Organic Letters

pubs.acs.org/OrgLett

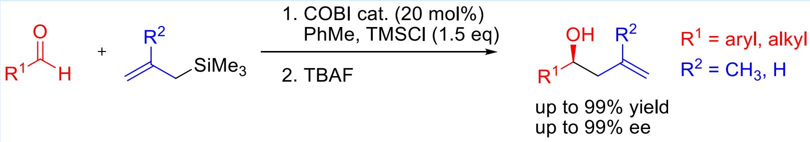
Letter

Highly Enantioselective Allylation Reactions of Aldehydes with Allyltrimethylsilane Catalyzed by a Chiral Oxazaborolidinium Ion

Taehyeong Kim, Hye-Min Jeong, Anipireddy Venkateswarlu, and Do Hyun Ryu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01820

Read Online



ABSTRACT: A highly enantioselective allylation reaction of aldehydes with silyl reagents was developed for the synthesis of a variety of chiral homoallylic alcohols. In the presence of a chiral oxazaborolidinium ion (COBI) catalyst, the reaction proceeded in high yield (up to 99%) with excellent asymmetric induction (up to 99% ee).

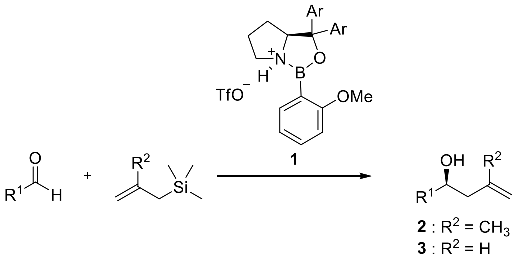
The enantioselective allylation reaction of carbonyl compounds is one of the most powerful carbon−carbon bond-forming methods for the stereoselective construction of optically active homoallylic alcohols, which are valuable and versatile chiral building blocks that, after simple transformation to other functional groups, have been used for the synthesis of numerous biologically active compounds and natural products.[1a−d] Because of their importance, allylation reactions have attracted considerable attention of organic chemists, and notable asymmetric versions of this reaction have been discovered over the past several decades.[1] Several effective asymmetric catalytic methodologies with numerous achiral allyl reagents such as allylstannanes,[2] allyl halides,[3] allyl acetates,[4] and allylboronates[5] have been developed. Among them, allylsilanes are broadly used in modern organic synthesis, benefiting from nontoxicity, air and moisture stability, and easy preparation and handling.[6−8]

The asymmetric allylation of aldehydes with allylsilanes, known as the Hosomi−Sakurai reaction,[9] is typically catalyzed by Lewis acids, and notable catalytic asymmetric versions of the reaction have been reported by several research groups.[6] Since the first catalytic asymmetric reaction with chiral (acyloxy)borane[6a] was reported in 1993, titanium-[6b] and cerium-based[6e] catalysts have provided the corresponding homoallylic alcohols in moderate to good yields with asymmetric induction. Recently, silylium-based Lewis acid organocatalysts[6d,f] were developed by List et al. to catalyze enantioselective allylation reactions with methallyltrimethylsilane and the less nucleophilic allytrimethylsilane. However, many of these reactions were limited to electron-rich aldehydes. Moreover, both the yield and the enantiomeric excess could be further improved by the development of new catalytic enantioselective methods.

Our research group recently reported highly enantioselective nucleophilic addition reactions with silyl reagents catalyzed by chiral oxazaborolidinium ions (COBIs, **1**)[10] as a strong Lewis acid catalyst. In particular, enantioselective cyanosilylation[10a,b] and hydrosilylation[10d] reactions of carbonyl compounds were successfully developed. Inspired by these previous developments, we anticipated that a COBI would be a suitable Lewis acid catalyst for enantioselective allylation reactions of aldehydes with allylsilane reagents. Herein we disclose enantioselective methallylation and allylation reactions of various aldehydes with allylsilanes catalyzed by a COBI (**1**) in high yields (up to 99%) with excellent enantiomeric excess (up to 99%) (Scheme 1).

