SELECTIVE REACTIONS USING ORGANOALUMINUM REAGENTS

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Abstract-With the aid of selected examples an overview is given of the development trends in highly discriminative reactions using organoaluminum compounds. 1) A new approach has been demonstrated for the selective synthesis of α-arylated amines and enaminones. 2) Nucleophilic aromatic substitution by organoaluminum reagents provides new entry to a variety of aromatic amines. Utility of new methodologies is illustrated by the straightforward synthesis of indole and the related heterocycles.

Although their role in the olefin oriented world of petrochemicals is well-established, organoaluminum reagents are relatively newcomers as tools in selective organic synthesis. The characteristic properties of these reagents derived mainly from the high Lewis acidity of the organoaluminum monomers. The unusually high Lewis acidity, indeed, appears to account for their great tendency to form 1:1 complexes, even with neutral bases such as ethers. These properties (commonly identified with oxygenophilicity) are of great value in the design of slective synthetic reactions. The coordination of a molecule invariably causes a change of reactivity, and the coordinated group may be activated or deactivated depending upon the type of reaction. Furthermore, on coordination of an organic molecule an auxiliary bond can become coupled to the reagent and promote the desired reaction. These elements underlie the studies on synthetic methodology described herein.

A careful examination of the mechanism of Beckmann rearrangement led us to consider that organoaluminum compounds might be employed as amphoteric reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary iminocarbocation by the nucleophile which is originally attached to aluminum.[1]
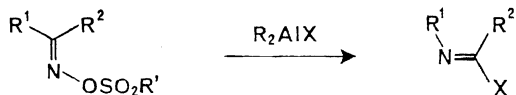

X = Alkyl, Alkynyl, SR', SeR', CN

For example, treatment of a wide variety of oxime sulfonates with several equivalents of alkylaluminum reagents in methylene chloride resulted in formation of the imines, which were directly reduced with excess diisobutylaluminum hydride to give the corresponding amines.[1] Although this method provides a simple route to many substances hitherto accessible by lengthy or complicated syntheses, the drawback of the methodology is the less reactive nucleophile, e.g. sp[2]-carbon nucleophiles and enolate ion, generally gave us poor results.

Reaction of cyclohexanone oxime mesylate **1** with diethylaluminum iodide (2 equiv) produced cleanly the imidoyl iodide, which was directly alkylated by the use of phenylmagnesium bromide (3 equiv) and then reduced with DIBAH (4 equiv) to furnish α-phenylated amine **2** in 81% yield.[2]
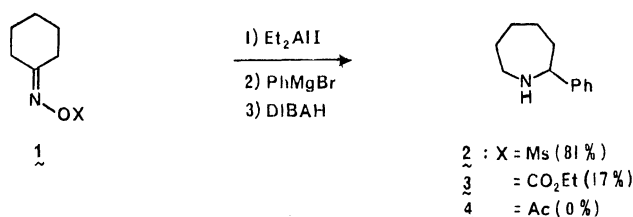

The effectiveness of this method is apparent from the following list of α-phenylated amines prepared from ketoxime mesylates by the aluminum method. Yields are indicated in parenthesis for each product. A darkened bond appearing in a formula reflects the carbon-carbon bond created in the reaction of imidoyl iodides with Grignard reagents.

(93 %)   (63 %)   (44 %)
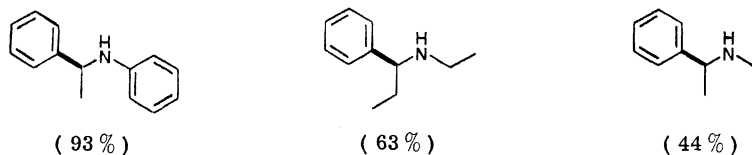
Thus, the method for the conversion of oxime substrates to imidoyl iodides disclosed above makes available α-phenylated amines which are not accessible by previously described reactions.[1]

We next outline a new process which leads to the formation of enaminones by the combination of enol silyl ethers and oxime sulfonates in the presence of organoaluminum reagents.[3] Enaminones are an important class of compounds in view of the fruitful chemical properties and high synthetic utility, particularly as building blocks for the elaboration of fused carbocycles and polyhetero-cycles. The general synthetic method involves reaction between β-diketones and amines that usually causes the lack of regiochemical control over the position of amino group in the enaminone moiety.

