



Published in final edited form as:

Angew Chem Int Ed Engl. 2016 April 11; 55(16): 4983–4987. doi:10.1002/anie.201600766.

Mixed-Ligand Chiral Rhodium(II) Catalyst Enables the Enantioselective Total Synthesis of Piperarborenine B

Robert A. Panish, Srinivasa R. Chintala, and Prof. Joseph M. Fox

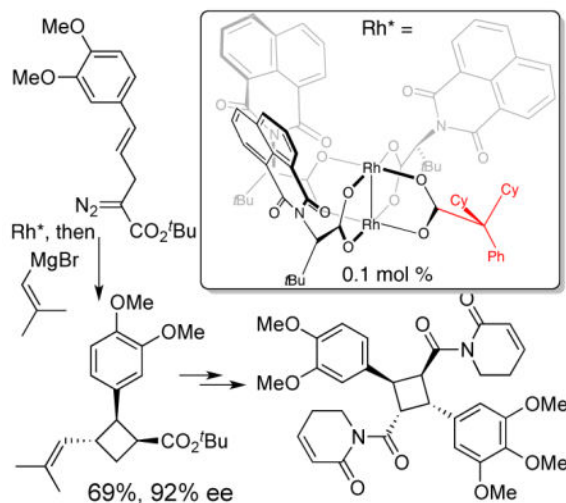
Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, United States

Joseph M. Fox: jmfox@udel.edu

Abstract

A novel, mixed-ligand chiral rhodium(II) catalyst, $\text{Rh}_2(\text{S-NTTL})_3(\text{dCPA})$, has enabled the first enantioselective total synthesis of the natural product piperarborenine B. A crystal structure of $\text{Rh}_2(\text{S-NTTL})_3(\text{dCPA})$ reveals a “chiral crown” conformation with a bulky dicyclohexylphenyl acetate ligand and three N-naphthalimido groups oriented on the same face of the catalyst. The natural product was prepared on large scale using rhodium-catalyzed bicyclobutanation/copper-catalyzed homoconjugate addition chemistry in the key step. The route proceeds in ten steps with an 8% overall yield and 92% ee.

Graphical abstract



Mixing Ligands: A new mixed-ligand chiral rhodium(II) catalyst, $\text{Rh}_2(\text{S-NTTL})_3(\text{dCPA})$, has enabled the first enantioselective total synthesis of the natural product piperarborenine B. Key to the synthesis is a rhodium-catalyzed bicyclobutanation/copper-catalyzed homoconjugate addition

Correspondence to: Joseph M. Fox, jmfox@udel.edu.

Supporting information for this article is given via a link at the end of the document. CCDC 1449073 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

for complex cyclobutane synthesis. The natural product was prepared on 400 mg scale and 8% overall yield.

Keywords

chiral rhodium catalyst; bicyclobutane; strained molecule; homoconjugate addition; piperarborenine B

Truxillate and truxinate natural products exhibit diverse biological activities. These molecules and their derivatives display potential as therapeutic leads in areas including oncology, neurology, infectious diseases, and respiratory diseases.^[1] Despite the significant number of natural lead compounds, the underrepresentation^[2] of cyclobutane-containing drugs is a reflection of an area in organic chemistry where concise, general and stereoselective methods for cyclobutane synthesis are still needed.

Piperarborenine B, a cyclobutane-containing natural product isolated from *Piper arborescens*, has exhibited activity against P-388, A-549, and HT-29 cancer cell lines (IC₅₀ = 0.13, 1.4, and 2.4 μM, respectively).^[3] Other cyclobutane-containing natural products such as incarvillateine,^{[4][5]} paufferol A^[1d] and the synthetic SB-FI-26^[6] have also exhibited exciting biological activities, with the cyclobutane core proving to be an essential feature.

