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Direct Wittig Olefination of Alcohols

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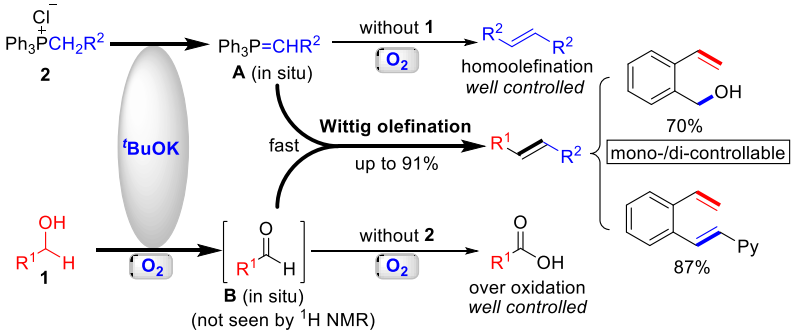


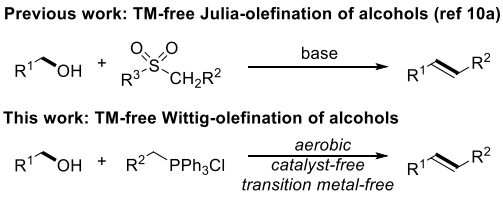
ABSTRACT: A base-promoted transition metal-free approach to substituted alkenes using alcohols under aerobic conditions using air as the inexpensive and clean oxidant is described. Aldehydes are relatively difficult to handle compared to corresponding alcohols due to their volatility and penchant to polymerize and autoxidize. Wittig ylides are easily oxidized to aldehydes and consequently form homo-olefination products. By the strategy of simultaneously in situ generation of ylides and aldehydes, for the first time, alcohols are directly transferred to olefins with no need of pre-preparation of either aldehydes or ylides. Thus the di-/mono-controllable olefination of diols is accomplished. This synthetically practical method has been applied in the gram-scale synthesis of pharmaceuticals such as DMU-212 and Resveratrol from alcohols.

INTRODUCTION

While the success of using alcohols as nucleophiles prevails for the direct access to various functional groups, the development of simple, low-cost and mild reaction conditions capable of utilizing alcohols to react with nucleophiles seems to be challenging due to the high energy of C-O bonds (~90 kcal/mol).[1] It requires an activation of alcohols with excess Brønsted or normally stoichiometric amounts of Lewis acids or the usage of a Mitsunobu protocol, where massive amounts of waste are produced.[2] Besides, applying alcohols as electrophiles under the basic conditions proves to be even more difficult as C-O bonds' energy is increased as a result of their deprotonation in the presence of base.

Wittig olefination[3] is a versatile and reliable method for the production of substituted alkenes from aldehydes in both industry and laboratory preparations,[4] whereas using alcohols instead of corresponding aldehydes would be valuable because aldehydes are relatively difficult to handle compared to corresponding alcohols due to their volatility and penchant to polymerize and autoxidize. In addition, alcohols are more inexpensive, less toxic and more stable than the corresponding aldehydes. In this sense, a variety of oxidizing systems have been implemented for the in situ oxidation–Wittig olefination of primary alcohols but using stoichiometric amount of toxic or hazardous oxidants.[5] Some aerobic oxidation/Wittig procedures based on noble metals also have been applied with stabilized Wittig reagents, however, high temperature is usually needed.[6] A borrowing hydrogen method, which involves catalytic removal of hydrogen from the alcohol, nucleophilic attack of the new carbonyl, and hydrogenation, enables the possibility of "electrophilic alcohols" but forming C-C single bonds instead.[7]

Scheme 1. Olefination of Alcohols



Several examples have been documented in the indirect Wittig olefination of alcohols in recent years using dehydrogenation strategy with noble metal complexes such as ruthenium as catalysts[8] or in the presence of stoichiometric nickel nanoparticles.[9] For example Milstein et al. have reported a P,N,N-Ru-complex catalyzed olefination reaction of alcohols using Wittig reagents.[8a] Albeit transition metal catalysts have been used, harsh reaction conditions with excess ^{t}BuOK at 110 ^{o}C were necessary. The advantage of such in situ dehydrogenation of alcohols to aldehydes is the no need of extra oxidants. But the flip side is that it must face the liberation of hydrogen gas, which may give rise to a safety problem in chemistry laboratory, and the subsequent rehydrogenation of final olefins by the simultaneously generated hydrogen. On

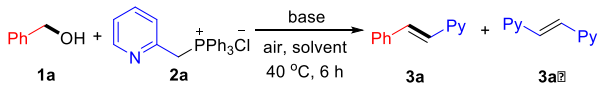
another hand, the use of noble metal-catalysts will not only increase costs but also generate metal residues, which must be avoided in a pharmaceutical-oriented olefination. Therefore, a direct transition metal-free Wittig-olefination of alcohols avoiding hazardous oxidants or the emission of flammable H_2 by a clean aerobic in situ oxidation of alcohols, would be a big breakthrough in the activation and transformation of alcohols.

