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Pd-Catalyzed Tandem Isomerization/Cyclization for the Synthesis of Aromatic Oxazaheterocycles and Pyrido[3,4-*b*]indoles

Linglong Ding, Yan-Ning Niu, and Xiao-Feng Xia*

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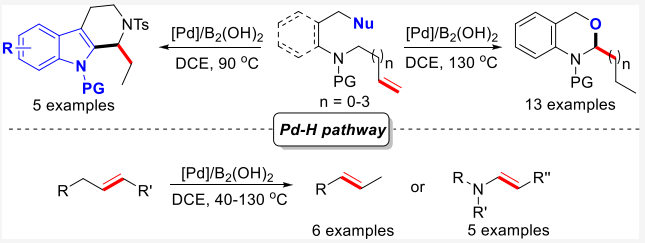
ABSTRACT: An effient tandem process consisting of palladium-catalyzed double-bond isomerization of long-chain olefins and subsequent intramolecular cyclization promoted by $B_2(OH)_2$ for the synthesis of aromatic oxazaheterocycles is disclosed. This strategy can also provide rapid access to pyrido[3,4-*b*]indoles, *trans*-2-olefins, and eneamides bearing various functional groups with high regio- and stereoselectivity.



INTRODUCTION

Metal-catalyzed alkene isomerization has emerged as a powerful strategy with wide application for the synthesis of high-value chemicals in industry and academia. During the past few decades, a great number of C−C double-bond isomerization protocols have been developed using catalysts derived from noble metals[1] as well as base metals.[2] Despite the remarkable developments and applications in organic synthesis with these strategies, its use for C−C or C−X bond formation in the synthesis of heterocyclic compounds has not been well investigated.[3] As early as 2012, Kochi and co-workers developed a complex Pd-catalyzed alkene isomerization strategy for catalytic cycloisomerization of 1,*n*-dienes.[4] Later on, Nielsen, Scheidt, and other groups reported a variety of metal-catalyzed alkene isomerization of N- and O-allylic systems to access structurally complex and diverse heterocycles (Scheme 1).[5] In 2016, a tandem long-distance chain-walking/cyclization reaction via $RuH_2(CO)(PPh_3)_3$/Brønsted acid cocatalysis leading to aromatic oxazaheterocycles was realized by the Saá group.[6] Recently, a complex nickel hydride/Brønsted acid-cocatalyzed tandem isomerization/cyclization reaction of allyl ethers and amines was disclosed by Fleischer and co-workers.[7] Although a series of catalysts have been reported for the alkene isomerization/cyclization, developing an efficient and simple catalytic system capable of expanding the boundaries of long-distance alkene isomerization/cyclization is imperative in modern organic synthesis.

Recently, boranes or boronates have been reported as efficient ancillary ligands with metal catalysts for activation of olefins due to their potential to engage in Lewis acid coligand−metal−substrate bridging interaction.[8] In light of this strategy, in 2016, Stokes, Song, and Prabhu groups developed a series of diboron-assisted palladium-catalyzed transfer hydrogenations of olefins and N-heteroaromatics, respectively (Scheme 2a).[9] Later on, this was further explored by the Prabhu group in palladium-boronate/borane-system-catalyzed isomerization of olefins (Scheme 2a).[10] Very recently, a similar strategy involving a palladium/borane-catalyzed selective synthesis of prenylated indoles was reported by Chen.[11] In these transformations, a B−Pd−H active species was involved as the key catalyst. To continue our interest in Pd−H catalysis,[12] we report, herein, an expedient pathway for alkene isomerization/cyclization by harnessing the versatility of B_2X_4 reagents, which can serve as both a transition metal oxidant and as a Lewis acid for cyclization (Scheme 2b).

RESULTS AND DISCUSSION

We commenced our investigation using **1a** as a model substrate in the presence of previously reported conditions;[13] cycloisomerization product **2a** was obtained in a 43% yield (Table 1, entry 1). However, glycerol and ethanol in place of glucose as a hydrogen source failed miserably to give the desired products (entries 2 and 3). Then, D-mannitol in place of glucose as the hydrogen source improved the yield of benzoxazine **2a** to 67% (entry 4). Compared with B_2Pin_2, $B_2(OH)_4$ is more environmentally benign and much atom economic; therefore, we decided to replace B_2Pin_2 with $B_2(OH)_4$.[14] To our delight, when 3 equiv of $B_2(OH)_4$ was used, the yield of **2a** was increased to 79% (entry 5). Subsequent fine tuning the reaction by reducing the amount of $B_2(OH)_4$ to 2 equiv indicated that the yield of **2a** was improved further to 81% (entry 6). Moreover, when the amount of $B_2(OH)_4$ was kept at 1.2 equiv, the yield of **2a** was

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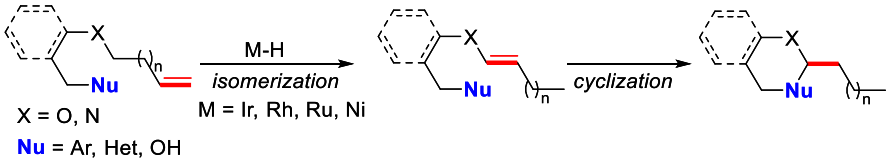
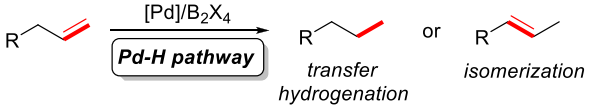
Scheme 1. Previous Works on Tandem Alkene Isomerization/Cyclization



Scheme 2. Pd-Catalyzed Transfer Hydrogenations or Isomerization of Olefins

(a) Previous works: *Pd-Boron-catalyzed transfer hydrogenations or isomerization of olefins*



(b) Our work: *Long distance olefin cycloisomerization*

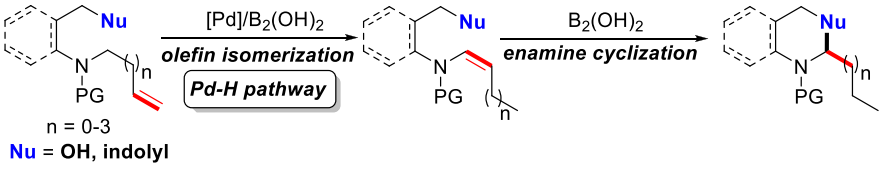
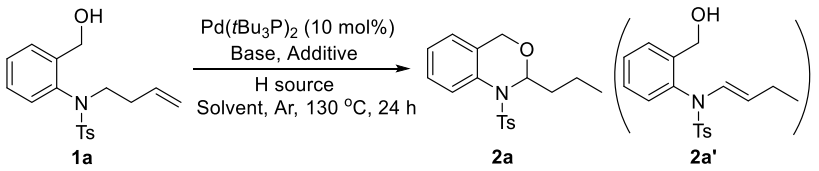


Table 1. Optimization of Reaction Conditions[a]



					yield (%)[b]
entry	H source	additive (equiv)	solvent (mL)	**2a**	**2a′**
1	glucose	B_2Pin_2 (3.0)	DCE (1.0)	43	
2	glycerol	B_2Pin_2 (3.0)	DCE (1.0)	<5	
3	EtOH	B_2Pin_2 (3.0)	DCE (1.0)		
4	D-mannitol	B_2Pin_2 (3.0)	DCE (1.0)	67	
5	D-mannitol	$B_2(OH)_4$ (3.0)	DCE (1.0)	79	
6	D-mannitol	$B_2(OH)_4$ (2.0)	DCE (1.0)	81	
7	D-mannitol	$B_2(OH)_4$ (1.2)	DCE (1.0)	19	48
8[c]	D-mannitol	$B_2(OH)_4$ (2.0)	DCE (1.0)	58	
9	Fructose	$B_2(OH)_4$ (2.0)	DCE (1.0)	73	
10	Sucrose	$B_2(OH)_4$ (2.0)	DCE (1.0)	79	
11[d]		$B_2(OH)_4$ (2.0)	DCE (2.0)	82	
12[e]		$B_2(OH)_4$ (2.0)	DCE (2.0)	55	
13		$B_2(OH)_4$ (2.0)	DMF (2.0)	0	0
14		$B_2(OH)_4$ (2.0)	toluene (2.0)	0	0
15	EtOH	$B_2(OH)_4$ (1.2)	toluene (1.0)	52	25
16	EtOH	$B_2(OH)_4$ (60%)	toluene (1.0)	43	22
17	EtOH	B_2Pin_2 (30%)	toluene (1.0)	<5	51
18	H_2O	B_2Pin_2 (30%)	toluene (1.0)	55	30

