Cationic Iron(III) Porphyrin-Catalyzed [4 + 2] Cycloaddition of Unactivated Aldehydes with Simple Dienes

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S *Supporting Information*

ABSTRACT: Cationic iron(III) porphyrin was found to be an efficient catalyst for the highly chemoselective hetero-Diels–Alder-type reaction of aldehydes with 1,3-dienes. The catalyzed process did not require the use of electron-deficient aldehydes such as glyoxylic acid derivatives or activated electron-rich 1,3-dienes such as Danishefsky's diene and Rawal's diene. The high functional group tolerance and robustness of the catalyst were demonstrated. Further, the potential utility of the catalyst was demonstrated by performing the cycloaddition in the presence of water and by carrying out cycloaddition of an unactivated ketone such as cyclohexanone with a diene.

The hetero-Diels–Alder reaction is one of the most powerful synthetic methods for the construction of six-membered heterocyclic compounds. In particular, the cyclo-addition of aldehydes to dienes, which affords the pyran scaffold, has been widely applied in the preparation of natural products and physiologically active substances.[1,2] However, the majority of these reactions involve the use of activated aldehydes such as glyoxylates or electron-rich dienes such as Danishefsky's diene and Rawal's diene.[3] Only a limited number of hetero-Diels–Alder reactions in which unactivated aldehydes and simple dienes are employed have been reported. Furthermore, the use of a very strong Brønsted acid or Lewis acid is mandatory to activate the poorly reactive hetero-dienophile to a sufficient extent in order to compensate for the low reactivity of simple dienes. These requirements impose strict limitations on the choice of functional groups that can be tolerated under the reaction conditions adopted.[4] Thus, the development of an efficient catalyst that overcomes such drawbacks remains a challenging research topic in organic synthesis. Herein we report the reaction of unactivated aldehydes with simple dienes in the presence of a cationic iron(III) porphyrin catalyst to afford pyrans. This catalyst has high functional group tolerance, chemoselectivity, and robust-ness in the reaction.

Initially, we prepared the cationic iron(III) porphyrin catalyst [Fe(TPP)]SbF$_6$ (TPP = *meso*-tetraphenylporphyrinato) by treating [Fe(TPP)]Cl with AgSbF$_6$ in CH$_2$Cl$_2$ at ambient temperature for 12 h (Scheme 1).[5,6] Treatment of the resulting [Fe(TPP)]SbF$_6$ with 2 equiv of 1-naphthaldehyde afforded [Fe(TPP)(C$_{10}$H$_7$CHO)$_2$]SbF$_6$, in which two molecules of naphthaldehyde are coordinated as axial ligands to the iron(III) center (Figure 1). Therefore, we presumed that [Fe(TPP)]-SbF$_6$ would be an efficient Lewis acid for converting

