Organic Letters
Letter
pubs.acs.org/OrgLett

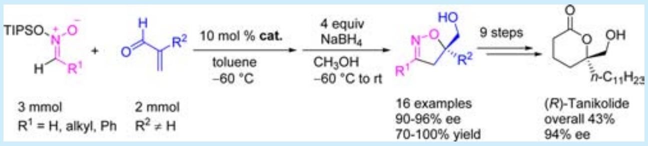
Catalytic Asymmetric Synthesis of Isoxazolines from Silyl Nitronates

Xiaoyu Han, Li Dong, Caiwei Geng, and Peng Jiao*

Key Laboratory of Radiopharmaceuticals, College of Chemistry, Beijing Normal University, Beijing 100875, P. R. China

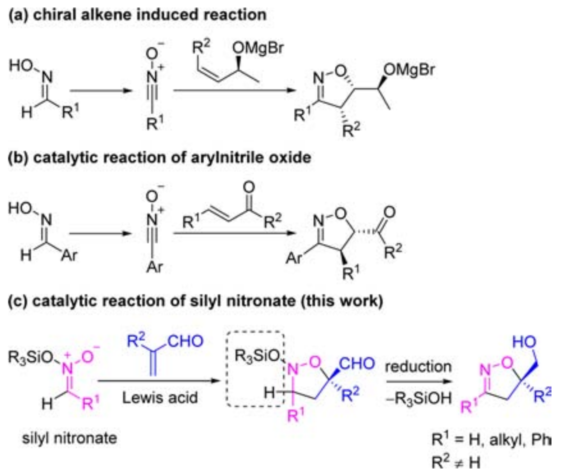
Supporting Information

ABSTRACT: 1,3-Dipolar cycloadditions of triisopropylsilyl nitronates and 2-alkylacroleins produced isoxazolines bearing a chiral quaternary center in high yields and enantioselectivities with the aid of a chiral oxazaborolidine catalyst. One chiral isoxazoline product was converted to (*R*)-(+)-Tanikolide in 9 steps in a total yield of 43%.



Chiral 2-isoxazolines are valuable intermediates for the synthesis of a variety of organic molecules of significant importance, including many natural products of medicinal or biological activity.[1] To date, the methodology for 2-isoxazoline synthesis has mainly relied on the cycloaddition of nitrile oxide.[1] An enantiomerically pure allyl alcohol *in situ* forms allyloxymagnesium bromide, which reacts with an *in situ* generated nitrile oxide to afford the chiral isoxazoline with high asymmetric induction [Scheme 1a]. Mapp and Carreira used this method to synthesize structurally diversified *β*-amino acids and polyketide building blocks via isoxazolines.[2−4] Due to the typical basic conditions for the generation of nitrile oxide or the Lewis basicity of the nitrile oxide, few examples of catalytic asymmetric synthesis of isoxazolines have been documented: "bisoxazoline-MgI_2" and "chiral ligand-$Ni(ClO_4)_2$" complexes were used by Sibi, Suga, and Feng, respectively, as catalysts for isoxazoline syntheses from mainly arylnitrile oxides, and regioselectivity problems were encountered [Scheme 1b].[5]

Scheme 1. Access to Different Chiral Isoxazolines



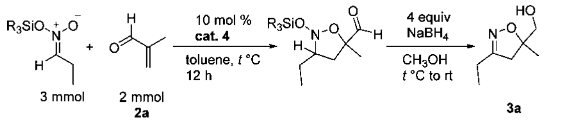
In the presence of a base, a nitroalkane reacts with a silyl chloride to form the corresponding silyl nitronate, which could be used as an equivalent of nitrile oxide for 1,3-dipolar cycloadditions and is fairly stable in comparison with nitrile oxide. In his pioneering work, Torssell reported the reactions of silyl nitronates with various alkenes under thermal conditions.[6] Isoxazolines were obtained in racemic forms. Asymmetric syntheses of isoxazolines from silyl nitronates were scarcely reported, in which a chiral auxiliary or a chiral center was introduced into the dipolarophile molecule.[7] Herein, we report our efforts in discovering a new method of chiral isoxazoline synthesis starting from readily available silyl nitronates and 2-alkylacroleins [Scheme 1c]. We hope to accomplish the catalytic asymmetric synthesis of novel isoxazolines, which cannot be prepared in the known procedures, in uniformly high regio-, diastereo-, and enantioselectivities.