At the outset of this study, the enantioselective allylation reaction between benzaldehyde and methallyltrimethylsilane was examined in the presence of 20 mol % of COBI catalyst **1** activated by triflic acid. The reaction was carried out at −78 °C

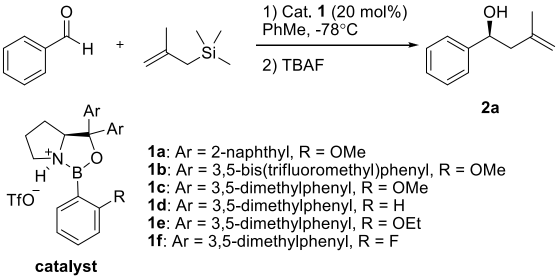
Scheme 1. Catalytic Enantioselective Methallylation and Allylation Reactions of Aldehydes Using COBI Catalyst 1



Received: May 30, 2020

in toluene and was quenched by tetrabutylammonium fluoride (TBAF) solution after completion of the reaction to give chiral homoallylic alcohol **2a** in 89% yield with 74% ee (Table 1, entry 1). Encouraged by this initial attempt, we screened the catalyst structure and found that the catalyst **1c** with 3,5-dimethylphenyl (Ar) and methoxy (R) substituents activated by triflic acid gave the best result with 80% yield and 87% ee (entries 1–6). Because the reaction mixture of catalyst **1b** was heterogeneous at −78 °C, the reaction was performed at −40 °C to provide **2a** in 87% yield with 76% ee (entry 2). In the COBI catalyst system, the 2-methoxyphenyl substituent appeared to be superior to phenyl, 2-ethoxyphenyl, and 2-fluorophenyl substituents in terms of asymmetric induction (entries 3–6). Interestingly, the reaction rate and enantiomeric excess slightly increased with the addition of 20 mol % of trimethylsilyl chloride[11] (TMSCl) (entry 3 vs entry 7). Other additives, such as TMSBr, TMSI, and TMSOTf, gave lower enantiomeric excess compared with TMSCl. From investigating the amount of TMSCl, it emerged that 1.5 equiv of TMSCl provided the best result (entries 7–9). The use of 3 equiv of TMSCl gave lower enantiomeric excess due to probable competing pathways of carbonyl activation through cationic silicon species[12] that resulted in racemic products (entry 9).

Table 1. Optimization of the Asymmetric Methallylation of Benzaldehyde[a]



2a

1a: Ar = 2-naphthyl, R = OMe
1b: Ar = 3,5-bis(trifluoromethyl)phenyl, R = OMe
1c: Ar = 3,5-dimethylphenyl, R = OMe
1d: Ar = 3,5-dimethylphenyl, R = H
1e: Ar = 3,5-dimethylphenyl, R = OEt
1f: Ar = 3,5-dimethylphenyl, R = F

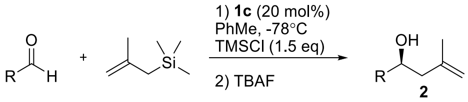
catalyst

entry	cat.	additive (equiv)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	none	13	89	74
2[d]	**1b**	none	1.5	87	76
3	**1c**	none	13	80	87
4	**1d**	none	13	84	43
5	**1e**	none	18	70	56
6	**1f**	none	4	98	71
7	**1c**	TMSCl (0.2)	13	85	89
8	**1c**	TMSCl (1.5)	8	92	94
9	**1c**	TMSCl (3.0)	5	98	40

[a] Unless otherwise noted, the reactions of benzaldehyde (0.2 mmol) with methallyltrimethylsilane (0.3 mmol) were performed in the presence of **1** (20 mol %) in 1.2 mL of toluene at −78 °C. [b] Isolated yield of **2a**. [c] ee of **2a** was determined by chiral HPLC. [d] Reaction was performed at −40 °C.

Using optimized reaction conditions (Table 1, entry 8) for the catalytic enantioselective allylation reaction, we evaluated this methodology with a range of substituted aldehydes (Table 2). Regardless of the electronic and steric properties of substituents on the aldehydes, highly optically active homoallylic alcohols **2** were obtained (entries 2–9). Whereas benzaldehydes substituted with electron-withdrawing groups showed high reactivities (entries 2–5), electron-donating group substitution gave low reactivities and decreased enantiomeric excess in the presence of catalyst **1c**. To overcome this issue, the reactions for electron-donating-group-substituted benzaldehydes were performed in the presence of catalyst **1b** at −40 °C (entries 6–9). Notably, excellent results were obtained with sterically hindered ortho-substituted benzaldehydes (entries 5 and 7). This catalytic system was also successfully applied to reactions of various other aromatic aldehydes such as furyl, naphthyl, and cinnamyl (entries 10–13). However, the strongly Lewis-acidic COBI catalyst was prone to trimerize aliphatic aldehydes. To prevent trimerization, hydrocinnamaldehyde was added to the solution of methallyltrimethylsilane and catalyst **1c** in toluene to provide product **2n** in 92% yield with 78% ee (entry 14). In the presence of TMSCl, chiral homoallylic alcohol **2n** was obtained in 94% yield with 69% ee (entry 15).