As part of our continuous research interests in the clean activation and functionalization of alcohols,[10-12] we have previously reported a base-promoted transition metal-free direct Julia-olefination of alcohols under oxygen-free conditions, where the starting alcohols could act as a reductant instead of Na-Hg in the reductive cleaving of C-S and C-O bonds.[10] In this work, we report our recent result of the direct Wittig olefination, in which alcohols were used as formal electrophiles to react with Wittig reagent under basic conditions, avoiding transition metals, hazardous oxidants, and the emission of flammable hydrogen gas.[8a]

RESULTS AND DISCUSSION

Reaction conditions. Initial studies were carried out using benzyl alcohol **1a** and triphenyl(2-pyridylmethyl)phosphonium chloride **2a**. We noticed that in the presence of ^{t}BuOK, in situ alcohol oxidative Wittig reaction could be proceeded very well under very mild conditions (Table 1, entry 7). The effect of ^{n}BuLi was not good as ^{t}BuOK (entry 11). However, the reaction didn't occur when using KOH and Cs_2CO_3 (entries 9 and 10). Among the solvents, tetrahydrofuran gave a better result in olefination process. After screening the amount of base and starting material, we found that benzyl alcohol **1a** (110 mol %) and ^{t}BuOK (200 mol %) could efficiently lead to high conversion and selectivity (entry 15). This condition was chosen as the standard condition for further investigation of substrate scope and limitation. What should be pointed out is that the ICP-MS test reveals that no obvious amount of trace transition metals (Ru/Rh/Pd/Ir/Pt < 1 ppm) in ^{t}BuOK.

Table 1. Reaction Conditions[a]

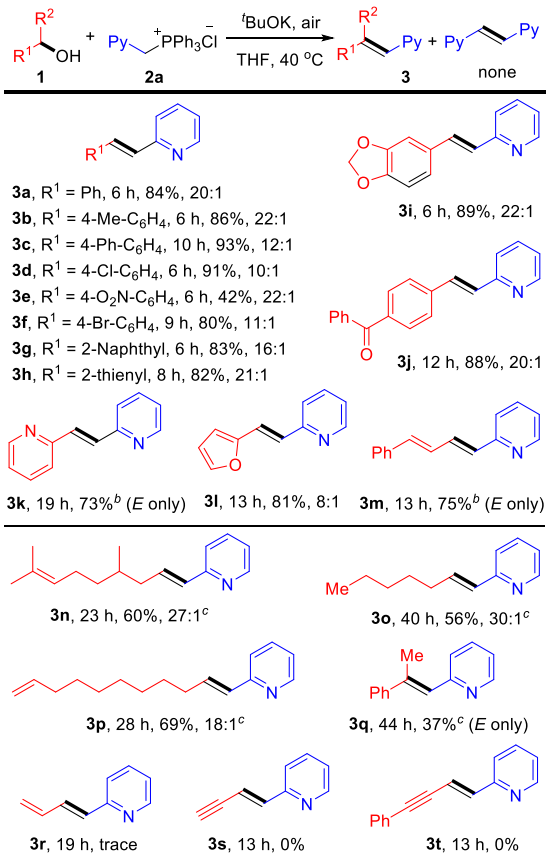


entry	**1a:2a**	base	solvent	*E*/*Z*[b]	**3a**(%)[b]
1	1.3	^{t}BuOK (2.0)	dioxane	27	83
2	1.3	^{t}BuOK (2.0)	toluene	15	80
3	1.3	^{t}BuOK (2.0)	DMSO	19	39
4	1.3	^{t}BuOK (2.0)	DME	10	11
5	1.3	^{t}BuOK (2.0)	octane	11	84
6	1.3	^{t}BuOK (2.0)	CH_3CN	6	21
7	1.3	^{t}BuOK (2.0)	THF	11	87
8	1.3	NaH (2.0)	THF	33	68
9	1.3	KOH (2.0)	THF	–	0
10	1.3	Cs_2CO_3 (2.0)	THF	–	0
11	1.3	^{n}BuLi (2.0)	THF	4	10
12	1.3	^{t}BuOK (1.5)	THF	16	69
13	1.3	^{t}BuOK (1.8)	THF	13	85
14	1.3	^{t}BuOK (2.3)	THF	16	83
15	1.1	^{t}BuOK (2.0)	THF	20	**85**
16	1.5	^{t}BuOK (2.0)	THF	16	85
17	1.7	^{t}BuOK (2.0)	THF	9	81

[a] Conditions: **1a** (1.1-1.7 equiv), **2a** (1.0 mmol), base (2.0 mmol), solvent (1.5 mL), 40 °C, 6 h. [b] Determined by ^{1}H NMR.

Reaction scope. Various alcohols were subjected to the standard condition to prepare alkenes (Scheme 2). A wide range of aryls as well as heteroaryls, including phenyl and substituted phenyls, 2-naphthyl, 2-thienyl, 2-pyridyl, 2-furyl, were all performed well to afford desired alkenes **3a**–**3l** in generally good yields. For all cases, *E*/*Z* selectivity of alkenes has been well controlled in the range of 8 to 30. Aliphatic alcohols could also be converted to corresponding alkenes (**3n** and **3p)** With respect to the secondary alcohols, similar to the Wittig olefination of ketones, the reactivity was much lower than that of primary alcohols. Except **3m**, other olefins (**3r-t**) from allylic or propargylic alcohols are not obtained, whereas only decomposed byproduct 2-methyl pyridine is obtained.

