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Cobalt(III) Porphyrin Catalyzed Aza-Diels–Alder Reaction

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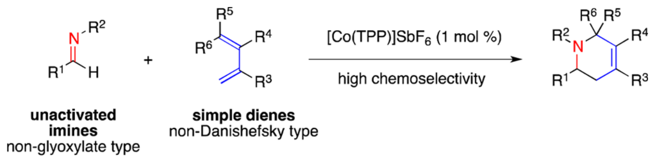
ABSTRACT



An efficient protocol for the aza-Diels–Alder reaction of electron-deficient 1,3-dienes with unactivated imines in the presence of a cationic cobalt(III) porphyrin complex was developed. The transformation proceeded smoothly to afford the desired piperidine scaffold within 2 h at ambient temperature. Highly chemoselective cycloaddition of imines with dienes in the presence of a variety of carbonyl compounds was also demonstrated.

The [4 + 2] cycloaddition of dienes with imines, namely, the aza-Diels–Alder reaction, is a versatile method for constructing privileged scaffolds such as the piperidine scaffold and is hence considered to have potential applications in the synthesis of natural products and pharmaceuticals. Therefore, the development of [4 + 2] cycloaddition strategies involving the use of a catalyst and a mediator has been a research topic of great interest.[1] Many of the precedent aza-Diels–Alder reactions demonstrate high regioselectivity and enantioselectivity but require the use of electron-rich and extremely reactive Danishefsky-type dienes, which severely restricts their widespread application in organic synthesis.[2] Herein, we report that the aza-Diels–Alder reaction of simple 1,3-dienes, which are less reactive than Danishefsky dienes, with imines is efficiently catalyzed by a cationic cobalt-porphyrin complex to afford piperidines.

Metalloporphyrins have been used as catalysts in various organic transformations that are difficult to perform using other metal complexes. The distinct catalytic ability of metalloporphyrins can be attributed to their characteristic structure, in which the tetradentate porphyrin ligand shows rigid in-plane coordination to the metal. Hence, we presumed that a hard Co^{3+} Lewis acid catalyst could be prepared using a porphyrin ligand and a weakly coordinating axial ligand, so that the cationic nature of Co^{3+} is revealed.[3] Such a complex would preferentially coordinate with a hard Lewis base such as an imine and chemoselectively activate simple dienes, thus compensating for their low reactivity; consequently, [4 + 2] cycloaddition would proceed efficiently to afford the corresponding piperidines.[4] To test our hypothesis, we carried out the reaction of imine **1a** with diene **2a** in the presence of $[Co(TPP)]BF_4$ (1 mol %) in toluene. The reaction proceeded to completion within 2 h at ambient temperature to afford piperidine **3aa** in 79% yield (Table 1, entry 1). We also examined the effect of various counteranions such as ClO_4^-, SbF_6^-, OTf^-, and Cl^-, which would act as axial ligands, on the cationic nature of Co^{3+} (entries 2–5). When $[Co(TPP)]SbF_6$ was used as the catalyst, **3aa** was obtained in 92% isolated yield (entry 3). The desired

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(1) (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (c) Weinreb, S. M. Hetero Dienophile Additions to Dienes. In *Comprehesive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 401.

(2) Leighton and coworkers reported novel silicon Lewis acid mediated aza-Diels–Alder reactions of an unactivated imine with three different dienes, see: Tambar, U. K.; Lee, S. K.; Leighton, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 10248.

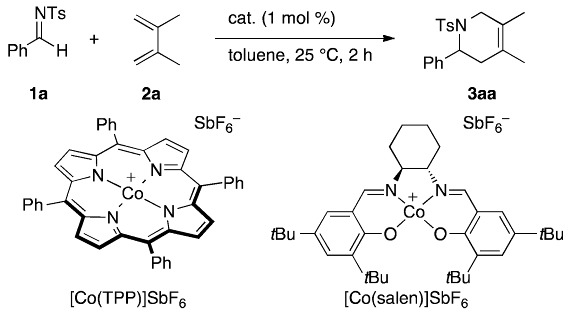
(3) For some selected examples on the synthesis and properties of cationic cobalt-porphyrin complexes, see: (a) Satoh, M.; Ohba, Y.; Yamauchi, S.; Iwaizumi, M. *Inorg. Chem.* **1992**, *31*, 298. (b) Sakurai, T.; Yamamoto, K.; Naito, H.; Nakamoto, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3042. (c) Fukuzumi, S.; Okamoto, K.; Tokuda, Y.; Gros, C. P.; Guilard, R. *J. Am. Chem. Soc.* **2004**, *126*, 17059.

