Organocatalytic Asymmetric Tandem Nazarov Cyclization/ Semipinacol Rearrangement: Rapid Construction of Chiral Spiro[4.4]nonane-1,6-diones

Bin-Miao Yang,[†,§] Pei-Jun Cai,[‡] Yong-Qiang Tu,*[,†,§] Zhi-Xiang Yu,[‡] Zhi-Min Chen,[†,§] Shuang-Hu Wang,[†,§] Shao-Hua Wang,[†,§] and Fu-Min Zhang[†,§]

[†]State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

[‡]Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, P. R. China

[§]Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072, P. R. China

S *Supporting Information*

ABSTRACT: A novel organocatalytic asymmetric tandem Nazarov cyclization/semipinacol rearrangement reaction using "unactivated" substrates has been developed, generating a series of chiral spiro[4.4]nonane-1,6-diones in up to 96% yield and 97% enantiomeric excess. Significantly, it is the first direct example for asymmetric synthesis of cyclopentanones with four stereocenters using Nazarov cyclization. DFT calculations have been applied to understand the reaction mechanism, stereochemistry, and substituent effects.

Figure 1. Examples of chiral ligand and natural products containing the key spiro[4.4]nonane skeleton.

Scheme 1. Designing the Tandem Nazarov Cyclization/ Semipinacol Rearrangement Approach to Spiro[4.4]nonane-1,6-diones

The Nazarov 4π-conrotatory electrocyclization reaction, a useful and powerful method for constructing cyclopentenones, has played an important role in synthetic chemistry since its discovery in 1941.[1] In particular, with the development of its asymmetric variation and the ingenious design of new substrates, this method has found wide applications in the synthesis of natural products.[2] In general, most asymmetric Nazarov cyclizations are achieved by the use of "activated" substrates (substituted by an α-carboxy or α-ether group, or both) to improve the reactivity and enantioselectivity,[1k,l,3] which limits the substrate types. The corresponding Nazarov reactions with "unactivated" substrates have not been investigated to a large extent due to the requirement for harsh reaction conditions and the poor regioselectivity compared to the reactions with "activated" substrates.[4] Notably, the "interrupted" Nazarov reaction has been developed, using nucleophilic species to trap the Nazarov oxyallyl intermediate,[1j,5] which generally occurs under mild conditions and benefits the formation of multiple chemical bonds and stereocenters. Nevertheless, the asymmetric—especially the catalytic asymmetric—interrupted Nazarov reaction has rarely been reported[6] and is worth investigating further.

Spiro[4.4]nonane skeletons, as key structural motifs, broadly exist in not only many important chiral ligands of asymmetric catalysis (Figure 1, **a**)[7] but also a lot of biologically important natural products (Figure 1, **b** and **c**).[8] Until now, however, constructing this type of skeleton has required multi-step and complicated approaches. Accordingly, realizing the correspond-

ing asymmetric version is even more challenging. For example, for the synthesis of chiral spiro[4.4]nonane-1,6-dione, chemical[9] and kinetic resolution[10] are generally needed. Furthermore, the synthesis of its derivatives is rarely achieveable.[11] Thus, exploring more direct and asymmetric strategies is still necessary. Considering that the Nazarov cyclization normally involves a carbocation intermediate (Scheme 1), a key prerequisite for inducing semipinacol rearrangement,[12] we hypothesized that if a suitable cyclobutanol motif is designed to connect to the α-position of the cyclization precursor **I**, the oxyallyl intermediate **II** would induce a subsequent semipinacol rearrangement to generate spiro[4.4]nonane-1,6-dione **III**. West et al. also tested such an "interrupted" Nazarov reaction of "unactivated" substrates of 2-hydroxyalkyl-1,4-dien-3-ones **I** with a series of rearrangement precursors (cyclobutyl, cyclopentyl, cyclohexyl,
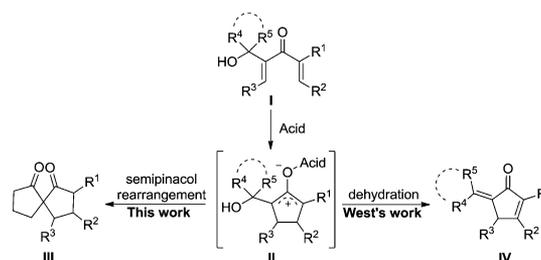
Table 1. Optimizing the Nazarov Cyclization/Semipinacol Rearrangement Sequence[a]

