JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

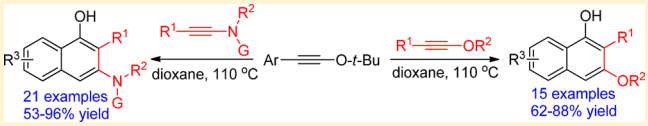
Construction of 1-Naphthols via Benzannulation Based on the Reaction of Aryl *tert*-Butyl Ynol Ethers with Ynamides or Ynol Ethers

Yihui Bai, Jing Yin, Zhicheng Liu, and Gangguo Zhu*

Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, China

Supporting Information

ABSTRACT: A new version of benzannulation featuring the use of aromatic *tert*-butyl ynol ethers as the convenient precursors for arylketenes has been developed. Both ynamides and ynol ethers undergo this reaction smoothly, giving 3-amino and 3-alkoxy 1-naphthols in good to excellent yields under the heated reaction conditions. The high efficiency, excellent regioselectivity, good functional group compatibility, and broad substrate scope render this reaction particularly valuable for organic synthesis.



INTRODUCTION

Naphthol and its derivatives are privileged scaffolds in a variety of natural products, pharmaceutical reagents, and highly valued chemicals. For instance, mollugin (**A**, Figure 1) is found to possess significant antiviral activity against the hepatitis B virus.[1] Rubioncolin B (**B**, Figure 1), a compound isolated from the roots of *Rubia oncotricha* and *R. cordifolia*, has shown a potent cytotoxic and antitumor activity.[2] Other noteworthy examples include gossypol (**C**, Figure 1),[3] an *anti*-cancer reagent, and rifampicin (**D**, Figure 1), a medicine for the treatment of mycobacterium infections, including tuberculosis and Hansen's disease.[4] As such, the invention of new methods for the synthesis of naphthols with certain substitution patterns is of significant importance. While a number of protocols[5] are available for this purpose, few methods provide a rapid and regiocontrolled approach to 1-naphthols.

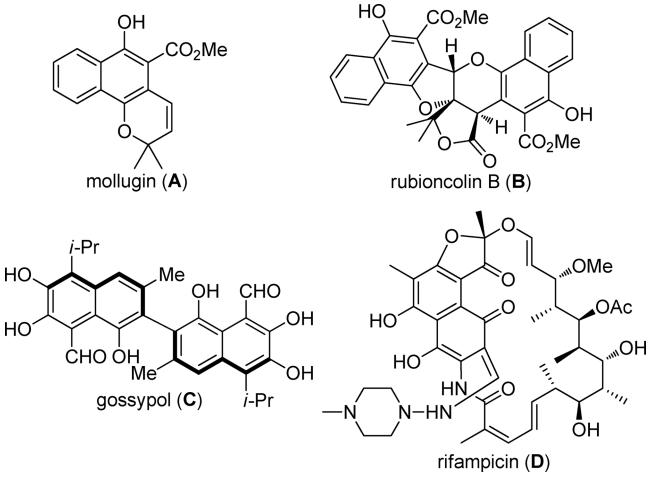
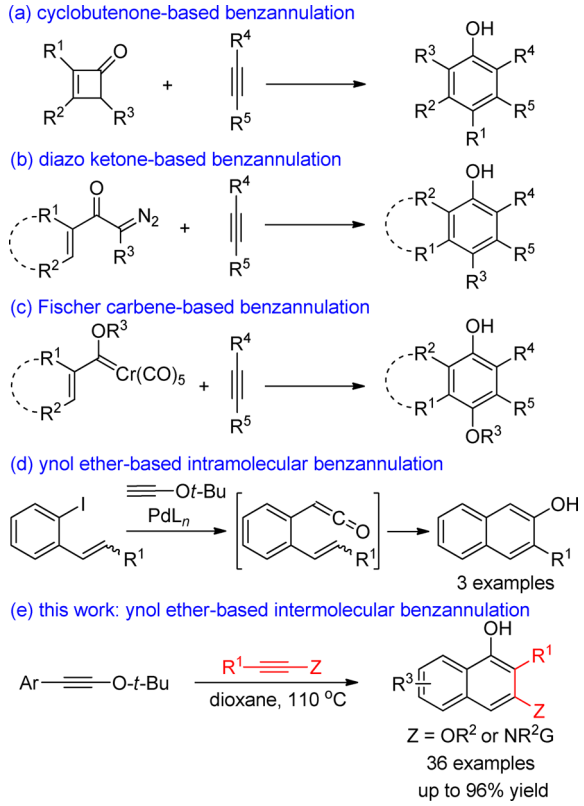


Figure 1. Selected bioactive compounds containing 1-naphthol and its derivatives.

The benzannulation strategy, well developed by Danheiser,[6] Moore,[7] Wulff,[8] and others,[9] has stood out as a straightforward and efficient method for assembling aromatic compounds (Scheme 1a–c). It typically depends on the [2 + 2] cycloaddition of alkynes with vinylketenes resulting from cyclobutenones, diazo ketones, or Fischer carbenes, respec-

Scheme 1. Benzannulation Strategy Featuring Ketene Intermediates



Received: August 11, 2015

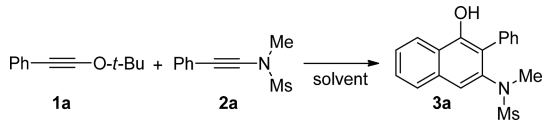
DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX

tively, followed by a four electron electrocyclic cleavage/six electron electrocyclic closure/tautomerization domino process. Indeed, this method has been successfully applied to the total synthesis of a variety of natural products.[10] However, most of the preceding methods have focused on the construction of phenols and related compounds, while less attention has been paid to the access of naphthols. Furthermore, there are only limited types of ketene precursors for this annulation, consequently, the exploration of novel benzannulation using readily accessible and benchtop stable starting materials as ketene equivalents is highly desirable. A recent work done by Zhang and Ready[11] stood out as a significant advance in this field, in which a rapid elaboration of 2-naphthols was achieved by an intramolecular benzannulation featuring the in situ generation of arylketenes via a thermolysis of aryl *tert*-butyl ynol ethers[12−14] (Scheme 1d). In contrast, the intermolecular version is much more challenging and remains an underdeveloped process. Pursuing our recent interest in the transformations of ynol ethers,[14] we report here a new benzannulation protocol based on aryl *tert*-butyl ynol ethers, delivering 3-amino and 3-alkoxy 1-naphthols in a single synthetic step (Scheme 1e). The high efficiency, excellent regioselectivity, good functional group compatibility, and utilization of aromatic *tert*-butyl ynol ethers as the effective precursors for labile arylketenes make this reaction very appealing for synthetic applications.

