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Copper-catalysed benzofuran synthesis: developing aryl bromide–alkenyl triflates as general heterocycle precursors

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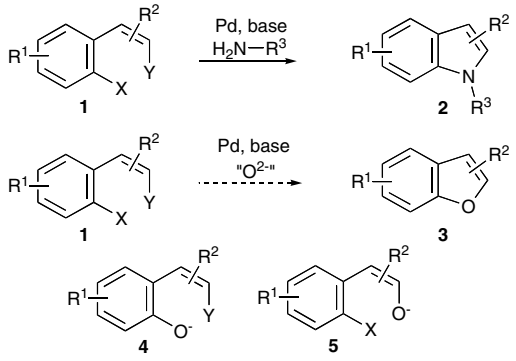
Abstract—A range of conjugated aryl bromide–alkenyl triflates, previously described as indole precursors, are efficiently converted to the corresponding benzofurans when treated with CuI/TMEDA and potassium hydroxide.

The importance of heterocyclic compounds cannot be overstated; around one half of all known organic compounds contain a heterocyclic ring.[1] These compounds, be they natural products or designed molecules, are responsible for an amazing variety of biological processes and they feature in the majority of pharmaceuticals. They are also used as agrochemicals, colourants and as new materials. The synthesis of heterocyclic compounds has a long and extensive history in which many classic syntheses have been developed; however, significant challenges still remain, with certain compound classes remaining difficult to prepare.[1] Modern discovery chemistry also places new demands on synthetic routes, requiring rapid access to related structures through simple late-stage modifications.

An attractive approach to address this latter issue would be to develop a single class of precursor that could be used to access several different heterocycle types. For example, could a single precursor be utilised to access indoles, benzofurans and benzothiophenes? We recently introduced a new series of indole precursors; when treated with an N-nucleophile under palladium catalysis, aryl–alkenyl-dihalides (**1**, X and Y = halogen),[2] or the corresponding halo-triflates (**1**, X = halogen, Y = OTf),[3] undergo sequential inter- and intramolecular amination reactions to deliver indole products in good yields (**1**→**2**, Scheme 1). In this Letter, we present a strategy that starts to address the idea of a common heterocycle precursor, and demonstrates the efficient Cu-catalysed conversion of the same family of acyclic difunctionalised precursors into benzofurans (**1**→**3**).



Scheme 1.

In order to convert precursors such as **1** into the corresponding benzofurans we required a suitable oxygen-based nucleophile. Although a number of water equivalents have been employed in Pd-catalysed arylation reactions,[4] we were particularly attracted to the recent report from Buchwald documenting the use of KOH as a coupling partner for aryl halides under catalytic palladium conditions.[5,6] We reasoned that the

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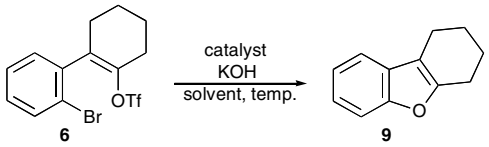
Table 1. Identification of conditions for the conversion **6**→**9**[a]



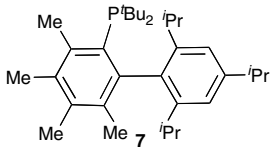
6 **9**

Entry	Catalyst/additive	Solvent[b]	Temp (°C)	Time (h)	Yield (%)
1	$Pd_2(dba)_3$/**7**	Dioxane/H_2O	100	24	0[c]
2	—	Dioxane/H_2O	100	20	0[c]
3	CuI/TMEDA (3.5 equiv.)	H_2O	120	16	36[d]
4	CuI/TMEDA (3.5 equiv)	H_2O	120	16	13[e]
5	CuI/TMEDA (3.5 equiv)	H_2O	120	16	81
6	*CuI/TMEDA (3.5 equiv)*	*Dioxane/H_2O*	*120*	*16*	*99*
7	CuI/TMEDA (0.17 equiv)	Dioxane/H_2O	120	16	47
8	CuI/TMEDA (1.0 equiv)	Dioxane/H_2O	120	16	79
9	CuI/TMEDA (3.5 equiv)	Dioxane/H_2O	65	16	56
10	CuI/TMEDA (3.5 equiv)	Dioxane/H_2O	90	16	74

[a] Conditions for CuI catalysis: CuI (8.5 mol %), KOH (4.0 equiv).
[b] Dioxane/H_2O, 1:1.
[c] Ketone **8** isolated as exclusive product.
[d] 2.5 equiv of KOH used.
[e] 1.1 equiv of KOH used.

application of this protocol to substrates such as **1** would lead to benzofurans via the intermediacy of either phenolates **4** or enolates **5**.

