COMMUNICATION

DOI: 10.1002/cjoc.201400186

Fc-PIP Catalyzed Asymmetric Synthesis of *cis*-2,3-Dihydrobenzofurans†

Shanshan Jiang, Bin Hu, Xingxin Yu,* and Weiping Deng*

Shanghai Key Laboratory of New Drug Design, *School of Pharmacy*,
East China University of Science and Technology, *Shanghai 200237*, *China*

A highly enantioselective intramolecular Michael addition-Lactonization domino reaction of a range of enon acids catalyzed by nuleophilic organocatalyst (Fc-PIP) was developed, furnishing *cis*-2,3-dihydrobenzofuran derivatives with excellent enantioselecitivities (94%—98% *ee*) and good diastereoselectivities (up to 99/1).

Keywords Michael addition-Lactonization, dihydrobenzofuran, Fc-PIP

Introduction

Chiral 2,3-dihydrobenzofuran equivalents have been found extensively as crucial motifs in numerous biologically active natural products and pharmaceuticals,[1-3] such as macrocyclic spermine alkaloid,[1a] (+)-lithospermic acid,[1b] aperindine[1c] and neolignan natural products (+)-conocarpan[1d] (Figure 1). These molecules exhibited potent biological acitivities,[2,3] including hypotensive,[2a,2b] anti-HIV,[2c] insecticidal,[2e] antifungal[2f] properties, *etc.*

Among the developed asymmetric catalytic methodologies for the construction of chiral 2,3-dihydrobenzofuran scaffolds, C—H insertion process of aryldiazoacetates catalyzed by Rh(II) complexes, developed by Davies,[4] Fukuyama,[1a,5] and Hashimoto[6] was one of the most significant routes, which achieved moderate to good enantioselectivities (up to 99% *ee*). Furthermore, organocatalytic cascade reaction developed by Jørgensen and co-workers[7] employing prolinol derivative as the catalyst offered an easy entry to prepare optically active 2,3-dihydrobenzofurans with excellent enantioselection, in spite of involving relatively intricate reaction process. Recently, tetramisole was employed to the intramolecular Michael addition-Lactonization reaction of an array of enone acids by Smith[8a] (introduced by Birman[8b] *et al.*), giving *cis*-2,3-disubstitute-2,3-dihydrobenzofurans with good enantiselectivities and excellent diastereoselectivities, which exhibited several merits for organocatalytic method. The method toward enolization *in situ* generated from carboxylic acids promoted by nucleophilic catalysts was established by Romo and co-workers precedently.[9] In 2013, Zhou[9j] reported intramolecular Michael addition of keto-enones with bifunctional primary amine-squaramide catalyst in excellent yields with good to excellent diastereo- and enantioselectivities.

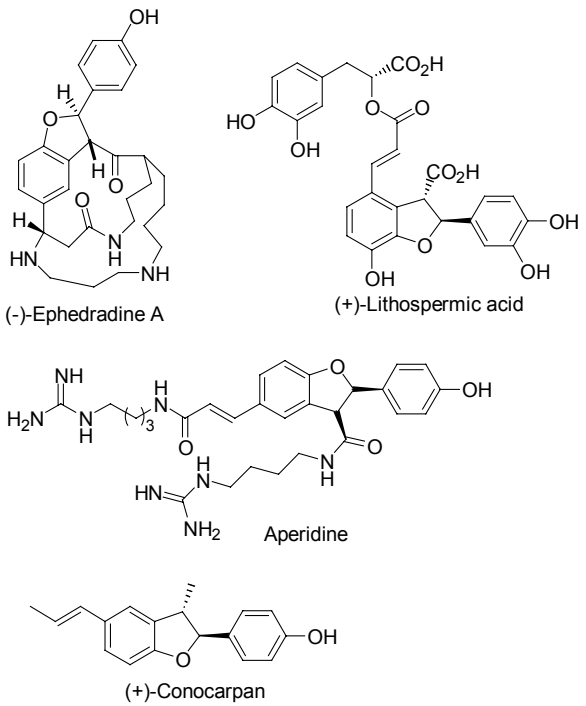


Figure 1 Natural products containing chiral 2,3-dihydrobenzofuran motifs.

