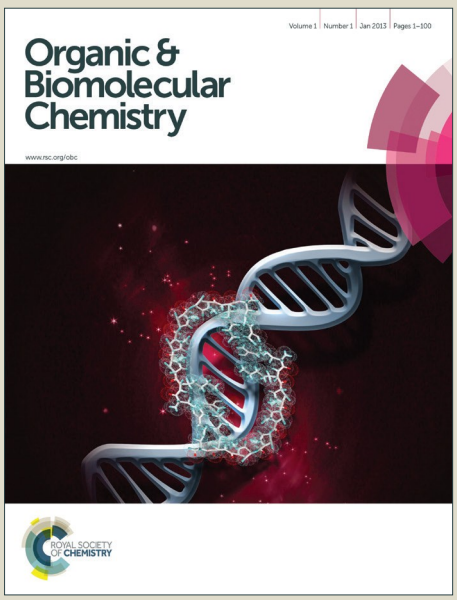
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

PAPER

Highly Enantioselective Catalytic 1, 3-Dipolar Cycloadditions of α-Alkyl Diazoacetates: Efficient Synthesis of Functionalized 2-Pyrazolines

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Sung Il Lee,[a,b] Ka Eun Kim,[b] Geum-Sook Hwang[a,*] and Do Hyun Ryu[b,*]

Highly enantioselective 1,3-dipolar cycloaddition reactions of α-substituted diazoacetates are accomplished by catalysis of the chiral oxazaborolidinium ion. Functionalized 2-pyrazolines are synthesized in high to excellent enantiomeric ratios (up to >99:1). The synthetic utility of 2-pyrazoline was expanded via preparation of 2,4-diamino ester compounds bearing a chiral quaternary carbon center.

Introduction

Pyrazolines, five-membered heterocycles with two continuous nitrogen atoms and one double bond, have received considerable attention from synthetic and medicinal chemists because of their diverse range of biological properties, including antimicrobial, antiviral, anti-inflammatory, antidepressant, and anticancer activities[1]. Pyrazoline derivatives can also be used as chiral building blocks for the synthesis of more complex nitrogen-containing molecules[2].

The chiral Lewis acid-catalyzed 1,3-dipolar cycloaddition reaction between diazo compounds and olefinic dipolarophiles is a powerful method for the stereoselective synthesis of pyrazolines. Since Kanemasa's first report of chiral Lewis acid-catalyzed enantioselective 1,3-dipolar cycloaddition in 2000[3], various synthetic strategies and chiral catalysts have been developed. The Maruoka research group developed a Ti(IV)-BINOLate-catalyzed cycloaddition reaction of α-substituted acroleins and ethyl diazoacetate[4]. In 2009, our research group extended the substrate scope to α,β-disubstituted acroleins with an oxazaborolidinium catalyst[5]. A novel pyrazolidinone imide auxiliary was introduced to dipolarophiles by Sibi et al.[6]. Simple diazoacetates[4-6] have mainly been used as 1,3-dipoles, although various α-substituted diazoacetates have been applied for useful asymmetric reactions[7] catalyzed by Lewis acids. This is likely because other reaction types would be competitive, such as cyclopropanation[7d,8] or C-H insertion[7b,c] reactions. Highly enantioselective catalytic 1,3-dipolar cycloaddition reactions of α-substituted diazoacetates have not been reported to date. However, Suga and co-workers[8] reported a chiral nickel(II)-catalyzed asymmetric cycloaddition reaction of benzyl-substituted diazoacetate with moderate enantioselectivity (77%).

The chiral oxazaborolidinium ion **1**, which is prepared from the corresponding oxazaborolidine by protonation with trifluoromethanesulfonic acid, behaves as a powerful Lewis acid. It has been shown to be a suitable catalyst for diazo compounds involving various asymmetric reactions (Fig. 1)[5,7a-d]. In addition, there is substantial evidence for the formation of a complex between oxazaborolidinium ions and α,β-unsaturated carbonyl compounds[7b,9a,10,11].