(4) (a) Person, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1. (c) Woodward, S. *Tetrahedron* **2002**, *58*, 1017.

10.1021/ol3020946

product **3aa** was not obtained when using other cobalt catalysts such as [Co(salen)]SbF_6 and $CoCl_2$ or when using $AgSbF_6$ (entries 6−11). Moreover, noncobalt cationic metalloporphyrin complexes such as [Fe(TPP)]SbF_6 and [Mn(TPP)]SbF_6 did not show any catalytic activity (entries 12 and 13).

Table 1. Cobalt-Catalyzed Cycloaddition of **1a** with **2a**[a]

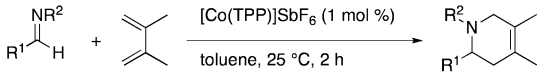


entry	catalyst	yield (%)[b]
1	[Co(TPP)]BF_4	79
2	[Co(TPP)]ClO_4	71
3	[Co(TPP)]SbF_6	99 (92)[c]
4	[Co(TPP)]OTf	69
5	[Co(TPP)]Cl	<1
6	[Co(salen)] SbF_6	<1
7	$CoCl_2$	<1
8	$CoCl_2$·$(bpy)_2$	<1
9	$CoCl_2$·$TPPH_2$	<1
10	$CoCl_2(tmeda)_2$	<1
11	$AgSbF_6$	<1
12	[Fe(TPP)]SbF_6	<1
13	[Mn(TPP)]SbF_6	<1

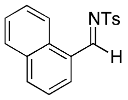
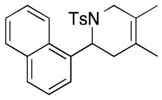
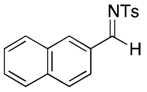
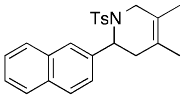
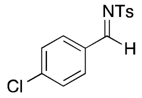
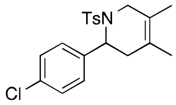
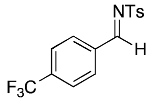
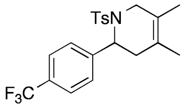
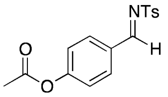
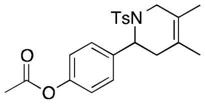
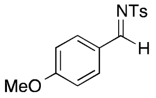
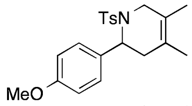
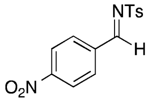
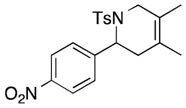
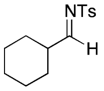
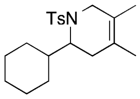
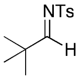
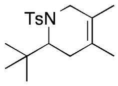
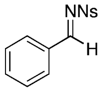
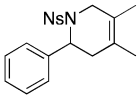
[a] Reactions were carried out using catalyst (1 mol %), imine **1a** (0.4 mmol), and 1,3-diene **2a** (0.8 mmol, 2 equiv) in 4 mL toluene at 25 °C for 2 h. [b] NMR yields based on imine **1a**. [c] Isolated yields based on imine **1a**.

With the optimized reaction conditions in hand, we examined the [Co(TPP)]SbF_6-catalyzed [4 + 2] cycloaddition of various imines with **2a**. The results are summarized in Table 2. Naphthyl aldimines **1b** and **1c** reacted with **2a** in the presence of the cobalt catalyst to furnish the correspondingly substituted piperidines **3ba** and **3ca** in 89% and 83% yields, respectively (entries 1 and 2). Imines possessing electron-withdrawing substituents on the phenyl group, such as **1d** and **1e**, also reacted with **2a** to afford the correspondingly substituted piperidines **3da** and **3ea** in excellent yields (entries 3 and 4). Acetoxy, methoxy, and nitro substituents were well tolerated under the present reaction conditions, as seen from the reactions of **1f**, **1g**, and **1h**, and the corresponding cycloaddition products were isolated in good to moderate yields (entries 5, 6, and 7), although a longer reaction time was required in the latter two cases. Notably, aliphatic aldimines such as **1i** and **1j** also reacted with the simple diene **2a** to afford piperidines **3ia** and **3ja** in 87% and 83% yields, respectively (entries 8 and 9). Imine **1k** bearing a nosyl (Ns: 2-nitrobenzenesulfonyl) substituent, which is more easily removable than the tosyl group, reacted with **2a** to yield **3ka** in moderate yield (entry 10).

