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Direct Access to Highly Substituted 1-Naphthols through Palladium-Catalyzed Oxidative Annulation of Benzoylacetates and Internal Alkynes

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The synthesis of aromatic and heterocyclic molecules is a topic of continued interest owing to the presence of these skeletal motifs in countless natural products and synthetic compounds that display important chemical, biological, and medicinal properties.[1] 1-Naphthol and its highly substituted derivatives fall into this category. For example, mollugin (Figure 1a) and its analogues have shown antiviral activity

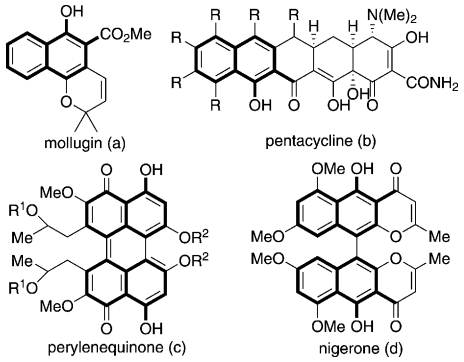
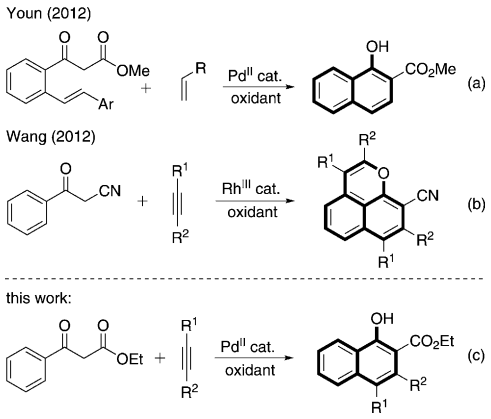


Figure 1. Important examples of substituted-1-naphthols.

against the hepatitis B virus.[2] Pentacycline (Figure 1b) displays a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative organisms.[3] Cercosporin, phleichropme, and calphostins belong to a class of perylenequinone natural products (Figure 1c) and have been identified as potent protein kinase C inhibitors and photodynamic cancer therapies.[4] Nigerone (Figure 1d) is a class of bis-naphthopyrone natural products that exhibits antitumor and antibacterial activities.[5]

Despite some progress that has been made in constructing the 1-naphthol scaffold,[6] these methods suffer from drawbacks such as the use of high reaction temperature,[6e,f] rarely used starting materials,[6e–g] multiple synthetic steps,[6h–j] and limited substrate scope.[6k] Recently, transition-metal-catalyzed direct C–H functionalizations have attracted much attention owing to their atom-economy, simple protocol, and environmentally benign features.[7] Although the transition-metal-catalyzed oxidative annulations[8] through direct C–H functionalization have proven to be a powerful tool in the assembly of numerous structural motifs,[9] a detailed survey of the literature reveals that the one-step synthesis of highly substituted 1-naphthols from readily available starting materials has so far remained a major challenge. It is well known that a direct and efficient synthetic method that utilizes simple and readily available starting material would not only enable the construction of a new class of scaffolds but would also facilitate the late-stage structural modification of existing compounds. Very recently, Youn's group reported a palladium-catalyzed method to prepare 1-naphthols from alkenyl 1,3-dicarbonyl compounds or aryl-substituted alkenyl β-keto esters (Scheme 1a).[10]



Scheme 1. Challenges in the synthesis of 1-naphthols.

Wang and co-workers independently reported an example of rhodium-catalyzed cascade oxidative annulation reactions of benzoylacetonitriles with alkynes, thereby affording substituted naphthopyrans through an in situ formed 1-naphthol key intermediate (Scheme 1b).[11] As part of our continued interest in transition-metal-mediated C–C bond-forming processes, we recently disclosed palladium-catalyzed oxidative annulations of isatins and unactivated internal alkynes to access the benzazepine scaffold.[12a] Herein, we report our new results on a straightforward approach: palladium-catalyzed oxidative annulation reactions of readily available benzoylacetates with unactivated internal alkynes, which il-

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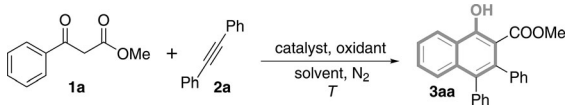
lustrated an efficient preparation of more substituted 1-naphthols (Scheme 1c).

