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One-Pot Cycloisomerization/ Hetero-Diels–Alder Reaction of 1,6-Enynes with Aldehydes Catalyzed by Rhodium and a Brønsted Acid

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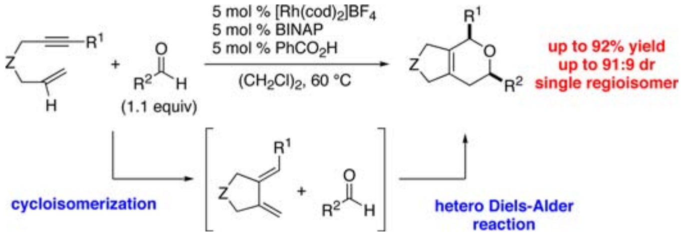
ABSTRACT



A rhodium and Brønsted acid catalyzed one-pot cycloisomerization/hetero-Diels–Alder reaction of 1,6-enynes with unactivated aldehydes was established under mild conditions. This one-pot catalytic protocol produced a wide variety of annulated dihydropyrans from readily available starting materials in a highly atom economical manner.

The hetero-Diels-Alder reaction has been utilized for the convenient synthesis of six-membered heterocycles. Several examples of [4 + 2] cycloaddition reactions of 1,3-dienes with aldehydes leading to six-membered oxacyclic compounds have been reported to date.[1] However, the successful examples are largely limited to the use of electron-deficient aldehydes and/or electron-rich 1,3-dienes.[2] Although a few examples using unactivated aldehydes and 1,3-dienes have been reported, these reactions employed very strong Brønsted[3] or Lewis acids[4] in order to activate poorly reactive heterodienophiles. Furthermore, the product yields are insufficient and the substrate scope is limited. Recently, Matsubara, Kurahashi, and a co-worker achieved the highly efficient hetero-Diels–Alder reaction of unactivated aldehydes and 1,3-dienes under mild reaction conditions (benzene, 80 °C) by using a cationic Fe(III) porphyrin complex as a novel Lewis acid catalyst.[5] This mild catalyst system significantly broadened the substrate scope. However, a few examples of exocyclic 1,3-dienes, which afford annulated dihydropyrans,[6] were tested due to the poor availability of exocyclic 1,3-dienes.[5] Herein, we disclose the one-pot cycloisomerization/hetero-Diels–Alder reaction of 1,6-enynes with unactivated aldehydes catalyzed

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(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.

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

(3) (a) Ansell, M. F.; Charalambides, A. A. *J. Chem. Soc., Chem. Commun.* **1972**, 739. (b) Griengl, H.; Geppert, K. P. *Monatsh. Chem.* **1976**, *107*, 675. (c) Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, C. *Tetrahedron Lett.* **1997**, *38*, 2569.

(4) (a) Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996**, *37*, 6351. (b) Hanamoto, T.; Sugimoto, Y.; Jin, Z. Y.; Inanaga, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1421.

(5) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2012**, *134*, 5512.

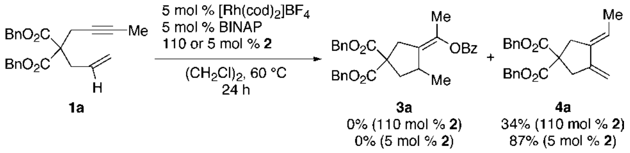
(6) For recent examples of biologically active compounds possessing annulated dihydropyran cores, see: (a) Stokl, J.; Hofferberth, J.; Pritschet, M.; Brummer, M. *J. Chem. Ecol.* **2012**, *38*, 331. (b) Feng, C.-L.; Gong, M.-F.; Zeng, Y.-B.; Dai, H.-F.; Mei, W.-L. *Molecules* **2010**, *15*, 2473.

10.1021/ol4005849

by rhodium and a Brønsted acid under mild conditions. This unprecedented one-pot catalysis produces a wide variety of annulated dihydropyrans from readily available starting materials.