[a]Conditions: **1a** (0.05 mmol), H source (0.15 mmol), $Pd(tBu_3P)_2$ (10 mol %), NaOAc (0.15 mmol), and solvent (1 mL) at 130 °C for 24 h. [b]Isolated yields. [c]115 °C. [d]**1a** (0.1 mmol). [e]$Pd(tBu_3P)_2$ (5 mol %).

dramatically reduced to 19% and enamine **2a′** was obtained in a 48% yield concomitantly (entry 7). By decreasing the temperature to 115 °C, a slightly reduced yield was observed (entry 8). In addition, fructose and sucrose in place of D-mannitol as the hydrogen source also gave the desired product **2a** in 73 and 79% yields, respectively (entries 9 and 10). Interestingly, in the absence of extra hydrogen sources and bases, the cycloisomerization also smoothly occurred to give the desired product **2a** in 82% yields (entry 11). Further, decreasing the catalyst loading to 5 mol % reduced the reaction yield (55%, entry 12). Solvent screening revealed that dichloroethane (DCE) was the best solvent, whereas dimethylformamide (DMF) and toluene failed to give the desired product (entries 13 and 14). Notably, when the reaction was carried out under an ethanol/toluene system, corresponding product **2a** and enamine **2a′** were both obtained (entries 15 and 16). When B_2Pin_2 (30 mol %) was used, only enamine **2a′** was detected (entry 17). In addition,

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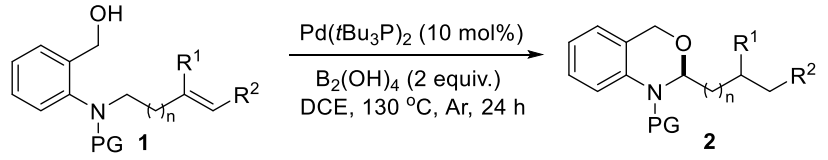
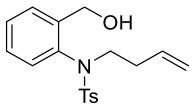
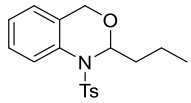
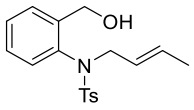
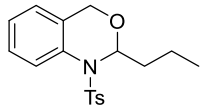
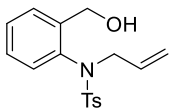
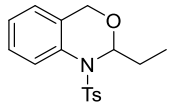
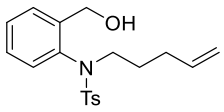
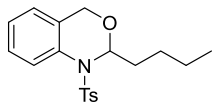
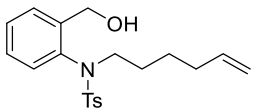
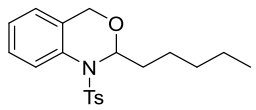
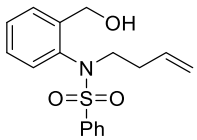
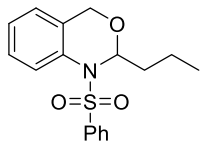
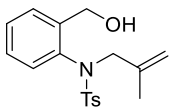
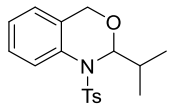
Table 2. Variations in an Alkene-Bearing Chain[a]



Entry	Substrate	Product	Yield (%)[b]
1		 **2a**	82 (85)[c]
2		 **2a**	81
3		 **2b**	76
4[d]		 **2c**	44
5[d]		 **2d**	38
6		 **2e**	87
7[e]		 **2f**	45

[a]Conditions: **1** (0.20 mmol), $Pd(tBu_3P)_2$ (10 mol %), and $B_2(OH)_4$ (0.40 mmol) in 3 mL of DCE at 130 °C for 24 h. [b]Isolated yields. [c]1.0 mmol **1a** was used. [d]48 h. [e]12 h.

using H_2O in place of ethanol as the hydrogen source, the yield of **2a** was increased to 55% and enamine **2a′** was obtained in a 30% yield (entry 18). Therefore, the optimized reaction conditions for this cycloisomerization were defined as $Pd(tBu_3P)_2$ (10 mol %), and $B_2(OH)_4$ (2 equiv) in DCE at 130 °C under an argon atmosphere for 24 h (entry 11).

Under the optimized reaction conditions (Table 1, entry 11), the substrate scope of this reaction was examined (Table 2). Substrates with various long-distance olefins were subjected to the cycloisomerization reactions and smoothly converted into benzoxazines in moderate to good yields. Short-distance-chain olefin derivatives were well tolerated, leading to the corresponding products **2a** and **2b** in 82 and 76% yields, respectively (entries 1 and 3). Long-distance-chain olefin derivatives **1c,d** cycloisomerized to benzoxazines **2c,d**; lower yields were obtained (44 and 38%, respectively, entries 4 and

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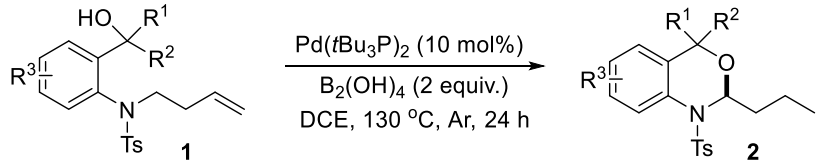
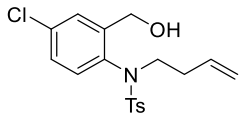
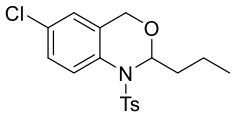
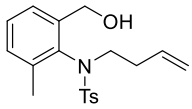
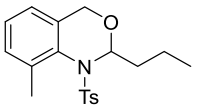
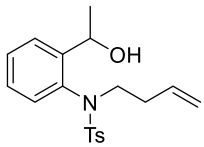
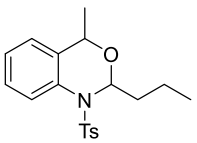
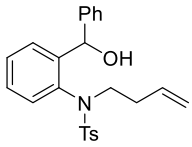
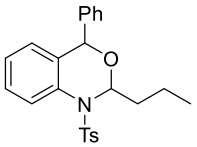
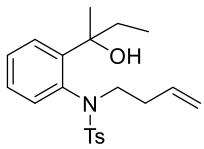
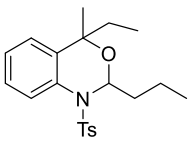
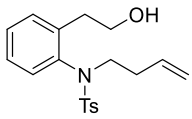
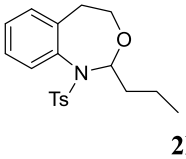
Table 3. Variations in Aryls and Oxygenated Nucleophiles[a]



Entry	Substrate	Product	Yield (%)[b]
1		 **2g**	60
2		 **2h**	73
3		 **2i**	82 (dr 3.4:1)
4[c]		 **2j**	60 (dr 3.7:1)
5[c]		 **2k**	30
6		 **2l**	70

[a]Conditions: **1** (0.20 mmol), $Pd(tBu_3P)_2$ (10 mol %), and $B_2(OH)_4$ (0.40 mmol) in 3 mL of DCE at 130 °C for 24 h. [b]Isolated yields. [c]36 h.

5) even though the reaction was prolonged to 48 h. An internal olefin derivative could also afford the desired product **2a** in a good yield (81%, entry 2). Substrate **1e** with a sulfonamide protecting group was compatible with this transformation to give benzoxazine **2e** in an 87% yield (entry 6). Notably, 1,1-disubstituted alkene **1f** can be also tolerated in this transformation, affording **2f** below average yield (45%, entry 7). A scale-up experiment (1.0 mmol) was carried out and cycloisomerization product **2a** was obtained in an 85% yield (entry 1).

An electron-withdrawing group such as −Cl and an electron-donating group such as −Me slightly influenced the yields, and the corresponding cycloisomerization products **2g** and **2h** were obtained in 60 and 73% yields, respectively (Table 3, entries 1 and 2). Secondary alcohol **1i** had no effect on the reaction, giving an excellent yield of product **2i** (82%, entry 3). However, due to the steric hindrance, substrates **1j** and **1k** cycloisomerized to give benzoxazine **2j** and **2k** in fairly lower yields (60 and 30%, respectively, entries 4 and 5). Finally, the substrate having a long hydroxyl chain was also suitable for the cycloisomerization reaction to give the seven-membered benzoxazepines **2l** in a good yield (70%, entry 6).

