Preprint Title	Cascade Intramolecular Prins/Friedel–Crafts Cyclization for the Synthesis of 4-Aryl-tetralin-2-ols and 5-Aryl-tetrahydro-5*H*-benzo[7]annulen-7-ols
Authors	Jie Zheng, Shuyu Meng and Quan Rui Wang
Publication Date	08 März 2021
Article Type	Full Research Paper
Supporting Information File 1	BJOC SI Manuscrip ZJ.docx; 13.0 MB
ORCID® iDs	Jie Zheng - https://orcid.org/0000-0002-2974-296X; Shuyu Meng - https://orcid.org/0000-0003-4527-4243; Quan Rui Wang - https://orcid.org/0000-0001-7593-9176

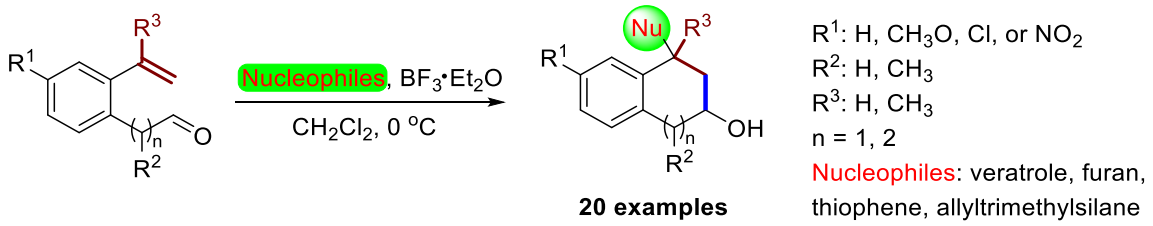
BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cascade Intramolecular Prins/Friedel–Crafts Cyclization for the Synthesis of 4-Aryl-tetralin-2-ols and 5-Aryl-tetrahydro-5*H*-benzo[7]annulen-7-ols

Jie Zheng, Shuyu Meng, and Quanrui Wang*

Address: Department of Chemistry, Fudan University, 2005 Songhu Road, Shanghai 200438, People's Republic of China

Email: Quanrui Wang* - qrwang@fudan.edu.cn
* Corresponding author



Abstract:
Treatment of 2-(2-vinylphenyl)acetaldehydes or 3-(2-vinylphenyl)propanals with $BF_3{\cdot}Et_2O$ results in intramolecular Prins reaction affording intermediary benzyl carbenium ions, which are then trapped by a variety of electron-rich aromatics via Friedel–Crafts alkylation. This cascade Prins/Friedel–Crafts cyclization protocol paves an expedient path to medicinally useful 4-aryl-tetralin-2-ol and 5-aryl-tetrahydro-5*H*-benzo[7]annulen-7-ol derivatives.

Keywords:
Prins/Friedel–Crafts; cascade; 4-aryl-tetralin-2-ol

Introduction

2,4-Disubstituted tetralins (Figure 1, **I**) especially 2-functionalized tetralins are privileged building blocks for medicinal chemistry applications which are known to exhibit a wide spectrum of biological activities.[1-3] Several prominent representative compounds with such a skeleton are

illustrated in Figure 1. Cycloolivil (Figure 1, **II**)[4] isolated from the bark of olea europaea has been recognized as inhibitor of cyclic AMP dependent phosphodiesterase, can act as a Ca^{2+} antagonist and exhibits promising antioxidant properties. 4-Phenyl-2-propionamidotetralin (4-P-PDOT) (Figure 1, **III**)[5] is a melatonin MT_2 selective antagonist that can be used to map melatonin receptor subtypes in tissue and serves as a chemical biology tool to identify sub-type selective analogues with therapeutic potential. In addition, *trans*-4-phenyl-*N*,*N*-dimethyl-2-aminotetralin **(***trans*-H_2-PAT**)** (Figure 1, **IV**)[6] has been determined to modulate tyrosine hydroxylase activity and dopamine synthesis in rodent forebrain and is also a ligand binding to histamine H_1 receptors, and thus potentially useful therapeutic for psychoses, addiction, and other neuropsychiatric disorders.

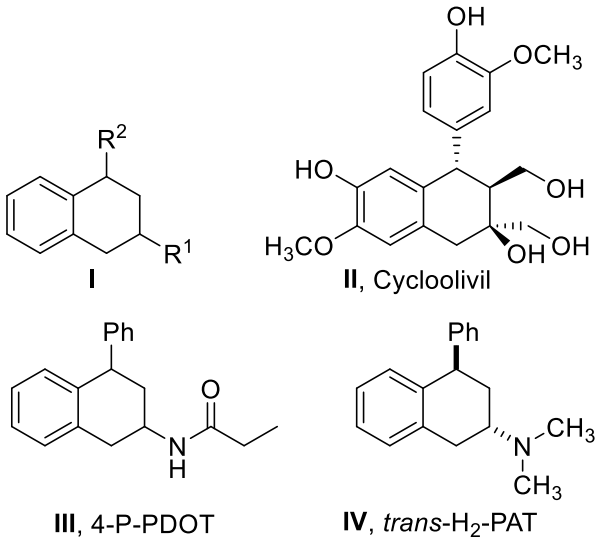
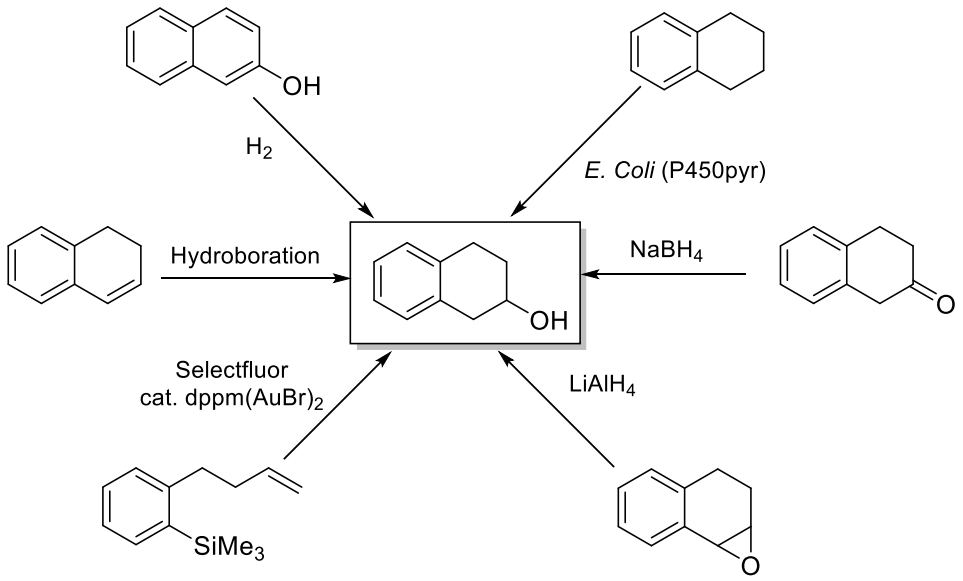


