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Synthesis of Carbazoles and Dihydrocarbazoles by a Divergent Cascade Reaction of Donor–Acceptor Cyclopropanes

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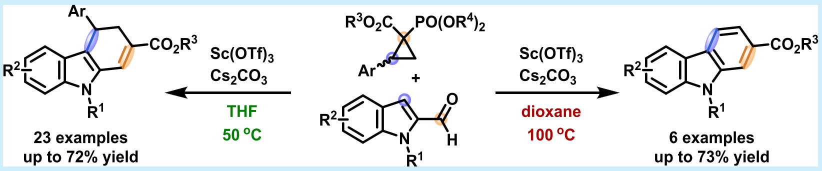
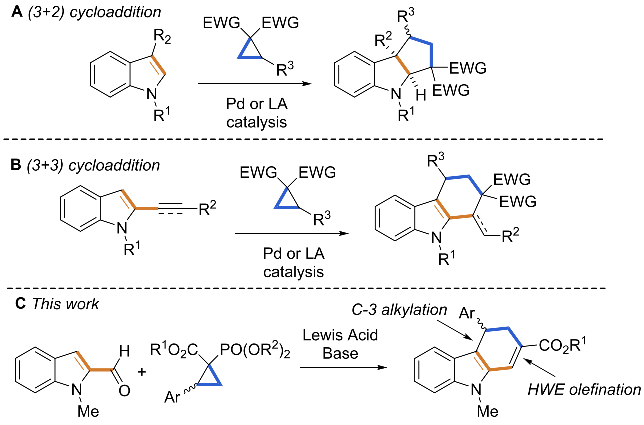


ABSTRACT: An alkylation/olefination cascade of indolecarboxaldehydes and phosphonate-functionalized donor–acceptor cyclopropanes affords functionalized dihydrocarbazoles and cyclohepta[*cd*]indoles in formal (3 + 3) and (4 + 3) cycloadditions. A minor modification to the reaction conditions also allows access to the fully aromatic heterocyclic scaffolds by thermal loss of an electron-rich aryl moiety.

Carbazoles and their di- and tetrahydro derivatives have gained considerable interest from the synthetic community owing to their presence in a wide range of natural products and their diverse biological activities.[1] Consequently, these scaffolds are highly relevant for drug discovery.[2] Despite the development of diverse synthetic methods for the construction of carbazoles and their dihydro derivatives,[3] efficient new methods allowing alternative substitution patterns remain urgently required. Therefore, we set out to develop an efficient and versatile approach based on donor–acceptor cyclopropanes (DACs). DACs have emerged as highly valuable building blocks in organic synthesis:[4] Their high ring strain, combined with a vicinal substitution pattern of donor and acceptor groups, allows the facile generation of a reactive 1,3-zwitterion. Although numerous reactions of DACs have been reported over the years, (3 + 2) cycloadditions[5] have received considerably more attention compared with their (3 + 3)[6] and (3 + 4)[7] counterparts. This is due to the high number of 1,2-dipolarophiles compared with 1,3- and 1,4- dipolar reaction partners. Owing to their frequent occurrence in natural products,[8] indole derivatives have been extensively used as 1,2-dipolarophiles in (3 + 2) cycloadditions.[9] However, the vast majority of indole-based natural products feature a tetrahydrocarbazole or β-carboline framework,[10] accessible only via (3 + 3) cycloaddition. Unfortunately, given the natural reactivity of indoles as 1,2-dipolarophiles, (3 + 3) and other types of cycloadditions are considerably more difficult to achieve. To tackle this issue, it is necessary to introduce dedicated functionalities that could divert the usual reaction pathway (Scheme 1B). However, these examples are rare and substrate-limited and require multistep synthesis of the starting materials.[11]

Scheme 1. (A) (3 + 2) Cycloaddition of DACs and Indoles, (B) (3 + 3) Cycloaddition of DACs and Alkenyl/Alkynylindoles, and (C) (3 + 3) Cycloaddition of DACs and Indolecarboxaldehydes



Typically, the acceptor moiety of DACs comprises two ester functionalities, which may be replaced with sulfones, ketones, nitriles, or electron-poor arenes.[12] We recently demonstrated that the previously neglected phosphonates are suitable acceptor moieties, allowing Horner–Wadsworth–Emmons (HWE) olefination with aldehydes upon activation of the DAC. Thus vinylcyclopropanes react with salicylaldehydes