In the course of developing new organocatalytic system, we have demonstrated that our own amidine-ferrocene hydrid (Fc-PIP) displayed exciting enantioselectivities in the Kinetic Resolution (KR) of arylalkyl carbinols (*S* up to 1892),[10a] bulkyl (hetero)arylalkyl

* E-mail: xxyu@ecust.edu.cn, weiping_deng@ecust.edu.cn; Tel.: 0086-021-64252431; Fax: 0086-021-64252431
Received March 26, 2014; accepted May 2, 2014; published online June 13, 2014.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201400186 or from the author.
† Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai on the occasion of their 90th birthdays.

CHINESE JOURNAL OF CHEMISTRY

carbinols furnishing the unreacted alcohols with more than 99% *ee* and good yields for all tested substrates,[10b] and the challenging arylalkenyl carbinols (*S* up to 24).[10c] In this paper, Michael addition-Lactonization tandem reaction of enone acids catalyzed by Fc-PIP was reported, furnishing *cis*-2,3-dihydrobenzofuran with excellent *ee* (94% to 98%) and good diastereoselectivities (*dr* up to 99/1).

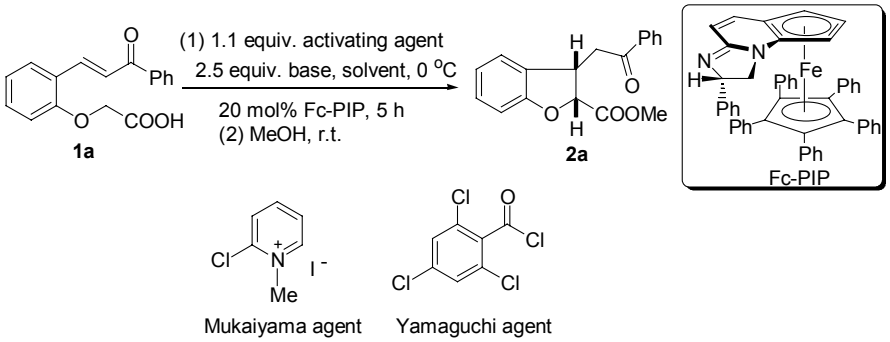
Results and Discussion

Since the significance of the combination of activating agents and catalyst in such transformations mentioned by Romo[9f] and Smith,[8a] our studies began by exploring the influence of activating agents on this process. Enone acid **1a** treated as the model substrate was subjected to the Michael addition-Lactonization reaction using Fc-PIP as the catalyst in $CHCl_3$ at 0 ℃, and a range of commercially available activating agents, which were frequently applicable to the preparation of mixed anhydride and regarded as condensation reagents were investigated. Mukaiyama agent gave the desired product **2a** with good enantioselectivity and diastereoselectivity (Table 1, Entry 1). Interestingly, the use of Yamaguchi agent, EDCI, DCC and pivaloyl chloride led to lower diastereoselectivities, but better enantioselectivities (Entries 2—5), so it was clear that pivaloyl chloride was relatively superior to others with regard to the enantioselctivity.

Further screening of solvents showed that pivaloyl chloride allowed the synthesis of **2a** with improved *dr* value of 91/9 and no loss in the enantioselectivity by switching $CHCl_3$ to CH_2Cl_2 (Table 1, Entry 11). Other solvents displayed low enatioselectivities or yields, although the diastereoselectivities were improved compared with that of $CHCl_3$ (Entries 6—10).

In addition, we also examined the influence of bases on the reaction. Et_3N proved to be inferior to DIPEA in terms of both stereoselectivity and yield (Table 1, Entries 11 vs. 12). The other two proton scavengers, proton sponge and lutidine, as well as weakly

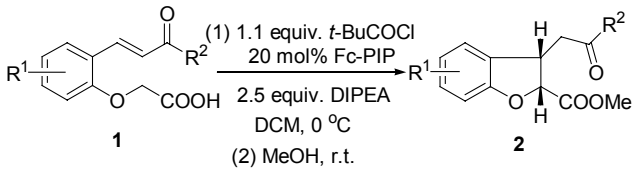
Table 1 Optimization of the reaction conditions