Scheme 2. Scope of Alcohols[a]



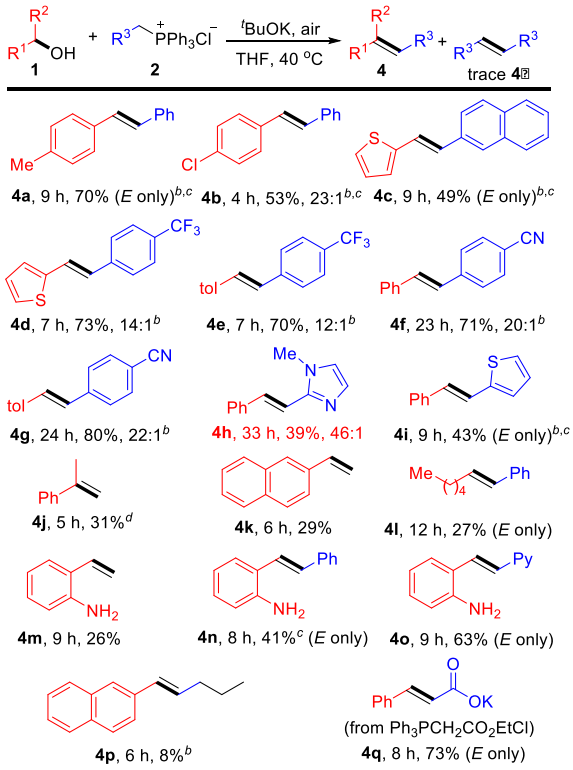
[a] Condition A: **1** (1.1 mmol), **2a** (1 mmol), ^{t}BuOK (2 mmol), THF (1.5 mL), air, 40 °C (the data in parenthesis refer to *E*/*Z* ratios). [b] I_2 (0.5 mmol), THF (3 mL), 90 °C (4 days for **3k** and 2.5 days for **3m**). [c] **1** (1 mmol), **2a** (2 mmol), NaH (4 mmol), dioxane (1.5 mL), air, 70 °C.

Next, various alcohols and Wittig reagents have been subjected to the standard condition to prepare alkenes (Scheme 3). In most cases, mainly or only (*E*)-isomers were obtained (**4a**–**4c** and **4h**–**4o**). For the cases with *E*/*Z*-ratios lower than 10:1, the reaction were treated with iodine under heating conditions to afford (*E*)-isomers (**4d**–**4g**). In some cases with low yields, the homo-olefination of ylides were observed. In all cases, the olefination with stable ylides was unsuccessful. Thus this Wittig olefination of alcohols is limited to hemistable and unstable ylides.

Mono-/di-selectivity control. One advantage of current method is control the regioselectivity for the substrates with two reactive sites. As shown in Scheme 4, the synthesis of

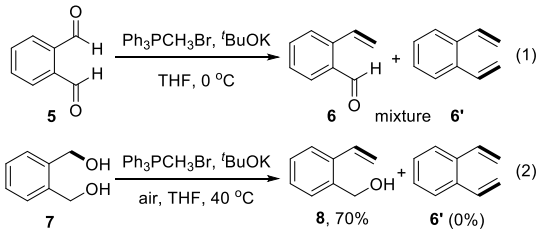
mono-alkene **6** from dialdehyde **5** was not successful because of low regioselectivity. However, when diol **7** was used as the starting material, mono-olefin **8** was obtained as the sole product in 70% of yield. The slow in situ generation of aldehyde intermediate by this method enabled the high regioselectivity for such substrates. In another case, the asymmetric olefination of diol **7** was achieved to afford dialkene **9** in 70% of yield (Scheme 5). The mono-olefination of **7** afforded (*E*)-**10** in 87% of yield in 12:1 regioselectivity. Therefore, this method is powerful complement to Wittig olefination of dialdehydes. The reaction with $BuPPh_3Br$ afforded corresponding olefin **4p** in only 8% of yield. Terminal olefins were obtained in 26-31% of yields (**4j**, **4k** and **4m**). The stabilized ylide $Ph_3P{=}CHCO_2Et$ afforded the product **4q** as a salt in 73% of yield.

Scheme 3. Scope and Limitation[a]



[a] Condition A: **1** (1.1 mmol), **2** (1 mmol), ^{t}BuOK (2 mmol), THF (1.5 mL), air, 40 °C. [b] I_2 (0.5 equiv), THF (3 mL), 90 °C (1-7 days, see experimental section for details). [c] 0 °C. [d] NaH instead of ^{t}BuOK.

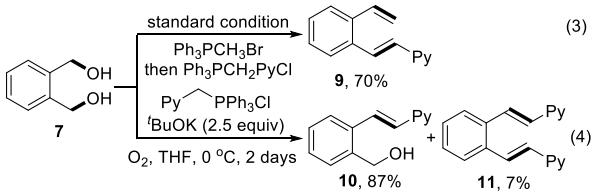
Scheme 4. Wittig Olefination: Aldehyde vs Alcohol



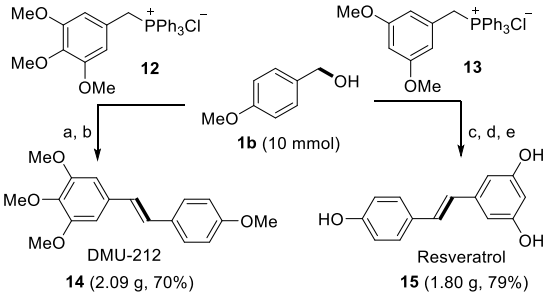
Synthetic applications. This method has been applied in the synthesis of bioactive molecules. The cytotoxic activity of DMU-212 has been shown to vary in cell lines derived from the same type of cancer, i.e. ovarian, breast and colorectal ones. Using present method, 2 g of DMU-212 was synthesized from **1b** in 70% of yield. Resveratrol possesses chemopreventive and cytostatic properties against a variety of human tumour cell lines, including several prostate cancer cell lines. Resveratrol could be prepared from **1b** in 79% in gram-scale (Scheme 6).

To further explore the application of this method in organic synthesis, optically active helicene **21** was prepared from 2-naphthyl methanol **16** (Scheme 7). Racemic **21** was achieved in 5 steps, followed by the resolution with **22** to afford both enantiomers of **21**.