Figure 1. Parent structure of 2,4-disubstituted tetralins (**I**) and selected medicinally useful derivatives (**II**-**IV**).

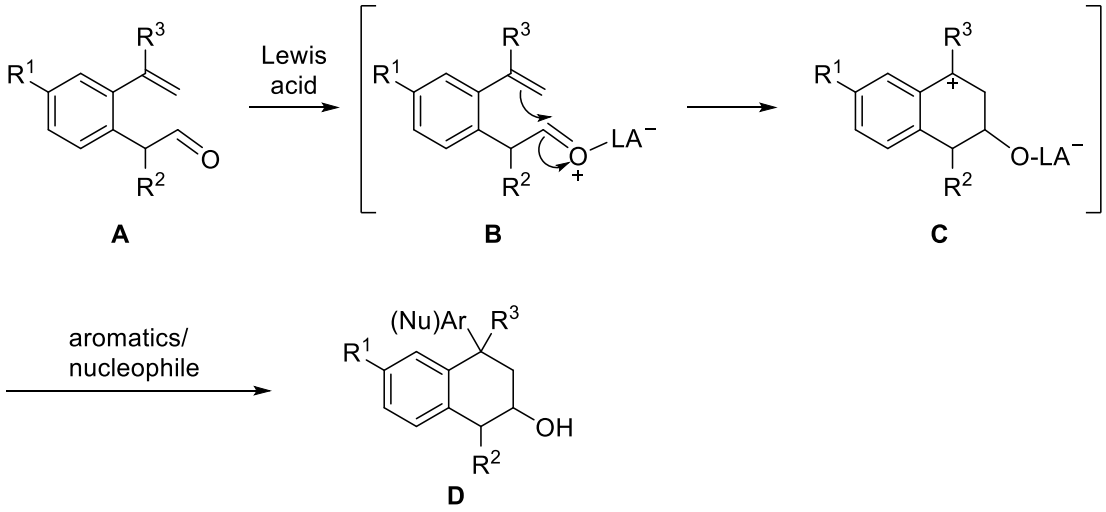
Although 4-substitituted tetralin-2-ols and derivatives with significant pharmaceutical activities have been identified, only a limited number of synthetic methods have been documented in the literature (Scheme 1).[7-9] Moreover, these methods generally require multiple steps, proceed in low overall yields and have a limited ability for structural modification to prepare analogues with new substitution patterns for enhancing activities. Consequently, it is highly desirable to develop new synthetic methods that provide efficient access to 2,4-disubstituted tetralin compounds and thus facilitate their biological investigations.



Scheme 1. Reported Strategies for the Synthesis of Tetralin-2-ol Ring Systems

Cascade Prins/Friedel–Crafts reaction to form multiple chemical bonds in one operation has emerged as a very important atom-economic strategy for the construction of oxygen-containing heterocycles.[10-12] For example, Nagumo and coworkers have developed a Prins/Friedel–Crafts cyclization of homocinnamyl alcohols with aromatic aldehydes under action with $BF_3{\cdot}Et_2O$ affording 2*H*-indeno[1,2-*b*]furan derivatives.[13] Likewise, Hinkle and coworkers reported in 2017 a three-step domino alkynyl-Prins cyclization, Friedel–Crafts alkenylation, and dehydration/aromatization reaction between 1-aryl-3-hexyne-2,6-diol derivatives and aldehydes, and this led to the formation of 1,4-dihydro-2*H*-benzo[*f*]isochromenes.[14]

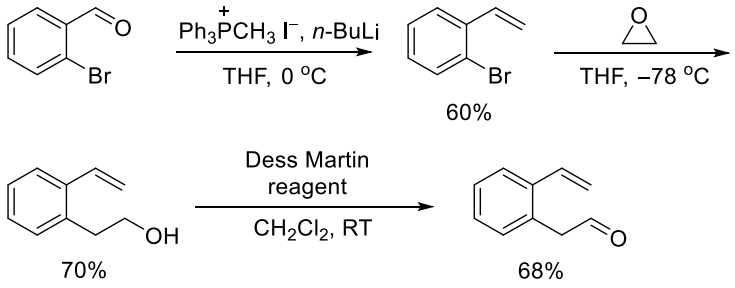
The Prins-induced cyclization, inter alia, become a significant tool for assembly of complex molecules from relatively simple and inexpensive materials/reagents in a single operation. It continues to be an interesting and profitable field of research with impact upon synthetic organic chemistry.[15,16] Many of the existing protocols rely on an acid-promoted condensation of a homoallylic alcohol and an aldehyde to give an oxocarbenium ion, which is then reacted with olefinic/alkynic bond generating a new carbocation for Friedel–Crafts reaction. Given the potential value of tetralin-2-ol scaffolds to drug research programs, we decided to develop a novel Prins/Friedel–Crafts cyclization strategy for the synthesis of 4-aryl-2-hydroxy tetralins starting from 2-(2-vinylphenyl)acetaldehydes (Scheme 2). In this protocol, we envisioned that aldehyde **A** would give rise to an oxocarbenium ion specie **B** upon action of a Lewis acid. Intermediate **B** would undergo Prins-type cyclization with the olefinic bond to produce a stable benzyl carbocation **C**, which may be trapped by Friedel–Crafts alkylation with aromatic ring or reaction with an external nucleophile to afford the target product **D**.