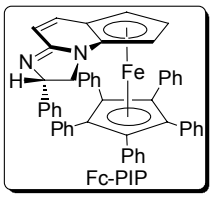


Entry	Activating agent	Solvent	Base	Yield[a]	*dr*[b]	*ee*[c]
1	Mukaiyama agent	$CHCl_3$	DIPEA	64%	94/6	90%
2	Yamaguchi agent	$CHCl_3$	DIPEA	44%	66/34	97%
3	EDCI	$CHCl_3$	DIPEA	47%	80/20	93%
4	DCC	$CHCl_3$	DIPEA	54%	68/32	97%
5	*t*-BuCOCl	$CHCl_3$	DIPEA	57%	66/34	98%
6	*t*-BuCOCl	PhMe	DIPEA	27%	90/10	95%
7	*t*-BuCOCl	THF	DIPEA	61%	89/11	86%
8	*t*-BuCOCl	CH_3CN	DIPEA	64%	96/4	94%
9	*t*-BuCOCl	DMF	DIPEA	47%	90/10	95%
10	*t*-BuCOCl	$ClCH_2CH_2Cl$	DIPEA	51%	72/28	95%
11	*t*-BuCOCl	CH_2Cl_2	DIPEA	54%	91/9	98%
12	*t*-BuCOCl	CH_2Cl_2	Et_3N	34%	85/15	87%
13	*t*-BuCOCl	CH_2Cl_2	Proton sponge	trace	—	—
14	*t*-BuCOCl	CH_2Cl_2	Lutidine	trace	—	—
15	*t*-BuCOCl	CH_2Cl_2	K_3PO_4	trace	—	—
16	*t*-BuCOCl	CH_2Cl_2	KOBu-*t*	34%	85/15	95%
17	*t*-BuCOCl	CH_2Cl_2	Cs_2CO_3	31%	87/13	96%

[a] Isolated yield. [b] Calculated by ^1H NMR data of the crude reaction product. [c] Determined by chiral HPLC analysis.

Table 2 Generality of the Michael addition-lactonization of enone acids catalyzed by Fc-PIP





Entry	R^1	R^2	Time/h	Yield[a]/%	*dr*[b]	*ee*[c,d]/%
1	H (**1a**)	Ph	5	54	91/9	98 (94)
2	H (**1b**)	Me	8	NP	—	—
3	H (**1c**)	*p*-MePh	8	55	92/8	98 (94)
4	H (**1d**)	*o*-MeOPh	8	64	95/5	98
5	H (**1e**)	*m*-MeOPh	8	55	83/17	96
6	H (**1f**)	*p*-MeOPh	8	52	89/11	98
7	H (**1g**)	*p*-ClPh	8	57	>99/1	94 (84)
8	H (**1h**)	*o*-BrPh	8	53	>99/1	97
9	H (**1i**)	*m*-BrPh	8	59	96/4	96
10	H (**1j**)	*p*-BrPh	8	59	92/8	96
11	H (**1k**)	*p*-FPh	8	57	95/5	97
12	H (**1l**)	2,4-di-ClPh	8	55	91/9	96
13	H (**1m**)	2-Naphthyl	8	55	91/9	98
14	4-Cl (**1n**)	Ph	1	60	97/3	95
15	2-MeO (**1o**)	Ph	8	58	>99/1	97
16[e]	H (**1a**)	Ph	8	51	88/12	90

[a] Isolated yield. [b] Calculated by ^{1}H NMR data of the crude reaction product. [c] Determined by chiral HPLC analysis. [d] Data in the parentheses are *ee* values reported by Smith. [e] Using Cl-PIQ as the catalyst instead.

inorganic base led to trace product, probably due to the poor ability of deprotonation in the context of this tandem transformation (Entries 13－15). However, the improvement of basicity did not deliver better enantioselectivity and diastereoselectivity (Entries 16 and 17).

With the optimum reaction conditions in hand, the scope of this domino process was then investigated. As illustrated in the Table 2, by contrast with the work of Smith and co-workers[8a], when R^2 of the chalcone was alkyl group instead of aryl, none of the desired product was obtained (Table 2, Entries 2). In the case of aryl groups, a wide range of enone acids, which bear electron-donating and electron-withdrawing substitutes on the *o*-, *m*-, *p*-positions of benzene ring, performed smoothly under the optimized conditions to furnish *cis*-2,3-hydrobenzofuran compounds with moderate to excellent diastereoselectivities (83/17－99/1 *dr*) and high enantioselectivities (94%－98% *ee*), respectively (Table 2, Entries 3－15).

