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Synthesis of Polysubstituted 2-Naphthols by Palladium-Catalyzed Intramolecular Arylation/Aromatization Cascade

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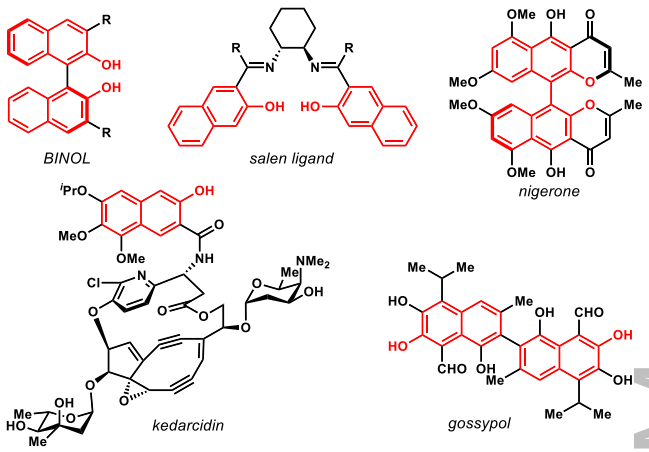
Abstract: A palladium-catalyzed intramolecular α-arylation and defluorinative aromatization strategy for the synthesis of polysubstituted 2-naphthols is reported. With *ortho*-bromobenzyl-substituted α-fluoroketones as the substrates and palladium acetate/triphenylphosphine as the catalyst, this method features good functional group tolerance, readily available catalyst and starting materials, and high yields. The applications of the strategy are demonstrated by the synthesis of useful building blocks, such as naphtha[2,3-*b*]furan, naphthol AS-D, and ligands/catalysts.

Keywords: aromatization; C–C bond formation; cyclization; defluorination; 2-naphthol; palladium.

Polysubstituted naphthols have found wide applications in organic synthesis and drug development (Scheme 1).[1,2] For instance, BINOLs and naphthol derived salen-type ligands are extensively applied in asymmetric catalysis.[3,4] A number of biologically active natural products, such as nigerone,[5] gossypols,[6] and kedarcidin,[7] possess a 2-naphthol backbone. Moreover, naphthols are precursors that can be readily transformed into naphthalene and naphthoquinone, which are core structures of many natural products exemplified in nanaomycin A[8] and rifampicin.[9] Therefore, the development of efficient strategies toward the regioselective synthesis of polysubstituted naphthol derivatives is of great importance.

Electrophilic aromatic substitution of naphthols is a conventional approach to synthesize their derivatives, however, this method enables the introduction of functional groups only at specific positions of the substrates (i.e., C2 of 1-naphthols and C1 of 2-naphthols).[10] Alternatively, multisubstituted naphthols have been efficiently synthesized by de novo strategies, which are particularly attractive in natural products synthesis, allowing the aromatic ring formation at the late stage.[11] Transition metal catalysis (i.e., Pd, Au, Ag, Rh) is a powerful tool for the de novo synthesis of naphthol (Scheme 2a).[12–15] However, previously reported methods are mainly



Scheme 1. Representative ligands and bioactive compounds with 2-naphthol skeletons.

limited to accessing 1-naphthol derivatives. To date, only a handful of examples of the de novo construction of polysubstituted 2-naphthols have been reported.[16–18] Larock et al reported a 6-*endo*-*dig* cyclization of alkynyl benzyl ketones by treatment with excess iodine monochloride (Scheme 2b).[17] Recently, the Zi group realized an efficient rhodium-catalyzed oxidative cyclization of enynes in the construction of 2-naphthols and phenols with remarkable substrate scope, albeit necessitating an external oxidant (Scheme 2c).[18] During our study toward intramolecular α-arylation reactions,[19] we found that *ortho*-bromobenzyl-substituted α-fluoroketones **1** under palladium catalysis resulted in the formation of 2-naphthols **2**. These electron-deficient naphthols are not easily accessed by conventional methods. We proposed that the reaction probably involves an oxidative addition of aryl bromide to palladium (**1** to **I**), α-arylation of ketone (**I** to **II**), and defluorinative aromatization (**II** to **2**, Scheme 2d).[20] Given the synthetic challenge of electronic deficient 2-naphthols, our approach provides facile access to this unit. In particular, the functional groups (hydroxy and ketone) introduced