Upon establishment of the synthetic goal, we prepared the triisopropylsilyl (TIPS) nitronate **1a** from 1-nitropropane and studied the reaction of **1a** with methacrolein (**2a**) in anhydrous toluene. At the outset, we tested the "BINOL-Ti(IV)" complex (Table 1, cat. **4a**) as a chiral Lewis acid catalyst.[8] At −10 °C, the cycloaddition reaction proceeded to generate a new compound. After silica gel chromatography, <15% yield of the cycloaddition product was isolated. We recognized this was possibly caused by the instability of the cycloadduct bearing both a sensitive *N*-silyloxy and a sensitive aldehyde group. Indeed, when the cycloaddition product was reduced with $NaBH_4$ in a methanolic solution, the isoxazoline product (**3a**) bearing a hydroxymethyl group at the newly formed chiral quaternary center was isolated in 68% yield and 77% ee (Table 1, entry 1). This one-pot reduction step spontaneously eliminated triisopropylsilanol from the *N*-silyloxy isoxazolidine. "Salen-Cr(III)" (cat. **4c**) was also tested.[9,10] A good yield and ee were obtained for the isoxazoline product (Table 1, entry 3). When Corey's chiral oxazaborolidine activated by TfOH (cat. **4e**) was used as the catalyst,[11] the cycloaddition proceeded at −60 °C furnishing the isoxazoline in quantitative yield and 90% ee (Table 1, entry 5). When CH_2Cl_2 was used as the solvent, the reaction went smoothly to give the isoxazoline **3a** in the same ee but with a decreased yield of 81% (Table 1, entry 6). Replacing TIPS with other silyl groups resulted in significantly

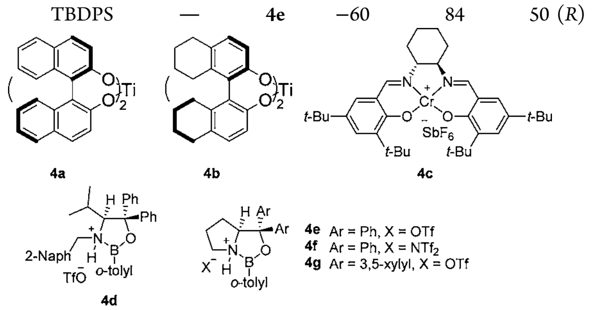
Received: March 20, 2015
Published: June 17, 2015

DOI: 10.1021/acs.orglett.5b00826
Org. Lett. 2015, 17, 3194−3197

Table 1. Screening of Catalyst and Nitronate for 1,3-Dipolar Cycloaddition Using Methacrolein[a]

