Umpolung Reaction

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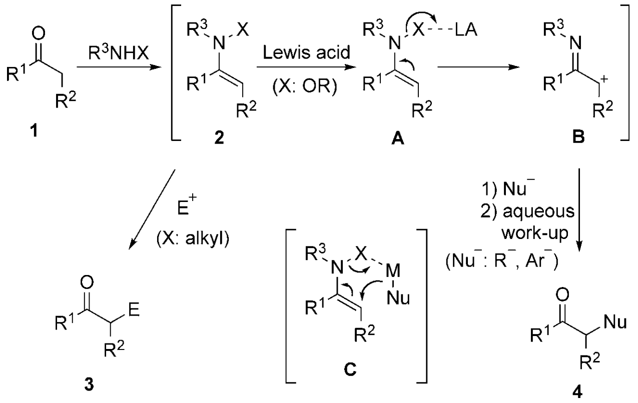
# Nucleophilic α-Arylation and α-Alkylation of Ketones by Polarity Inversion of *N*-Alkoxyenamines: Entry to the Umpolung Reaction at the α-Carbon Position of Carbonyl Compounds**

*Tetsuya Miyoshi, Takayuki Miyakawa, Masafumi Ueda, and Okiko Miyata**

Umpolung reactions have been developed as unconventional methods for the synthesis of biologically active target molecules. Polarity inversions of the carbonyl group are known in stoichiometric dithiane chemistry[1] and more recently in catalytic NHC chemistry,[2] in which acyl anion equivalents that are generated by the umpolung of reactivity of the carbonyl carbon react with the electrophile. The umpolung reaction of the α-carbon atom on the carbonyl structure is an attractive reaction because it allows the direct introduction of various types of substituents into the α position through the use of nucleophiles. To the best of our knowledge, less is known about the umpolung reaction at the α position of the carbonyl group except for the use of α-halogenated carbonyl compounds.[3] There are a few reports of the umpolung reactions of enamine derivatives such as vinyl azides,[4] *N*-sulfonylazoalkenes,[5] and enammonium salts with an indolo[2,3-a]quinolizine structure.[6] Most umpolung reaction of these enamine derivatives have been carried out using nucleophilic alkylation reagents; however, the umpolung arylation reactions of enamines have been much less investigated.[7]

Our research group has developed a strategy for the efficient umpolung α-alkylation and α-arylation of ketones via enamine intermediates (Scheme 1). Generally, enamine **2** (X = alkyl) reacts with an electrophile to give a 2-substituted ketone **3**. We anticipated that enamine **2** carrying a heteroatom substituent (X = OR) would generate the corresponding α-carbonyl carbocation equivalent **B** by coordination with a Lewis acid followed by N−X bond cleavage of the resulting complex **A**. The subsequent desired reaction with a nucleophile would occur at an electrophilic α-carbon atom to form the imine which is unstable enough to undergo hydrolysis upon aqueous work-up. Herein, we present the umpolung α-alkylation and α-arylation of ketones via *N*-alkoxyenamines under mild reaction conditions.[8]



***Scheme 1.*** Umpolung strategy using an enamine intermediate. LA = Lewis acid, Nu = nucleophile.

This method is remarkable in its ability to deliver α-aryl ketones, which are normally difficult to prepare by using the reaction of an enamine with electrophiles.[9] There have been no reports of polarity reversal of *N*-alkoxyenamine and we are aware of only one example of electrophilic alkylation of *N*-alkoxyenamine which occurred much more slowly than the corresponding pyrrolidine enamine.[10] Organoaluminum reagents were chosen as the nucleophile because we expected that the desired reaction with a nucleophile such as trialkylaluminum, which has Lewis acidic character, could proceed efficiently by sequential coordination, N−O bond cleavage, and addition of the nucleophile (complex **C** in Scheme 1).