Scheme 1. Synthesis of the [Fe(TPP)(C$_{10}$H$_7$CHO)$_2$]SbF$_6$ Complex
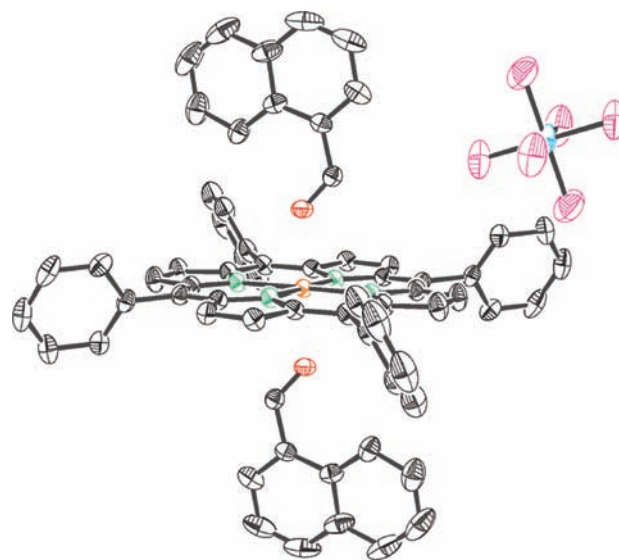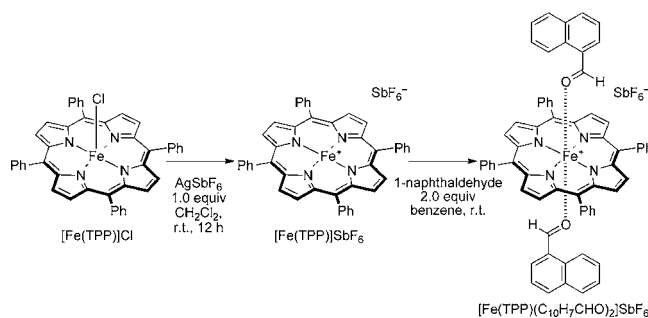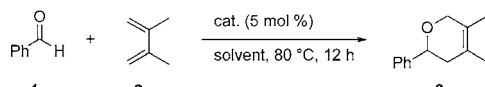
Figure 1. ORTEP drawing of [Fe(TPP)(C$_{10}$H$_7$CHO)$_2$]SbF$_6$.

unactivated aldehydes into stronger heterodienophiles for cycloaddition with simple dienes.

Indeed, the reaction of benzaldehyde (**1a**) with 2,3-dimethyl-1,3-butadiene (**2a**) in the presence of the cationic iron(III) porphyrin catalyst (5 mol %) in benzene at 80 °C for 12 h afforded pyran **3aa** in 81% isolated yield (Table 1, entry 1). In other solvents such as toluene, 1,4-dioxane, and MeCN or in the absence of a reaction medium, the yields were even lower (entries 2–5). Upon optimization of the counteranion of the
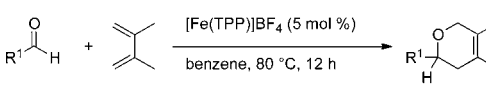
Table 1. Iron-Catalyzed Cycloaddition of 1a with 2a[a]
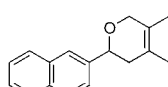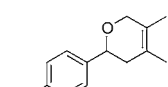
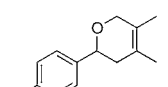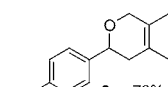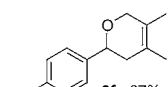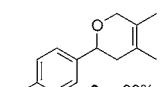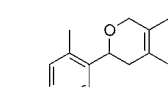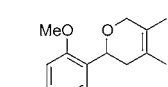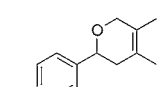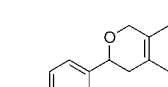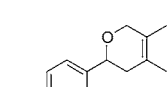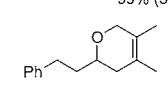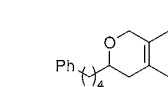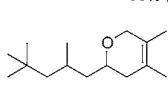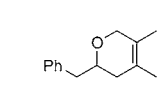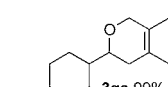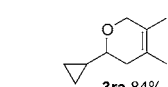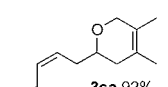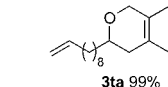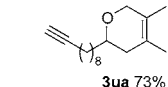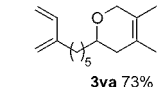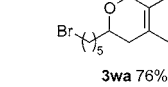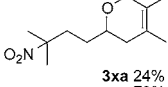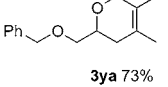| entry	catalyst	solvent	yield (%)[b]
1	[Fe(TPP)]SbF$_6$	benzene	81
2	[Fe(TPP)]SbF$_6$	toluene	66
3	[Fe(TPP)]SbF$_6$	1,4-dioxane	<1
4	[Fe(TPP)]SbF$_6$	MeCN	<1
5	[Fe(TPP)]SbF$_6$	—	49
6	[Fe(TPP)]Cl	benzene	<1
7	[Fe(TPP)]OTf	benzene	<1
8	[Fe(TPP)]BF$_4$	benzene	92
9	[Fe(TPP)]PF$_6$	benzene	<1
10	FeCl$_3$	benzene	38
11	FeCl$_3$·(tmeda)$_2$	benzene	3
12	FeCl$_3$·(bpy)$_2$	benzene	5
13	FeCl$_3$·TPPH$_2$	benzene	<1
14	FeCl$_2$	benzene	4
15	FeF$_3$	benzene	<1
16	AgBF$_4$	benzene	<1