3a Ar = 2,6-(iPr)$_2$C$_6$H$_3$
3b Ar = 4-(1-Ad)-2,6-(iPr)$_2$C$_6$H$_2$
3c Ar = 9-anthracenyl
3d Ar = 1-naphthyl
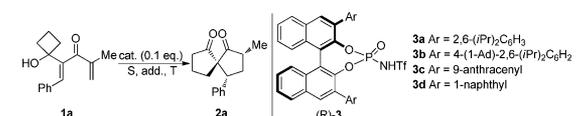
entry	cat., solv., add.,[b] T	yield./%[c] (t/h)	ee[d] (dr)[d]
1	BF$_3$·Et$_2$O,[e] DCM, –, –78 °C	87 (0.1)	– (89:11)
2	silica gel,[f] DCM, –, rt	79 (43)	– (82:18)
3	3a, CHCl$_3$, –, rt	97 (1)	90% (98:2)
4	3b, CHCl$_3$, –, rt	74 (4)	85% (>99:1)
5	3c, CHCl$_3$, –, rt	86 (40)	57% (98:2)
6	3d, CHCl$_3$, –, rt	84 (2)	33% (>99:1)
7	3a,[g] CHCl$_3$, –, rt	98 (3.5)	88% (93:7)
8	3a, CHCl$_3$, –, 0 °C	89 (3)	93% (98:2)
9	3a, DCM, –, 0 °C	98 (1)	89% (99:1)
10	3a, DCE, –, 0 °C	92 (2)	88% (99:1)
11	3a, CCl$_4$, –, 0 °C	81 (5)	79% (97: 3)
12	3a',[h] CHCl$_3$, –, 0 °C	96 (6)	–90% (95:5)
13	3a, CHCl$_3$, 3 Å MS, 0 °C	98 (1.5)	91% (98:2)
14	3a, CHCl$_3$, 4 Å MS, 0 °C	97 (1.5)	92% (>99:1)
15	3a, CHCl$_3$, 5 Å MS, 0 °C	98 (1.5)	88% (98:2)
16	3a, CHCl$_3$, 4 Å MS, –10 °C	99 (3.5)	93% (>99:1)
17	3a, CHCl$_3$, 4 Å MS, –20 °C	87 (9)	97% (>99:1)
18	3a, CHCl$_3$, 4 Å MS, –30 °C	88 (12)	96% (>99:1)

[a]All reactions were performed with 0.1 mmol 1a in 1.0 mL of solvent. Abbreviations: cat. = catalyst; solv. = solvent; add. = additive; T = temperature, t = time; ee = enantiomeric excess; dr = diastereomer ratio; DCM = dichloromethane; DCE = 1,2-dichloroethane; rt = room temperature; MS = molecular sieves. [b]50 mg. [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]1.0 equiv. [f]3.0 equiv of mass relative to 1a. [g]0.05 equiv. [h]3a' is the enantiomer of 3a.

Table 2. Substrate Scope of the Tandem Nazarov Cyclization/Semipinacol Rearrangement[a]

[a]Substrate 1 (0.1 mmol) was dissolved in 1.0 mL of CHCl$_3$ at –20 °C under Ar atmosphere, and then 4 Å MS (50 mg) was added; 5 min later, catalyst 3a (0.01 mmol) was added. The ee and dr were determined by chiral HPLC analysis. [b]1.09 mmol scale of 1a: 97% yield, 95% ee, >99:1 dr, 9 h. [c]Isolated yield. [d]X-ray crystallography of 2m–o, see SI. [e]Determined by ^{1}H NMR (400 MHz).

and chain structure alkyls).[13] Although no desired rearrangement product was obtained except the dehydration product of alkylidenecyclopentenones **IV**, it provided the message that the tandem process might be feasible under proper conditions. In this study, we present our research results toward the first organocatalytic asymmetric tandem Nazarov cyclization/semipinacol rearrangement reaction using "unactivated" substrates. Preliminary density functional theory (DFT) studies of the reaction mechanism, stereochemistry, and substituent effects were also performed.