RESULTS AND DISCUSSION

The initial studies were focused on the reaction between aryl *tert*-butyl ynol ether **1a** and ynamide[15] **2a**, and the results are summarized in Table 1. By treating **1a** (0.25 mmol) and **2a** (0.3 mmol) under a nitrogen atmosphere in toluene at 110 °C for 10 h, 3-amino 1-naphthol **3a** was obtained in 30% yield (Table 1, entry 1). We envisioned that a low concentration of ketene intermediates might decrease the undesirable dimerization and related side reactions. As expected, an improved yield (55%) was observed when **1a** was added via a syringe pump within 2 h (Table 1, entry 2). Increasing the loading of **2a** led to a better yield (Table 1, entry 3). Meanwhile, the solvent was varied, and we were delighted to find that the use of dioxane, instead of toluene, improved the yield to 87% (Table 1, entries 4−9). In contrast, a diminished yield was observed when the reaction was carried out under an air atmosphere or at a lower temperature (Table 1, entries 10 and 11). As such, the further substrate screening was conducted in dioxane under N_2 at 110 °C for 10 h.

Table 1. Optimization of the Reaction Conditions[a]

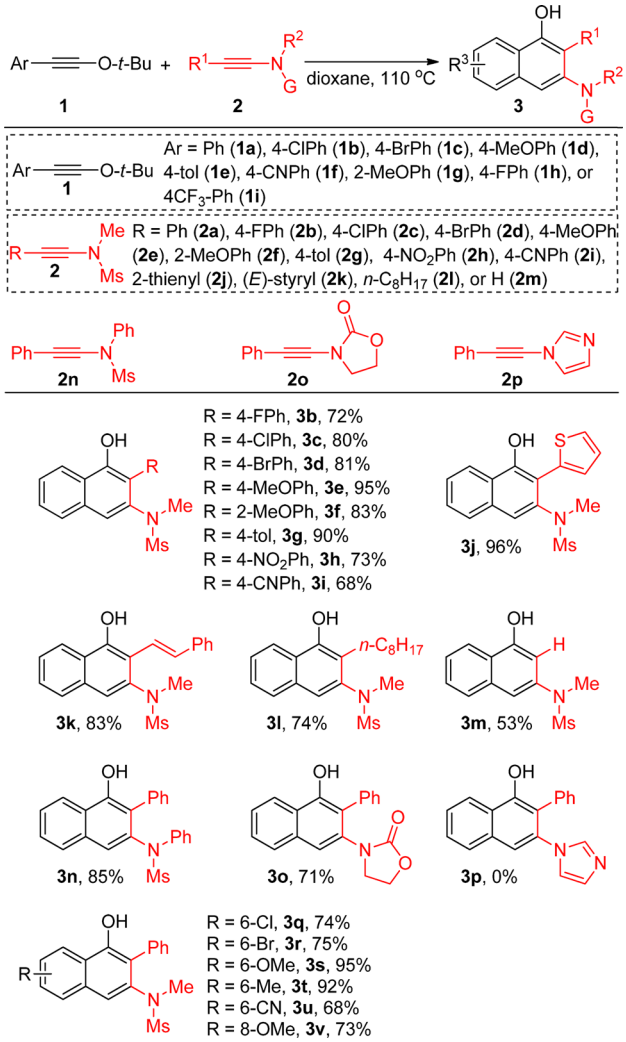


entry	**2a** (equiv)	solvent	yield (%)[b]
1	1.2	toluene	30
2[c]	1.2	toluene	55
3[c]	2.0	toluene	71
4[c]	2.0	THF	64
5[c]	2.0	$ClCH_2CH_2Cl$	81
6[c]	2.0	MeCN	76
7[c]	2.0	NMP	trace
8[c]	2.0	DMSO	trace
9[c]	2.0	dioxane	87
10[c,d]	2.0	dioxane	46
11[c,e]	2.0	dioxane	66

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), solvent (2 mL), under N_2, 110 °C, 10 h. [b]Isolated yield. [c]**1a** was added via a syringe pump within 2 h. [d]Under an air atmosphere. [e]Run at 80 °C.

With the optimized reaction conditions in hand, we first investigated the substrate scope of ynamides, and the results are summarized in Table 2. A series of *N*-sulfonyl ynamides bearing different substituents were initially surveyed. Halogen atoms such as F, Cl, and Br were well tolerated to give 1-naphthols **3b−3d** in high yields. The electron-rich ynamides **2e−2g** afforded the desired products in particularly good yields, while the electron-poor substrates **2h** and **2i** furnished **3h** and **3i** in somewhat lower yields, probably due to the reduced ketenophilicity of latter cases. Moreover, ynamide **2e**, derived from 4-methoxyphenyl acetylene, produced 1-naphthol **3e** in 95% yield, while that derived from 2-methoxyphenyl acetylene led to **3f** in a slightly decreased yield (83%). This transformation proceeded successfully with thiophene function, giving rise to **3j** in almost quantitative yield (96%). Alkenyl and alkyl ynamides, **2k** and **2l**, for example, participated well in this reaction to form **3k** and **3l** in 83% and 74% yield, respectively.

Table 2. Scope of the Synthesis of 3-Amino 1-Naphthols[a]



[a]Reaction conditions: see Table 1; yields refer to the isolated yields.

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX

Terminal ynamide **2m** was also suitable for the production of 1-naphthol **3m**, albeit in a moderate yield. In addition, 3-(phenylethynyl)oxazolidin-2-one (**2o**) exhibited good reactivity to generate **3o** in a satisfactory yield. In contrast, **2p**, an imidazole-derived ynamide, was found to be unreactive under the reaction conditions (**3p**).

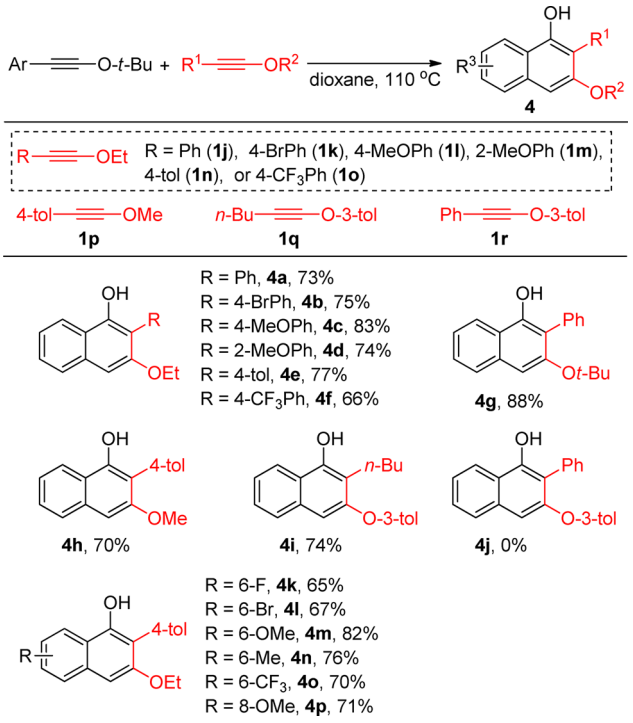
Subsequently, we turned our attention to the reactivity of diverse aryl *tert*-butyl ynol ethers (Table 2). Pleasingly, both electron-poor and electron-rich ynol ethers were competent substrates for this reaction, forming the desired products in good to excellent yields (**3q**–**3v**). The reaction occurred uneventfully with Cl and Br atoms (**3q** and **3r**), which may be utilized for further functionalization via the transition-metal-catalyzed cross-coupling reactions.

