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A catalyst-free bis(triflyl)ethylation/benzannulation reaction: rapid access to carbazole-based superacidic carbon acids from alkynols^{†‡}

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Carbazoles possessing Tf_2CHCH_2 groups were obtained by the reaction of 1-(indol-2-yl)but-3-yn-1-ols with *in situ*-generated $\text{Tf}_2\text{C}=\text{CH}_2$ through vicinal difunctionalisation of the alkyne moiety, where the vinyl-type carbocation intermediate was selectively attacked by the indole moiety and not by the carbanion moiety.

Carbanions are inherently reactive chemical species and the isolation of carbanion-containing salts is significantly limited. Delocalisation of the negative charge by an electron-withdrawing mesomeric (resonance) effect is a general approach for the improvement of thermodynamic stability. Some 'free' triphenylmethanides¹ and cyclopentadienides² have been isolated and characterised. Stabilisation of the carbanion is also achieved by substitution of the anionic carbon atom by fluorine atom(s) or fluorine-containing substituents. For example, Farnham and co-workers isolated and characterised a 'free' perfluorocarbanion.³ Carbanions bearing two triflyl groups ($\text{Tf} = \text{CF}_3\text{SO}_2$), which are known to be one of the strongest electron-withdrawing groups, attract much attention.⁴ Yanai reported several intramolecular salts **1–4** (Fig. 1A).^{5–9} For the stability of such $[\text{Tf}_2\text{CR}]^-$ species, an orbital interaction between an occupied p orbital of the anionic carbon atom and adjacent $\sigma_{\text{S-C}(\text{F}_3)}^*$ orbitals, called negative hyperconjugation,¹⁰ is pointed out to be a key factor (Fig. 1B).⁸ It is easily predictable that nucleophilicity of $[\text{Tf}_2\text{CR}]^-$ is strongly suppressed due to the steric crowding around the anionic carbon atom and the charge-delocalised nature.

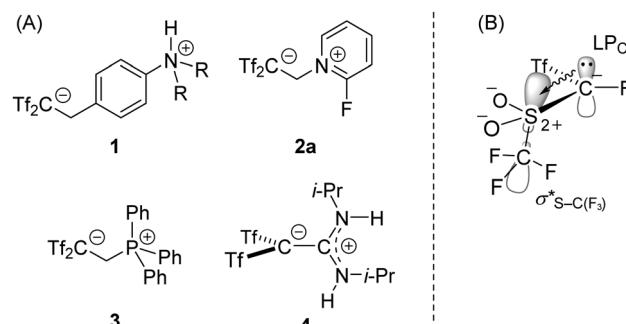


Fig. 1 (A) Zwitterions bearing a $[\text{Tf}_2\text{CR}]^-$ structure, and (B) negative hyperconjugation in $[\text{Tf}_2\text{CR}]^-$.

Actually, compound **3** was the first example of a well-defined phosphorous carba-betaine, which did not undergo ring-closure into the corresponding phosphacyclopropane.⁸ Recently, a chemically inert property of $[\text{Tf}_2\text{CR}]^-$ was applied to push-pull π systems. Push-pull ethylene **4** with a large distortion around the central C–C bond axis showed clearly charge-separated characters on the C–C bond in a complementary bonding analysis.⁹ These examples reveal that σ - or π -bonding with the $[\text{Tf}_2\text{CR}]^-$ moiety is not favourable.

With such background, we were interested in the ring-closing reaction of vinyl-type carbocation **INT-1** bearing a $[\text{Tf}_2\text{CR}]^-$ moiety as the counter anion and a nucleophilic indole moiety (eqn (1)). As a pioneering work, Alcaide and Almendros reported a *gem*-bis(triflyl)cyclobutene synthesis through the stepwise (2+2) cycloaddition of several alkynes with $\text{Tf}_2\text{C}=\text{CH}_2$,^{11,12} which was *in situ*-generated from 2-fluoropyridinium salt **2a**⁷ developed by Yanai (eqn (2)).¹³ In the case of **INT-1** derived from 1-(indol-2-yl)but-3-yn-1-ols **5** with $\text{Tf}_2\text{C}=\text{CH}_2$, two reaction paths would be possible as follows: path (a) cyclobutene formation through a C–C bond forming reaction between the anionic carbon atom and the cationic C4 atom; path (b) carbazole formation induced by nucleophilic attack of the indole moiety on the C4 atom. Such a reaction system would allow further understanding of the chemical behaviour of the $[\text{Tf}_2\text{CR}]^-$