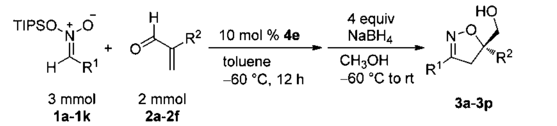


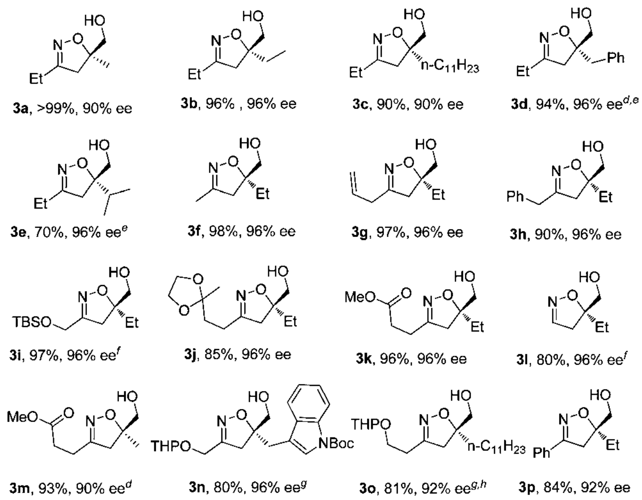
entry	R_3Si	nitronate	cat.	t (°C)	yield (%)	ee (%)[b,c]
1	TIPS	**1a**	**4a**	−10	68	77 (*S*)
2		**1a**	**4b**	−10	19	4 (*S*)
3		**1a**	**4c**	−10	84	90 (*S*)
4		**1a**	**4d**	−60	75	9 (*R*)
5[d]		**1a**	**4e**	−60	>99	90 (*R*)
6[e]		**1a**	**4e**	−60	81	90 (*R*)
7		**1a**	**4f**	−60	75	81 (*R*)
8		**1a**	**4g**	−60	95	90 (*R*)
9	TMS	—	**4e**	−60	30	75 (*R*)
10	TBS	—	**4e**	−60	70	81 (*R*)
11	TBDPS	—	**4e**	−60	84	50 (*R*)



[a]Yields and ee's were for **3a**. All yields were isolated ones. [b]Ee was determined by chiral HPLC analysis of the benzoate of **3a** using AD-H column. [c]Abs. configuration in the parentheses was assumed by analogy. [d]Acrolein did not react with **1a**. [e]The solvent was CH_2Cl_2.

Scheme 2. Asymmetric 1,3-Dipolar Cycloadditions of TIPS Nitronates with 2-Alkylacroleins[a,b,c]





[a]All yields were isolated ones. [b]Ee was determined by chiral HPLC analysis of the corresponding benzoate. [c]Abs. configurations were assumed by analogy. [d]Abs. configuration was determined by XRD analysis. [e]4 mmol of silyl nitronate were reacted for 24 h. [f]4 mmol of silyl nitronate were used. [g]Ee was for the bisbenzoate of the diol obtained by removing the THP group. [h]Abs. configuration determined by chemical correlation to (*R*)-Tanikolide.

decreased yields and ee's under otherwise identical conditions (Table 1, entries 9−11).

With the promising results obtained by the catalysis of catalyst **4e**, scopes of both the triisopropylsilyl nitronate and the acrolein substrates for the asymmetric 1,3-dipolar cycloaddition were carefully investigated (Scheme 2). 2-Alkylacroleins were prepared from aliphatic aldehydes by methylenation with formalin.[12] 2-Ethyl or 2-undecylacrolein (**2b**, **2c**) reacted with the TIPS nitronate **1a** to give the products (**3b**, **3c**) in excellent yields and ee's (Scheme 2). When the acrolein (**2d**, **2e**) bearing a 2-benzyl or 2-isopropyl group was used, a longer reaction time (24 h) and more nitronate (2 equiv) were required for a complete conversion of the acrolein substrate. 96% ee was obtained for each compound (**3d**, **3e**). The crystal structure of the *p*-bromobenzoate of **3d** definitely indicated the absolute configuration was (*R*).[13] The scope of the nitroalkane was then examined. For this purpose, 2-ethylacrolein (**2b**) was selected as the dipolarophile. The nitronate (**1b**) of nitroethane gave isoxazoline **3f** in 98% yield and 96% ee. The nitronate of 4-nitro-1-butene and 2-nitro-1-phenylethane (**1c**, **1d**) gave the isoxazoline **3g** and **3h** in 96% ee, respectively. The TBS ether of nitroethanol was converted to the silyl nitronate **1e**, which was rapidly used in the cycloaddition reaction to deliver product **3i** in 97% yield and 96% ee. When the nitronate of 5-nitro-2-pentanone was reacted with 2-ethylacrolein under standard conditions, no cycloaddition was observed. Ethylene ketal protection of the strongly coordinating ketone carbonyl group and subsequent silylation afforded the nitronate (**1f**), which gave **3j** in 85% yield and 96% ee. An ester group in nitronate **1g** obtained from 4-nitrobutanoic acid methyl ester was totally tolerated, as shown by the good yield and ee of product **3k**. Encouraged by the exciting results obtained for the nitro alkanes bearing an alkene, phenyl, ester, potential ketone, or hydroxy group, we hope to further apply TIPS methylenenitronate (**1h**) as a reactant, which is from CH_3NO_2 and needs particular attention due to its instability. After many failures, we could finally prepare the nitronate **1h** from 1 equiv of CH_3NO_2, 1 equiv of TIPS-Cl, and 0.9 equiv of DBU in CH_2Cl_2 at 0 °C. After removing DBU·HCl, the crude **1h** was suitable for the cycloaddition and successfully produced isoxazoline **3l** in 96% ee and 80% yield. Obviously, this result was comparable to those of nitronates **1a**−**1g**. Thus, structural variation of the acrolein and the nitronate would produce more chiral isoxazolines of possible interest. **3m** was obtained from methacrolein (**2a**) and silyl nitronate **1g** in 90% ee. A single crystal of the *p*-bromobenzoate of **3m** was used for XRD analysis. The absolute configuration was confirmed to be (*R*).[13] The THP ether of nitroethanol was converted into the TIPS nitronate (**1i**). When **1i** was reacted with the indolylmethylacrolein **2f**, the isoxazoline (**3n**) was obtained in 96% ee, which is a potential precursor for the synthesis of monatin, a natural sweetener of possible commercial interest.[14] The reaction of 2-undecylacrolein (**2c**) with 3-nitro-1-propanol derived silyl nitronate (**1j**) afforded the isoxazoline (**3o**) in 92% ee, which was used for the synthesis of (*R*)-Tanikolide. The nitronate (**1k**) of phenylnitromethane gave the isoxazoline (**3p**) in 84% yield and 92% ee.