Some examples of the reaction are summarized in Table 1. This method is applicable to a variety of enol silyl ethers and ketoxime sulfonates. Of all the Lewis acids examined diethylaluminum chloride and ethylaluminum dichloride (2~3 equiv) have proven to be the most efficacious, and other Lewis acids ($AlCl_3$, $SnCl_4$, $FeCl_3$, $TiCl_4$, Me_3SiOTf, Me_3SiI, etc.) gave less satisfactory results
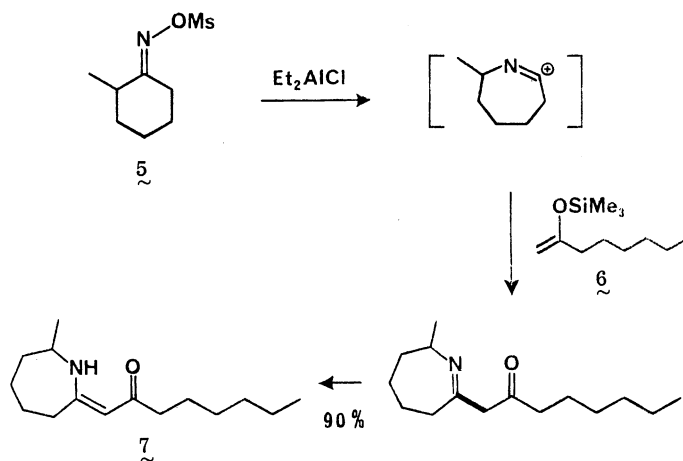
(0 ~ 35% yield). Notably, this condensation takes place regiospecifically in both substrates. For example, reaction of 1-trimethylsiloxy-6-methylcyclohexene (8) or 1-trimethylsiloxy-2-methyl-cyclohexene (9) with cyclohexanone oxime mesylate furnished 10 or 11, respectively, as a sole isolable product (entry 8, 9). The regiospecific Beckmann rearrangement was observed in case of unsymmetrical oxime sulfonates (entry 3, 4, 12). Another striking feature of the reaction is the high chemospecificity (entry 13). It should be added that oxime sulfonate of aromatic ketone and cyclopentanone systems are not employable; attempted condensation of various oxime substrates resulted in the formation of deteriorated reaction mixtures.

The versatility of enaminones in synthetic as well as heterocyclic chemistry serves a stimulus for exploration of the potential applications of this methodology. Accordingly, we have devised a new stereoselective approach to γ-amino alcohols by a direct hydrogenation of the enaminones. Thus, the selective hydrogenation of the enaminone 12 leading to the γ-amino alcohol 13 was realized in 90% yield with reasonable stereoselectivity (~94%) by using 10% platinum on charcoal as a catalyst in EtOH-CHCl$_3$ (30:1) at 20°C for 6 h and 1 atm of H$_2$.
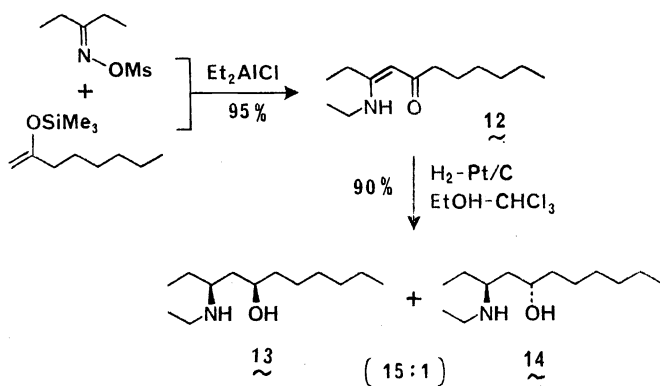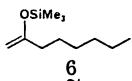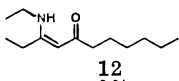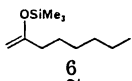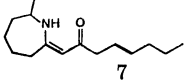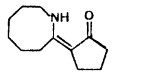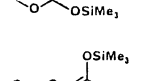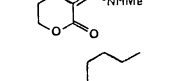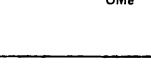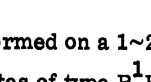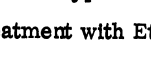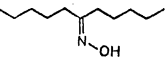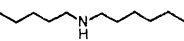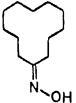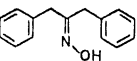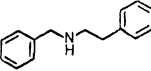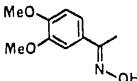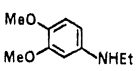
Table I. Condensation of Enol Silyl Ethers with Oxime Mesylates by Organoaluminum Reagents.[a]