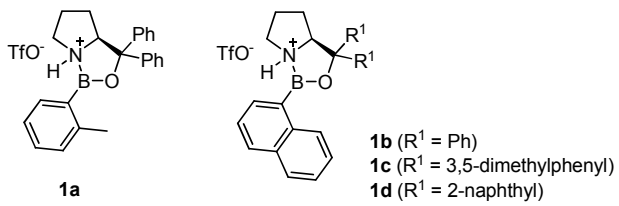
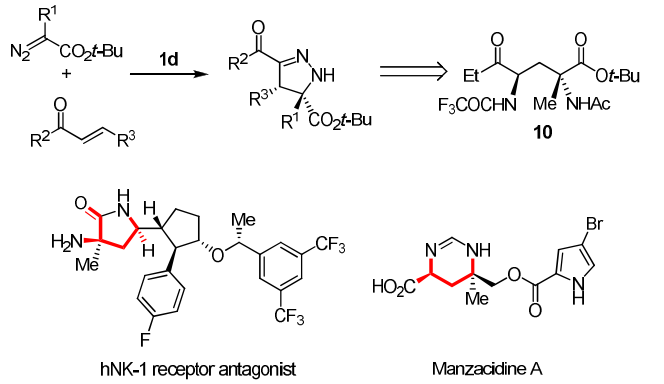


Fig. 1 Structures of the oxazaborolidinium ions.

We anticipated that the oxazaborolidinium ion would be a suitable Lewis acid catalyst for the enantioselective 1,3-dipolar cycloaddition of α-substituted diazoacetates. In this report, we introduce a highly efficient synthetic methodology for optically active 2-pyrazoline rings. The utility of pyrazoline rings is demonstrated by synthesis of a quaternary carbon-bearing 2,4-diamino ester, which has high potential as a chiral building block for natural products and drug candidates (Scheme 1)[12].

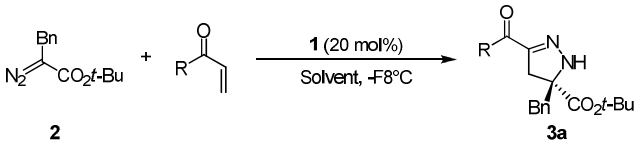


Scheme 1 Asymmetric 1,3-dipolar cycloaddition reaction and potential application to 2,4-diamino carbonyl compound synthesis.

Results and discussion

The investigation was performed by screening various *α,β*-unsaturated carbonyl compounds in the presence of *tert*-butyl benzyldiazoacetate (**2**) and 20 mol% chiral oxazaborolidinium ions 1 (Table 1). Acrolein (R=H) did not yield the desired 2-pyrazoline (entry 1). When the reaction was carried out with acrylic acid (R=OH), the desired cycloadduct was isolated in low yield (31 %), although the product was a racemic mixture (entry 2). The 2-pyrazoline ring was obtained in considerable yield and an enantiomeric ratio with the ester dipolarophile (entries 3 and 4). Unfortunately, further attempts to increase enantioselectivity were not satisfactory. The focus was then shifted to *α,β*-enone dipolarophile. In the presence of 20 mol% oxazaborolidinium ion **1a**, which was prepared by precursor activation with triflic acid, a 1,3-dipolar cycloaddition reaction was rapidly carried out to afford 2-pyrazoline in high yield with a moderate enantiomeric ratio (entry 5). Various substituents at the boron center were examined. We found that oxazaborolidinium ion catalyst **1b** with a 1-naphthyl substituent at the boron center produced a cycloaddition product with promising stereoselectivity without a decrease in yield (entry 6). Next, we investigated the effect of solvent with catalyst **1b** and found that toluene produced the best enantioselectivity and yield (entries 6-8). To further improve enantioselectivity, a sterically bulkier diaryl group was introduced. The 3,5-dimethylphenyl-substituted oxazaborolidinium ion (**1c**) furnished 2-pyrazoline in a 90:10 enantiomeric ratio (entry 9). Finally, high enantioselectivity was obtained using the 2-naphthyl-substituted oxazaborolidinium catalyst **1d** (entry 10).