Scheme 5. Selectivity Control

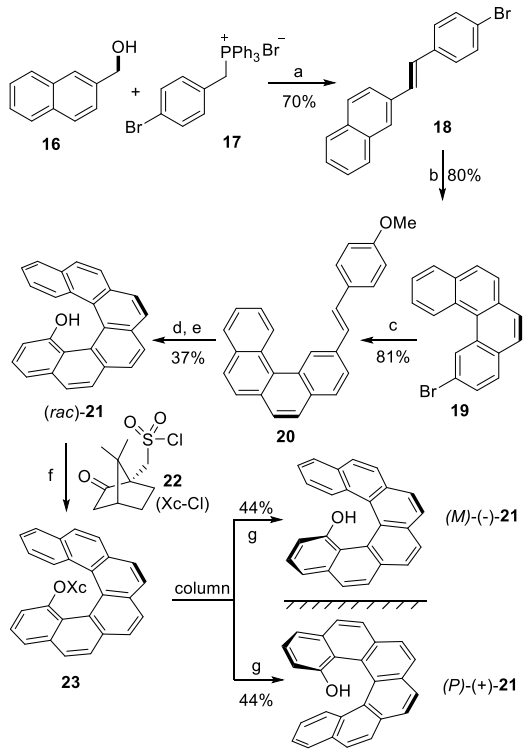


Scheme 6. Gram-Scale Synthesis of Pharmaceuticals[a]



[a] Conditions: a) ^{t}BuOK, THF, air, 0 °C, 16 h; b) I_2 (20 mol %), THF, argon, 90 °C, 11 hr; c) ^{t}BuOK, THF, air, 0 °C; d) I_2 (15 mol %), argon, THF, 90 °C, 79% for two steps; e) BBr_3, DCM, 0 to 30 °C, quant.

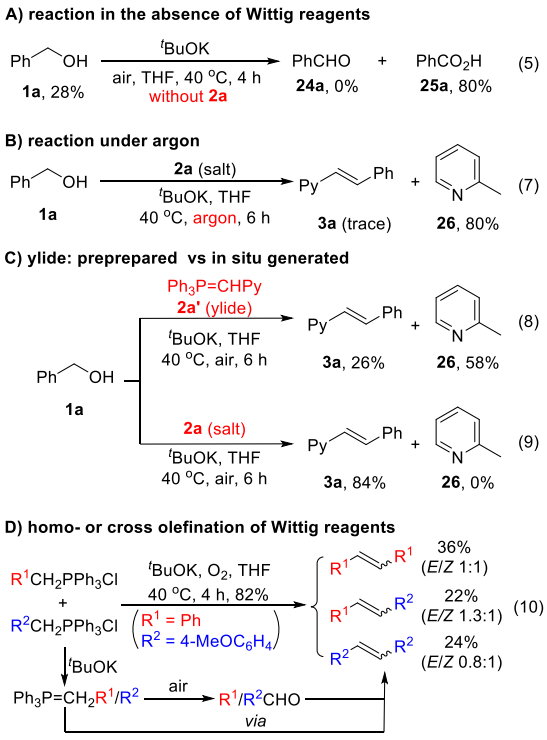
Scheme 7. Synthesis of Enantioenriched 21[a]



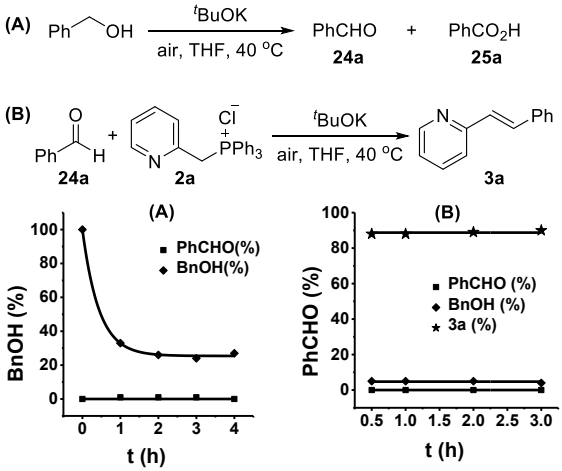
[a] Conditions: a) ^{t}BuOK, air, THF, 0 °C, 43 hr; b) I_2 (1 equiv), toluene, hν (400 W), HPMV, 1.5 hr; c) 4-MeO-styrene, $Pd(OAc)_2$ (3 mol %), dppp (4.5 mol %), K_2CO_3, TBAB (20 mol %), DMA, 40 h; d) I_2 (1 equiv), propylene oxide, toluene, hν (400 W), 2.5 h; e) BBr_3, DCM, rt, 9 hr. f) **22** (2 equiv), DMAP (0.2 equiv), Et_3N (2 equiv), CH_2Cl_2, R.T., 12 h; g) KOH (10 equiv), THF, MeOH, 80 °C, 9 h.

Control experiments. The treatment of **1a** in the absence of Wittig reagent gives rise to the over oxidation of aldehydes intermediates to acid (Scheme 8, eq 5). The kinetic study further reveals that BnOH is slowly oxidized to PhCHO in the absence of Wittig reagent (Scheme 9A). The olefination is very fast (Scheme 9B). The rapid olefination enables the quick trap of in situ generated aldehydes, avoids the over oxidation of aldehydes intermediates to acids. The reaction in under argon does not afford olefin **3a**, whereas 2-methyl pyridine **26** is produced via the decomposition of Wittig reagent (eq 7).[13] The olefination with pre-prepared ylide **2a'** yields only 26% of **3a**, whereas **26** is obtained in 58% yield (eq 8). Compared to above results, the olefination with in situ generated ylide affords **3a** in 84% yield without the formation of **26** (eq 9). This is a remarkable advantage of olefination of alcohols over aldehydes under aerobic conditions. In addition, ylides are normally unstable under aerobic condition due to the fast oxidation of ylides to the corresponding aldehydes which are followed by the homo-olefination (eq 10). Actually, such homo-olefination of Wittig has been inhibited by the competing oxidation of alcohols.