As such, we have developed a facile and efficient method for the construction of 3-amino 1-naphthols using a novel benzannulation featuring the coupling of aryl *tert*-butyl ynol ethers with ynamides. Next, we explored the possibility of assembling 3-alkoxy 1-naphthols via the cross-coupling of aryl *tert*-butyl ynol ethers with another class of ynol ethers (Table 3). Pleasingly, using ynol ether **1j** instead of **2a** as the alkyne partner for this benzannulation, 3-alkoxy 1-naphthol **4a** was generated in 73% yield, and only a trace amount (<5%) of byproducts resulting from the homocoupling of **1j** was observed. Both electron-rich and electron-poor ynol ethers **1k**–**1o** were compatible with this transformation, affording 3-alkoxy 1-naphthols **4b**–**4f** in yields of 66–83%. In the meantime, the scope with regard to the R^2 group of ynol ethers was briefly investigated. Ynol ethers **1p** and **1q** were also competent substrates, whereas no detectable product **4j** was observed when **1r** was employed as the coupling partner (**4h**–**4j**). Likewise, this reaction tolerated a wide range of electronically and sterically different substituents, as well demonstrated by the assembly of products **4k**–**4p**. The structure of 1-naphthols **3v** and **4a** was determined by the X-ray diffraction analysis.[16] Of note, this method generally offers higher yields when compared with the traditional benzannulation based on diazo ketones.[6b]

To probe the reaction mechanism of this benzannulation, the reaction of **1a** and **2a** was conducted at 60 °C for 10 h. As a result, a cyclobutenone compound **5a** was isolated in 87% yield, which was successfully transformed into **3a** in 93% yield after being stirred at 110 °C for 10 h (Scheme 2). Similarly, the production of 1-naphthol **4g** was achieved via the identical sequence. These results indicate that cyclobutenones may be the key intermediates for this new benzannulation reaction.

In light of the above results and previous reports,[6,7,11] a possible mechanism for this new variant of benzannulation is proposed in Scheme 3. The reaction begins from the H[1,5]-shift[11,17] to deliver an arylketene intermediate **I** accompanied by the extrusion of isobutylene, which undergoes a [2 + 2] cycloaddition with ynamides or ynol ethers to form the cyclobutenone species **II** in a regiocontrolled manner. The polarization of the C–C triple bonds of ynamides or ynol ethers may account for the observed regioselectivity. Then, the cyclobutenone species **II** undergoes the four electron electrocyclic cleavage/six electron electrocyclic closure/tautomerization domino process to produce polysubstituted 1-naphthols under the heated conditions.

Table 3. Scope of the Access of 3-Alkoxy 1-Naphthols[a]

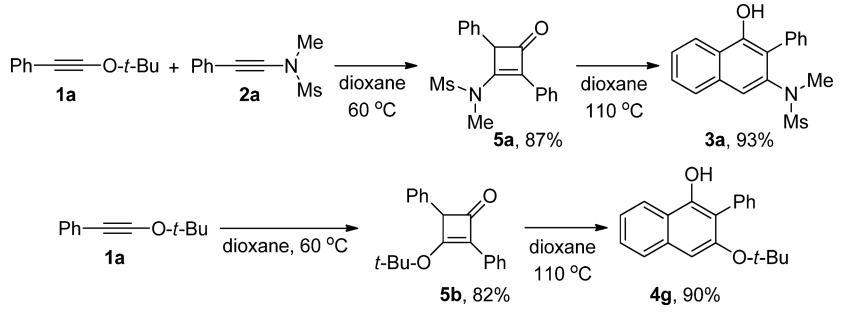


[a]Reaction conditions: see Table 1; yields refer to the isolated yields.

CONCLUSION

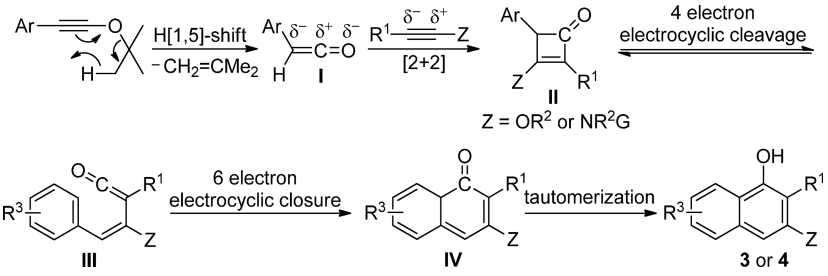
In summary, we have realized a new benzannulation protocol featuring the use of readily accessible aryl *tert*-butyl ynol ethers as suitable precursors for labile arylketene intermediates. Both ynamides and ynol ethers can serve as the alkyne components for this annulation to form 3-amino and 3-alkoxy 1-naphthols in good to excellent yields with excellent regioselectivity. A wide selection of functional groups such as F, Cl, Br, NO_2, CN, CF_3, OMe, oxazolidinyl, (hetero)aryl, alkenyl, and alkyl substituents

Scheme 2. Preliminary Studies on the Reaction Mechanism



DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 3. A Plausible Mechanism



are well tolerated. Further investigations on the synthetic application of this protocol are currently underway.

EXPERIMENTAL SECTION

General. Unless otherwise noted, materials obtained from commercial suppliers were used directly without further purification. Dioxane, toluene, and THF were distilled from sodium prior to use. Column chromatography was carried out using silica gel (300–400 mesh) with petroleum ethers/EtOAc as the eluent. ^{1}H and ^{13}C NMR spectra were measured on a 600 or 400 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent (see Supporting Information). The chemical shifts are given in δ relative to TMS, and the coupling constants are given in Hertz. The high-resolution mass spectra (HRMS) analyses were conducted using a TOF MS instrument with an ESI source. Melting points were measured by a melting point instrument and were uncorrected.