Building upon these results, it revealed that in this reaction our designed nucleophilic catalyst Fc-PIP was superior to tetramisole employed by Smith, in whose system only 84% － 94% *ee*s were obtained for aryl-substituted chalcone (Table 2, data in the parentheses of Entries 1, 3, 7). Furthermore, we also studied the influence of functionality of aromatic ether on the reaction. When weak electron-withdrawing group was introduced in the *para*-position, the reaction proceeded faster than others, giving the corresponding chiral 2,3-hydrobenzofuran derivative **2n** with 97/3 *dr* and 95% *ee*, respectively (Entry 14). Whereas **1o**, bearing electron-rich substitution on the *orth*-position, displayed both excellent enantioselectivity and diastereoselectivity (Entry 15). By contrast the Michael addition-Lactonization cascade reaction of **1a** using Birman's Cl-PIQ catalyst gave 88/12 *dr* and 90% *ee* (Entry 16).

We reasoned that the catalytic cycle of this reaction was analogous to that postulated by Smith,[8a,11] involving the formation of the mixed anhydride, then acylation with Fc-PIP giving acyl ammonium intermediate **I**, followed by deprotonation in the presence of base to deliver (*Z*)-ammonium enolate intermediate **II**, which then proceeds with asymmetric Michael addition, intramolecular cyclization and methanolysis to generate *cis*-2,3-dihydrobenzofuran derivatives (Figure 2). Based on the results, we deduced that excellent enantioselecitivity demonstrated in the asymmetric Michael addition was probably attributed to the synergy of central and planar chirality of our catalyst Fc-PIP.

Conclusions

In summary, we have established that highly selective acyl transfer catalyst Fc-PIP proved to be effective in the intramolecular Michael addition-Lactonization tandem reaction of a variety of enone acids to afford *cis*-2,3-dihydrobenzofuran derivatives with moderate to excellent diastereoselectivities (83/17－99/1 *dr*) and excellent enantioselectivities (94%－98% *ee*), repectively. Futher applications of Fc-PIP to alternative catalytic system are ongoing in our laboratory.

General Procedure

In a flame dried round bottom flask was dissolved the corresponding enone-acid (1.0 equiv., 0.1 mmol), Fc-PIP (0.2 equiv., 0.02 mmol) and DIPEA (1.0 equiv., 0.1 mmol) in dry DCM (1 mL) at 0 ℃. Pivaloylchloride (1.1 equiv., 0.11 mmol) was then added dropwise at the same temperature. After 20 min, DIPEA (1.5 equiv., 0.15 mmol) was added and the reaction mixture was sterred for a specified period of time. The reaction was then quenched with MeOH and stirred for 1.5 h at r.t. The solvent was evaporated and the residue was puri-