Our investigation began with the Pd-catalyzed oxidative annulation of benzoylacetate **1a** and diphenylacetylene **2a** to give the corresponding 1-naphthol **3aa** (Table 1).[13] On

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	–[c]	$Cu(OAc)_2$	DMSO	–[d]
2	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	22
3	$[Pd(PPh_3)_2Cl_2]$	$Cu(OAc)_2$	DMSO	24
4	$Pd(TFA)_2$	$Cu(OAc)_2$	DMSO	16
5	$PdCl_2$	$Cu(OAc)_2$	DMSO	15
6	$Pd(OAc)_2$	AgOAc	DMSO	–[d]
7	$Pd(OAc)_2$	CuOAc	DMSO	12
8	$Pd(OAc)_2$	$CuCl_2$	DMSO	–[d]
9	$Pd(OAc)_2$	$PhI(OAc)_2$	DMSO	<5
10	$Pd(OAc)_2$	oxones	DMSO	–[d]
11	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO	–[d]
12	$Pd(OAc)_2$	BQ[e]	DMSO	–[d]
13	$Pd(OAc)_2$	$Cu(OAc)_2$	anisole	–[d]
14	$Pd(OAc)_2$	$Cu(OAc)_2$	1,4-dioxane	–[d]
15	$Pd(OAc)_2$	$Cu(OAc)_2$	EtOH	–[d]
16	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_3CN	–[d]
17	$Pd(OAc)_2$	$Cu(OAc)_2$	DMA[f]	<5
18	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	50[g]
19	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	51[h]
20	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**DMSO**	**76[i]**
21	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	24[j]

[a] Reaction conditions: DMSO (2 mL), **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv), 80°C, 24 h, N_2 (TFA = trifluoroacetic acid). [b] Isolated yield after purification by column chromatography. [c] No catalyst. [d] No desired product. [e] 1,4-Benzoquinone. [f] Dimethylacetamide. [g] $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (2.0 equiv), 80°C. [h] $Pd(OAc)_2$ (100 mol%), $Cu(OAc)_2$ (2.0 equiv), 80°C. [i] $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (3.0 equiv), 80°C. [j] $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (3.0 equiv), 120°C.