General Procedure for the Benzannulation between Aryl *tert*-Butyl Ynol Ethers and Ynamides. To a solution of **2a** (104 mg, 0.5 mmol) in 1 mL of dioxane was added a solution of **1a** (44 mg, 0.25 mmol) in 1 mL of dioxane via a syringe pump at 110 °C (oil bath) within 2 h. After refluxing for 8 h, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (petroleum ether/EtOAc = 2:1) gave 71 mg (yield: 87%) of **3a** as a white solid, mp: 158–161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30–8.24 (m, 1H), 7.90–7.80 (m, 1H), 7.60–7.48 (m, 8H), 5.64 (s, 1H), 3.12 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.7, 138.2, 133.5, 133.4, 131.0, 129.5, 128.8, 127.5, 127.3, 126.3, 123.8, 122.6, 121.9, 119.1, 39.3, 38.2; IR (KBr) 3376, 3042, 1594, 1570, 1495, 1441, 1318, 1124 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}NNaO_3S$ (M + Na)$^+$ 350.0827, found 350.0820.

*Compound **3b**.* White solid, 62 mg, 72% yield, mp: 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.29–8.20 (m, 1H), 7.96–7.93 (m, 1H), 7.67 (s, 1H), 7.60–7.53 (m, 2H), 7.43–7.38 (m, 2H), 7.31–7.26 (m, 2H), 2.98 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9 (d, J = 243.8 Hz), 151.2, 139.6, 133.6, 133.4 (d, J = 8.7 Hz), 132.1 (d, J = 3.3 Hz), 128.2, 127.3, 126.4, 125.3, 123.9, 122.8, 118.6, 115.1 (d, J = 21.2 Hz), 39.2, 38.1; IR (KBr) 3381, 3021, 1593, 1571, 1498, 1455, 1316, 1123 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}FNNaO_3S$ (M + Na)$^+$ 368.0733, found 368.0718.

*Compound **3c**.* White solid, 72 mg, 80% yield, mp: 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.30–8.20 (m, 1H), 8.00–7.90 (m, 1H), 7.68 (s, 1H), 7.60–7.53 (m, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 2.98 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.1, 139.4, 134.9, 133.6, 133.3, 132.2, 128.2, 128.1, 127.4, 126.4, 125.3, 123.7, 122.8, 118.5, 39.3, 37.9; IR (KBr) 3376, 3055, 1591, 1571, 1491, 1447, 1315, 1122 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}ClNNaO_3S$ (M + Na)$^+$ 384.0437, found 384.0423.

*Compound **3d**.* White solid, 82 mg, 81% yield, mp: 165–168 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.27–8.22 (m, 1H), 7.97–7.93 (m, 1H), 7.69 (s, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.60–7.55 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 2.98 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 151.0, 139.3, 135.3, 133.7, 133.6, 131.1, 128.2, 127.4, 126.4, 125.3, 123.7, 122.8, 120.9, 118.5, 39.3, 37.9; IR (KBr) 3385, 3033, 1587, 1486, 1458, 1317, 1127 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}BrNNaO_3S$ (M + Na)$^+$ 427.9932, found 427.9924.

*Compound **3e**.* White solid, 85 mg, 95% yield, mp: 168–170 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.64 (s, 1H), 7.60–7.50 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 3.82 (s, 3H), 2.96 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.8, 151.1, 139.9, 133.4, 132.5, 128.1, 127.7, 127.1, 126.2, 125.2, 124.4, 122.8, 118.6, 113.8, 55.5, 39.2, 38.4; IR (KBr) 3463, 3018, 1591, 1567, 1496, 1464, 1323, 1140 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_4S$ (M + Na)$^+$ 380.0932, found 380.0925.

*Compound **3f**.* White solid, 74 mg, 83% yield, mp: 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32–8.26 (m, 1H), 7.86–7.80 (m, 1H), 7.58–7.47 (m, 4H), 7.41 (d, J = 7.1 Hz, 1H), 7.20–7.14 (m, 1H), 7.10 (d, J = 8.3 Hz, 1H), 5.70 (s, 1H), 3.82 (s, 3H), 3.18 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.0, 138.9, 133.6, 133.3, 130.5, 127.4, 127.2, 126.1, 124.0, 122.7, 121.4, 118.9, 118.8, 111.4, 55.6, 38.8, 37.6; IR (KBr) 3359, 1539, 1505, 1449, 1324, 1119 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_4S$ (M + Na)$^+$ 380.0932, found 380.0921.

*Compound **3g**.* White solid, 77 mg, 90% yield, mp: 160–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30–8.20 (m, 1H), 7.85–7.80 (m, 1H), 7.58–7.54 (m, 2H), 7.53 (s, 1H), 7.45–7.35 (m, 4H), 5.61 (s, 1H), 3.12 (s, 3H), 2.71 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.8, 138.7, 138.2, 133.4, 130.8, 130.2, 130.1, 127.5, 127.3, 126.3, 123.7, 122.6, 121.9, 119.0, 39.3, 38.2, 21.4; IR (KBr) 3364, 3016, 1594, 1570, 1498, 1448, 1315, 1129 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_3S$ (M + Na)$^+$ 364.0983, found 364.0974.

*Compound **3h**.* White solid, 68 mg, 73% yield, mp: 194–196 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.32 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.76 (s, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.64–7.57 (m, 2H), 3.06 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 151.1, 146.8, 144.0, 138.9, 133.9, 133.0, 128.3, 127.7, 126.6, 125.3, 123.3, 123.2, 122.9, 118.6, 39.4, 37.4; IR (KBr) 3393, 3029, 1594, 1571, 1448, 1321, 1138 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_5S$ (M + Na)$^+$ 395.0678, found 395.0657.

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX–XXX

Compound ***3i***. White solid, 60 mg, 68% yield, mp: 182−185 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.40−8.20 (m, 1H), 8.01−7.87 (m, 3H), 7.74 (s, 1H), 7.65−7.50 (m, 4H), 3.03 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 151.0, 141.7, 139.0, 133.9, 132.7, 132.0, 128.3, 127.6, 126.6, 125.3, 123.7, 122.9, 119.7, 118.6, 110.1, 39.4, 37.6; IR (KBr) 3368, 3029, 1595, 1570, 1495, 1448, 1322, 1138 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}N_2NaO_3S$ $(M + Na)^+$ 375.0779, found 375.0761.

Compound ***3j***. White solid, 80 mg, 96% yield, mp: 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31−8.24 (m, 1H), 7.84−7.78 (m, 1H), 7.61−7.53 (m, 4H), 7.30−7.22 (m, 2H), 6.11 (s, 1H), 3.20 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 138.5, 133.8, 133.6, 129.9, 128.6, 127.9, 127.8, 127.5, 126.5, 123.6, 122.9, 119.4, 114.2, 39.5, 38.1; IR (KBr) 3487, 3064, 1594, 1569, 1494, 1446, 1321, 1141 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}NNaO_3S_2$ $(M + Na)^+$ 356.0391, found 356.0374.