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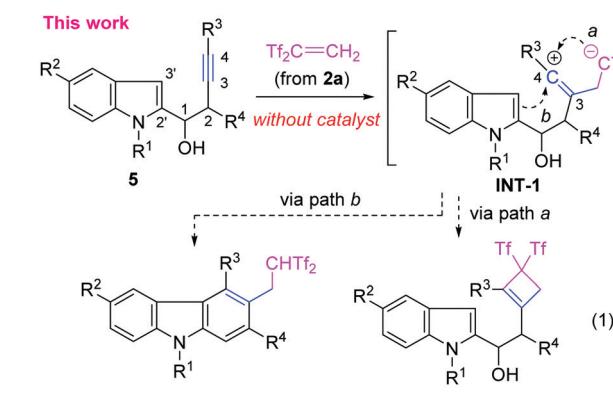
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† Dedicated to Prof. Benito Alcaide on the occasion of his retirement.

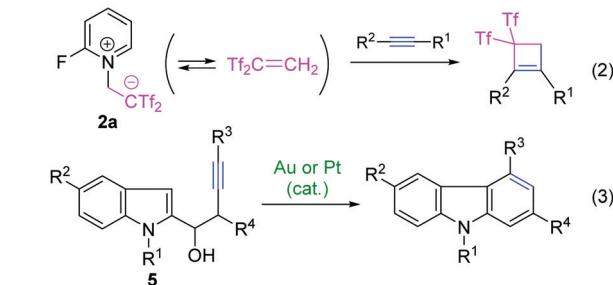
‡ Electronic supplementary information (ESI) available: Computational details, experimental procedures, characterization data of new compounds, crystallographic details, and copies of NMR spectra for all new compounds. CCDC 1911534. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc08930f



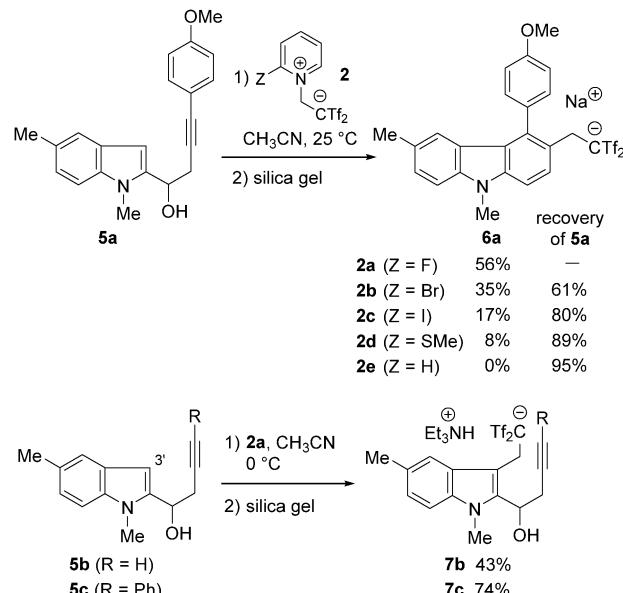
species. In this paper, we report that the latter path selectively proceeds to give Tf_2CHCH_2 -decorated carbazoles as the final products. Carbazoles are an important class of natural products, biologically active molecules, and advanced materials.¹⁴ Therefore, synthetic interests in them are renewed. In particular, transition metal-catalysed cyclisations of indolyl-3-alkyn-1-ols 5 have been developed to complement classical approaches (eqn (3)).¹⁵ The present results clearly demonstrate that non-ionic $\text{Tf}_2\text{C}=\text{CH}_2$ effectively activates the internal alkynes in an electrophilic fashion. In addition, this is a rare example where attack of the non-ionic carbon-centred nucleophile is faster than that of the carbanion.



