

Highly Regio-, Diastereo-, and Enantioselective 1,6- and 1,8-Additions of Azlactones to Di- and Trienyl *N*-Acylpyrroles

Daisuke Uraguchi, Ken Yoshioka, Yusuke Ueki, and Takashi Ooi*

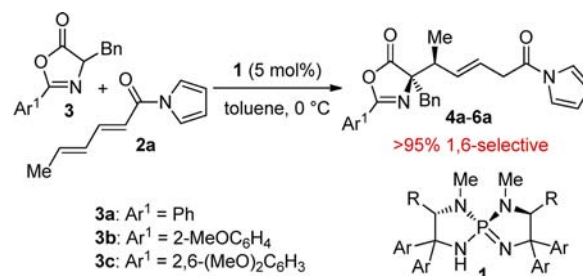
Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan

S Supporting Information

ABSTRACT: A vinylog of Michael addition (1,6-addition) of azlactones to δ -substituted dienyl *N*-acylpyrroles has been developed with virtually complete 1,6-, diastereo-, and enantioselectivities by means of chiral *P*-spiro triaminoiminophosphorane as a catalyst. This system has been successfully extended to an unprecedented bis-vinylog of Michael addition (1,8-addition) of azlactones to ζ -substituted trienyl *N*-acylpyrroles with high levels of regio- and stereocontrol.

In contrast to the considerable progress in the field of catalytic asymmetric Michael addition (1,4-addition) of carbon nucleophiles to electron-deficient alkenes, research on the development of the vinylog of Michael addition (1,6-addition) to extended conjugated systems, such as dienyl carbonyl compounds, has largely been sporadic, despite the potential synthetic utility of the reaction.¹ While the principle of vinylogy states that the reactivity is, in theory, maintained by the propagation of the electronic effect of the directing functional group through a conjugated π system,² it is well recognized that 1,4-addition is generally favored over 1,6-addition even with electron-deficient dienes.³ Several transition-metal catalysts have been shown to be effective for overcoming this regioselectivity issue, enabling the introduction of carbanionic nucleophiles to the δ -carbon of δ -substituted dienyl acceptors with high levels of enantiocontrol.^{4–7} On the other hand, there is only one example of the catalytic asymmetric 1,6-addition of enolates, in which δ -unsubstituted dienyl carbonyl and sulfonyl compounds were employed to appreciate the spatial accessibility of the terminal double bond for governing the regioselectivity.⁸ This methodological deficiency poses a formidable challenge associated with control of not only the regiochemistry but also the stereochemistry in the addition of prochiral enolates to δ -substituted, electron-deficient dienes, where simultaneous discrimination of both enantiofaces of the enolate and the vinylogous Michael acceptor should be realized. Alexakis and Stephens recently demonstrated the effectiveness of using 1,3-bis(sulfonyl)-butadiene as an acceptor for guiding the initial 1,6-addition of a chiral enamine intermediate in a catalytic stereoselective formal [4+2] cycloaddition with aldehydes to give optically active 1,3-bis(sulfonyl)cyclohexadienes.^{9,10} In conjunction with our continuous efforts to explore the potential of *P*-spiro chiral triaminoiminophosphorane¹¹ of type **1** (see Table 1) as a strong organic base catalyst,^{12–14} we disclose herein our solution to this problem: the development of a highly diastereo-

Table 1. Effect of the Structure of Catalyst **1** and Ar¹ of Azlactone **3** on the Stereoselectivity^a



entry	catalyst R, Ar (1)	3	yield ^b (%)	dr ^{c,d}	ee ^{d,e} (%)	prod
1	^t Pr, Ph (1a)	3a	93	10:1	79	4a
2	Me, Ph (1b)	3a	96	12:1	84	4a
3	Bn, Ph (1c)	3a	91	2:1	38	4a
4	^t Bu, Ph (1d)	3a	95	13:1	92	4a
5	^t Bu, 4-MeC ₆ H ₄ (1e)	3a	93	11:1	86	4a
6	^t Bu, 4-FC ₆ H ₄ (1f)	3a	99	12:1	94	4a
7	1f	3b	96	14:1	91	5a
8	1f	3c	97	>20:1	98	6a

^aReactions were performed with 0.11 mmol of **2a** and 0.1 mmol of **3** in toluene (1.0 mL) in the presence of **1** (5 mol %) at 0 °C for 1–2 h.

