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An Asymmetric Pathway to Dendrobine by a Transition-Metal-Catalyzed Cascade Process

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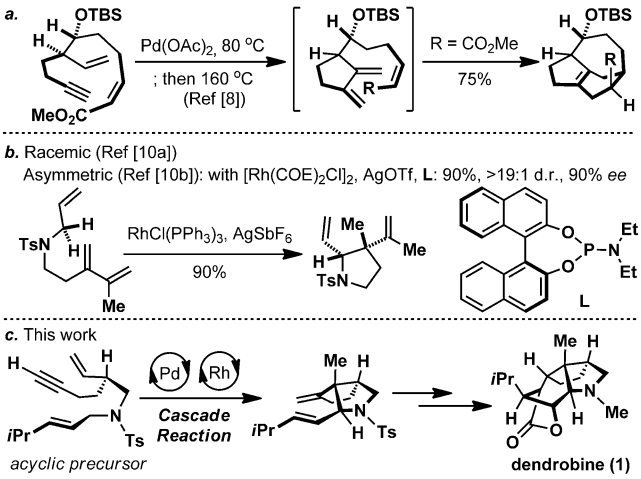
Abstract: *An asymmetric pathway to the caged tetracyclic pyrrolidine alkaloid, dendrobine, is reported. The successful synthetic strategy features a one-pot, sequential palladium-catalyzed enyne cycloisomerization and rhodium-catalyzed diene-assisted pyrrolidine formation by allylic CH activation. The developed transition-metal-catalyzed cascade process permits rapid access to the dendrobine core structure and circumvents the handling of labile intermediates. An intramolecular aldol condensation under carefully defined reaction conditions takes place with a concomitant detosylation, followed by reductive amine methylation, to afford a late-stage intermediate (previously identified by several prior dendrobine syntheses) in only 10 synthetic steps overall.*

Synthetic organic chemistry has made significant strides in terms of reducing the high step-count traditionally associated with the total synthesis of complex architectures.[1] Synthetic strategies that embrace redox[2] and protecting group[3] economy are particularly attractive, together with complexity-generating transformations in the context of cascade and domino reactions.[4] In connection with the latter, there is a growing interest in concurrent introduction of several non-interfering reagents, either simultaneously or sequentially, to a single reaction vessel.[5] In doing so, workup and purification are significantly reduced, and the isolation of potentially hazardous and/or labile intermediates is circumvented. However, realization of such one-pot operations are non-trivial, and require in depth understanding of the individual reagents, the anticipated byproduct(s) derived from each reagent, and substrate/product compatibility with each reagent and its byproduct(s). Furthermore, implementation of catalytic transformations poses an even greater challenge, primarily because of concerns over catalyst inhibition and turnover efficiency. In spite of these challenges, several reports of multimetal and multiligand catalytic transformations have appeared recently,[6] most notably the contributions from the Lautens laboratory.[7]

We have previously demonstrated an enyne cycloisomerization/Diels–Alder cascade process to assemble the core structure of the echinopines (Scheme 1 a).[8] In connection with this study, we pondered whether an enyne cycloisomerization product could further participate in other conjugated diene-specific transformations. Specifically,



Scheme 1. a) Previously reported cascade enyne cycloisomerization/intramolecular Diels–Alder reaction. b) Diene-assisted CH activation in the synthesis of substituted pyrrolidines. c) Proposed dienyne cascade reaction to access the core structure of dendrobine (**1**). Key: isopropyl (*i*Pr), *tert*-butyldimethylsilyl (TBS), cyclooctene (COE), *para*-toluenesulfonyl (Ts).

several transition-metal-mediated, conjugated diene-specific transformations have been reported,[9] and more recently the Yu laboratory demonstrated a serendipitous conjugated diene-assisted CH-activation process in the synthesis of substituted pyrrolidines together with its asymmetric variant (Scheme 1 b).[10] All facts considered, and mindful of the structural framework of the anticipated cascade reaction product, the polycyclic alkaloid dendrobine (**1**)[11] was selected to showcase the newly developed synthetic technology and as a significant advance in comparison with the prior art (Scheme 1 c).[12] Furthermore, realization of the proposed synthetic strategy also represents a conceptually unique approach that exploits an entirely acyclic starting material—in stark contrast to the cyclic building blocks employed in all past dendrobine syntheses.