Scheme 8. Control Experiments

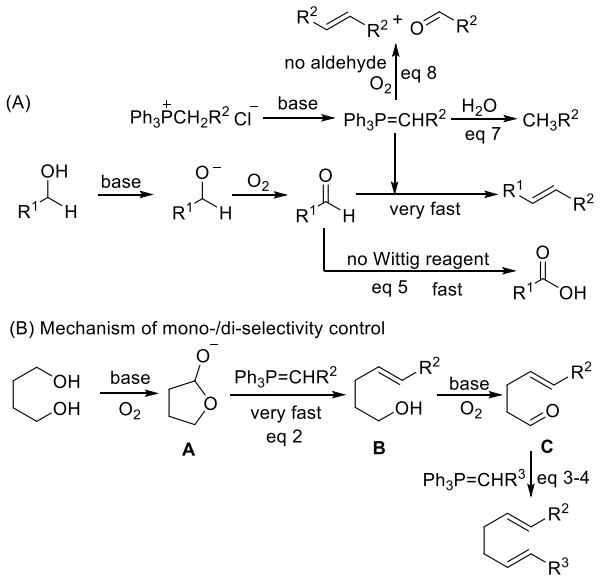


Scheme 9. Kinetic Study



Reaction mechanism. A mechanism is proposed in Scheme 10. The in situ generated ylides and aldehydes react fast to produce olefins. The side reactions such as homo-olefination of Wittig reagents and over oxidation of aldehyde intermediates have been inhibited under alcohol media. The mechanism of mono-/di-selectivity control has been realized by the formation of intermediate **A**. Thus during the olefination of one side, another side is "protected". The further olefination affords asymmetric olefination of diols (Scheme 10B).

Scheme 10. Mechanism



CONCLUSION

In conclusion, we have developed a pharmaceutical-oriented scalable and practical catalyst- and transition-metal-free Wittig olefination of alcohols at 40 °C with an alcohol umpolung strategy. Using air as the inexpensive and clean oxidant, various olefins could be synthesized. This synthetically practical method has been applied in the synthesis of optical active helicenes and the gram-scale synthesis of pharmaceuticals such as DMU-212 and resveratrol, demonstrating potential application in pharmaceutical synthesis.

EXPERIMENTAL SECTION

General Procedure for Condition A. Wittig reagent (1.0 mmol) and ^{t}BuOK (2.0 mmol, 224.4 mg, 2.0 equiv) were weighed into a 25 mL Schlenk tube. After dried under vacuum, 1.5 mL of THF and an alcohol was added. The reaction mixture was stirred at 40 °C under an atmosphere of air (1 atm balloon), monitored by TLC. And quenched by filtering through Celite and silica gel, washed with ethyl acetate and purified on silica gel column using petroleum ether (PE) /ethyl acetate (EA) (v/v 10/1) as eluent. Compounds **3a**, **3b**, **3d-3i**, **3k-3m**, **3o**, **3q**, **4a**, **4b**, **4d-4q**, **8**, **10**, **11**, **14**, **15**, **18**, **19**, **20**, and **21** were known compounds and have been reported previously.[14]

General Procedure for Condition B (3k, 3m, 4d-4g). After the reaction under Condition A, iodine (0.50 equiv) was added and stirred under argon at 90 °C (oil bath). The mixture was washed with saturated solution of sodium thiosulfate, dried with sodium sulfate and purified on silica gel.

*(E)-2-styrylpyridine (**3a**):*[14a] White solid; 6 h; yield 84% (151.9 mg, *E/Z* = 12:1).

*(E)-2-(4-methylstyryl)pyridine (**3b**):* [14a] White solid; 6 h; yield 86% (167.3 mg, *E/Z* = 22:1).

*(E)-2-(2-([1,1'-biphenyl]-4-yl)vinyl)pyridine (**3c**):* White solid; 10 h; yield 93% (241.1 mg, *E/Z* = 12:1); R_f = 0.3 (PE/EA 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.0 Hz, 1H), 7.70–7.61 (m, 8H), 7.47–7.40 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 16.0 Hz, 1H), 7.16 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.7, 149.8, 141.2, 140.7, 136.7, 135.8, 132.4, 129.0, 128.0, 127.7, 127.6, 127.1, 122.3, 122.2. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{19}H_{16}N$ 258.1283, found 258.1281.

*(E)-2-(4-chlorostyryl)pyridine (**3d**):* [14b] White solid; 6 h; yield 91% (196.3 mg, *E/Z* = 10:1)

*(E)-2-(4-nitrostyryl)pyridine (**3e**):* [14c] Yellow solid; 6 h; yield 42% (95.6 mg, *E/Z* = 22:1).

*(E)-2-(4-bromostyryl)pyridine (**3f**):*[14q] White solid; 9 h; yield 80% (219.1 mg, *E/Z* = 11:1).

(E)-2-(2-(naphthalen-2-yl)vinyl)pyridine (**3g**): [14b] Yellow solid; 6 h; yield 83% (191.7 mg, E/Z = 16:1).

