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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.

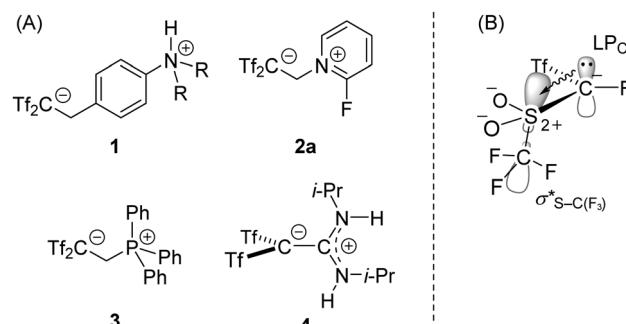


Fig. 1 (A) Zwitterions bearing a $[\text{Tf}_2\text{CR}]^-$ structure, and (B) negative hyperconjugation in $[\text{Tf}_2\text{CR}]^-$.

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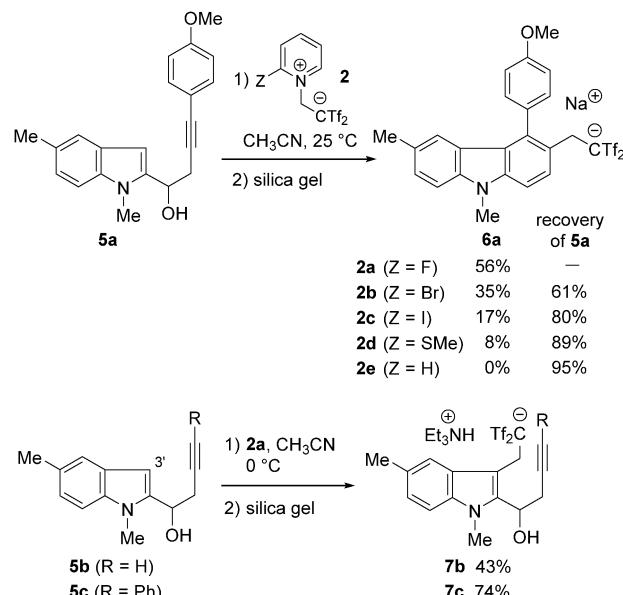
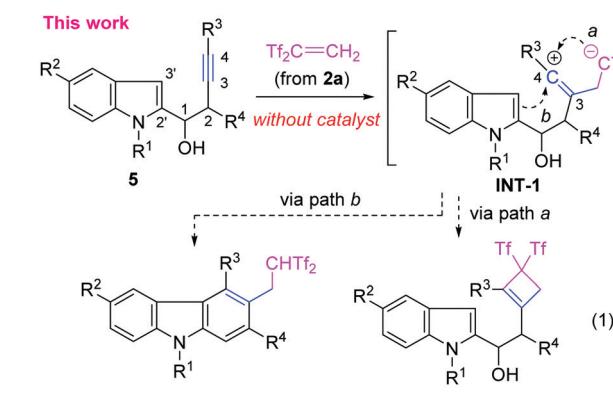
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† Dedicated to Prof. Benito Alcaide on the occasion of his retirement.

‡ 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.



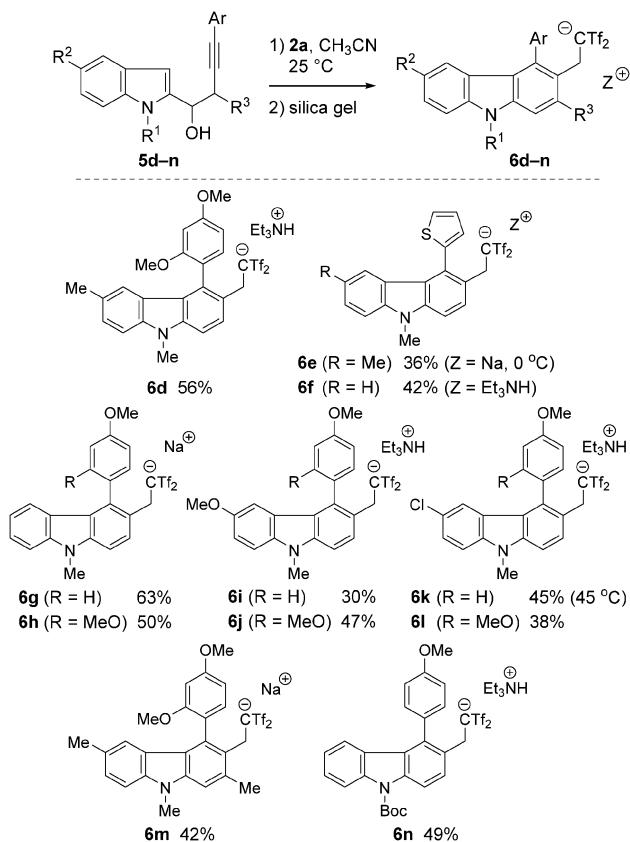
Scheme 1 Reactions of indolyl-3-alkyn-1-ols 5a-c with 2a.