Table 1 Reaction optimization for the oxazaborolidinium ion-catalyzed asymmetric 1,3-dipolar cycloaddition reaction[a]



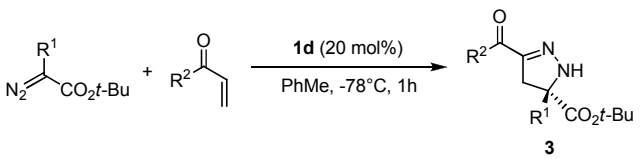
2 **3a**

Entry	R	Cat.	Solvent	Yield (%)[b]	e.r[c]
1	H	**1d**	PhMe	0	-
2	OH	**1b**	CH_2Cl_2	31	0
3	OMe	**1b**	CH_2Cl_2	20	73:27
4	OCH_2CF_3	**1b**	CH_2Cl_2	97	77:23
5	Et	**1a**	CH_2Cl_2	91	72:28
6	Et	**1b**	CH_2Cl_2	93	76:24
7	Et	**1b**	EtCN	99	54:46
8	Et	**1b**	PhMe	98	88:12
9	Et	**1c**	PhMe	97	90:10
10	Et	**1d**	PhMe	85	94.5:5.5

[a] Reaction conditions: α,β-unsaturated carbonyl compound (1.2 equiv.), **2** (0.25 mmol), **1** (20 mol%), -78ºC, solvent (1 ml), 1h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

After optimization of the asymmetric 1,3-dipolar cycloaddition reaction, the scope of this methodology was investigated with various *α*-substituted diazoacetates and enones. Regardless of the structure of the *α*-substituent of the *tert*-butyl diazoacetate, the cycloaddition reaction was carried out in a highly stereoselective manner with ethyl vinyl ketone and methyl vinyl ketone. The corresponding 2-pyrazolines were obtained in good to excellent yield (Table 2).

Table 2 Substrate scope of the chiral oxazaborolidinium ion-catalyzed 1,3-dipolar cycloaddition reaction[a]



3

Entry		R^1	R^2	Yield (%)[b]	e.r[c]
1	**a**	Bn	Et	85	94.5:5.5
2	**b**	Allyl	Et	90	93:7
3	**c**	n-Hex	Et	96	90:10
4[d,e]	**d**	Me	Et	97	91:9
5	**e**	Bn	Me	82	95.5:4.5
6	**f**	Allyl	Me	74	96.5:3.5
7	**g**	n-Hex	Me	90	94:6

[a] Reaction conditions: enone (1.2 equiv.), *tert*-butyl alkyl diazoacetate (0.25 mmol), **1d** (20 mol%), -78ºC, toluene (1 ml), 1h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 8.34 mmol of diazoacetate and 10 mol% of **1d** used. [e] The absolute configuration was determined to be (*S*) (see the Supporting Information).

To further investigate the substrate scope of the present catalytic system, we performed the catalytic asymmetric 1,3-dipolar cycloaddition reaction with a range of *β*-substituted enones in order to obtain highly functionalized chiral 2-

pyrazolines containing two stereogenic centers (Table 3). Interestingly, the chiral oxazaborolidinium ion **1d**-catalyzed 1,3-dipolar cycloaddition reaction of *β*-substituted enones proceeded in a highly *syn*-stereoselective manner. Only *syn* product **3** was detected on 1H NMR spectral analysis. Remarkably, good results were obtained with (*E*)-pent-3-en-2-one (entries 1−6). However, sterically hindered R^1 substituents such as isopropyl groups caused significant reductions in yield and product enantioselectivity (entry 7). High chemical yields and enantioselectivities were attained using (*E*)-hex-3-en-2-one or (*E*)-4-phenylbut-3-en-2-one as dipolarophiles (entries 8-13). The use of (*E*)-4-cyclohexylbut-3-en-2-one or (*E*)-5-methylhex-3-en-2-one containing bulkier substituents at the *β*-position of the enone provided corresponding chiral 2-pyrazolines with moderate yield and enantioselectivity (entries 14 and 15).

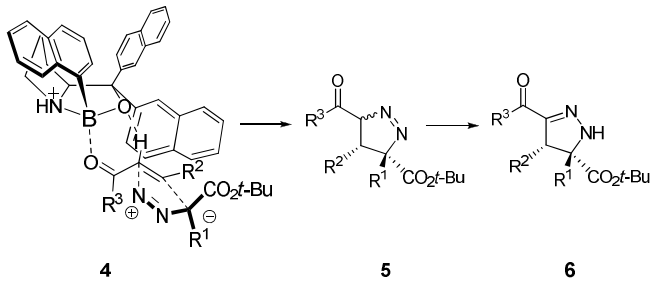
Table 3 Substrate scope of the chiral oxazaborolidinium ion-catalyzed 1,3-dipolar cycloaddition reaction: β-substituted enones[a]