To gain some insight into the stereocontrol of the catalyzed reaction, we performed an instant NMR analysis of the concentrated reaction mixture of 2-indolylmethylacrolein (**2f**)

DOI: 10.1021/acs.orglett.5b00826
Org. Lett. 2015, 17, 3194−3197

with the TIPS nitronate of 2-*tert*-butyldimethylsilyloxy-1-nitroethane (**1e**). One set of signals for the cycloadduct [Figure 1a] were observed, which clearly indicated an extra high

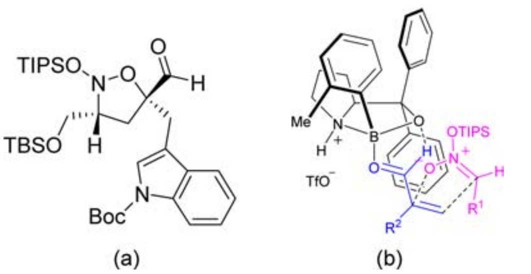
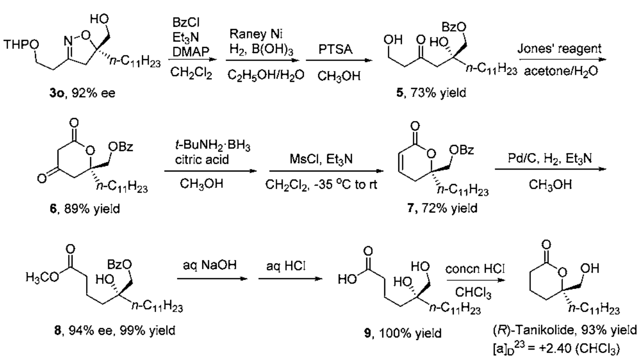


Figure 1. (a) Suggested structure for an isoxazolidine cycloadduct. (b) Possible transition state for cycloaddition.

endo selectivity of the cycloaddition process.[15] Though we have no direct information about the absolute configuration of the chiral center (C_3) next to the N atom, a prevailed *endo* selectivity for concerted cycloaddition made us to conclude an (*R*) configuration based on the proposed transition state structure [Figure 1b]. 2-Alkylacrolein coordinated to the oxazaborolidine catalyst possessed an *s-trans* configuration, and the nitronate approached from the *Re* face to give the cycloadduct with R^1 and R^2 in a *cis* configuration. Similarly, ^{1}H NMR analysis of the reaction mixture of the TBS nitronate of 1-nitropropane with methacrolein also supported the conclusion of a highly *endo* selective cycloaddition.[15]