As outlined in Scheme 2, our synthetic investigation began with the preparation of the proposed cycloisomerization precursor **8**. *Trans*-1,4-dibromo-2-butene (**2**) was treated with alkynyl Grignard reagent **3** in the presence of a catalytic amount of $CuBr{\cdot}SMe_2$ (5 mol%) to afford the S_N2' product **4** exclusively. Subjecting homoallylic bromide **4** to a variety of protected and unprotected aliphatic amines and ammonia largely resulted in elimination; therefore, an azide displacement (NaN_3, 84% overall yield from **2**) followed by reduction ($LiAlH_4$) was implemented to furnish amine **6**. Reductive amination between amine **6** and enal **7** ($NaBH_4$), followed by

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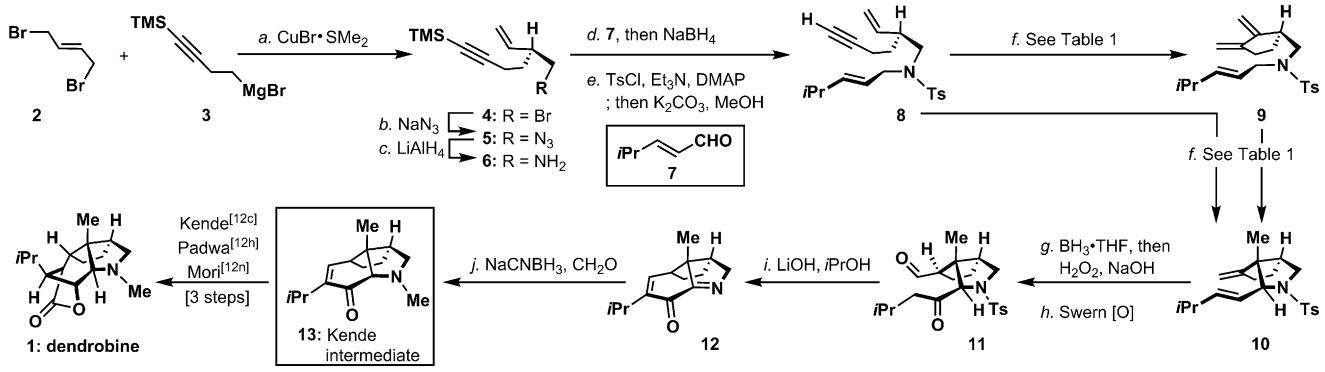
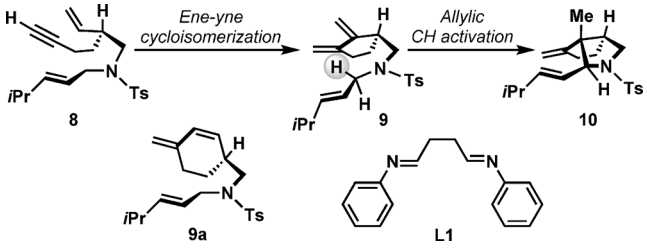


Scheme 2. Synthesis of dendrobine (**1**) via Kende Intermediate **13**. Reagents and Conditions: a) **3** (1.5 equiv), CuBr·SMe_2 (5.0 mol%), CH_2Cl_2, −78 °C, 1 h; b) NaN_3 (1.1 equiv), DMF, 23 °C, 16 h, 84% for two steps; c) $LiAlH_4$ (1.5 equiv), Et_2O, −78 to 23 °C, 2 h; d) **7** (1.0 equiv), $MgSO_4$ (1.0 wt. equiv), Et_2O, 23 °C, 2 h; then $NaBH_4$ (0.8 equiv), MeOH, 23 °C, 1 h; e) Et_3N (0.8 equiv), DMAP (0.17 equiv), TsCl (0.8 equiv), CH_2Cl_2, 23 °C, 16 h; followed by K_2CO_3 (1.7 equiv), MeOH, 23 °C, 16 h, 40% overall yield from **5**; f) see Table 1; g) BH_3·THF (10 equiv), THF, 0 °C, 2 h; followed by NaOH (10% aq.)/H_2O_2 (35% aq.) (1:1), THF, 0 to 50 °C, 1 h, 87%; h) $(COCl)_2$ (10 equiv), DMSO (20 equiv), CH_2Cl_2, −78 °C, 1 h; followed by Et_3N (30 equiv), −78 to 23 °C, 1 h, 86%; i) LiOH (0.1 equiv), *i*PrOH, 23 °C, 24 h, 80%; j) HCHO (37% aq., 20 equiv), $NaCNBH_3$ (10 equiv), AcOH (3.0 equiv), MeOH, −78 to 23 °C, 5 h, 53%. Key: acetic acid (AcOH), *N*,*N*′-(dimethylamino)pyridine (DMAP), *N*,*N*′-dimethylformamide (DMF), dimethylsulfoxide (DMSO), isopropanol (*i*PrOH), *para*-toluenesulfonyl chloride (TsCl), trimethylsilyl (TMS).