Scheme 2. Designed Cascade Reactions to 4-Substitued Tetralin-2-ols

Results and Discussion

Our research began with the preparation of 2-(2-vinylphenyl)acetaldehydes (**5**) required as substrates for the Prins/Friedel–Crafts cyclization reactions. Commonly, aldehydes **5** have previously been prepared via a three step process as exemplified in Scheme 3, which consists of the following steps: (i) Wittig reaction of the lithium anion of methylphosphonium iodide with 2-bromobenzaldehyde; (ii) Lithiation of the resultant ortho-bromo-styrene with BuLi and reaction of the aryl lithium species with ethylene oxide; (iii) Oxidation of the resultant primary alcohol using Dess-Martin periodinane.[17,18] The conditions involved the exposure to carcinogenic/volatile ethylene oxide and use of highly reactive *n*-BuLi, and required cryogenic temperatures (–78 °C).

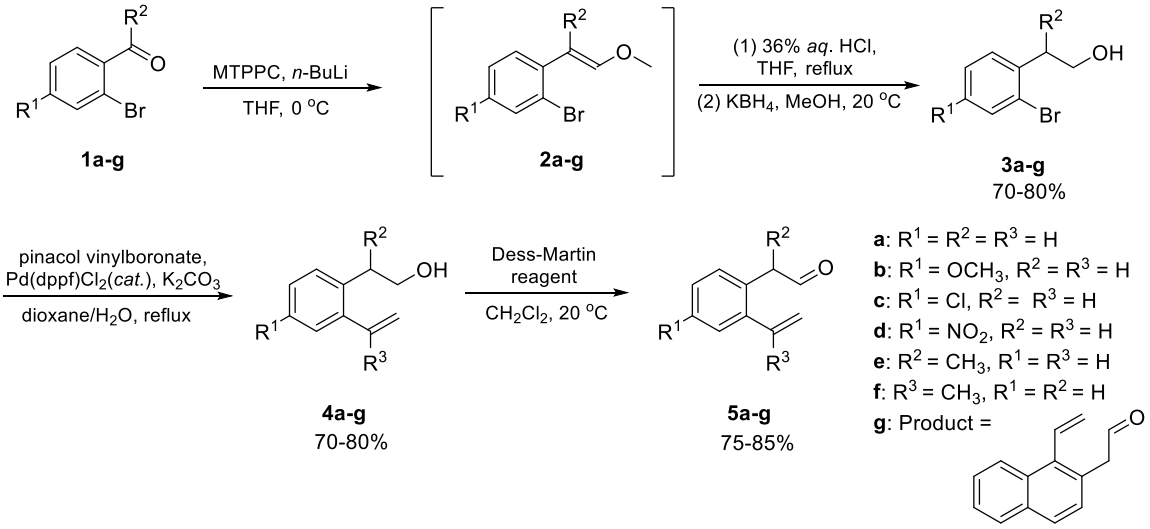


Scheme 3. The Documented Synthesis of 2-(2-Vinylphenyl)acetaldehyde (5a)

This prompted us to work out a more practical and flexible method to access these aromatic enal compounds **5**. At the offset, we examined the synthesis of substrate **5a** using the route as outlined in Scheme 4. Thus, the Wittig reaction of 2-bromobenzaldehyde **1a** with methoxymethyl triphenylphosphonium chloride (MTPPC) upon action with *n*-butyllithium in THF at 0 °C gave the vinyl-ether **2a** that was subjected to acidic hydrolysis using 36% *aq*. HCl to furnish the corresponding aldehyde.[19] Without purification, the resultant aldehyde intermediate was

then directly reduced using potassium borohydride to the corresponding primary alcohol **3a** in 74% yield starting from **1a**. Pd-catalyzed cross-coupling of **3a** with pinacol vinylboronate afforded the styrene **4a** in 78% yield.[20,21] Next, Dess-Martin oxidation of alcohol **4a** was carried out, and the desired 2-(2-vinylphenyl)acetaldehyde **5a** was successfully obtained in 85% yield. Obviously, this modified method has the advantages of mild reaction condition, operation simplicity, and using cheap and non-toxic reagents.

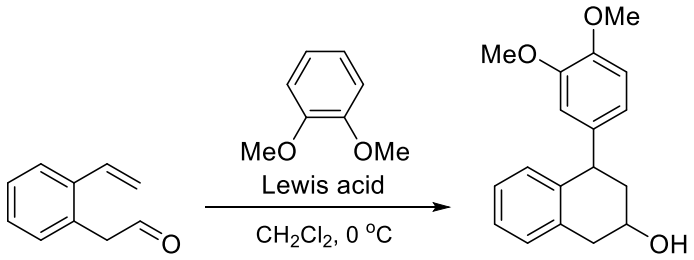
This modified procedure was then expanded to the synthesis of a set of 2-(2-vinylphenyl)acetaldehydes **5b**-**f** starting from differently substituted 2-bromobenzaldehydes **1** or 1-(2-bromophenyl)ethan-1-one **1e** in comparable yields. Likewise, 2-(1-vinylnaphthalen-2-yl)acetaldehyde **5g** was prepared from 1-bromo-2-naphthaldehyde in 48% yield over the three steps. It should be noted that the nitro-substituted intermediate **3d** was prepared by nitration of **3a** with nitric acid under the promotion of acetic anhydride.