As we required a route that would allow access to 2,3-disubstituted benzofurans, a substitution pattern that can be difficult to obtain using several alternative Pd-based methods,[7] we selected triflate **6** as our test substrate (Table 1).[8] Unfortunately, treatment of triflate **6** with KOH under Buchwald's conditions ($Pd_2(dba)_3$, ligand **7**) provided ketone **8** as the exclusive product (entry 1). The use of a number of alternative ligands produced the same result.[9] It appeared that we were able to access an enolate corresponding to **5**; however, we could not identify a Pd-based catalyst that would achieve the final ring-closure, even though the Pd-catalysed conversion of ketones such as **8** to benzofurans is known.[10] A reaction excluding any catalyst established that KOH was responsible for the observed triflate hydrolysis (entry 2). Alternative bases, such as Cs_2CO_3, K_2CO_3 or K_3PO_4, or water alone, were not sufficient to cause hydrolysis. Despite our failure to identify a Pd catalyst capable of the overall transformation we were drawn to a report from SanMartin and Domínguez detailing the Cu-catalysed cyclisation of enolates leading to benzofurans;[11] importantly, the process was conducted 'on-water'.[12,13] Application of the SanMartin conditions, with the addition of 2.5 equiv of KOH, delivered benzofuran **9** in 36% yield (entry 3). Employing 1.1 equiv of KOH lowered the yield to 13%; however, if 4.0 equiv were employed this was increased to 81% (entries 4 and 5). The addition of dioxane as co-solvent increased the yield further to 99% (entry 6). The final entries in the table established that decreasing the amount of TMEDA, or lowering the reaction temperature, resulted in reduced yields (entries 7–10).



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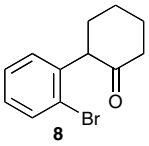

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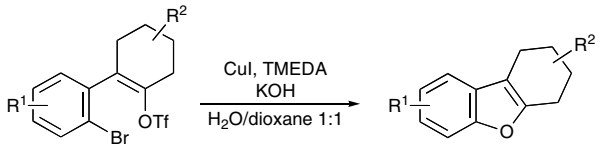
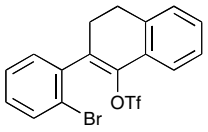
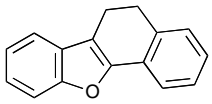
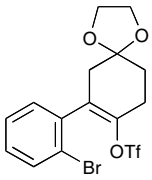
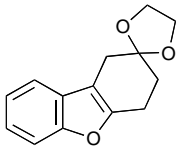
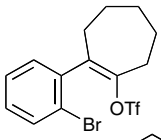
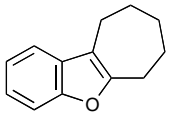
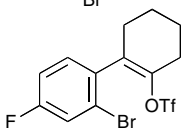
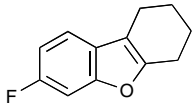
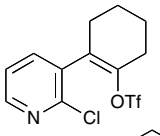
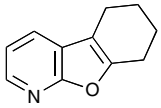
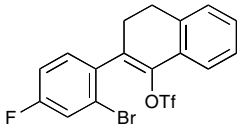
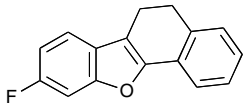
With optimised conditions for the conversion of aryl bromides–alkenyl triflates into benzofurans available, we undertook a brief investigation of the scope of the process (Table 2).[14,15] Variation of the alkenyl triflate portion of the substrates to include fused benzene rings, dioxolane substituents and larger ring sizes proceeded without incident to deliver the corresponding benzofurans in good yields (entries 1–3). Entries 4 and 5 show that the introduction of a simple fluoro-substituent and the exchange of a benzene for a pyridine-based substrate were also tolerated well. The final entry demonstrates the successful variation of both the triflate and bromide segments of the substrate.