CHINESE JOURNAL OF CHEMISTRY

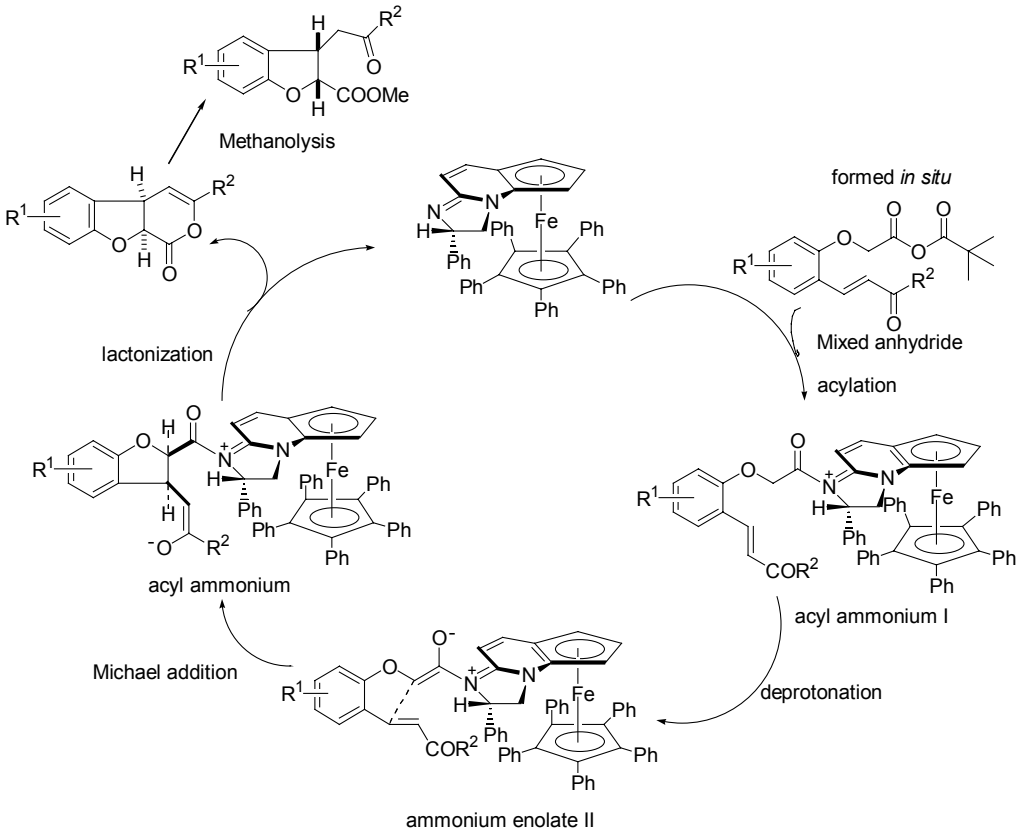


Figure 2 Postulated catalytic cycle.

fied by chromatography column to yield indene carboxylates **2a**—**2o**.

Acknowledgement

The authors are grateful to the Fundamental Research Funds for the Central Universities, the National Natural Science Foundation of China (No. 21372074).

References

[1] (a) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11633; (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75; (c) Antus, S.; Kurtán, T.; Juhász, L.; Kiss, L.; Hollósi, M.; Májer, Z. *Chirality* **2001**, *13*, 493; (d) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112; (e) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496; (f) García-Muñoz, S.; Jiménez-González, L.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Synlett* **2005**, 3011; (g) Jiménez-González, L.; García-Muñoz, S.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Eur. J.* **2006**, *12*, 8762; (h) Natori, Y.; Tsutsui, H.; Sato, N.; Nakamura, S.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2009**, *74*, 4418; (i) Meng, J.; Jiang, T.; Bhatti, H. A.; Siddiqui, B. S.; Dixon, S.; Kilburn, J. D. *Org. Biomol. Chem.* **2010**, *8*, 107; (j) Wakimoto, T.; Miyata, K.; Ohuchi, H.; Asakawa, T.; Nukaya, H.; Suwa, Y.; Kan, T. *Org. Lett.* **2011**, *13*, 2789; (k) Calter, M. A.; Li, N. *Org. Lett.* **2011**, *13*, 3686.

[2] (a) Tamada, M.; Endo, K.; Hikino, H.; Kabuto, C. *Tetrahedron Lett.* **1979**, 873; (b) Dätwyler, P.; Bosshardt, H.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2712; (c) Abd-Elazem, I. S.; Chen, H. S.; Bates, R. B.; Huang, R. C. C. *Antiviral Res.* **2002**, *55*, 91; (d) Yokoo, Y.; Fujii, W.; Hori, H.; Nagao, K.; Suwa, Y.; Taniyama, K.; Tsuji, K.; Yoshida, T.; Nukaya, H. *Alcohol.*: *Clin. Exp. Res.* **2004**, *28*, 129S; (e) Chauret, D. C.; Bernard, C. B.; Arnason, J. T.; Durst, T. *J. Nat. Prod.* **1996**, *59*, 152; (f) De Campos, M. P.; Filho, V. C.; Da Silva, R. Z.; Yunes, R. A.; Zacchino, S.; Juarez, S.; Bella Cruz, R. C.; Bella Cruz, A. *Biol. Pharm. Bull.* **2005**, *28*, 1527.