entry	enol silyl ether	oxime mesylate[b] R^1	R^2	method[c]	product	yield (%)
1	**6**	Et	Et	A	**12**	95
2				B		67
3		$-CHCH_3(CH_2)_4-$		A	**7**	90
4				B		86
5		$-(CH_2)_6-$		A		74
6		Me	Me	A		30
7				B		69
8	**8**	$-(CH_2)_5-$		B	**10**	82
9	**9**	$-(CH_2)_5-$		B	**11**	42
10		Me	Me	A		65
11				B		31
12		$-CHCH_3(CH_2)_4-$		A		66
13		$-(CH_2)_{11}-$		A		80
14		$-(CH_2)_5-$		B		53
15		Me	Me	A		48
16		Et	Et	B		73

[a] Reaction performed on a 1~2 mmol scale.

[b] Oxime mesylates of type $R^1R^2C=NOMs$ were employed.

[c] Method A: Treatment with Et_2AlCl (3 equiv, a 1 M hexane solution) at -78°C for 30 min and at 20°C for 1 h.

Method B: Treatment with $EtAlCl_2$ (2 equiv, a 2 M toluene solution) at -78°C for 30 min and at 20°C for 0.5~1 h.

So far, we have ignored the direct exposure of oximes to organoaluminum reagents. It is well known that the lithium aluminum hydride reduction of oximes produces the corresponding primary amines, isomeric secondary amines, and aziridines depending on the nature of oxime substrates and the reduction conditions. During an investigation into the chemistry of Beckmann rearrangement-alkylation sequence,[1] we have found a simple and highly convenient procedure for obtaining secondary amines exclusively from oximes by the use of DIBAH.[4] Several examples are listed in Table 2.

Table 2. Reduction of Oximes with Diisobutylaluminum Hydride

| entry	oxime	conditions temp (°C), time (h)	product	yield (%)
1		0, 2		92
2		0, 1; 20, 2		92
3		0, 1; 20, 2		85
4		0, 1; 20, 2		70
5		0, 1; 20, 2		71
6		0, 3		74