[a]Reactions were carried out using the iron catalyst (5 mol %), aldehyde **1a** (0.5 mmol), and diene **2a** (2.0 mmol, 4 equiv) in 2 mL of solvent at 80 °C for 12 h. [b]Isolated yields based on aldehyde **1a**.

cationic iron porphyrin complex, **3aa** was obtained in excellent yield. When [Fe(TPP)]BF$_4$ was used, **3aa** was obtained in 92% yield (entry 8). The use of other iron catalysts such as FeCl$_3$, FeCl$_3$·(tmeda)$_2$, FeCl$_3$·(bpy)$_2$, FeCl$_2$, and FeF$_3$ or the use of AgBF$_4$ in place of the cationic iron(III) porphyrin complex resulted in the formation **3aa** in trace amounts or much lower yields (entries 10−16).

With the optimized reaction conditions in hand, we first evaluated the cationic iron(III) porphyrin-catalyzed hetero-Diels−Alder-type reaction of various aldehydes **1** with **2a** [Table 2; for details, see the Supporting Information (SI)]. 2-Naphthaldehyde (**1b**) participated in the reaction with **2a** to afford **3ba** in 88% isolated yield. Benzaldehydes with electron-withdrawing substituents such as trifluoromethyl, fluoride, chloride, and bromide afforded pyrans **3** in good yields. Benzaldehyde **1i**, which has an electron-donating methoxy substituent, reacted with **2a** to furnish **3ia** in excellent yield (99%). Nitro and nitrile substituents on benzaldehyde were well-tolerated under the present reaction conditions, and the corresponding cycloaddition products (**3ja** and **3ka**, respectively) were isolated in excellent yields. Furthermore, the reaction of p-acetylbenzaldehyde (**1l**) with **2a** gave **3la** in 98% yield, but a considerably long reaction time (5 days) was required. The cationic iron(III) porphyrin complex was also found to be effective for the reaction of aliphatic aldehydes with **2a**. Notably, phenylacetaldehyde (**1p**), a highly enolizable aldehyde, also underwent cycloaddition with **2a** to afford pyran **3pa** in 72% yield. Cyclopropanecarboxaldehyde (**1r**) reacted with **2a** to afford the corresponding substituted pyran **3ra** in 84% yield. Aldehydes with unsaturated moieties such as a double bond, triple bond, or even a conjugated diene also furnished cycloadducts **3** in moderate to excellent yields (**3sa**, 92%; **3ta**, 99%; **3ua**, 73%; **3va**, 73%). Moreover, various functional groups such as bromide, nitro, ether, and imide on aliphatic aldehydes were tolerated under the reaction conditions, and functionalized pyrans were obtained (**3wa**, 76%; **3xa**, 73%; **3ya**, 73%; **3za**, 92%).

Table 2. Iron Porphyrin-Catalyzed Cycloaddition of Aldehydes 1 with 2a[a]

product[b]

[a]Reactions were carried out using [Fe(TPP)]BF$_4$ (5 mol %), aldehyde **1** (0.5 mmol), and diene **2a** (2.0 mmol, 4 equiv.) in 2 mL of benzene at 80 °C for 12 h, unless otherwise noted. [b]Isolated yields based on aldehyde **1** are shown. [c]A diastereomeric ratio of 1/1 was observed.