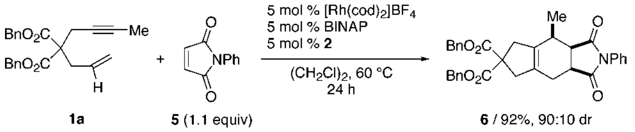
We previously reported that a cationic Rh(I)/bisphoshine complex catalyzes the cyclization of 1,6-diynes with benzoic acid (**2**) leading to dienyl benzoates under mild conditions.[7] Thus, we attempted the reaction of 1,6-enyne **1a** in the presence of a stoichiometric amount of **2** and a catalytic amount of a cationic Rh(I)/BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] complex. Although the expected carboxylative cyclization product **3a** was not generated, exocyclic 1,3-diene **4a** was generated in low yield (Scheme 1). When using a catalytic amount of **2**, the yield of **4a** significantly improved (Scheme 1).

Scheme 1



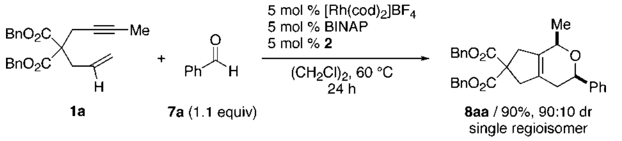
Chatani, Murai, and co-workers reported the cycloisomerization of 1,6-enynes leading to exocyclic 1,3-dienes[8] by using a neutral Ir(I) complex and acetic acid.[9] Subsequently, Yamamoto, Itoh, and co-workers reported the trapping of the thus generated exocyclic 1,3-dienes[8] from nitrogen-linked 1,6-enynes with *N*-phenylmaleimide (**5**) by the Diels–Alder reaction under toluene reflux conditions.[10] Thus, we attempted the one-pot cycloisomerization/Diels–Alder reaction of **1a** with **5**.[11] Pleasingly, the expected product **6** was obtained in high yield under mild reaction conditions (Scheme 2).

Scheme 2



On the other hand, Oi and co-workers reported the hetero-Diels–Alder reaction of unactivated aldehydes and 1,3-dienes under mild reaction conditions ($CHCl_3$, 50 °C) by using a cationic Pd(II)/bisphosphine catalyst.[4a] As the one-pot reaction shown in Scheme 2 employs the Lewis acidic cationic Rh(I) complex as a catalyst,[12] we anticipated that the same Rh(I) complex would catalyze the hetero-Diels–Alder reaction with an unactivated aldehyde in one pot. As we expected, the unprecedented one-pot cycloisomerization/hetero-Diels–Alder reaction of 1,6-enyne **1a** with benzaldehyde (**7a**) proceeded in the presence of the cationic Rh(I)/BINAP complex (5 mol %) and **2** (5 mol %) to give annulated dihydropyran **8aa** as a single regioisomer in high yield with high diastereoselectivity (Scheme 3).

Scheme 3



The effect of Brønsted acids and counteranions on the reaction of 1,6-enyne **1a** with benzaldehyde (**7a**) was examined (Table 1). With respect to Brønsted acids, use of more acidic sulfonic acid **10** and phosphoric acid **11** increased the yield of the undesired olefin isomerization product **9a** (entries 2 and 3), and use of less acidic phenol (**12**) lowered the yield of **8aa** due to the formation of the corresponding [2 + 2 + 2] cyclization product as a byproduct.[13] The use of the most acidic sulfonic acid **10** significantly decreased the diastereoselectivity (entry 2). With respect to counteranions, use of the more ionic [SbF_6] anion afforded a complex mixture of byproducts other than the desired product **8aa** (entry 5), and use of less ionic [OTf] anion afforded **9a** as a major product (entry 6). In both cases, lower diastereoselectivities were observed. The neutral Rh(I)/BINAP complex did not catalyze the reaction (entry 7). Thus, use of benzoic acid (**2**) as the Brønsted acid and the [BF_4] anion as the counteranion is optimal (entry 1).