To further investigate the scope of this novel cycloisomerization system, the reaction of N-tosyl tryptamine

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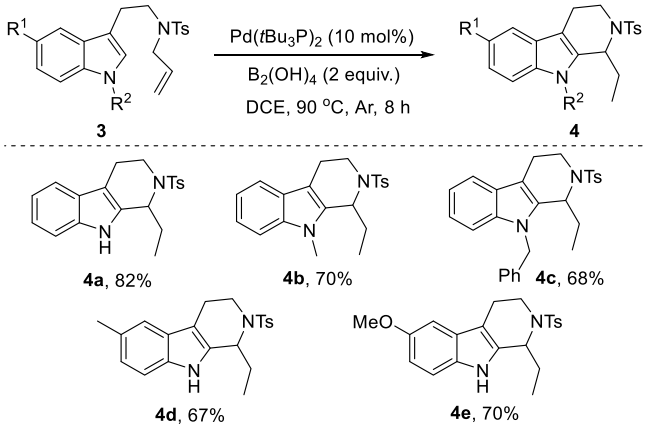
derivatives was carried out under the slightly modified reaction conditions (Scheme 3). It is worth noting that the conversion

Scheme 3. Scope for the Synthesis of Pyrido[3,4-*b*]indoles



efficiency was improved significantly when the reaction temperature decreased to 90 °C, as the reaction could be completed within 8 h. The unprotected indole could undergo cyclization to give a high yield of product **4a** (82%). Methyl- or benzyl-protected indoles gave the corresponding products **4b** and **4c** in 70 and 68% yields, respectively. In addition, the C-5 substituted unprotected indoles with a methyl or a methoxyl group smoothly underwent cyclization to give products **4d** and **4e** in 67 and 70% yields, respectively.

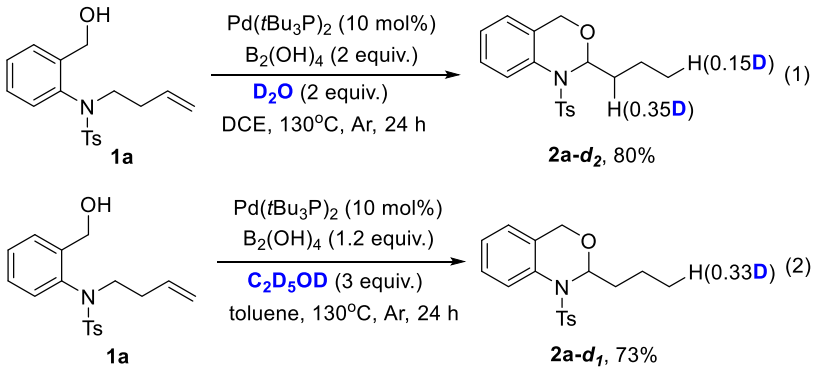
The isomerization process was further investigated on the simple olefins with functionalized chains.[15] As shown in Table 4, a series of *trans*-2-olefins bearing various functional groups were obtained in good yields. 1-Phenylbut-3-en-1-ol, which contains a −OH group, showed good compatibility with the metal catalyst and furnished the isomerized products (*E*)-1-phenylbut-2-en-1-ol (**6a**) instead of thermodynamically more favored butyrophenone at a mild reaction condition (40 °C).[11] In addition, substrate **5b** containing a phenolic −OH group can also give the isomerized product **6b** in a 71% yield (entry 2). The corresponding isoeugenol derivative (*E*)-1,2-dimethoxy-4-(prop-1-en-1-yl)benzene (**6c**) was obtained in an excellent yield (96%, entry 3). Further, substrates with allyl ether can be also tolerated in this transformation, affording the isomerized products **6d** and **6e** in good yields with moderate selectivities (entries 4 and 5). Similarly, the isomerization of the substrate with *N*-allyl **5f** was also facile and afforded the corresponding enamine *E*-isomer **6f** in a 67% yield at 40 °C (entry 6). As expected, long-distance olefin substrates **5g** and **5h** can go through the chain-walking process over two positions to give the corresponding *E*-isomer **6g** and **6h** in 60 and 64% yields at high temperatures, respectively (entries 7 and 8). Similarly, the 1,2-disubstituted alkenes **5i** can also give the isomerized product **6h** in a lower yield (entry 9). Substrates **5j** and **5k** had no effect on the reaction and the corresponding isomerized products **6i** and **6j** were obtained in 42 and 80% yields, respectively (entries 10 and 11). However, simple terminal alkenes such as 1-dodecene and 5-hexen-1-ol were not tolerated in these isomerization conditions (not shown in Table 4).

To better understand the mechanism of this cycloisomerization, deuterium-labeled experiments were carried out with **1a** under different reaction conditions. As expected, the cycloisomerization went smoothly when D_2O was added in the standard condition. NMR analysis of purified **2a-*d*$_2$** indicated that deuterium had been embedded at two different positions (Scheme 4(1)). Deuteration on the *β*-position of a N atom in **2a-*d*$_2$** meant that there was a process of tautomerization between enamine and imine before the cyclization. The reaction of **1a** with ethanol-d_6 gave product **2a-*d*$_1$**, whose NMR spectra revealed that a deuterium atom had been incorporated mainly at the terminal carbon position (Scheme 4(2)). These phenomena were in accordance with previous reports.[9,10]

Control experiments were performed to gain insight into the mechanism of this transformation (Scheme 5). Treatment of **1a** with 3 equiv of ethanol and 1.2 equiv of B_2Pin_2 in toluene under otherwise standard conditions gave rise to enamine **2a′** in a 79% yield (Scheme 5(1)), which can go through intramolecular cyclization to afford **2a** in the presence of $B_2(OH)_2$ at 80 °C (Scheme 5(2)). The reaction of **1a** with ethanol and B_2Pin_2 systems could also give 2-olefin **2a″** in an 85% yield after 30 min, which could further go through isomerization/cyclization to afford **2a** in an 81% yield under standard conditions (Scheme 5(3),(4)). These phenomena meant that chain-walking of a double bond and cyclization were involved as the key steps in this transformation.[6]

According to deuterium experiments and mechanistic investigations, a possible transformation pathway has been proposed in Scheme 6. First, a Pd catalyst goes through oxidative addition with $B_2(OH)_4$ to give active Pd species **A**; water then coordinates to one boron atom to give adduct **B**, which goes through H atom transfer to afford Pd−hydride **C**. Migratory insertion of a double bond of **1a** with Pd−hydride **C** could afford Pd−alkyl intermediate **D**, which give intermediate **E** through *β*-H elimination. Enamine intermediate **F** could be

Scheme 4. Deuterium Experiments



https://doi.org/10.1021/acs.joc.1c00770
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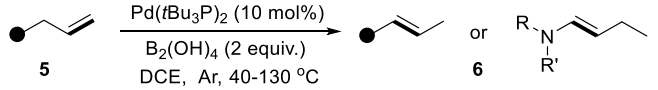
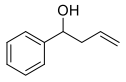
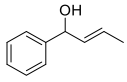
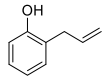
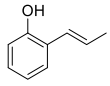
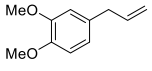
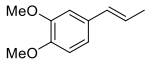
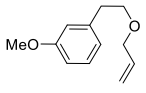
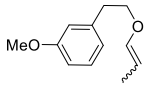
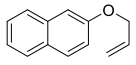
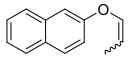
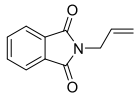
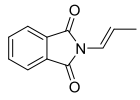
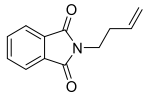
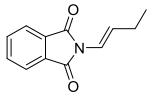
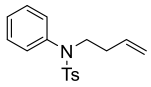
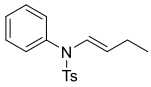
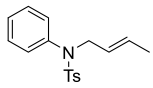
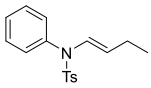
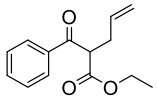
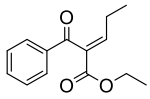
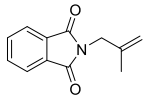
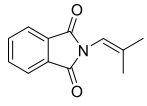
Table 4. Scope for Isomerization of Alkenes[a]