There are several ways to access truxillate and truxinate natural products, but most are focused on the preparation of compounds with symmetrical cyclobutane cores. The photochemical [2+2] reaction has factored significantly in the total synthesis of *symmetrical* truxillic acid and related derivatives,^[7] including elegant solutions from crystal engineering^[8] and advances from redox photocatalysis.^[9] Alternatively, truxinic acid derivatives have been formed in modest diastereoselectivity by [2+2] photocycloaddition in flow.^[10] However, direct photodimerization is extremely limited for the construction of cyclobutane natural products where the core is chiral and the alkene precursors are non-equivalent such as the compounds displayed in Figure 1.^[8b]

In recent years, catalytic C–H activation methods have factored prominently in the elaboration of cyclobutane natural products.^[11] Recently, Baran has shown that racemic tri- and tetrasubstituted cyclobutanes can be prepared from disubstituted cyclobutanes through sequential arylation and vinylation reactions,^[12] using directing groups and catalytic conditions originally developed by Daugulis^[11b, 13] and also popularized by Chen.^[14] Baran's synthesis of piperarborenine B showcased sequential cyclobutane C(sp³)–H activation to construct the unsymmetrical truxillate core. This approach provided racemic piperarborenine B in 7% overall yield in 7 steps.

Several enantioselective approaches to unsymmetrical cyclobutane cores have been described in recent years.^[15–20] Tang has reported the synthesis of the initially assigned structures of pipericyclobutanamide A and piperchabamide G via Rh(I)-catalyzed conjugate addition of arylboronic acid to a cyclobutenoate derived from enantiospecific cyclopropane ring expansion.^[15] Rh₂(5*S*-MEPY)₄-catalyzed cyclopropanation was used to set the

stereochemistry of the core in 80% ee. This study revised the assignments to the six-membered ring isomers chabamide and nigramide F, respectively.

Recently, our group has introduced a modular new approach to chiral cyclobutane synthesis involving tandem Rh(II)-catalyzed enantioselective ‘bicyclobutanation’^[21]/Cu(I)-catalyzed homoconjugate addition of α -cinnamyl- α -diazoesters (Scheme 1).^[22, 23] Inspired by the unique bioactivities of a number of cyclobutane-containing natural products, we sought to demonstrate the power of our strategy for enantioselective synthesis of unsymmetrical cyclobutanes. Additionally, we realized this would potentially enable rapid diversification of complex cyclobutanes for SAR studies. Herein, we report the first enantioselective total synthesis of piperarborenine B (**1**). Critical to the synthesis was the development of a new, chiral Rh(II)-carboxylate complex that catalyzes the key bicyclobutanation step with high enantioselectivity and turnover number. Additional key aspects of the synthesis include improved ‘on water’ conditions for cyclobutane C–H activation and a streamlined route that was used to produce the natural product on 400 mg scale in only one week from veratraldehyde.

Retrosynthetically, we envisioned the α -truxillate core of **7** arising from a Baran late stage C–H activation using a properly installed directing group. The stereotriad **5** would be constructed using our previously developed enantioselective bicyclobutanation/homoconjugate addition chemistry. The required diazoester **3** would arise from commercially available veratraldehyde using a Tsuji-Trost allylation in a key step.

The synthesis commenced by developing a synthesis of the diazoester (**3**). Several efficient routes to the compound were developed (see supporting information). In the most time and scale efficient route (Scheme 3), veratraldehyde was treated with vinylMgBr to provide a vinyl alcohol that was shown to be an effective substrate for an ‘on water’ Tsuji-Trost allylation of *tert*-butyl acetoacetate using Pd(OAc)₂ (2 mol %), PPh₃ (10 mol %), and adamantoic acid (10 mol %).^[24] Treatment of ketoester **2** with *p*-ABSA, and NaOH in a mixture of acetonitrile/H₂O provided the desired diazoester **3** in 47% yield over three steps. This three step process for diazoester synthesis was accomplished in one day and represents an efficient new strategy for α -allyl- α -diazoester synthesis.

Recently, our group^[22] and that of Davies^[21] have described complementary catalyst systems for enantioselective bicyclobutanation. Our system provides access to *tert*-butyl bicyclobutane carboxylates that can be combined *in situ* with Grignard reagents to produce functionalized, enantiomerically enriched cyclobutanes.^[22] In our previous work, we described Rh₂(*S*-NTTL)₄ as an effective catalyst for bicyclobutanation in terms of enantioselectivity and yield. However, our efforts to apply this catalyst produced the bicyclobutane intermediate **4** in only 84% ee (Scheme 4). Screening efforts with other symmetrical catalysts were unsuccessful (see SI for full optimization table).