To demonstrate the scope of this cycloaddition, we next examined the reaction of aldehyde **1a** with various conjugated dienes **2** (Table 3; for details, see the SI). Under the optimized reaction conditions, 2-aryl-1,3-butadienes having an electron-withdrawing substituent on the phenyl moiety reacted with **1a** to afford the corresponding substituted pyrans regioselectively in good yields. On the other hand, when the butadiene had an electron-donating methoxy substituent on the phenyl moiety, as in **2f**, cycloaddition with **1a** was retarded, and oligomerization of **2f** proceeded predominantly. Oligomerization was prevented by slow addition of **2f** to the reaction mixture over 3 h, and as a result, the desired cycloadduct **3af** was obtained, but in a very

Table 3. Iron Porphyrin-Catalyzed Cycloaddition of 1a with Dienes 2[a]
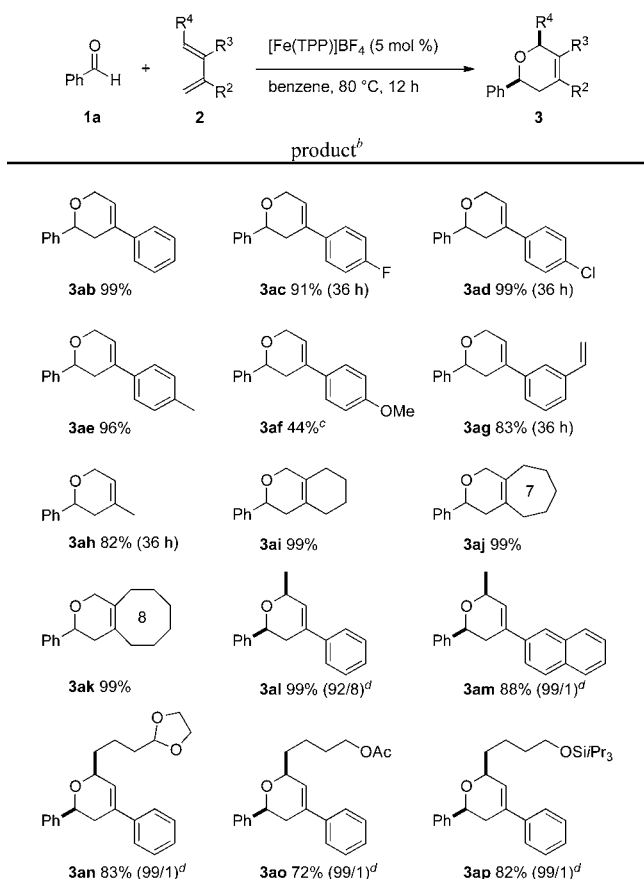
^{a}Reactions were carried out using [Fe(TPP)]BF$_4$ (5 mol %), aldehyde **1a** (0.5 mmol), and diene **2** (2.0 mmol, 4 equiv) in 2 mL of benzene at 80 °C for 12 h, unless otherwise noted. ^{b}Isolated yields based on aldehyde **1** are shown. ^{c}Diene **2f** was added to the reaction mixture over 3 h. ^{d}Ratio of diastereomers (*cis/trans*).

