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# Nafion-H-catalyzed Mukaiyama aldol condensations and hetero Diels–Alder reactions using aldehydes and imines. Part 15: General synthetic methods[†]

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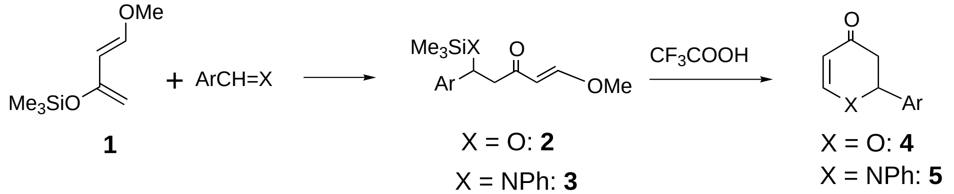
**Abstract**—Nafion-H catalyzes the Mukaiyama aldol condensation between aromatic aldehydes and the Danishefsky diene whereas the corresponding imines directly undergo hetero Diels–Alder cyclization to form 2,3-dihydro-γ-pyridones. Some chiral acetal derived aldehydes were found to undergo Mukaiyama aldol condensation in the presence of Lewis acids but not with Nafion-H.

The hetero Diels–Alder reaction[2] between a reactive carbonyl compound or an imine and the Danishefsky diene **1** (Scheme 1) is an excellent pathway to obtain γ-pyrones or γ-pyridones due to its highly electron rich nature. Aldehydes and imines react easily with **1**. A variety of achiral[3] as well as chiral[4] catalysts have been used to catalyze this reaction. The achiral catalysts that have been employed include $MgBr_2$,[5] $ZnI_2$,[6] $LiClO_4$,[7] $CF_3SO_3H$.[8] Likewise, metallocenium complex $[Cp_2Ce]^+[BPh_4]^-$ catalyzes[9] hetero Diels–Alder reactions and more recently, the use of microwaves has also been found[10] to accelerate the hetero Diels–Alder reaction.

Solid acid catalysts such as zeolites,[11] clays,[12] and Nafion-H[13] have enjoyed immense popularity in organic synthesis. They offer selectivities in addition to making the work-up simpler involving mere filtration of the catalysts. We have been interested in making use of the zeolite H-ZSM 5,[14,15] montmorillonite K 10[15] and Nafion-H[15,16] in various organic transformations. Nafion-H was found by us[16] to be an excellent catalyst for ionic Diels–Alder reactions where the acetal moiety of dienophiles remained unaffected. It was, therefore, of interest to explore the behavior of Nafion-H towards hetero Diels–Alder reactions. Since the acidity of Nafion-H is comparable[13] to 100% $H_2SO_4$, we wondered if the second step involving exposure of the Mukaiyama aldol products (Scheme 1) to trifluoroacetic acid could be avoided to obtain the cyclized products directly. Our efforts in this direction using aldehydes and imines as dienophiles are described in this letter. Accordingly, it was found that aromatic aldehydes react readily with **1** to form the corresponding Mukaiyama aldol products **2** (Scheme 1) (1.5–3.5 h/room temperature) upon treatment with Nafion-H (30 mg/1 mmol of aldehyde). However, contrary to our expectations, no trace of the cyclized product **4** was formed. But, when the catalyst was removed by filtration and the filtrate treated with 0.1 ml of $CF_3CO_2H$, the expected cyclized products were obtained in good yields. Our results are summarized in Table 1. Interestingly, the corresponding aromatic imines underwent direct cyclization to 2,3-dihydro-γ-pyridones upon



**Scheme 1.**

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*Keywords*: hetero Diels–Alder reaction; Nafion-H; Danishefsky diene; chiral acetal; $ZnI_2$.

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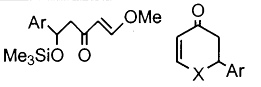
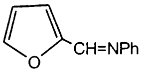
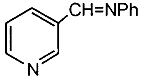
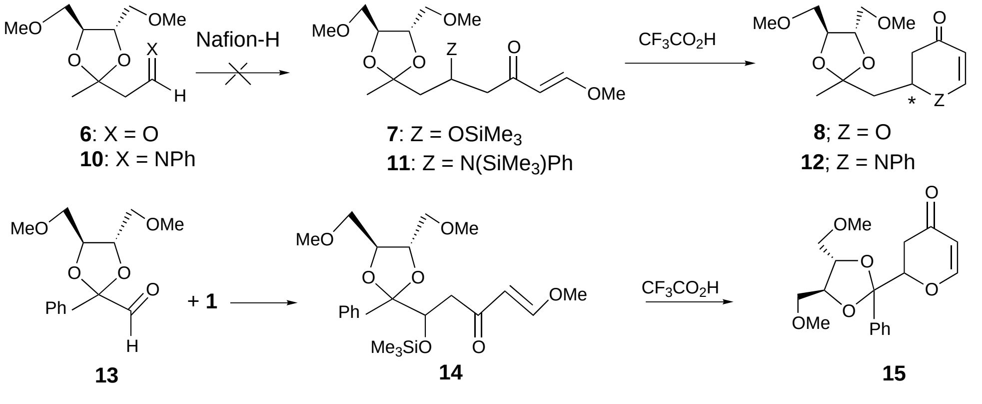
**Table 1.** Hetero Diels–Alder reaction using aromatic aldehydes and imines and Nafion H as the catalyst

