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# Solvent switchable cycloaddition: a (one-pot) metal-free approach towards *N*-substituted benzo[e]- *or* [*f*]isoindolones *via* $C_{sp^2}$–H functionalization†

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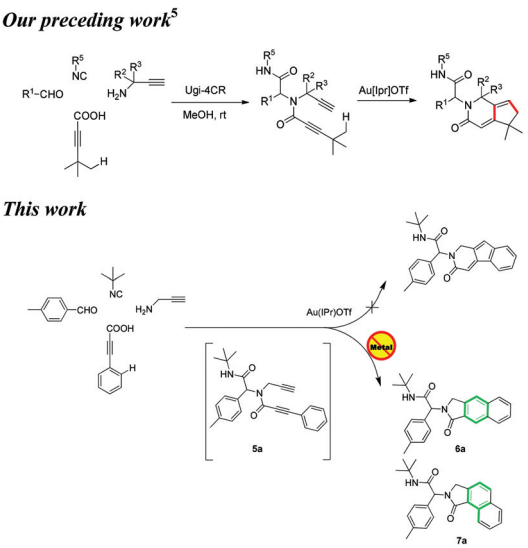
The tuning of selective ring closure is a nontrivial challenge in synthetic organic chemistry. Herein we report a solvent switchable metal-free [4 + 2] cycloaddition approach *via* $C_{sp^2}$–H functionalization. The protocol is highly atom economical with water being the only by-product, delivering *N*-substituted benzo[*e*]- or [*f*]isoindolones in high yields.

The elaboration of methodologies to selectively access heterocycles, while guaranteeing molecular diversity and eco-compatibility, represents a great challenge to organic chemists. In this regard, multi-component reactions (MCR) inherently bequeath molecular diversity and complexity in a single step.[1] Moreover, post-MCR transformations could provide powerful ways to generate libraries of unprecedented molecular skeletons.[2,3] Employing this strategy, merged with gold-catalyzed dual σ–π activation,[4] we recently reported a post-Ugi gold-catalyzed regioselective tandem cyclization *via* $C_{sp^3}$–H functionalization (Scheme 1).[5]

Stimulated by these findings and our recent endeavours regarding post-Ugi transformations,[6] we aimed to extend this methodology to the $C_{sp^2}$–H functionalization employing cascade cyclizations[4c] of *N*-propynyl phenylpropiolamides to access indenopyridinones (Scheme 1). These compounds are known to possess antihistaminic and antidepressant activity.[7]

According to the literature, cationic gold,[4c,5] palladium,[8–10] zinc,[11] copper,[12] and iron[13] have been used alongside phosphorous containing ligands,[9] Lewis acids and excess of pheno-




**Scheme 1** Different cyclization of *N*-propynyl propiolamides.

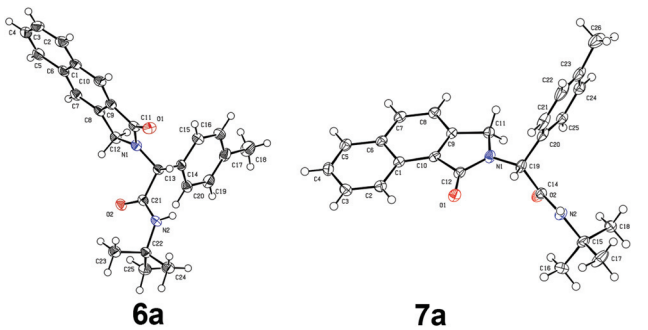



**Fig. 1** Crystal structure of compound **6a** and **7a**. Thermal ellipsoids set at 50% probability.[17] Only one molecule is shown for **6a**.

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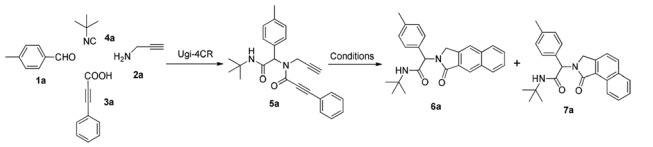
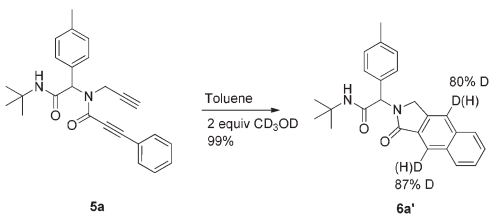
**Table 1** Optimization of the metal-free intramolecular [4 + 2] cycloaddition[a]