Recently, our group described the mixed-ligand Rh(II)-catalyst, Rh₂(*S*-PTTL)₃(TPA), a dirhodium paddlewheel complex that is substituted by three chiral ligands and one achiral ligand.^[25] This catalyst displayed superior results in certain enantioselective cyclopropanation, cyclopropenation and indole functionalization reactions. Our

computational and crystallographic studies showed that it adopts a ‘chiral crown’ conformation, where the *N*-phthalimido groups are all presented on the same face. In the bicyclobutanation of **3**, Rh₂(*S*-PTTL)₃(TPA) gave the bicyclobutane **4** in a promising 60% ee. We speculated that replacing TPA with a ligand that makes non-covalent contacts between the chiral ligand and substrate may be beneficial to asymmetric induction. We further speculated that a large achiral ligand may rigidify the chiral crown arrangement of the chiral ligands. Accordingly we designed a new mixed-ligand Rh(II)-catalyst, Rh₂(*S*-NTTL)₃(dCPA), which contains a bulky dicyclohexylphenylacetate group (dCPA) as the achiral ligand. A crystal structure of Rh₂(*S*-NTTL)₃(dCPA) revealed that the chiral crown conformation was conserved with the bulky dCPA ligand. As shown in Figure 2, the *N*-naphthalimido groups are oriented on the same face of the catalyst with the sterically demanding *tert*-butyl groups on the opposite face blocking reactivity on the bottom face of the catalyst. Indeed, this new mixed-ligand complex gave 92% ee and 79% yield of the bicyclobutane. With this optimal catalyst in hand, we used it in the key step in a one-pot bicyclobutanation/homoconjugate addition sequence to assemble the core of piperarborenine **B**. Hence, treatment of diazoester **3** with 0.1 mol % Rh₂(*S*-NTTL)₃(dCPA) at -78 °C in toluene followed by cuprate addition using CuBr•SMe₂, PPh₃, and 2-methyl-1-propenylmagnesium bromide in THF provided the desired trisubstituted cyclobutane **5** in 69% yield, 92% ee and 4:1 dr after kinetic protonation with BHT.

In order to set the desired stereochemical relationship of the cyclobutane ring, kinetic protonation with a bulky proton source was required. BHT was an effective proton source providing the desired diastereomer in 4:1 dr.^[22] An even higher 6:1 dr was obtained with the sterically demanding 2,6-di(adamantan-1-yl)-4-(*tert*-butyl)phenol, but unfortunately this high selectivity was poorly reproducible upon scale up. For this reason, BHT was chosen for large scale synthesis of the enantiomerically enriched cyclobutane **5**, which was prepared in gram quantities.

We next sought to install the amide directing group to facilitate subsequent Pd-catalyzed C–H activation. The carboxylate functionality was unveiled by an ozonolysis/Pinnick oxidation sequence. First, vinylcyclobutane **5** was treated with O₃ in the presence of 1,3,5-trimethoxybenzene, an additive found to suppress over-oxidation of the electron-rich 1,2-dimethoxyphenyl group. After reductive quench with PPh₃, the aldehyde intermediate was oxidized to the carboxylic acid by Pinnick oxidation. The crude carboxylic acid was used in a HATU-enabled coupling with 2-(methylthio)aniline to install the desired directing group providing cyclobutane **6** in 66% yield, along with an additional 14% yield of a separable diastereomer derived from the minor diastereomer of **5**.

Initial attempts at C–H activation using known conditions^[12a] (Ar-I, Pd(OAc)₂, Ag₂CO₃, *tert*-BuOH, 75 °C) provided the arylated product in 45% yield and incomplete conversion of starting material. Gratifyingly, we discovered that the yield was significantly improved by running the reaction ‘on water.’^[26] Thus, the combination of 3,4,5-trimethoxyiodobenzene, Pd(OAc)₂, PivOH, and K₂CO₃ on water gave the desired cyclobutane **7** in 69% yield. These conditions avoid the use of Ag₂CO₃ and also proceed considerably faster with full consumption of starting material after 12 h (as opposed to 45% yield and 80% conversion after 36 h in *tert*-BuOH at 75 °C). Running the reaction neat led to a slightly diminished

56% yield. Interestingly, microwave heating at 100 °C resulted in 55% yield with incomplete conversion after only 20 minutes but was not further investigated due to scalability limitations of our microwave reactor.