(E)-2-(2-(thiophen-2-yl)vinyl)pyridine (**3h**): [14a] Yellow solid; 8 h; yield 82% (153.6 mg, E/Z = 21:1).

(E)-2-(2-(benzo[1,3]dioxol-5-yl)vinyl)pyridine (**3i**): [14a] White solid; 6 h; yield 89% (199.5 mg, E/Z = 22:1).

*(E)-phenyl(4-(2-(pyridin-2-yl)vinyl)phenyl)methanone (**3j**):* White solid; 12 h; yield 88% (251.3 mg, *E/Z* = 20:1); R_f = 0.4 (PE/EA 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.4 Hz, 1H), 7.83 (t, *J* = 8.8 Hz, 4H), 7.73–7.67 (m, 4H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 16.0 Hz, 1H), 7.20 (dd, *J* = 7.2, 5.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.2, 155.0, 149.9, 140.8, 137.7, 136.9, 136.7, 132.4, 131.5, 130.7, 130.4, 130.0, 128.3, 126.9, 122.7. HRMS (ESI-TOF) m/*z* [M + Na]$^+$ calcd. for $C_{20}H_{15}NONa$ 308.1046, found 308.1050.

*(E)-1,2-di(pyridin-2-yl)ethane (**3k**):* [14a] Yellow solid; 19 h for step 1, 4 days for step 2; yield 73% two steps (132.6 mg, *Z* not detected).

(E)-2-(2-(furan-2-yl)vinyl)pyridine (**3l**): [14r] White solid; 13 h; yield 81% (138.7 mg, E/Z = 8:1).

*2-((1E,3E)-4-phenylbuta-1,3-dien-1-yl)pyridine (**3m**):* [14d] Brown solid; 13 h for step 1, 2.5 days for step 2; yield 75% two steps (156.4 mg, *Z* not detected).

*(E)-2-(4,8-dimethylnona-1,7-dien-1-yl)pyridine (**3n**):* Brown oil; 23 h; yield 60% (136.9 mg, *E/Z* = 27:1); R_f = 0.3 (PE/EA 25 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.60 (td, *J* = 8.0, 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.08 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H), 6.72 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 2.32–2.25 (m, 1H), 2.15–2.07 (m, 1H), 2.04–1.95 (m, 2H), 1.68 (s, 3H), 1.66–1.63 (m, 1H), 1.61 (s, 3H), 1.47–1.38 (m, 1H), 1.26–1.16 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.2, 149.5, 136.5, 134.8, 131.3, 131.1, 124.8, 121.6, 121.0, 40.5, 36.9, 32.8, 25.8, 25.7, 19.7, 17.7. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{16}H_{24}N$ 230.1909, found 230.1905.

*(E)-2-(hept-1-en-1-yl)pyridine (**3o**):*[14e] Yellow oil; 40 h; yield 56% (98.5 mg, *E/Z* = 30:1).

*(E)-2-(undeca-1,10-dien-1-yl)pyridine (**3p**):* Brown oil; 28 h; yield 69% (157.6 mg, *E/Z* = 18:1); R_f = 0.3 (PE/EA 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.59 (td, *J* = 7.6, 1.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.08 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.73 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 5.86–5.76 (m, 1H), 5.01–4.91 (m, 2H), 2.26 (q, *J* = 6.8 Hz, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.52–1.48 (m, 2H), 1.40–1.30 (m, 8H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.3, 149.5, 139.3, 136.4, 136.2, 129.9, 121.6, 121.0, 114.2, 33.9, 32.9, 29.4, 29.3, 29.1, 29.0. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{16}H_{24}N$ 230.1909, found 230.1918.

*(E)-2-(2-phenylprop-1-en-1-yl)pyridine (**3q**):* [14f] Brown solid; 44 h; yield 37% (71.4 mg, *Z* not detected).

*(E)-1-methyl-4-styrylbenzene (**4a**):* [14g] White solid; 9 h for step 1, 1.5 days for step 2; yield 70% two steps (136.9 mg, *Z* not detected).

*(E)-1-chloro-4-styrylbenzene (**4b**):* [14g] Yellow solid; 4 h for step 1, 6 days for step 2; yield 53% two steps (113.7 mg, *E/Z* = 23:1).

*(E)-2-(2-(naphthalen-2-yl)vinyl)thiophene (**4c**):* White solid; 9 h for step 1, 21 h for step 2; yield 49% two steps (115.7 mg, *Z* not detected); R_f = 0.5 (PE/EA 70 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.79 (m, 4H), 7.68 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48–7.41 (m, 2H), 7.36 (d, *J* = 16.0 Hz, 1H), 7.21 (d, *J* = 5.2 Hz, 1H), 7.11–7.07 (m, 2H), 7.02 (dd, *J* = 5.2, 3.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.1, 134.6, 133.8, 133.1, 128.6, 128.5, 128.1, 127.9, 127.8, 126.6, 126.5, 126.4, 126.1, 124.6, 123.4, 122.3. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{16}H_{13}S$ 237.0738, found 237.0735.

*(E)-2-(4-(trifluoromethyl)styryl)thiophene (**4d**):* White solid; 7 h for step 1, 2.6 days for step 2; yield 73% two steps (185.5 mg, *E/Z* = 14:1).

*(E)-1-methyl-4-(4-(trifluoromethyl)styryl)benzene (**4e**):*[7] White solid; 7 h for step 1, 6.6 days for step 2; yield 70% two steps (183.9 mg, *E/Z* = 12:1).