| Entry | Solvent | Temp (°C) | Time (h) | Yield[b] (%) | Ratio (**6a** : **7a**)[b] |
|---|---|---|---|---|---|
| 1 | Toluene | 120 | 16 h | 71 | 54 : 46 |
| 2 | Toluene | 140 | 15 h | 76 | 31 : 69 |
| 3 | Xylene | 140 | 15 h | 73 | 49 : 51 |
| 4 | DCE | 140 | 15 h | 78 | 47 : 53 |
| 5 | **Toluene** | **150** | **15 h** | **95** | **19 : 81** |
| 6 | Toluene–MeOH (1 : 1) | 140 | 15 h | 99 | 99 : 01 |
| 7 | iPrOH | 140 | 15 h | 99 | 97 : 03 |
| 8 | *n*-BuOH | 140 | 15 h | 97[c] | >99 : 01 |
| 9 | 2,2,2-Trifluoroethanol | 140 | 15 h | 95 | >99 : 01 |
| 10 | *n*-BuOH | 140 | 8 h | 98[c] | >99 : 01 |
| 11 | *n*-BuOH | 140 | 3 h | 98[c] | >99 : 01 |
| **12** | ***n*-BuOH**[d] | **50/140** | **8 h/3 h** | **97**[c] | **>99 : 01** |

[a] Unless otherwise stated, all reactions were performed using 0.1 mmol of **5a** in the indicated solvent (1 mL), under $N_2$ atmosphere and conventional heating. [b] The combined yield and ratio of **6a** and **7a** was estimated on the basis of $^1$H NMR analysis using 2,4,6-trimethoxy benzaldehyde as an internal standard (0.1 mmol). [c] Isolated yields. [d] A one-pot sequence was applied using *n*-BuOH as common solvent; for the Ugi-4CR 8 h at 50 °C; followed by 3 h at 140 °C.



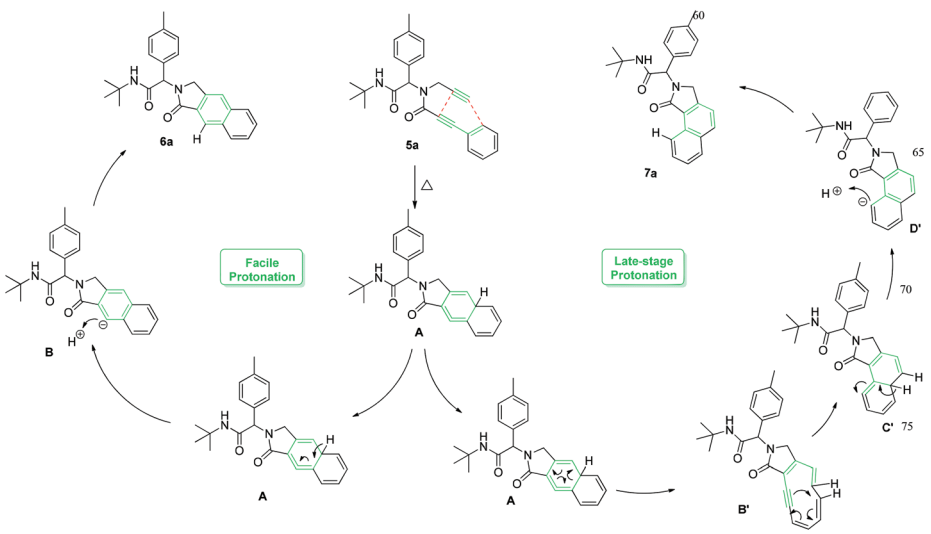

**Scheme 2** Deuterium labelling experiment with compound **5a**.

lic additives,[13–15] to catalyze similar intramolecular cyclizations. The access to the precursors for such cyclizations is often rather tedious.[13,15,16]

To investigate the workability of the concept, *N*-propynyl phenylpropiolamide (**5a**), synthesized *via* Ugi four-component reaction (U-4CR)[17] of *p*-tolualdehyde (**1a**) with propargyl amine (**2a**), 3-phenylpropiolic acid (**3a**) and *tert*-butyl isonitrile (**4a**) in methanol, was subjected to our established reaction conditions using 5 mol% of *in situ* generated IPrAuOTf.[5] To our surprise, we did not observe, by NMR spectroscopy, the desired product. Instead, as revealed by MS-analysis, we observed two other products with similar molecular weight as the starting material. Finally, $^1$H NMR and X-ray crystallographic analysis[18] proved that 38% of the benzo[*f*]isoindolone **6a** was furnished,[4c] next to 36% of the benzo[*e*]isoindolone **7a** (Scheme 1 and Fig. 1). Interestingly, this benzo[*f*]isoindolones are known to act as potent human 17,20-lyase inhibitors for the treatment of castration-resistant prostate cancer (CRPC).[8] Further, a control experiment ruled out the necessity of the metal-catalyst (Table 1, entry 1).