With the optimized reaction conditions in hand, we explored the scope of this one-pot catalysis (Table 2). With respect to unactivated aldehydes, a variety of aromatic and heteroaromatic aldehydes **7a**–**f** could participate in this reaction to give the corresponding dihydropyrans **8aa**–**f** in high yields with high diastereoselectivities (entries 1–6). Importantly, both electron-rich and -deficient aromatic aldehydes **7d**,**e** equally reacted with **1a** (entries 4 and 5). Not only aromatic aldehydes but also aliphatic aldehydes

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[7] Tanaka, K.; Saito, S.; Hara, H.; Shibata, Y. *Org. Biomol. Chem.* **2009**, *7*, 4817.

[8] For examples of the transition-metal-catalyzed cycloisomerization of 1,6-enynes leading to exocyclic 1,3-dienes, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Mori, M.; Kozawa, Y.; Nishida, M.; Kanamaru, M.; Onozuka, K.; Takimoto, M. *Org. Lett.* **2000**, *2*, 3245. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (d) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (e) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753. (f) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268.

[9] (a) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433. (b) Kezuka, S.; Okada, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711.

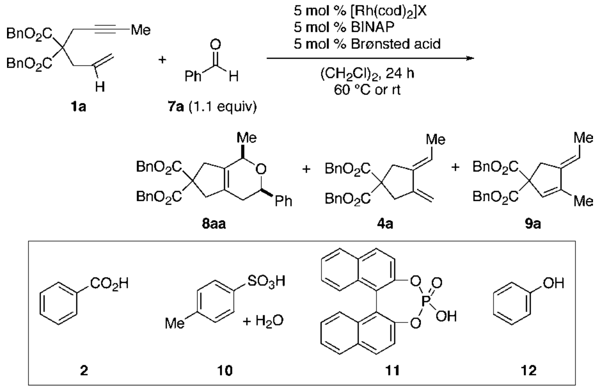
[10] Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804.

[11] For examples of the one-pot cycloisomerization/Diels–Alder reaction, see: (a) Van Boxtel, L. J.; Körbe, S.; Noltemeyer, M.; De Meijere, A. *Eur. J. Org. Chem.* **2001**, 2283. (b) Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291.

[12] Our research group recently reported that a cationic Rh(I)/biaryl bisphoshine complex catalyzes the carbonyl ene reaction; see: Okazaki, E.; Okamoto, R.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6722.

[13] Ishida, M.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Chem.—Eur. J.* **2011**, *16*, 12578.

Table 1. Effect of Brønsted Acids and Counteranions on Reaction of 1,6-Enyne **1a** with Benzaldehyde (**7a**)[a]