Compound ***3k***. White solid, 73 mg, 83% yield, mp: 143−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31−8.25 (m, 1H), 7.80−7.75 (m, 1H), 7.62−7.53 (m, 4H), 7.46−7.34 (m, 5H), 7.10 (d, J = 17.0 Hz, 1H), 6.43 (s, 1H), 3.31 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 138.2, 136.3, 135.1, 133.0, 128.9, 128.6, 127.4, 127.4, 126.7, 126.5, 124.2, 122.8, 122.5, 118.8, 118.1, 39.2, 37.7; IR (KBr) 3385, 3059, 1591, 1569, 1496, 1146, 1318, 1128 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{19}NNaO_3S$ $(M + Na)^+$ 376.0983, found 376.0969.

Compound ***3l***. Yellow oil, 67 mg, 74% yield;^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09−8.05 (m, 1H), 7.75−7.70 (m, 1H), 7.48−7.43 (m, 2H), 7.39 (s, 1H), 5.80 (s, 1H), 3.35 (s, 3H), 3.09 (s, 3H), 1.70−1.10 (m, 14H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 139.3, 132.2, 127.3, 126.4, 126.1, 124.4, 122.8, 121.5, 118.2, 40.1, 35.9, 31.9, 30.1, 29.6, 29.5, 29.3, 26.0, 22.7, 14.2; IR (KBr) 3489, 3011, 1594, 1571, 1491, 1457, 1330, 1144 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{29}NNaO_3S$ $(M + Na)^+$ 386.1766, found 386.1746.

Compound ***3m***. White solid, 33 mg, 53% yield, mp: 118−121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.56−7.48 (m, 2H), 7.35 (s, 1H), 7.29 (s, 1H), 7.03 (d, J = 1.5 Hz, 1H), 3.43 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.6, 139.1, 134.3, 127.5, 127.4, 125.7, 123.7, 122.0, 115.4, 108.4, 38.4, 35.2; IR (KBr) 3355, 3061, 1595, 1579, 1451, 1310, 1138 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}NNaO_3S$ $(M + Na)^+$ 274.0514, found 274.0497.

Compound ***3n***. White solid, 83 mg, 85% yield, mp: 183−185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.61−7.46 (m, 6H), 7.18−7.10 (m, 4H), 6.97 (d, J = 7.1 Hz, 2H), 5.52 (s, 1H), 3.03 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.1, 140.5, 137.0, 133.3, 132.8, 129.3, 128.9, 128.8, 127.7, 127.4, 126.4, 123.8, 122.7, 122.0, 120.2, 40.1; IR (KBr) 3533, 3051, 1592, 1570, 1490, 1456, 1326, 1145 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}NNaO_3S$ $(M + Na)^+$ 412.0983, found 412.0976.

Compound ***3o***. White solid, 54 mg, 71% yield, mp: 80−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.23 (m, 1H), 7.85−7.81 (m, 1H), 7.60−7.49 (m, 8H), 5.70 (s, 1H), 4.14 (t, J = 8.16 Hz, 2H), 3.44 (t, J = 7.72 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.5, 133.6, 133.4, 132.8, 130.3, 129.9, 129.0, 127.6, 127.4, 126.2, 123.7, 122.6, 119.8, 119.0, 62.2, 47.8; IR (KBr) 3362, 3058, 1740, 1595, 1570, 1495, 1458, 1211 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}NNaO_3$ $(M + Na)^+$ 328.0950, found 328.0922.

Compound ***3q***. White solid, 67 mg, 74% yield, mp: 163−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.61−7.47 (m, 7H), 5.59 (s, 1H), 3.11 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.4, 133.0, 132.3, 131.7, 130.8, 129.6, 129.1, 129.0, 128.2, 124.4, 122.9, 121.9, 119.0, 39.2, 38.3; IR (KBr) 3516, 3067, 1592, 1567, 1490, 1443, 1322, 1147 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}ClNNaO_3S$ $(M + Na)^+$ 384.0437, found 384.0410.

Compound ***3r***. White solid, 76 mg, 75% yield, mp: 161−164 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.65−7.47 (m, 7H), 5.58 (s, 1H), 3.12 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.9, 138.6, 133.0, 131.9, 130.9, 130.8, 129.6, 129.1, 129.0, 125.2, 124.8, 122.9, 120.5, 119.1, 39.2, 38.3; IR (KBr) 3516, 3066, 1588, 1564, 1498, 1442, 1323, 1147 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}BrNNaO_3S$ $(M + Na)^+$ 427.9932, found 427.9920.

Compound ***3s***. White solid, 85 mg, 95% yield, mp: 157−159 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 9.0 Hz, 1H), 7.60−7.44 (m, 7H), 7.23 (dd, J = 8.9, 2.5 Hz, 1H), 5.58 (s, 1H), 3.96 (s, 3H), 3.11 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.2, 148.6, 135.8, 133.7, 130.9, 129.4, 129.1, 128.9, 128.8, 124.8, 122.5, 120.3, 118.9, 100.7, 55.5, 39.4, 38.1; IR (KBr) 3517, 3012, 1591, 1563, 1499, 1455, 1320, 1150 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_4S$ $(M + Na)^+$ 380.0932, found 380.0924.

Compound ***3t***. White solid, 78 mg, 92% yield, mp: 154−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.61−7.37 (m, 7H), 5.54 (s, 1H), 3.11 (s, 3H), 2.66 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 137.2, 136.3, 133.6, 131.7, 131.0, 129.6, 129.4, 128.7, 127.4, 123.9, 121.9, 121.5, 118.9, 39.3, 38.1, 22.0; IR (KBr) 3517, 3018, 1604, 1566, 1491, 1442, 1323, 1138 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_3S$ $(M + Na)^+$ 364.0983, found 364.0979.

Compound ***3u***. White solid, 60 mg, 68% yield, mp: 173−177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.94−7.88 (m, 1H), 7.70−7.45 (m, 7H), 5.78 (s, 1H), 3.14 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2, 141.4, 134.7, 132.7, 132.5, 130.8, 129.7, 129.4, 129.3, 128.7, 127.7, 123.8, 122.9, 119.1, 109.4, 39.1, 38.4; IR (KBr) 3309, 3030, 1627, 1559, 1457, 1318, 1136 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}N_2NaO_3S$ $(M + Na)^+$ 375.0779, found 375.0779.

