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Sequential Retro-Ene Arylation Reaction of *N*-Alkoxyenamides for the Synthesis of *tert*-Alkylamines

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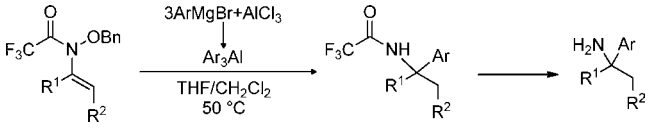
ABSTRACT

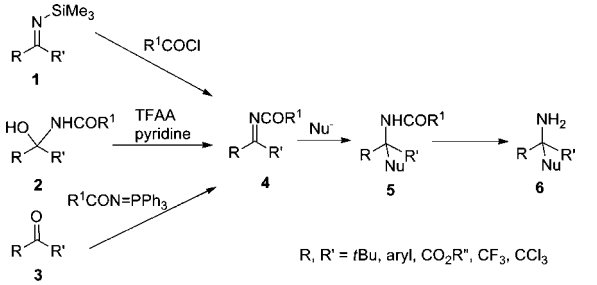


A sequential retro-ene arylation reaction has been developed for the conversion of *N*-alkoxyenamides to the corresponding *tert*-alkylamines in good yields via the nucleophilic addition of a triarylaluminum reagent to an in situ generated *N*-acylketimine. The reaction is tolerant of a range of functional groups and provides facile access to a series of *tert*-alkylamines that would be otherwise difficult to access using conventional procedures.

Biologically active small molecules bearing *N*-substituted quaternary carbon atoms (i.e., *tert*-alkylamines) are ubiquitous in natural products and pharmaceuticals.[1] Compounds of this type are usually prepared using the Ritter reaction, where tertiary alcohols or substituted alkenes capable of generating stable carbocations are treated with a nitrile-containing species under acidic conditions to give the corresponding amides, which can then be hydrolyzed to give the amines.[2] These compounds can also be generated via the reduction of *tert*-alkyl azides[3] or nucleophilic addition to nitriles.[4] Nucleophilic addition to ketimine derivatives also represents a powerful method for the construction of *tert*-alkylamine derivatives. Unfortunately, however, *N*-alkyl and *N*-arylketimines are limited in terms of the scope of their reactivity and can only react successfully with a narrow range of nucleophilic reagents.

In contrast, *N*-acylketimines are particularly attractive substrates for the preparation of *tert*-alkylamine derivatives using the nucleophilic addition reaction because of their higher electrophilicity, which enables them to overcome the poor reactivity observed using *N*-alkyl or *N*-arylimines.[5] *N*-Acylketimines **4** have been prepared in a number of ways, including (1) the reaction of *N*-silylimines **1** with acyl chlorides;[6] (2) the dehydration of

Scheme 1. Methods for the Formation of *N*-Acylketimines and Their Nucleophilic Addition Reaction



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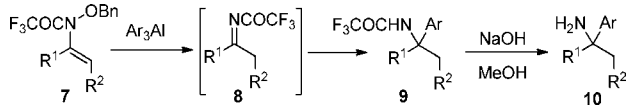
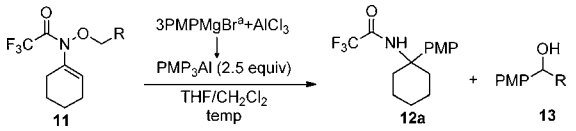
hemiaminals **2**;[7] and (3) the aza-Wittig reaction of ketones **3** with iminophosphoranes (Scheme 1).[8] The scope of the addition reaction of nucleophiles to *N*-acylketimines is limited, however, to the use of nontautomerizable *N*-acylketimines because tautomerizable *N*-acylketimines can readily tautomerize to give the corresponding enamides, which are more stable.[9] For this reason, tautomerizable *N*-acylketimines have not been well-utilized for nucleophilic addition reactions.[10]

Scheme 2. Retro-Ene Arylation Reaction of *N*-Alkoxyenamides



It was envisaged that nucleophilic addition to a tautomerizable *N*-acylketimine could be achieved via the in situ generation of an *N*-acylketimine in the presence of a suitable nucleophile. Herein, we describe the development of a novel preparative method for the synthesis of *N*-acylketimines **8** bearing α-protons via the retro-ene reaction of the corresponding *N*-alkoxyenamides **7** and their subsequent reaction with triarylaluminum reagents to afford the *tert*-alkylamides **9** (Scheme 2). The presence of the strongly electron-withdrawing trifluoroacetyl group effectively enhanced the electrophilicity of the imine in this system, and the group could be readily removed following the addition reaction to give the corresponding *tert*-alkylamines **10**.

