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# An intramolecular, Pd-mediated α-arylation route to 4-aryl-2-naphthols

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ABSTRACT

1-Aryl-1-(2-bromophenyl)but-2-yn-1-ols, obtained from the addition of prop-1-yn-1-yllithium to 2-bromobenzophenones, readily rearrange to 4-aryl-4-(2-bromophenyl)but-3-en-2-ones upon treatment with TFA. Subsequent intramolecular Pd-mediated α-arylation of these but-3-en-2-ones gave 4-aryl-2-naphthols which were smoothly transformed into photochromic naphthopyrans.



Substituted 2-naphthols are extremely valuable substrates for the preparation of biologically active molecules and pharmaceuticals,[1] BINOL ligands,[2] azo-dyes and pigment lakes,[3,4] photochromic naphthopyrans,[5] electroluminescent materials,[6] organometallic macrocycles[7] and molecular machines.[8] Given the versatility of these compounds it is somewhat surprising that versatile strategies to prepare 3- and or 4- substituted 2-naphthols are relatively few in number.[9] Recent approaches to give 3,4-disubstituted 2-naphthols include an effective, base free, 6-*endo*-*dig* electrophilic cyclisation of 1-phenyl-3-alkyn-2-ones to afford 3-iodo-4-phenyl-2-naphthol (Scheme 1a).[10] Base-free reaction conditions were also used in the $Pd(CF_3CO_2)_2$(dppe) mediated annulation of methyl *o*-(BPin)phenyl acetates to 1,2-bis(4-methoxyphenyl)ethyne resulting in 3,4-di(4-methoxyphenyl)-2-naphthol (Scheme 1b).[11] 4-Aryl-2-naphthols, devoid of additional substituents, have recently been reported by strategies employing C–C bond insertion of benzyne into aroylacetones with subsequent intramolecular aldol condensation and dehydration, typically affording isomeric mixtures of 3-aryl-1-naphthols and 4-aryl-2-naphthols (Scheme 1c).[2a,12] Moreover a $Pd(OAc)_2$-catalysed *meta*-selective direct arylation protocol has been employed to synthesise 2-carbamoyloxy-4-arylnaphthalenes.[13] 2-Methoxy-4-trifloxynaphthalene, derived from relatively expensive 1,3-dihydroxynaphthalene, has been subjected to Suzuki couplings with a range of arylboronic acids to give 4-aryl-2-naphthols in good yields after demethylation (Scheme 1d).[14] 4-Phenyl-2-naphthol has been obtained by the Friedel–Crafts acylation of phenylacetylene with phenylacetyl chloride[15] and by the gold-catalysed carbocyclization of 2-(prop-2-yn-1-yl)benzophenone.[16] Given the general lack of a relatively inexpensive and simple regiospecific approach to preparing such naphthols from either commercial or readily available starting materials, combined with our interest in photochromic naphthopyrans[17] which are derived from the acid-catalysed condensation between 1,1-diarylprop-2-yn-1-ols and substituted 2-naphthols,[18] we were interested in exploring new 2-naphthol constructs. On this theme, the Pd-mediated ring closure employed to obtain the key tricycle (Scheme 1e), in an alternative synthesis of duocarmycins involving the coupling between a silyl enol ether and a triflate, attracted our attention.[19]

Considering the above reaction leading to an *O*-protected 'heterocyclic naphthol' to be the forerunner of an α-arylation protocol[20] it was postulated that suitably functionalized 4,4-diarylbut-3-en-2-ones could be subjected to an intramolecular α-arylation reaction to afford 4-arylnaphthalen-2(1*H*)-ones which would readily tautomerise to the required 2-naphthols.

Thus, addition of prop-1-yn-1-yllithium, efficiently generated from the reaction of excess LDA to 1,2-dibromopropane,[21] to readily available 2-bromobenzophenones[22] **1a**,**b** gave butynols **2a**,**b** in excellent yield (Scheme 2). Subsequent Meyer–Schuster rearrangement[23] of **2a**,**b** to afford 4-aryl-4-(2-bromophenyl)but-3-en-2-ones **3a**,**b** was accomplished in high yield using TFA in toluene at room

