

A Mild and Efficient Synthesis of 2,5-Disubstituted 2,3-Dihydro-4-pyridones Catalyzed by Yb(OTf)₃

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Abstract: A highly efficient aza-Diels–Alder reaction of *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with *N*-benzhydryl imines was catalyzed by Yb(OTf)₃ in toluene at room temperature to give corresponding 2,5-disubstituted 2,3-dihydro-4-pyridones in high yields. Three-component reactions of diene with aldehydes and amines were also performed smoothly to afford the desired cycloadducts under solvent-free condition in 51–86% yields.

Key words: Diels–Alder reaction, *N*-benzhydryl imines, solvent-free, Lewis acid, three-component reaction

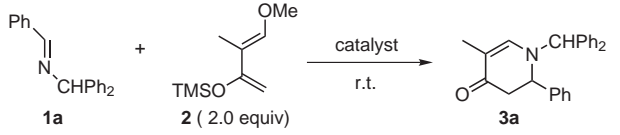
Aza-Diels–Alder reactions provide a powerful strategy for the construction of nitrogen-containing six-membered ring compounds.¹ While recent advances have been made in a number of Lewis acid-catalyzed aza-Diels–Alder reactions in organic solvents^{2–5} and aqueous media,⁶ asymmetric versions using chiral catalysts have also been reported.^{7–12} Among these reactions imino dienophiles have different imino-nitrogen protecting groups including *N*-phosphoryl,^{2g} *N*-tosyl,^{10,11} or *N*-aryl and alkyl, which can activate the imine towards the aza-Diels–Alder reaction. *N*-Benzhydryl imines have been widely used in Strecker reaction with HCN or TMS-CN affording the corresponding α -amino nitriles.¹³ In this communication, aza-Diels–Alder reactions between *N*-benzhydryl imines¹⁴ and *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3 diene¹⁵ were carried out to give 2,5-disubstituted 2,3-dihydro-4-pyridones. Herein, we wish to report our preliminary studies in this field.

In 2002, Ding et al. reported a highly efficient aza-Diels–Alder reaction in methanol without catalyst.⁵ Recently, Kobayashi and co-workers carried out the reaction catalyzed by AgOTf^{6a} or alkaline salt^{6b} in water. However, to the best of our knowledge, no report has been described to date using *N*-benzhydryl imines as dienophiles in aza-Diels–Alder reaction. In the course of our effort to obtain the aza-Diels–Alder reaction cycloadduct of imine **1a** with diene **2**, we found that normal Lewis acids such as ZnCl₂, TiCl₄, Et₂Zn and Et₂AlCl promoted this reaction sluggishly and gave the desired product **3a** in very poor yield. But moderate yield was achieved in the presence of a catalytic amount of Zn(OTf)₂. Initiated by the results,

different metal triflates were screened, and Yb(OTf)₃ exhibited more promising catalytic capability than others (entries 1–5, Table 1). Then the reaction was optimized in term of yield under varying conditions including solvent, catalyst loading and the concentration of the imine. Several solvents including polar and non-polar ones were employed for the reaction. As shown in Table 1, solvent has remarkable effect on the yield of the reaction. Compared with other solvents, toluene was the best solvent, which gave the pyridone **3a** in 92% yield with 20 mol% Yb(OTf)₃ (entry 9, Table 1). An attempt to carry out the reaction in H₂O gave no product at all (entry 6, Table 1). Reducing the catalyst loading from 20 mol% to 10 mol% and 5 mol%, the yield dropped sharply down from 92% to 60% and 49%, respectively (entries 10 and 11, Table 1). However, increasing the concentration of imine from 0.125 M to 0.625 M, the reaction rate was greatly enhanced with a shortened reaction time from 24 hours to 6 hours (entry 13, Table 1).

Encouraged by the results obtained in the reaction of imine **1a**, a variety of *N*-benzhydryl imines **1** were then investigated in the presence of 20 mol% Yb(OTf)₃ at room temperature in toluene. The reactions of aldimines **1** with diene **2** took place smoothly to afford the corresponding adducts **3** in good to excellent yields. It should be noted that the electron-withdrawing groups of aldimines decreased the yield compared with the electron-donating ones generally (entry 5 vs. 7, Table 2). Heteroaromatic aldimines, both **1h** and **1i**, afforded the corresponding products **3h,i** with high yields, 84% and 99%, respectively (entries 8 and 9, Table 2). The α,β -unsaturated aldimine also worked well giving the cycloadduct in good yield (entry 10, Table 2).

To the best of our knowledge, imines, particularly those derived from aliphatic aldehydes, are not always stable. So it is synthetically interesting to construction aza-Diels–Alder products using a three-component one-pot reaction manner especially for aliphatic aldimines, in which the aldimines were prepared in situ and reacted with diene. Accordingly, the aldehyde was first allowed to react with amine and diene **2** was introduced successively. Primary experiment results proved that three-component aza-Diels–Alder reactions proceeded smoothly under solvent-free condition.¹⁶ As shown in Table 3, the three-component condensation reaction was carried out smoothly to afford the corresponding 2,5-disubstituted 2,3-dihydro-4-pyridones in moderate to high yields without solvent. The

Table 1 Aza-Diels–Alder Reaction of Diene **2** with Imine **1a**^a


Entry	Catalyst	Catalyst loading (mol%)	Solvent	Yield (mol%) ^b
1	LiOTf	20	THF	36
2	Cu(OTf) ₂	20	THF	45
3	Sc(OTf) ₃	20	THF	60
4	Zn(OTf) ₂	20	THF	62
5	Yb(OTf) ₃	20	THF	70
6	Yb(OTf) ₃	20	H ₂ O	N.R.
7	Yb(OTf) ₃	20	CH ₂ Cl ₂	71
8	Yb(OTf) ₃	20	Et ₂ O	81
9	Yb(OTf) ₃	20	Toluene	92
10	Yb(OTf) ₃	10	Toluene	60
11	Yb(OTf) ₃	5	Toluene	49
12 ^c	Yb(OTf) ₃	20	Toluene	83
13 ^d	Yb(OTf) ₃	20	Toluene	94

^a All reactions were performed over 24 h with concentration of imine = 0.125 M, unless otherwise indicated.