We first tested the feasibility of the designed tandem reaction with 2-hydroxyalkyl-1,4-dien-3-one **1a** as the model substrate (Table 1). Fortunately, the initial attempt with BF$_3$·Et$_2$O as the promoter in DCM at –78 °C successfully afforded the desired product of 2-methyl-4-phenylspiro[4.4]nonane-1,6-dione (**2a**) in 87% yield (entry 1). Silica gel was found to promote the cyclization/rearrangement process to afford **2a** under mild conditions (entry 2). Based on the results above, the corresponding enantioselective transformation was then investigated. Because of the environmental friendliness of organocatalysis, N-triflylphosphoramide,[8c,g,14] a classical type of chiral Brønsted acid, was used to perform the expected enantioselective reaction (entries 3–6). Among the catalysts screened, **3a**[15] was the most effective, giving **2a** in 97% yield and 90% ee along with 98:2 dr (entry 3). Reducing the loading of **3a** to 0.05 equiv did not affect the yield much but led to a little lower enantioselectivity (entry 7). Lowering the reaction temperature to 0 °C could enhance the enantioselectivity, but with a reduced yield of

89% (entry 8). Furthermore, the solvent effect was observed, and the best enantioselectivity was obtained with CHCl$_3$ as the solvent (entries 8–11). Similarly, the use of catalyst **3a'**, the enantiomer of **3a**, could also give the corresponding enantiomer of **2a** in excellent yield and enantioselectivity (entry 12). The influence of different molecular sieves on the reaction was tested, and the presence of 4 Å MS afforded the best diastereo- and enantioselectivity (entries 13–15). Finally, we tried to further improve the enantioselectivity of this transformation by lowering the reaction temperature (entries 16–18). To our delight, the ee of **2a** could be increased to 97% at –20 °C, with an unchanged dr and a yield of 87% (entry 17).

With the optimized conditions in hand (Table 1, entry 17), we investigated the scope and limitation of this tandem reaction with a variety of substrates containing different R^1, R^2, and R^3 groups. As shown in Table 2, substrates **1a–o** reacted to give the desired chiral spiro[4.4]nonane-1,6-diones **2a–o** with good to excellent diastereo- and enantioselectivities. Further observations indicated the reaction rate was dependent, to some extent, upon the properties of the substituents R^1 and R^3 of the substrates. For example, when the substituent at the aromatic ring of R^3 was an electron-neutral group, changing R^1 from methyl (Me) to ethyl (Et) significantly reduced the rate of the reaction (**2a** vs **2b**, **2c** vs **2d**). Furthermore, when the aromatic ring of R^3 had an electron-donating group at the 2- or 3-position, reactions generally were fast and completed within 5–10 h, regardless of whether R^1 = Me or Et (**2e–g**). In contrast, when an electron-withdrawing group was present at the 2-position of the aromatic ring, the reaction was generally slow and needed several days to complete (**2h**). However, if an electron-donating or -withdrawing substituent was present at the 4-position of the aromatic ring, the reaction time did not vary so much, regardless of whether R^1 = Me or Et (**2i–k**). In particular, a chloro substituent resulted in a long reaction time when placed at either the 2- or 4-position of the aromatic ring of R^3 (**2l** and **2m**).
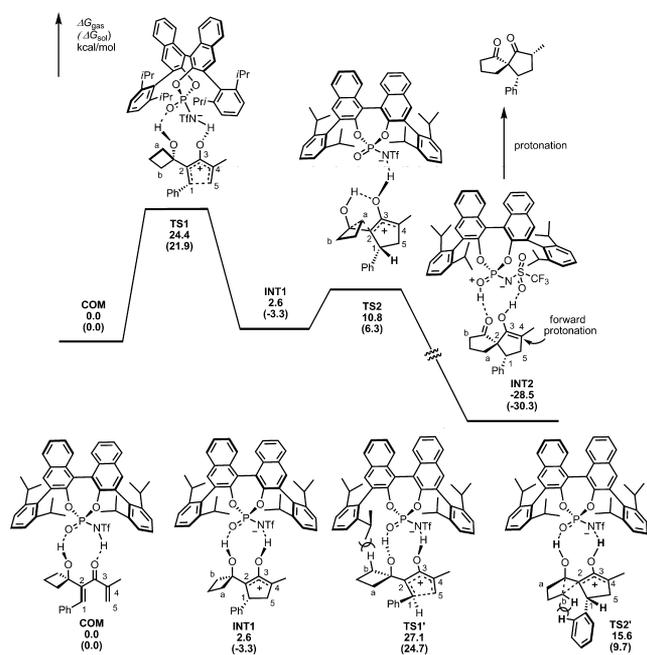
Figure 2. B3LYP/6-311++G**//B3LYP/6-31G* calculated free energy surface of the catalytic cycle of the tandem reaction between **1a** and **3a** (see computed key structures in SI).