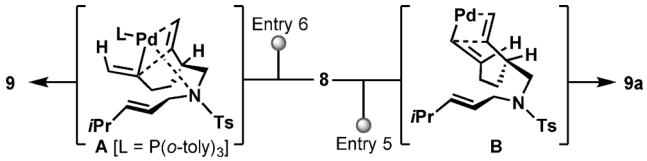
a one-pot tosylation (TsCl, Et_3N, DMAP) and desilylation (K_2CO_3, MeOH) provided the targeted dienyne **8** in 40% overall yield from azide **5**. In this manner, every reaction along the established pathway employed inexpensive and easily handled reagents, and required only two trivial chromatographic purifications (**5** and **8**) over the entire synthetic sequence.

With dienyne **8** in hand, the stage was set to investigate the proposed transition-metal-mediated cascade process. To obtain a clear picture of the individual processes, cycloisomerization of dienyne **8** was first examined.[13] In this context, while the desired reaction pathway involving the terminal alkene and alkyne in **8** was anticipated based on both kinetic and thermodynamic grounds, we were conscious of potential side reactions that might engage the pendant *trans*-disubstituted alkene prior to the desired cycloisomerization event. Pleasingly, enyne cycloisomerization product **9** was obtained from a variety of palladium catalytic systems (Table 1). However, certain conditions afforded varying amounts of the enyne-cycloisomerization product **9a** as a consequence of alkyne moiety participation in an *endo*- rather than the desired *exo*-mode (Table 1, Entries 1–6).[14] Trost had previ-

Table 1: Transition-metal-mediated cycloisomerization of dienyne **8** and diene-assisted CH activation of triene **9**.



Entry	Substrate	Conditions	Yield [%][c]
1	**8**	$Pd(OAc)_2$, benzene, 80 °C, 2 h	**9**+**9a** (35%), (**9**:**9a** 3:5)
2	**8**	$Pd(OAc)_2$, PPh_3, benzene or DCE, 80 °C, 2 h	**9** (76% or 69%)
3	**8**	$Pd(OAc)_2$, **L1**, benzene, 80 °C, 2 h	**9**+**9a** (24%), (**9**:**9a** 10:1)
4	**8**	$Pd(OAc)_2(PPh_3)_2$, benzene, 80 °C, 2 h	**9** (60%)
5	**8**	$Pd_2(dba)_3$, AcOH, benzene, RT, 12 h	**9**+**9a** (41%), (**9**:**9a** 1:8)
6	**8**	$Pd_2(dba)_3$, P(*o*-tolyl)$_3$, AcOH, benzene, RT, 12 h	**9**+**9a** (67%), (**9**:**9a** 10:1)
7	**8**	$Pd_2(dba)_3$, P(*o*-tolyl)$_3$, benzene, RT, 12 h	**8** (72%)
8	**8**	$[Rh(COD)Cl]_2$, $AgSbF_6$, PPh_3, DCE, 80 °C, 3 h	**8** (50%)
9[a]	**8**	$RhCl(PPh_3)_3$, $AgSbF_6$, DCE, 80 °C, 3 h	**8** (40%)
10[b]	**9**	$[Rh(COD)Cl]_2$, $AgSbF_6$, PPh_3, DCE, 80 °C, 3 h	**10** (43%)
11[b]	**9**	$RhCl(PPh_3)_3$, AgOTf, DCE, 80 °C, 3 h	**10** (35%)
12[a]	**9**	$RhCl(PPh_3)_3$, $AgSbF_6$, DCE, 80 °C, 3 h	**10** (67%)
13[b]	**9**	$RhCl(PPh_3)_3$, $AgSbF_6$, DCE, 80 °C, 3 h	**10** (15%)
14[a]	**8**	$Pd(OAc)_2$, PPh_3, DCE, 80 °C, 2 h; then $RhCl(PPh_3)_3$, $AgSbF_6$, DCE, 80 °C, 2 h	**10** (60%)
15[a]	**8**	$Pd(OAc)_2$, PPh_3, DCE, $RhCl(PPh_3)_3$, $AgSbF_6$, DCE, 80 °C, 2 h	**9** (70%)

