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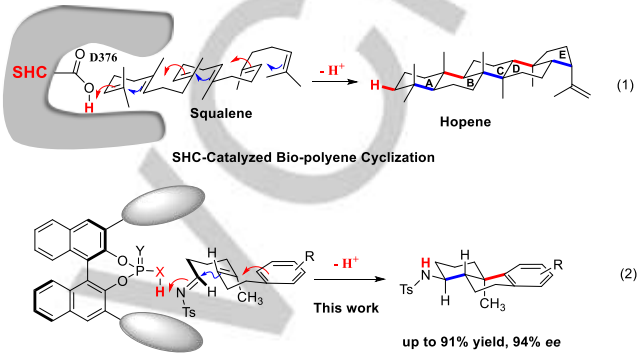
Enantioselective Polyene Cyclization Catalyzed by a Chiral Brønsted Acid

Liwen Fan †, Chunyu Han †, Xuerong Li †, Jiasheng Yao, Zhengning Wang, Chaochao Yao, Weihao Chen, Tao Wang, and Junfeng Zhao*

Dedicated to Professor E. J. Corey on the occasion of his 90th birthday.

Abstract: The first enantioselective polyene cyclization initiated by a BINOL-derived chiral *N*-phosphoramide (NPA)-catalyzed protonation of imine is described. The ion pair formed between the iminium ion and chiral counter anion of NPA plays an important role for controlling the stereochemistry of the overall transformation. This strategy offers a highly efficient approach to fused tricyclic frameworks containing three contiguous stereocenters, which are widely found in natural products. In addition, the first catalytic asymmetric total synthesis of (−)−ferruginol was accomplished with the NPA **5g**-catalyzed enantioselective polyene cyclization as the key step for the construction of the tricyclic core with excellent yield and enantio-selectivity.

Terpenes and steroids are ubiquitous natural products with a broad range of interesting biological activities, which render them and their derivatives valuable candidates for drug discovery.[1] However, the construction of their complex structures which contain polycyclic frameworks and multiple contiguous chiral centers, including all-carbon quaternary ones, is a great challenge for synthetic chemists.[2] Their biosyntheses involve highly efficient enzyme-catalyzed highly efficient domino cyclizations of linear poly-alkenes (polyene cyclization).[3] One typical example is the biosynthesis of optical pure hopene which involves a squalene hopene cyclases (SHC) catalyzed polyene cyclization triggered by enantioselective protonation of the terminal isoprene functionality of squalene to initiate the polyene cyclization (Scheme 1, Eq. 1).[4] Notably, up to five C-C bonds and nine chiral carbon centers are formed in such bio-polyene cyclization. Theoretically, thousands of isomers would be formed attributing to the chemo-, regio-, and stereo-selectivity, and owing to premature termination resulting from elimination and rearrangement of the carbocation intermediates. Amazingly, only one isomer among thousands of possibilities is produced in the SHC-catalyzed polyene cyclization.



Scheme 1. Enantioselective polyene cyclization

The breathtaking high selectivity and efficacy of enzyme-catalyzed polyene cyclization have drawn great interests of many organic chemists, and enormous efforts have been made to understand how nature works and to mimic such fantastic bio-reactions in the laboratory. Stork[5] and Eschenmoser[6] independently proposed that the ring-junction stereochemistry of polyene cyclization is stereospecific with *E*-alkenes giving *trans*-ring junctions while *Z*-alkenes giving *cis*-ring junctions. The Stork-Eschenmoser postulate (SEP) offers a theoretical foundation for biomimetic polyene cyclization, which has evolved into the most powerful strategy for the total syntheses of terpene and steroid natural products.[2] Despite this, almost all of the acid-catalyzed polyene cyclizations reported in the last century were diastereo-selective. Enantioselective polyene cyclization reaction remained an unexplored challenge untill 1999, when Yamamoto and Ishihara employed a stoichiometric Lewis acid-assisted Brønsted acid (LBA) as a chiral proton promoter.[7] Later, several LBAs,[8] Lewis base-assisted Brønsted acids[9] and other catalysts have been developed to catalyze the enantioselective polyene cyclization, in which the enantioselective protonation or electrophilic halogenation[10] of terminal isoprene acted as the initiating event. Aside from terminal isoprene, only few functional groups that can produce carbocations[11] or radicals[12] upon interacting with chiral catalysts have been used as initiators for enantioselective polyene cyclization.[13] Thus, the development of a superior catalytic enantioselective polyene cyclization is still of great significance owing to the structural diversity of terpenes and steroids. Herein, we report the first enantioselective polyene cyclization initiated by a BINOL-derived chiral *N*-phosphoramide (NPA)-catalyzed protonation.