3

Entry		R^1	R^2	T (ºC)	Yield (%)[b]	e.r[c]
1	**h**	Bn	Me	-40	90	>99:1
2	**i**	Allyl	Me	-40	92	98.5:1.5
3	**j**	n-Hex	Me	-40	92	98.5:1.5
4	**k**	4-BrBn	Me	-40	91	98.5:1.5
5[d]	**l**	Me	Me	-40	85	97:3
6	**m**	Et	Me	-40	74	97.5:2.5
7	**n**	i-Pr	Me	-20	54	91.5:8.5
8	**o**	Bn	Et	-40	96	95.5:4.5
9	**p**	Allyl	Et	-40	86	93:7
10	**q**	n-Hex	Et	-40	92	94.5:5.5
11	**r**	Bn	Ph	-20	73	93:7
12	**s**	Allyl	Ph	-20	80	94:6
13	**t**	n-Hex	Ph	-20	71	95:5
14	**u**	Bn	c-Hex	-20	46	86:14
15	**v**	Bn	i-Pr	-20	82	72:28

[a] Reaction conditions: enone (1.2 equiv.), *tert*-butyl alkyl diazoacetate (0.25 mmol), **1d** (20 mol%), toluene (1 ml), 1h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The relative stereostructure was determined to be *syn* by 1D NOE NMR spectra (see the Supporting Information).

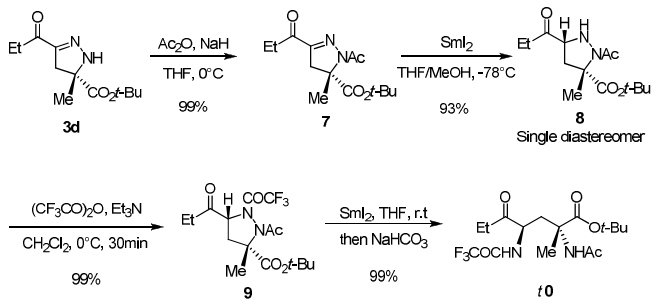
The transition state model proposed in Fig. 2 explains the observed stereoselectivity of the oxazaborolidinium ion-catalyzed asymmetric 1,3-dipolar cycloaddition reaction. The mode of alkenone coordination to **1d** is the same as that previously shown for enantioselective Diels−Alder[10e], Michael[10b], and C−H functionalization[7b]. In the transition state complex (**4** in Fig. 2), the electron-deficient *α*,*β*-enone subunit attracts the 2-naphthyl group through a π−π donor−acceptor interaction, and the enone double bond is situated above the 2-naphthyl group. This fixed structure shields the rear of the *α*,*β*-unsaturated enone from approach by the *α*-alkyl diazoacetate. The dipole-dipole interaction between two polar carbonyl groups[7c,d] and steric repulsion between R^1 and R^2 elevate the transition state energy so the *tert*-butyl ester group is positioned away from the ketone group. The oxazaborolidinium ion-catalyzed asymmetric cycloaddition reaction leads to (4*S*,5*S*)-pyrazoline **6** as the major enantiomer after 1,3-proton migration of relatively unstable 1-pyrazoline **5**.



4 5 6

Fig. 2 Transition state model for oxazaborolidinium catalyzed asymmetric 1,3-dipolar cycloaddition reaction of enones.

To highlight the chemical utility of 2-pyrazolines, this catalytic asymmetric cycloaddition reaction was applied to construction of an optically active diamino carbonyl compound. After acetylation of 2-pyrazoline **3d**, the imine bond adjacent to the ketone moiety was chemoselectively reduced by samarium diiodide to give **8** with complete diastereoselectivity. The relative stereostructure of **8** was unambiguously determined by 1D NOE NMR spectral analysis. The 1D NOE NMR spectra of **8** revealed correlations between the *α*-proton of the ketone and the *α*-methyl group of the *tert*-butyl ester. Trifluoroacetylation of the resulting pyrazolidine ring was readily executed in the presence of trifluoroacetic anhydride. Finally, the electron-deficient N-N single bond of **9** was rapidly cleaved by SmI_2 to afford 2,4-diamino carbonyl compound **10** bearing a quaternary carbon center in 99% yield (Scheme 2)[13].