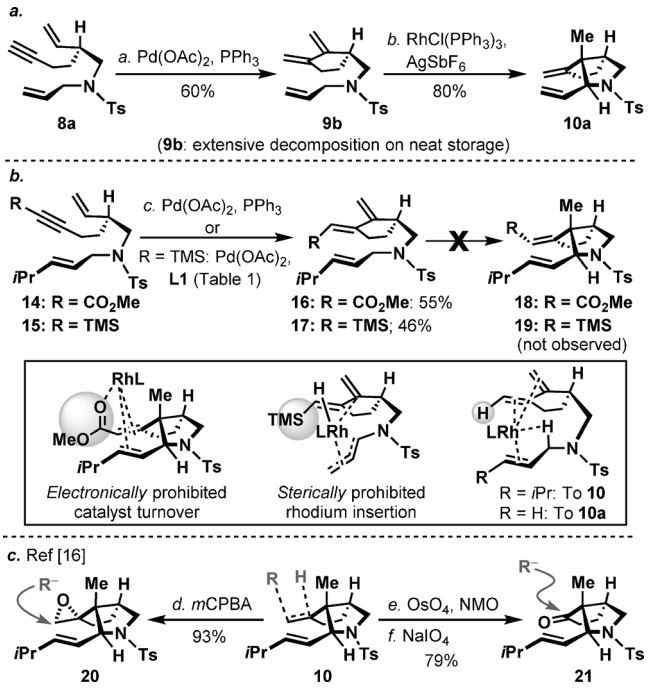


[a] Rhodium catalyst prepared by initially stirring at 80 °C for 1 h; [b] rhodium catalyst prepared by initially stirring at 23 °C for 1 h; [c] chromatographically isolated yield and product ratio determined by ^{1}H NMR analysis of the crude reaction mixture. Key: acetic acid (AcOH), acetate (OAc), 1,5-cyclooctadiene (COD), dibenzylideneacetone (dba), 1,2-dichloroethane (DCE), *ortho*-methylphenyl (*o*-tolyl).

ously suggested the $Pd(OAc)_2$ catalytic system operates by a different mechanistic pathway compared to the Pd^0/HX system (for example, X = acetate (OAc)); the latter process is believed to involve the initial generation of a H-Pd-X species followed by its hydropalladation of the terminal alkyne.[14d] Trost and coworkers further demonstrated that the cycloisomerization reaction under the Pd^0/HX catalytic system could be carried out in the presence or absence of a phosphine ligand ($P(o\text{-tolyl})_3$) to yield an identical product.[14d] However, in our studies the Pd^0/acetic acid (AcOH) system afforded the *endo*-enyne cycloisomerization product **9a** preferentially in the absence of phosphine ligand (Table 1, Entry 5), and more surprisingly, the *exo*-selectivity could be restored by introduction of $P(o\text{-tolyl})_3$ (Table 1, Entry 6). We speculate that the presence of phosphine ligand had a pronounced effect on the electronic nature of the palladium center and its coordinative ability with the proximal tosylamide nitrogen, as depicted by the post-hydropalladation transition states **A** and **B** leading to the corresponding cycloisomerization products **9** and **9a**, respectively. No productive cycloisomerization was observed under the Pd^0 system in the absence of AcOH (Table 1, Entry 7). During the course of reaction optimization, we routinely observed that the isolated yield of **9** was highly dependent on the storage duration of the neat crude reaction mixture. Further inspection by thin layer chromatography and ^1H NMR profiling of the crude reaction mixture was revealing. The lability of cycloisomerization product **9** was ultimately confirmed when insoluble polymeric materials were isolated from purified **9** that had been stored neat; this phenomenon was more pronounced for cycloisomerization product **9b** (Scheme 3a; Supporting Information). These counterproductive events strengthened the impetus of our investigation and highlighted the value of the synthetic technology described herein (see proceeding text).

With cycloisomerization product **9** secured (with care), its participation in the proposed conjugated diene-assisted CH-activation process was examined (Table 1, Entries 10–13). In this instance, while the originally developed procedure reported by Yu and Li was effective,[10a] we found the best result was obtained with a preheated and aged catalyst mixture containing $RhCl(PPh_3)_3$ and $AgSbF_6$, followed by introduction to a solution of freshly prepared triene **9**. This remarkable transformation required little fine-tuning compared to the originally reported method, and generated highly functionalized diene **10** (and **10a**; Scheme 3a) reproducibly. Bicyclic pyrrolidine **10** (and **10a**) was obtained as a single stereoisomer, and demonstrated excellent stability upon storage in solution and neat, at low or ambient temperatures.