Table 2. Asymmetric Methallylation Reactions of Various Aldehydes[a,b]



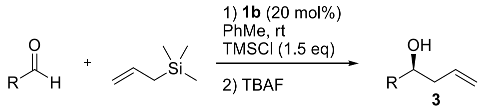
2

entry	2	R	time (h)	yield (%)[c]	ee (%)[d]
1	**2a**	Ph	13	92	94
2	**2b**	4-$NO_2C_6H_4$	2	95	96
3[e]	**2c**	4-$CF_3C_6H_4$	2	96	96
4	**2d**	4-BrC_6H_4	3	98	95
5	**2e**	2-BrC_6H_4	3	94	99
6[f]	**2f**	4-$CH_3C_6H_4$	12	92	79
7[f]	**2g**	2-$CH_3C_6H_4$	6	96	93
8[f]	**2h**	4-$BnOC_6H_4$	18	95	86
9[f]	**2i**	4-$MeOC_6H_4$	18	92	78
10	**2j**	2-furyl	12	86	99
11	**2k**	1-naphthyl	8	99	83
12	**2l**	2-naphthyl	12	98	89
13	**2m**	(*E*)-PhCH=CH	6	72	85
14[g]	**2n**	$PhCH_2CH_2$	0.5	92	78
15	**2n**	$PhCH_2CH_2$	0.5	94	69

[a] Unless otherwise noted, the reactions of aldehydes (0.2 mmol) with methallyltrimethylsilane (0.3 mmol) were performed in the presence of **1c** (20 mol %) and TMSCl (0.3 mmol) in 1.2 mL of toluene at −78 °C. [b] Absolute configurations of **2** shown in Table 2 were assigned by measurements of optical rotation and comparisons with the known substances. For details, see the Supporting Information. [c] Isolated yield of **2**. [d] ee of **2** was determined by chiral HPLC. [e] 1 mmol scale reaction was also performed to give **2c** in 97% yield with 97% ee. [f] Reaction was performed in the presence of **1b** (20 mol %) at −40 °C. [g] Reaction was performed in the absence of TMSCl.

Encouraged by the good results exhibited in Table 2, we applied our new catalytic method to the more challenging enantioselective Hosomi–Sakurai reaction with allyltrimethylsilane to obtain chiral homoallylic alcohols **3** (Table 3). Concentrated conditions and an elevated reaction temperature were needed to complete the reaction due to the low nucleophilicity of allyltrimethylsilane.[13] An evaluation of COBI catalysts with benzaldehyde identified **1b** as the optimal catalyst instead of **1c**. The effect of TMSCl is evident. (See the Supporting Information for details.) As summarized in Table 3, the reactions produced the corresponding chiral homoallylic alcohols **3** in good yields with high enantiomeric excess regardless of the electronic properties and position of substituents on the aromatic ring (entries 1–13). The combination of TMSCl and **1b** increased the yield and enantiomeric excess of **3j** up to 91 and 87%, respectively (entry

Table 3. Asymmetric Allylation Reactions of Various Aromatic Aldehydes[a,b]



entry	3	R	time (h)	yield (%)[c]	ee (%)[d]
1	**3a**	Ph	12	97	94
2[e,f]	**3b**	4-$NO_2C_6H_4$	18	94	98
3[e]	**3c**	4-$CF_3C_6H_4$	5	99	96
4[g]	**3d**	4-BrC_6H_4	8	98	93
5	**3e**	2-BrC_6H_4	8	96	84
6[e]	**3f**	4-FC_6H_4	12	99	96
7[e]	**3g**	3-FC_6H_4	6	95	95
8[e]	**3h**	2-FC_6H_4	6	99	96
9[e]	**3i**	2,4-$Cl_2C_6H_3$	1	94	94
10	**3j**	4-$CH_3C_6H_4$	14	91	87
11[h]	**3j**	4-$CH_3C_6H_4$	18	12	38
12	**3k**	2-$CH_3C_6H_4$	5	94	88
13	**3l**	1-naphthyl	13	97	79

