ORGANIC LETTERS

2013
Vol. 15, No. 9
2120–2123

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

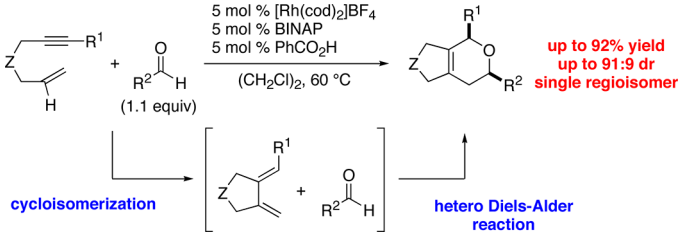
Mana Ishida[†] and Ken Tanaka[*,†,‡]

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan, and JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan

tanaka-k@cc.tuat.ac.jp

Received March 4, 2013

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

[†] Tokyo University of Agriculture and Technology.
[‡] JST, ACT-C.

(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.

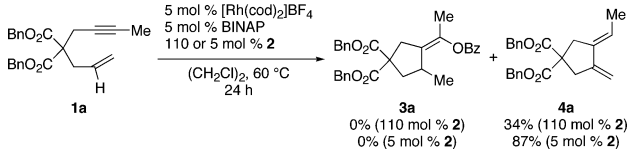
(6) For recent examples of biologically active compounds possessing annulated dihydropyran cores, see: (a) Stokl, J.; Hofferberth, J.; Pritschet, M.; Brummer, M. *J. Chem. Ecol.* **2012**, *38*, 331. (b) Feng, C.-L.; Gong, M.-F.; Zeng, Y.-B.; Dai, H.-F.; Mei, W.-L. *Molecules* **2010**, *15*, 2473.

10.1021/ol4005849
Published on Web 04/22/2013

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).

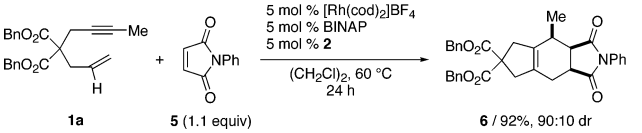
Scheme 1



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).

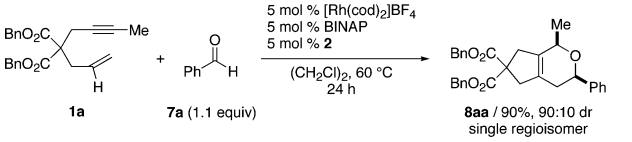
On the other hand, Oi and co-workers reported the hetero-Diels–Alder reaction of unactivated aldehydes and 1,3-dienes under mild reaction conditions ($CHCl_3$, 50 °C) by using a cationic Pd(II)/bisphosphine catalyst.[4a] As the one-pot reaction shown in Scheme 2 employs the

Scheme 2



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

(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.

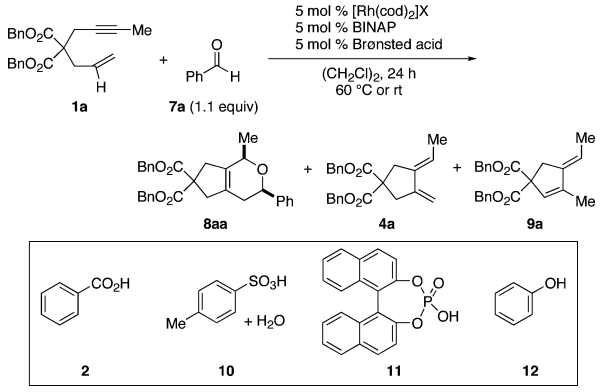
(10) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804.

(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

(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.

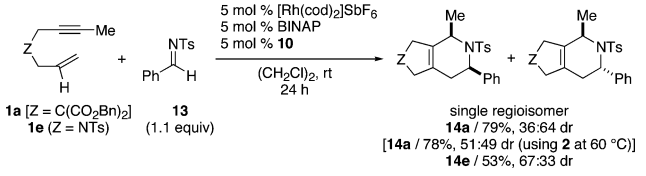
(17) For other examples of the aza-Diels–Alder reaction of unactivated imines and 1,3-dienes, see: (a) Tambar, U. K.; Lee, S. K.; Leighton, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 10248. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.

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

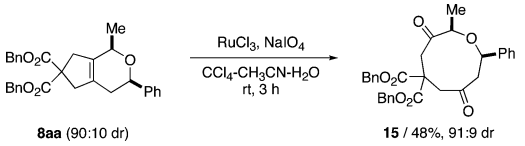
entry	**1**	**7**	**8** / yield[b], dr
1	**1a**	**7a**	**8aa** / 90%, 90:10
2	**1a**	**7b**	**8ab** / 87%, 89:11
3	**1a**	**7c**	**8ac** / 85%, 71:29
4	**1a**	**7d** (R = OMe)	**8ad** / 79%, 82:18
5	**1a**	**7e** (R = CF_3)	**8ae** / 75%, 85:15
6	**1a**	**7f**	**8af** / 70%, 80:20
7	**1a**	**7g** (R = 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-Br$C_6H_4CH_2$)	**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.

Scheme 4



Scheme 5



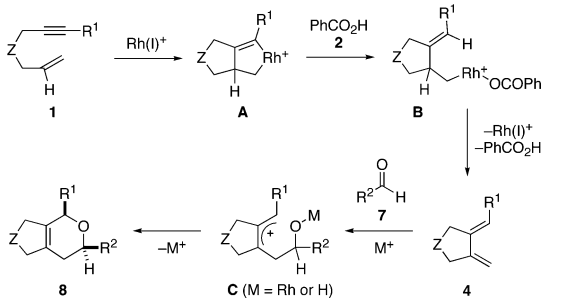
attempted the one-pot cycloisomerization/aza-Diels–Alder reaction by using the cationic Rh(I)/BINAP complex and Brønsted acids. Gratifyingly, 1,6-enynes **1a**,**e** reacted with unactivated imine **13** at rt in the presence of 5 mol % of the cationic Rh(I)/BINAP complex with the more ionic [SbF_6] 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).

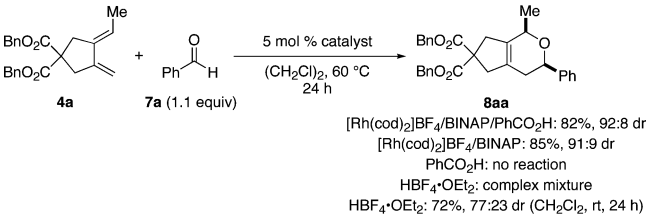
Scheme 6 depicts a plausible mechanism for the present one-pot catalysis. 1,6-Enyne **1** reacts with rhodium affording rhodacyclopentene **A**. The reaction of **A** with benzoic acid (**2**) affords rhodium benzoate **B**. β-Hydride elimination from **B** followed by elimination of benzoic acid affords 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.

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

Scheme 6



Scheme 7



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•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•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]

Acknowledgment. This work was supported partly by Grants-in-Aid for Scientific Research (Nos. 20675002 and 23105512) from MEXT and ACT-C from JST (Japan). We are grateful to Umicore for the generous support in supplying rhodium complexes.

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

(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.

The authors declare no competing financial interest.