Iron-catalyzed annulations of 2-(2-alkynyl)phenoxy)-1-arylethanones leading to substituted naphthalen-1-ols†

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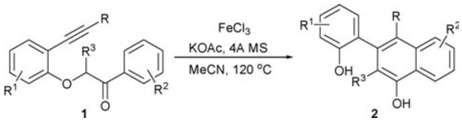
A novel intramolecular annulation of 1-(2-alkynylphenoxy)-propan-2-ones catalyzed by iron, an economical and environmentally-benign transition metal, has been developed; this new atom-economical route includes dual C–H functionalizations to construct the naphthalen-1-ol or anthracen-1-ol skeletons.

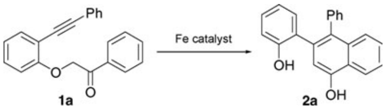
The regio- and chemoselective synthesis of polysubstituted polycyclic aromatic hydrocarbons is of continuing interest because these compounds play important roles in the chemical and pharmaceutical industries.[1–6] There are two common types of transformation: one involves the introduction of substituents onto a pre-existing aromatic ring[1] and the other are transition metal-catalyzed annulation reactions, such as Diels–Alder reactions, the [2 + 2 + 2]-cyclotrimerization of alkynes and the [4 + 2]-benzannulations of enynes.[1–6] However, these methods are restricted to relatively harsh reaction conditions, unaccessible substrates and/or expensive catalysts; moreover, regio- and chemoselectivity are unsatisfactory in many cases. To overcome these drawbacks, herein we report a novel intramolecular annulation of 1-(2-alkynylphenoxy)propan-2-ones catalyzed by iron, an economical and environmentally-benign transition metal,[7] to regioselectively synthesize substituted naphthalen-1-ols in the presence of KOAc (Scheme 1).

The reaction of 2-(2-(2-phenylethynyl)phenoxy)-1-phenylethanone (**1a**) was investigated to optimize the reaction conditions (Table 1).[8,9] We found that base played an important role in the reaction (Table 1, entries 1–6). While the reaction of substrate **1a** with $FeCl_3$ did not occur without base (Table 1, entry 1), two equivalents of KOAc provided the target 3-(2-hydroxyphenyl)-4-phenylnaphthalen-1-ol (**2a**) in a 73% yield (Table 1, entry 2). To our delight, the yield of **2a** was enhanced to 92% by using 4 equivalents of KOAc (Table 1, entry 3). However, other bases, including NaOAc, K_2CO_3 and Et_3N, were less effective (Table 1, entries 4–6). Among the Fe catalysts examined, $FeCl_3$ was superior to the others, such as $FeBr_3$, $Fe_2(SO_4)_3$ and FeF_3 (Table 1, entries 7–9). The results demonstrate that decreasing the amount of $FeCl_3$ reduced the yield, and the target product **2a** was not observed without Fe catalysts (Table 1, entries 10 and 11). Finally, the reaction temperature was investigated, and it was found that a lower temperature disfavored the reaction (Table 1, entry 12).



Scheme 1 Iron-catalyzed annulations of 2-(2-(2-alkynyl)phenoxy)-1-arylethanones.

Table 1 Screening conditions[a]



Entry	Fe catalyst	Base (equiv.)	Isolated yield (%)
1	$FeCl_3$	—	0
2[b]	$FeCl_3$	KOAc (2)	73
3	$FeCl_3$	KOAc (4)	92
4	$FeCl_3$	NaOAc (4)	22
5	$FeCl_3$	K_2CO_3 (4)	Trace
6	$FeCl_3$	Et_3N (4)	7
7	$FeBr_3$	KOAc (4)	9
8	$Fe_2(SO_4)_3$	KOAc (4)	8
9	FeF_3	KOAc (4)	12
10[c]	$FeCl_3$	KOAc (4)	35
11	—	KOAc (4)	0
12[d]	$FeCl_3$	KOAc (4)	47

[a] Reaction conditions: **1a** (0.2 mmol), Fe catalyst (20 mol%), base, anhydrous 4 Å molecular sieve (100 mg) and MeCN (2 mL) at 120 °C for 24 h. [b] For 60 h. [c] $FeCl_3$ (10 mol%). [d] At 80 °C.

