Supporting Information

Copper-catalyzed Tandem Annulation/Enol Nucleophilic Addition to Access Multisubstituted Indoles

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1. General Remarks

All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been oven dried prior to use unless noted otherwise. Anhydrous solutions were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates and visualized with UV light at 254 nm. Flash column chromatography was performed with silica gel (40-60 μm). $^1$H and $^{13}$C nuclear magnetic resonance spectra (NMR) were obtained on a Bruker Avance II 400 MHz or Bruker Avance III 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in CDCl$_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet(t), quartet (q), quintet (quint), or multiplet (m), with coupling constants ($J$) in hertz (Hz). High resolution mass spectra (HRMS) were performed by an Agilent apparatus (TOF mass analyzer type) on an Electron Spray Injection (ESI) mass spectrometer. Melting points were determined by an XP-4 melting point apparatus.

2. General procedure for the preparation of substrates 1:

Following a slight modification of the literature procedure.$^{S1-S6}$

To a stirred solution of 2-aminobenzonitrile S1 (1 equiv, 4 mmol) in anhydrous THF (4 mL) was added $R^2$MgBr (2 equiv, 8 mmol) at 0 °C over 10 min. The reaction mixture was allowed to warm to room temperature and stir at this temperature
overnight. When the reaction was completed as determined by TLC, the mixture was quenched with 1 M HCl and then extracted with EtOAc. The organic phase was washed by brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the residue by column chromatography gave the corresponding S₂.

To a stirred solution of S₂ (1 equiv, 2 mmol) in anhydrous THF (20 mL) was added ethynylmagnesium bromide (20 mL, 0.5 M in THF, 5 equiv, 10 mmol) at 0 °C over 10 min. The reaction mixture was allowed to warm to room temperature and stir at this temperature overnight. When the reaction was completed as determined by TLC, the mixture was quenched with saturated aqueous NH₄Cl and then extracted with EtOAc. The organic phase was washed by brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the residue by column chromatography gave the corresponding S₃.

To a solution of S₃ (1 equiv, 1 mmol) was added tosyl chloride (1.05 equiv) in pyridine (0.8 M) and the resulting solution was stirred at 105 °C for 30 min under argon. The reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with 3 M HCl and brine, dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was purified with flash column chromatography to give the 1.

To a stirred solution of S₃ (1 equiv, 1 mmol) in anhydrous THF (10 mL) was added Boc anhydride (1.05 equiv, 1.05 mmol) at room temperature. The reaction mixture was stirred overnight under reflux. When the reaction was complete as determined by TLC, the volatile solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate = 85:15) to give the corresponding Boc-aniline product 1h (90% yield) as a white solid.

All substrates 1a-1l were prepared by the similar procedure.

### 3. Unsuccessful substrates for the copper-catalyzed tandem reactions

For the following substrates used in the copper-catalyzed tandem reactions, the reaction was very sluggish with the internal alkynes substrates. For the secondary propargylic alcohols, unknown products were afforded instead of the desired multisubstituted indoles.
4. Reference:


5. NMR Spectra
Ts 3a
31

[Chemical structure diagram]
3m