The directing group was removed by converting to the Bocamide followed by hydrolysis with lithium hydroperoxide. ^{[12a],[27]} The remaining *tert*-butylester monoacid was treated with TFA to afford the diacid **8**. The synthesis of piperarborenine B was completed by dihydropyridinone addition to *in situ* generated diacyl chloride in 75% yield (Scheme 6).

In conclusion, the highly efficient, enantioselective total synthesis (8% overall yield) can be completed in only one week to produce 400 mg of the natural product, piperarborenine B. Key features include a new protocol for α -allyl- α -diazoester synthesis that can be completed in one day while avoiding unstable intermediates. A new mixed-ligand Rh(II)-catalyst was designed, synthesized and demonstrated to be effective for the key bicyclobutanation step in 92% ee with only 0.1 mol % of the catalyst. This catalytic enantioselective reaction can be employed in a one-pot bicyclobutanation/homoconjugate addition cascade to establish the cyclobutane core. ‘On water’ conditions for cyclobutane C–H activation were found to be particularly effective in forming the truxillate core. The use of aqueous media factored prominently in this total synthesis with two steps conducted ‘on water’ (Tsuji-Trost allylation and C–H activation) and three other steps conducted in aqueous/organic mixtures. The reported route is especially modular featuring several points of derivatization that can enable straightforward synthesis of enantiomerically enriched analogues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

For funding we thank NSF CHE 1300329. RAP thanks NIH T32GM008550 for a training grant. For instrumentation we thank NIH P20GM104316, P30GM110758, S10RR026962-01, S10OD016267-01 and NSF grants: CHE 0840401, CHE-1229234 and CHE-1048367. We are grateful to Glenn Yap for the determining the crystal structure of Rh₂(S-NTTL)₃(dCPA).

References

1. a) Dembitsky VM. *J Nat Med.* 2008; 62:1–33. [PubMed: 18404338] b) Sergeiko A, Poroikov VV, Hanuš LO, Dembitsky VM. *Open Med Chem J.* 2008; 2:26–37. [PubMed: 19696873] c) Tan JJ, Tan CH, Wang YQ, Jiang SH, Zhu DY. *Helv Chim Acta.* 2006; 89:117–121. d) Nozaki H, Hayashi KI, Kido M, Kakumoto K, Ikeda S, Matsuura N, Tani H, Takaoka D, Iinuma M, Akao Y. *Tetrahedron Lett.* 2007; 48:8290–8292.
2. McGrath NA, Brichacek M, Njardarson JT. *J Chem Ed.* 2010; 87:1348–1349.
3. a) Lee FP, Chen YC, Chen JJ, Tsai IL, Chen IS. *Helv Chim Acta.* 2004; 87:463–468. b) Tsai IL, Lee FP, Wu CC, Duh CY, Ishikawa T, Chen JJ, Chen YC, Seki H, Chen IS. *Planta Med.* 2005; 71:535–542. [PubMed: 15971125]
4. a) Nakamura M, Chi YM, Yan WM, Nakasugi Y, Yoshizawa T, Irino N, Hashimoto F, Kinjo J, Nohara T, Sakurada S. *J Nat Prod.* 1999; 62:1293–1294. [PubMed: 10514316] b) Nakamura M, Chi YM, Kinjo J, Yan WM, Nohara T. *Phytochemistry.* 1999; 51:595–597.
5. a) Chi YM, Nakamura M, Yoshizawa T, Zhao XY, Yan WM, Hashimoto F, Kinjo J, Nohara T, Sakurada S. *Biol Pharm Bull.* 2005; 28:1989–1991. [PubMed: 16204962] b) Nakamura M, Chi YM,