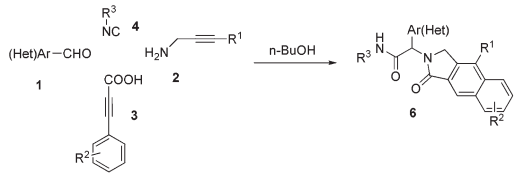
To get some mechanistic insight, a deuterium labelling experiment was performed with compound **5a** (Scheme 2). Use of 2 equiv. of $CD_3OD$ in the reaction resulted in ~87% of deuterium incorporation in the product **6a′**. However, incorporation of deuterium was also observed on the terminal carbon from the propargyl amine part, probably due to facile deprotonation of the terminal acetylene. Based on these observations and previous mechanistical studies,[15] a plausible mechanism with two distinct possibilities is depicted in Scheme 3.

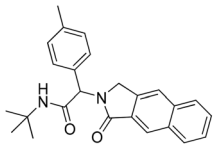
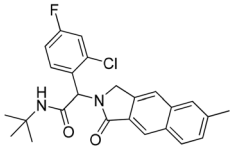
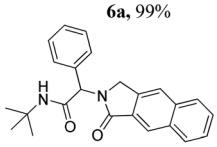
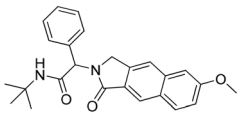
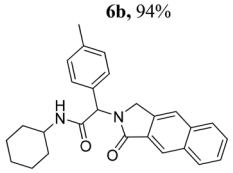
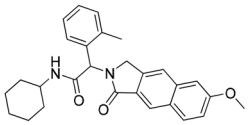
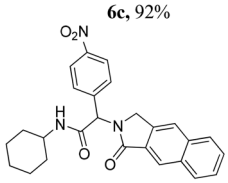
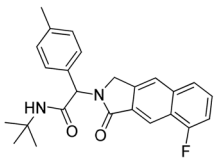
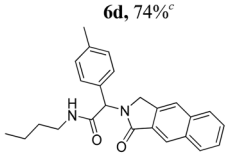
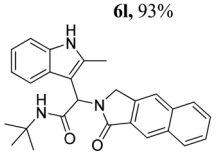
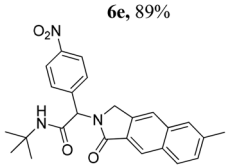
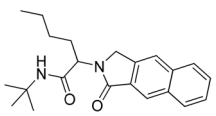
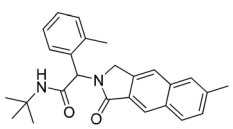
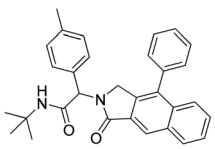
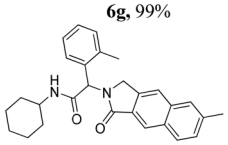
The cyclohexatriene **A**, formed by initial [4 + 2] cyclization, can undergo either isomerization followed by protonation to deliver benzo[*f*]isoindolone **6a**, or a six-electron electrocyclic ring-opening process to afford 1,2-dehydro-[10]annulene **B′**. [1,6]-Electrocyclization of **B′** then leads to cyclic allene **C′**, which upon aromatization, results in the formation of the rearranged benzo[*e*]isoindolone **7a**.




**Scheme 3** Plausible mechanism for the metal-free post-Ugi cyclization.

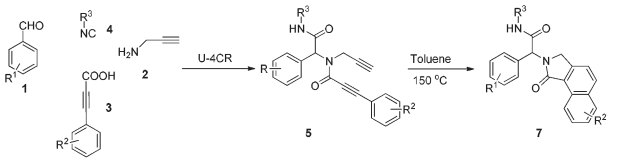
**Table 2** Scope of the protocol for the formation of benzo[*e*]isoindolones **6**[a,b]