With the optimal reaction conditions for the umpolung reaction in hand (see entry 5 of Table S1 in the Supporting Information), we investigated the umpolung alkylation of various ketones with several commercially available trialkylaluminum compounds (Table 1). At first, we evaluated the reaction of cyclohexanone derivatives **1a–c**. The expected reaction of the *N*-cyclohexenylisoxazolidine intermediate **2a**,[11] which was formed in situ, with $Et_3Al$ proceeded and afforded **4a** in 76% yield (Table 1, entry 1). Similarly, the reaction of **2a** with $i\mathrm{Bu}_3\mathrm{Al}$ gave **4b** in 69% yield (Table 1, entry 2). The *N*-alkenylisoxazolidine **2b** prepared from **1b**, successfully underwent the umpolung alkylation to provide **4c–e** in more than 70% yield (Table 1, entries 3–5). In the case of 2-methylcyclohexanone (**1c**), 2-ethyl-6-methylcyclohexanone (**4f**) was obtained as a result of regioselective formation of trisubstituted *N*-alkoxyenamine **2c** as an intermediate. Next, we turned our attention to investigating the umpolung reaction using acyclic ketones. The 5-nonanone (**1d**) provided good yield of the corresponding ethylated

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[*] T. Miyoshi, T. Miyakawa, Dr. M. Ueda, Prof. Dr. O. Miyata
Kobe Pharmaceutical University
Motoyamakita, Higashinada, Kobe 658-8558 (Japan)
Fax: (+81) 78-441-7554
E-mail: miyata@kobepharma-u.ac.jp

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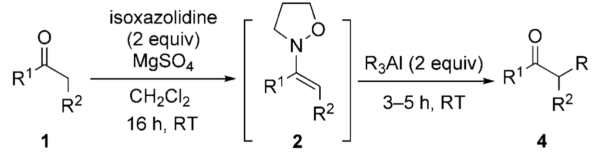
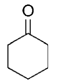
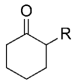
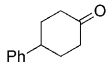
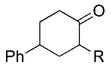
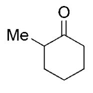
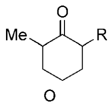
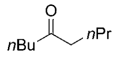
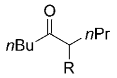
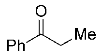
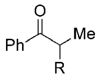
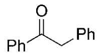
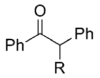
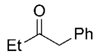
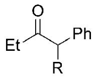
**Table 1:** Umpolung alkylation of various ketones.



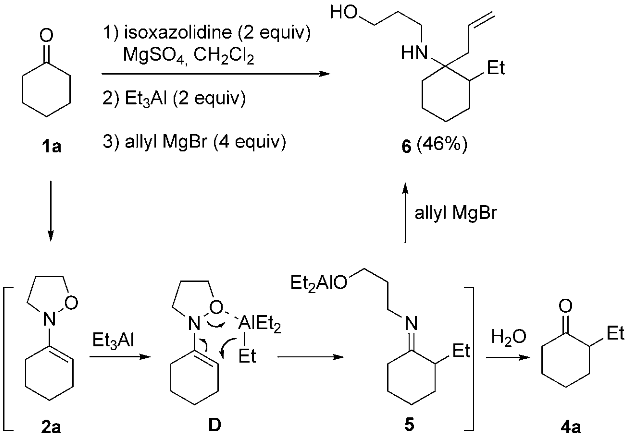
| Entry | Substrate | | Product: R | Yield [%][a] |
|---|---|---|---|---|
| 1 |  | **1a** |  **4a**: Et | 76 |
| 2 | | | **4b**: *i*Bu | 69 |
| 3 |  | **1b** |  **4c**: Me | 72<br>(*trans*/*cis* = 1:1)[b] |
| 4 | | | **4d**: Et | 71<br>(*trans*/*cis* = 1:1)[b] |
| 5 | | | **4e**: *i*Bu | 70<br>(*trans*/*cis* = 1:3)[b] |
| 6 |  | **1c** |  **4f**: Et | 74<br>(*trans*/*cis* = 5:2)[b] |
| 7 |  | **1d** |  **4g**: Et | 78 |
| 8 |  | **1e** |  **4h**: Et | 51 |
| 9 |  | **1f** |  **4i**: Et | 44 |
| 10 |  | **1g** |  **4j**: Et | 61 |

[a] Yield of isolated product. [b] The diastereomeric ratio was determined by $^1$H NMR spectroscopy of the crude product.

product **4g** (Table 1, entry 7). Similarly, acyclic ketones **1e** and **1f** gave **4h** and **4i**, respectively, in moderate yields (Table 1, entries 8 and 9). In the case of ketone **1g**, **4j** was obtained in a regioselective manner via a more stable *N*-alkoxyenamine intermediate **2g** (Table 1, entry 10).