Entry	Substrate	Product/Yield (%)[b]	Temp.(°C)/ Time (h)
1	 **5a**	 **6a**, 74%	40/6
2	 **5b**	 **6b**, 71%	40/12
3	 **5c**	 **6c**, 96%	80/1
4	 **5d**	 **6d**, 68%, E/Z=55:45[c]	40/30
5	 **5e**	 **6e**, 74%, E/Z=68:32[c]	80/1
6	 **5f**	 **6f**, 67%	40/8
7	 **5g**	 **6g**, 60%[d]	100/12
8	 **5h**	 **6h**, 64%	130/24
9	 **5i**	 **6h**, 38%[e]	100/4
10	 **5j**	 **6i**, 42%	130/36
11	 **5k**	 **6j**, 80%	80/12

[a]Conditions: **5** (0.20 mmol), $Pd(tBu_3P)_2$ (10 mol %), and $B_2(OH)_4$ (0.40 mmol) in 3 mL of DCE. [b]Isolated yields. [c]Determined by ^1H NMR. [d]**5g** (0.20 mmol), $Pd(tBu_3P)_2$ (10 mol %), B_2Pin_2 (1.2 equiv), and C_2H_5OH (3.0 equiv) in 3 mL of toluene. [e]Anhydrous DCE is used.

obtained after isomerization from **E**. In the presence of $B_2(OH)_4$, enamine intermediate can easily transform into imine intermediate **G**, which could go through intramolecular cyclization to afford product **2a**.

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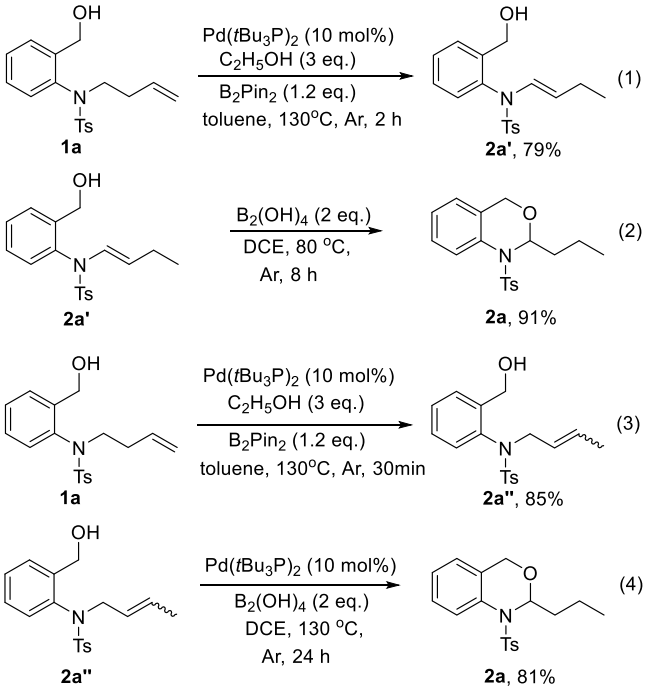
Scheme 5. Mechanistic Investigations



CONCLUSIONS

In summary, we have developed an efficient double-bond isomerization/intramolecular cyclization process for the synthesis of six- or seven-membered 1,3-oxazaheterocycles and pyrido[3,4-*b*]indoles. A series of *trans*-2-olefins and eneamides bearing various functional groups can be also obtained with high regio- and stereoselectivity. B_2X_4 reagents were crucial for this Pd−H catalytic procedure and intramolecular cyclization as a Lewis acid. This protocol serves as a platform to open new approaches in palladium hydride-catalyzed tandem transformations.

EXPERIMENTAL SECTION

General Remarks. Column chromatography was carried out on a silica gel. Unless noted, ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$, ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$, and IR spectra were recorded on an FTIR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS (high-resolution mass spectra); high-resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF-Q instrument equipped with an ESI source. Copies of their ^{1}H NMR and ^{13}C NMR spectra are provided. Pd(tBu$_3$P)$_2$, $B_2(OH)_4$, and the substrate **5f** were purchased from Sigma-Aldrich. All reagents or catalysts were directly used as purchased without further purification. The substrates **1a**−**1l**, **3a**−**3e**, **5a**, **5b** were synthesized according to a previous report.[5a,6] The solvent for recrystallization of all solid compounds was CH_2Cl_2.

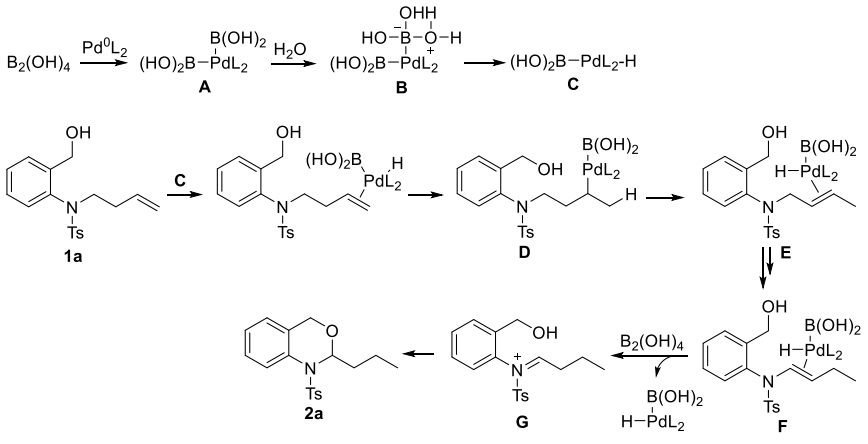
General Procedure for the Synthesis of Products 2, 4, and 6. A mixture of *N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-phenyl)-4-methyl-benzene-sulfonamide **1a** (0.20 mmol), $B_2(OH)_4$ (0.40 mmol), and Pd(tBu$_3$P)$_2$ (0.02 mmol) was combined in DCE (3.0 mL) at 130 °C in an oil bath for 24 h under an argon atmosphere. After the reaction, 10 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **2a** (petroleum ether/ethyl acetate = 6:1).

A mixture of *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-allyl-4-methylbenzene-sulfonamide **3a** (0.20 mmol), $B_2(OH)_4$ (0.40 mmol), and Pd(tBu$_3$P)$_2$ (0.02 mmol) was combined in DCE (3.0 mL) at 90 °C in an oil bath for 8 h under an argon atmosphere. After the reaction, 10 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **4a** (petroleum ether/ethyl acetate = 3:1).

A mixture of 1-phenylbut-3-en-1-ol **5a** (0.20 mmol), $B_2(OH)_4$ (0.40 mmol), and Pd(tBu$_3$P)$_2$ (0.02 mmol) was combined in DCE (3.0 mL) at 40 °C in an oil bath for 6 h under an argon atmosphere. After the reaction, 10 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **6a** (petroleum ether/ethyl acetate = 10:1).

Scale-Up Experiment for the Synthesis of 2a. A mixture of *N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)-phenyl)-4-methyl-benzene-sulfonamide **1a** (1.0 mmol), $B_2(OH)_4$ (2.0 mmol), and Pd(tBu$_3$P)$_2$ (0.1 mmol) was combined in DCE (10 mL) at 130 °C in an oil bath for 24 h under an argon atmosphere. After the reaction, 20 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. Purification by column chromatography on a silica gel (petroleum ether/ethyl acetate = 6:1) provided the product **2a** (281 mg, 85%) as a yellow solid.

Scheme 6. Proposed Mechanism



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*2-Propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2a**).* Mp = 100−102 °C, 82%, yellow solid, 54 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-22-6;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.30−7.25 (m, 1H), 7.14 (dd, J = 23.0, 7.8 Hz, 3H), 6.83 (d, J = 7.6 Hz, 1H), 5.79 (t, J = 7.0 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.66−1.60 (m, 2H), 1.44 (dt, J = 14.7, 7.3 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 135.5, 132.5, 129.0, 128.3, 127.7, 127.2, 127.1, 126.1, 124.2, 83.7, 60.7, 33.2, 21.5, 18.2, 13.5; IR (cm^{-1}): 2959, 2871, 1598, 1492, 1457, 1378, 1348, 1306, 1239, 1202, 1168, 1107, 1088, 1059, 1020, 917, 804, 760, 704, 681, 649.