When substrates **1n** and **1o** with cyclic $R^1 \cdots R^2$ were subjected to the general reaction conditions, the corresponding products **2n** and **2o**, with tricyclic framework and four consecutive stereogenic centers, were obtained with good to excellent ee and dr values. To further demonstrate the potential synthetic utility of the reaction, the transformation with substrate **1a** was carried out on ~1.0 mmol scale, and the expected product was still produced with 97% yield, 95% ee, and >99:1 dr.

Substrates **1p–r** have also been synthesized to study the process. Compared with **1a**, **1p** (with $R^1 = R^2 = H$, $R^3 = Ph$) reacted to give an intractable mixture gradually upon treatment with BF$_3$·Et$_2$O. Similar results could be observed when substrates **1q** (with $R^1 = Me$, $R^2 = R^3 = Ph$) and **1r** (with R^1, R^2, and $R^3 =$ alkyls, see SI for detailed structure) were investigated. Furthermore, no spiro[4.4]nonane-1,6-dione was detected when the substrates reacted with **3a**. These facts indicated that $R^1 = H$, $R^2 = Ph$, and $R^3 = Me$ were not favorable to the cyclization/rearrangement sequence (see SI).

With the experimental results above, DFT calculations[16] with B3LYP functional[17] were performed to rationalize the reaction process and its stereochemistry with **1a** and **3a** (Figure 2, with computed free energies in both the gas phase and CHCl$_3$ solution; here we use gas-phase values to discuss the reaction).[18] The reaction starts by forming a hydrogen-bonding complex, **COM**, between the substrate and the catalyst. The substrate in **COM** is protonated by the catalyst and can be regarded as a pentadienyl cation, which then undergoes 4π-conrotatory electrocyclization via two competing transition states, **TS1** and **TS1′**, with activation free energies of 24.4 and 27.1 kcal/mol, respectively. The Nazarov reaction step here is irreversible, since the following ring expansion transition state **TS2** is much lower in energy than both **TS1** and **TS1′**. Consequently, the Nazarov reaction step prefers to occur via **TS1** to set up the stereochemistry at C$_1$. In **TS1′**, the phenyl and hydroxyl groups of the substrate point in the same direction, and this arrangement pushes the cyclobutyl group of the substrate toward the isopropyl
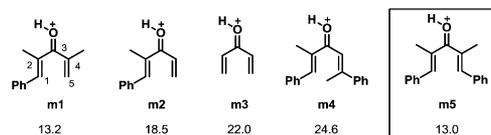
group in the catalyst, causing it to suffer steric repulsion. In contrast, such repulsion is absent in **TS1**, where the hydroxyl group binds to the catalyst and its cyclobutyl group stays away from the catalyst.

Once the chiral center in C$_1$ is determined by the first Nazarov reaction, this chiral information can influence the stereo-chemistry at C$_2$ in the ring expansion step. DFT calculations found that the C$_a$ atom, which is in the *trans* configuration with respect the Ph group at the C$_1$ atom, undergoes easier [1,2] migration via **TS2** to give **INT2**, while migration of the C$_b$ atom, which is in the *cis* configuration with respect to the Ph group at C$_1$ and experiences steric repulsion from the Ph group in **TS2′**, is disfavored by 4.8 kcal/mol in the gas phase. Consequently, this step sets up the stereochemistry at C$_2$. The [1,2]-C$_a$ migration requires an activation free energy of 8.2 kcal/mol and is exergonic by 31.1 kcal/mol.

INT2 can be protonated to give the final product. We proposed that this could be an outer-sphere process via the proton source in the reaction system, which prefers a forward attack in the position *trans* to the Ph group at C$_1$ to avoid steric repulsions from both the catalyst and the product (for detail, see SI).