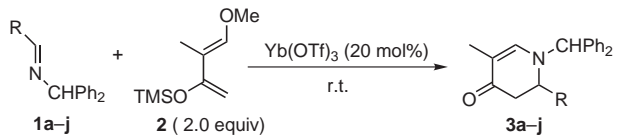
^b Isolated yields.

^c Reaction was carried out over 6 h, concentration of imine = 0.25 M.

^d Reaction was carried out over 6 h, concentration of imine = 0.625 M.

yields of the reaction were slightly lower than those obtained by the reaction of isolated aldimines. The reaction tolerated various aldehydes, such as aromatic, aliphatic, olefinic and heteroaromatic aldehydes. Interestingly, aliphatic aldehydes could react successfully with amines and diene **2** to afford corresponding pyridones (entries 7–9, Table 3), which could not be obtained in the stepwise system above.

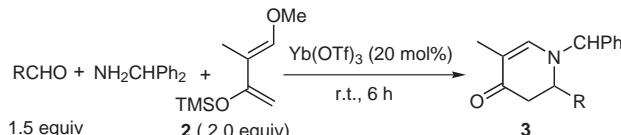
In conclusion, we have developed a mild and highly efficient protocol for the synthesis of racemic 2,5-disubstituted 2,3-dihydro-4-pyridones from diene **2** with *N*-benzhydryl imines or aldehydes and benzhydrylamines. The mild experiment conditions, short reaction time and the wide substrate generality represent the notable features of this procedure. Further investigations on asymmetric aza-Diels–Alder reactions of *N*-benzhydryl imines with diene **2** are now in progress.

Table 2 Yb(OTf)₃-Catalyzed Aza-Diels–Alder Reaction of Diene **2** with Imines **1a**^a


Entry	R	Product	Yield (%) ^b
1	C ₆ H ₅	3a	94
2	2-MeC ₆ H ₄	3b	78
3	4-MeC ₆ H ₄	3c	80
4	2-MeOC ₆ H ₄	3d	84
5	4-MeOC ₆ H ₄	3e	90
6	4-ClC ₆ H ₄	3f	76
7	4-FC ₆ H ₄	3g	70
8	2-Furyl	3h	84
9	2-Pyridyl	3i	99
10	PhCH=CH	3j	62

^a All reactions were performed over 6 h with concentration of imine = 0.625 M, unless otherwise noted.

^b Isolated yields. All compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS analyses.

Table 3 Yb(OTf)₃-Catalyzed Three-Component Aza-Diels–Alder Reaction under Solvent-Free Conditions^a


Entry	R	Yield (%) ^b
1	C ₆ H ₅	77
2	4-MeC ₆ H ₄	72
3	3-MeOC ₆ H ₄	78
4	2-ClC ₆ H ₄	76
5	2-Pyridyl	75
6	PhCH=CH	58
7	<i>c</i> -C ₆ H ₁₁	86
8	(CH ₃) ₂ CH	54
9	CH ₃ CH ₂ CH ₂	51

^a All reactions performed on a 0.125 mmol scale at r.t.

^b Isolated yields. All compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS analyses.

Stepwise Procedure for the Aza-Diels–Alder Reaction of Diene 2 with Imines

All reactions were carried out using anhyd toluene and under nitrogen in over-dried tubes. Yb(OTf)₃ (15.5 mg, 0.025 mmol) and *N*-benzhydryl imine (**1a**, 33.9 mg, 0.125 mmol) were placed in tube. Toluene (0.2 mL) and diene **2** (56 µL, 0.25 mmol) were then added successively. After stirring for 6 h at r.t., the reaction was quenched with 0.5 mL of 1.0 M HCl. The mixture was extracted with CH₂Cl₂ and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a** as white crystal (mp 120–121 °C) in 94% yield. ¹H NMR (600 MHz, CDCl₃): δ = 7.33–6.98 (m, 15 H, Ph-H), 6.91 (s, 1 H, =CH), 5.29 (s, 1 H, -CHPh₂), 4.42–4.39 (m, 1 H, N-CHPh), 2.74–2.72 (m, 2 H, -CH₂), 1.59 (s, 3 H, CH₃). ¹³C NMR (150 MHz, CDCl₃): δ = 190.5, 149.6, 139.4, 138.9, 138.4, 129.5, 129.1, 129.0, 128.8, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 127.3, 106.4, 67.5, 66.0, 62.8, 44.1, 13.1. HRMS (ESI): *m/z* calcd for C₂₅H₂₃NO [M – Na]⁺: 376.1672; found: 376.1671.

One-Pot Procedure for the Three-Component Aza-Diels–Alder Reaction without Solvent

Yb(OTf)₃ (15.5 mg, 0.025 mmol) was placed in the tube. Then, benzaldehyde (19 µL, 0.1875 mmol) and benzhydrylamine (22 µL, 0.125 mmol) were sequentially introduced, and diene **2** (56 µL, 0.25 mmol) was added successively. After stirring for 6 h, the reaction was quenched with 0.5 mL of 1.0 M HCl. The mixture was extracted with CH₂Cl₂ and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a** in 77% yield.

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