*2-Ethyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2b**).* Mp = 69−71 °C, 76%, yellow solid, 48 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-26-0;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.30−7.25 (m, 1H), 7.18−7.10 (m, 3H), 6.83 (d, J = 7.6 Hz, 1H), 5.69 (t, J = 7.1 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.72−1.64 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 135.5, 132.5, 129.0, 128.3, 127.7, 127.2, 127.1, 126.0, 124.2, 85.2, 60.7, 24.6, 21.5, 9.3; IR (cm^{-1}): 3065, 2969, 2935, 2876, 1598, 1492, 1457, 1378, 1347, 1272, 1208, 1170, 1114, 1087, 1050, 1019, 949, 935, 877, 809, 762, 704, 682, 649.

*2-Butyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2c**).* Mp = 83−85 °C, 44%, yellow solid, 31 mg, 48 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-27-1;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.27 (t, J = 7.0 Hz, 1H), 7.19−7.09 (m, 3H), 6.83 (d, J = 7.6 Hz, 1H), 5.77 (t, J = 7.0 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.65 (dt, J = 8.6, 6.2 Hz, 2H), 1.44−1.28 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 135.5, 132.5, 129.0, 128.3, 127.7, 127.2, 127.1, 126.1, 124.2, 84.0, 60.7, 30.9, 27.0, 22.1, 21.5, 13.9; IR (cm^{-1}): 2955, 2859, 1598, 1492, 1457, 1379, 1348, 1230, 1168, 1089, 1052, 1019, 808, 760, 704, 681, 649.

2-Pentyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (2d). Mp = 76−78 °C, 38%, yellow solid, 27 mg, 48 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-28-2;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.18−7.10 (m, 3H), 6.83 (d, J = 6.2 Hz, 1H), 5.77 (t, J = 7.0 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.64 (qd, J = 7.1, 2.1 Hz, 2H), 1.46−1.38 (m, 2H), 1.30−1.23 (m, 4H), 0.89−0.83 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 135.5, 132.5, 129.0, 128.3, 127.7, 127.2, 127.1, 126.1, 124.2, 84.0, 60.7, 31.2, 31.1, 24.6, 22.4, 21.5, 13.9; IR (cm^{-1}): 2928, 2858, 1598, 1492, 1457, 1378, 1349, 1212, 1168, 1090, 1053, 1019, 969, 917, 805, 761, 704, 681, 649.

*1-(Phenylsulfonyl)-2-propyl-1,4-dihydro-2H-benzo[d][1,3]-oxazine (**2e**).* Mp = 99−101 °C, 87%, white solid, 55 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (d, J = 9.4 Hz, 1H), 7.57−7.50 (m, 2H), 7.47 (t, J = 7.5 Hz, 1H), 7.34−7.25 (m, 3H), 7.17 (t, J = 6.9 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.80 (t, J = 7.0 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 4.07 (d, J = 15.6 Hz, 1H), 1.63 (dt, J = 8.9, 6.4 Hz, 2H), 1.46 (p, J = 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 138.3, 132.7, 132.4, 128.4, 128.3, 127.7, 127.2, 127.1, 126.2, 124.2, 83.8, 60.7, 33.2, 18.2, 13.5; IR (cm^{-1}): 3060, 2961, 2925, 2863, 1607, 1584, 1491, 1456, 1377, 1337, 1240, 1204, 1169, 1104, 1087, 1061, 1025, 981, 960, 941, 917, 875, 803, 755, 725, 709, 690, 662, 600; HRMS (ESI) m/z calcd for $C_{17}H_{19}NO_3S^+$ $(M + Na)^+$ 340.0983, found 340.0978.

*2-Isopropyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2f**).* Mp = 106−108 °C, 45%, yellow solid, 30 mg, 12 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-33-9;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.30−7.25 (m, 1H), 7.19−7.10 (m, 3H), 6.83 (d, J = 7.8 Hz, 1H), 5.30 (d, J = 10.0 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 4.08 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.85 (dp, J = 9.9, 6.6 Hz, 1H), 0.99 (dd, J = 6.6, 4.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 135.6, 132.5, 129.1, 128.7, 127.7, 127.2, 127.1, 126.1, 124.2, 89.0, 60.8, 28.6, 21.5, 18.6, 18.1; IR (cm^{-1}): 3065, 2961, 2925, 2871, 1598, 1492, 1457, 1346, 1306, 1224, 1209, 1168, 1110, 1078, 1051, 1022, 952, 905, 808, 759, 704, 683, 650.

*6-Chloro-2-propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2g**).* Mp = 87−89 °C, 60%, yellow solid, 44 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 6.85 (s, 1H), 5.77 (t, J = 7.0 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 4.10 (d, J = 15.9 Hz, 1H), 2.36 (s, 3H), 1.64−1.59 (m, 2H), 1.44 (dq, J = 15.3, 7.6 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.8, 135.3, 131.7, 131.2, 129.8, 129.2, 128.4, 127.7, 127.6, 124.2, 83.7, 60.4, 33.1, 21.5, 18.2, 13.5; IR (cm^{-1}): 2959, 2871, 1598, 1480, 1417, 1351, 1240, 1197, 1168, 1119, 1088, 1032, 983, 921, 837, 812, 769, 705, 684, 662; HRMS (ESI) m/z calcd for $C_{18}H_{20}ClNO_3S^+$ $(M + Na)^+$ 388.0750, found 388.0745.

*8-Methyl-2-propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2h**).* Mp = 113−115 °C, 73%, white solid, 50 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 7.8 Hz, 1H), 7.15 (dt, J = 7.6, 3.5 Hz, 3H), 6.66 (d, J = 7.5 Hz, 1H), 5.68 (t, J = 6.4 Hz, 1H), 4.30 (d, J = 15.2 Hz, 1H), 3.51 (d, J = 15.1 Hz, 1H), 2.54 (s, 3H), 2.38 (s, 3H), 1.40 (td, J = 12.5, 12.0, 7.4 Hz, 4H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.6, 138.9, 135.7, 132.5, 131.6, 130.1, 128.9, 128.4, 127.0, 121.8, 84.5, 61.9, 34.9, 21.5, 18.9, 18.2, 13.5; IR (cm^{-1}): 2920, 2850, 1594, 1458, 1349, 1240, 1197, 1181, 1162, 1142, 1132, 1076, 1047, 1017, 924, 911, 880, 809, 776, 727, 703, 675, 635; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_3S^+$ $(M + Na)^+$ 368.1296, found 368.1291.

*4-Methyl-2-propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2i**).* Mp = 84−86 °C, 82%, white solid, 56 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1), dr = 3.4:1; CAS: 1863980-34-0;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (dd, J = 8.0, 1.2 Hz, 1Hdiast1), 7.71 (dd, J = 8.0, 1.2 Hz, 1Hdiast2), 7.42 (d, J = 8.3 Hz, 1Hdiast1), 7.34 (d, J = 8.4 Hz, 3Hdiast2), 7.29 (d, J = 18.8 Hz, 1Hdiast2), 7.21 (qd, J = 7.5, 1.3 Hz, 1Hdiast1), 7.11 (d, J = 8.1 Hz, 2Hdiast1, 2Hdiast2), 6.98 (d, J = 7.6 Hz, 1Hdiast2), 6.89 (d, J = 8.0 Hz, 1Hdiast1), 5.79 (t, J = 7.0 Hz, 1Hdiast1), 5.59 (t, J = 6.2 Hz, 1Hdiast2), 4.74 (q, J = 6.4 Hz, 1Hdiast1), 3.61 (q, J = 6.6 Hz, 1Hdiast2), 2.35 (s, 3Hdiast2), 2.33 (s, 3Hdiast1), 1.72−1.38 (m, 4Hdiast1, 4Hdiast2), 1.30 (d, J = 6.6 Hz, 3Hdiast2), 0.92 (t, J = 7.3 Hz, 3Hdiast1), 0.89 (d, J = 7.2 Hz, 3Hdiast2), 0.72 (d, J = 6.5 Hz, 3Hdiast1); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.5, 143.4, 136.3, 135.6, 133.1, 132.9, 131.9, 129.2, 128.9, 128.1, 127.7, 127.7, 127.5, 127.3, 127.1, 126.5, 126.2, 124.6, 123.6, 85.2, 83.8, 68.2, 66.1, 38.0, 33.0, 21.5, 21.4, 20.9, 20.6, 18.3, 18.1, 13.6, 13.5; IR (cm^{-1}): 2959, 2872, 1598, 1486, 1456, 1351, 1306, 1245, 1202, 1168, 1090, 1021, 813, 758, 705, 684, 664.