Owing to their rigid chiral backbones and adjustable acidities, BINOL-derived chiral Brønsted acids, especially BINOL-derived chiralphosphoric acids (CPA) with various acidities, provide a platform for development of artificial protonases, which would be effective for polyene cyclization.[14] However, enantioselective

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[**] Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

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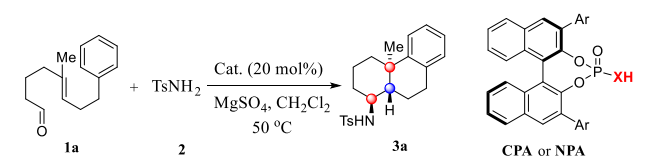
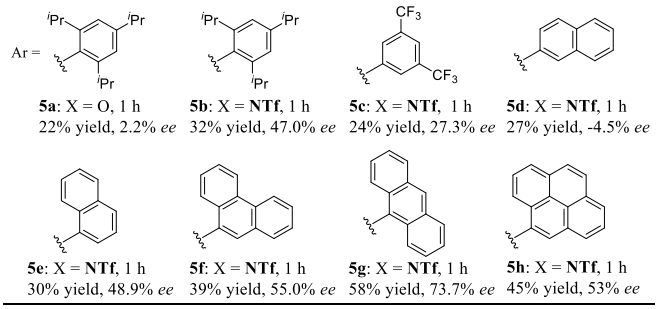
Table 1. Optimization of reaction conditions[a]





Entry	Cat.	Additive	T (°C)	Time (h)	Yield (%)[b]	*ee*[c]
1	**5g**	-	50	72	51	70.0
2	**5g**	4 Å MS	50	72	50	61.0
3	**5g**	Na_2SO_4	50	18	42	69.2
4	**5g**	$Mg(OAc)_2$	50	18	25	74.8
5	**5g**	$MgS_2O_3 \cdot 6H_2O$	50	1	58	79.3
6	**5g**	TFA	50	1	32	72.8
7	**5g**	$MgS_2O_3 \cdot 6H_2O$	25	2	55	80.9
8	**5g**	$MgS_2O_3 \cdot 6H_2O$	0	6	57	82.4
9	**5g**	$MgS_2O_3 \cdot 6H_2O$	-40	18	58	88.9
10	**5g**	**$MgS_2O_3 \cdot 6H_2O$**	**-60**	**24**	**65**	**91.7**
11	**Mg(5g-H)$_2$**	-	25	48	0	n.d.

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.4 mmol), additive (0.2 mmol), CPA or NPA (0.02 mmol) in CH_2Cl_2 (4 mL). [b] Isolated yield. [c] Enantiomeric excess (*ee*) determined by HPLC analysis using Chiralpak OJ-H column. TFA: trifluoroacetic acid.

polyene cyclization initiated by CPA-catalyzed protonation remains an unconquered challenge because of the low proton affinity of π-bond of the isoprene initiator.[10b] According to the SEP, the stereochemistry of the first formed chiral center is crucial for controlling the overall enantioselectivity of the biomimetic polyene cyclization. Successful pioneering works revealed that the appropriate combination of a chiral catalyst and an initiating functional group (initiator) is crucial for enantioselective polyene cyclization. Imines have been proven to be efficient substrates in organic transformations catalyzed by BINOL-based chiral Brønsted acids.[15] We envisioned that the imine functionality would be an ideal initiator because it could produce an iminium upon protonation to initiate the polyene cyclization. Importantly, the ion pair[16] formed between the iminium ion and the chiral counter anion of the Brønsted acid would offer an opportunity for controlling enantioselectivity (Scheme 1, Eq. 2). Although this looks like a straight-forward strategy, it is indeed challenging because of the potential competition from aldehyde-ene-reaction-initiated polyene cyclization.[17] Furthermore, 6-exo-cyclization would result in 4*α/β*-NH selectivity, which would complicate the stereo-selectivity of the overall transformation.