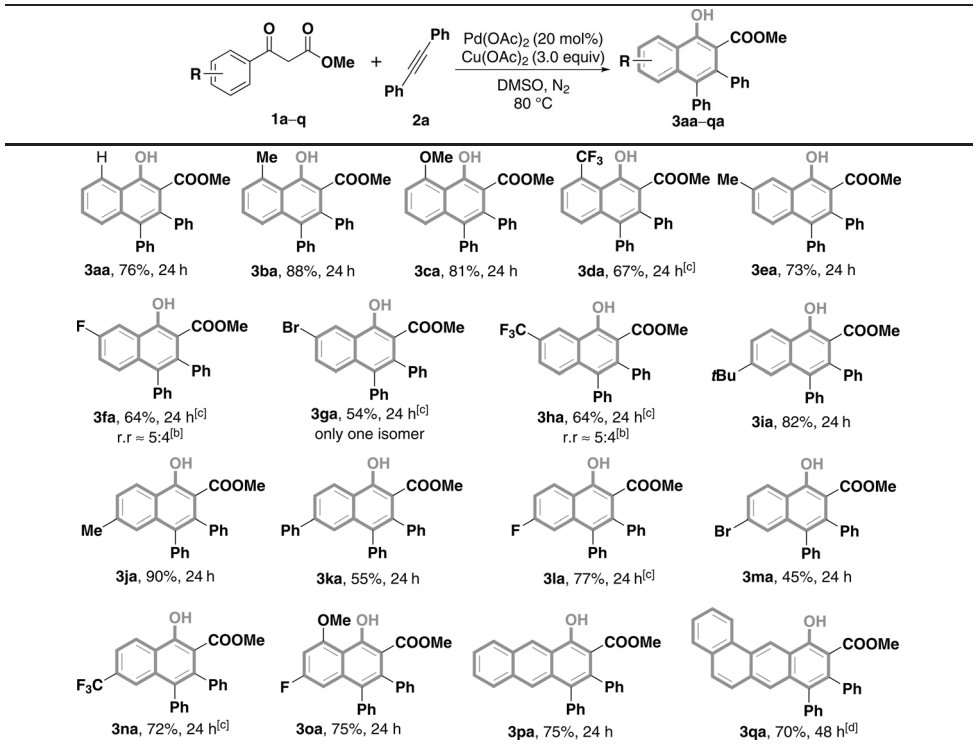
the basis of optimization experiments, the best results were obtained using $Pd(OAc)_2$ as catalyst with stoichiometric amounts of $Cu(OAc)_2$ as the oxidant in DMSO (Table 1, entry 20). Under these conditions, the conversion was complete within 24 h at 80°C (Table 1, entry 20; 76% isolated yield). No reaction was observed in the absence of palladium catalyst (Table 1, entries 1–5). A variation of oxidants (Table 1, entries 6–12) or solvents (Table 1, entries 13–18) led to a significant decrease in chemical yield. The effects of temperature are summarized in Table 1 (Table 1, entries 20 and 21), and a low yield was achieved at a high temperature owing to the potential decomposition of starting materials (Table 1, entry 21; 120°C, 24%). However, lowering the temperature further also led to a slow reaction conversion (see the details in the Supporting Information). Moreover, production was highly sensitive to the loading of $Pd(OAc)_2$ and $Cu(OAc)_2$ used. When the loading of $Pd(OAc)_2$ was decreased proportionally from 20 to 10%, a significant decrease in yield was observed (Table 1, entry 18; 50% versus Table 1, entry 2; 22%). However, the use of 100% $Pd(OAc)_2$ did not improve the production of **3aa** (Table 1, entry 19; 51%). Notably, the amount of $Cu(OAc)_2$ was identified to be another crucial factor (Table 1, entries 19 and 20; ultimately, 3.0 equiv of $Cu(OAc)_2$ were used). Additionally, the use of an inert atmosphere (N_2) was found to be essential to avoid the side aerobic oxidation of alkynes.

With the optimized conditions in hand, our attention turned to an evaluation of the scope and limitations of this reaction (Tables 2 and 3). Given the great value of benzoylacetates, we used the simple diphenylacetylene **2a** to examine the scope. To our delight, the optimized reaction conditions allowed the oxidative annulations of benzoylacetates **1**, which contained a variety of functional groups, regardless of electron-donating or electron-withdrawing properties, thereby delivering the corresponding products in moderate to high yields (Table 1; 45–90%). Notably, methoxy (**3ca**, **3oa**), trifluoromethyl (**3da**, **3ha**, **3na**), and bromo (**3ga**, **3ma**) were valuable functional groups amenable for further decoration of the products. Excellent regioselectivity was observed when 3-bromo-substituted β-keto ester (**1g**) was employed (only one regioisomer detected), thereby favoring activation of the less hindered C–H bond (**3ga**). However, 3-fluoro- or 3-trifluoro-substituted benzoylacetates (**1f** and **1h**) led to limited regioselective control owing to both *ortho* and *para* C–H bond activation by means of strong electron-drawing groups (F or CF_3). It is noteworthy that the naphthalene ring and anthracene ring were well tolerated in substrates, thereby leading to valuable π-conjugated aromatic compounds (**3pa** and **3qa**).