It seemed logical to expect that the reduced hydroxylamine might play a significant role of the above rearrangement, though the possibility of a direct rearrangement mechanism has not yet been ruled out. We thus examined the behavior of the hydroxylamine 15 with DIBAH. Indeed, the amine 16 was obtained cleanly.
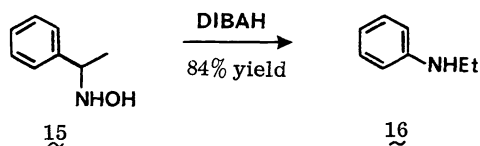
Similarly, the reaction of trimethylaluminum with derivatives of hydroxylamines led to efficient rearrangements as indicated.[5]
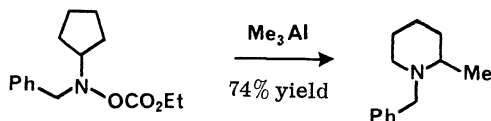
While the overall mode of rearrangement of trialkylaluminum reagents with hydroxylamines parallels the reactions with oxime sulfonates, there are nevertheless significant differences. Indeed, reaction of trialkylaluminum with the derivative of hydroxylamine $\underset{\sim}{17}$ gave the alkylated products $\underset{\sim}{18}$ and $\underset{\sim}{19}$.[6] Thus, disclosed herein is a new and efficient method for the nucleophilic introduction of an alkyl group such as methyl or alkynyl on the aromatic nuclei of arylhydroxylamine derivatives by organoaluminum reagents.   In other words, it could become possible using organoaluminum reagents to restructure the reactivity profile of the arene from nucleophile to electrohile.
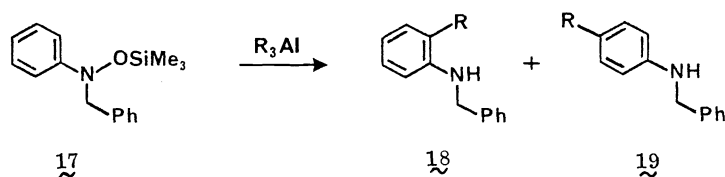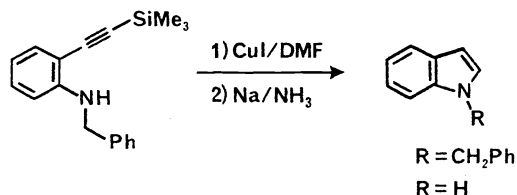

Several examples are listed in Table 3. The characteristic features of the reaction follow. (1) As indicated in Table 3, the reaction appears general with respect to the structural types of aryl-hydroxylamine derivatives, which can be readily accessible from a wide variety of nitro compounds in 55–65% overall yield by the following sequence: (i) reduction of nitroarenes with zinc and aq NH_4Cl in EtOH; (ii) alkylation using benzyl bromide and K_2CO_3 in degassed MeOH; (iii) silyation with trimethylsilyl chloride and NEt_3 in CH_2Cl_2. (2) The high oxygenophilic aluminum reagent is capable of cleaving N–O bond heterolytically to yield the discrete anilenium ion which is readily susceptible toward nucleophilic attack of trialkylaluminum at either ortho or para position. (3) Any double alkylation products was not detected from the reaction products. (4) The choice of trimethylsilyl ether is essential for obtaining C alkylation products selectively. (5) The use of 1-phenethyl group as substituent effected the clean alkylation to furnish 2,4-disubstituted anilines as sole isolable products.

The availability of aromatic amines bearing the ortho alkynyl moiety allowed the development of a convenient access to indoles. Thus, treatment of N-benzyl (2-trimethylsilylethynyl)aniline with CuI (0.5 equiv) and $CaCO_3$ (1 equiv) in DMF at 120°C for 2 h led to smooth cyclization and concurrent elimination of trimethylsilyl group to furnish 1-benzylindole in 73% yield. No trace of the intermediate 1-benzyl-2-trimethylsilylindole could be detected. Deprotection with Na/NH_3 gave rise to indole in 80% yield.

Table 3. Nucleophilic Aromatic Substitution by Trialkylaluminums. [a]

entry	substrate	R₃Al	product	yield (ratio) [b]
1		R = Me		71 (3:2)
2		= n-BuC≡C		77 (1:1)
3	17	= Me₃SiC≡C	18 19	55 (1:1)
4		= PhC≡C		68 (3.7:1)
5		R = Me		69 (1:1)
6		= n-BuC≡C		83 (2.4:1)
7		= Me₃SiC≡C		70 (1:2)
8	R' = CH₂Ph	R = Me		42 [c]
9		= n-BuC≡C		40 [c]
10	R' = CHMePh	R = n-BuC≡C		61
11		= Me₃SiC≡C		83
12	R' = CH₂Ph	R = Me		43 [c]
13		= n-BuC≡C		39 [c]
14	R' = CHMePh	R = n-BuC≡C		61
15		= Me₃SiC≡C		66

[a] Reaction was carried out in CH_2Cl_2 under argon atmosphere by using 4 equiv of R_3Al at 0°C for 30 min.

[b] Isolated ratio of ortho- and para-alkylated aromatic amines.

[c] A considerable amount of imine resulting from the elimination of benzylic proton was formed.

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