Compound ***3v***. White solid, 65 mg, 73% yield, mp: 168−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.76 (s, 1H), 7.50−7.45 (m, 3H), 7.41−7.34 (m, 3H), 7.03 (d, J = 7.7 Hz, 1H), 4.00 (s, 3H), 2.99 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 151.0, 139.0, 136.0, 131.3, 128.2, 127.5, 126.6, 126.4, 125.6, 125.2, 114.9, 112.7, 105.6, 56.1, 39.3, 38.2; IR (KBr) 3420, 3008, 1593, 1536, 1494, 1442, 1320, 1125 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_4S$ $(M + Na)^+$ 380.0932, found 380.0920 (see Supporting Information). Crystal data for **3v** ($C_{19}H_{19}NO_4S$, 357.41): orthorhombic, space group *Pbca*, a = 16.4246(5) Å, b = 11.9941(4) Å, c = 17.9328(5) Å, U = 3532.73(19) Å^3, Z = 8, T = 296(2) K, absorption coefficient 0.207 mm^{-1}, reflections collected 28721, independent reflections 4137 [R(int) = 0.0736], refinement by full-matrix least-squares on F^2, data/restraints/parameters 4137/0/242, goodness-of-fit on F^2 = 1.007, final R indices [$I > 2s(I)$] R_1 = 0.0453, wR_2 = 0.1201, R indices (all data) R_1 = 0.0597, wR_2 = 0.1402, largest diff peak and hole 0.299 and −0.422 e·Å^{-3}. Crystallographic data for the structure **3v** have been deposited

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX

with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 1412471.

General Procedure for the Benzannulation between Aryl *tert*-Butyl Ynol Ethers and Ynol Ethers. To a solution of **1j** (73 mg, 0.5 mmol) in 1 mL of dioxane was added a solution of **1a** (44 mg, 0.25 mmol) in 1 mL of dioxane via a syringe pump at 110 °C for 1 h. After stirring at 110 °C for 6 h, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (petroleum ether/EtOAc = 20:1) gave 48 mg (yield: 73%) of **4a** as a white solid, mp: 93−95 °C (see Supporting Information). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.58−7.46 (m, 6H), 7.38 (t, J = 7.5 Hz, 1H), 6.87 (s, 1H), 5.66 (s, 1H), 4.13 (q, J = 6.9 Hz, 2H), 1.34 (t, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.8, 149.1, 134.4, 132.8, 131.0, 129.2, 128.1, 127.0, 126.3, 123.1, 122.5, 120.0, 114.9, 99.1, 63.9, 14.6; IR (KBr) 3488, 3049, 1595, 1575, 1503, 1455, 1127 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1221. Crystal data for **4a** ($C_{18}H_{16}O_2$, 264.31): monoclinic, space group $P2_1/N$, a = 12.9443(8) Å, b = 10.3400(6) Å, c = 21.8826(13) Å, U = 2909.3(3) Å^3, Z = 8, T = 296(2) K, absorption coefficient 0.078 mm^{-1}, reflections collected 19243, independent reflections 6554 [R(int) = 0.0905], refinement by full-matrix least-squares on F^2, data/restraints/parameters 6554/0/365, goodness-of-fit on F^2 = 1.071, final R indices [$I > 2s(I)$] R_1 = 0.0739, wR_2 = 0.1831, R indices (all data) R_1 = 0.1166, wR_2 = 0.2278, largest diff peak and hole 0.253 and −0.419 e·Å^{-3}. Crystallographic data for the structure **4a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 1412472.

Compound ***4b***. White solid, 64 mg, 75% yield, mp: 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 1H), 7.73−7.66 (m, 3H), 7.52−7.46 (m, 1H), 7.40−7.32 (m, 3H), 6.84 (s, 1H), 5.48 (s, 1H), 4.11 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 149.0, 134.4, 132.8, 132.4, 131.7, 127.2, 126.3, 123.2, 122.4, 122.3, 119.9, 113.6, 99.1, 63.9, 14.6; IR (KBr) 3489, 3052, 1596, 1575, 1503, 1488, 1128 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}BrNaO_2$ $(M + Na)^+$ 365.0153, found 365.0144.

Compound ***4c***. White solid, 61 mg, 83% yield, mp: 127−130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.49−7.47 (m, 1H), 7.40−7.35 (m, 3H), 7.09 (d, J = 8.1 Hz, 2H), 6.85 (s, 1H), 5.68 (s, 1H), 4.13 (q, J = 6.9 Hz, 2H), 3.91 (s, 3H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 155.0, 149.2, 134.2, 132.2, 128.7, 127.4, 126.9, 126.2, 123.0, 122.4, 119.9, 114.7, 99.0, 63.8, 55.3, 14.6; IR (KBr) 3496, 3064, 1598, 1570, 1509, 1447, 1128 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NaO_3$ $(M + Na)^+$ 317.1154, found 317.1147.

Compound ***4d***. Yellow oil, 54 mg, 74% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26−8.20 (m, 1H), 7.74−7.72 (m, 1H), 7.50−7.44 (m, 2H), 7.40−7.35 (m, 2H), 7.13−7.10 (m, 2H), 6.89 (s, 1H), 5.84 (s, 1H), 4.15−4.12 (m, 2H), 3.85 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.3, 155.2, 149.6, 134.5, 133.2, 129.7, 126.8, 126.2, 122.9, 122.6, 121.4, 121.2, 120.5, 112.0, 111.6, 99.4, 63.9, 55.8, 14.6; IR (KBr) 3527, 3066, 1594, 1574, 1491, 1458, 1113 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NaO_3$ $(M + Na)^+$ 317.1154, found 317.1146.

Compound ***4e***. Colorless oil, 54 mg, 77% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.50−7.37 (m, 6H), 6.86 (s, 1H), 5.67 (s, 1H), 4.13 (q, J = 6.96 Hz, 2H), 2.48 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.9, 149.2, 137.8, 134.2, 130.8, 129.9, 129.6, 126.9, 126.2, 122.9, 122.4, 119.9, 114.7, 99.0, 63.8, 21.4, 14.6; IR (KBr) 3527, 3049, 1598, 1576, 1499, 1446, 1129 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1369.

Compound ***4f***. White solid, 55 mg, 66% yield, mp: 96−98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.52−7.50 (m, 1H), 7.41−7.38 (m, 1H), 6.88 (s, 1H), 5.45 (s, 1H), 4.13 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.3, 149.1, 136.9, 134.6, 131.6, 130.0 (q, J = 32.5 Hz), 127.4, 126.4, 126.0 (q, J = 3.7 Hz), 124.1 (q, J = 270.1 Hz), 123.3, 122.4, 119.9, 113.5, 99.2, 63.9, 14.5; IR (KBr) 3228, 3061, 1599, 1578, 1498, 1443, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}F_3O_2$ $(M + H)^+$ 333.1102, found 333.1073.

Compound ***4g***. White solid, 64 mg, 88% yield, mp: 86−89 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.57−7.43 (m, 7H), 7.21 (s, 1H), 5.74 (s, 1H), 1.23 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 148.9, 134.0, 133.8, 131.4, 129.0, 127.9, 126.8, 126.7, 123.9, 122.5, 121.1, 119.5, 111.0, 79.9, 29.0; IR (KBr) 3528, 3052, 1597, 1575, 1495, 1456, 1134 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NaO_2$ $(M + Na)^+$ 315.1361, found 315.1378.