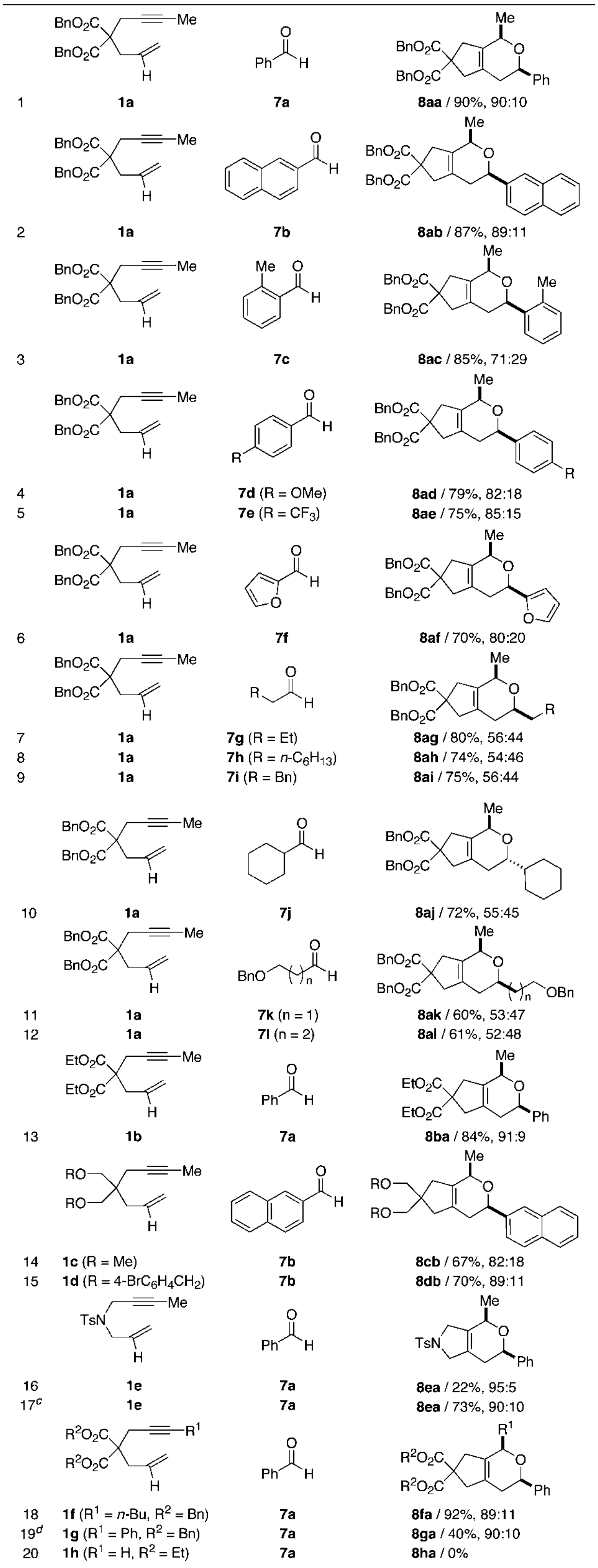
entry	Brønsted acid	counteranion (X)	temp (°C)	**8aa** % yield[b] (dr)	**4a** % yield[b]	**9a** % yield[b]
1	**2**	BF_4	60	90 (90:10)	0	<5
2	**10**	BF_4	rt	53 (71:29)	0	39
3	**11**	BF_4	rt	60 (91:9)	0	20
4	**12**	BF_4	60	66 (92:8)	0	0
5	**2**	SbF_6	60	47 (75:25)	0	5
6	**2**	OTf	60	20 (64:36)	0	61
7[c]	**2**	Cl	60	0	0	0

[a] $[Rh(cod)_2]X$ (0.010 mmol), BINAP (0.010 mmol), Brønsted acid (0.010 mmol), **1a** (0.20 mmol), **7a** (0.22 mmol), and $(CH_2Cl)_2$ or CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield. [c] $[RhCl(cod)]_2$ (2.5 mol %) was used.

7g–**j** could be employed, although diastereoselectivities were low (entries 7–10). Furthermore, acid-sensitive benzyloxy-substituted aldehydes **7k**,**l** smoothly reacted with **1a** (entries 11 and 12). With respect to 1,6-enynes, not only malonate- (entries 1–13) but also 1,3-diol-derived ones **1c**, **d** (entries 14 and 15) were suitable substrates for this process. In the reaction of tosylamide-linked 1,6-enyne **1e** with **7a**, the use of *p*-toluenesulfonic acid (**10**) at rt gave the corresponding dihydropyran **8ea** in a higher yield (entry 17) than the use of **2** at 60 °C (entry 16). Not only 1,6-enynes **1a**–**e** possessing the methyl group at the alkyne terminus but also 1,6-enynes **1f**,**g** possessing the *n*-butyl or phenyl group at the alkyne terminus, respectively, reacted with **7a** to give dihydropyrans **8fa** and **8ga**[14] in moderate to high yields (entries 18 and 19). Unfortunately, the reaction of terminal 1,6-enyne **1h** and **7a** did not afford dihydropyran **8ha** (entry 20).[15]

Very recently, Matsubara, Kurahashi, and a co-worker reported the aza-Diels–Alder reaction of unactivated imines and 1,3-dienes at rt by using a cationic Co(III) porphyrin complex as a Lewis acid catalyst.[16,17] We also