[a] Unless otherwise noted, the reactions of aldehydes (0.2 mmol) with allyltrimethylsilane (0.3 mmol) were performed in the presence of **1b** (20 mol %) and TMSCl (0.3 mmol) in 0.2 mL of toluene at room temperature. [b] Absolute configurations of **3** shown in Table 3 were assigned by measurements of optical rotation and comparisons with known substances. For details, see the Supporting Information. [c] Isolated yield of **3**. [d] ee of **3** was determined by chiral HPLC. [e] 1.2 mL of toluene was used. [f] Reaction was performed at 0 °C. [g] 1 mmol scale reaction was also performed to give **3d** in 96% yield with 93% ee. [h] Reaction was performed in the absence of TMSCl.

10 vs entry 11). To the best of our knowledge, this is first highly enantioselective boron-catalyzed Hosomi−Sakurai reaction with allyltrimethylsilane.

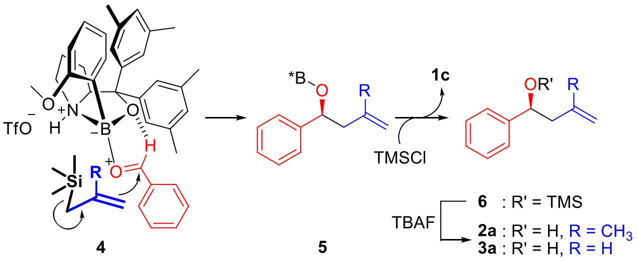


Figure 1. Transition-state model of the asymmetric allylation of benzaldehyde catalyzed by **1c**.

The observed stereochemistry of the catalytic asymmetric allylation reaction catalyzed by COBI **1c** can be rationalized using the transition-state model shown in Figure 1. The mode of coordination of benzaldehyde to **1c** would be the same as has been previously observed in other enantioselective nucleophilic additions.[10e] In the pretransition state assembly **4**, shown in Figure 1, the benzaldehyde group is located above the 3,5-dimethylphenyl group, which effectively shields the *re* face (back) from addition by the allylsilane. Nucleophilic addition of the allylsilane from the *si* face (front) of benzaldehyde leads to intermediate **5**. The apparent function of TMSCl is to increase the reaction rate by regenerating COBI **1c**.[11] After deprotection of the silyl group of compound **6**, chiral homoallylic alcohol **2a** or **3a** is obtained as the major enantiomer. Comparisons of the optical rotation data with literature values confirmed the absolute (*S*) stereochemistry of products **2a** and **3a**.

We presented the first highly enantioselective boron-catalyzed Hosomi−Sakurai reactions of a broad range of aldehydes with allylsilanes. Notably, enantioselective reactions of both electron-rich and electron-poor aldehydes were achieved using the same catalysts. This mild protocol delivers efficient access to a variety of chiral homoallylic alcohols in high yields with excellent asymmetric induction. These studies revealed that TMSCl is an essential additive that increased the reaction rate as a promoter of catalyst regeneration. The absolute configurations of the major products were the same as those predicted by the transition-state model in Figure 1. Further investigations concerning the role of TMSCl in this reaction as well as an extension of the reaction scope are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01820.

General information, experimental procedures, optimization tables of allylation reactions, characterization of products, and full analytical data with spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Do Hyun Ryu − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea;* orcid.org/0000-0001-7615-4661; Email: dhryu@skku.edu

Authors

Taehyeong Kim − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea*
Hye-Min Jeong − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea*
Anipireddy Venkateswarlu − *Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01820

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIP) (nos. NRF-2019R1A2C2087018, 2019R1A4A2001440, and 2019R1H1A2080189).

■ REFERENCES

(1) For selected books and recent reviews on asymmetric allylation reactions, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, Germany, 2004; supplement 2, p 97. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793. (c) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774−7854. (d) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595−5698. For catalytic asymmetric allylation of imines, see: (e) Momiyama, N.; Nishimoto, H.; Terada, M. *Org. Lett.* **2011**, *13*, 2126−2129. (f) Kang, K.-T.; Park, S. H.; Ryu, D. H. *Org. Lett.* **2019**, *21*, 6679−6683.