Encouraged by these results, we next explored the scope of internal alkynes **2** that could potentially react with **1a** to study the generality of the scheme for further synthetic exploitation. The reaction showed broad substrate tolerance among internal alkynes. Electron-rich alkynes reacted to give high reaction yields (Table 3, **3ab–ad, 3ah–ag**; 75–88%), whereas electron-deficient systems were slightly less facile (Table 3, **3ae–ag**, **3ao**; 36–68%). Heteroaryl, ester-containing, and aliphatic alkynes were all tolerated (**3ap**, **3aq**, **3ar**). When asymmetrical internal alkynes were employed, two regioisomers were usually both observed (**3al–aq**; ratio of regioisomers was 1:1 to 4:1). In the event that the internal alkyne (**2r**) was highly electron deficient, the only regioisomer (**3ar**) was formed by following Markovnikov's rule in the alkyne addition step.

To further understand the electronic effects of functional groups, two comparative experiments were conducted (Schemes 2 and 3). As outlined in Scheme 2, electron-rich alkyne **2b** generally proceeded slightly faster than its electron-deficient counterpart **2e** (**3ab**/**3ae** 10:7). Similarly, electron-rich benzoylacetate **1j** also exhibited a similar reactivity as well as electron-deficient benzoylacetate **1l** when they were treated with diphenylacetylene **2a** (Scheme 3; **3ja**/**3la** 5:4). These results suggested that the electronic effects of functional groups from both benzoylacetates and internal al-

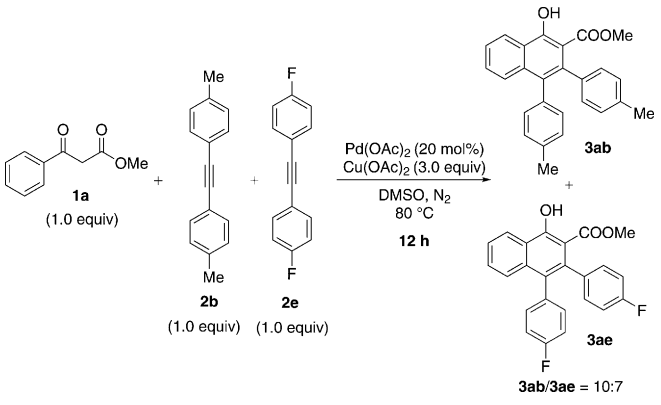
Table 2. Scope of β-keto esters.[a]



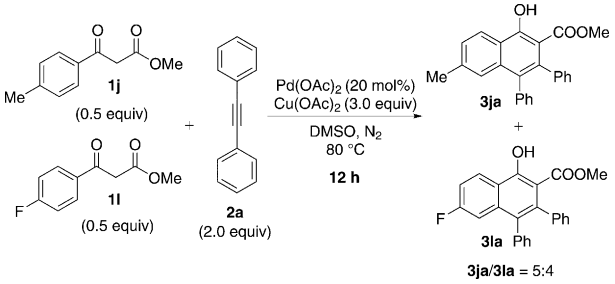
[a] Reaction conditions: DMSO (2 mL), **1a–q** (0.2 mmol, 1.0 equiv), **2a** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (3.0 equiv), 80 °C, 24 h, N_2. [b] The ratio of regioisomers was determined by NMR spectroscopy. [c] $Pd(OAc)_2$ (30 mol%). [d] $Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (4.0 equiv).

kynes might have limited effects on the chemoselectivity of this reaction.