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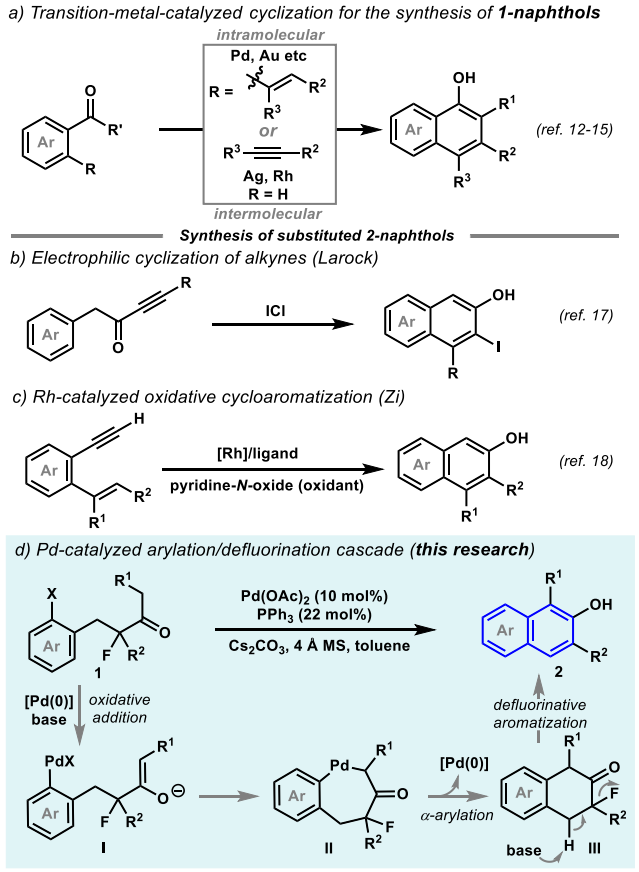
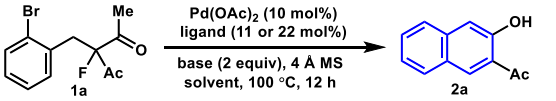
can potentially serve as synthetic handles for downstream transformations to further access their valuable derivatives. Herein we report the detailed studies of this methodology.



Scheme 2. Selected Synthetic Methods of Naphthol Derivatives.

We began our investigation using 3-(2-bromobenzyl)-3-fluoroacetylacetone **1a** as a model substrate to optimize the reaction parameters (Table 1). Treatment of substrate **1a** with catalytic amount of $Pd(OAc)_2$ in the presence of 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) delivered the desired 2-naphthol **2a** in 82% yield (entry 1). However, other examined palladium sources, including $Pd(TFA)_2$, $Pd(MeCN)_2Cl_2$ and $Pd_2(dba)_3$, all led to diminished yields (entries 2–4). The use of other bisphosphine ligands (i.e., Xantphos, dppp, and dppf) resulted in slightly inferior yields (entries 5–7). We were pleased to find that the catalyst derived from $Pd(OAc)_2$ and the readily available PPh_3 provided the product in equally good yields as the reaction using the more expensive BINAP ligand (entry 8). Further screening of other reaction conditions with a variety of bases (K_2CO_3, Na_2CO_3, K_3PO_4, and Et_3N, entries 9–11) and solvents (dioxane, THF, DCE, and DMF, entries 12–15) did not result in improved yields. A dramatically lower yield was obtained with reduced catalyst loading (with 5 mol% catalyst, entry 16). Control experiments revealed that both $Pd(OAc)_2$ and PPh_3 are essential to the reaction (entries 17 and 18). The reaction without the addition of 4 Å MS resulted in only 46% yield (entry 19). Finally, we identified the optimal reaction conditions as: 10 mol% of $Pd(OAc)_2$, 22 mol% of PPh_3, 2 equiv of Cs_2CO_3 in toluene with 4 Å MS as the additive (entry 8).