To elucidate the reaction pathway, we investigated the one-pot double nucleophilic alkylation of **2a** (Scheme 2). The treatment of **2a** with $Et_3Al$ and subsequent reaction with allylmagnesium bromide gave dialkylated amino alcohol **6** in 46 % yield. This result indicates that this umpolung reaction would proceed via intermediate imine **5**. Finally, addition of allylmagnesium bromide to imine **5** gave the amine **6**. Instead of allylation, the treatment of **5** with water during work-up afforded 2-alkylated ketone **4a**.

Encouraged by these results, this umpolung reaction was extended to α-arylation (Table 2). We expected that this type of umpolung reaction would be able to easily furnish α-aryl ketone derivatives. The majority of recent progress in the preparation of α-aryl ketone compounds has focused on the development of transition-metal-catalyzed couplings of enolate species with aryl halides.[12] However, the two major drawbacks of these reactions are that a high temperature is required for a successful reaction and an expensive transition metal reagent is needed.

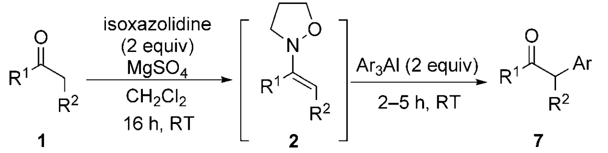


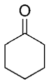
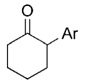
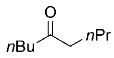
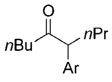
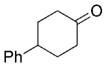
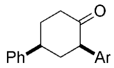
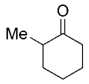
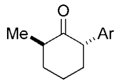
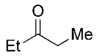
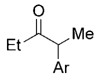
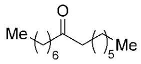
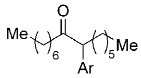
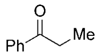
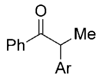
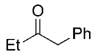
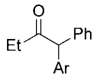
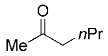
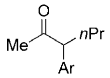
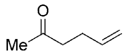
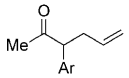
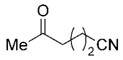
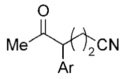
**Scheme 2.** One-pot double nucleophilic reaction.

We first examined the arylation of **2a** with various types of triarylaluminum compounds.[13] The expected reaction using $Ph_3Al$ proceeded smoothly and gave α-phenylated product **7a** in 60 % yield (Table 2, entry 1). The scope of triarylaluminum compounds used was expanded (Table 2, entries 2–5). The electronic nature of the substituents on the benzene ring had little effect on the reaction efficiency. The higher yields of desired α-aryl ketone derivatives were observed when *N*-alkoxyenamine **2d** was subjected to the arylation reaction (Table 2, entries 6–10). We next examined α-arylation of various types of ketones with $(4\text{-MeOC}_6H_4)_3Al$. The cyclohexanone derivatives **1b** and **1c** gave the corresponding α-arylated products **7k** and **7l** in a stereoselective manner in 68 and 60 % yields, respectively (Table 2, entries 11 and 12). The reaction of acyclic ketones **1h** and **1i** gave desired products **7m** and **7n** in good yields, respectively (Table 2, entries 13 and 14). However, the ketones **1e** and **1g** bearing a phenyl group gave the products **7o** and **7p** in diminished yield (Table 2, entries 15 and 16). Interestingly, unsymmetrical aliphatic ketones **1j–l** underwent regioselective α-arylation to yield **7q–s** (Table 2, entries 17–19). Notably, functional groups such as the alkenyl and cyano groups were tolerated during this reaction (Table 2, entries 18 and 19).