^bIsolated yield. ^cDiastereomeric ratios of 1,6-adducts were indicated, which were determined by ¹H NMR (400 MHz) analysis of crude aliquot. ^dAbsolute configurations of **4a–6a** were assigned by analogy to that of **6d**. ^eEnantiomeric excesses of the major diastereomer were indicated, which were analyzed by chiral stationary phase HPLC.

and enantioselective 1,6-addition of azlactones¹⁵ to simple δ -monosubstituted dienyl *N*-acylpyrroles **2**^{3a,d,h} by the utilization of chiral iminophosphorane **1f** as a requisite catalyst for total yet rigorous selectivity control. Furthermore, this system can be successfully extended to the hitherto unknown bis-vinylog of Michael addition (1,8-addition) to ζ -substituted trienyl acceptors with high levels of regio- and stereocontrol.

As a vinylogous Michael acceptor, we employed dienyl *N*-acylpyrrole **2** in consideration of its synthetic utility, i.e., the *N*-acylpyrrole moiety can be easily converted into various carbonyl functionalities with different oxidation states.^{16,17} The initial attempt was made by treating *N*-(2*E*,4*E*)-hexadienylpyrrole **2a** with azlactone **3a** in the presence of 5 mol % of *L*-valine-derived iminophosphorane **1a** in toluene at 0 °C. The reaction proceeded to completion in 2 h, and

Received: October 16, 2012

Published: November 12, 2012

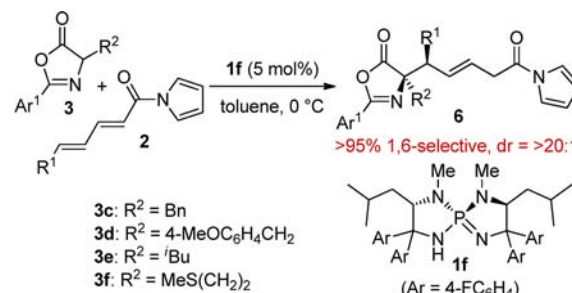
interestingly, ^1H NMR (400 MHz) analysis of the crude aliquot revealed the exclusive formation of the 1,6-adduct, β,γ -unsaturated *N*-acylpyrrole **4a**, with a diastereomeric ratio of 10:1 (Table 1, entry 1). Since no evidence for the concomitant production of the isomeric, α,β -unsaturated analog of **4a** was detected, the intermediary generated vinylogous enolate was thought to be protonated predominantly at the α -position of the carbonyl group. After purification by standard silica gel column chromatography, the diastereomeric mixture of **4a** was isolated in 93% yield with promising enantioselectivity for the major diastereomer (79% ee). Encouraged by this prime finding of the extraordinarily regioselective 1,6-addition, we next investigated the effect of the catalyst structure on the stereochemical outcome. In accordance with our anticipation, appropriate choice of the alkyl group (R) originating from the parent α -amino acid and the geminal aromatic substituents (Ar) on the diazaphosphacycles of **1** turned out to be crucial for improving the stereoselectivity. This scrutiny led to the identification of *L*-leucine-derived iminophosphorane **1f** bearing 4-fluorophenyl substituents as an optimal catalyst, and **4a** was isolated with good diastereoselectivity (dr = 12:1) and high enantiomeric excess of 94% (entries 1–6). It should be noted that the diastereo- and enantioselectivities were further enhanced by the modification of the aromatic substituent at the 2-position of azlactone **3**. Introduction of a 2,6-dimethoxyphenyl group (**3c**) allowed for the addition of **2a** to proceed with virtually complete selectivity control in the presence of **1f** to afford almost stereochemically pure **6a** in 97% yield (entries 7 and 8).