Table 1. Optimization of the Reaction Conditions.[a]



entry	ligand (%)	base	solvent	yield (%)[b]
1	BINAP (11)	Cs_2CO_3	toluene	82
2[c]	BINAP (11)	Cs_2CO_3	toluene	48
3[d]	BINAP (11)	Cs_2CO_3	toluene	27
4[e]	BINAP (11)	Cs_2CO_3	toluene	30
5	DPPP (11)	Cs_2CO_3	toluene	79
6	Xantphos (11)	Cs_2CO_3	toluene	80
7	dppf (11)	Cs_2CO_3	toluene	80
8	**PPh_3 (22)**	**Cs_2CO_3**	**toluene**	**82**
9	PPh_3 (22)	K_2CO_3	toluene	53
10	PPh_3 (22)	Na_2CO_3	toluene	18
11	PPh_3 (22)	Et_3N	toluene	15
12	PPh_3 (22)	Cs_2CO_3	dioxane	41
13	PPh_3 (22)	Cs_2CO_3	THF	23
14	PPh_3 (22)	Cs_2CO_3	DCE	36
15	PPh_3 (22)	Cs_2CO_3	DMF	trace
16[f]	PPh_3 (11)	Cs_2CO_3	toluene	61
17[g]	PPh_3 (22)	Cs_2CO_3	toluene	n.r.
18	–	Cs_2CO_3	toluene	9
19[h]	PPh_3 (22)	Cs_2CO_3	toluene	46

[a]Reactions conducted on a 0.1 mmol scale.
[b]Isolated yield.
[c]With 10 mol% of $Pd(TFA)_2$.
[d]With 10 mol% of $Pd(MeCN)_2Cl_2$.
[e]With 5 mol% of $Pd_2(dba)_3$.
[f]With 5 mol% of $Pd(OAc)_2$.
[g]Without $Pd(OAc)_2$.
[h]Without 4 Å MS.

Next, the substrate scope was explored. The influence of substituents on the efficacy of the α-arylation/aromatization reaction was first investigated under the optimal reaction conditions. Electron-donating groups, such as methyl (**2b**–**d**), methoxy (**2e** and **2f**), and dimethoxy (**2g**) were well tolerated in good yields. A substrate with a methyl group at the *ortho*-position to bromide resulted in a slightly decreased yield (**2d**, 65% yield). When the benzo[*d*][1,3]dioxole-derived substrate **1h** was employed, only a moderate yield was achieved (**2h** 46% yield). Subsequently, a series of electron-withdrawing substituents, including F, Cl, NO_2 at different positions of the aryl ring, were also studied. The resultant products **2i**–**l** were formed in 74–88% yields. In general, the electronic nature of the substituents on the substrates proved to have less influence on the efficiency of our method. Then we investigated substrates derived from different dicarbonyl compounds. Benzoyl- and propionyl-substituted 2-naphthols (**2m** and **2n**) were synthesized smoothly in 93% and 78% yields, respectively. Notably, a 10 mmol scale reaction with