Scheme 2 Synthesis of 2,4-diamino carbonyl compound **10**

Conclusion

This is the first example of a highly enantiocontrolled catalytic 1,3-dipolar cycloaddition reaction of *α*-substituted diazoacetates into vinyl ketones or *β*-substituted vinyl ketones. Functionalized 2-pyrazolines are synthesized in high yield and enantioselectivity. The resulting 2-pyrazoline can be easily

converted into a 2,4-diamino carbonyl compound that bears a chiral quaternary carbon center. These enantiomerically enriched pyrazolines and diamino esters may be useful chiral building blocks for synthesis of natural products or drug candidates containing two nitrogen atoms.

Experimental

Preparation of (*S*)-oxazaborolidine solution (0.05M in Toluene)

A 50 ml, one-necked, round-bottomed flask and a Dean-Stark apparatus (containing ca. 10 g of 4 Å molecular sieves) fitted on top with a reflux condenser and a nitrogen inlet adaptor were charged with (*S*)-(-)-*α*,*α*-di-2-naphthyl-2-pyrrolidinemethanol (0.707 g, 2.0 mmol), tri-1-naphthylboroxine (0.308 g, 0.67 mmol), and 35 ml of toluene. The resulting mixture was heated to reflux (bath temperature 145 ºC). After 3 h, the reaction mixture was cooled to ca. 60 ºC, and the Dean-Stark apparatus and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated to a volume of ca. 5 ml by distillation (air-cooling). This distillation protocol was repeated three times by re-charging with 20 ml of toluene. The solution was then allowed to cool to room temperature, and the distillation head was quickly replaced with a vacuum adaptor. Concentration in *vacuo* (ca. 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil. Oxazaborolidine was dissolved in 40 ml of PhMe and stored at -40 ºC.

General Procedure for the Enantioselective Synthesis of 2-Pyrazolines (Table 2)

A freshly prepared solution of trifluoromethanesulfonic acid in PhMe (0.20 M solution, 0.25 mL, 0.05 mmol) was added dropwise to an oxazaborolidine solution (0.05M for oxazaborolidine in PhMe, 1.2 ml, 0.06 mmol for oxazaborolidine) at -40 ºC under nitrogen. After stirring for 20 min at -40 ºC, a pale yellow homogeneous solution of oxazaborolidinium catalyst was obtained. Enone (0.30 mmol) was then added in one portion to the solution of oxazaborolidinium catalyst at -78 ºC. After 20 min of stirring, diazoacetate (0.25 mmol) was added in one portion. TLC was used to monitor the reaction. After completion, the reaction was quenched at -78 ºC by adding Et_3N (14 µl, 0.1 mmol). The reaction mixture was directly purified by flash chromatography on silica gel by eluting with ethyl acetate/hexanes (v/v, 1/9) to give a 2-pyrazoline product.

General Procedure for the Enantioselective Synthesis of 2-Pyrazolines (Table 3)

A freshly prepared solution of trifluoromethanesulfonic acid in PhMe (0.20M solution, 0.25 mL, 0.05 mmol) was added dropwise to an oxazaborolidine solution (0.05M for oxazaborolidine in PhMe, 1.2 ml, 0.06 mmol for oxazaborolidine) at -40 ºC or -20 ºC under nitrogen. After stirring for 20 min (10 min at -20 ºC), a pale yellow homogeneous solution of oxazaborolidinium catalyst was obtained. Enone (0.30 mmol) was then added in one portion to the solution of oxazaborolidinium catalyst. After 10 min of stirring, diazoacetate (0.25 mmol) was added in one portion. TLC was used to monitor the reaction. After completion, the reaction was quenched by adding Et_3N (14 µl, 0.1 mmol). The reaction mixture was directly purified by flash chromatography on silica gel by eluting with ethyl acetate/hexanes (v/v, 1/9) to give a 2-pyrazoline product.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(NRF-2013R1A1A2059838) and the Ministry of Science, ICT & Future Planning(NRF-2013R1A1A2073207).