In conclusion, we have demonstrated that the combination of KOH and CuI/TMEDA is effective for the conversion of aryl bromide–alkenyl triflates to the corresponding benzofurans. The reactions proceed via hydrolysis of the alkenyl triflates to generate enolates, which are then converted to the benzofurans under the action of Cu(I). The process tolerates variation of both the alkenyl triflate and aryl bromide portions of the substrate. The successful conversion of aryl bromide–alkenyl triflates to benzofurans is significant as it demonstrates that a single class of difunctionalised acyclic precursor can be used to access both indoles and benzofurans. Studies to utilise these simple precursors for the synthesis of further classes of heterocycles are underway and will be reported in due course.

Table 2. The Cu(I) catalysed conversion of aryl bromide–alkenyl triflates to benzofurans[a]



Entry	Substrate	Product	Yield[b] (%)
1			95
2			83
3			75
4			96
5			81
6			91

[a] Conditions: CuI (8.5 mol %), TMEDA (3.5 equiv), KOH (4.0 equiv), dioxane/H_2O, 1:1, 120 °C, 16 h.
[b] Isolated yields.

Acknowledgements

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14. *General experimental procedure*: A screw cap tube (20 mL) was charged with 2-(2-bromophenyl)cyclohexen-1-yl triflate **6** (124 mg, 0.32 mmol), CuI (5.2 mg, 0.0272 mmol), TMEDA (170 μL, 1.12 mmol), ground potassium hydroxide pellets (72 mg, 1.28 mmol), water (1.9 mL) and dioxane (1.9 mL). The tube was sealed and the reaction mixture was heated at 120 °C for 16 h. The reaction mixture was allowed to cool to room temperature and diluted with DCM (5 mL). The product was extracted with DCM (3 × 5 mL), dried over $MgSO_4$, filtered and reduced in vacuo. The product was purified via flash column chromatography (1% Et_2O–petroleum ether) to yield benzofuran **9** (55 mg, 99%) as a colourless oil. Data consistent with that reported in the literature.[10b]
15. All subtrates and products described in this Letter are known compounds (see Ref. 10b), except for: *Trifluoromethanesulfonic acid 2-(2-bromo-4-fluoro-phenyl)-3,4-dihydronaphthalen-1-yl ester (Table 2, entry 6 substrate);* white solid: mp 69.5–71 °C (petroleum ether–Et_2O); ν_{max} (Nujol mull)/cm^{-1} 3072, 2943, 1655, 1579, 1487, 1417, 1213, 1140, 1077, 1010, 908, 885, 837, 764, 731, 606; δ_H (400 MHz, $CDCl_3$) 7.52–7.47 (1H, m, Ar–H), 7.43 (1H, dd, $J = 8.3$ and 2.5, Ar–H), 7. 36–7.22 (4H, m, Ar–H), 7.10 (1H, dt, $J = 11.1$ and 2.5, Ar–H), 3.22–3.12 (1H, m, CH*H*–C(Ar)=C), 3.03–2.86 (2H, m, Ar–CH_2–CH_2), 2.67–2.57 (1H, m, C*H*HC(Ar)=C); δ_C (100 MHz, $CDCl_3$) 162.2. (d, $^1J_{CF} = 252.5$), 142.1, 136.2, 133.2 (d $^4J_{CF} = 3.2$), 132.0 (d, $^3J_{CF} = 8.8$), 130.6, 129.3 (d, $^2J_{CF} = 22.4$), 127.7, 127.0, 123.6 (d, $^3J_{CF} = 9.6$), 122.2, 120.4 (d, $^2J_{CF} = 24.8$), 118.0 (q, $^1J_{CF} = 320.4$), 114.9, 114.6, 29.8, 27.4; *m/z* LRMS (EI$^+$) 452.0 (^{81}Br−M$^+$, 55), 450.0 (^{79}Br−M$^+$, 55), 317.1 (30), 291.1 (95), 289.1 (100%); HRMS (EI) 449.9540 (M$^+$ $C_{17}H_{11}O_3{}^{79}BrF_4S$ requires 449.9543).