- Yan WM, Yonezawa A, Nakasugi Y, Yoshizawa T, Hashimoto F, Kinjo J, Nohara T, Sakurada S. *Planta Med.* 2001; 67:114–117. [PubMed: 11301854]
6. Berger WT, Ralph BP, Kaczocha M, Sun J, Balius TE, Rizzo RC, Haj-Dahmane S, Ojima I, Deutsch DG. *PLoS ONE.* 2012; 7:e50968. [PubMed: 23236415]
7. a) Iriondo-Alberdi J, Greaney MF. *Eur J Org Chem.* 2007; 2007:4801–4815. b) Bach T, Hehn JP. *Angew Chem Int Ed.* 2011; 50:1000–1045. c) Crimmins MT. *Chem Rev.* 1988; 88:1453–1473.
8. a) Ichikawa M, Takahashi M, Aoyagi S, Kibayashi C. *J Am Chem Soc.* 2004; 126:16553–16558. [PubMed: 15600360] b) Skiredj A, Beniddir MA, Joseph D, Leblanc K, Bernadat G, Evanno L, Poupon E. *Angew Chem Int Ed.* 2014; 53:6419–6424. c) Biradha K, Santra R. *Chem Soc Rev.* 2013; 42:950–967. [PubMed: 23223680]
9. a) Ischay MA, Anzovino ME, Du J, Yoon TP. *J Am Chem Soc.* 2008; 130:12886–12887. [PubMed: 18767798] b) Du J, Yoon TP. *J Am Chem Soc.* 2009; 131:14604–14605. [PubMed: 19473018] c) Ischay MA, Ament MS, Yoon TP. *Chem Sci.* 2012; 3:2807–2811. [PubMed: 22984640] d) Riener M, Nicewicz DA. *Chem Sci.* 2013; 4:2625–2629.
10. Telmesani R, Park SH, Lynch-Colameta T, Beeler AB. *Angew Chem Int Ed.* 2015; 54:11521–11525.
11. a) Engle KM, Mei TS, Wasa M, Yu JQ. *Acc Chem Res.* 2012; 45:788–802. [PubMed: 22166158] b) Nadres ET, Santos GI, Shabashov D, Daugulis O. *J Org Chem.* 2013; 78:9689–9714. [PubMed: 24090404] c) Neufeldt SR, Sanford MS. *Acc Chem Res.* 2012; 45:936–946. [PubMed: 22554114]
12. a) Gutekunst WR, Baran PS. *J Am Chem Soc.* 2011; 133:19076–19079. [PubMed: 22066860] b) Gutekunst WR, Baran PS. *J Org Chem.* 2014; 79:2430–2452. [PubMed: 24548142] c) Gutekunst WR, Gianatassio R, Baran PS. *Angew Chem Int Ed.* 2012; 51:7507–7510.
13. a) Shabashov D, Daugulis O. *J Am Chem Soc.* 2010; 132:3965–3972. [PubMed: 20175511] b) Zaitsev VG, Shabashov D, Daugulis O. *J Am Chem Soc.* 2005; 127:13154–13155. [PubMed: 16173737]
14. a) He G, Chen G. *Angew Chem Int Ed.* 2011; 50:5192–5196. b) Feng Y, Chen G. *Angew Chem Int Ed.* 2010; 49:958–961.
15. a) Liu R, Zhang M, Wyche TP, Winston-McPherson GN, Bugni TS, Tang W. *Angew Chem Int Ed.* 2012; 51:7503–7506. b) Xu H, Zhang W, Shu D, Werness JB, Tang W. *Angew Chem Int Ed Engl.* 2008; 47:8933–8936. [PubMed: 18850597]
16. a) Albrecht L, Dickmeiss G, Cruz Acosta F, Rodriguez-Escrich C, Davis RL, Jørgensen KA. *J Am Chem Soc.* 2012; 134:2543–2546. [PubMed: 22280440] b) Halskov KS, Kniep F, Lauridsen VH, Iversen EH, Donslund BS, Jørgensen KA. *J Am Chem Soc.* 2015; 137:1685–1691. [PubMed: 25575040]
17. Du J, Skubi KL, Schultz DM, Yoon T. *Science.* 2014; 344:392–396. [PubMed: 24763585]
18. Johnson T, Choo K-L, Lautens M. *Chem Eur J.* 2014; 20:14194–14197. [PubMed: 25233924]
19. a) Chen G, Shigenari T, Jain P, Zhang Z, Jin Z, He J, Li S, Mapelli C, Miller MM, Poss MA, Scola PM, Yeung KS, Yu JQ. *J Am Chem Soc.* 2015; 137:3338–3351. [PubMed: 25697780] b) Xiao KJ, Lin DW, Miura M, Zhu RY, Gong W, Wasa M, Yu JQ. *J Am Chem Soc.* 2014; 136:8138–8142. [PubMed: 24815880]
20. Chen Y-J, Hu T-J, Feng C-G, Lin G-Q. *Chem Commun.* 2015; 51:8773–8776.
21. Concomitant with our previous work Davies has independently described complementary bicyclobutanation conditions: Qin C, Davies HML. *Org Lett.* 2013; 15:310–313. [PubMed: 23286365]
22. Panish R, Chintala SR, Boruta DT, Fang Y, Taylor MT, Fox JM. *J Am Chem Soc.* 2013; 135:9283–9286. [PubMed: 23758288]
23. Homoconjugate additions of arylsulfonyl-substituted bicyclobutanes: Gianatassio R, Lopchuck JM, Wang J, Pan C-M, Malins LR, Prieto L, Brandt TA, Collins MR, Gallego GM, Sach NW, Spangler JE, Zhu H, Zhu J, Baran PS. *Science.* 2016; 351:241–246. [PubMed: 26816372]
24. a) Manabe K, Kobayashi S. *Org Lett.* 2003; 5:3241–3244. [PubMed: 12943397] b) Shibuya R, Lin L, Nakahara Y, Mashima K, Ohshima T. *Angew Chem Int Ed.* 2014; 53:4377–4381.
25. Boruta DT, Dmitrenko O, Yap GPA, Fox JM. *Chem Sci.* 2012; 3:1589–1593. [PubMed: 23125912] For heteroleptic Rh(II) complexes composed solely of chiral ligands, see: Lindsay VNG, Charette AB. *ACS Catal.* 2012; 2:1221–1225.