Table 2. Scope of Imines **1** in the Cycloaddition[a]



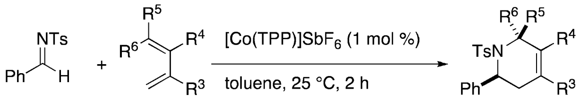
1 **2a** **3**

entry	1	imine	3	product	yield (%)[b]
1	**1b**		**3ba**		89
2	**1c**		**3ca**		83
3	**1d**		**3da**		90
4	**1e**		**3ea**		85
5	**1f**		**3fa**		85
6	**1g**		**3ga**		83[c]
7	**1h**		**3ha**		77[d]
8	**1i**		**3ia**		87
9	**1j**		**3ja**		83
10[e]	**1k**		**3ka**		64[d]

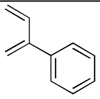
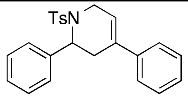
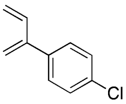
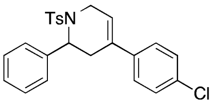
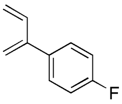
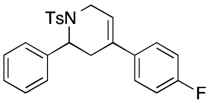
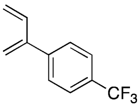
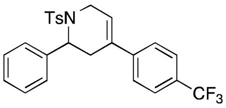
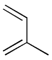
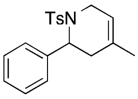
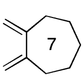
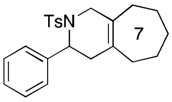
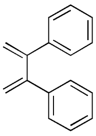
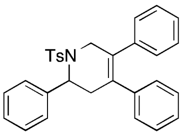
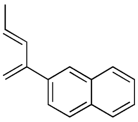
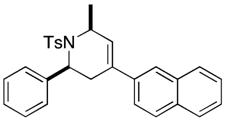
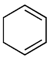
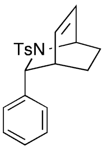
[a] Reactions were carried out using [Co(TPP)]SbF_6 (1 mol %), imine **1** (0.4 mmol), and 1,3-diene **2a** (0.8 mmol, 2 equiv) in 4 mL toluene at 25 °C for 2 h, unless otherwise noted. [b] Isolated yields based on imine **1**. [c] [Co(TPP)]SbF_6 (2.5 mol %), 25 °C, for 12 h. [d] [Co(TPP)]SbF_6 (2.5 mol %), 50 °C, for 6 h. [e] NNs, 2-nitrobenzenesulfonamide.

To demonstrate the scope of this cycloaddition in more detail, we examined the reaction of **1a** with various dienes **2** having different functional groups and substitution patterns (Table 3). 2-Phenyl-1,3-butadienes reacted with **1a** to afford the corresponding substituted piperidines **3** regioselectively in good yield (entries 1−4). On the other hand,

Table 3. Scope of Dienes **2** in the Cycloaddition[a]



1a **2** **3**

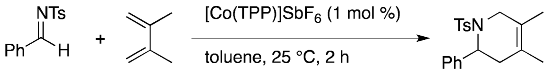
entry	2	diene	3	product	yield (%)[b]
1	**2b**		**3ab**		91
2	**2c**		**3ac**		87
3	**2d**		**3ad**		90
4	**2e**		**3ae**		83
5	**2f**		**3af**		71
6	**2g**		**3ag**		88[c]
7	**2h**		**3ah**		50[c]
8	**2i**		**3ai**		83 (85:15)[d]
9	**2j**		**3aj**		63[e] (88:12)[d]