The success of the palladium-catalyzed cycloisomerization and rhodium-catalyzed allylic CH functionalization as individual processes was a prerequisite for the proposed tandem process. We had already established that, under the palladium-catalyzed cycloisomerization conditions, diene **10** was not observed, and control experiments indicated that the rhodium catalyst system developed for the allylic CH-activation process was ineffective on dienyne **8** (Table 1, Entries 8 and 9). Gratifyingly, merging the palladium and rhodium catalyst systems as a one-pot process was realized by



Scheme 3. a) Palladium-catalyzed cycloisomerization of dienyne **8a** and rhodium-catalyzed formation of pyrrolidine **10a**; b) cycloisomerization of dienynes **14** and **15**, and attempted pyrrolidine formation; c) transformations projected for diene **10** and selected oxidative transformations (details in the Supporting Information). Key: *meta*-chloroperbenzoic acid (*m*CPBA), *N*-methylmorpholine *N*-oxide (NMO).

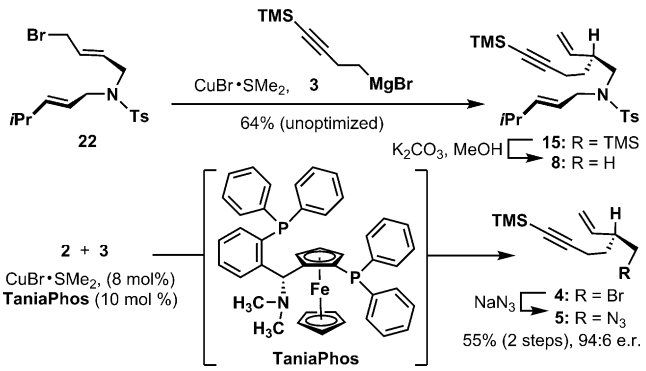
sequential introduction of the preformed catalyst blends, to generate bicyclic diene **10** directly from dienyne **8** (Table 1, Entry 14). The catalyst systems developed for the individual processes could be applied directly without modifications, while maintaining the low catalyst loading without increasing the reaction time. Furthermore, the stability issue associated with the cycloisomerization products **9** (and **9b**) was completely avoided, and on a practical scale the one-pot method afforded a slightly higher yield compared to the combined individual processes. Interestingly, simultaneous introduction of palladium and rhodium reagent blends to a solution of dienyne **8** only afforded the cycloisomerization product **9** (Table 1, Entry 15), and introduction of additional rhodium catalyst only marginally promoted the formation of pyrrolidine **10**.

Recognizing bicyclic pyrrolidine **10** harbors 15 of the 16 carbon atoms required for dendrobine (**1**), we pondered whether a slightly revised substrate could provide the entire carbon backbone of the target molecule. In this context, dienynoate **14** was envisaged as a suitable candidate. While the cycloisomerization of **14** proceeded smoothly, we were not able to execute the subsequent allylic CH-functionalization reaction (Scheme 3b). Although TMS–dienyne **15** was considered a more electronically compatible substrate, it shared a similar fate as dienynoate **14**. The precise reason(s) for these observations are yet to be uncovered; however, preliminary computational studies suggest dienoate **18** may suffer from inefficient catalyst turnover, whereas the vinylsilane in **17** may be prohibitive to the post-CH-activation rhodium

insertion. Furthermore, we also speculate that the initial rhodium catalyst complexation may be disfavored in CO_2Me and TMS bearing dienes **16** and **17**, respectively, compared to the sterically less-demanding diene in **9** (and **9b**).[15]