Thus, DFT calculations indicated that the most difficult step of the process is the Nazarov cyclization, and the catalyst's stereochemistry determines the stereochemistry at C$_1$ by the cyclization step; then the C$_1$ center in **INT1** affects the chiral center at C$_2$ via a [1,2]-C$_a$ migration. Finally, the chiral catalyst environment influences the protonation from the forward face of **INT2** and builds the chiral center at the C$_4$ atom.

Preliminary investigations of how substituents affect the Nazarov reaction have been performed, based on the model reaction of protonated divinyl ketones **m1–m5** (Scheme 2). Compound **m1** is similar to substrate **1a**, with the Me group at position 2 representing the cyclobutanol group in **1a**. DFT calculations showed that Ph group at C$_1$ and two Me groups at C$_2$ and C$_4$ are beneficial for the Nazarov reaction by 8.8 kcal/mol when we compare the relative reactivities of **m1** and **m3**. Without a Me group at C$_4$, **m2** becomes less favorable than **m1** by 5.3 kcal/mol, and this explains why **1p** cannot give the expected reaction (see SI). Compound **m4** is similar to the West compound,[13] and it is the worst substrate for the Nazarov reaction, explaining why a stoichiometric amount of Lewis acid is required for the Nazarov reaction, and implicating that it is not a good substrate for our reaction. DFT calculations predicted that **m5** is a good substrate, with reactivity similar to that of both **m1** and **1a**, but experimentally we did not observe the expected tandem reaction of **1q**. We reasoned that steric repulsions between substrate and catalyst could decrease the reactivity of substrate **1q** (for more discussion of substitution effects, see SI).

In summary, we have developed an asymmetric tandem Nazarov cyclization/semipinacol rearrangement reaction of "unactivated" substrates to yield a series of chiral spiro[4.4]-nonane-1,6-diones using chiral Brønsted acid as the catalyst.

Within this tandem process, up to four consecutive stereocenters, one being the all-carbon quaternary stereogenic center, were successfully constructed in excellent enantioselectivities. Significantly, it is the first direct example to synthesize asymmetrically cyclopentanones with four stereocenters by using the Nazarov cyclization. The reaction mechanism, stereochemistry, and substituent effects have also been studied by DFT calculations. Further studies of the process and application of the transformation in organic synthesis are under investigation.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental and computational details; spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04049.

■ AUTHOR INFORMATION

Corresponding Author
*tuyq@lzu.edu.cn
Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1941**, 211. (b) Nazarov, I. N.; Zaretskaya, I. I. *Bull. Acad. Sci. U.R.S.S. Classe Sci. Chim.* **1942**, 200. (c) Nazarov, I. N.; Zaretskaya, I. I. *Zh. Obshch. Khim.* **1957**, *27*, 693. (d) Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746. (e) Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*, Vol. 45; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; pp 1−158. (f) Harmata, M. *Chemtracts* **2004**, *17*, 416. (g) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (h) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (i) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (j) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (k) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851. (l) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531. (m) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, 3621. (n) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979. (o) Wenz, D. R.; Read de Alaniz, J. *Eur. J. Org. Chem.* **2015**, 23.

(2) Recent examples of Nazarov cyclizations used in natural products synthesis: (a) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022. (b) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498. (c) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915. (d) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 300. (e) Gao, S.; Wang, Q.; Chen, C. *J. Am. Chem. Soc.* **2009**, *131*, 1410. (f) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560. (g) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891. (h) Leboeuf, D.; Wright, C. M.; Frontier, A. J. *Chem.—Eur. J.* **2013**, *19*, 4835. (i) Moritz, B. J.; Mack, D. J.; Tong, L.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2988. (j) Carlsen, P. N.; Mann, T. J.; Hoveyda, A. H.; Frontier, A. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9334. (k) Shvartsbart, A.; Smith, A. B. *J. Am. Chem. Soc.* **2014**, *136*, 870. (l) Shi, Y.; Yang, B.; Cai, S.; Gao, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9539. (m) Wang, J.; Wang, J.; Li, C.; Meng, Y.; Wu, J.; Song, C.; Chang, J. *J. Org. Chem.* **2014**, *79*, 6354. (n) Shvartsbart, A.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 3510.