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.

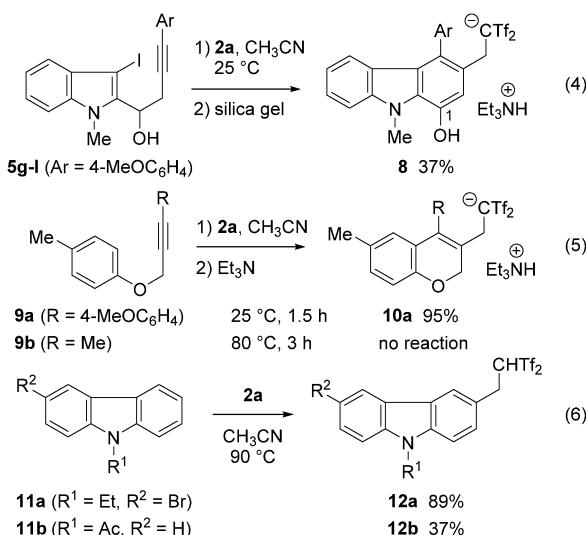
The scope of the bis(triflyl)ethylation/benzannulation reaction was studied by using a series of indolyl-3-alkyn-1-ols 5 (Scheme 2). The reaction was applicable to 5-methylindoles **5d** and **5e** bearing electron-rich aryl groups including 2,4-dimethoxyphenyl and 2-thienyl groups on the alkyne terminus 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)).

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 **2e**¹⁷ 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**,

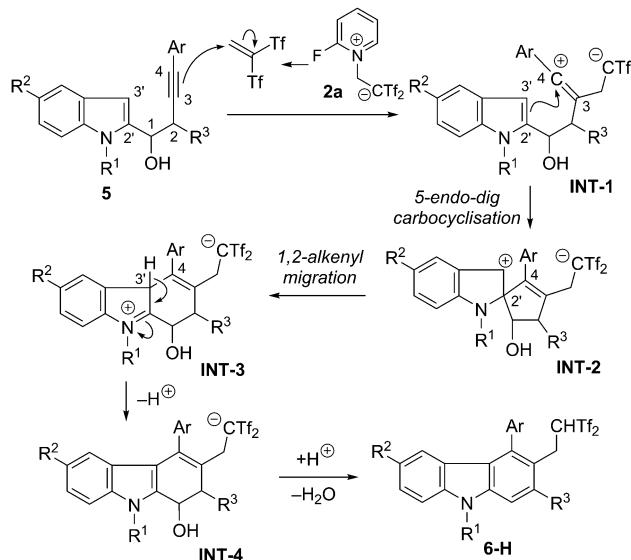


Scheme 2 Catalyst-free reaction of indolyl-3-alkyn-1-ols **5d–n** with **2a**.

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.