While the structural resemblance between bicyclic pyrrolidine **10** and dendrobine (**1**) was encouraging, we envisaged the two olefins within **10** had to be differentiated for the ensuing transformations (Scheme 3c).[16] In this regard, we discovered under carefully controlled conditions that diene **10** could be epoxidized by *meta*-chloroperbenzoic acid or dihydroxylated (OsO_4, *N*-methylmorpholine *N*-oxide) selectively at its 1,1-disubstituted olefin. However, upon contemplating the limited reaction scope and the number of synthetic steps forecasted to reach dendrobine (**1**), epoxide **20** and ketone **21** soon became less appealing. Continued redox investigations eventually revealed diene **10** could undergo a highly regio- and stereoselective hydroboration at both of its olefins ($BH_3{\cdot}SMe_2$) to afford the corresponding diol after oxidative workup (H_2O_2, NaOH, 87% yield), and could be further oxidized under Swern conditions (86% yield) to furnish ketoaldehyde **11** (Scheme 2). We were excited by the prospect of ketoaldehyde **11** participation in an intramolecular aldol condensation reaction; thereby delivering an enone structure closely resembling the Kende intermediate (**13**, Scheme 2) intercepted by several of the past dendrobine syntheses.[12c,h,n] However, we soon encountered uncertainty and failure with a variety of conventional and unconventional aldol condensation conditions.[17] Gratifyingly, continued efforts ultimately uncovered LiOH/*i*PrOH as an uniquely effective reagent system for the desired transformation,[18] together with an unexpected but fortuitous detosylation by β-elimination to afford enone **12** in a pleasing 80% yield. This latter observation was particularly noteworthy because it removed the need for the strong reducing conditions usually associated with detosylation, and the so-obtained imine **12** was converted to the known Kende intermediate (**13**) under reductive amination conditions ($NaCNBH_3$, AcOH, CH_2O_{aq})[19] (Scheme 2). Overall, the developed synthetic sequence—comprising designed and serendipitously discovered reactions—constituted one of the most efficient entries to dendrobine (**1**) to date. Finally, this expedient synthesis was streamlined through a related S_N2' reaction between allylic bromide **22**[20] and Grignard reagent **3** (Scheme 4), and became asymmetric under the allylic alkylation condition developed by Feringa and coworkers (TaniaPhos)[21] to afford optically active bromide **4** and azide **5** (94:6 e.r.).[22]

In conclusion, an expedient transition-metal-catalyzed synthetic pathway to dendrobine (**1**) was realized. Salient features of the developed synthesis include a copper-catalyzed asymmetric allylic alkylation, a palladium-catalyzed enyne cycloisomerization, a rhodium-catalyzed diene-assisted pyrrolidine formation by allylic CH activation, and a late-stage intramolecular aldol condensation with concomitant detosylation. Notably, the palladium and rhodium reagent systems could be introduced sequentially to a single reaction vessel, and in doing so reduced compound handling and obviated the isolation of the sensitive triene intermediate **9** (and **9a**). The mutual compatibility of the reagent systems discussed herein opens up opportunities for the discovery of new tandem catalytic transformations, which are currently under investigation in our laboratory.



Scheme 4. Alternative synthesis of dienyne **8** and synthesis of optically active bromide **4** and azide **5** (details in the Supporting Information).

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · cascade reactions · homogeneous catalysis · total synthesis · transition metals

[1] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40.
[2] T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010.
[3] I. S. Young, P. S. Baran, *Nature* **2009**, *457*, 193.
[4] For reviews of cascade reactions in total synthesis, see: a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; b) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p. 617; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; *Angew. Chem.* **2006**, *118*, 7292; d) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993; e) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167.

[5] a) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3605; *Angew. Chem.* **2011**, *123*, 3685; b) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866.

[6] For recent examples and a review on dual-metal cascade catalysis, see: a) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2004**, *126*, 16066; b) C. Kammerer, G. Prestat, T. Gaillard, D. Madec, G. Poli, *Org. Lett.* **2008**, *10*, 405; c) M. Zhang, H.-F. Jiang, H. Neumann, M. Beller, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2009**, *48*, 1681; *Angew. Chem.* **2009**, *121*, 1709; d) T. A. Cernak, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 3124; e) K. Yamamoto, T. Bruun, J. Y. Kim, L. Zhang, M. Lautens, *Org. Lett.* **2016**, *18*, 2644. For a review, see f) C. Bruneau, S. Derien, P. H. Dixneuf, *Top. Organomet. Chem.* **2006**, *19*, 295.

[7] For seminal contributions from the Lautens group on multiligand, multimetal catalysis, see: a) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem. Int. Ed.* **2011**, *50*, 9089; *Angew. Chem.* **2011**, *123*, 9255; b) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh, M. Lautens, *Angew. Chem. Int. Ed.* **2013**, *52*, 9755; *Angew. Chem.* **2013**, *125*, 9937; c) L. Zhang, L. Sonaglia, J. Stacey, M. Lautens, *Org. Lett.* **2013**, *15*, 2128; d) J. Tsoung, J. Panteleev, M. Tesch, M. Lautens, *Org. Lett.* **2014**, *16*, 110; e) L. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 13850; *Angew. Chem.* **2014**, *126*, 14070.