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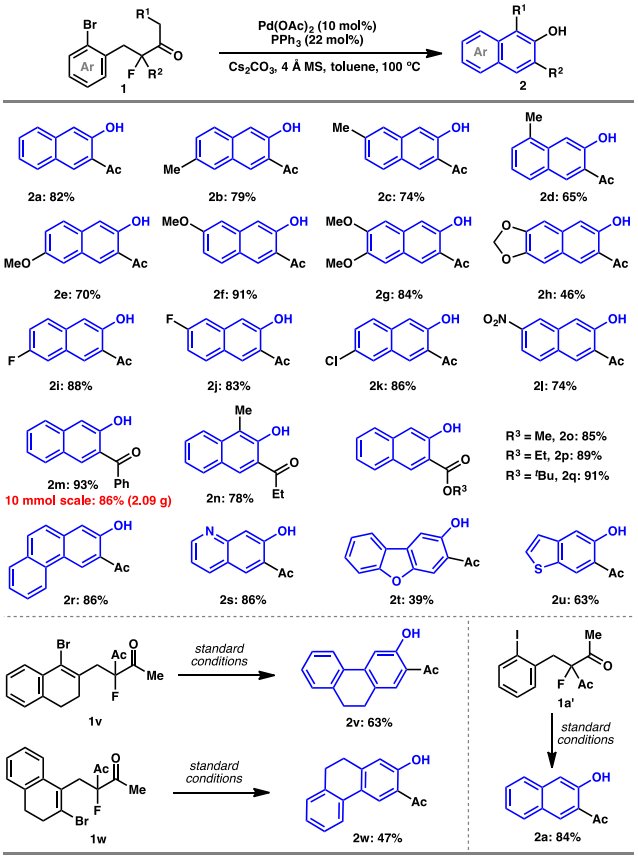
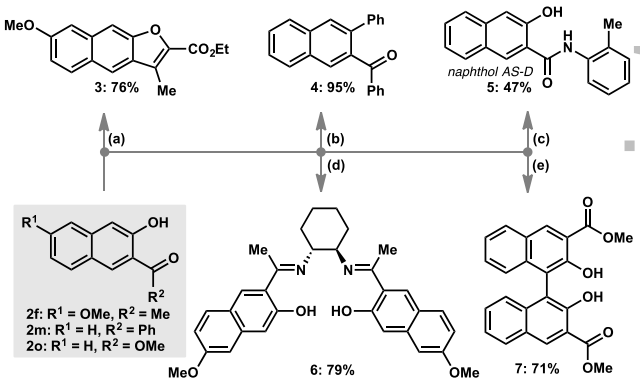
substrate **1m** was also carried out and delivered 2-naphthol **2m** in 86% yield (2.09 g). Gratifyingly, acetoacetate-derived substrates **1o**–**q** were also well tolerated providing ester-containing 2-naphthols **2o**–**q** in 85–91% yields.



Scheme 3. Substrate Scope. Reactions conducted under the conditions of entry 8, Table 1. Percentages represent isolated yields.

Particularly interesting are the heteroaromatic products **2s**, **2t**, and **2u**, featuring a quinoline, a dibenzofuran, and a benzothiophene core, respectively, which are difficult to synthesize by other methods. Finally, it is noteworthy to report that alkenyl bromides were also compatible substrates. The reactions with dihydronaphthalenyl substrates provided 9,10-dihydrophenanthernols **2v** and **2w** in 63% and 47% yields, respectively. The conditions were also capable with the iodobenzyl substrate without loss of the efficiency as demonstrated by the reaction of **1a'**. Although the corresponding α-Cl- and α-Br-analogs of **1a** are readily prepared, the reaction with either of those two substrates (**1x** or **1y**) delivered the desired product **2a** inefficiently in dramatically decreased yields (Scheme S1 in the SI), which highlights the crucial role of the fluorinated substrates to this transformation. Additionally, the synthesis of substrates with R^2 being alkyl and aryl substituents is problematic.[21]

To showcase the utility of the palladium-catalyzed 2-naphthol synthesis, a number of transformations were carried out (Scheme 4). Nucleophilic substitution of 2-bromoacetate with **2f** followed by a tandem intramolecular aldol condensation furnished polysubstituted naphtho[2,3-*b*]furan **3** in 76% yield. Conversion of free naphthol to its triflate and subsequent Suzuki-Miyaura cross-coupling reaction afforded naphthalene **4** in 95% yield over two steps. Naphthol AS-D **5**, a molecule used for histochemical localization of esterases, was synthesized in 47% yield over three steps. Furthermore, the reaction of the ketone group in **2f** with (*R*,*R*)-cyclohexane-1,2-diamine provided chiral salen ligand **6** in 79% yield. Finally, 1,1'-binaphthol **7** was obtained in 71% yield by an iron-catalyzed dehydrogenative coupling reaction of **2o**.