As shown in Table 2, the scope was explored under the standardised conditions. Initially, a set of substituents at the terminal alkyne moiety were evaluated in the presence of $FeCl_3$ and KOAc (Table 2, entries 1–10). The results indicated that substituted aryl groups were perfectly tolerated (Table 2, entries 1–7). The treatment of methyl-substituted substrates **1b** or **1c**, for instance, with $FeCl_3$ and KOAc afforded the corresponding products in good yields (Table 2, entries 1 and 2). Meanwhile, a moderate yield was achieved from the reaction of substrate **1d**, having a 4-F–C_6H_4 group, with 20 mol% $FeCl_3$ (Table 2, entry 3); 80 mol% or 100 mol% $FeCl_3$ enhanced the yield to over 70% (Table 2, entries 4 and 5). We found that both 4-CF_3–C_6H_4-substituted substrate **1e** and thiophen-2-ylalkyne **1f** required a greater loading of $FeCl_3$ in order to give satisfactory yields (Table 2, entries 6 and 7). Gratifyingly, the standard conditions were compatible with alkynes having alkyl groups: **1g** and **1h** (Table 2, entries 8 and 9). It was discovered that the annulation of trimethylsilyl-substituted alkyne **1i** afforded the de-trimethylsilylated

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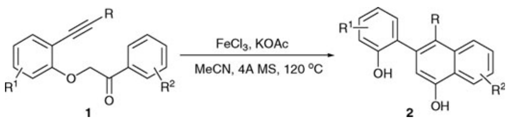
† Electronic supplementary information (ESI) available: Experimental procedures, analytical data and spectra. See DOI: 10.1039/b911669a

Table 2 FeCl$_3$-catalyzed annulations[a]



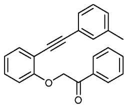
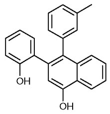
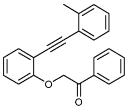
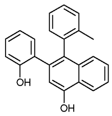
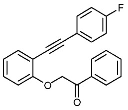
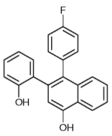
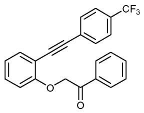
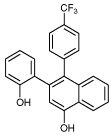
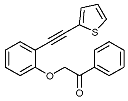
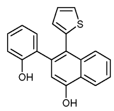
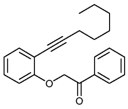
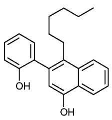
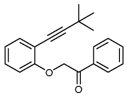
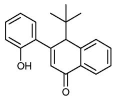
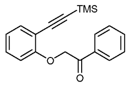
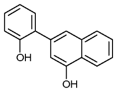
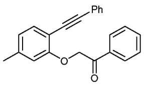
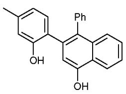
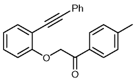
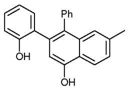
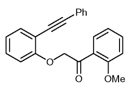
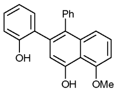
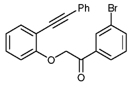
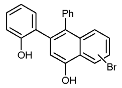
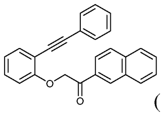
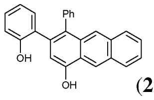
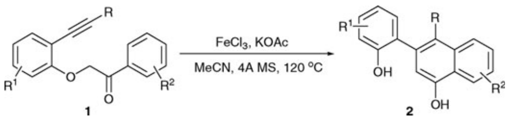
Entry	Substrate **1**	Product **2**	Time/h	Yield (%)[b]
1	 **(1b)**	 **(2b)**	26	77
2	 **(1c)**	 **(2c)**	24	89
3	 **(1d)**	 **(2d)**	48	47
4[c]	**(1d)**	**(2d)**	24	75
5[d]	**(1d)**	**(2d)**	24	72
6[c]	 **(1e)**	 **(2e)**	24	75
7[c]	 **(1f)**	 **(2f)**	44	54
8	 **(1g)**	 **(2g)**	48	58
9	 **(1h)**	 **(2h)**	48	40
10[c]	 **(1i)**	 **(2i)**	24	56
11	 **(1j)**	 **(2j)**	24	27
12[c]	**(1j)**	**(2j)**	22	46
13	 **(1k)**	 **(2k)**	24	84
14[c]	 **(1l)**	 **(2l)**	24	55
15[c,e]	 **(1m)**	 **(2m)**	24	56
16[c,f]	 **(1n)**	 **(2n)**	48	45

Table 2 (*continued*)