Scheme 4. Modified Synthesis of 2-(2-Vinylphenyl)acetaldehydes (5a-f) and 1-Vinyl naphth-2-ylacetaldehyde 5g

With the accessibility of the aromatic vinyl aldehydes **5**, the cascade Prins/Friedel–Crafts reaction was examined. Our investigations were commenced by applying aldehyde **5a** as the model substrate (Scheme 5). A Lewis acid screening was carried out to identify the best catalyst for carrying out the tandem intramolecular Prins/Fridel–Crafts reaction (Table 1). Thus, portion-wise addition of $AlCl_3$ (1.1 eq.) to a stirred mixture of **5a** (1.0 eq.) and veratrole (1.05 eq.) in CH_2Cl_2 at 0 °C resulted in an intramolecular Prins reaction to generate a benzyl carbenium ion that concurrently underwent Friedel–Crafts reaction with veratrole, leading to the formation of the expected 4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-ol **6a** (51:49 mixture of *cis-/trans*- diastereomers) as a colorless oil in 50% yield (Table 1, entry 1). Use of Et_2AlCl as Lewis acid gave tetralin **6a** in a slightly improved 55% yield. However, use of $AlMe_3$ resulted in competing reduction of **5a** 2-bromophenylethanol **4a** as the major product (Table 1,

entry 3). Switching to the weaker Lewis acid $In(OTf)_3$ failed to induce any intramolecular Prins cyclization (Table 1, entry 4), whilst use of $FeCl_3$ produced **6a** in a similar 52% yield as observed for $AlCl_3$ (Table 1, entry 5). To our delight, 1.1 equivalents of $BF_3{\cdot}Et_2O$ were found to promote the transformation efficiently, and 70% isolated yield of **6a** was obtained (Table 1, entry 6). However, experiments with $BF_3{\cdot}Et_2O$ content below the stoichiometric one afforded significantly decreased yields of **6a** (Table 1, entries 7 and 8).



5a **6a**

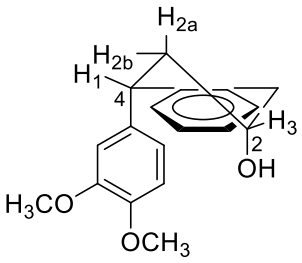
Scheme 5. Lewis acid catalyzed Prins/Friedel–Crafts Reaction of 5a with Veratrole

Table1. Screening of Lewis Acid Catalysts[a]

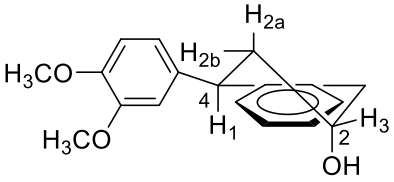
Entry	Lewis acid	Amount of LA [mol%]	*cis*-/*trans*-ratio[b]	Yield [%][c]
1	$AlCl_3$	110	51/59	50
2	Et_2AlCl	110	50/50	55
3	$AlMe_3$	110	NA	0[d]
4	$In(OTf)_3$	110	NA	0
5	$FeCl_3$	110	50/50	52
6	$BF_3{\cdot}Et_2O$	110	49/51	70
7	$BF_3{\cdot}Et_2O$	80	50/50	50
8	$BF_3{\cdot}Et_2O$	50	50/50	35

[a] Conditions: a mixture of **5a** (1.40 mmol), veratrole (1.47 mmol) and Lewis acid (1.54 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 °C for 2 h.
[b] *Cis*-/*trans*- ratio were determined by ^1H NMR spectrum.
[c] Isolated yield by chromatography.
[d] Reduction product **4a** instead of the desired **6a** was identified.

The relative cis and trans configuration of the C-2 hydroxy group and the C-4 aryl substituent were assigned on the basis of analyzing ^1H-^1H COSY. If there is a NOE effect between H^1 and H^3, and meanwhile H^1 and H^3 also have a strong NOE effect with H^{2a}, it is assigned to be *cis*-configuration. Otherwise, it is the *trans* isomer. For more details, please see SI.



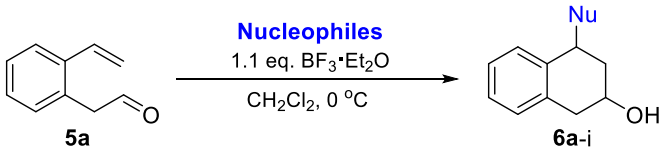
cis-**6a**



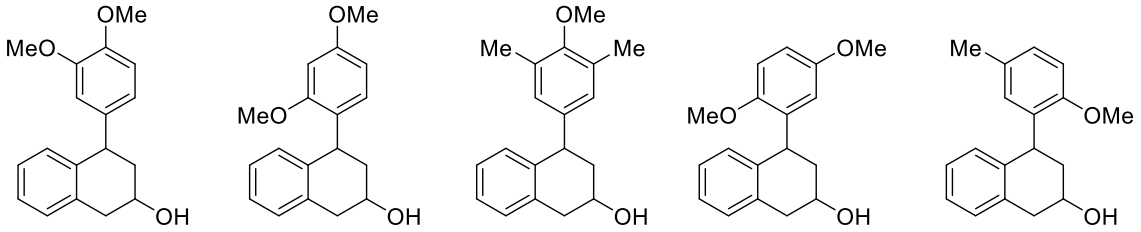
trans-**6a**

Having determined the suitable reaction conditions, we surveyed the scope and limitation of the cascade protocol. To start, we explored the range of nucleophiles that were used to intercept the benzyl carbenium ion. The results are summarized in Table 2. All reactions with electron-rich aromatics containing *p*- and/or *o*-methoxy substituent as the nucleophile proceeded well to give the desired 2-hydroxy-4-aryl tetralin compounds **6a-e** as 49:51 to 60:40 mixtures of *cis*-/*trans*- diastereomers in moderate to good yields.