The reaction conditions were evaluated extensively by screening various amines and amides, solvents, BINOL-based chiral Brønsted acids, and additives with aldehyde **1a** as the model substrate. The representative results are listed in Table 1 (see Supporting Information for details). Preliminary studies revealed that our proposal is feasible. The reaction was sensitive to solvent, and dichloromethane was identified to be optimal. As expected, poor results with respect to the yield and enantioselectivity were obtained when BINOL-derived CPA **5a** was used as the catalyst (Table 1). Meanwhile, a remarkable improvement in enantioselectivity was observed with more acidic NPA **5b** (Table 1). Inspired by the cation–π interactions found in enantioselective cationic polycyclization,[11d, 18] we evaluated the BINOL-derived NPAs with different-sized aryl substituents at the 3,3′-positions. Interestingly, a significant improvement of the reactivity and enantioselectivity was observed as the size of the aryl substituents increased (Table 1, **5c**, **5e**, **5f**, **5g**).[19] The 2-naphthyl (**5d**) and 4-pyrenyl (**5h**) groups were exceptions, indicating that not only the cation–π interaction but also the steric interaction related to the arrangement of the aryl substituents plays an important role in asymmetric induction. Notably, the additive significantly affected the reaction rate (Table 1, entries 1–6). $MgS_2O_3 \cdot 6H_2O$ was the best additive, which led to the fastest reaction rate with good enantioselectivity and yield (Table 1, entry 5). Further optimization revealed that the enantioselectivity of the polyene cyclization increased steadily with decreasing reaction temperature (Table 1, entries 7–10). Enantioselective polyene cyclization product **3a** was obtained in 65% yield and with 91.7% *ee* when the reaction was carried out at −60 °C in the presence of $MgS_2O_3 \cdot 6H_2O$ with 20 mol% of NPA **5g** as the catalyst. Control experiment illustrated that magnesium salt of **5g** is not effective for this transformation (Table 1, entry 11). The π–π interaction between the phenyl group of 4-methylbenzene sulfonamide and the anthracenyl group of NPA **5g** would also be involved in the asymmetric induction event because other amides provided poor results (see Supporting Information for details). Although a 1:1 ratio of 4*α/β*-NH diastereomers was produced when a nonchiral Brønsted acid, such as TFA, was used as the catalyst for the racemic version, only the enantioenriched *α*-NH diastereomer was furnished for all of the chiral-NPA-catalyzed reactions.

Under the optimal reaction conditions, the substrate scope of this highly efficient transformation was investigated. As shown in Table 2, a broad range of substituted phenyl rings proved to be efficient terminators for this enantioselective domino cyclization. Both electron-donating and electron-withdrawing groups were tolerated on the terminator phenyl ring. However, the position and electronic effect of the substituents significantly influenced the reaction efficiency. In general, the electron-rich substituents at the *para* position benefitted the reaction remarkably with respect to both reactivity and enantioselectivity (**3b-3m**). The electronic properties of the terminator significantly affected the reaction yield (**3b-3e**). Interestingly, *meta* Cl- and Br- were compatible; the corresponding domino-cyclized products were generated in moderate to high yields with excellent enantioselectivity (**3d**, **3e**,

