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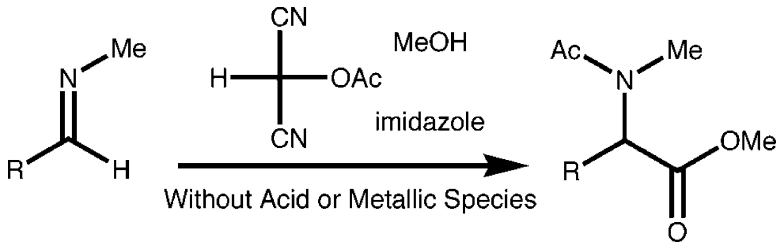

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A Highly Efficient Carbon−Carbon Bond Formation Reaction via Nucleophilic Addition to *N*-Alkylaldimines without Acids or Metallic Species

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Nucleophilic addition reactions to imines have often served as a straightforward method for the synthesis of amines.[1] However, activations of the C═N bond, which is generally poor in reactivity, are necessary to obtain satisfactory efficiencies of these nucleophilic addition reactions.[2] As shown in Figure 1, such activations can be classified as either post- or preactivation. In the case of postactivation, the C═N bond is not substituted with an activating group, and therefore, a Brønsted or Lewis acid or a metallic species is essential to effectively activate the formation of iminium cations or the equivalent species.[3] On the other hand, in the case of preactivation, the C═N bond is substituted with an activating group, such as carbonyl,[4a−d] sulfonyl,[4e−g] sulfinyl,[4h] phosphoryl,[4i,j] or silyl group,[4k] to facilitate the addition reaction. To the best of our knowledge, efficient carbon−carbon bond formation via nucleophilic attack reactions to *ordinary N-alkylated imines without pre- or postactivation* has yet to be reported.

Herein, we describe a methodology for efficient carbon−carbon bond formation via nucleophilic attack of *N*-methylaldimines **1** with neither pre- nor postactivation (Scheme 1). Using this methodology, α-*N*-methylacetamino acid methyl ester **3** was synthesized as a one-pot reaction;[5] the key reagent was **2**, which is a masked acyl cyanide (MAC) reagent[6] (H−MAC−R: MAC = $-C(CN)_2O-$), with an acetyl group (R = $COCH_3$). Although the preparation of **2** has been described in our recent paper,[7] the herein report is the first application toward the chemical reaction of **1**.

Typical MAC reagents (R = $SiMe_2tBu$ or OCHMeOEt) have been shown to be effective in promoting addition reactions to preactivated imines, such as *N*-sulfonylated imines[8] and sulfinimides.[9] These reagents, however, did not exhibit similar effectiveness toward ordinary *N*-alkylated imines, even in the presence of a Lewis or Brønsted acid.

In contrast, the use of novel reagent **2** was effective in facilitating the reaction of *N*-methyl benzaldimine **1a** to give **3a** without the use of a Brønsted acid, Lewis acid, or metal species (Table 1). Reaction of **2** (1.2 mmol) and **1a** (1 mmol) with triethylamine (2.5 mmol) in anhydrous methanol (5 mL) at room temperature for 30 min gave **3a** in 21% yield (entry 1). (*Caution*: The key reaction produces 2 equiv of hydrogen cyanide. Carry out the reaction in a hood.) In the case of entry 1, although the yield of **3a** was low, the success of the reaction without pre- or postactivation demonstrated its feasibility and prompted further investigations to optimize the reaction conditions. To examine the influence of the base, reactions were carried out under various mild basic conditions (entries 2−5); among the bases, the use of imidazole exhibited the best result (entry 5). Subsequent reactions at various temperatures (entries 5−8) indicated the optimum reaction temperature of −40 °C.

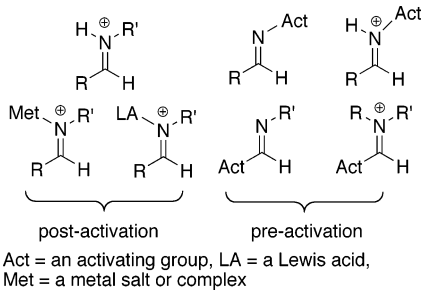
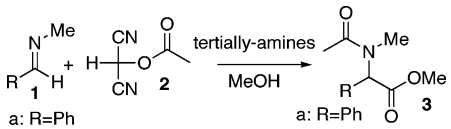


Figure 1. Ordinary methods of C═N bond activation.

Scheme 1



Using the optimized conditions (Table 1, entry 7), reactions of various **1** were carried out to afford **3** in good to excellent yields. Our results showed that the electron density of the aromatic ring has a slight influence on the yields and reaction times (entries 1−8). Aliphatic aldimines were also converted to **3** in excellent yields (entries 9 and 10). It is noteworthy that the aldimine having an *acid-sensitive acetal* was transformed to **3** in excellent yield (entry 11).