Literature works



We first examined the reaction of indolyl-3-alkyn-1-ols 5 with 2-(2-fluoropyridinium-1-yl)-1,1-bis(triflyl)ethan-1-ide 2a under the optimised conditions for the cyclobutene-forming reaction (at 25 °C, in CH_3CN)¹¹ (Scheme 1). The reaction of (*p*-methoxyphenyl)alkyne 5a with 1.0 equiv. of 2a selectively produced the desired carbazole acid 6a–H, which was isolated as the corresponding sodium salt 6a in 56% yield after column chromatography on silica gel.¹⁶ In this case, the expected by-products including 3-bis(triflyl)ethylated indole and cyclobutene products were not obtained. For the present molecular transformation, the reaction solvents are critical. The use of DMF led to complexation of the reaction, while the reaction using ethanol or dichloromethane was not productive due to low solubility of 2a. During screening with several pyridinium salts 2b–e, we refound that a non-fluorinated salt 2e¹⁷ did not react with 5a under similar conditions and other 2-substituted pyridinium salts caused very slow conversion of 5a.^{7b} Unfortunately, in the case of terminal alkyne 5b, 2,2-bis(triflyl)ethylation of the indole 3-position (C3' atom) selectively occurred to give indole acid 7b–H,

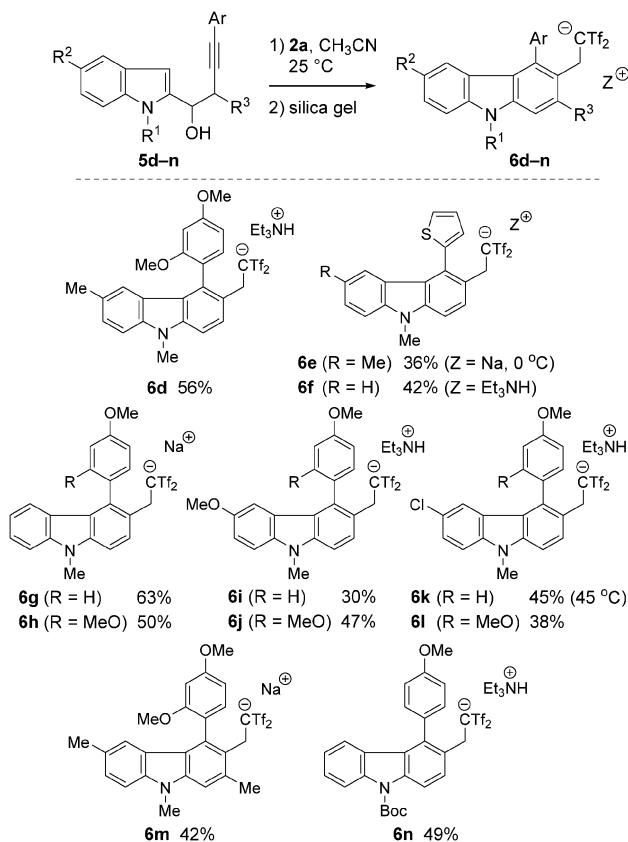


Scheme 1 Reactions of indolyl-3-alkyn-1-ols 5a–c with 2a.

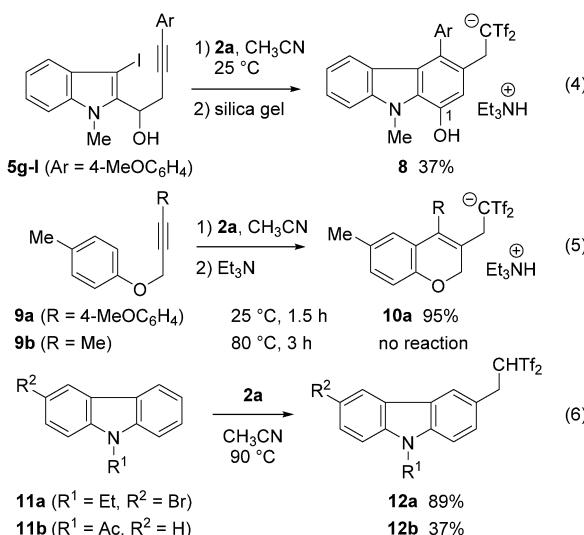
which was isolated as the corresponding triethylammonium salt 7b after column chromatography on silica gel pre-treated by Et_3N for neutralisation.¹⁶ A similar result was observed in the reaction of phenylalkyne 5c. These results imply that alkyne-selectivity observed in the reaction of 5a is enhanced by the electron-donating aryl group on the alkyne terminus. Indeed, by applying common Lewis acids such as ZnI_2 and InCl_3 , we observed no evidence of the formation of carbazoles from 5c. The adduct 7c gave only a complex mixture by heating at 80 °C. On this basis, we conclude that the 3-alkylated products 7 are formed in an irreversible manner and the possible carbazoles 6 did not generate from them.