*4-Phenyl-2-propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**2j**).* Mp = 85−87 °C, 60%, yellow solid, 48 mg, 36 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1), dr = 3.7:1; CAS: 1863980-35-1;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (d, J = 8.2 Hz, 1Hdiast1), 7.74 (d, J = 6.8 Hz, 1Hdiast2), 7.56 (d, J = 8.3 Hz, 2Hdiast1), 7.42 (d, J = 8.3 Hz, 2Hdiast2), 7.38−7.19 (m, 6Hdiast1, 6Hdiast2), 7.08 (t, J = 7.6 Hz, 2Hdiast1, 2Hdiast2), 6.94 (dd, J = 6.7, 2.8 Hz, 1Hdiast1, 1Hdiast2), 6.61 (d, J = 7.6 Hz, 1Hdiast1), 6.35 (dd, J = 15.1, 7.2 Hz, 1Hdiast1, 2Hdiast2), 6.01 (t, J = 7.0 Hz, 1Hdiast1), 5.72 (t, J = 5.9 Hz, 1Hdiast2), 5.65 (s, 1Hdiast1), 4.03 (s, 1Hdiast2), 2.45 (s, 3Hdiast1), 2.44 (s, 3Hdiast2), 1.90−1.81 (m, 2Hdiast1), 1.79−1.72 (m, 2Hdiast2), 1.63−1.52 (m, 2Hdiast1), 1.47−1.39 (m, 2Hdiast2), 0.99 (t, J = 7.4 Hz, 3Hdiast1), 0.90 (t, J = 7.4 Hz, 3Hdiast2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.9, 143.6, 139.9, 138.1, 137.2, 135.9, 135.7, 133.9, 132.5, 130.3, 129.6, 129.4, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.6, 127.4, 126.7, 126.3, 125.8, 125.2, 85.8, 84.9, 75.3, 73.7, 38.9, 33.2, 21.5, 18.3, 17.8, 13.7, 13.6; IR (cm^{-1}): 3064, 3030, 2959, 2930, 2871, 1598, 1481, 1455, 1355, 1305, 1289, 1242, 1168, 1108, 1088, 1019, 867, 814, 757, 700, 664.

*4-Ethyl-4-methyl-2-propyl-1-tosyl-1,4-dihydro-2H-benzo[d][1,3]-oxazine (**2k**).* Mp = 73−75 °C, 30%, yellow solid, 20 mg, 36 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); ^{1}H NMR (400 MHz, CDCl3): 7.80 (dd, J = 8.1, 3.6 Hz, 1H), 7.47 (dd, J = 14.6, 8.3 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.22−7.17 (m, 1H), 7.14 (dd, J = 8.2, 4.1 Hz, 2H),

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6.97−6.92 (m, 1H), 5.77−5.68 (m, 1H), 2.33 (d, J = 3.9 Hz, 3H), 1.78−1.50 (m, 4H), 1.45 (dd, J = 15.5, 6.9 Hz, 2H), 1.33 (s, 1H), 0.95−0.84 (m, 5H), 0.51−0.45 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.5, 143.5, 138.0, 137.6, 136.4, 136.4, 131.4, 131.3, 129.2, 129.1, 128.5, 128.3, 128.1, 127.9, 127.2, 126.9, 126.8, 126.4, 126.2, 125.2, 125.1, 83.8, 83.7, 75.3, 75.0, 37.6, 36.7, 36.4, 35.0, 27.2, 27.1, 21.4, 21.4, 19.0, 18.9, 13.5, 7.9, 7.5; IR (cm^{-1}): 3064, 3029, 2961, 2935, 2874, 1598, 1485, 1447, 1350, 1305, 1288, 1249, 1212, 1168, 1100, 1057, 1019, 953, 874, 812, 761, 679, 648; HRMS (ESI) m/z calcd for $C_{21}H_{27}NO_3S^+$ $(M + Na)^+$ 396.1609, found 396.1604.

2-Propyl-1-tosyl-1,2,4,5-tetrahydrobenzo[d][1,3]oxazepine ***(2l)***. Mp = 148−150 °C, 70%, white solid, 48 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 6:1); CAS: 1863980-38-4;[6] ^1H NMR (400 MHz, $CDCl_3$): 7.55 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 6.8 Hz, 1H), 7.25−7.18 (m, 4H), 7.02−6.98 (m, 1H), 5.94 (t, J = 6.8 Hz, 1H), 3.60−3.50 (m, 2H), 2.40 (s, 3H), 2.19 (d, J = 16.1 Hz, 1H), 2.02 (ddd, J = 15.2, 9.8, 5.2 Hz, 1H), 1.40 (dq, J = 32.4, 7.0 Hz, 4H), 0.86 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.3, 139.8, 138.0, 135.2, 132.4, 129.9, 129.2, 128.5, 127.7, 127.2, 84.9, 59.1, 36.3, 32.5, 21.5, 18.2, 13.5; IR (cm^{-1}): 3071, 2958, 2879, 1595, 1488, 1451, 1388, 1340, 1247, 1166, 1110, 1089, 1070, 1027, 996, 934, 864, 820, 773, 750, 709, 670, 636.

1-Ethyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ***(4a)***. Oil, 82%, 58 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 3:1); CAS: 864953-98-0;[16b] ^1H NMR (400 MHz, $CDCl_3$): 8.09 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.31−7.25 (m, 2H), 7.13−7.00 (m, 4H), 5.09 (dd, J = 8.8, 4.9 Hz, 1H), 4.12 (dd, J = 15.1, 5.2 Hz, 1H), 3.43−3.34 (m, 1H), 2.48 (dd, J = 15.1, 4.2 Hz, 1H), 2.38−2.29 (m, 1H), 2.25 (s, 3H), 1.97−1.79 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.2, 138.1, 135.8, 133.1, 129.4, 126.7, 126.5, 121.8, 119.2, 117.9, 110.9, 107.4, 54.5, 39.6, 28.8, 21.3, 19.7, 10.8; IR (cm^{-1}): 3387, 3054, 2966, 2930, 1596, 1492, 1451, 1377, 1332, 1303, 1158, 1091, 1034, 974, 929, 813, 727, 710, 696, 652.

1-Ethyl-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ***(4b)***. Mp = 146−148 °C, 70%, white solid, 50 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 3:1); ^1H NMR (400 MHz, $CDCl_3$): 7.57 (d, J = 8.2 Hz, 2H), 7.29−7.23 (m, 2H), 7.20−7.14 (m, 1H), 7.03 (t, J = 7.9 Hz, 3H), 5.04 (dd, J = 10.3, 3.7 Hz, 1H), 4.09 (dd, J = 14.9, 6.2 Hz, 1H), 3.65 (s, 3H), 3.46−3.38 (m, 1H), 2.48 (dd, J = 16.0, 5.4 Hz, 1H), 2.42−2.32 (m, 1H), 2.21 (s, 3H), 1.88−1.73 (m, 2H), 1.17 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.1, 137.9, 137.0, 134.8, 129.2, 126.7, 126.3, 121.4, 119.0, 118.1, 108.7, 106.2, 53.7, 38.5, 29.8, 27.9, 21.3, 19.5, 11.2; IR (cm^{-1}): 2953, 2921, 2849, 1466, 1377, 1334, 1196, 1180, 1161, 1141, 1132, 1076, 972, 814, 742, 714, 635; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_2S^+$ $(M + H)^+$ 369.1637, found 369.1631.