Scheme 4. Product Transformations. Conditions: (a) **2f** (0.1 mmol), $BrCH_2CO_2Et$ (4 equiv), K_2CO_3 (4 equiv), DMF, 120 °C, 6 h; (b) i) **2m** (0.4 mmol), Tf_2O (1.1 equiv), pyridine, rt, overnight; ii) $PhB(OH)_2$ (1.5 equiv), $PdCl_2$ (10 mol%), PPh_3 (20 mol%), Na_2CO_3 (2 equiv), THF:H_2O (1:1), 80 °C, 36 h; (c) i) **2o** (0.9 mmol), KOH (4 equiv, 10 wt%), EtOH, rt, 12 h; ii) DMF (cat), $(COCl)_2$ (1.5 equiv), DCM, 30 °C; then *o*-toluidine (1.5 equiv), Et_3N (3 equiv), DCM, rt, 12 h; (d) (1*R*,2*R*)-cyclohexane-1,2-diamine (0.1 mmol), **2f** (2 equiv), 4 Å MS, MeOH, reflux, overnight; (e) **2o** (0.1 mmol), $FeCl_3$ (10 mol%), TBHP (1.5 equiv), DCE:HFIP (1:1), rt, 12 h.

In summary, we have developed a palladium-catalyzed α-arylation and aromatization strategy for the synthesis of polysubstituted 2-naphthol derivatives. This method employs commercially available palladium salt and PPh_3 ligand along with readily synthesized substrates. A variety of 2-naphthols were accessed in good to excellent yields with good functional group tolerance. We have also demonstrated the utility of the synthesized 2-naphthols as building blocks to access their valuable derivatives. Efforts toward the application of this method in the synthesis of complex bioactive natural products are ongoing in our laboratory.

Experimental Section

General Procedure for the Synthesis of Polysubstituted 2-Naphthols by Palladium-Catalyzed Intramolecular Arylation/Aromatization Cascade

To a 4 mL vial equipped with a magnetic stirring bar were added substrate **1a** (28.6 mg, 0.1 mmol, 1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 10 mol%), PPh_3 (5.9 mg, 0.022 mmol, 22 mol%), Cs_2CO_3 (65.2 mg, 0.2 mmol, 2 equiv), 4 Å MS (100.0 mg) and 1 mL of toluene under an argon atmosphere. After the vial was sealed and stirred at 100 °C for 12 h, the reaction was cooled to room temperature. The mixture was filtered through celite and washed with EA (20 mL). Then the filtration was concentrated under reduced pressure. The desired product **2a** (15.3 mg) was obtained in 82% yield as a yellow solid after purification by silica gel chromatography (PE:EA = 100:1).

Acknowledgements

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[20] Another pathway involving the formation of an α,β-unsaturated carbonyl followed by intramolecular α-arylation is also possible.

[21] Attempts to synthesize a substrate with R^2 = Ph [4-(2-bromophenyl)-3-fluoro-3-phenylbutan-2-one] failed due to the low efficiency of the α-fluorination of 4-(2-bromophenyl)-3-phenylbutan-2-one.

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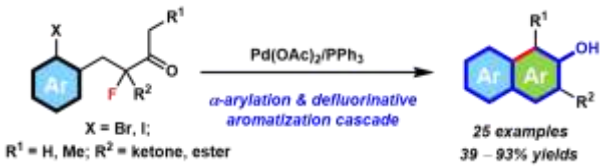

J. Cai, Z.-K. Wang, Y.-H. Zhang, F. Yao, X.-D. Hu, and W.-B. Liu*