26. Li, B.; Dixneuf, PH. Metal-Catalyzed Reactions in Water. Wiley-VCH Verlag GmbH & Co., KGaA; 2013. p. 47-86.
27. Evans DA, Britton TC, Ellman JA. Tetrahedron Lett. 1987; 28:6141–6144.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

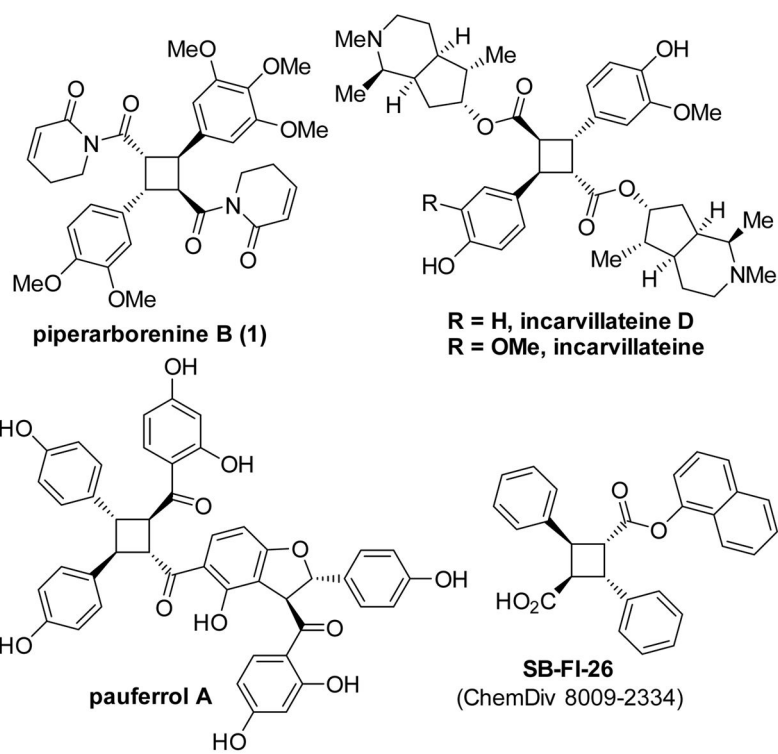


Figure 1.
Cyclobutane-containing natural products and drug leads.