9-Benzyl-1-ethyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ***(4c)***. Oil, 68%, 60 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 3:1); ^1H NMR (400 MHz, $CDCl_3$): 7.39 (d, J = 8.3 Hz, 2H), 7.33−7.27 (m, 4H), 7.17 (d, J = 8.2 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 6.7 Hz, 1H), 6.97 (t, J = 7.9 Hz, 4H), 5.38 (d, J = 16.9 Hz, 1H), 5.17 (d, J = 16.9 Hz, 1H), 4.93 (dd, J = 9.0, 4.8 Hz, 1H), 4.16 (dd, J = 15.0, 6.2 Hz, 1H), 3.49−3.40 (m, 1H), 2.52 (dd, J = 16.2, 4.5 Hz, 1H), 2.38 (s, 1H), 2.25 (s, 3H), 1.78−1.70 (m, 2H), 1.09 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 142.9, 138.1, 137.3, 136.9, 134.9, 129.3, 128.9, 127.7, 126.7, 126.2, 121.8, 119.3, 118.2, 109.6, 107.2, 53.8, 46.9, 38.5, 28.2, 21.4, 19.6, 11.2; IR (cm^{-1}): 3029, 2966, 2931, 1597, 1495, 1464, 1335, 1305, 1180, 1161, 1091, 1032, 971, 932, 910, 813, 736, 714, 648; HRMS (ESI) m/z calcd for $C_{27}H_{28}N_2O_2S^+$ $(M + H)^+$ 445.1950, found 445.1944.

1-Ethyl-6-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ***(4d)***. Oil, 67%, 49 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 3:1); ^1H NMR (400 MHz, $CDCl_3$): 7.84 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 3H), 6.95 (d, J = 8.2 Hz, 1H), 5.05 (dd, J = 8.6, 5.0 Hz, 1H), 4.11 (dd, J = 14.8, 5.6 Hz, 1H), 3.42−3.33 (m, 1H), 2.44 (dd, J = 15.1, 4.1 Hz, 1H), 2.39 (s, 3H), 2.37−2.29 (m, 1H), 2.27 (s, 3H), 1.96−1.79 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.1, 138.2, 134.1, 133.2, 129.4, 128.6, 126.9, 126.7, 123.3, 117.8, 110.5, 107.2, 54.5, 39.7, 28.9, 21.3, 19.7, 10.8; IR (cm^{-1}): 3328, 2962, 2925, 1696, 1596, 1495, 1463, 1335, 1156, 1091, 1034, 968, 914, 853, 815, 735, 662; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_2S^+$ $(M + H)^+$ 369.1637, found 369.1631.

1-Ethyl-6-methoxy-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ***(4e)***. Oil, 70%, 53 mg, 24 h, R_f = 0.6 (petroleum ether/EtOAc = 3:1); ^1H NMR (400 MHz, $CDCl_3$): 8.00 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 6.3 Hz, 2H), 6.79−6.74 (m, 2H), 5.05 (dd, J = 8.7, 5.0 Hz, 1H), 4.14−4.08 (m, 1H), 3.79 (s, 3H), 3.43−3.34 (m, 1H), 2.44 (dd, J = 16.2, 4.2 Hz, 1H), 2.37−2.29 (m, 1H), 2.26 (s, 3H), 1.93−1.75 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 153.8, 143.1, 138.1, 134.0, 130.9, 129.4, 126.9, 126.7, 111.5, 111.4, 107.2, 100.3, 55.8, 54.5, 39.6, 28.8, 21.3, 19.8, 10.8; IR (cm^{-1}): 3331, 2967, 2935, 1695, 1596, 1492, 1331, 1287, 1216, 1156, 1090, 1029, 972, 912, 851, 815, 734, 662; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_3S^+$ $(M + H)^+$ 385.1586, found 385.1580.

(E)-1-Phenylbut-2-en-1-ol ***(6a)***. Oil, 74%, 22 mg, 40 °C, 6 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 52755-39-2;[15d] ^1H NMR (400 MHz, $CDCl_3$): 7.39−7.32 (m, 4H), 7.29−7.25 (m, 1H), 5.80−5.65 (m, 2H), 5.16 (d, J = 3.5 Hz, 1H), 1.90 (d, J = 3.2 Hz, 1H), 1.72 (d, J = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 143.3, 133.6, 128.5, 127.5, 126.1, 75.2, 17.7; IR (cm^{-1}): 3349, 3061, 3027, 2963, 2914, 2854, 1672, 1601, 1491, 1450, 1377, 1194, 1115, 1068, 1004, 964, 912, 845, 754, 698, 630.

(E)-2-(Prop-1-en-1-yl)phenol ***(6b)***. Oil, 71%, 19 mg, 40 °C, 12 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 23619-59-2;[7] ^1H NMR (400 MHz, $CDCl_3$): 7.29 (d, J = 6.0 Hz, 1H), 7.12−7.07 (m, 1H), 6.91−6.86 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 6.25−6.16 (m, 1H), 4.95 (s, 1H), 1.92 (dd, J = 6.6, 1.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 152.4, 128.2, 127.9, 127.3, 125.3, 125.0, 120.8, 115.7, 18.9; IR (cm^{-1}): 3397, 2960, 2921, 1643, 1615, 1576, 1495, 1454, 1343, 1285, 1257, 1195, 1180, 1132, 1105, 1076, 1028, 972, 877, 841, 796, 750, 698, 635.

(E)-1,2-Dimethoxy-4-(prop-1-en-1-yl)benzene ***(6c)***. Oil, 96%, 34 mg, 80 °C, 1 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 6379-72-2;[10] ^1H NMR (400 MHz, $CDCl_3$): 6.90−6.78 (m, 3H), 6.34 (d, J = 15.7 Hz, 1H), 6.15−6.06 (m, 1H), 3.88 (d, J = 9.1 Hz, 6H), 1.86 (dd, J = 6.6, 1.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 149.0, 148.1, 131.1, 130.6, 123.7, 118.6, 111.2, 108.5, 55.9, 55.7, 18.3; IR (cm^{-1}): 2998, 2954, 2932, 2833, 1602, 1582, 1513, 1464, 1415, 1376, 1333, 1263, 1231, 1156, 1138, 1026, 962, 921, 855, 816, 783, 764, 614.

1-Methoxy-3-(2-(prop-1-en-1-yloxy)ethyl)benzene ***(6d)***.[5f] E/Z = 55:45, oil, 68%, 26 mg, 40 °C, 30 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); ^1H NMR (400 MHz, $CDCl_3$): 7.22 (dd, J = 15.4, 7.9 Hz, 1H), 6.83−6.75 (m, 3H), 5.95 (dd, J = 6.2, 1.7 Hz, 1H), 4.44−4.37 (m, 1H), 3.92 (t, J = 7.1 Hz, 1H), 3.84 (t, J = 7.1 Hz, 1H), 3.79 (s, 3H), 2.91 (t, J = 7.1 Hz, 2H), 1.56 (ddd, J = 14.5, 6.8, 1.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 159.6, 159.6, 146.3, 145.3, 139.9, 139.9, 129.4, 129.3, 121.3, 121.2, 114.7, 114.7, 111.7, 111.7, 101.3, 98.7, 72.6, 69.6, 55.1, 36.4, 35.8, 12.6, 9.3; IR (cm^{-1}): 3038, 2936, 2867, 2834, 1667, 1601, 1489, 1454, 1436, 1378, 1356, 1259, 1152, 1093, 1044, 931, 874, 778, 696.

2-(Prop-1-en-1-yloxy)naphthalene ***(6e)***. E/Z = 68:32, oil, 74%, 27 mg, 80 °C, 1 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 831-27-6;[7] ^1H NMR (400 MHz, $CDCl_3$): 7.75 (dd, J = 18.7, 8.5 Hz, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 6.9 Hz, 1H), 7.29−7.17 (m, 2H), 6.58−6.47 (m, 1H), 5.04−4.89 (m, 1H), 1.74 (ddd, J = 18.8, 6.9, 1.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 155.4, 155.3, 141.8, 140.8, 134.3, 129.7, 129.6, 127.7, 126.9, 126.5, 124.2, 118.6, 118.6, 110.2, 110.0, 108.9, 108.1, 12.3, 9.5; IR (cm^{-1}): 3055, 2918, 2858, 1670, 1628, 1599, 1509, 1465, 1392, 1357, 1255, 1214, 1173, 1123, 1084, 1016, 959, 927, 844, 810, 745, 614.

(E)-2-(Prop-1-en-1-yl)isoindoline-1,3-dione ***(6f)***. Mp = 147−149 °C, 67%, yellow solid, 25 mg, 40 °C, 8 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 93250-83-0;[10] ^1H NMR (400 MHz, $CDCl_3$): 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 6.61−6.53 (m, 2H), 1.84 (d, J = 5.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 166.7, 134.2, 131.7, 123.4, 118.3, 118.1, 16.3; IR (cm^{-1}):

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2936, 1771, 1712, 1609, 1466, 1396, 1381, 1323, 1196, 1141, 1063, 1016, 948, 876, 783, 712, 626.