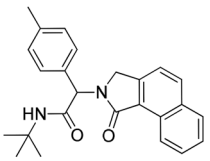
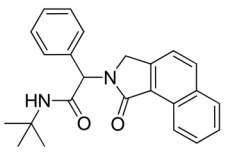
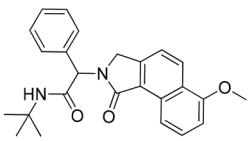
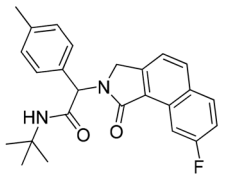
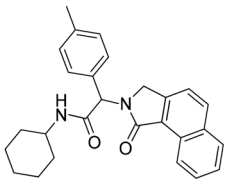
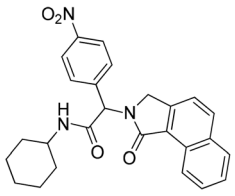



| One-pot cycloadduct | One-pot cycloadduct |
|---|---|
|  **6a,** 99% |  **6i,** 93% |
|  **6b,** 94% |  **6j,** 94% |
|  **6c,** 92% |  **6k,** 91% |
|  **6d,** 74%[c] |  **6l,** 93% |
|  **6e,** 89% |  **6m,** 84% |
|  **6f,** 77%[c] |  **6n,** 37% |
|  **6g,** 99% |  **6o,** 0% |
|  **6h,** 99% | |

[a] Unless otherwise stated, all reactions were performed using aldehyde **1** (0.1 mmol), amine **2** (1.05 equiv.), acid **3** (1.05 equiv.) and isonitrile **4** (1.05 equiv.) in *n*-butanol (2 mL) at 50 °C for 8–12 h followed by heating at 140 °C for 3–8 h. [b] Yields are isolated yields. [c] Isolated after chromatographic purification.

**Table 3** Scope of the protocol for the formation of rearranged benzo[*f*]isoindolones **7**[a,b]




| Product 7 | Product 7 |
|---|---|
|  **7a**, 67% |  **7b**, 77% |
|  **7c**, 58% |  **7d**, 78% |
|  **7e**, 57% |  **7f**, 52% |

[a] For U-4CR: all reactions were performed using aldehyde **1** (0.1 mmol), amine **2** (1.05 equiv.), acid **3** (1.05 equiv.) and isonitrile **4** (1.05 equiv.) in *n*-butanol (2 mL) at 50 °C for 8–12 h. [b] For cycloaddition: reactions were run using **5** (0.25 mmol) in dry toluene (2 mL) under $N_2$ atmosphere at 150 °C for 8–15 h.

Motivated by these findings, we further investigated the conditions to optimize the selective ring closure. Among different solvents screened, toluene was found to be the best, when used at elevated temperature, for the formation of benzo[*e*]isoindolone **7a** (Table 1, entries 2–5). The use of a polar protic solvent solely, or as co-solvent with toluene, dramatically shifts the pendulum towards the formation of benzo[*f*]isoindolone **6a** (Table 1, entries 6–11). To our great satisfaction, an attempt to carry out the sequence in a tandem fashion resulted in an almost quantitative yield with complete selectivity for **6a** (Table 1, entry 12). Besides the atom economy and the catalyst free process, the application of *n*-BuOH also contributes to the green aspect of this protocol.[19,20]

Having optimized the regioselective cycloadditions (Table 1, entries 5 and 12), we first explored the substrate scope for the one-pot synthesis of benzo[*f*]isoindolones **6**. In most cases, compounds **6** were obtained in excellent yields (84–99%), without the need of further chromatographic purification

(Table 2). Ugi-product resulting from various aromatic aldehydes, isonitriles and acids were well tolerated.

Notably, 2-methylindole-3-carbaldehyde afforded the indolyl-benzo[*f*]isoindolone **6m** in high yield. However, a significant loss of the yield was observed when aliphatic valeraldehyde was used (**6n**, Table 2). The use of phenyl propargylamine failed to give the desired product (**6o**, Table 2).

Next, we turned our attention to generate a small library of rearranged benzo[*e*]isoindolones **7**, employing our optimized conditions (Table 1, entry 5). The reaction proved to be versatile with respect to aldehyde, acid and isonitrile used in the Ugi-reaction, giving the desired compounds **7** in 52–78% yield (Table 3). The presence of an electron withdrawing group on the acid improves the yield of desired product, while the use of an electron deficient aldehyde and electron rich acid lowered the yields (Table 3, **7c, d and f**). Importantly, employment of Ugi-product **5d**, derived from an *o*-substituted acid, under optimized condition for the formation of rearranged product **7** (Table 1, entry 5), resulted in only one isomer of benzo[*e*]isoindolone **7d** (Table 3, **7d**). The structures of compounds **7** are well characterized by NMR spectroscopy and compounds **7b** and **7d** were also unambiguously assigned by X-ray crystallography (Table 3, entries 3 and 4).[18]

## Conclusions

We have developed a (one-pot) facile metal-free and atom economical protocol for the synthesis of diversely substituted benzo[*e*]isoindolones **6** and benzo[*f*]isoindolones **7** from readily available starting materials. This one of the rare examples where the selectivity of the ring-closure could be controlled by a simple switch of the solvent.

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