[a] Reactions were carried out using $[Co(TPP)]SbF_6$ (1 mol %), imine **1a** (0.4 mmol), and 1,3-diene **2** (0.8 mmol, 2 equiv) in 4 mL toluene at 25 °C for 2 h, unless otherwise noted. [b] Isolated yields based on imine **1**. [c] $[Co(TPP)]SbF_6$ (2.5 mol %), 50 °C, for 2 h. [d] Ratio of isomers. [e] $[Co(TPP)]SbF_6$ (5 mol %), 50 °C, 5 h.

when the butadiene had an electron-donating methoxy substituent on the phenyl moiety, cycloaddition with **1a** was retarded, and oligomerization of the diene proceeded predominantly. Cycloaddition of isoprene **2f** with **1a** afforded the desired product **3af** in moderate yield (entry 5). The reaction of conformationally fixed 1,2-bismethylenecycloheptane **2g** with **1a** gave the bicyclic compound **3ag** in 88% yield (entry 6). 2,3-Diphenyl-1,3-butadiene **2h** showed rather low reactivity, and hence, **3ah** was obtained only in moderate yield (entry 7). (*E*)-2-Naphthyl-1,3-pentadiene **2i** reacted with **1a** in a regioselective manner to give *cis*-**3ai** in 83% yield, with a stereoisomer ratio of 85:15 (entry 8).[5,6] Further, the reaction of 1,3-cyclohexadiene **2j** with **1a** afforded **3aj** as the predominant cycloadduct. Single-crystal X-ray analysis of **3aj** confirmed that this compound was an *exo*-adduct (see the Supporting Information).[7]

Chemoselective activation of imines by the cationic cobalt catalyst $[Co(TPP)]SbF_6$ was demonstrated by the [4 + 2] cycloaddition of **1a** with **2a** in the presence of various carbonyl compounds (Scheme 1). The reaction proceeded effectively to afford the desired piperidine product **3aa** in high yields (> 84%), irrespective of the presence of the carbonyl compound. No cycloadduct formed by the reaction of **2a** with the carbonyl compound was observed in any of these cases. These results clearly highlighted the excellent chemoselectivity of the $[Co(TPP)]SbF_6$-catalyzed cycloaddition of imines with dienes.

Scheme 1. Chemoselective Cycloaddition of **1a** with **2a** in the Presence of Various Carbonyl Compounds



1a **2a**

in the presence of	3aa
PhCHO	88%
PhCOMe	85%
$PhCO_2Me$	89%
PhNCO (1 equiv)	84%

In summary, we demonstrated the catalytic efficiency of the cationic cobalt-porphyrin complex $[Co(TPP)]SbF_6$ for the aza-Diels–Alder reaction of imines with dienes. The use of this catalyst allowed for the reaction of unactivated dienes, that is, non-Danishefsky-type dienes, with unactivated imines such as nonglyoxylate imines to construct the piperidine framework. The high activation ability of the catalyst that competes with the high chemoselectivity could be attributed to the hard Lewis acidity of Co^{3+}, which in turn was due to the rigid tetradentate planar porphyrin ligand and the weakly coordinating axial SbF_6^- ligand. Efforts toward the development of an asymmetric variant of the aza-Diels–Alder reaction and elucidation of

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(5) The reaction of **1a** with (*Z*)-2-naphthyl-1,3-pentadiene **2i′** in the presence of the $[Co(TPP)]SbF_6$ catalyst afforded cycloadduct in 81% yield as a stereoisomer mixture (*cis*/*trans* = 57:43), whereas the reaction of **1a** with (*E*)-2-naphthyl-1,3-pentadiene **2i** afforded *cis*-**3ai** as the predominant product (Table 3, entry 8). These results indicated that the cobalt-catalyzed cycloaddition of imines with dienes proceeds through a stepwise mechanism.

(6) The cycloadditon of **1b** with **2i** afforded **3bi** as a major isomer in 59% isolated yield. The configuration of **3bi** was unambiguously confirmed by an X-ray crystal structure analysis (see the Supporting Information).

(7) The *exo*-selectivity can be explained by a stepwise reaction mechanism, which would start with the Alder-ene-type reaction of the carbon–carbon double bond with the imine to form an allyl cation intermediate and subsequent cyclization. Thus, geometric isomerization is induced by the allyl cation formation.

the unique reactivity of the cationic cobalt-porphyrin complex are underway.

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Supporting Information Available. Experimental procedures including spectroscopic and analytical data of new compounds. CIF files of **3aj** and **3bi**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.