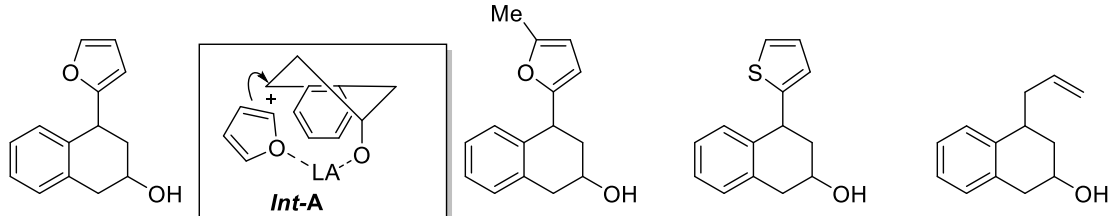
Table 2. Use of Different Nucleophiles for the Cascade Reaction with 5a[a]



5a **6a**-i



6a, 70%[b] *cis-/trans-* = 49/51 | **6b**, 72% *cis-/trans-* = 55/45 | **6c**, 60% *cis-/trans-* = 54/46 | **6d**, 68% *cis-/trans-* = 51/49 | **6e**, 65% *cis-/trans-* = 60/40



6f, 40% *cis-/trans-* = 1/99 | **6g**, 35% *cis-/trans-* = 1/99 | **6h**, 37% *cis-/trans-* = 41/59 | **6i**, 65% *cis-/trans-* = 44/56

[a] Reaction conditions: a mixture of **5a** (1.40 mmol), nucleophile (1.47 mmol), $BF_3{\cdot}Et_2O$ (1.54 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred at 0 °C for 2 h.
[b] Isolated yield by chromatography.

The electron-rich 5-membered heterocycles like furans and thiophene participated also smoothly in the reaction sequence, leading to clean formation of the respective 2-hydroxy-4-

heteroaryl tetralins **6f-h**, although the yields were lower than that with substituted anisole derivatives. On comparing the results from anisole-type nucleophiles or thiophene with that from furans, it was observed that the reactions with furans furnished predominantly *trans*-**6f** and *trans*-**6g** with high degree of diastereoselectivity (*cis*-/*trans*- ratio = 1:99). The preferential formation of *trans*- products for furan nucleophiles may be due to interaction with the inherent oxyphilic property of BF_3, making the furan ring located on the other side as the generated oxy ion. A plausible intermediate structure ***Int-A*** is proposed to tentatively account for the stereo outcome. In ***Int-A*** the tetrahydro benzene ring is expected to exist in the half-chair conformation.

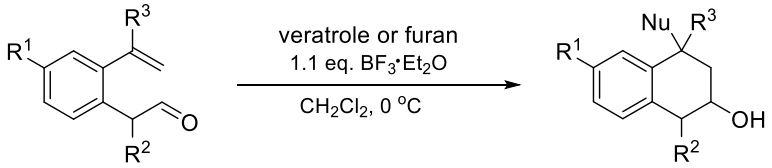
To further expand the substitution pattern, we then tried the reaction of **5a** with allysilane as a carbon-nucleophile. As expected, the expected 4-allyl substituted tetrahydronaphthalen-2-ol **6i** was obtained, again, as a mixture of *cis*-/*trans*- products (ratio 44:56). This example demonstrated the general synthetic utility of this cascade protocol.

Encouraged by the success of using **5a** as the substrate, the reaction with other prepared 2-(2-vinylphenyl)ethanals **5b-g** carrying different substituents on the benzene nucleus or on the side chain with veratrole and furan as the nucleophiles were investigated. As can be seen from Table 3, under the comparable conditions, most of the reactions proceeded smoothly with the attempted alkene-aldehydes **5** to furnish the corresponding 2,4-disubstituted tetralins **6j-t** in acceptable to good isolated yields (Table 3). For instance, the reaction with aldehydes **5** containing π-donating substituents like methoxy and chloro substituents offered 2-hydroxy-4-aryl tetralin products **6j-m** in 38-72% yield. To our gladness, an electron-deficient nitro group residing on the benzene ring of aldehyde **5d** didn't retard the reaction. Under the standard conditions, **5d** reacted with veratrole delivering tetralin **6n** in 55% yield. However, using furan as the nucleophile component, the reaction sequence with **5d** failed to give the tetralin product. Instead, we only isolated 30% yield of the trivial bis-furan **7** as the major product.

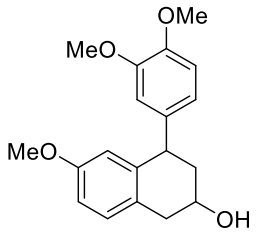
In addition, aldehydes **5e** or **5f** bearing a methyl group at the acetaldehyde side or the benzylic position of the alkene side were also competent substrates for this cascade strategy, thus 1,2,4-trisubsitituted tetralins **6o** and **6p** as well as 2,4,4-trisubsitituted tetralins **6q** and **6r** were achieved in moderate to reasonable yields. This cyclization methodology was also applicable to the 2-(1-vinylnaphthalen-2-yl)acetaldehyde **5g**, for which the reaction with veratrole or furan lead to the formation of the respective tricyclic 4-aryl-1,2,3,4-tetrahydrophenanthren-2-ols **6s** and **6t** in 73% and 43% yields, respectively.

From the above results, conclusion can be made that the reaction using furan as the nucleophile underwent with nearly complete *trans*-stereoselectivity whereas the reactions using veratrole as a nucleophile occurred with no or much lower *cis*-/*trans*-selectivity (*cis*-/*trans*- ratio ranged from 37:63 to 60:40).

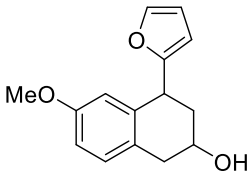
Table 3. Reaction of 5b-g with Veratrole or Furan[a]