Scheme 2. Effects of the Cationic Iron(III) Porphyrin Catalyst
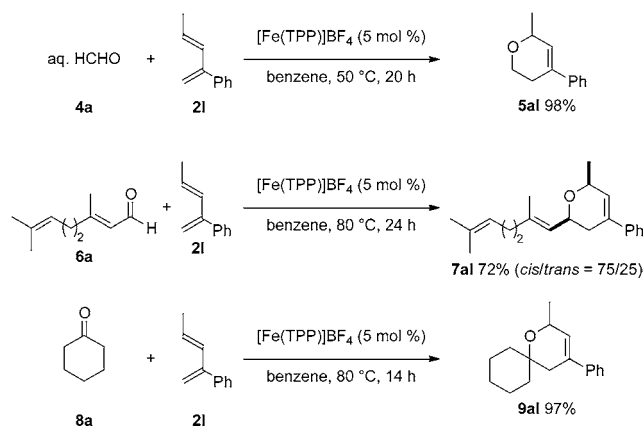
low yield (44%).[7] A 1,3-butadiene possessing a highly polymerizable styryl moiety also reacted with **1a** to give **3ag** in 83% yield. Cycloaddition of conformationally fixed *s-cis*-dienes such as 1,2-bis(methylene)cyclohexane (**2i**) with **1a** also proceeded successfully to give hexahydro-1*H*-isochromene **3ai** in 99% yield. Likewise, 1,2-bis(methylene)cycloheptane (**2j**)

and 1,2-bis(methylene)cyclooctane (**2k**) reacted with **1a** to furnish polycyclic cycloadducts **3aj** and **3ak**, respectively, in excellent yields. Furthermore, cycloadditions of **1a** with 1,4-disubstituted-1,3-dienes proceeded with high regio- and stereoselectivity. 2-Phenyl-1,3-pentadiene (**2l**) reacted with **1a** to afford *cis*-**3al** in 99% yield in a regioselective manner, with a stereoisomer ratio of 92/8. Cycloaddition of **2m** with **1a** gave **3am** as the single isomer in 88% yield (for details of X-ray crystal structure analysis, see the SI).[8] Acid-sensitive functional groups such as acetal, acetoxy, and siloxy groups were also tolerated under the reaction conditions, giving the corresponding substituted pyrans (**3an**, 83%; **3ao**, 72%; **3ap**, 82%). These results clearly highlighted the excellent chemoselectivity of the [Fe(TPP)]BF$_4$-catalyzed cycloaddition of aldehydes with dienes.

Notably, the [Fe(TPP)]BF$_4$-catalyzed [4 + 2] cycloaddition was feasible in the presence of water. An aqueous solution of formaldehyde (**4a**) could be made to react with **2l** to obtain pyran **5al** in 98% yield (Scheme 2). It is also noteworthy that the α,β-unsaturated aldehyde **6a** behaved as a heterodienophile but not as a heterodiene, reacting with **2l** to afford **7al** in 72% yield with a diastereomeric ratio of 75/25. Moreover, unactivated ketones, which are much poorer heterodienophiles than are aldehydes as a result of steric and electronic effects, also participated in the cycloaddition with the diene; cyclohexanone (**8a**) reacted with **2l** to afford oxaspiro compound **9al** in 97% isolated yield.[9]

In summary, we have developed an unprecedented catalyst for the hetero-Diels–Alder-type [4 + 2] cycloaddition of unactivated aldehydes with simple dienes. The readily available cationic iron(III) porphyrin effectively catalyzes the cycloaddition with high functional group tolerance and robustness. Furthermore, the use of this catalyst in the cycloaddition of an unactivated ketone and a simple diene has been demonstrated for the first time. Efforts directed toward the development of an asymmetric variant of the reaction and detailed studies to elucidate the mechanism underlying the unique reactivity of the cationic iron(III) porphyrin complex are underway.[10,11]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic and analytical data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) For reviews of the hetero-Diels−Alder reaction, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero- Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Tietze, L.-F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1 and references therein.

(2) For some selected examples, see: Avermectin: (a) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119. Laulimalide: (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, I. *Tetrahedron Lett.* **1997**, *38*, 2427. Ambruticin: (c) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. Phorboxazole A: (d) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749. Calyxin: (e) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606. Isomigrastatin: (f) Krauss, I. J.; Mandal, M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5576. For reviews, see: (g) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (h) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250. (i) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 661.