Having established the optimized conditions, we studied the scope of this new catalytic, highly stereoselective 1,6-addition protocol. The representative results are listed in Table 2. Generally, the reaction reached completion within 3 h using 5 mol % of **1f** to give **6** in nearly quantitative yield, and neither the isomeric α,β -unsaturated 1,6-adducts nor the 1,4-adducts were formed to a detectable extent. With respect to the vinylogous Michael acceptor, the present system tolerated the incorporation of various linear and branched terminal substituents (R¹, **2b–e**), and excellent stereoselectivities were uniformly observed (entries 1–4). Dienyl *N*-acylpyrroles **2f–h** bearing a functional group, such as olefin, ether, and ester, also appeared to be good candidates for the reaction (entries 5–7).¹⁸ In addition to the benzyl-substituted **3c**, other azlactones with different alkyl appendages at the 4-position (R², **3d–f**) could be employed as donor substrates, and high levels of stereochemical control were achieved regardless of their structural features (entries 8–10).

The *N*-acylpyrrole and azlactone moieties of the 1,6-adducts **6** could be separately derivatized into various carbonyl functionalities.^{15,16} For example, the *N*-acylpyrrole moiety could be readily converted into the corresponding esters by treatment with sodium methoxide, as shown by the illustrative transformation from **6d** to **7** in Scheme 1. Subsequent ring opening of the azlactone component¹⁹ with 4-chloroaniline afforded secondary amide **8**, and its single-crystal X-ray diffraction analysis allowed us to determine the absolute configuration of **6d**.²⁰

The significant potential of our approach based on the catalysis of *P*-spiro chiral triaminoiminophosphorane **1f** was amply demonstrated by applying it to the development of the bis-vinylogous 1,8-addition of **3** to trienyl *N*-acylpyrroles **9** (Table 3).²¹ Reaction of **3c** with (2*E*,4*E*,6*E*)-octatrienoylpyrrole **9a** under the same conditions as those for 1,6-addition,

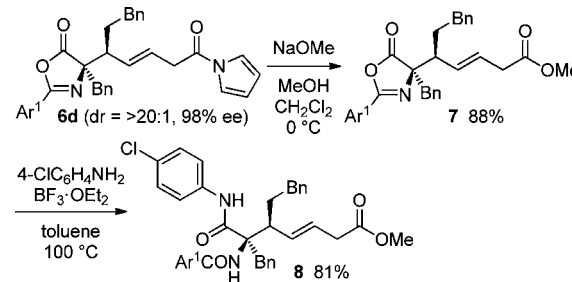
Table 2. Substrate Scope of the 1,6-Addition of Azlactones **3 (Ar¹ = 2,6-(MeO)₂C₆H₃) to δ -Substituted Dienyl *N*-Acylpyrroles **2**^a**



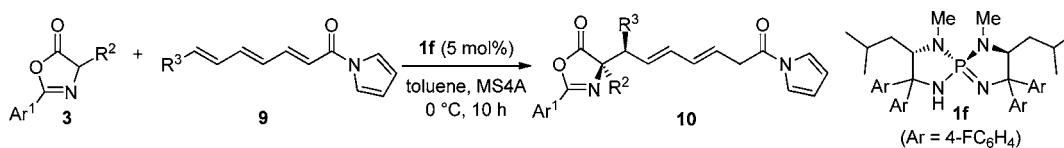
entry	R ¹ (2)	3	time (h)	yield ^b (%)	ee ^{c,d} (%)	6
1	Me(CH ₂) ₂ (2b)	3c	2	94	98	6b
2	Me(CH ₂) ₆ (2c)	3c	2	84	98	6c
3	Ph(CH ₂) ₂ (2d)	3c	3	99	98	6d
4	^t Bu (2e)	3c	2	95	98	6e
5	CH ₂ =CH(CH ₂) ₃ (2f)	3c	2	98	98	6f
6	BnOCH ₂ (2g)	3c	2	93	97	6g
7	BzOCH ₂ (2h)	3c	2	96	94	6h
8	Me (2a)	3d	2	98	98	6i
9	Me (2a)	3e	3	97	94	6j
10	Me (2a)	3f	1	95	90	6k

^aReactions were performed with 0.11 mmol of **2** and 0.1 mmol of **3** in toluene (1.0 mL) in the presence of **1f** (5 mol %) at 0 °C. Diastereomeric ratios of **6** were >20:1 as indicated, which were determined by ^1H NMR (400 MHz) analysis of crude aliquot. ^bIsolated yield. ^cAbsolute configuration of **6d** was determined by X-ray crystallographic analysis of its derivative **8**, see Scheme 1 and the SI for details. Absolute configurations of **6b,c**, and **6e–k** were assigned by analogy to that of **6d**. ^dEnantiomeric excesses of the major diastereomer of **6** were indicated, which were analyzed by chiral stationary phase HPLC.