*(E)-2-(But-1-en-1-yl)isoindoline-1,3-dione (**6g**).* Mp = 53−55 °C, 60%, yellow solid, 24 mg, 12 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 184947-06-6;[15d] ^{1}H NMR (400 MHz, $CDCl_3$): 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 6.66−6.58 (m, 2H), 2.27−2.15 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 168.4, 166.7, 134.2, 133.8, 132.2, 131.7, 124.5, 123.4, 123.1, 116.9, 24.3, 13.7; IR (cm^{-1}): 2963, 2926, 1771, 1718, 1610, 1465, 1387, 1309, 1197, 1151, 1128, 1077, 962, 911, 875, 713, 622.

*(E)-N-(But-1-en-1-yl)-4-methyl-N-phenylbenzenesulfonamide (**6h**).* Mp = 126−128 °C, 64%, white solid, 38 mg, 24 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 1863980-42-0;[6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (d, J = 8.3 Hz, 2H), 7.36−7.31 (m, 3H), 7.27 (d, J = 8.2 Hz, 2H), 7.00−6.95 (m, 2H), 6.91 (d, J = 14.0 Hz, 1H), 4.43 (dt, J = 13.8, 6.8 Hz, 1H), 2.43 (s, 3H), 2.00−1.92 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.6, 137.1, 136.1, 130.2, 129.5, 129.3, 128.7, 128.1, 127.5, 114.8, 23.0, 21.5, 14.3; IR (cm^{-1}): 2957, 2910, 2841, 1651, 1595, 1486, 1449, 1380, 1352, 1320, 1247, 1169, 1117, 1100, 1089, 1019, 970, 948, 912, 872, 812, 741, 696, 662, 619.

*(E)-Ethyl-2-benzoylpent-2-enoate (**6i**).* Oil, 42%, 19 mg, 130 °C, 36 h, R_f = 0.5 (petroleum ether/EtOAc = 20:1); CAS: 39626-68-1;[16a] ^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (d, J = 7.0 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.16 (t, J = 7.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.13 (p, J = 7.6 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 194.4, 164.6, 149.5, 136.8, 133.6, 133.2, 129.0, 128.7, 61.1, 23.0, 13.9, 12.8; IR (cm^{-1}): 2975, 2935, 1723, 1674, 1640, 1596, 1580, 1448, 1367, 1233, 1178, 1143, 1076, 1031, 944, 909, 716, 689, 671.

*2-(2-Methylprop-1-en-1-yl)isoindoline-1,3-dione (**6j**).* Mp = 86−88 °C, 80%, white solid, 32 mg, 12 h, R_f = 0.5 (petroleum ether/EtOAc = 10:1); CAS: 73286-68-7;[16c] ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 5.90 (s, 1H), 1.93 (d, J = 1.6 Hz, 3H), 1.67 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 167.4, 139.1, 134.1, 132.0, 123.4, 112.1, 22.7, 18.9; IR (cm^{-1}): 3065, 2973, 2934, 2914, 1766, 1715, 1609, 1464, 1393, 1340, 1286, 1224, 1110, 1085, 1066, 981, 890, 798, 784, 730, 712, 531.

*(E)-N-(But-1-en-1-yl)-N-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (**2a′**).* Oil, 51%, 17 mg, R_f = 0.5 (petroleum ether/EtOAc = 6:1); CAS: 1863980-66-8; [6] ^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.44−7.39 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.18−7.13 (m, 1H), 6.96 (d, J = 13.9 Hz, 1H), 6.38 (d, J = 7.9 Hz, 1H), 4.76 (d, J = 11.1 Hz, 1H), 4.53−4.43 (m, 1H), 4.27 (dt, J = 13.8, 6.8 Hz, 1H), 2.77−2.64 (m, 1H), 2.46 (s, 3H), 1.96 (p, J = 7.4 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 144.2, 141.8, 135.5, 134.5, 131.0, 129.8, 129.7, 129.4, 128.5, 127.9, 127.6, 114.9, 61.0, 22.9, 21.6, 14.4; IR (cm^{-1}): 3438, 2960, 2927, 2871, 1653, 1596, 1488, 1452, 1356, 1165, 1129, 1088, 1039, 972, 941, 894, 813, 767, 747, 711, 662, 579.

*(E)-N-(But-2-en-1-yl)-N-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (**2a″**).*[6] Oil, 73%, 24 mg, R_f = 0.5 (petroleum ether/EtOAc = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (dd, J = 15.9, 8.0 Hz, 4H), 7.33−7.27 (m, 3H), 7.16−7.11 (m, 1H), 6.43 (d, J = 6.7 Hz, 1H), 5.39−5.35 (m, 1H), 4.96 (d, J = 9.0 Hz, 1H), 4.53−4.40 (m, 2H), 3.68 (dd, J = 13.5, 7.1 Hz, 1H), 3.10−3.06 (m, 1H), 2.46 (s, 3H), 1.53 (d, J = 4.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 143.8, 142.4, 137.2, 134.9, 131.5, 130.9, 129.5, 128.9, 128.2, 128.0, 127.7, 124.4, 61.2, 54.4, 21.5, 17.5; IR (cm^{-1}): 3515, 2921, 1597, 1491, 1451, 1340, 1160, 1090, 1038, 966, 920, 861, 814, 764, 747, 710, 655, 575.

Deuterium Labeling Experiments. A mixture of *N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)phenyl)-4-methyl-benzenesulfonamide **1a** (0.20 mmol), C_2D_5OD (0.60 mmol), $B_2(OH)_4$ (0.24 mmol), and $Pd(tBu_3P)_2$ (0.02 mmol) was combined in toluene (3.0 mL) at 130 °C in an oil bath for 24 h under an argon atmosphere. After the reaction, 10 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **2a−d$_1$** (petroleum ether/ethyl acetate = 6:1) in a 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78−7.79 (m, 1 H), 7.40−7.42 (m, 2 H), 7.28−7.29 (m, 1 H), 7.10−7.18 (m, 3 H), 6.82−6.84 (m, 1 H), 5.79 (m, 1 H), 4.59 (d, J = 16.0 Hz, 1 H), 4.11 (d, J = 16.0 Hz, 1 H), 2.34 (s, 3 H), 1.50−1.66 (m, 2 H), 1.40−1.48 (m, 2 H), 0.92 (t, J = 4.0 Hz, 2.67 H).

A mixture of *N*-(but-3-en-1-yl)-*N*-(2-(hydroxymethyl)phenyl)-4-methyl-benzenesulfonamide **1a** (0.10 mmol), D_2O (0.20 mmol), $B_2(OH)_4$ (0.20 mmol), and $Pd(tBu_3P)_2$ (0.01 mmol) was combined in anhydrous DCE (2.0 mL) at 130 °C in an oil bath for 24 h under an argon atmosphere. After the reaction, 10 mL of water was added to quench the reaction, and the resulting mixture was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography afforded the product **2a−d$_2$** (petroleum ether/ethyl acetate =6:1) in an 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78−7.79 (m, 1 H), 7.40−7.42 (m, 2 H), 7.27−7.29 (m, 1 H), 7.10−7.18 (m, 3 H), 6.82−6.84 (m, 1 H), 5.79 (m, 1 H), 4.59 (d, J = 16.0 Hz, 1 H), 4.11 (d, J = 16.0 Hz, 1 H), 2.34 (s, 3 H), 1.50−1.66 (m, 1.65 H), 1.40−1.50 (m, 2 H), 0.92 (t, J = 4.0 Hz, 2.85 H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00770.

^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xiao-Feng Xia − *Key Laboratory of Synthetic and Biological Colloids, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi, Jiangsu 214122, China; Guangxi Key Laboratory of Agricultural Resources Chemistry and Biotechnology, College of Chemistry and Food Science, Yulin Normal University, Yulin, Guangxi 537000, China;* orcid.org/0000-0002-1837-0638; Email: xiaxf@jiangnan.edu.cn

Authors

Linglong Ding − *Key Laboratory of Synthetic and Biological Colloids, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi, Jiangsu 214122, China*

Yan-Ning Niu − *Department of Teaching and Research, Nanjing Forestry University, Huaian, Jiangsu 223003, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00770

Notes

The authors declare no competing financial interest.

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