pentafluorobenzoyloxime was found to be suitable for this cyclization reaction. That is, without the Beckmann rearrangement, *O*-pentafluorobenzoyloxime **6b** was converted to pyrrole **8b** in good yield by the Heck-type cyclization followed by isomerization of the crude products with trimethylsilyl chloride. It was also noted that the stereochemistry of the oximes exhibited no significant influence in the cyclization reaction.



This nitrogen-Heck-type reaction found a wide application to prepare pyrrole derivatives. Various γ,δ-unsaturated ketone oximes having terminal and substituted methylene groups cyclized to the corresponding pyrroles smoothly.

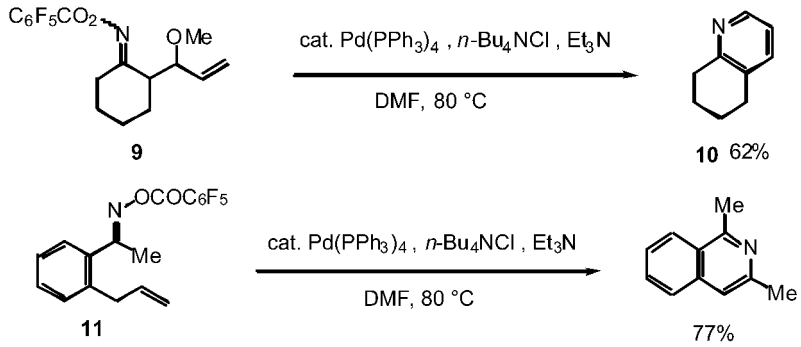


Thus, 5-*exo* cyclization proceeds generally on γ,δ-unsaturated ketone *O*-pentafluorobenzoyloximes via alkylideneaminopalladium species, while 6-*endo* cyclization was observed in the Heck-type reaction of γ,δ-unsaturated ketone oximes having β-methoxy group **9**. Particularly, in the presence of tetrabutylammonium chloride, pyridine derivatives **10** are obtained in a reasonable yield. The reaction

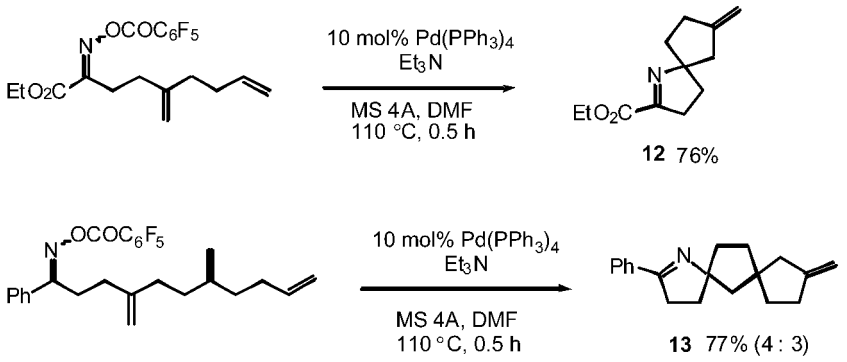


pathway of this formal 6-*endo* cyclization has not been clear, but the reaction certainly starts by the oxidative addition of the oximes.

Under these reaction conditions with tetrabutylammonium chloride, *o*-allylphenyl ketone *O*-pentafluorobenzoyloxime **11** also cyclized to give various isoquinoline derivatives.

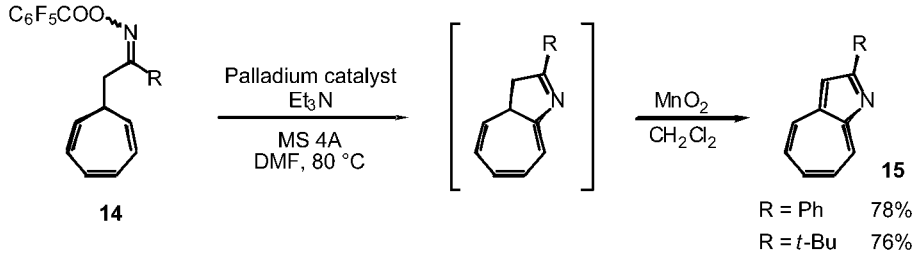


Various methods have been developed toward the construction of an interesting 1-azaspiro[4.4]-nonane skeleton, including a recent metal-catalyzed allylation reaction [11]. This nitrogen-Heck-type reaction provides another metal-catalyzed method for the synthesis of 1-azaspiro[4.4]nonane derivatives. Bicyclic and tricyclic imines, such as **12** and **13**, could be prepared in one step from dienyl and trienyl ketone oximes.



A straightforward method is also developed for the synthesis of aza-azulenes by the palladium-catalyzed cyclization. 1-Aza-azulenes **15** were obtained by treatment of cycloheptatrienylmethyl ketone

O-pentafluorobenzoyloximes **14** with a palladium catalyst and triethylamine and successive oxidation with MnO_2.



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