Table 1. Optimization of the Retro-Ene Arylation Reaction



				yield (%)	
entry	substrate	R	temp (°C)	**12a**	**13**
1	**11a**	H	rt	–	–
2	**11a**	H	50	58	34
3[b]	**11a**	H	90	50	–
4	**11b**	Ph	50	72	53
5	**11c**	4-$CF_3C_6H_4$	50	68	67
6	**11d**	4-$MeOC_6H_4$	50	30	25

[a] PMP: *p*-methoxyphenyl. [b] $(CH_2Cl)_2$ was used instead of CH_2Cl_2.

The reaction of *N*-methoxyenamide **11a**[11] with 2.5 equiv of tris(4-methoxyphenyl)aluminum, which was prepared from the reaction of trichloroaluminum with 4-methoxyphenylmagnesium bromide, was initially selected as a model reaction to optimize the reaction conditions.[12] When the reaction was conducted at ambient temperature, it did not provide any of the desired product, and only the starting material was recovered (Table 1, entry 1). Pleasingly, however, when the reaction was conducted at a temperature of 50 °C, the *tert*-alkylamide **12a** and 4-methoxybenzylalcohol (**13a**) were obtained in 58 and 34% yields, respectively (Table 1, entry 2). A further increase in the reaction temperature to 90 °C led to a minor reduction in the yield of the reaction (Table 1, entry 3). When we used 4-methoxyphenylmagnesium bromide instead of tris(4-methoxyphenyl)aluminum, a complex mixture was obtained.

The *N*-alkoxyenamides **11b**–**d** were used to investigate the substituent effects of the different alkoxy groups. When *N*-benzyloxyenamide **11b** was used as the substrate, the reaction proceeded smoothly to afford **12a** and **13b** in 72 and 53% yields, respectively (Table 1, entry 4). The application of the same reaction conditions to substrate **11c** bearing an electron-withdrawing 4-trifluoromethylbenzyloxy group provided similar results (Table 1, entry 5). In contrast, the application of the reaction conditions to substrate **11d** bearing an electron-donating 4-methoxybenzyloxy group resulted in lower levels of reactivity and a poorer yield (Table 1, entry 6).

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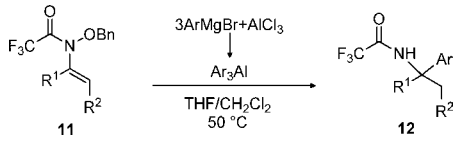
(11) Preparation of *N*-alkoxyenamides **11a**: To a solution of cyclohexanone *O*-methyl oxime (551 mg, 4.3 mmol) in CH_2Cl_2 (20 mL) was added TFAA (1.2 mL, 8.6 mmol) dropwise at 0 °C. After stirring for 4 h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/AcOEt = 50/1) to give **11a** (921 mg, 96%).

(12) Triarylaluminum reagents were prepared the same as in our previous work. See: (a) Miyoshi, T.; Miyakawa, T.; Ueda, M.; Miyata, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 928. (b) Miyoshi, T.; Sato, S.; Tanaka, H.; Hasegawa, C.; Ueda, M.; Miyata, O. *Tetrahedron Lett.* **2012**, *53*, 4188.