(3) (a) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075. (b) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. (c) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (d) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315. (e) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266. (f) Cao, P.; Deng, C.; Zhou, Y.-Y.; Sun, X.-L.; Zheng, J.-C.; Xie, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4463. (g) Jolit, A.; Walleser, P. M.; Yap, G. P. A.; Tius, M. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 6180.

(4) First example of an asymmetric Nazarov reaction using "unactivated" substrates: Hutson, G. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 4988.

(5) (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430. (b) Wu, Y.-K.; Dunbar, C. R.; McDonald, R.; Ferguson, M. J.; West, F. G. *J. Am. Chem. Soc.* **2014**, *136*, 14903.

(6) (a) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256. (b) Huang, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 8060. (c) Yaji, K.; Shindo, M. *Synlett* **2009**, *15*, 2524. (d) Leboeuf, D.; Huang, J.; Gandon, V.; Frontier, A. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10981.

(7) (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P. *J. Am. Chem. Soc.* **1997**, *119*, 9570. (b) Ding, K.; Han, Z.; Wang, Z. *Chem.—Asian J.* **2009**, *4*, 32. (c) Xie, J.; Zhou, Q. *Acta Chim. Sinica* **2014**, *72*, 778.

(8) (a) Guella, G.; Dini, F.; Pietra, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1134. (b) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Guella, G. *J. Am. Chem. Soc.* **2010**, *132*, 7153. (c) Kupta, J.; Anke, T.; Oberwinkler, F.; Schramm, G.; Steglich, W. *J. Antibiot.* **1979**, *32*, 130. (d) Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 709. (e) Shinohara, C.; Chikanish, T.; Nakashima, S.; Hashimoto, A.; Hamanaka, A.; Endo, A.; Hasumi, K. *J. Antibiot.* **2000**, *53*, 262. (f) Li, Y.-Y.; Shen, Y.-M. *Helv. Chim. Acta* **2010**, *93*, 2151. (g) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (h) D'yakonov, V. A.; Trapeznikova, O. A.; Meijere, A.; Dzhemilev, U. M. *Chem. Rev.* **2014**, *114*, 5775.

(9) (a) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587. (b) Gerlach, H.; Müller, W. *Helv. Chim. Acta* **1972**, *55*, 2277. (c) Harada, N.; Ochiai, N.; Takada, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1977**, 495. (d) Nieman, J. A.; Keay, B. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1973. (e) Chan, A. S. C.; Lin, C.-C.; Sun, J.; Hu, W.; Li, Z.; Pan, W.; Mi, A.; Jiang, Y.; Huang, T.-M.; Yang, T.-K.; Chen, J.-H.; Wang, Y.; Lee, G.-H. *Tetrahedron: Asymmetry* **1995**, *6*, 2953. (f) Feng, X. M.; Zeng, D. C.; Li, Z.; Jiang, Y. Z. *Chin. Chem. Lett.* **1999**, *10*, 559. (g) Nieman, J. A.; Keay, B. A. *Synth. Commun.* **1999**, *29*, 3829.

(10) Han, Z.; Wang, Z.; Ding, K. *Adv. Synth. Catal.* **2011**, *353*, 1584.

(11) (a) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747. (b) Qian, D.; Zhang, J. *Chem.—Eur. J.* **2013**, *19*, 6984.

(12) (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823. (c) Leemans, E.; D'hooghe, M.; Kimpe, N. D. *Chem. Rev.* **2011**, *111*, 3268. (d) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523. (e) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207. (f) Wang, S.-H.; Li, B.-S.; Tu, Y.-Q. *Chem. Commun.* **2014**, *50*, 2393.

(13) Scadeng, O.; West, F. G. *Eur. J. Org. Chem.* **2014**, 1860.

(14) (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78. (c) Rueping, M.; Ieawsuwan, W. *Chem. Commun.* **2011**, *47*, 11450. (d) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706. (e) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (f) Raja, S.; Ieawsuwan, W.; Korotkov, V.; Rueping, M. *Chem.—Asian J.* **2012**, *7*, 2361. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(15) Yang, M.; Zhao, Y.-M.; Zhang, S.-Y.; Tu, Y.-Q.; Zhang, F.-M. *Chem.—Asian J.* **2011**, *6*, 1344.

(16) Frisch, M. J.; et al. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013　(see SI for full citation).

(17) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(18) Recent DFT studies of the Nazarov reaction: (a) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379. (b) Shi, F. Q.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503.