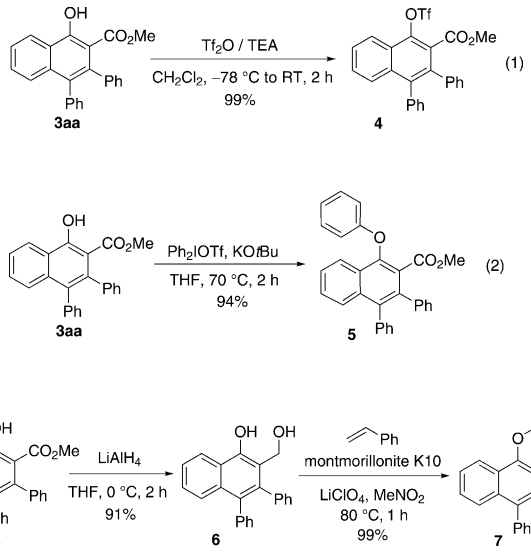
The versatility of this palladium-catalyzed oxidative annulation can be exploited in chemoselective transformations to access various frameworks with high degrees of molecular complexity. As outlined in Equation (1), **3aa** was readily converted to the important Tf-protected 1-naphthanol **4** by the addition of 1.5 equivalents of trifluoromethanesulfonic anhydride (Tf_2O). Under conditions of diphenyliodonium trifluoromethanesulfonate (Ph_2IOTf) and potassium *tert*-butoxide (KO*t*Bu), **3aa** was expectedly converted to a diaryl ether **5** with a 95% yield in 2.0 h [Eq. (2)]. The reduction of **3aa** followed and intermediate **6** was generated and further converted to a polycyclic dihydropyran **7** in high yield [Eq. (3)].



Scheme 2. Competition experiments of diphenylacetylenes.

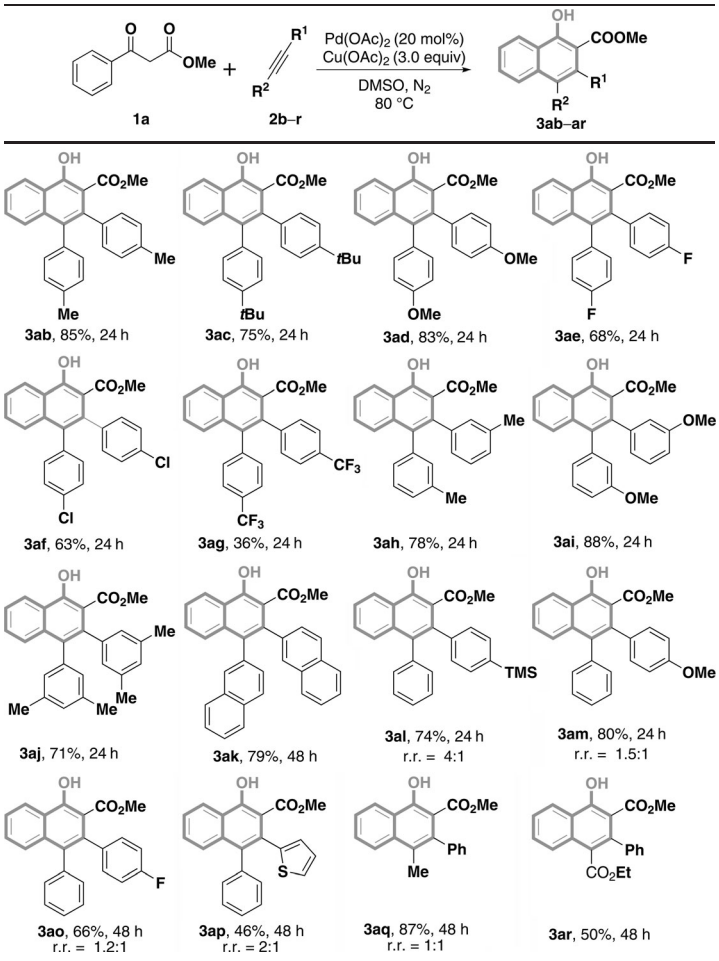


Scheme 3. Competition experiments of β-keto esters.



Facile manipulation of intermediate **4** offers an additional synthetic opportunity. For example, the −OTf group in **4** could be replaced by an alkyne group to yield **8** in 93% yield by means of $[Pd(PPh_3)_2Cl_2]$-catalyzed Sonogashira coupling (Scheme 4a). $Pd(OAc)_2$-promoted Heck-type alkenation of **4** led to the formation of **9** in 94% yield (Scheme 4b). When Tf-protected 1-naphthanol **4** was treated with phenylboronic acid or isobutylboronic acid catalyzed by [Pd-

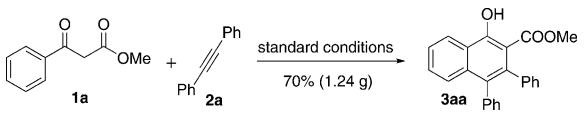
Table 3. Scope of internal alkynes.[a]