(3) For representative references, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (c) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (d) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (e) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

(4) Sulfuric acid: (a) Griengl, H.; Geppert, K. P. *Monatsh. Chem.* **1976**, *107*, 675. [Pd(dppp)(PhCN)$_2$]BF$_4$: (b) Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996**, *37*, 6351. Trifluoromethanesulfonic acid: (c) Aggarwal, V.; Vennall, G. P.; Davey, P. N.; Newman, C. *Tetrahedron Lett.* **1997**, *38*, 2569. Scandium perfluorooctanesulfonate: (d) Hanamoto, T.; Sugimoto, Y.; Jin, Z. Y.; Inanaga, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1421.

(5) (a) Baldwin, J. E.; Haraldsson, G. G. *Inorg. Chem. Acta.* **1981**, *51*, 29. (b) Malek, A.; Latos-Grazynski, L.; Bartczak, T. J.; Zadlo, A. *Inorg. Chem.* **1991**, *30*, 3222. (c) Fang, M.; Wilson, S. R.; Suslick, K. S. *J. Am. Chem. Soc.* **2008**, *130*, 1134.

(6) High-valent cationic iron porphyrins such as [Fe(TPP)]ClO$_4$ and [Fe(TPP)]OTf are useful Lewis acid catalysts for the rearrangement of epoxides to carbonyl compounds. For pioneering examples, see: (a) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554. (b) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Tetrahedron Lett.* **1999**, *40*, 7243. (c) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* **2002**, 2570.

(7) Danishefsky's dienes such as *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene failed to participate in the iron-catalyzed reaction with **1a** because of oligomerization of the diene.

(8) The reaction of **1a** with (*Z*)-2-naphthyl-1,3-pentadiene (**2m′**) in the presence of the [Fe(TPP)]BF$_4$ catalyst afforded *cis*-**3am** as the major cycloadduct in 61% yield, along with its stereoisomer *trans*-**3am′** in 38% yield, whereas the reaction of **1a** with (*E*)-2-naphthyl-1,3-pentadiene (**2m**) afforded *cis*-**3am** in 88% yield. These results indicate that the iron-catalyzed cycloaddition of aldehydes with dienes proceeds through an asynchronous stepwise mechanism. For a theoretical study of the mechanism of the hetero-Diels−Alder reaction, see: McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330.

(9) There are very few reports on the hetero-Diels−Alder reaction of unactivated ketones with dienes. For cycloaddition with Rawal's dienes, see: (a) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321. (b) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. For cycloaddition with Brassard's dienes, see: (c) Guay, V.; Brassard, P. *Tetrahedron* **1984**, *40*, 5039. (d) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294.

(10) For reviews of the asymmetric hetero-Diels−Alder reaction, see: (a) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839. (b) Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147. (c) Gouverneur, V.; Reiter, M. *Chem.—Eur. J.* **2005**, *11*, 5806. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

(11) Cationic iron porphyrins may undergo spin-state transition and/or mixing, which contributes to an increase in the catalytic activity for the cycloaddition. For the spin state of cationic iron porphyrins, see: (a) Dolphin, D. H.; Sams, J. R.; Tsin, T. B. *Inorg. Chem.* **1977**, *16*, 711. (b) Shelly, K.; Bartczak, T.; Robertscheidt, W.; Reed, C. A. *Inorg. Chem.* **1985**, *24*, 4325. (c) Reed, C. A.; Guiset, F. *J. Am. Chem. Soc.* **1996**, *118*, 3281. (d) Ikeue, T.; Ohgo, Y.; Yamaguchi, T.; Takahashi, M.; Takeda, M.; Nakamura, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2617. For a study of spin-state mixing of cytochromes, see: (f) Maltempo, M. M. *J. Chem. Phys.* **1974**, *61*, 2540. For a related theoretical study of a spin-state transition that enhances the reactivity of cobalt catalysts for the hetero-Diels−Alder reaction, see: (e) Iwakura, I.; Ikeno, T.; Yamada, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2524.