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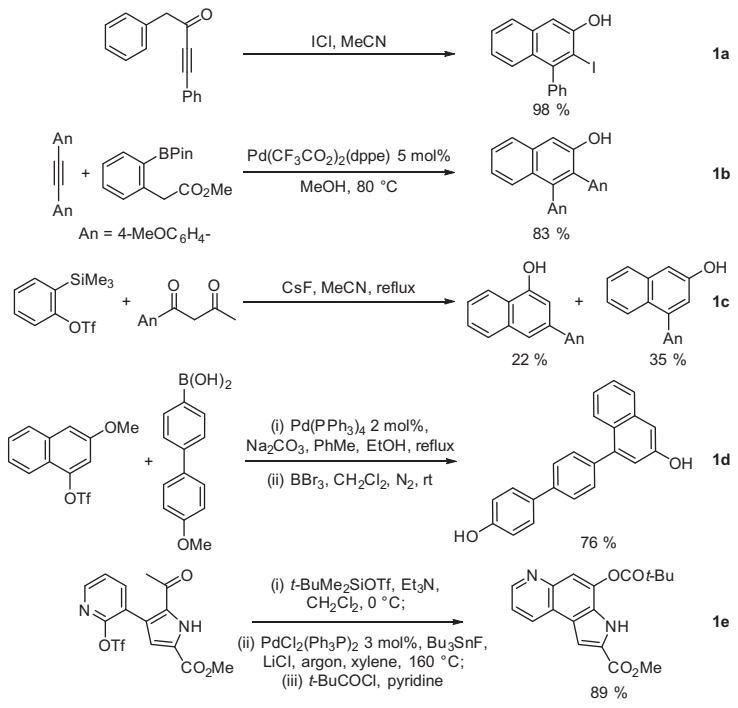
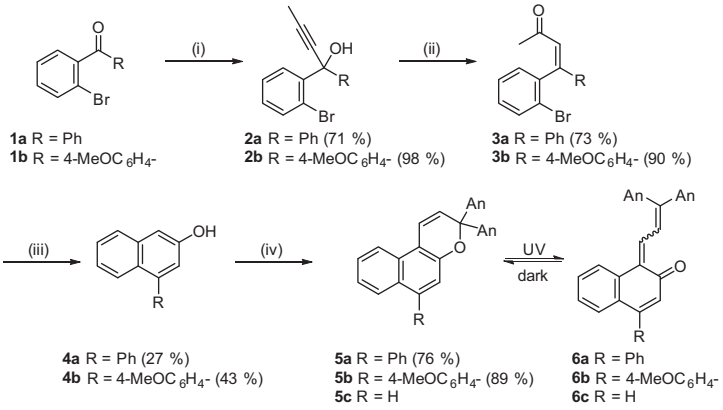



**Scheme 1.**




**Scheme 2.** Reagents and conditions: (i) *n*-BuLi, diisopropylamine, anhyd. THF, $N_2$, −70 °C to rt then 1,2-dibromopropane, −60 °C to rt; (ii) $CF_3CO_2H$, PhMe, rt; (iii) $Pd_2(dba)_3$ (5 mol %), (*t*-Bu)$_3$PHBF$_4$, KO*t*-Bu, anhyd PhMe; (iv) 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol, $(MeO)_3CH$, PPTS, 1,2-DCE, reflux.

temperature. The geometry of **3b** was established as the *Z*-isomer through NOE interactions between the alkene proton which resonated at $\delta$ 6.73 and the protons *meta*- to the methoxy group in the anisole ring which appeared at $\delta$ 7.28. No other NOE interactions were observed between the alkene proton and any other aromatic protons (see ESI). It is of interest to note that **3b** has been previously obtained in two steps, in 20% overall yield, through the addition of isopropenylmagnesium bromide to **1b** followed by a Pd-catalysed oxidative rearrangement of the 1,1-diaryl-2-methylprop-2-en-1-ol.[24] The present two step transformation of **1b** into **3b** was accomplished more efficiently (88% over two steps).

Widely used conditions ($Pd_2(dba)_3$, (*t*-Bu)$_3$PHBF$_4$, KO*t*-Bu, PhMe, reflux) for routine intermolecular $\alpha$-arylation chemistry[20] were adopted for a preliminary investigation into the ring closure of **3a**,**b** to the naphthols **4a**,**b**. The $\alpha$-arylation step currently represents the weak link in this three step transformation offering only poor to moderate yields (**4a** 27%; **4b** 43%) and there remains much scope to explore the impact of various ligands, catalysts and base combinations on the yield of this useful transformation. Evidence for the formation of the desired naphthols was accrued from NMR spectroscopy which exhibited key signals for the protons of the hydroxyl-substituted naphthalene ring, for example, **4a** $\delta$ 5.4 (1H, s, OH ($D_2O$ exchangeable), $\delta$ 7.04 (1H, d, $J$ = 2.0 Hz, 3-H), $\delta$ 7.14 (1H, d, $J$ = 2.0 Hz, 1-H) and mass spectrometry which gave good agreement between the found and required molecular ions (see ESI). The usefulness of compounds such as **4** was demonstrated by their facile transformation into novel naphthopyrans **5a**,**b** in excellent yields using pyridinium *p*-toluenesulfonate (PPTS) in conjunction with an alkynol and $(MeO)_3CH$ as a dehydrating agent.[25] The naphthopyrans exhibited characteristic signals for 2-H in their NMR spectra at $\delta$ 6.2 ($J$ = 10 Hz) and at $\delta$ 82.2 for 3-C; both of which were indicative of the pyran unit.[26] UV irradiation (365 nm, 8 W) of toluene solutions (ca. $1 \times 10^{-6}$ mol dm$^{-3}$) of **5a**,**b** together with the established naphthopyran **5c** for comparative purposes resulted in the generation of orange–red coloured photomerocyanines **6a**–**c** with

absorption maxima at ca. 470 nm (see ESI) in accord with their substitution pattern.[26]

In summary, we have developed a short route to 4-aryl-2-naphthols which relies upon the efficient generation and Meyer–Schuster rearrangement of a 1,1-diarylbutynol. The C-**1**–C-**8a** bond of the naphthol was generated by an intramolecular α-arylation reaction which we believe constitutes a new approach to the 2-naphthol moiety. Optimisation of the key Pd-mediated naphthol ring-forming step and examination of other aryl and heteroaryl substituents are ongoing.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.081.

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