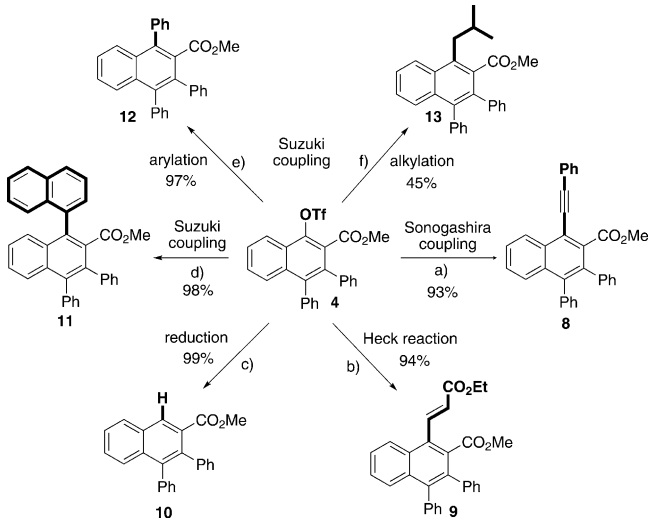
[a] Reaction conditions: DMSO (2.0 mL), **1a** (0.2 mmol, 1.0 equiv), **2b–r** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (3.0 equiv), 80°C, N_2; the ratio of regioisomers was determined by NMR spectroscopy.

$(PPh_3)_4$], Suzuki coupling reactions took place and afforded aryl- or alkyl-functionalized products **12** and **13** (Scheme 4e,f). If formic acid was employed to react with Tf-protected 1-naphthanol **4**, a reductive product **10** was obtained in 99% yield (Scheme 4c). Gratifyingly, $[Pd(PPh_3)_4]$-promoted Suzuki coupling allowed Tf-protected 1-naphthanol **4** to readily convert into binaphthyl product **11** (Scheme 4d), which could potentially be used as a ligand in organometallic and coordination chemistry, or as a functional material due to its extended π-conjugated system. In addition to indicating the potentially synthetic practicability, a Gram-scale synthesis was examined under standard conditions and gave **3aa** in 70% yield (Scheme 5; 1.24 g).

On the basis of known transition-metal-catalyzed C–H activation/oxidative annulation reactions, we propose a plausi-

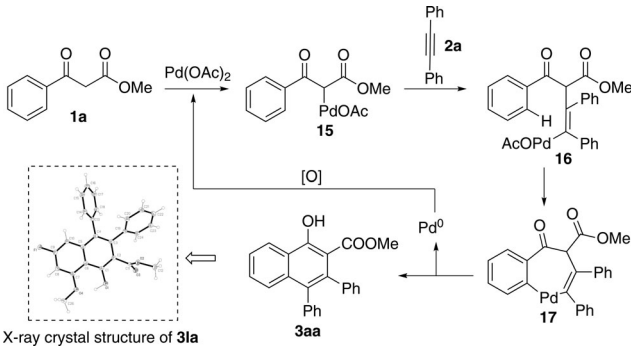


Scheme 5. Gram-scale synthesis of **3aa**.