Compound ***4h***. Colorless oil, 46 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.52−7.46 (m, 1H), 7.39−7.34 (m, 5H), 6.87 (s, 1H), 5.62 (s, 1H), 3.87 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 149.2, 138.1, 134.2, 130.8, 130.2, 129.4, 127.0, 126.3, 123.1, 122.4, 120.0, 114.4, 97.9, 55.7, 21.4; IR (KBr) 3524, 3052, 1597, 1576, 1499, 1459, 1130 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1219.

Compound ***4i***. Colorless oil, 57 mg, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.08 (m, 1H), 7.65−7.59 (m, 1H), 7.44−7.39 (m, 2H), 7.29−7.25 (m, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.91−6.84 (m, 3H), 5.36 (s, 1H), 2.89−2.82 (m, 2H), 2.38 (s, 3H), 1.70−1.64 (m, 2H), 1.51−1.41 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 154.5, 149.8, 140.0, 132.9, 129.5, 126.9, 126.2, 124.1, 123.9, 121.3, 121.1, 119.6, 116.1, 115.9, 106.9, 31.6, 23.8, 22.8, 21.5, 14.0; IR (KBr) 3503, 3027, 1578, 1485, 1457, 1244, 1135 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}O_2$ $(M + H)^+$ 307.1698, found 307.1689.

Compound ***4k***. Colorless oil, 48 mg, 65% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80−7.78 (m, 1H), 7.69−7.67 (m, 1H), 7.37−7.33 (m, 4H), 7.28−7.24 (m, 1H), 6.85 (s, 1H), 5.66 (s, 1H), 4.11 (q, J = 7.0 Hz, 2H), 2.47 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2 (d, J = 241.9 Hz), 154.3 (d, J = 2.3 Hz), 148.6 (d, J = 5.0 Hz), 138.0, 131.0, 130.7, 130.0, 129.2, 128.3 (d, J = 8.5 Hz), 120.3 (d, J = 8.8 Hz), 116.9 (d, J = 25.2 Hz), 115.6, 106.4 (d, J = 22.3 Hz), 99.0, 63.9, 21.4, 14.6; IR (KBr) 3526, 3021, 1579, 1504, 1437, 1150, 1081 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}FO_2$ $(M + H)^+$ 297.1291, found 297.1277.

Compound ***4l***. Colorless oil, 60 mg, 67% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36−8.34 (m, 1H), 7.59−7.52 (m, 2H), 7.38−7.34 (m, 4H), 6.81 (s, 1H), 5.68 (s, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.48 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.3, 148.4, 138.1, 132.7, 130.8, 130.7, 130.1, 130.1, 127.9, 124.9, 121.4, 121.1, 116.5, 98.9, 63.9, 21.4, 14.6; IR (KBr) 3523, 3024, 1587, 1572, 1491, 1453, 1136 cm^{-1};

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX

HRMS (ESI) calcd for $C_{19}H_{17}BrNaO_2$ $(M + Na)^+$ 379.0310, found 379.0300.

Compound ***4m***. White solid, 63 mg, 82% yield, mp: 112−115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 8.9 Hz, 1H), 7.50−7.49 (m, 1H), 7.38−7.36 (m, 4H), 7.18 (dd, J = 8.9, 2.6 Hz, 1H), 6.84 (s, 1H), 5.64 (s, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 2.48 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.9, 153.2, 148.1, 137.8, 130.8, 130.0, 129.7, 129.4, 127.9, 120.4, 119.5, 115.3, 100.9, 99.3, 63.9, 55.4, 21.4, 14.7; IR (KBr) 3523, 3021, 1587, 1575, 1491, 1453, 1186 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NaO_3$ $(M + Na)^+$ 331.1310, found 331.1298.

Compound ***4n***. White solid, 55 mg, 76% yield, mp: 98−101 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.39−7.36 (m, 4H), 7.34 (d, J = 8.3 Hz, 1H), 6.84 (s, 1H), 5.65 (s, 1H), 4.12 (q, J = 6.8 Hz, 2H), 2.55 (s, 3H), 2.49 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.2, 148.6, 137.7, 132.5, 132.4, 130.8, 129.9, 129.7, 129.1, 126.2, 121.4, 120.0, 114.8, 99.0, 63.8, 21.7, 21.4, 14.6; IR (KBr) 3527, 3021, 1594, 1573, 1511, 1458, 1167 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}O_2$ $(M + H)^+$ 293.1542, found 293.1535.

Compound ***4o***. White solid, 61 mg, 70% yield, mp: 95−98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.64 (dd, J = 8.6, 1.7 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.88 (s, 1H), 5.78 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 2.49 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 149.9, 138.3, 135.7, 130.6, 130.1, 128.8, 127.0, 124.7 (q, J = 271.7 Hz), 124.6 (q, J = 32.3 Hz), 122.5 (q, J = 3.1 Hz), 120.7 (q, J = 4.6 Hz), 118.8, 115.8, 98.8, 64.0, 21.4, 14.5; IR (KBr) 3525, 3024, 1611, 1578, 1519, 1463, 1176 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}F_3NaO_2$ $(M + Na)^+$ 369.1078, found 369.1070.

Compound ***4p***. White solid, 55 mg, 71% yield, mp: 107−110 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 1H), 7.40−7.36 (m, 4H), 7.32−7.28 (m, 1H), 7.26 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.65 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 4.04 (s, 3H), 2.47 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.6, 154.2, 149.1, 137.8, 130.8, 129.9, 129.6, 126.1, 122.8, 120.8, 115.2, 114.7, 104.9, 93.5, 63.9, 55.5, 21.4, 14.6; IR (KBr) 3525, 3051, 1598, 1584, 1497, 1449, 1122 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}O_3$ $(M + H)^+$ 309.1491, found 309.1482.

Compound ***5a***. It was prepared from **1a** and **2a** at 60 °C for 10 h to give 71 mg of **5a** (87% yield) as a white solid, mp: 175−178 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 7.1 Hz, 2H), 7.45−7.34 (m, 8H), 5.15 (s, 1H), 3.33 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.0, 160.3, 135.3, 129.1, 129.1, 128.6, 128.5, 128.4, 128.2, 67.2, 39.2, 37.6; IR (KBr) 3021, 1687, 1614, 1599, 1493, 1453, 1316, 1132 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}NNaO_3S$ $(M + Na)^+$ 350.0827, found 350.0821.

Compound ***5b***.[17b] Colorless oil, 60 mg, 82% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88−7.83 (m, 2H), 7.39−7.26 (m, 8H), 4.82 (s, 1H), 1.38 (s, 9H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01858.