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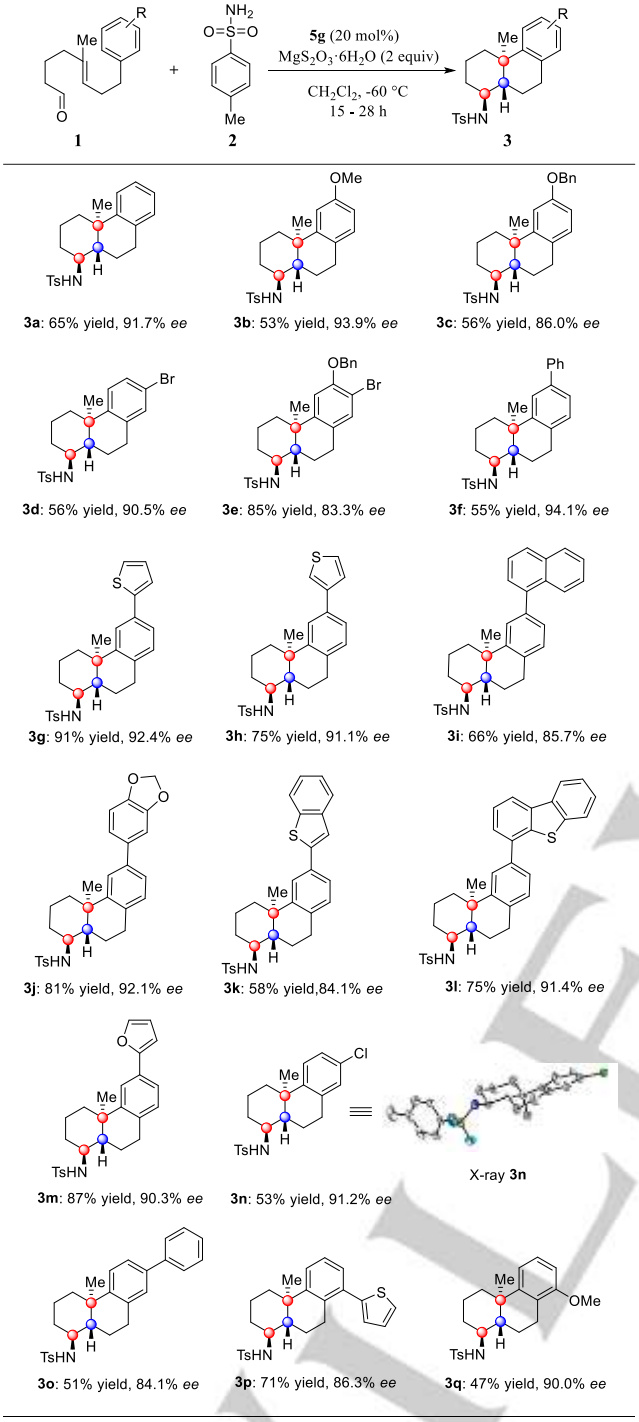
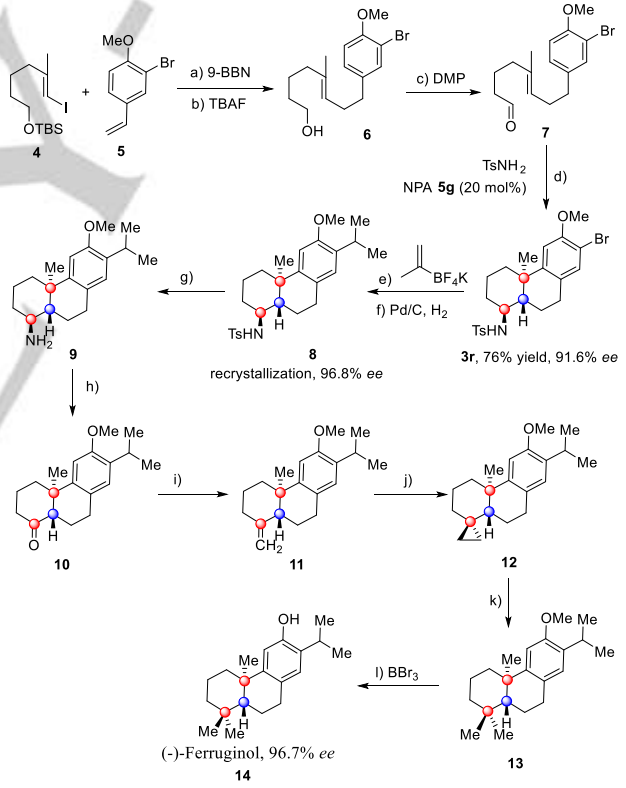