Through further investigation, we identified a one-pot umpolung arylation reaction involving enamine formation. We expected that triarylaluminum would preferentially react with *N*-alkoxyenamine over the ketone unit owing to the steric hindrance caused by the bulky substituents of the triarylaluminum reagent. We therefore examined a simple one-pot procedure involving enamine formation without $MgSO_4$ and the umpolung arylation reaction (Scheme 3). Pleasingly, treatment of 5-nonanone (**1d**) with both isoxazolidine and triphenylaluminum in $CH_2Cl_2$ cleanly afforded the desired product **7f** in 73 % yield. Similar results were obtained when triarylaluminum compounds such as *p*-tolyl, 4-methoxylphenyl and 4-fluorophenyl aluminum regents were employed. This method is equivalent to direct umpolung α-arylation of carbonyl compounds which proceeds smoothly in the presence of isoxazolidine and it provides an efficient alternative synthetic route to 2-aryl carbonyl compounds using a simplified procedure.

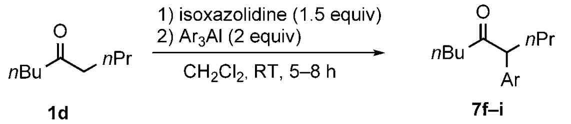
***Table 2:*** Umpolung arylation of various ketones.



| Entry | Substrate | | | Product: Ar | Yield [%][a] |
|---|---|---|---|---|---|
| 1 |  | **1a** |  | **7a**: Ph | 60 |
| 2 | | | | **7b**: *p*-tolyl | 64 |
| 3 | | | | **7c**: 4-MeOC$_6$H$_4$ | 68 |
| 4 | | | | **7d**: 4-FC$_6$H$_4$ | 60 |
| 5 | | | | **7e**: 4-ClC$_6$H$_4$ | 61 |
| 6 |  | **1d** |  | **7f**: Ph | 83 |
| 7 | | | | **7g**: *p*-tolyl | 74 |
| 8 | | | | **7h**: 4-MeOC$_6$H$_4$ | 83 |
| 9 | | | | **7i**: 4-FC$_6$H$_4$ | 75 |
| 10 | | | | **7j**: 4-*t*BuC$_6$H$_4$ | 85 |
| 11 |  | **1b** |  | **7k**: 4-MeOC$_6$H$_4$ | 68 |
| 12 |  | **1c** |  | **7l**: 4-MeOC$_6$H$_4$ | 60 |
| 13 |  | **1h** |  | **7m**: 4-MeOC$_6$H$_4$ | 86 |
| 14 |  | **1i** |  | **7n**: 4-MeOC$_6$H$_4$ | 71 |
| 15 |  | **1e** |  | **7o**: 4-MeOC$_6$H$_4$ | 29 |
| 16[b] |  | **1g** |  | **7p**: 4-MeOC$_6$H$_4$ | 47 |
| 17 |  | **1j** |  | **7q**: 4-MeOC$_6$H$_4$ | 81 |
| 18 |  | **1k** |  | **7r**: 4-MeOC$_6$H$_4$ | 75 |
| 19 |  | **1l** |  | **7s**: 4-MeOC$_6$H$_4$ | 80 |

[a] Yield of isolated product. [b] The regioisomer was obtained in 7% yield.

In conclusion, we have presented the first development of an efficient umpolung reaction by polarity inversion at the $\beta$ position of *N*-alkoxyenamines. The reaction is characterized by mild reaction conditions and simple transformation of ketones into $\alpha$-substituted ketones without isolation of enamine derivatives and intermediate imines. This method provides an attractive alternative to chemistry involving enolate and enamine species. Furthermore, this reaction allows transition-metal-free $\alpha$-arylation of ketones under mild conditions. Further development of this umpolung reaction is currently underway.



**1d**

**7f–i**

**7f**: Ar = Ph (73%)
**7g**: Ar = *p*-tolyl (68%)
**7h**: Ar = 4-MeOC$_6$H$_4$ (70%)
**7i**: Ar = 4-FC$_6$H$_4$ (67%)

***Scheme 3.*** One-pot $\alpha$-arylation of 5-nonanone.

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**Keywords:** aluminum · enamines · ketones · nucleophilic addition · umpolung

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