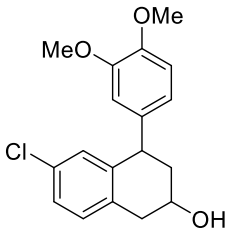
5b-g **6j-t**



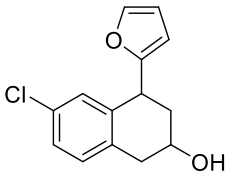
6j, 72%[b]
cis-/trans- = 48:52



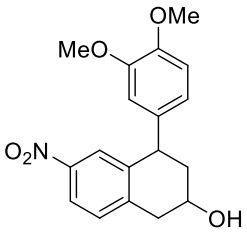
6k, 41%
cis-/trans- = 1:99



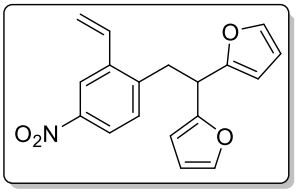
6l, 67%
cis-/trans- = 44:56



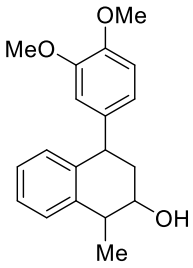
6m, 38%
cis-/trans- = 1:99



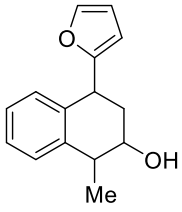
6n, 55%
cis-/trans- = 56:44



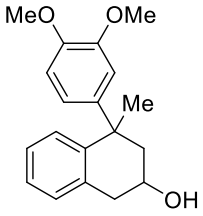
7, 30%



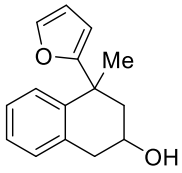
6o, 65%



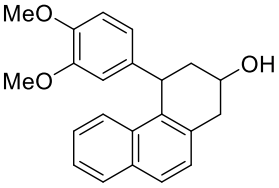
6p 36%



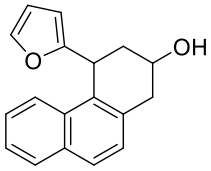
6q, 50%
cis-/trans- = 37:63



6r, 25%
cis-/trans- = 1:99



6s, 73%
cis-/trans- = 52:48



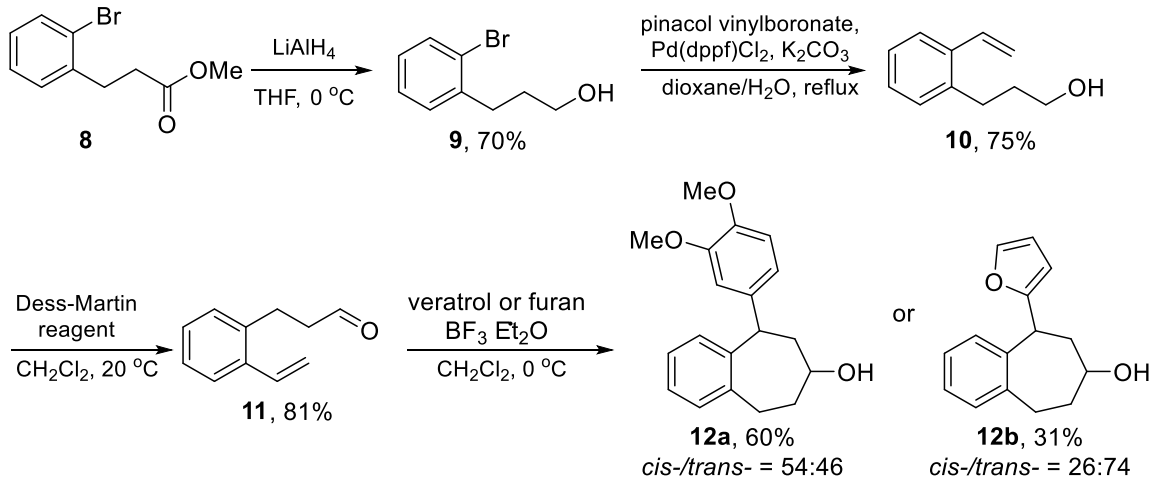
6t, 43%
cis-/trans- = 1:99

[a] Reaction conditions: a mixture of **5b-g** (1.40 mmol), nucleophile (1.47 mmol), $BF_3{\cdot}Et_2O$ (1.54 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred at 0 °C for 2 h.
[b] Isolated yield by chromatography.

In order to further explore the generality of this cascade Prins/Friedel–Crafts cyclization, the established methodology was also applied to the formation of tetrahydro-5*H*-benzocyclohepten-7-ol ring systems. As shown in Scheme 6, the required homo-aldehyde substrate **11** was prepared starting from methyl 3-(2-bromophenyl)propionate **8** analogously as for **5**. Reduction of ester **8** with $LiAlH_4$ in THF at 0 °C afforded the alcohol **9** that was subjected to Suzuki

reaction with pinacol vinylboronate using Pd(dppf)Cl_2 as catalyst to produce 3-(2-vinylphenyl)propan-1-ol **10**. Oxidation of the alcohol **10** with Dess-Martin oxidizing reagent furnished the requisite aldehyde **11** in 43% yield over the three steps.

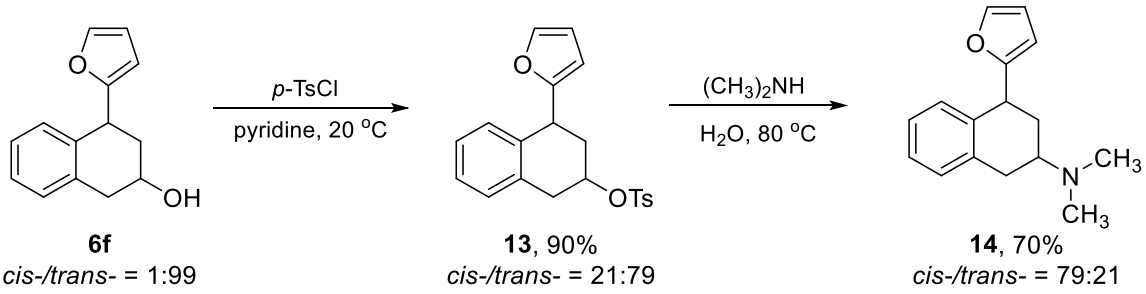
Under the standard conditions, aldehyde **11** underwent satisfactorily the cascade Prins/Friedel–Crafts cyclization with veratrole or furan as the nucleophile furnishing the tetrahydro-5*H*-benzo[7]annulen-7-ol **12a** (*cis*-/*trans*- ratio = 54:46) and **12b** ((*cis*/*trans* ratio = 26:74) in 60% and 31% yields, respectively. Predominance of the *trans*-product for the reaction with furan further verified the oxyphilic character of the employed BF_3, although the stereoselectivity considerably decreased in comparison with the formation of tetralin ring system as the distance between the reaction sites is increased. It is of worthy to mention that the tetrahydro-5*H*-benzo[7]annulen-7-ol skeleton is also of considerable medicinal significance and has attracted much synthetic efforts.[22,23]