Scheme 2. Enantioselective polyene cyclization catalyzed by NPA **5g**[a] [a] Reaction conditions: Unless otherwise specified, the reactions were carried out with **1** (0.1 mmol), **2** (0.4 mmol), $MgS_2O_3 \cdot 6H_2O$ (0.2 mmol), NPA **5g** (0.02 mmol) and CH_2Cl_2 (4 mL) at -60 °C. Isolated yields. *ee* determined by HPLC analysis using Chiralpak OJ-H or AD-H column.

and **3n**). These halogen substituents offer opportunities for further functionalization via transition-metal-catalyzed cross-coupling reactions. Although strong electron-donating groups, such as MeO- and BnO-, were tolerated, no reaction occurred when strong electron-withdrawing substituents, such as nitro and cyano groups, were present on the terminator phenyl ring (data not shown). The relative configuration of the polyene cyclization product was determined using NMR spectroscopy and X-ray crystallographic analysis of racemic **3a**. The absolute configuration was established on the basis of the X-ray crystallographic analysis of **3n**, whereas the stereochemistries of the other products were assigned by analogy (see Supporting Information).[20]

This method provides an efficient strategy to enantioselectively construct fused tricyclic frameworks with three contiguous stereocenters, which are widely found in terpene and steroid natural products. To further demonstrate the power of this method, the first catalytic asymmetric total synthesis of (−)−ferruginol was conducted with the **5g**-catalyzed enantioselective polyene cyclization as the key step. Ferruginol is isolated from Lamiaceae plants and exhibits important bioactivities, such as antifungal, antimicrobial, antitumor, and anti-inflammatory activities.[21] In addition, it is an important intermediate in the syntheses of other abietane diterpene natural products. The previous total syntheses



Scheme 3. First catalytic asymmetric total synthesis of (-)-ferruginol[a] [a] Reagents and conditions: (a) 9-BBN, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol%), aq NaOH, 40%; (b) Bu_4NF (1.5 equiv), THF, 92%; (c) DMP (1.5 equiv), CH_2Cl_2, 86%; (d) NPA **5g** (20 mol%), $TsNH_2$ (4.0 equiv), $MgS_2O_3 \cdot 6H_2O$ (2.0 equiv), CH_2Cl_2, -60 °C, 18 h, 76%, 91.6% *ee*; (e) potassium isopropenyltrifluoroborate (1.5 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mol%), Cs_2CO_3 (3 equiv), THF:H_2O = 10:1, reflux 12 h, 88%; (f) Pd/C, H_2 balloon, CH_3OH, 97%; (g) Li, naphthalene, THF, rt, 80%; (h) TPAP, NMO,CH_2Cl_2, rt, 24 h, 78%; (i) $Ph_3P{=}CH_2$, THF, reflux, 8 h, 79%; (j) Et_2Zn, CH_2I_2, toluene, reflux 8 h, 68%; (k) H_2 balloon, PtO_2 (1 equiv), AcOH, 10 h, 78%; (l) BBr_3 (3.5 equiv), CH_2Cl_2, 0 °C, 83%. 9-BBN = 9-borabicyclo[3.3.1] nonane, DMP = Dess Martin periodinane, TPAP = tetra-n-propylammonium perruthenate, NMO = N-methylmorpholine N-oxide.