The enantiomerically pure isoxazoline prepared in our method contains a masked tertiary alcohol unit. To demonstrate the utility of our new method of chiral isoxazoline synthesis, an efficient synthesis of (*R*)-(+)-Tanikolide was completed and the results are shown in Scheme 3.[16] Starting

Scheme 3. Synthesis of (+)-Tanikolide



from the product **3o** (92% ee), protection of the free hydroxy group with benzoyl, followed by Raney Ni catalyzed hydrogenation and ring opening,[17] and deprotection of the THP group afforded product **5** in 73% yield (3 steps). Oxidation of **5** with Jones' reagent gave the tetrahydropyran-2,4-dione (**6**) in 89% yield. Removal of the undesired ketone group at the 4-position of the lactone ring turned out to be more challenging than expected. Pd/C catalyzed hydrogenation under 50 atm of H_2 or $NaBH_4$ (10 equiv) reduction made no change to the molecule of **6**. This special ketone carbonyl was finally reduced with the *tert*-butylamine borane complex in the presence of citric acid.[18] ^{13}C NMR indicated the carbonyl was reduced with no facial selectivity.[15] A 60:40 diastereomeric mixture was obtained, which gave product **7** in 72% yield (2 steps) when subjected to dehydration via the methanesulfonate. Pd/C catalyzed hydrogenation of **7** under atmospheric pressure gave **8** quantitatively when Et_3N was added to the reaction mixture. The ee of **8** was determined to be 94% by HPLC analysis.[16] Saponification of both ester groups in the molecule of **8** gave the dihydroxy acid **9**, which readily converted to (*R*)-Tanikolide in the presence of a catalytic amount of concentrated aqueous hydrochloric acid.

In summary, we disclosed a catalytic asymmetric synthesis of chiral isoxazolines from silyl nitronates of various nitroalkanes with high enantioselectivity. Chiral oxazaborolidine activated by TfOH was the Lewis acid catalyst of choice. Preparation of silyl nitronates bearing useful functional groups was carefully investigated. The isoxazoline prepared in our method contains a chiral quaternary center. One chiral isoxazoline was used for the efficient synthesis of (*R*)-Tanikolide. We believe the enantiomerically pure isoxazolines obtained in our method will find more applications in organic syntheses.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00826.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pjiao@bnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research reported in this publication was supported by the National Natural Science Foundation of China (21002008). We thank Prof. Jiaxin Zhang (College of Chemistry, Beijing Normal University) for assistance with NMR experiments and Prof. Xiang Hao (ICCAS, Beijing) for XRD analysis.

■ REFERENCES

(1) For books and reviews, see: (a) Huisgen, R. 1,3-Dipolar Cycloaddition-Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. *1*, pp 1−176. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988. (c) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (d) Ono, N. *The Nitro Group in Organic Synthesis*; VCH: New York, 2001. (e) Denmark, S. E.; Cottell, J. J. Nitronates In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; Vol. *59*, pp 83−167. (f) *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: New York, 2007.

(2) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324−2339.

(3) (a) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846−6847. (b) Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 10504−10505. (c) Buhrlage, S. J.; Brennan, B. B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 12456−12457. (d) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376−5383. (e) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *Synlett* **2004**, 1409−1413.

(4) (a) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082−2085. (b) Muri, D.; Lohse-Fraefel, N.;

DOI: 10.1021/acs.orglett.5b00826
Org. Lett. 2015, 17, 3194−3197

Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4036−4038. (c) Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857−3858. (d) Kleinbeck, F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 578−581. (e) Muri, D.; Carreira, E. M. *J. Org. Chem.* **2009**, *74*, 8695−8712.