Scheme 6. Synthesis of 5-Aryl-tetrahydro-5*H*-benzo[7]annulen-7-ols (12a,b)

Finally, the ability to structurally diversify the 2-hydroxy-4-substituted tetralin skeletons into medicinally useful derivatives was then demonstrated by converting 2-hydroxy-4-furyl-tetralin **6f** into the PAT analogue **14** (see Figure 1).[24] Reaction of **6f** with *p*-toluene sulfonyl chloride in pyridine afforded the tosylate **13** in 90% yield, which was then treated with 40% aqueous dimethylamine to produce the tertiary amine containing PAT analogue **14** (*cis/trans* ratio 79:21) in 70% yield (Scheme 7). Obviously, conversion of **13** to **14** proceeded in a typical S_N2 manner resulting in the expectable configuration inversion.

To unequivocally support the configuration assignment made by NMR analysis, the sulfonate derivative **13** from **6f** was prepared by reaction with tosyl chloride. For compound **13**, we were able to develop single crystals suitable for X-ray analysis. Thus, X-ray diffraction studies on **13** confirmed undoubtedly its *trans*-configuration.[25] The ORTEP structure is shown in Figure 2



6f
cis-/trans- = 1:99

13, 90%
cis-/trans- = 21:79

14, 70%
cis-/trans- = 79:21

Scheme 7. Conversion of 2-Hydroxy-4-Furyl-Tetralin 6f into PAT Analogue 14

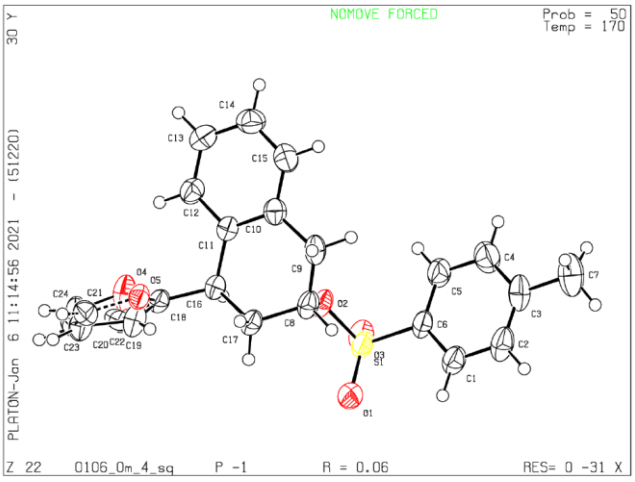


Figure 2. Crystal structure of the tosylate **13**. The displacement ellipsoids are drawn at the 30% probability level.

Conclusion

In summary, a Prins cyclization and Friedel–Crafts cascade reaction strategy for the synthesis of 4-aryl-tetralin-2-ols as well as 5-aryl-tetrahydro-5*H*-benzo[7]annulen-7-ols has been established. The sequence involved the Prins cyclization of 2-(2-vinylphenyl)acetaldehydes or 3-(2-vinylphenyl)propanal by action with BF_3 to generate benzyl carbenium ions that can be captured by Friedel–Crafts alkylation reaction with a range of electron rich benzenes or heteroaromatics. The method has a relatively broad applicability allowing variation in the benzene ring as well as the side chain. Further manipulation of the hydroxyl group demonstrated the synthetic potential for accessing medicinally useful analogues.

Supporting Information

The Supporting Information contains experimental procedures, characterization data of all

isolated products as well as copies of NMR spectra and **13**'s XRPD data.
Supporting Information File 1: Experimental section.

Acknowledgements

The authors acknowledge the financial support from the National Natural Science Foundation of China (21971042). We thank Mr. G. Tang for acquiring high-resolution mass spectrometry data.

ORCID® iDs

Quanrui Wang: https://orcid.org/0000-0001-7593-9176

Jie Zheng: https://orcid.org/0000-0002-2974-296X

Shuyu Meng: https://orcid.org/0000-0003-4527-4243

References

1. Ichikawa, K.; Kinoshita, T.; Nishibe, S.; Sankawa, U. The Ca^{2+} antagonist activity of lignans. *Chem. Pharm. Bull.* **1986**, *34*, 3514-3517. doi: 10.1248/cpb.34.3514
2. Dubocovich, M. L.; Masana, M. I.; Iacob, S.; Sauri, D. M. Melatonin receptor antaǵonists that differentiate between the human Mel_{1a} and Mel_{1b} recombinant subtypes are used to assess the pharmacoloǵical profile of the rabbit retina ML_1 presynaptic heteroreceptor. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *355*, 365-375. doi: 10.1007/pl00004956
3. Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Owens, C. E.; Kula, N. S.; Baldessarini, R. J.; McPhail, A. T.; Mailman, R. B. Synthesis and pharmacological evaluation of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as ligands for a novel receptor with σ-like neuromodulatory activity. *J. Med. Chem.* **1993**, *36*, 2542-2551. doi: 10.1021/jm00069a013
4. Moritani, Y.; Ukita, T.; Ohmizu, H.; Iwasaki, T. The first synthesis of (±)-Cycloolivil: a highly stereoselective synthesis of 3-hydroxy-1-aryltetralin lignans based on the stereoselective hydroxylation of α, β-dibenzyl-γ-butyrolactones. *J. Chem. Soc., Chem. Commun.* **1995**, 671-672. doi: 10.1039/C39950000671
5. Lucarini, S.; Bedini, A.; Spadoni, G.; Piersanti, G. An improved synthesis of cis-4-phenyl-2-propionamidotetralin (4-P-PDOT): a selective MT_2 melatonin receptor antagonist. *Org. Biomol. Chem.* **2008**, *6*, 147-150. doi: 10.1039/b713904g
6. Bucholtz, E. C.; Brown, R. L.; Tropsha, A.; Booth, R. G.; Wyrick, S. D. Synthesis, evaluation, and comparative molecular field analysis of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as ligands for histamine H_1 receptors. *J. Med. Chem.* **1999**, *42*, 3041-3054. doi: 10.1021/jm980428x
7. Makowski, P.; Cakan, R. D.; Antonietti, M.; Goettmann, F.; Titirici, M.-M. Selective partial

hydrogenation of hydroxy aromatic derivatives with palladium nanoparticles supported on hydrophilic carbon. *Chem. Commun.* **2008**, *999*, 999-1001. doi: 10.1039/b717928f