The proposed mechanism[4,5] for the formation of **3** is illustrated in Scheme 2. Initially, a tertiary amine deprotonates **2** to generate carbanion **4** (step A), which is then involved in the nucleophilic attack of **1** to form **5** (step B). Although step B may be reversible, anionic nitrogen of **5** can intramolecularly attack[5] the carbonyl group (step C), which is irreversible, thus driving the reaction forward. Subsequently, the anionic oxygen of **6** can trigger the elimination of a cyanide anion to generate the acyl cyanide **7** (step D). Finally, **3** can be produced from **7** with methanol (step E).

In general, it is unfavorable to propose a scheme that involves generation of a *species that possesses a vacant orbital* (Lewis acids). In the case of Scheme 2, metal coordination was not present.

Table 1. Synthesis of **3a** from **1a** and **2** in Methanol

entry	base (equiv)	temp	time (h)	yield (%)
1	Et_3N (2.5)	rt	0.5	21
2	DMAP (0.1)	rt	0.5	37
3	DMAP (2.5)	rt	0.5	44
4	pyridine (2.5)	rt	0.5	38
5	imidazole (2.5)	rt	0.5	62
6	imidazole (2.5)	0 °C	1	68
7	imidazole (2.5)	−40 °C	3	99
8	imidazole (2.5)	−78 °C	5	99

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Scheme 2

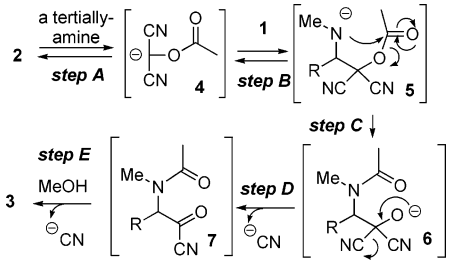


Table 2. Synthesis of **3** from **2** and Various *N*-Methylaldimines **1** in Methanol with Imidazole at −40 °C

entry	**3**	R	time (h)	yield (%)
1	**3a**	C_6H_5	3	99
2	**3b**	4-CH_3−C_6H_4	3	90
3	**3c**	4-CH_3O−C_6H_4	3	88
4	**3d**	4-CN−C_6H_4	5	64
5	**3e**	4-NO_2−C_6H_4	5	64
6	**3f**	3-pyridinyl	5	80
7	**3g**	2-furanyl	2	76
8	**3h**	2-thiophenyl	2	75
9	**3i**	$C_6H_5CH_2CH_2$	3	83
10	**3j**	$(C_2H_5)_2CH$	5	81
11	**3k**	4-$(C_2H_5O)_2CHC_6H_4$	5	82

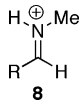
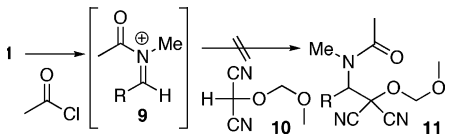


Figure 2.

Measurements of the pH of the reaction solution revealed that the pH was approximately 9−10,[10] indicating the acetal was stable under the conditions (Table 2, entry 11). The generation of iminium cation **8**, therefore, can be ruled out (Figure 2). When the reaction of **1**, acetyl chloride, and a MAC reagent with a nonmigratory group (H−MAC−MOM, **10**)[11] was carried out in ether or dichloromethane in the presence of various kinds and amounts of tertiary amines, even a trace amount of **11** was not detected (Scheme 3). Thus, the generation of acetylated iminium cation **9** can be also ruled out.

Scheme 3



To date, efficient addition reactions to imines have involved either pre- or postactivation. In contrast, the propulsive force for the reaction reported herein is the *termination of the reversible process triggered by the migration* of an acetyl group (step C), followed by the elimination of two cyano groups (steps D and E). Accordingly, these addition reactions can be carried out under very mild basic conditions.

Our novel methodology highlights the discriminatory characteristic of **2** *not only* against other MAC reagents *but also* against previously reported nucleophiles/catalyst systems. We are now pursuing further development of the unique reactivities of novel acylated MAC reagents.

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Supporting Information Available: Experimental data for the compounds listed in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The MAC reagent **2** was not decomposed at room temperature for a few weeks. By way of precaution, we have usually stored **2** in a refrigerator, where **2** was not decomposed at all for more than a year. Preparation of **2**: Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73−75.

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(10) Presumably, the mild basic condition of this reaction is maintained by a slightly excess amount of imidazole (2.5 equiv), even if **2** (1.2 equiv) could be consumed to generate hydrogen cyanide (ca. 2.4 equiv).

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