The scope of the bis(triflyl)ethylation/benzannulation reaction was studied by using a series of indolyl-3-alkyn-1-ols 5 (Scheme 2). The reaction was applicable to 5-methylindoles 5d and 5e bearing electron-rich aryl groups including 2,4-dimethoxyphenyl and 2-thienyl groups on the alkyne terminus to give carbazoles 6d and 6e in moderate to good yields. 5-Unsubstituted indoles 5f–h and 5-methoxyindoles 5i and 5j were successfully converted to the desired carbazoles 6f–j. Likewise, 5-chloroindoles 5k and 5l reacted with $\text{Tf}_2\text{C}=\text{CH}_2$ to give carbazoles 6k and 6l, respectively. Taking into account the low reactivity of the halogenated carbazoles in the direct aromatic electrophilic substitution (S_{EAr}) reaction with *in situ*-generated $\text{Tf}_2\text{C}=\text{CH}_2$ (*vide infra*), the present results show some synthetic advantages. The reactions of 2-methylbut-3-yn-1-ol 5m and *N*-Boc indole 5n also worked well to give carbazoles 6m and 6n, respectively. As shown in eqn (4), the reaction of iodoindole 5g–I with 2a gave 1-hydroxycarbazole 8. These examples suggest that the present reaction is potent for a regio-controlled synthesis of highly substituted carbazoles. The cyclisation methodology initiated by highly electrophilic $\text{Tf}_2\text{C}=\text{CH}_2$ is not limited to carbazole formation. For example, the reaction of propargyl ether 9a with 2a produced 2*H*-chromene 10a in 95% yield (eqn (5)).

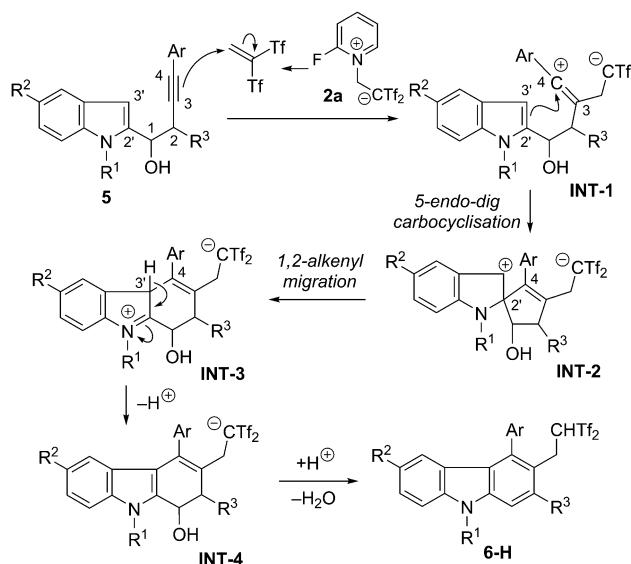


Scheme 2 Catalyst-free reaction of indolyl-3-alkyn-1-ols **5d–n** with **2a**.

Unfortunately, dialkyl alkyne **9b** was significantly less reactive and its consumption was not observed even under heating conditions.



The Tf_2CH -type superacidic molecules behave as carbon acids with unique catalytic activity.^{18,19} In the synthetic context,⁵ direct $\text{S}_{\text{E}}\text{Ar}$ reaction of simple carbazoles with $\text{Tf}_2\text{C}=\text{CH}_2$ would be attractive to obtain the carbazole-based acids.²⁰ However, the reactions involving electron-deficient carbazoles **11a** and **11b** required heating conditions to form the products **12a** and **12b** (eqn (6); also, see ESI‡).



Scheme 3 Mechanistic explanation.