| Entry | Aldehyde/Imine |  <br>Mukaiyama Product (**2**)<br>Cycloadduct (**4**/**5**) | %Yield/ Time (h) |
|---|---|---|---|
| 1 | benzaldehyde | **4a**: X = O, Ar = Ph | 62/2 |
| 2 | PhCH=NPh | **5a**: X = NPh, Ar = Ph | 72/10 |
| 3 | 3-tolualdehyde | **4b**: X = O; Ar = 3-Me-$C_6H_4$ | 60/2 |
| 4 | 3-$CH_3$-$C_6H_4$CH=NPh | **5b**: X = NPh; Ar = 3-Me-$C_6H_4$ | 81/16 |
| 5 | 2-nitrobenzaldehyde | **4c**: X = O; Ar = 2-$NO_2$-$C_6H_4$ | 65/1.5 |
| 6 | 2-$NO_2$-$C_6H_4$CH=NPh | **5c**: X = NPh; Ar = 2-$NO_2$-$C_6H_4$ | 76/15 |
| 7 | furfural | **2d**: Ar = 2-furyl | 70/2 |
| 8 |  | **4d**: X = O; Ar = 2-furyl | 89/10 |
| 9 | 3-pyridine aldehyde | **2e**: Ar = 3-pyridyl | 72/3 |
| 10 |  | **5e**: Ar = 3-pyridyl | 88/14 |
| 11 | 4-tolualdehyde | **4f**: Ar = 4-tolyl | 65/3 |
| 12 | 4-$CH_3$-$C_6H_4$CH=NPh | **5f**: Ar = 4-tolyl | 73/4 |
| 13 | 4-anisaldehyde | **4g**: Ar = 4-anisyl | 64/3 |
| 14 | 4-$OCH_3$-$C_6H_4$CH=NPh | **5g**: Ar = 4-anisyl | 77/12 |
| 15 | 4-bromobenzaldehyde | **4h**: Ar = 4-bromophenyl | 62/3.5 |
| 16 | 4-Br-$C_6H_4$CH=NPh | **5h**: Ar = 4-bromophenyl | 74/13 |

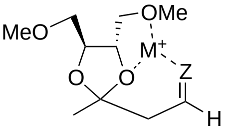
treatment with Nafion-H (entries 2, 4, 6, 8, 10, 12, 14, 16: Table 1). No trace of the Mukaiyama imino aldol product was formed suggesting that the Mukaiyama imino aldol products, if formed, underwent direct cyclization. Furthermore, unlike the reactions of furfural and 3-pyridine aldehyde with **1** in which the Mukaiyama aldol products were found to decompose upon treatment with $CF_3CO_2H$, the corresponding imines (Table 1, entries 8 and 10) underwent direct cyclization with Nafion-H alone. After the reaction was over, the catalyst was filtered off and the products purified by column chromatography.

Our interest[17] in using chiral acetals in organic synthesis led us to investigate whether the aldehyde **6**[18] would act as a dienophile in the presence of Nafion-H as a catalyst. Unfortunately, our attempts to effect this reaction met with no success. Some simple aliphatic aldehydes such as butyraldehyde and phenyl acetaldehyde also did not react with **1** under the present reaction conditions. However, **6** underwent a Mukaiyama aldol condensation with **1** under the influence of Lewis acids such as $ZnCl_2$, $Yb(OTf)_3$, $ZnI_2$ and even $LiClO_4$. Among these, $ZnI_2$ gave the best results leading to the Mukaiyama aldol adduct **7** which was treated with $CF_3CO_2H$ to obtain the cyclized product **8**[19] in 70% yield (Scheme 2). The diastereomeric ratio[20] was only 60:40 indicating that the intermediate **9** is not very rigid. In addition, the corresponding imine did not react cleanly with **1** in presence of Nafion-H, but in the presence of $ZnI_2$, it gave the cycloadduct **12**[19] in 90% yield, via **11**, in a diastereomeric ratio of 65:35. The non-enolizable aldehyde **13**[21] did not react with **1** in the presence of Nafion-H, but in the presence of $ZnI_2$, the

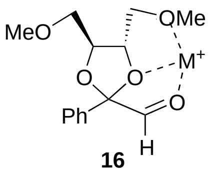


**Scheme 2.**

corresponding cyclized product **15**[19] was formed, via **14**, in a diastereomeric ratio of 80:20. This suggests that the intermediate **16** is more rigid than **9** offering a somewhat better diasteroselectivity. Efforts are underway to explore whether other catalysts will give higher diastereoselectivities in these reactions.