*(E)-4-styrylbenzonitrile (**4f**):* [14g] White solid; 23 h for step 1, 4.7 days for step 2; yield 71% two steps (145.7 mg, *E/Z* = 20:1).

*(E)-4-(4-methylstyryl)benzonitrile (**4g**):* [14h] White solid; 24 h for step 1, 4.6 days for step 2; yield 80% two steps (174.0 mg, *E/Z* = 22:1).

*(E)-1-methyl-2-styryl-1H-imidazole (**4h**):* [14i] Yellow solid; 33 h; yield 39% (72.7 mg, *E/Z* = 46:1). *(E)-2-styrylthiophene (**4i**):* [14g] Brown solid; 9 h for step 1, 1.5 days for step 2; yield 43% two steps (79.6 mg, *Z* not detected).

*2-Phenyl-1-propene (**4j**):* [14o] Colorless oil; 5 h; yield 31% (36.2 mg).

*2-vinylnaphthalene (**4k**):* [14j] White solid; 6 h; yield 29% (44.7 mg).

*(E)-hept-1-en-1-ylbenzene (**4l**):* [14k] Yellow oil; 12 h for step 1, 2.5 days for step 2; yield 27% two steps (46.3 mg, *Z* not detected).

*2-vinylaniline (**4m**):* [14u] Colorless oil; 9 h; yield 26% (31.0 mg).

*(E)-2-styrylaniline (**4n**):* [14t] Yellow solid; 8 h for step 1, 8 h for step 2; yield 41% two steps (80.1 mg, *Z* not detected).

*(E)-2-(2-(pyridin-2-yl)vinyl)aniline (**4o**):* [14t] Orange solid; 9 h; yield 63% (122.6 mg, *Z* not detected).

*(E)-2-(pent-1-en-1-yl)naphthalene (**4p**): [14v] White solid; 6 h; yield 8% (15.7 mg, Z not detected)*

*(E)- potassium cinnamate (**4q**): [14w] White solid; 8 h; yield 73% (136.0 mg, Z not detected)*

*(2-vinylphenyl)methanol (**8**):* [14s] Colorless oil; 19 h; yield 70% (94.4 mg).

*(E)-2-(2-vinylstyryl)pyridine (**9**):* Colourless oil; 55 h; yield 70% (143.7 mg, *Z* not detected); R_f = 0.3 (PE/EA 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.4 Hz, 1H), 7.96 (d, *J* = 16.0 Hz, 1H), 7.69–7.62 (m, 2H), 7.52–7.49 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.31–7.29 (m, 2H), 7.22–7.15 (m, 2H), 7.05 (d, *J* = 16.0 Hz, 1H), 5.67 (d, *J* = 4.4 Hz, *J* = 17.6 Hz, 1H), 5.39 (d, *J* = 10.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.7, 149.7, 137.1, 136.6, 134.9, 130.5, 130.3, 128.3, 127.9, 126.6, 126.5, 122.2, 116.9. HRMS (ESI-TOF) m/*z* [M + Na]$^+$ calcd. for $C_{15}H_{13}NNa$ 230.0940, found 230.0942.

*(E)-(2-(2-(pyridin-2-yl)vinyl)phenyl)methanol (**10**)* Colourless oil; 48 h; yield 87% (184.3 mg, *Z* not detected).

*1,2-bis((E)-2-(pyridin-2-yl)vinyl)benzene (**11**):* White solid; 48 h; yield 7% (19.9 mg, *Z* not detected).

*(E)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene (**14**):* [14l] Yellow solid; 16 h for step 1, 11 h for step 2; yield 70% two steps (2.09 g).

(E)-1,3-dimethoxy-5-(4-methoxystyryl)benzene: [14l] Brown solid; 25 h for step 1, 4 h for step 2; yield 79% two steps (2.14 g).

(E)-5-(4-hydroxystyryl)benzene-1,3-diol (**15**): [14l] Brown solid; 6 h; yield 100% (1.80 g).

*2-(4-bromostyryl)naphthalene (**18**):* [14m] By Condition B, white solid; 43 h; yield 70% (430.6 mg, *E/Z* = 0.7:1).

*2-bromobenzo[c]phenanthrene (**19**):* [14n] Compound **18** and I_2 (353 mg) were dissolved in 1.2 L toluene. The mixture was transferred into a quartz reactor. Then it was irradiated by 400W HMPV lamp for 1.5 h. The reaction mixture was washed with saturated sodium thiosulfate solution and dried with sodium sulfate. The solvent was removed under reduced pressure and purified on silica gel column to give the **19** (341.0 mg, 80%). White solid; 24 h; yield 80% (341.0 mg).

*3-(4-methoxystyryl)benzo[c]phenanthrene (**20**):* [14p] Palladium acetate (7.5 mg, 0.0333 mmol) and 1,3-bis(diphenylphospino)propane (20.6 mg, 0.0500 mmol) were dissolved in *N,N*-dimethylacetamide (5.00 mL) under argon atmosphere. The mixture was stirred at room temperature until it became homogeneous. In another 100 mL round flask, **19** (341.0 mg, 1.11 mmol), potassium carbonate (306.8 mg, 2.22 mmol), tetrabutylammonium bromide (71.6 mg, 0.222 mmol) were added into 25.0 mL *N,N*-dimethylacetamide. The mixture was heated to 60 °C and styrene (300 μL, 2.22 mmol) was added. Then the mixture was heated to 100 °C and the previously prepared solution of Pd catalyst was added. The resulting mixture was heated to 140 °C for 40 h and monitored by TLC. After completion of the reaction, the reaction mixture was poured into 1 M HCl and extracted with dichloromethane. The organic phase was combined and washed with brine. Then it was dried with sodium sulfate. The organic solvent was evaporated under reduced pressure and purified on silica gel column with petroleum ether and ethyl acetate to give **20** (324.4 mg, *E/Z* = 7:1, 81%). White solid; 40 h; yield 81% (324.4 mg, *E/Z* = 7:1).