Scheme 1. Derivatization of 1,6-Adduct **6d (Ar¹ = 2,6-(MeO)₂C₆H₃) for Determination of Absolute Configuration**



except for the use of powdered 4A molecular sieves (MS4A),²² resulted in carbon–carbon bond formation at the ζ -position of **9a** to afford the 1,8-adduct, $\beta,\gamma,\delta,\epsilon$ -unsaturated *N*-acylpyrrole **10a**, almost exclusively in 89% yield (1,8-/1,6-/1,4-adducts = >20:<1:1) (entry 1). Further, ^1H NMR (400 MHz) analysis indicated that **10a** was obtained virtually as a single diastereomer (dr = >20:1), and the enantiomeric excess was determined to be 99% by chiral HPLC measurement. A brief survey of the possible variation in the structures of the pronucleophile **3** and the bis-vinylogous Michael acceptor **9** showed the promising generality of this unprecedented, regioselective 1,8-addition of enolates to electron-deficient trienes efficiently catalyzed by **1f** with remarkably high relative and absolute stereocontrol (entries 2–5, Table 3).

Table 3. Catalytic, Regio- and Stereoselective 1,8-Addition of Azlactones **3** ($\text{Ar}^1 = 2,6\text{-}(\text{MeO})_2\text{C}_6\text{H}_3$) to Trienyl *N*-Acylypyrroles 9^a 

entry	R ³ (9)	R ² (3)	yield ^b (%)	rr ^c (1,8:1,6:1,4)	dr ^{d,e}	ee ^{e,f} (%)	prod
1	Me (9a)	Bn (3c)	89	>20:<1:1	>20:1	99	10a
2	Me(CH ₂) ₆ (9b)	3c	94	>20:<1:1	18:1	99	10b
3	BnOCH ₂ (9c)	3c	98	14:1:<1	>20:1	98	10c
4	9a	4-MeOC ₆ H ₄ CH ₂ (3d)	90	>20:<1:1	>20:1	99	10d
5	9a	^t Bu (3e)	90	>20:<1:1	8:1	99	10e

^aReactions were performed with **1f** (5 mol %), 0.11 mmol of **9**, and 0.1 mmol of **3** in toluene (1.0 mL) containing 100 mg of MS4A at 0 °C for 10 h. ^bIsolated yield. ^cRegioisomeric ratios (rr) were determined by ¹H NMR (400 MHz for entries 1, 3, and 4, 700 MHz for entries 2 and 5) analysis of crude aliquot. ^dDiastereomeric ratios of 1,8-adduct **10** were indicated, which were determined by ¹H NMR (400 MHz for entries 1, 3, and 4, 700 MHz for entries 2 and 5) analysis of crude aliquot. ^eAbsolute configurations of **10a**–**e** were assigned by analogy to that of **6d**. ^fEnantiomeric excesses of the major diastereomer of **10** were indicated, which were analyzed by chiral stationary phase HPLC.

In conclusion, we have developed the 1,6-addition of azlactones to δ -monosubstituted dienyl *N*-acylpyrroles with essentially complete control of regio-, diastereo-, and enantioselectivities by virtue of chiral *P*-spiro triaminoimino-phosphorane as a strong organic base catalyst. This methodology has further been evolved into the highly regio- and stereoselective 1,8-addition to ζ -substituted trienyl acceptors. We believe that the present study would provide a new perspective of coping with the selectivity issues associated with the conjugate addition of prochiral enolates to prochiral electron-deficient polyenes and of exploiting rich chemistry involved in this type of selective carbon–carbon bond-forming reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

tooi@apchem.nagoya-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Work was supported by NEXT program, a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from MEXT, Program for Leading Graduate Schools “Integrative Graduate Education and Research Program in Green Natural Sciences” in Nagoya University, Grants of JSPS for Scientific Research, and the Asahi Glass Foundation. Y.U. acknowledges JSPS for financial support.

■ REFERENCES

- (1) For recent, excellent reviews on asymmetric 1,6-addition reactions, see: (a) Csáky, A. G.; de la Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080. (b) Biju, A. T. *ChemCatChem* **2011**, *3*, 1847. (c) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109.
- (2) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.