(5) For catalytic asymmetric syntheses of isoxazolines from nitrile oxides, see: (a) Sibi, M.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366−5367. (b) Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. *J. Org. Chem.* **2009**, *74*, 1099−1113. (c) Lian, X.; Guo, S.; Wang, G.; Lin, L.; Liu, X.; Feng, X. *J. Org. Chem.* **2014**, *79*, 7703−7710.

(6) (a) Torssell, K. B. G.; Zeuthen, O. *Acta Chem. Scand. B* **1978**, *32*, 118−124. (b) Sharma, S. C.; Torssell, K. B. G. *Acta Chem. Scand. B* **1979**, *33*, 379−383. (c) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569−5575.

(7) (a) Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27−30. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359−1370. (c) Stack, J. A.; Heffner, T. A.; Geib, S. J.; Curran, D. P. *Tetrahedron* **1993**, *49*, 995−1008. (d) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293−318. (e) Galley, G.; Jones, P. G.; Paetzel, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2073−2082. (f) Young, D. G. J.; Gomez-Bengoa, E.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 692−693. (g) Bonne, D.; Salat, L.; Dulcère, J.-P.; Rodriguez, J. *Org. Lett.* **2008**, *10*, 5409−5412. (h) Pitlik, J. *Synth. Commun.* **1994**, *24*, 243−252.

(8) For "BINOL-Ti(IV)" catalyzed asymmetric reactions, see: (a) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613−615. (b) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10−11. (c) Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478−5480. (d) Yuan, Y.; Wang, X.; Li, X.; Ding, K. *J. Org. Chem.* **2004**, *69*, 146−149. (e) Bao, H.; Zhou, J.; Wang, Z.; Guo, Y.; You, T.; Ding, K. *J. Am. Chem. Soc.* **2008**, *130*, 10116−10127. (f) Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem.* **2005**, *70*, 8533−8537. (g) He, L.; Zhao, L.; Wang, D.; Wang, M. *Org. Lett.* **2014**, *16*, 5972−5975.

(9) For "salen-M(III)" catalyzed asymmetric Diels−Alder reactions, see: (a) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844. (b) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628−4641. (c) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950−5951. (d) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163−1166.

(10) For "salen-M(III)" catalyzed asymmetric reactions, see: (a) Wang, S.; Wang, M.; Wang, D.; Zhu, J. *Org. Lett.* **2007**, *9*, 3615−3618. (b) Wang, S.; Wang, M.; Wang, D.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388−391. (c) Yue, T.; Wang, M.; Wang, D.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454−9457. (d) Yang, L.; Wang, D.; Huang, Z.; Wang, M. *J. Am. Chem. Soc.* **2009**, *131*, 10390−10391. (e) Tong, S.; Wang, D.; Zhao, L.; Zhu, J.; Wang, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4417−4420.

(11) For a review on chiral oxazaborolidine catalyzed reactions, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100−2117.

(12) (a) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538−2541. (b) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205−4216. (c) Marvel, C. S.; Myers, R. L.; Saunders, J. H. *J. Am. Chem. Soc.* **1948**, *70*, 1694−1699.

(13) CCDC 1046756: *p*-bromobenzoate of **3d**; CCDC 1046755: *p*-bromobenzoate of **3m**.

(14) (a) Vleggaar, R.; Ackerman, L. G. J.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3095−3098. (b) Bassoli, A.; Borgonovo, G.; Busnelli, G.; Morini, G.; Drew, M. G. B. *Eur. J. Org. Chem.* **2005**, 1652−1658. (c) Bassoli, A.; Borgonovo, G.; Busnelli, G.; Morini, G.; Merlini, L. *Eur. J. Org. Chem.* **2005**, 2518−2525.

(15) See Supporting Information for details.

(16) For references on the syntheses of Tanikolide, see: Gourdet, B.; Lam, H. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8733−8737, and ref 25 therein.

(17) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826−5833.

(18) (a) Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1157−1159. (b) Bennett, F.; Fenton, G.; Knight, D. W. *Tetrahedron* **1994**, *50*, 5147−5158. (c) Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001**, *42*, 8463−8465.

DOI: 10.1021/acs.orglett.5b00826
Org. Lett. 2015, 17, 3194−3197