*2-Hexahelicenol (rac-**21**):*[14p] Compound **20**, I_2 (228.4 mg, 0.90 mmol) and propylene oxide (38 mL, 540 mmol) were dissolved in 900 mL toluene. The mixture was transferred into a quartz reactor. Then it was irradiated by 400W HMPV lamp for 2.5 h. When the reaction completed, it was washed with saturated sodium thiosulfate solution and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was dissolved in 25 mL dichloromethane and cooled to 0 °C, BBr_3 (154 μL, 1.6 mmol) in dichloromethane (5.0 mL) was added dropwise. The resulting mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, it was quenched with 1.0 M HCl under 0 °C and extracted with dichloromethane. The organic phase was combined and washed with brine. Then it was dried with sodium sulfate. The organic solvent was evaporated under reduced pressure and purified on silica gel column with petroleum ether and ethyl acetate to give (*rac*)-**21** (117 mg, 37% two steps). Yellow solid; 9 h; yield 85% (117.0 mg).

*Hexahelicen-11-yl((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate (**23A**):* (*rac*)-**21,** *D*-(+)-10-camphorsulfonyl chloride (170.5 mg, 0.68 mmol)

and 4-dimethylaminepyridine (8.3 mg, 0.068 mmol) were dissolved in anhydrous dichloromethane. Then Et_3N (94 μL, 0.68 mmol) was added. The resulting mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, it was washed with water and dried with sodium sulfate. The organic solvent was evaporated under reduced pressure and purified on silica gel column with petroleum ether, dichloromethane and ethyl acetate (70:70:1) as eluent. The earlier eluting fractions gave diastereomer **23A** (83.8 mg, 44 %) while the later parts gave diastereomer **23B** (83.9 mg, 44 %). Yellow solid; 12 h; yield 44% (83.8 mg); R_f = 0.3 (PE/EA 50 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.94 (m, 5H), 7.91–7.89 (m, 3H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.27–7.22 (m, 2H), 6.72 (t, *J* = 8.4 Hz, 1H), 3.35 (d, *J* = 15.2 Hz, 1H), 2.69 (d, *J* = 15.6 Hz, 1H), 2.32–2.23 (m, 2H), 2.04–2.00 (m, 2H), 1.88 (d, *J* = 18.4 Hz, 1H), 1.42–1.38 (m, 1H), 1.26–1.22 (m, 1H), 0.98 (s, 3H), 0.71 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 213.5, 146.6, 133.2, 132.0, 131.7, 131.6, 131.0, 130.4, 129.5, 129.4, 128.1, 127.8, 127.7, 127.6, 127.3, 127.2, 127.0, 126.1, 126.0, 124.9, 124.0, 120.6, 119.9, 57.8, 47.8, 46.6, 42.6, 42.4, 26.9, 24.7, 20.0, 19.6. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{36}H_{31}O_4S$ 559.1938, found 559.1939.

*Hexahelicen-11-yl((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate (**23B**):* Yellow solid; 12 h; yield 44% (83.9 mg); R_f = 0.3 (PE/EA 50 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.90 (m, 8H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.28–7.24 (m, 2H), 6.72 (t, *J* = 8.0 Hz, 1H), 3.29 (d, *J* = 15.2 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 2.35–2.29 (m, 1H), 2.11–1.98 (m, 3H), 1.91 (d, *J* = 18.8 Hz, 1H), 1.54–1.47 (m, 1H), 1.44–1.38 (m, 1H), 0.78 (s, 3H), 0.71 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 213.8, 146.6, 133.2, 132.0, 131.6, 130.9, 130.4, 129.5, 129.4, 128.2, 127.9, 127.7, 127.5, 127.3, 127.2, 127.0, 126.2, 126.0, 124.9, 123.9, 120.4, 119.8, 57.8, 47.8, 46.9, 42.8, 42.4, 26.9, 24.6, 19.7, 19.6. HRMS (ESI-TOF) m/*z* [M + H]$^+$ calcd. for $C_{36}H_{31}O_4S$ 559.1938, found 559.1939.

*M-(-)-2-Hexahelicenol ((M)-(-)-**21**):* [14p] **23**A and KOH (85%) (99 mg, 1.5 mmol) were dissolved in THF/MeOH (1:1, v/v, 30 mL). The resulting mixture was refluxed at 80 ^{o}C for 10 hours. When the reaction finished, it was cooled to room temperature and poured into ice water. Then it was quenched with 1.0 M HCl and extracted with dichloromethane. Dried with sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified on silica gel column with petroleum ether and ethyl acetate to give the product (***M*)-(-)-21/(*P*)-(+)-21.**Yellow solid; 9 h; yield 99% (63.4 mg); $[\alpha]_D$ = -3282 (*c* 0.08, $CHCl_3$).

*P-(+)-2-Hexahelicenol ((P)-(+)-**21**):* [14p] **23**B was treated by same procedure as above. Yellow solid; 9 h; yield 99% (63.0 mg); $[\alpha]_D$ = +3721 (*c* 0.08, $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information

Spectra of products. This material is available free of charge *via* the Internet at http://pubs.acs.org.
SI (PDF)

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Notes

The authors declare no competing financial interest.

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