- (3) For recent, selected examples of asymmetric 1,4-additions to electron-deficient dienes, see: (a) Park, S.-Y.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 2815. (b) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430. (c) Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557. (d) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (e) Zhao, D.; Wang, Y.; Mao, L.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 10983. (f) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572. (g) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. (h) Li, Z.-B.; Luo, S.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2010**, *8*, 2505. (i) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3232. (j) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794. (k) Hayashi, Y.; Okamura, D.; Umemiya, S.; Uchimaru, T. *ChemCatChem* **2012**, *4*, 959.

- (4) For chiral transition-metal complex-catalyzed enantioselective 1,6-additions of carbanionic nucleophiles to $\alpha,\beta,\gamma,\delta$ -unsaturated systems, see: (a) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224. (b) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 5164. (c) Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957. (d) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398. (e) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (f) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (g) Nishimura, T.; Noishiki, A.; Hayashi, T. *Chem. Commun.* **2012**, *48*, 973. (h) Magrez, M.; Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2012**, *14*, 3576. (i) Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, DOI: 10.1021/ja309756k.

- (5) For an enantioselective silyl 1,6-addition to a β -substituted cyclic dienone, see: Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898.

- (6) Recently, an organocatalytic, 1,6-selective sulfa-Michael reaction was reported. Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439.

- (7) Sun, H.-W.; Liao, Y.-H.; Wu, Z.-J.; Wang, H.-Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2011**, *67*, 3991.

- (8) Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772.

- (9) For nonstereoselective examples, see: (a) Masuyama, Y.; Sato, H.; Kurusu, Y. *Tetrahedron Lett.* **1985**, *26*, 67. (b) Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B. H. *J. Org. Chem.* **1991**, *56*, 2713. (c) Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540.

- (10) Murphy, J. J.; Quintard, A.; McArdle, P.; Alexakis, A.; Stephens, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 5095.

(11) Triaminoiminophosphoranes are known as a P1-phosphazenes, which was developed by Schwesinger, see: (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167. For a review, see: (b) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; John Wiley & Sons: West Sussex, U.K., 2009.

(12) (a) Uraguchi, D.; Ooi, T. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1185. (b) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562. (c) Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842. (d) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685.

(13) For a review on organic base catalysis, see: Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

(14) For reviews on phosphonium salt catalyses, see: (a) Werner, T. *Adv. Synth. Catal.* **2009**, *351*, 1469. (b) Enders, D.; Nguyen, T. V. *Org. Biomol. Chem.* **2012**, *10*, 5327.

(15) For reviews of azlactones in organic syntheses, see: (a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. (b) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755. (c) Alba, A.-N. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720.

(16) For a review on the application of *N*-acylpyrroles, see: Goldys, A. M.; McErlean, C. S. P. *Eur. J. Org. Chem.* **2012**, 1877.

(17) For a pioneering study on the use of α,β -unsaturated *N*-acylpyrroles for the catalytic asymmetric conjugate addition, see: Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680.

(18) Although the reaction with δ -phenyl-substituted dienyl *N*-acylpyrrole **2** ($R^1 = \text{Ph}$) under the catalysis of **1f** exclusively yields 1,6-adduct **6** ($R^1 = \text{Ph}$), diastereo- and enantioselectivity are rather sensitive to the content of the water in the reaction media. So far, we have found that the presence of an appropriate amount of water is crucial for enhancing stereoselectivity, but establishment of a procedure for obtaining reproducible results is difficult at present. The details of the study on this problem will be reported in due course.

(19) Uraguchi, D.; Asai, Y.; Ooi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 733.

(20) See the SI for X-ray analysis details.

(21) For examples of nonstereoselective 1,8-addition reactions, see: (a) Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* **1988**, *345*, 239. (b) Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487. (c) Brocchini, S. J.; Lawton, R. G. *Tetrahedron Lett.* **1997**, *38*, 6319.

(22) Addition of MS4A is necessary in the 1,8-addition to bis-vinylogous Michael acceptors **9** for ensuring reproducibility, although the exact reason is unclear at present. In addition, we confirmed that comparable results were obtained with or without MS4A in the simple 1,6-addition to **2a**.