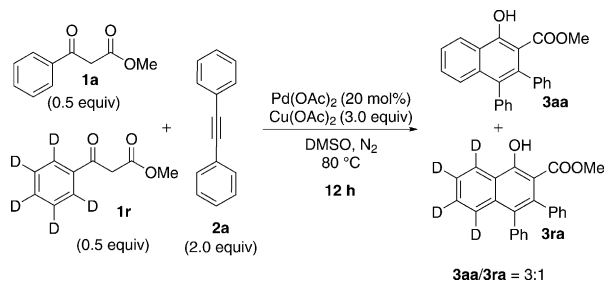
Scheme 4. Synthetic transformations. Reaction conditions: a) **4** (0.1 mmol), diphenylacetylene (0.3 mmol), $[Pd(PPh_3)_2Cl_2]$ (10 mol%), CuBr (5 mol%), *N*,*N*-diisopropylethylamine (DIPEA; 0.3 mmol), DMF (1 mL), 80°C, 5 h, N_2, 93%; b) **4** (0.1 mmol), ethyl acrylate (1.0 mmol), $Pd(OAc)_2$ (20 mol%), PPh_3 (60 mol%), toluene (1 mL), 110°C, 6 h, N_2, 94%; c) Compound **4** (0.1 mmol), HCOOH (0.3 mmol), $[Pd(PPh_3)_4]$ (10 mol%), triethylamine (TEA; 3.0 mmol), DMF (1 mL), 80°C, 2 h, N_2, 99%; d) **4** (0.1 mmol), 1-naphthylboronic acid (0.15 mmol), $[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3 (0.15 mmol), 4 Å MS (50 mg), toluene (1 mL), 80°C, 2 h, N_2, 98%; e) **4** (0.1 mmol), phenylboronic acid (0.15 mmol), $[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3 (0.15 mmol), toluene (1 mL), 80°C, 2 h, N_2, 97%; f) **4** (0.1 mmol), isobutylboronic acid (0.15 mmol), $[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3 (0.15 mmol), toluene (1 mL), 80°C, 2 h, N_2, 45%.

ble mechanism (Scheme 6). Formation of substituted 1-naphthol **3aa** presumably commences with the palladation of benzoylacetate **1a** to yield the palladium intermediate **15** (Scheme 6). The ensuing *syn* addition of intermediate **15** to



Scheme 6. Plausible mechanism.

diphenylacetylene **2a** generated the vinylpalladium intermediate **16**. Finally, intramolecular palladation of **16** led to the formation of palladabenzocycloheptanone **17**. The catalytic cycle was completed by the liberation of the product along with Pd^0 through reductive elimination. To gain insight into the mechanism, a significant kinetic isotope effect was measured by using **1a** and $[D_5]$**1r** as substrates (Scheme 7). A kinetic isotope effect (KIE) value of K_H/



Scheme 7. Kinetic study.

$K_D = 3.0$ was obtained (see the Supporting Information), thereby suggesting that the cleavage of the C–H bond of the phenyl ring was involved in the rate-determining step.[14]

In summary, we have developed an efficient synthesis of highly substituted 1-naphthols. The method utilizes simple and readily available benzoylacetates and unactivated internal alkynes, and employs a direct Pd^{II}-catalyzed oxidative annulation procedure that involves C–H activation. The reaction proceeds under mild conditions and exhibits a broad substrate scope with respect to the substituents. The significance of the 1-naphthol scaffold as a structural element should also render this method attractive for both synthetic and medicinal chemistry. We expect this new method to complement existing methods to access highly substituted 1-naphthols, which are of great interest in different disciplines.

Experimental Section

General procedure: A solution of β-keto ester **1a** (0.2 mmol, 1.0 equiv), diphenyl actylene **2a** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (20 mol%), and $Cu(OAc)_2$ (3.0 equiv) in DMSO (2 mL) was stirred at 80 °C for 24 h (Table 2). The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc (20:1, then 8:1) to afford the desired product **3aa** as a yellow solid (54 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 12.23$ (s, 1H), 8.55 (d, $J = 8.0$ Hz, 1H), 7.58–7.47 (m, 2H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.23–7.15 (m, 3H), 7.13–7.01 (m, 5H), 7.00–6.94 (m, 2H), 3.42 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.58$, 160.47, 141.88, 138.84, 137.25, 135.73, 131.66, 131.41, 129.79, 127.64, 126.82, 126.47, 125.80, 125.76, 124.24, 124.00, 106.58, 77.41, 77.16, 76.91, 51.93 ppm; HRMS (ESI): m/z calcd for $C_{24}H_{17}O_3$: 353.1183 $[M-H^+]$; found: 353.1170.

Acknowledgements

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Keywords: alkynes · annulation · C–H activation · naphthols · palladium

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