[8] P. A. Peixoto, R. Severin, C.-C. Tseng, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 3013; *Angew. Chem.* **2011**, *123*, 3069.

[9] For examples of the diene-effect in organic synthesis, see: a) P. A. Wender, N. M. Deschamps, T. J. Williams, *Angew. Chem. Int. Ed.* **2004**, *43*, 3076; *Angew. Chem.* **2004**, *116*, 3138; b) H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762; c) M. Gulıas, J. Duran, F. Lopez, L. Castedo, J. L. Mascarenas, *J. Am. Chem. Soc.* **2007**, *129*, 11026; d) S. W. Youn, J. I. Eom, *J. Org. Chem.* **2006**, *71*, 6705. For a review, see: e) M. P. Croatt, P. A. Wender, *Eur. J. Org. Chem.* **2010**, 19.

[10] a) Q. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 4542; b) Q. Li, Z.-X. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 2144; *Angew. Chem.* **2011**, *123*, 2192; c) Q. Li, Z.-X. Yu, *Organometallics* **2012**, *31*, 5185.

[11] a) H. Suzuki, I. Keimatsu, K. Ito, *J. Pharm. Soc. Jpn.* **1932**, *52*, 1049; b) H. Suzuki, I. Keimatsu, K. Ito, *J. Pharm. Soc. Jpn.* **1934**, *54*, 802; c) Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konika, J. Matsumoto, E. Katarao, J. Nakano, *Tetrahedron* **1964**, *20*, 2007; d) Y. Inubushi, Y. Sasaki, Y. Tsuda, J. Nakano, *Tetrahedron Lett.* **1965**, *6*, 1519.

[12] For racemic total syntheses, see: a) K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, Y. Hirata, *J. Am. Chem. Soc.* **1972**, *94*, 8278; b) Y. Inubushi, T. Kikuchi, T. Ibuka, T. Tanaka, I. Saji, K. Tokane, *J. Chem. Soc. Chem. Commun.* **1972**, 1252; c) A. S. Kende, T. J. Bentley, R. A. Mader, D. Ridge, *J. Am. Chem. Soc.* **1974**, *96*, 4332; d) W. R. Roush, *J. Am. Chem. Soc.* **1978**, *100*, 3599; e) C. H. Lee, M. Westling, T. Livinghouse, A. C. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 4089. For racemic formal syntheses, see: f) S. F. Martin, W. Li, *J. Org. Chem.* **1991**, *56*, 642; g) A. Padwa, M. Dimitroff, B. Liu, *Org. Lett.* **2000**, *2*, 3233; h) A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu, T. Wu, *J. Org. Chem.* **2001**, *66*, 3119. For asymmetric total syntheses, see: i) C.-K. Sha, R.-T. Chiu, C.-F. Yang, N.-T. Yao, W.-H. Tseng, F.-L. Liao, S.-L. Wang, *J. Am. Chem. Soc.* **1997**, *119*, 4130; j) J. Cassayre, S. Z. Zard, *J. Am. Chem. Soc.* **1999**, *121*, 6072; k) L. M. Kreis, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3436; *Angew. Chem.* **2012**, *124*, 3492. For asymmetric formal syntheses, see: l) B. M. Trost, A. S. Tasker, G. Ruether, A. Brandes, *J. Am. Chem. Soc.* **1991**, *113*, 670; m) Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708; n) N. Uesaka, F. Saitoh, M. Mori, M. Shibasaki, K. Okamura, T. Date, *J. Org. Chem.* **1994**, *59*, 5633.

[13] For a review on transition-metal-catalyzed cycloisomerization of 1,n-enynes, see: V. Michelet, P. Y. Toullec, J.-P. Genet, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268; *Angew. Chem.* **2008**, *120*, 4338.