Table 2. One-Pot Cycloisomerization/Hetero-Diels–Alder Reaction of 1,6-Enynes **1a**–**h** with Aldehydes **7a**–**l**[a]



entry	1	7	8 / yield[b], dr
1	**1a**	**7a**	**8aa** / 90%, 90:10
2	**1a**	**7b**	**8ab** / 87%, 89:11
3	**1a**	**7c**	**8ac** / 85%, 71:29
4	**1a**	**7d** (R = OMe)	**8ad** / 79%, 82:18
5	**1a**	**7e** (R = CF_3)	**8ae** / 75%, 85:15
6	**1a**	**7f**	**8af** / 70%, 80:20
7	**1a**	**7g** (R = Et)	**8ag** / 80%, 56:44
8	**1a**	**7h** (R = *n*-C_6H_{13})	**8ah** / 74%, 54:46
9	**1a**	**7i** (R = Bn)	**8ai** / 75%, 56:44
10	**1a**	**7j**	**8aj** / 72%, 55:45
11	**1a**	**7k** (n = 1)	**8ak** / 60%, 53:47
12	**1a**	**7l** (n = 2)	**8al** / 61%, 52:48
13	**1b**	**7a**	**8ba** / 84%, 91:9
14	**1c** (R = Me)	**7b**	**8cb** / 67%, 82:18
15	**1d** (R = 4-$BrC_6H_4CH_2$)	**7b**	**8db** / 70%, 89:11
16	**1e**	**7a**	**8ea** / 22%, 95:5
17[c]	**1e**	**7a**	**8ea** / 73%, 90:10
18	**1f** (R^1 = *n*-Bu, R^2 = Bn)	**7a**	**8fa** / 92%, 89:11
19[d]	**1g** (R^1 = Ph, R^2 = Bn)	**7a**	**8ga** / 40%, 90:10
20	**1h** (R^1 = H, R^2 = Et)	**7a**	**8ha** / 0%

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.010 mmol), BINAP (0.010 mmol), **2** (0.010 mmol), **1a**–**h** (0.20 mmol), and **7a**–**l** (0.22 mmol) in $(CH_2Cl)_2$ (2.0 mL) at 60 °C for 24 h. [b] Isolated yield. [c] A reaction was conducted using **10** in place of **2** at rt. [d] At 40 °C.

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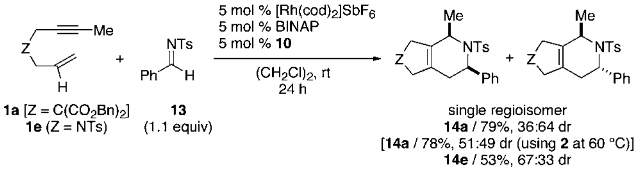
(14) Oligomerization of **4g** proceeded as a side reaction.

(15) As the corresponding exocyclic 1,3-diene **4h** was generated in ca. 40% yield, the subsequent hetero-Diels–Alder reaction of **4h** with **7a** did not proceed.

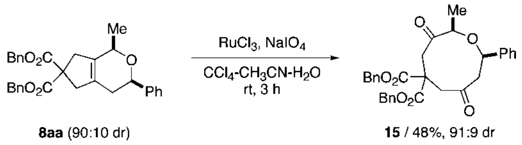
(16) Wakabayashi, R.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2012**, *14*, 4794.

(17) For other examples of the aza-Diels–Alder reaction of unactivated imines and 1,3-dienes, see: (a) Tambar, U. K.; Lee, S. K.; Leighton, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 10248. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.

Scheme 4



Scheme 5

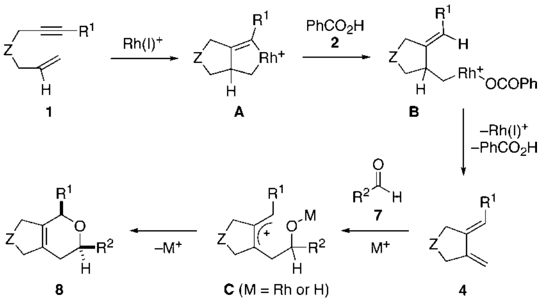


attempted the one-pot cycloisomerization/aza-Diels–Alder reaction by using the cationic Rh(I)/BINAP complex and Brønsted acids. Gratifyingly, 1,6-enynes **1a**,**e** reacted with unactivated imine **13** at rt in the presence of 5 mol % of the cationic Rh(I)/BINAP complex with the more ionic $[SbF_6]$ anion and **10** to give tetrahydropyridine **14a**,**e** as a single regioisomer in good yields with moderate diastereoselectivities (Scheme 4). The diastereoselectivity of **14a** was decreased by using **2** in place of **10** at 60 °C.