[3] (a) Tökés, A. L.; Litkei, G.; Gulácsi, K.; Antus, S.; Baitz-Gács, E.; Szántay, C.; Darkó, L. L. *Tetrahedron* **1999**, *55*, 9283; (b) Russell, M. G. N.; Baker, R.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 8667; (c) Seo, E.-K.; Kim, N.-C.; Mi, Q.; Chai, H.; Wall, M. E.; Wani, M. C.; Navarro, H. A.; Burgess, J. P.; Graham, J. G.; Cabieses, F.; Tan, G. T.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1483; (d) Apers, S.; Paper, D.; Bürgermeister, J.; Baronikova, S.; Dyck, S. V.; Lemière, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2002**, *65*, 718; (e) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Naganawa, H.; Chelladurai, V. *Tetrahedron* **2003**, *59*, 1255; (f) Li, X.-N.; Lu, Z.-Q.; Qin, S.; Yan, H.-X.; Yang, M.; Guan, S.-H.; Liu, X.; Hua, H.-M.; Wu, L.-J.; Guo, D.-A. *Tetrahedron Lett.* **2008**, *49*, 3797; (g) Wang, J.-F.; Yin, G.-F.; Zhou, X.-J.; Su, J.; Li, Y.; Zhong, H.-M.; Duan, G.; Cheng, Y.-X. *J. Asian Nat. Prod. Res.* **2011**, *13*, 80; (h) Reddy, N. K.; Vijaykumar, B. V. D.; Chandrasekhar, S. *Org. Lett.* **2012**, *14*, 299.

[4] (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459; (b) Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475; (c) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437; (d) Davies, H. M. L.; Pelphrey, P. M. In *Intermolecular C–H Insertions of Carbenoids*, Ed.: Denmark, S. E., Wiley-VCH, Weinheim, **2011**, p. 75; (e) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774.

[5] (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *Synthesis* **2003**, 1028; (b) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615; (c) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc.* **2008**, *130*, 16854.

[6] Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

[7] Albrecht, L.; Ransborg, L. K.; Lauridsen, V.; Overgaard, M.; Zweifel, T.; Jørgensen, K. A. *Angew. Chem.*, *Int. Ed.* **2011**, *50*, 12496.

[8] (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714; (b) Birman, V. B.; Li, X.-M. *Org. Lett*. **2006**, *8*, 1351.

[9] (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc*. **2001**, *123*, 7945; (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731; (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem*. **2005**, *70*, 2835; (d) Riyad, H. H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett*. **2006**, *8*, 4363; (e) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc*. **2008**, *130*, 10478; (f) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 9479; (g) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764; (h) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem*. **2011**, *76*, 2; (i) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496; (j) Liu, Y.; Lu, A.; Hu, K.; Wang, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2013**, 4836.

[10] (a) Hu, B.; Meng, M.; Wang, Z.; Du, W.; Fossey, J. S.; Hu, X.; Deng, W.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17041; (b) Hu, B.; Meng, M.; Fossey, J. S.; Mo, W.; Hu, X.; Deng, W.-P. *Chem. Commun.* **2011**, *47*, 10632; (c) Hu, B.; Meng, M.; Jiang, S.-S.; Deng, W.-P. *Chin. J. Chem*. **2012**, *30*, 1289.

[11] (a) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 3653; (b) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088; (c) Stark, D. G.; Morrill, L. C.; Yeh, P. P.; Slawin, A. M.; O'Riordan, T. J.; Smith, A. D. *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 11642; (d) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146; (e) Robinson, E. R.; Fallan, C.; Simal, C.; Slawin, A. M.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 2193; (f) Morrill, L. C.; Smith, S. M.; Slawin, A. M.; Smith, A. D. *J. Org. Chem*. **2014**, *79*, 1640; (g) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M.; Smith, A. D. *J. Org. Chem*. **2014**, *79*, 1626; (h) Morrill, L. C.; Ledingham, L. A.; Couturier, J. P.; Bickel, J.; Harper, A. D.; Fallan, C.; Smith, A. D. *Org. Biomol. Chem.* **2014**, *12*, 624; (i) Yeh, P. P.; Daniels, D. S.; Cordes, D. B.; Slawin, A. M.; Smith, A. D. *Org. Lett.* **2014**, *16*, 964; (j) Smith, S. R.; Leckie, S. M.; Holmes, R.; Douglas, J.; Fallan, C.; Shapland, P.; Pryde, D.; Slawin, A. M.; Smith, A. D. *Org. Lett*. **2014**, *16*, 2506.

(Zhao, X.)