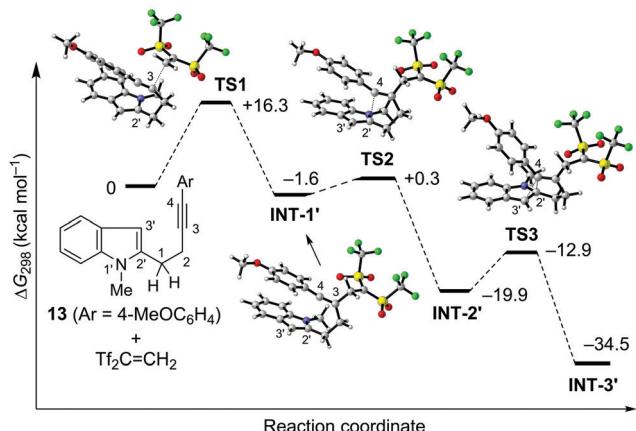


Fig. 2 Reaction profile of the bis(triflyl)ethylation/benzannulation reaction.

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.

Notes and references

- (a) W. Schlenk and J. Holtz, *Ber. Dtsch. Chem. Ges.*, 1916, **49**, 603; (b) S. Harder, *Chem. - Eur. J.*, 2002, **8**, 3229; (c) M. M. Olmstead and P. P. Power, *J. Am. Chem. Soc.*, 1985, **107**, 2174.
- (a) E. Le Goff and R. B. LaCount, *J. Am. Chem. Soc.*, 1963, **85**, 1354; (b) S. Matsumura and S. Seto, *Chem. Pharm. Bull.*, 1963, **11**, 126; (c) R. Kuhn and D. Rewicki, *Angew. Chem.*, 1967, **79**, 648; (d) K. Okamoto, T. Kitagawa, K. Takeuchi, K. Komatsu and K. Takahashi, *J. Chem. Soc., Chem. Commun.*, 1985, 173; (e) C. D. Gheewala, M. A. Radtke, J. Hui, A. B. Hon and T. H. Lambert, *Org. Lett.*, 2017, **19**, 4227.
- (a) W. B. Farnham, *Chem. Rev.*, 1996, **96**, 1633; (b) W. B. Farnham, D. A. Dixon and J. C. Calabrese, *J. Am. Chem. Soc.*, 1988, **110**, 2607.
- (a) A. Hasegawa, T. Ishikawa, K. Ishihara and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1401; (b) D. Höfler, R. Goddard, J. B. Lingnau, N. Nöthling and B. List, *Angew. Chem., Int. Ed.*, 2018, **57**, 8326; (c) L. Turowsky and K. Seppelt, *Inorg. Chem.*, 1988, **27**, 2135.