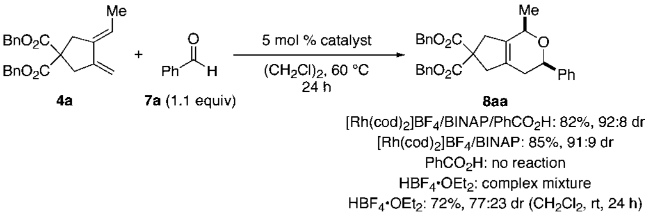
Importantly, the annulated dihydropyran product can serve as a precursor of a nine-membered oxacyclic compound. Ring expansion of the annulated dihydropyran **8aa** proceeded by the ruthenium-catalyzed C=C bond cleavage[18] to give nine-membered oxacyclic compound **15** in moderate yield (Scheme 5).

Scheme 6 depicts a plausible mechanism for the present one-pot catalysis. 1,6-Enyne **1** reacts with rhodium affording rhodacyclopentene **A**. The reaction of **A** with benzoic acid (**2**) affords rhodium benzoate **B**. β-Hydride elimination from **B** followed by elimination of benzoic acid affords exocyclic 1,3-diene **4**. Carbonyl activation by the cationic Rh(I) complex promotes the hetero-Diels–Alder reaction through cationic intermediate **C** to afford annulated dihydropyran **8**.[19] Small amounts of HBF_4, which may be generated in situ by the reaction of $Rh(I)^+{-}BF_4^-$ complexes and **2**, may also catalyze the hetero-Diels–Alder reaction.

Scheme 6



Scheme 7



In order to determine the active catalyst in the hetero-Diels–Alder reaction step, the reactions of isolated exocyclic 1,3-diene **4a** with **7a** were examined in the presence of various catalysts (Scheme 7). The cationic Rh(I)/BINAP complex smoothly catalyzed the reaction in the presence or absence of benzoic acid (**2**), while **2** did not catalyze the reaction at all. The use of $HBF_4{\bullet}OEt_2$ at 60 °C led to a complex mixture of products, although **8aa** was obtained at rt. However, the yield and diastereoselectivity using $HBF_4{\bullet}OEt_2$ were lower than those using the cationic Rh(I)/BINAP complex. Therefore, the hetero-Diels–Alder reaction might be mainly catalyzed by the cationic Rh(I)/BINAP complex and partly catalyzed by small amounts of in situ generated HBF_4.

In conclusion, a rhodium and Brønsted acid catalyzed one-pot cycloisomerization/hetero Diels–Alder reaction of 1,6-enynes with unactivated aldehydes was established under mild conditions. This one-pot catalytic protocol produced a wide variety of annulated dihydropyrans from readily available starting materials in a highly atom economical manner. Future studies will focus on developing an asymmetric variant of this one-pot catalysis.[20]

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[18] (a) Krishnan, K. S.; Kuthanapillil, J. M.; Rajan, R.; Suresh, E.; Radhakrishnan, K. V. *Eur. J. Org. Chem.* **2007**, 5847. (b) Molander, G. A.; Czako, B.; St. Jean, D. J., Jr. *J. Org. Chem.* **2006**, *71*, 1172.

[19] Similar cationic intermediate **C** was proposed in the cationic Pd(II)/bisphosphine complex-catalyzed hetero-Diels–Alder reaction; see ref 4a.

[20] Unfortunately, the reaction of **1a** and **7a** by using the cationic Rh(I)/(*R*)-BINAP catalyst afforded **8aa** with < 5% ee.