Spectroscopic data of products **3** and **4** (PDF)

X-ray data of **3v** (CIF)

X-ray data of **4a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*gangguo@zjnu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the Science Technology Department of Zhejiang Province (2015C31030), Natural Science Foundation of Zhejiang Province (LR12B02001 and LY14B020002), and National Natural Science Foundation of China (21172199).

■ REFERENCES

(1) (a) Itokawa, H.; Mihara, K.; Takeya, K. *Chem. Pharm. Bull.* **1983**, *31*, 2353. (b) Kawasaki, Y.; Goda, Y.; Yoshihira, K. *Chem. Pharm. Bull.* **1992**, *40*, 1504. (c) Ho, L.-K.; Don, M.-J.; Chen, H.-C.; Yeh, S.-F.; Chen, J.-M. *J. Nat. Prod.* **1996**, *59*, 330.

(2) (a) Itokawa, H.; Ibraheim, Z. Z.; Qiao, Y.-F.; Takeya, K. *Chem. Pharm. Bull.* **1993**, *41*, 1869. (b) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230.

(3) (a) Meyers, A. I.; Willemsen, J. J. *Tetrahedron* **1998**, *54*, 10493. (b) Boonsri, S.; Karalai, C.; Ponglimanont, C.; Chantrapromma, S.; Kanjana-opas, A. *J. Nat. Prod.* **2008**, *71*, 1173.

(4) Rinehart, K. L., Jr. *Acc. Chem. Res.* **1972**, *5*, 57.

(5) For selected reports since 2013, see: (a) Peng, S.; Wang, L.; Wang, J. *Chem. - Eur. J.* **2013**, *19*, 13322. (b) He, Y.; Zhang, X.; Shen, N.; Fan, X. *J. Org. Chem.* **2013**, *78*, 10178. (c) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 4884. (d) Xia, Y.; Qu, P.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2543. (e) Hammann, J. M.; Unzner, T. A.; Magauer, T. *Chem. - Eur. J.* **2014**, *20*, 6733. (f) Kim, H. Y.; Oh, K. *Org. Lett.* **2014**, *16*, 5934. (g) Chen, Y.; Wang, L.; Sun, N.; Xie, X.; Zhou, X.; Chen, H.; Li, Y.; Liu, Y. *Chem. - Eur. J.* **2014**, *20*, 12015 and references therein..

(6) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. (c) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852. (d) Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 11450. (e) Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396.

(7) (a) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 4024. (b) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 644.

(8) Bao, J.; Wulff, W. D.; Fumo, M. J.; Grant, E. B.; Heller, D. P.; Whitcomb, M. C.; Yeung, S.-M. *J. Am. Chem. Soc.* **1996**, *118*, 2166.

(9) (a) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (b) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3389.

(10) (a) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471. (b) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341. (c) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407. (d) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

(11) Zhang, W.; Ready, J. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8980.

(12) For the synthesis of aryl *tert*-butyl ynol ethers, see: (a) Marzo, L.; Parra, A.; Frías, M.; Alemán, J.; Ruano, J. L. G. *Eur. J. Org. Chem.* **2013**, *2013*, 4405. For the synthesis of other ynol ethers, see: (b) Jouvin, K.; Bayle, A.; Legrand, F.; Evano, G. *Org. Lett.* **2012**, *14*, 1652. (c) Tanaka, R.; Miller, S. I. *Tetrahedron Lett.* **1971**, *12*, 1753. (d) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.

(13) For selected reports on ynol ethers since 2014, see: (a) Ding, S.; Jia, G.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877. (b) Arai, S.; Nakajima, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5569. (c) D'Oyley, J. M.; Aliev, A. E.; Sheppard, T. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 10747. (d) Alford, J. S.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 10266. (e) Puri, S.; Thirupathi, N.; Reddy, M. S. *Org. Lett.* **2014**, *16*, 5246. (f) Babu, M. H.; Dwivedi, V.; Kant, R.; Reddy, M. S.

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX

Angew. Chem., Int. Ed. **2015**, *54*, 3783. (g) Fabig, S.; Haberhauer, G.; Gleiter, R. *J. Am. Chem. Soc.* **2015**, *137*, 1833. (h) Saito, N.; Sun, Z.; Sato, Y. *Chem. - Asian J.* **2015**, *10*, 1170. (i) Minami, Y.; Kanda, M.; Sakai, M.; Hiyama, T. *Tetrahedron* **2015**, *71*, 4522.

(14) For our recent works on ynol ethers, see: (a) Cai, H.; Yuan, Z.; Zhu, W.; Zhu, G. *Chem. Commun.* **2011**, *47*, 8682. (b) Bai, Y.; Yin, J.; Kong, W.; Mao, M.; Zhu, G. *Chem. Commun.* **2013**, *49*, 7650. (c) Cui, W.; Mao, M.; He, Z.; Zhu, G. *J. Org. Chem.* **2013**, *78*, 9815. (d) Cui, W.; Ying, J.; Zheng, R.; Cheng, C.; Bai, Y.; Zhu, G. *J. Org. Chem.* **2014**, *79*, 3487. (e) Yin, J.; Bai, Y.; Mao, M.; Zhu, G. *J. Org. Chem.* **2014**, *79*, 9179.

(15) For selected reviews on ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Gaumont, A.-C.; Alayrac, C.; Wrona, I. E.; Giguere, J. R.; Delacroix, O.; Bayle, A.; Jouvin, K.; Theunissen, C.; Gatignol, J.; Silvanus, A. C. *Tetrahedron* **2014**, *70*, 1529. For our recent works on ynamides, see: (c) Liu, G.; Kong, W.; Che, J.; Zhu, G. *Adv. Synth. Catal.* **2014**, *356*, 3314. (d) Yang, Y.; Wang, L.; Zhang, F.; Zhu, G. *J. Org. Chem.* **2014**, *79*, 9319. (e) Yang, Y.; Wang, L.; Zhang, J.; Jin, Y.; Zhu, G. *Chem. Commun.* **2014**, *50*, 2347. (f) Cheng, C.; Liu, S.; Zhu, G. *Org. Lett.* **2015**, *17*, 1581.

(16) CCDC 1412471 (**3v**) and 1412472 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(17) (a) Valentí, E.; Pericàs, M. A.; Serratosa, F. *J. Org. Chem.* **1990**, *55*, 395. (b) Gray, V. J.; Slater, B.; Wilden, J. D. *Chem. - Eur. J.* **2012**, *18*, 15582. (c) Tran, V.; Minehan, T. G. *Org. Lett.* **2011**, *13*, 6588.

DOI: 10.1021/acs.joc.5b01858
J. Org. Chem. XXXX, XXX, XXX−XXX