(2) (a) Li, Z.; Plancq, B.; Ollevier, T. *Chem. - Eur. J.* **2012**, *18*, 3144−3147. (b) Wang, T.; Hao, X.-Q.; Huang, J.-J.; Niu, J.-L.; Gong, J.-F.; Song, M.-P. *J. Org. Chem.* **2013**, *78*, 8712−8721.

(3) (a) Thorat, P. B.; Goswami, S. V.; Bhusare, S. R. *Tetrahedron: Asymmetry* **2013**, *24*, 1324−1330. (b) Chen, R.-Y.; Dhondge, A. P.; Lee, G.-H.; Chen, C. *Adv. Synth. Catal.* **2015**, *357*, 961−966. (c) Xiong, Y.; Zhang, G. *Org. Lett.* **2016**, *18*, 5094−5097. (d) Guo, R.; Yang, Q.; Tian, Q.; Zhang, G. *Sci. Rep.* **2017**, *7*, 1−12.

(4) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891−14899. (b) Cabrera, J. M.; Tauber, J.; Zhang, W.; Xiang, M.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9392−9395.

(5) (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716−2722. (b) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 11497−11500. (c) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303−320. (d) Clot-Almenara, L.; Rodrìguez-Escrich, C.; Osorio-Planes, L.; Pericàs, M. A. *ACS Catal.* **2016**, *6*, 7647−7651. (e) Gao, S.; Chen, M. *Org. Lett.* **2018**, *20*, 6174−6177. (f) Sedgwick, D. M.; Grayson, M. N.; Fustero, S.; Barrio, P. *Synthesis* **2018**, *50*, 1935−1957.

(6) For Lewis-acid-catalyzed asymmetric allylation of aldehydes with allylsilanes, see: (a) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495. (b) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363−2365. (c) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701−3703. (d) Mahlau, M.; Garcìa-Garcìa, P.; List, B. *Chem. - Eur. J.* **2012**, *18*, 16283−16287. (e) Zhao, S.; Zhang, X.; Zhang, Y.; Yang, H.; Huang, Y.; Zhang, K.; Du, T. *New J. Chem.* **2015**, *39*, 7734−7737. (f) Kaib, P. S. J.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 13200−13203. (g) Yanagisawa, A.; Yang, N.; Bamba, K. *Eur. J. Org. Chem.* **2017**, *2017*, 6614−6618. (h) Tomifuji, R.; Masuda, S.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2019**, *21*, 3834−3837.

(7) For Lewis-base-catalyzed asymmetric allylation of aldehydes with allylsilanes, see: (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021−12022. (b) Bai, B.; Shen, L.; Ren, J.; Zhu, H. J. *Adv. Synth. Catal.* **2012**, *354*, 354−358. (c) Ogasawara, M.; Kotani, S.; Nakajima, H.; Furusho, H.; Miyasaka, M.; Shimoda, Y.; Wu, W.-Y.; Sugiura, M.; Takahashi, T.; Nakajima, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13798−13802. (d) Staniland, S.; Adams, R. W.; McDouall, J. J. W.; Maffucci, I.; Contini, A.; Grainger, D. M.; Turner, N. J.; Clayden, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 10755−70759. (e) Reep, C.; Morgante, P.; Peverati, R.; Takenaka, N. *Org. Lett.* **2018**, *20*, 5757−5761.

(8) For Brønsted-acid-catalyzed asymmetric allylation of aldehydes with allylsilanes, see: Sai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 7091−7094.

(9) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295−1298. (b) *Name Reactions for Homologations*; Li, J. J., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; pp 539−575.

(10) (a) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106−8107. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384−5387. (c) Senapati, B. K.; Gao, L.; Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 5088−5091. (d) Kang, B. C.; Shin, S. H.; Yun, J.; Ryu, D. H. *Org. Lett.* **2017**, *19*, 6316−6319. (e) Shim, S. Y.; Ryu, D. H. *Acc. Chem. Res.* **2019**, *52*, 2349−2360.

(11) (a) Belokon, Y. N.; Chusov, D.; Borkin, D. A.; Yashkina, L. V.; Bolotov, P.; Skrupskaya, T.; North, M. *Tetrahedron: Asymmetry* **2008**, *19*, 459−466. (b) Barroso, S.; Adão, P.; Coelho, A. M.; Pessoa, J. C.; Martins, A. M. *J. Mol. Catal. A: Chem.* **2016**, *412*, 107−116.

(12) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326. (b) Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, *3*, 3561−3564. (c) Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046−10057.

(13) (a) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961. (b) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.