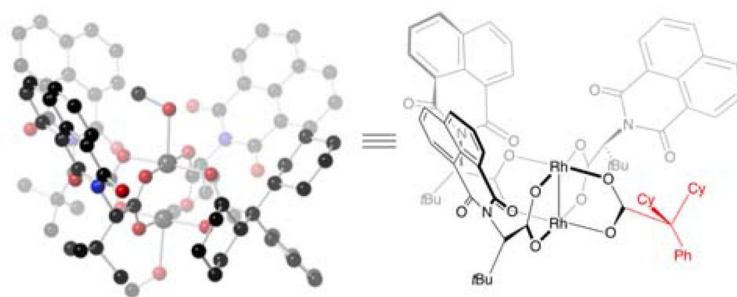
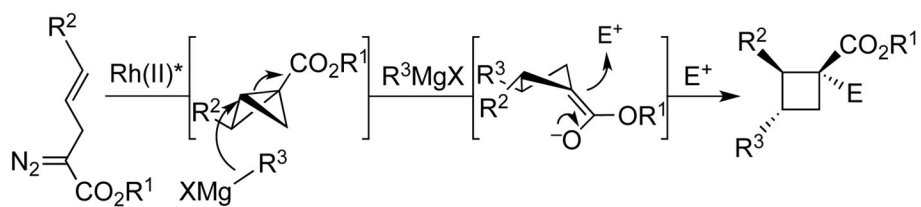
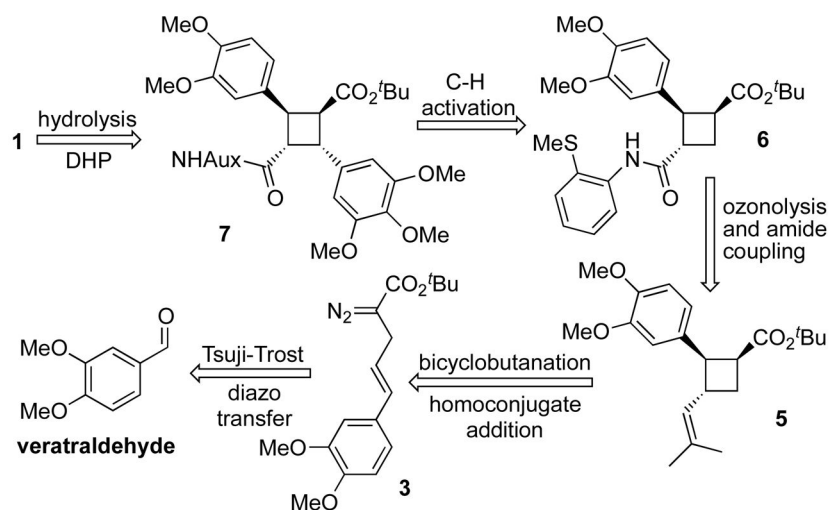


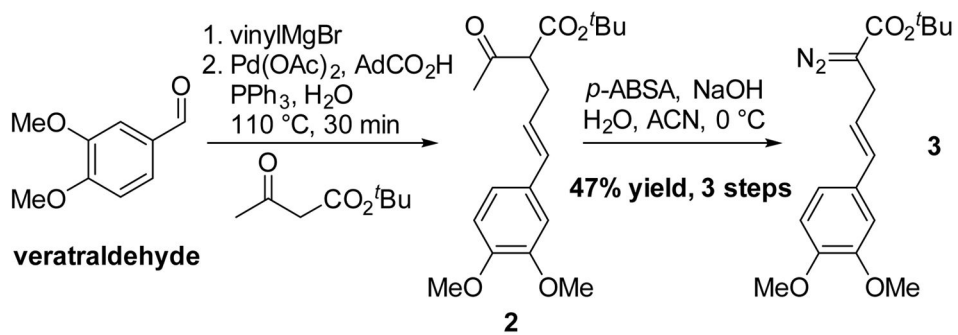
Figure 2.
X-ray crystal structure of $\text{Rh}_2(\text{S-NTTL})_3(\text{dCPA})$.