of ferruginol either were racemic or started from optically pure starting materials.[22] To the best of our knowledge, the catalytic asymmetric total synthesis of ferruginol was unexplored. We envisioned that **5g**-catalyzed enantioselective polyene cyclization product **3r** would be a valid intermediate for the asymmetric total synthesis of (−)−ferruginol. As shown in Scheme 3, the cyclization precursor **7** can be synthesized easily in accordance with the reported procedures from commercially available starting materials.[17] Under the standard reaction conditions, tricyclic product **3r** was obtained in good yield and with excellent enantioselectivity. Pd-catalyzed Suzuki coupling and Pd/C-catalyzed hydrogenation introduced the isopropyl group to the phenyl ring of the core structure. The deprotection of the tosyl group was removed by means of Li/naphthalene, furnishing compound **9**, the oxidation of which provided ketone **10**. The carbonyl functionality of ketone **10** was transformed into a gem-dimethyl group in good yield by employing a three-step strategy. Finally, demethylation of **13** with boron tribromide afforded the target (−)−ferruginol **14**. The as-synthesized (−)−ferruginol has the same NMR spectral data as those of (+)−ferruginol but an opposite optical rotation.[23] It should be noted that the analogs of ketone **10** are key intermediates for the total synthesis of natural products (+)-triptolide[24] and steviol,[25] which means that this method could also be used for the catalytic asymmetric total synthesis of enantioenriched triptolide and steviol.

In conclusion, we have developed the first BINOL-derived chiral NPA-catalyzed protonation of imine initiated enantioselective polyene cyclization. NPA **5g** functioned as an artificial protonase, which not only initiated but also controlled the stereochemistry of the overall transformation, in which one C–N bond and two C–C bonds were formed to furnish a tricyclic framework containing three contiguous stereocenters, including a quaternary carbon center. The noncovalent interactions,[26] including the cation–π interaction, π–π interaction, electrostatic interaction, and steric interaction between the iminium ion and the counter anion of the chiral NPA played crucial roles in controlling the stereoselectivity. The synthetic achievement of this cascade protocol could hardly be surpassed by stepwise techniques. The enantioenriched tricyclic products could be transformed into useful intermediates for the enantioselective total synthesis of natural products. The first catalytic asymmetric total synthesis of (−)−ferruginol using NPA **5g**-catalyzed enantioselective polyene cyclization as the key step further demonstrated the potential applicability of this method in complex molecular syntheses.

Experimental Section

To an oven-dried Schlenk tube equipped with a magnetic stir bar were added $TsNH_2$ (68.5 mg, 0.4 mmol, 4.0 equiv), BINOL-derived chiral N-phosphoramide (NPA) **5g** (16.6 mg, 0.02 mmol, 20 mol%), $MgS_2O_3{\cdot}H_2O$ (0.2 mmol, 2.0 equiv) and CH_2Cl_2 (4 mL) at room temperature. Then the reaction mixture was cooled to -60 ˚C and aldehyde **1** (0.1 mmol, 1.0 equiv) was added. The sealed Schlenk tube was stirred at -60 ˚C for 15 ~ 28 h. Upon the reaction completion (monitored by TLC), the solvent was removed in vacuo and the residue was purified by silica gel chromatography (eluent: petroleum ether/EtOAc = 20/1 to 4/1) to afford the desired products **3a**–**3r**.

Acknowledgements ((optional))

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Keywords: enantioselective polyene cyclization • asymmetric synthesis • chiral N-phosphoramide • total synthesis of ferruginol • terpene

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[20] CCDC 1577401 (racemic **3a**), 1577402 (racemic *β*-NH diastereomer **3a'**), 1577403 (enantioenriched **3r**) contain the complete crystallographic data for this paper. These data can be obtained free of charge upon request from the Cambridge Crystallographic Data Centre.

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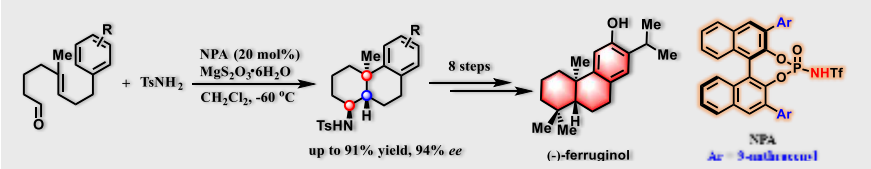

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Enantioselective Polyene Cyclization Catalyzed by Chiral Brønsted Acid

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