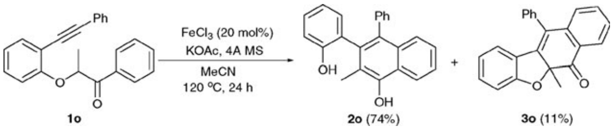
[a] Reaction conditions: **1** (0.2 mmol), FeCl$_3$ (20 mol%), KOAc (4 equiv.), 4 Å molecular sieve (100 mg) and MeCN (2 mL) at 120 °C. [b] Isolated yield. [c] FeCl$_3$ (80 mol%) was added. [d] FeCl$_3$ (100 mol%) was added. [e] 7-Br : 5-Br = 1.2 : 1. [f] Anthracen-1-ol : phenanthren-1-ol = 6.1 : 1.

product **2i** in 56% yield with 80 mol% FeCl$_3$ (Table 2, entry 10). A substituent at the phenoxy moiety was subsequently examined (Table 2, entries 11 and 12). The treatment of substrate **1j**, having a methyl group, with 20 mol% FeCl$_3$ gave product **2j** in 27% yield, and with 80 mol% FeCl$_3$, in 46% yield. It is pleasing to disclose that substrates **1k–1m**, bearing substituents on the aromatic ring of the arylethanone moiety, were annulated successfully in moderate to good yields (Table 2, entries 13–15). 1-(Naphthalen-2-yl)ethanone **1n** also smoothly underwent an annulation reaction with FeCl$_3$ and KOAc to afford anthracen-1-ol **2n** in 45% yield (Table 2, entry 16).

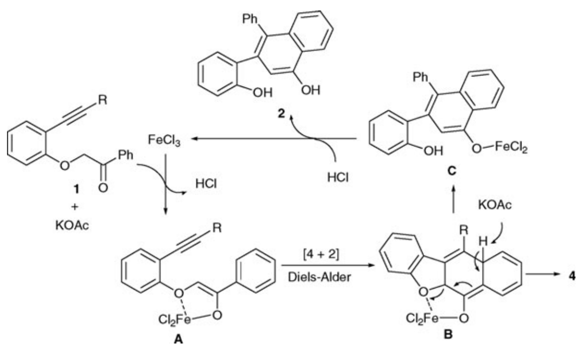
Substrates **1o** was also investigated under the standard conditions (Scheme 2). Interestingly, treatment of 2-(2-(2-phenylethynyl)phenoxy)-1-phenylpropan-1-one (**1o**) with FeCl$_3$ and KOAc afforded the target product **2o** in 74% yield along with a side-product **3o** in 11% yield.

A possible mechanism involving a Diels–Alder process was proposed as outlined in Scheme 3.[6,7] Complexation of a FeCl$_3$ with an arylethanone moiety yields intermediate **A** with the aid of KOAc. Intermediate **A** undergoes the [4 + 2] Diels–Alder reaction to afford intermediate **B**. Sequent deprotonation/C–O bond decomposation of intermediate **B** gives the product **2** and regenerates the active FeCl$_3$ species. Study of the true mechanism is in progress.

In summary, we have described the first example of intramolecular annulation of an alkyne with a sp^3 carbon nucleophile for the synthesis of substituted naphthalen-1-ols and anthracen-1-ol using economical and environmentally-benign



Scheme 2 Annulation of 2-(2-(2-phenylethynyl)phenoxy)-1-phenylpropan-1-one (**1o**).



Scheme 3 A possible mechanism.

iron catalyst. This new atom-economical route includes dual C–H functionalizations to construct the naphthalen-1-ol or anthracen-1-ol skelectons. Importantly, the present Fe-catalyzed method provides a potential route to designing the achiral/chiral hydroxy-containing ligands. Work to extend the reaction and study the detailed mechanism is currently underway in our laboratory.

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8 Both toluene and DMF were evaluated for the reaction of 2-(2-(2-phenylethynyl)phenoxy)-1-phenylethanone (**1a**). However, a trace amount of **2a** was observed.

9 To rule out the effect of Cu$_2$O, the reaction of **1a** was conducted in the presence of Cu$_2$O (1 mol% Cu$_2$O: 15% yield of **2a**, and 20 mol% Cu$_2$O: 20% yield of **2a**). See: S. L. Buchwald and C. Bolm, *Angew. Chem., Int. Ed.*, 2009, **48**, 5586.