8. Zhang, W.; Tang, W. L.; Wang, Z.; Li, Z. Regio- and stereoselective biohydroxylations with a recombinant *Escherichia coli* expressing $P450_{pyr}$ monooxygenase of sphingomonas Sp. HXN-200. *Adv. Synth. Catal.* **2010**, *352*, 3380-3390. doi: 10.1002/adsc.201000266

9. Brenzovich, W. E.; Brazeau, J.-F.; Toste, F. D. Gold-catalyzed oxidative coupling reactions with aryltrimethylsilanes. *Org. Lett.* **2010**, *12*, 4728-4731. doi: 10.1021/ol102194c

10. Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. Stereoselective synthesis of amido and phenyl azabicyclic derivatives via a tandem aza Prins-Ritter/Friedel–Crafts type reaction of endocyclic n-acyliminium ions. *J. Org. Chem.* **2013**, *78*, 10629-10641. doi: 10.1021/jo401450j

11. Reddy, B. V. S.; Sundar, C. S.; Reddy, M. R.; Reddy, C. S.; Sridhar, B. Tandem Prins and Friedel–Crafts cyclizations for the stereo-selective synthesis of *trans*-fused hexahydro-1H-benzo [*g*] iso-chromene derivatives. *Synthesis* **2015**, *47*, 1117-1122. doi: 10.1055/s-0034-1380177

12. Li, R.-Q.; He, Y.; Ding, Y.; Ang, C.-K.; Tian, J.-S.; Loh, T.-P. Formal synthesis of chelamidine alkaloids and their derivatives. *Chem. Commun.* **2018**, *54*, 3150–3153. doi: 10.1039/c7cc09875h

13. Sakata, Y.; Yasui, E.; Takatori, K.; Suzuki, Y.; Mizukami, M.; Nagumo, S. Syntheses of polycyclic tetrahydrofurans by cascade reactions consisting of five-membered ring selective Prins cyclization and Friedel–Crafts cyclization. *J. Org. Chem.* **2018**, *83*, 9103–9118. doi: 10.1021/acs.joc.8b01195

14. Hinkle, R. J.; Chen, Y.; Nofi, C. P.; Lewis, S. E. Electronic effects on a one-pot aromatization cascade involving alkynyl-Prins cyclization, Friedel–Crafts alkylation and dehydration to tricyclic benzo[*f*]isochromenes. *Org. Biomol. Chem.* **2017**, *15*, 7584–7593. doi: 10.1039/C7OB01412K

15. Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. Synthesis of tetrahydropyrans and related heterocycles via Prins cyclization; extension to aza-prins cyclization. *Tetrahedron.* **2010**, *66*, 413–445. doi: 10.1016/j.tet.2009.10.069

16. Padmaja, P.; Reddy, P. N.; Reddy, B. V. S. Tandem Prins cyclizations for the construction of oxygen containing heterocycles. *Org. Biomol. Chem.* **2020**, *18*, 7514–7532. doi: 10.1039/D0OB00960A

17. Grigg, R. D.; Hoveln, R. V.; Schomaker, J. M. Cu-catalyzed recycling of halogen activating groups *via* 1,3-halogen migration. *J. Am. Chem. Soc.* **2012**, *134*, 16131–16134. doi: 10.1021/ja306446m

18. Fustero, S.; Rodríguez, E.; Lázaro, R.; Herrera, L.; Catalán, S.; Barrio, P. Relay catalysis: enantioselective synthesis of cyclic benzo-fused homoallylic alcohols by chiral brønsted acid-catalyzed allylboration/ring closing metathesis. *Adv. Synth. Catal.* **2013**, *355*, 1058–1064. doi: 10.1002/adsc.201201095

19. Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. Highly stereoselective synthesis of indanes with four stereogenic centers *via* sequential Michael reaction and [3+2]

cycloaddition. *Chem. Commun.* **2010**, *46*, 7611–7613. doi: 10.1039/C0CC01577F
20. Dai, X.-J.; Engl, O. D.; León, T.; Buchwald, S. L. Catalytic asymmetric synthesis of α-arylpyrrolidines and benzo-fused nitrogen heterocycles. *Angew. Chem. Int. Ed.* **2019**, *58*, 3407–3411. doi: 10.1002/anie.201814331
21. Firmansjah, L.; Fu, G. C. Intramolecular Heck reactions of unactivated alkyl halides. *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341. doi: 10.1021/ja075245r
22. Singh, K. N.; Singh, P.; Sharma, E.; Kaur, M.; Deol, Y. S. Aryne-mediated arylation of the 3-benzazepine scaffold: one-pot synthesis of 1-aryl-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines. *Synthesis* **2015**, *47*, 3212–3220. doi: 10.1055/s-0034-1380453
23. Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Owens, C. E.; Bucholtz, E. C.; Hooper, P. C.; Kula, N. S.; Baldessarini, R. J.; Mailman, R. B. 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes and related derivatives as ligands for the neuromodulatory σ_3 receptor: further structure–activity relationships. *J. Med. Chem.* **1995**, *38*, 3857–3864. doi: 10.1021/jm00019a016
24. Booth, R. G. Therapeutic compounds. PCT Int. Appl. WO2010129048, **2010**.
25. CCDC 2060394 (13) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk./data_request/cif.