Notes and references

[a] Western Seoul Center, Korea Basic Science Institute, Seoul 120-140 Korea, E-mail: gshwang@kbsi.re.kr.
[b] Department of Chemistry, Sungkyunkwan University, Suwon 440-746 Korea, E-mail: dhryu@skku.edu.
†Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all products. See DOI: 10.1039/b000000x/

1 A. Marella, M. R. Ali, M. T. Alam, R. Saha, O. Tanwar, M. Akhter, M. Shaquiquzzaman and M. M. Alam, *Mini-Rev. Med. Chem*. 2013, **13**, 921 and references therein.
2 (a) T. Hashimoto, K. Maruoka, *Org. Bioorg. Chem*. 2008, **6**, 829; (b) F. M. Guerra, M. R. Mish, E. M. Carreira, *Org. Lett*. 2000, **2**, 4265; (c) G. A. Whitlock, E. M. Carreira, *J. Org. Chem*. 1997, **62**, 7916.
3 S. Kanemasa, T. Kanai, *J. Am. Chem. Soc*. 2000, **122**, 10710.
4 T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc*. 2006, **128**, 2174.
5 L. Gao, G.-S. Hwang, M. Y. Lee, D. H. Ryu, *Chem. Commun*. 2009, 5460.
6 M. P. Sibi, L. M. Stanley, T. Soeta, *Org. Lett*. 2007, **9**, 1553.
7 (a) L. Gao, B. C. Kang, D. H. Ryu, *J. Am. Chem. Soc*. 2013, **135**, 14556; (b) S. I. Lee, G.-S. Hwang, D. H. Ryu. *J. Am. Chem. Soc*. 2013, **135**, 7126; (c) L. Gao, B. C. Kang, G.-S. Hwang, D. H. Ryu, *Angew. Chem. Int. Ed*. 2012, **51**, 8322; (d) L. Gao, G.-S. Hwang, D. H. Ryu, *J. Am. Chem. Soc*. 2011, **133**, 20708; (e) W. Li, J. Wang, X. Hu, K. Shen, W. Wang, Y. Chu, L. Lin, X. Liu, X. Feng, *J. Am. Chem. Soc*. 2010, **132**, 8532; (f) W. Li, X. Liu, X. Hao, Y. Cai, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* 2012, **51**, 8644; (g) W. Li, X. Liu, F. Tan, X. Hao, J. Zheng, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* 2013, **52**, 10883; (h) T. Hashimoto, H. Miyamoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc*. 2009, **131**, 11280; (i) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc*. 2011, **133**, 8834.
8 H. Suga, Y. Furihata, A. Sakamoto, K. Itoh, Y. Okumura, T. Tsuchida, A. Kakehi, T. Baba, *J. Org. Chem*. 2011, **76**, 7377.

9 For selected reviews on cationic boron chiral catalyst, see: (a) E. J. Corey, *Angew. Chem. Int. Ed*. 2009, **48**, 2100; (b) T. S. De Vries, A. Prokofjevs, E. Vedejs, *Chem. Rev*. 2012, **112**, 4246.

10 (a) D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc*. 2007, **129**, 1498; (b) D. Liu, S. Hong, E. J. Corey, *J. Am. Chem. Soc*. 2006, **128**, 8160; (c) D. H. Ryu, G. Zhou, E. J. Corey, *Org. Lett*. 2005, **7**, 1633; (d) D. H. Ryu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc*. 2004, **126**, 4800; (e) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc*., 2003, **125**, 6388; (f) D. H. Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc*. 2002, **124**, 9992.

11 (a) S. H. Jung, G.-S. Hwang, S. I. Lee, D. H. Ryu, *J. Org. Chem*. 2012, **77**, 2513; (b) G. Zhou, E. J. Corey, *J. Am. Chem. Soc*. 2005, **127**, 11958. (c) Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc*. 2006, **128**, 6130.

12 (a) J. Kobayashi, F. Kanda, M. Ishibashi, H. Shigemori, *J. Org. Chem*. 1991, **56**, 4574; (b) K. R. Campos, A. Klapars, Y. Kohmura, D. Pollard, H. Ishibashi, S. Kato, A. Takezawa, J. H. Waldman, D. J. Wallace, C.-y, Chen, N. Yasuda, *Org. Lett.* 2011, **13**, 1004.

13 (a) T. Hashimoto, Y. Takiguchi, K. Maruoka, *J. Am. Chem. Soc*. 2013, **135**, 11473; (b) K. Tran, P. J. Lombardi, J. L. Leighton, *Org. Lett.* 2008, **10**, 3165-3167.