[14] For pioneering examples and selected reaction conditions for palladium-catalyzed enyne cycloisomerizations used herein, see: a) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. MacPherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255; b) B. Møller, K. Undheim, *Tetrahedron* **1998**, *54*, 5789; c) S. E. Gibson, P. R. Haycock, A. Miyazaki, *Tetrahedron* **2009**, *65*, 7498; d) B. M. Trost, D. C. Lee, F. Rise, *Tetrahedron Lett.* **1989**, *30*, 651. For a recent combined experimental and theoretical study, see: e) A. Mekareeya, P. R. Walker, A. Couce-Rios, C. D. Campbell, A. Steven, R. S. Paton, E. A. Anderson, *J. Am. Chem. Soc.* **2017**, *139*, 10104.

[15] A preliminary computational study was performed by Prof. Zhi-Xiang Yu and coworkers, Peking University, and more detailed studies are in progress.

[16] For selected synthetic investigations on the functionalization of diene **10**, epoxide **20**, and ketone **21**, see the Supporting Information.

[17] See the Supporting Information for details. For examples and conditions of intramolecular aldol condensation leading to the formation of cyclohexenone, see: (KOH–EtOH) a) K. C. Nicolaou, G. S. Tria, D. J. Edmonds, M. Kar, *J. Am. Chem. Soc.* **2009**, *131*, 15909; (*p*-TsOH – toluene) b) S. Wang, Y. Zhang, G. Dong, S. Wu, K. Fang, Z. Li, Z. Miao, J. Yao, H. Li, J. Li, W. Zhang, W. Wang, C. Sheng, *Org. Lett.* **2014**, *16*, 692; (piperidine – AcOH) c) A. Srikrishna, B. Beeraiah, *Tetrahedron: Asymmetry* **2007**, *18*, 2587; (K_2CO_3 – TBAB) d) D. F. Taber, T. D. Neubert, A. L. Rheingold, *J. Am. Chem. Soc.* **2002**, *124*, 12416; (DBU – benzene) e) N. Toyooka, M. Okumura, H. Takahata, H. Nemoto, *Tetrahedron* **1999**, *55*, 10673.

[18] For use of the LiOH–*i*PrOH system in intramolecular aldol condensation leading to the formation of cyclohexenone, see: a) J. Dardenne, S. Desrat, F. Guéritte, F. Roussi, *Eur. J. Org. Chem.* **2013**, 2116; b) K. Chen, Y. Ishihara, M. M. Galan, P. S. Baran, *Tetrahedron* **2010**, *66*, 4738.

[19] H. Satoh, H. Ueda, H. Tokuyama, *Tetrahedron* **2013**, *69*, 89.

[20] For synthesis of allylic bromide **22**, see the Supporting Information.

[21] For the use of the CuBr·SMe_2–TaniaPhos combination in copper-catalyzed asymmetric allylic alkylation reactions pioneered by the Feringa group, see: a) F. López, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2006**, 409; b) K. Geurts, S. P. Fletcher, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 15572; c) J. F. Teichert, S. Zhang, A. W. van Zijl, J. W. Slaa, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2010**, *12*, 4658; d) T. den Hartog, B. Macia, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.* **2010**, *352*, 999; e) M. Fañanas-Mastral, B. ter Horst, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2011**, *47*, 5843; f) Y. Huang, M. Fañanas-Mastral, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2013**, *49*, 3309; g) B. Mao, M. Fañanas-Mastral, M. Lutz, B. L. Feringa, *Chem. Eur. J.* **2013**, *19*, 761; h) V. Hornillos, M. Perez, M. Fañanas-Mastral, B. L. Feringa, *Chem. Eur. J.* **2013**, *19*, 5432.

[22] We synthesized TaniaPhos in 95% *ee* (chiral HPLC) by following the literature procedure: T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843.

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Communications

Natural Product Synthesis

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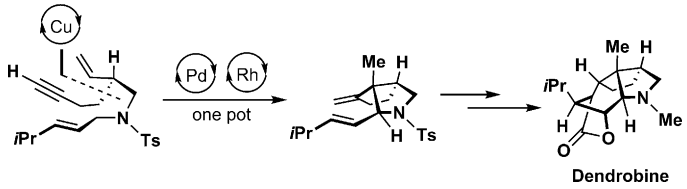
An Asymmetric Pathway to Dendrobine by a Transition-Metal-Catalyzed Cascade Process



An asymmetric pathway to polycyclic alkaloid dendrobine was developed comprising a one-pot palladium-catalyzed enyne cycloisomerization, and rhodium-catalyzed diene-assisted pyrrolidine formation by allylic CH activation. Intramolecular aldol condensation with concomitant detosylation, followed by reductive amination, afforded an advanced intermediate in only 10 synthetic steps.