Table 2. Sequential Retro-Ene Arylation Reactions of a Variety of Different *N*-Alkoxyenamides



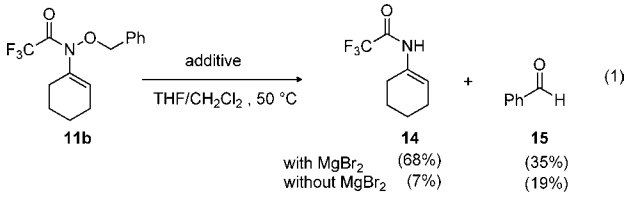
11 12

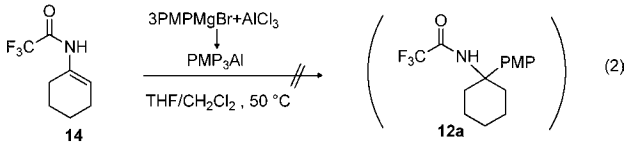
entry	substrate	product	Ar	time (h)	yield (%)
1			Ph	3	68
2[a]	11b	12b-d	Ph	3	23[b,c]
3			4-MeC_6H_4	3	65
4			4-FC_6H_4	3	63
5	11e	12e	4-$MeOC_6H_4$	15	45
6	11f	12f	4-$MeOC_6H_4$	3	70
7	11g	12g	4-$MeOC_6H_4$	3	63
8	11h	12h	4-$MeOC_6H_4$	3	73
9	11i	12i	4-$MeOC_6H_4$	3	62
10	11j	12j	4-$MeOC_6H_4$	8	51
11	11k	12k	4-$MeOC_6H_4$	7	62

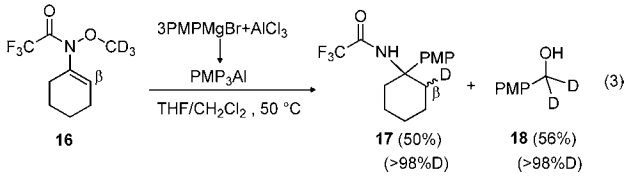
[a] Reaction was carried out with commercially available Ph_3Al. [b] Starting material **11b** was recovered in 41% yield. [c] Commercially available Ph_3Al with $MgBr_2$ improved the yield of product to 50%.

With an optimized procedure in hand, we proceeded to examine the scope of the reaction by reacting **11b** with a range of different triarylaluminum reagents (Table 2, entries 1−4). The use of the triphenylaluminum prepared in situ gave similar results to those observed above for the tris(4-methoxyphenyl)aluminum reagent (Table 2, entry 1). In contrast, the use of the commercially available triphenylaluminum reagent led to a significant reduction in the yield of amide **12b** (Table 2, entry 2). The commercially available triphenylaluminum reagent with $MgBr_2$ gave the product in 50% yield. These results demonstrated that the magnesium salt played an important role in this reaction. The tris(*p*-tolyl)aluminum and tris(4-fluorophenyl)aluminum reagents also performed well under the optimized conditions to give the desired amides **12c** and **12d** in relatively good yields (Table 2, entries 3 and 4, respectively).

Various cyclic and acyclic *N*-alkoxyenamides were then investigated under the optimized reaction conditions to further expand the scope of the reaction (Table 2, entries 5−11). To evaluate the impact of the ring size of cyclic enamides, a substrate bearing a cyclopentenyl group **11e** and a substrate bearing a cycloheptenyl group **11f** were subjected to the optimized reaction conditions (Table 2, entries 5 and 6, respectively). When the substrate bearing a cyclopentenyl group was subjected to the reaction conditions, the desired product was obtained in a 45% yield following an extended reaction time of 15 h (Table 2, entry 5). In contrast, the substrate bearing a cycloheptenyl group gave the corresponding amide in 70% yield following a reaction time of only 3 h (Table 2, entry 6). The reactions of the enamides **11g**−**i**, which contained substituents on their cyclohexene rings, were also examined (Table 2, entries 7−9). The results revealed that certain functional groups were well-tolerated under the optimized reaction conditions, such as an ethyl ester and an acetal. Compared with **11b**, the linear benzyloxyenamides **11j** and **11k** required extended reaction times to afford the desired amides in moderate yields (Table 2, entries 10 and 11).