**Scheme 1.**

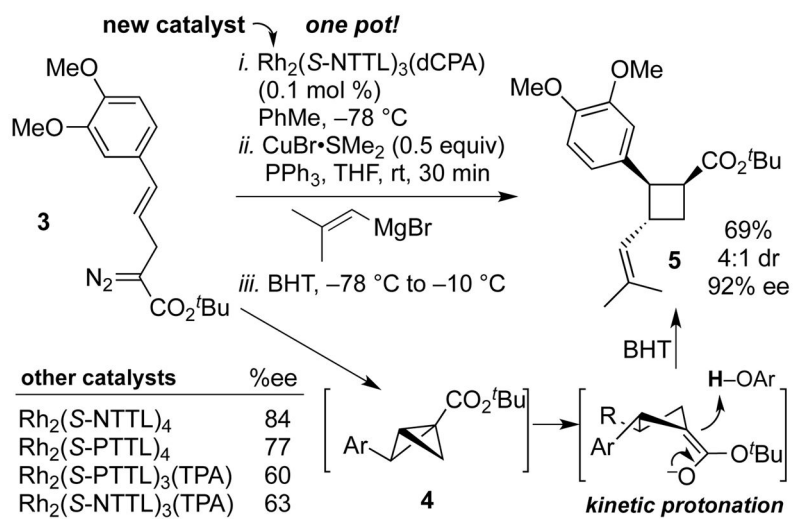
Bicyclobutanation/homoconjugate addition strategy for enantioselective cyclobutane synthesis.



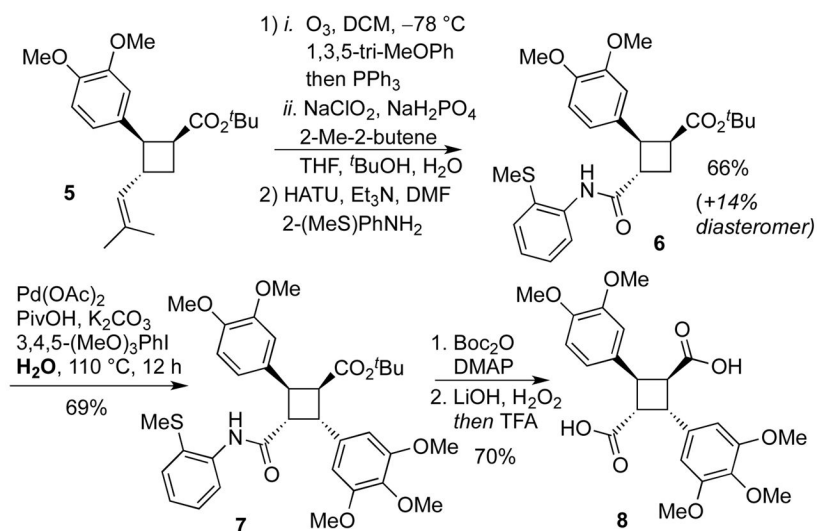
Scheme 2.
Retrosynthetic strategy for the enantioselective synthesis of piperarborenine B.

**Scheme 3.**

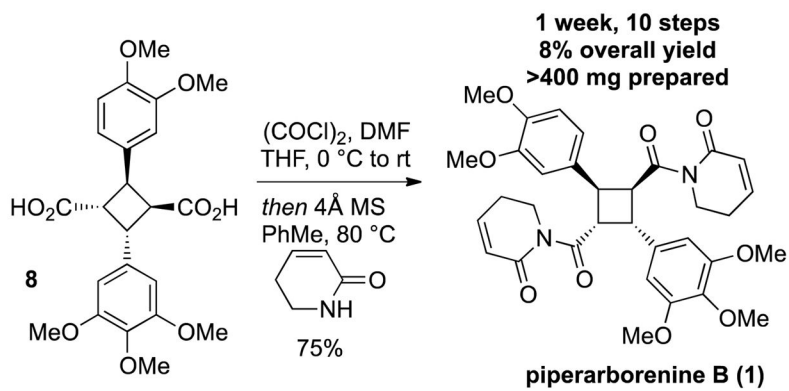
An efficient route to the substituted diazoester, **3**.

**Scheme 4.**

Rh(II)-catalyst screening and enantioselective synthesis of vinylcyclobutane, **5**.



Scheme 5.
 Directing group installation, Pd-catalyzed C–H activation and hydrolysis via lithium hydroperoxide.



Scheme 6.
Completion of piperarborenine B.