- For a review, see: H. Yanai and T. Taguchi, *J. Fluorine Chem.*, 2015, **174**, 108.
- H. Yanai, T. Yoshino, M. Fujita, H. Fukaya, A. Kotani, F. Kusu and T. Taguchi, *Angew. Chem., Int. Ed.*, 2013, **52**, 1560.
- (a) H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi and T. Matsumoto, *Chem. Commun.*, 2013, **49**, 10091; (b) H. Yanai, R. Takahashi, Y. Takahashi, A. Kotani, H. Hakamata and T. Matsumoto, *Chem. - Eur. J.*, 2017, **23**, 8203.
- H. Yanai, P. Almendros, S. Takahashi, C. Lázaro-Milla, B. Alcaide and T. Matsumoto, *Chem. - Asian J.*, 2018, **13**, 1956.
- H. Yanai, T. Suzuki, F. Kleemiss, H. Fukaya, Y. Dobashi, L. A. Malaspina, S. Grabowsky and T. Matsumoto, *Angew. Chem., Int. Ed.*, 2019, **58**, 8839.
- (a) J. D. Roberts, R. L. Webb and E. A. McElhill, *J. Am. Chem. Soc.*, 1950, **72**, 408; (b) O. Exner and S. Böhm, *New J. Chem.*, 2008, **32**, 1449; (c) G. Raabe, H.-J. Gais and J. Fleischhauer, *J. Am. Chem. Soc.*, 1996, **118**, 4622.
- (a) B. Alcaide, P. Almendros, I. Fernández and C. Lázaro-Milla, *Chem. Commun.*, 2015, **51**, 3395; (b) B. Alcaide, P. Almendros and C. Lázaro-Milla, *Chem. - Eur. J.*, 2016, **22**, 8998; (c) B. Alcaide, P. Almendros and C. Lázaro-Milla, *Adv. Synth. Catal.*, 2017, **359**, 2630.
- B. Alcaide, P. Almendros and C. Lázaro-Milla, *Chem. Commun.*, 2015, **51**, 6992.
- (a) H. Yanai, M. Fujita and T. Taguchi, *Chem. Commun.*, 2011, **47**, 7245; (b) H. Yanai, H. Ogura, H. Fukaya, A. Kotani, F. Kusu and T. Taguchi, *Chem. - Eur. J.*, 2011, **17**, 11747.
- For selected reviews, see: (a) M. Li, *Chem. - Eur. J.*, 2019, **25**, 1142; (b) X. Zhang and S. Ma, *Isr. J. Chem.*, 2018, **58**, 608; (c) G. Sathiyam, E. K. T. Sivakumar, R. Ganeshamoorthy, R. Thangamuthu and P. Sakthivel, *Tetrahedron Lett.*, 2016, **57**, 243; (d) A. W. Schmidt, K. R. Reddy and H.-J. Knöller, *Chem. Rev.*, 2012, **112**, 3193; (e) J. Roy, A. K. Jana and D. Mal, *Tetrahedron*, 2012, **68**, 6099; (f) H. J. Jiang, J. Sun and J. L. Zhang, *Curr. Org. Chem.*, 2012, **16**, 2014; (g) J. Li and A. G. Grimsdale, *Chem. Soc. Rev.*, 2010, **39**, 2399; (h) T. Janosik, N. Wahlstrom and J. Bergman, *Tetrahedron*, 2008, **64**, 9159; (i) H.-J. Knöller and K. R. Reddy, Chemistry and Biology of Carbazole Alkaloids, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, pp. 1–430.
- (a) Y. Qiu, W. Kong, C. Fu and S. Ma, *Org. Lett.*, 2012, **14**, 6198; (b) A. S. K. Hashmi, W. Yang and F. Rominger, *Chem. - Eur. J.*, 2012, **18**, 6576; (c) Y. Qiu, J. Zhou, C. Fu and S. Ma, *Chem. - Eur. J.*, 2014, **20**, 14589; (d) J. Zhou, Y. Qiu, J. Li, C. Fu, X. Zhang and S. Ma, *Chem. Commun.*, 2017, **53**, 4722.
- The most carbon acids were purified by column chromatography on acidic or Et_3N -pretreated silica gel. Therefore, chemical yields refer to the weight of isolated salts (see, ESI‡).
- L. L. Barber Jr and R. J. Koshar, *US Pat.*, 3962342, 1976.
- (a) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277; (b) C. H. Cheon and H. Yamamoto, *Chem. Commun.*, 2011, **47**, 3043.
- For selected examples, see: (a) K. Ishihara, A. Hasegawa and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2001, **40**, 4077; (b) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 3175; (c) A. Takahashi, H. Yanai and T. Taguchi, *Chem. Commun.*, 2008, 2385; (d) H. Yanai, O. Kobayashi, K. Takada, T. Isono, T. Satoh and T. Matsumoto, *Chem. Commun.*, 2016, **52**, 3280; (e) T. Gatzenmeier, M. van Gemmeren, Y. Xie, D. Höfler, M. Leutzscher and B. List, *Science*, 2016, **351**, 949; (f) D. Höfler, M. van Gemmeren, P. Wedemann, K. Kaupmees, I. Leito, M. Leutzscher, J. B. Lingnau and B. List, *Angew. Chem., Int. Ed.*, 2017, **56**, 1411.
- P. Almendros, H. Yanai, S. Hoshikawa, C. Aragoncillo, C. Lázaro-Milla, M. Toledano-Pinedo, T. Matsumoto and B. Alcaide, *Org. Chem. Front.*, 2018, **5**, 3163.
- A related spirocyclic intermediate has been recently proposed on the gold-catalysed synthesis of carbazoles: B. Alcaide, P. Almendros, C. Aragoncillo, E. Bustos, C. G. López-Calixto, M. Liras, V. A. de la Peña O'Shea, A. García-Sánchez and H. V. Stone, *Chem. - Eur. J.*, 2018, **24**, 7620.