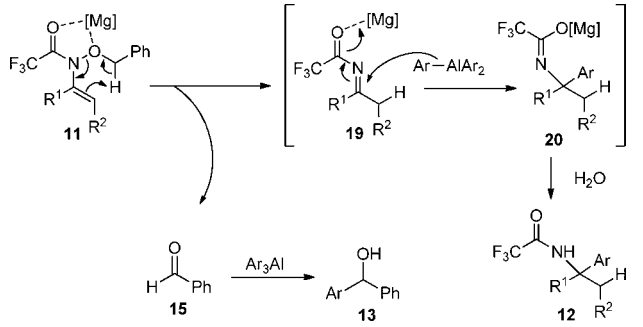




Various reaction conditions were also examined in an attempt to develop a deeper understanding of the reaction and elucidate the mechanism of the reaction. When the alkoxyenamide **11b** was treated with magnesium bromide at 50 °C, the N−O bond was cleaved to give enamide **14** and benzaldehyde (**15**) in 68 and 35% yields, respectively (eq 1). When the reaction was conducted in the absence of magnesium bromide, the enamide **14** was obtained in a much lower yield of only 7%, with 68% of the starting material also being recovered. These results demonstrated

that the magnesium salt was critical to the retro-ene step of the reaction, and that the enamide **14** could be an intermediate in this reaction. Interestingly, however, when the enamide **14** was subjected to the optimized conditions, no reaction was observed (eq 2). Deuterium labeling experiments were also conducted to investigate the mechanism of this transformation. The deuterated alkoxyenamide **16** was treated with tris(4-methoxyphenyl)aluminum that had been generated in situ at 50 °C and gave the β-deuterated amide **17** in a 50% yield (eq 3).

Scheme 3. Plausible Reaction Pathway



On the basis of these results, we have proposed a plausible reaction mechanism, as shown in Scheme 3. Although the role of the magnesium salt remains unclear, it is envisaged that the magnesium would coordinate with the oxygen atoms of the carbonyl and alkoxy groups to inhibit the free rotation of alkoxy groups and effectively fix the conformation in a way that way favors the retro-ene reaction. The N−O bond would then be cleaved, followed by a 1,5-hydrogen shift to give the *N*-acylimine **19** and benzaldehyde (**15**). The retro-ene reaction with concomitant N−O bond cleavage would proceed smoothly because of the formation of a strong C=O bond at the expense of the energy required to break the weak N−O bond.[13] The aryl groups would then add to the *N*-acylimine immediately before the occurrence of any tautomerization to the corresponding enamide. The benzaldehyde (**15**) also reacted with triarylaluminum to give the alcohol **13**.

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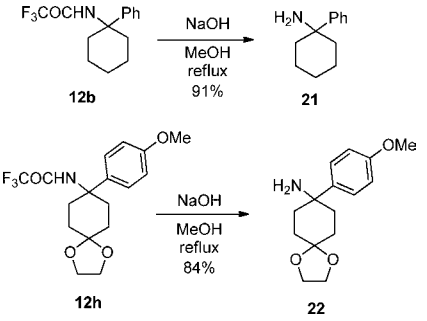
To complete this work, we proceeded to investigate the removal of the trifluoroacetyl group to afford the corresponding *tert*-alkylamine **21**. When the trifluoroacetamide **12b** was treated with NaOH in methanol, the *tert*-alkylamine **21** was obtained in 91% yield (Scheme 4). The cleavage conditions were also successfully applied to trifluoroacetamide **12h**, which contained an acetal-protecting group, to give the desired *tert*-alkylamine product **22** in good yield.

Scheme 4. Removal of the Trifluoroacetyl Group



In conclusion, we have successfully developed a new retro-ene reaction for the conversion of *N*-alkoxyenamides to tautomerizable *N*-acylketimines. The resulting *N*-acylketimines were immediately arylated with triarylaluminum reagents to afford the corresponding *tert*-alkylamides following the removal of the trifluoroacetyl group. This reaction represents a new procedure for accessing *N*-acylketimines. Further applications for this in situ generated *N*-acylimine are currently being investigated in our laboratory.

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Supporting Information Available. Experimental methods and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.