A plausible reaction pathway for carbazoles **6–H** is shown in Scheme 3. First, the alkyne moiety of indolyl-3-alkyn-1-ols **5** traps $\text{Tf}_2\text{C}=\text{CH}_2$ generated from reagent **2a** to produce the zwitterionic vinyl-type carbocation **INT-1**. This initial addition is followed by a 5-*endo*-dig carbocyclisation through nucleophilic attack of the C2' atom of the indole nucleus on the cationic C4 atom to give spirocyclic indolinium species **INT-2**.²¹ Next, a fused tricyclic intermediate **INT-3** arises through 1,2-alkenyl migration in the spirocyclic nucleus of **INT-2**. Further aromatisation including deprotonation of **INT-3** and dehydration of **INT-4** should generate **6–H**.

This reaction pathway including 5-*endo*-dig cyclisation followed by ring-expansion is supported by a DFT simulation [PCM(CH_3CN)-M06-2X/6-31+G(d) level of theory] of a model molecule **13**, where the hydroxyl group of substrate **5g** is replaced by a hydrogen atom (Fig. 2). For all optimised geometries, frequency calculations were conducted. The calculated Gibbs energy difference at 298 K (ΔG_{298}) for the initial electrophilic attack of $\text{Tf}_2\text{C}=\text{CH}_2$ on the alkyne C3 atom of **13** is only 16.3 kcal mol⁻¹, when the initial state is used as a reference (Fig. 2). A vinyl-type carbocation **INT-1'** corresponding to **INT-1** shown in Scheme 3 was found as a local minimum species. The transition state geometry of the 5-*endo*-dig cyclisation (TS2) is very close to **INT-1'**, and the activation barrier to give **INT-2'** is 1.9 kcal mol⁻¹ (from **INT-1'**). In **INT-1'**, the C4–C2' distance (275.1 pm) is obviously shorter than the C4–C3' distance (320.7 pm). The low activation barrier and the geometric similarity between **INT-1'** and **TS2** support that the 5-*endo*-dig path rather than the 6-*endo*-dig path is kinetically favourable. In addition, the (2+2) cycloaddition path requires a much higher activation energy (6.3 kcal mol⁻¹ from **INT-1'**; see, ESI‡). The following ring-expansion reaction (TS3) to give **INT-3'** is highly exothermic and requires a small activation energy (7.0 kcal mol⁻¹ from **INT-2'**). For each step on this pathway, the simulation well agrees with the fact that the reaction proceeds under really mild conditions.

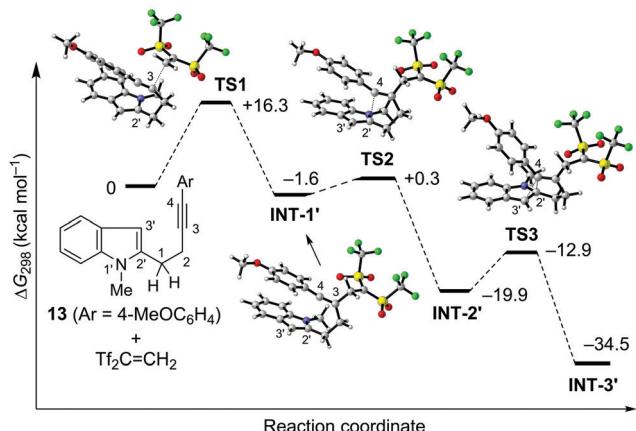


Fig. 2 Reaction profile of the bis(triflyl)ethylation/benzannulation reaction.

In conclusion, we successfully developed a sequential bis(triflyl)ethylation/benzannulation reaction to produce bis(triflyl)ethylated carbazoles from indolyl-3-alkyn-1-ols. This molecular transformation is triggered by a regioselective electrophilic attack of $\text{Tf}_2\text{C}=\text{CH}_2$, which is generated from the 2-fluoropyridinium salt **2a** in an *in situ* manner, on the alkyne moiety of the substrates. In vinyl-type carbocations thus generated, a ring-closing reaction between the cationic carbon atom and indole C2' atom predominantly takes place. This event clearly shows the chemically inert properties of $[\text{Tf}_2\text{CR}]^-$ in the chemical reaction.

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Conflicts of interest

There are no conflicts of interest to declare.

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