**9** M$^+$ = Lewis Acid



**16**

In summary, our findings suggest that Nafion-H is a good catalyst for effecting hetero Diels–Alder reactions between aromatic aldehydes and imines. However, chiral acetal derived aldehydes and imines are inert towards Nafion-H, but respond well to Lewis acids, especially ZnI$_2$.

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18. Aldehyde **6** was prepared by the Swern oxidation of the corresponding alcohol, which was obtained from the ketal of ethyl acetoacetate. All the compounds gave satisfactory spectral and analytical data.
19. Selected data: **Compound 8**: IR spectrum (neat) $\nu_{\text{max:}}$ 1650, 1580 cm$^{-1}$. $^1$H NMR spectrum (CDCl$_3$, 300 MHz): $\delta$ 1.44[a], 1.46[b] (2s, 3H, -CH$_3$), 1.95–2.45 (m, 2H, -CH$_2$-), 2.48–2.65 (m, 2H, -CO-CH$_2$-), 3.38[b], 3.4[a] (2s, 6H, 2×-OCH$_3$), 3.45–3.63 (m, 4H, 2×-C$\underline{H}_2$-OCH$_3$), 3.86–4.09 (m, 2H, 2×methines), 4.67–4.73 (m, 1H, methine on the pyrone ring), 5.4–5.42 (m, 1H, olefinic proton), 7.34–7.36 (m, 1H, olefinic proton); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 194.00, 163.59, 109.65, 107.50, 77.80, 77.34, 76.66, 72.90, 59.87, 45.55, 26.55; Mass spectrum (*m*/*z*): 286 (M$^+$), 255 (M$^+$ −31), 224 (M$^+$ −62). $[\alpha]_D^{25} = +7.2$ ($c = 1$, CH$_2$Cl$_2$). **Compound 12**: IR spectrum (neat) $\nu_{\text{max:}}$ 1640, 1570 cm$^{-1}$. $^1$H NMR spectrum (CDCl$_3$, 300 MHz): $\delta$ 1.39 (s, 3H), 1.95–2.59 (2m, 2H), 2.85–2.94 (m, 2H), 3.38, 3.39,[b] 3.40, 3.42[a] (4s, 6H), 3.46–3.62 (m, 4H), 3.83–3.94[a] and 4.04–4.17[b] (2m, 2H), 4.41–4.5[a] and 4.5–4.59[b] (2m 1H), 5.21 (d, 1H, $J = 7$ Hz), 7.12 (d, 1H, $J = 7$ Hz), 7.24–7.43 (m, 5H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 192.79, 147.93, 144.49, 130.03, 124.50, 118.84, 110.60, 102.20, 77.97, 77.60, 77.09, 73.47, 73.72, 68.50, 59.82, 54.36, 41.55, 38.62, 26.70, 19.20; Mass spectrum (*m*/*z*): 361 (M$^+$), 172 (M$^+$−189). $[\alpha]_D^{25} = +58.75$ ($c = 2$, CH$_2$Cl$_2$). **Compound 15**: IR spectrum (neat) $\nu_{\text{max:}}$ 1660, 1580 cm$^{-1}$. $^1$H NMR spectrum (CDCl$_3$, 300 MHz): $\delta$ 2.38–2.79 (m, 2H), 3.30, 3.42 (2s, 6H), 3.62–3.65 (m, 4H), 3.85–4.2 (m, 2H), 4.57[a] and 4.79[b] (2dd, 1H, $J = 8$, 5 Hz), 5.37 (d, 1H, $J = 6$ Hz), 7.27–7.54 (m, 6H). Mass spectrum (*m*/*z*): 334 (M$^+$), 303 (M$^+$−31), 272 (M$^+$−62). $[\alpha]_D^{25} = +19$ ($c = 1$, CH$_2$Cl$_2$). [Note: 'a' and 'b' refer to the peaks for major and minor diastereomers, respectively.]
20. The diastereoselectvity was determined from the $^1$H NMR by using Eu(hfc)$_3$ as a shift reagent.
21. This aldehyde was prepared by the Swern oxidation of the corresponding alcohol, which was obtained by the LiAlH$_4$ reduction of the ketal of ethyl benzoyl formate.