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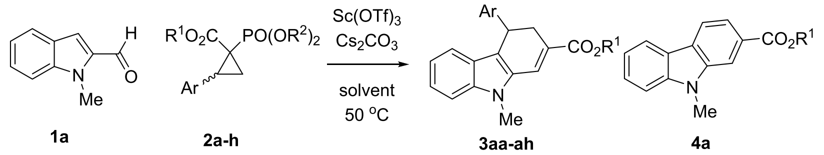
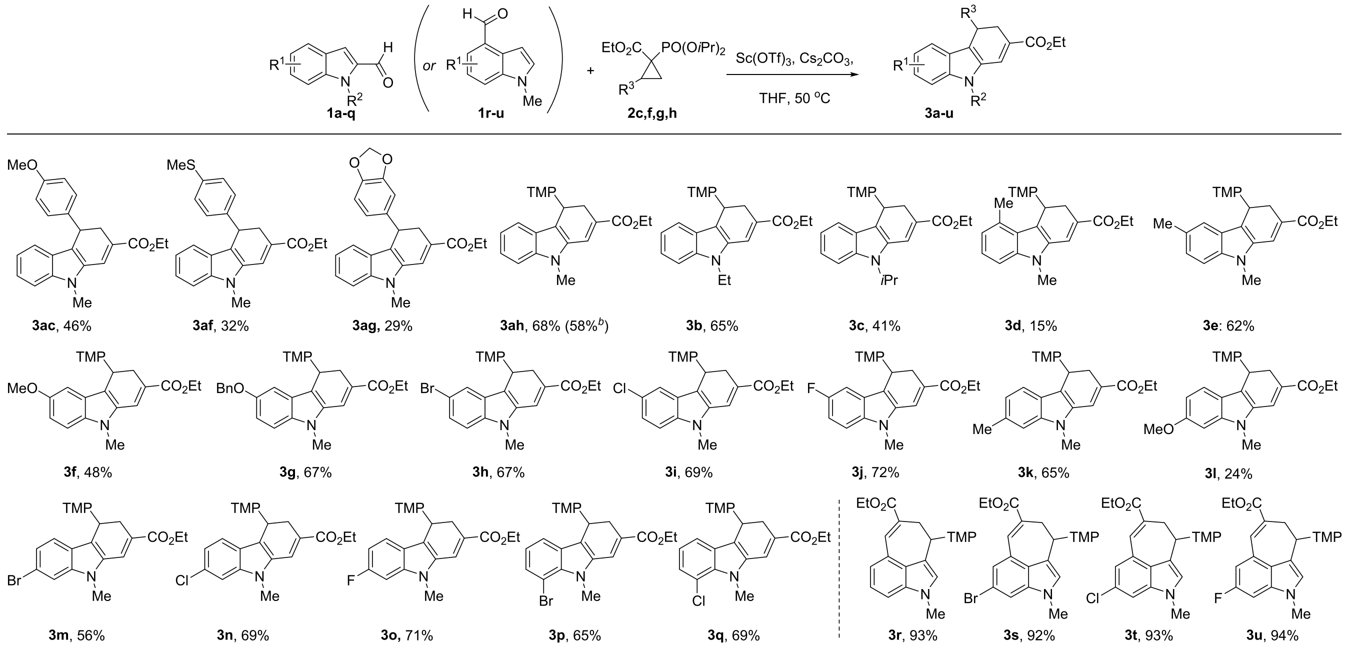
Table 1. Reaction Optimization[a]



entry	2	R^1	R^2	Ar	solvent	yield **3** (%)[b]	yield **4** (%)[b]
1[c]	**2a**	Me	Me	4-methoxyphenyl	THF	9	
2	**2a**	Me	Me	4-methoxyphenyl	THF	23	
3	**2b**	Et	Et	4-methoxyphenyl	THF	21	
4	**2c**	Et	*i*Pr	4-methoxyphenyl	THF	46[e]	
5	**2d**	*i*Pr	*i*Pr	4-methoxyphenyl	THF	30	
6	**2e**	*i*Pr	Me	4-methoxyphenyl	THF	26	
7	**2f**	Et	*i*Pr	4-methylthiophenyl	THF	32	
8	**2g**	Et	*i*Pr	3,4-methylenedioxyphenyl	THF	29	
9	**2h**	***i*Pr**	***i*Pr**	**2,4,6-trimethoxyphenyl**	**THF**	**68**[d]	
10	**2h**	*i*Pr	*i*Pr	2,4,6-trimethoxyphenyl	1,4-dioxane	33	
11	**2h**	*i*Pr	*i*Pr	2,4,6-trimethoxyphenyl	1,4-dioxane[e]	53	10
12	**2h**	***i*Pr**	***i*Pr**	**2,4,6-trimethoxyphenyl**	**1,4-dioxane**[f]		**73**[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a–h** (0.6 mmol), $Sc(OTf)_3$ (0.6 mmol), and Cs_2CO_3 (0.6 mmol) in 1 mL of solvent for 24 h. [b] Determined by ^1H NMR with internal standard. [c] Performed with **2a** (0.2 mmol), $Sc(OTf)_3$ (0.2 mmol), and Cs_2CO_3 (0.2 mmol). [d] Isolated yields. [e] Reaction performed at 80 °C. [f] Reaction performed at 100 °C.

Scheme 2. Scope of the Reaction toward Dihydrocarbazoles and Cyclohepta[*cd*]indoles[a]



[a] Reaction conditions: **1a–u** (0.2 mmol), **2a–h** (0.6 mmol), $Sc(OTf)_3$ (0.6 mmol), and Cs_2CO_3 (0.6 mmol) in THF (1 mL), 50 °C, 24 h. [b] Performed on a 1 mmol scale. TMP = 2,4,6-trimethoxyphenyl.

under palladium catalysis in an olefination/allylation cascade to give benzoxepins in a formal (4 + 3) cycloaddition.[13]

We realized that this concept could be more generally applicable to aldehydes with a nearby nucleophilic functionality. More specifically, we envisioned that indole-2-carboxaldehydes could react with DACs to give 3,4-dihydrocarbazoles in an all-carbon (3 + 3) cycloaddition (Scheme 1C). However, when we subjected **1a** to cyclization with the previously used vinylcyclopropane under palladium catalysis,[13] no conversion was observed.

Postulating that a more carbocationic character on the cyclopropane might more effectively promote the attack of the indole C3 position, we switched to arylcyclopropanes in combination with a Lewis acid and a noncoordinating base. Preliminary results proved the feasibility of this reaction, affording the desired dihydrocarbazole **3aa**, albeit in low yield (Table 1, entry 1).

We then began an extensive investigation of the types and stoichiometries of arylcyclopropanes, bases, and Lewis acids. (For details, see the Supporting Information.) Unfortunately, only scandium(III) triflate was able to promote the reaction and only in stoichiometric amount. We suspect that the dialkylphosphate ion formed during the olefination step may bind to the scandium cation, thereby lowering its Lewis acidity.

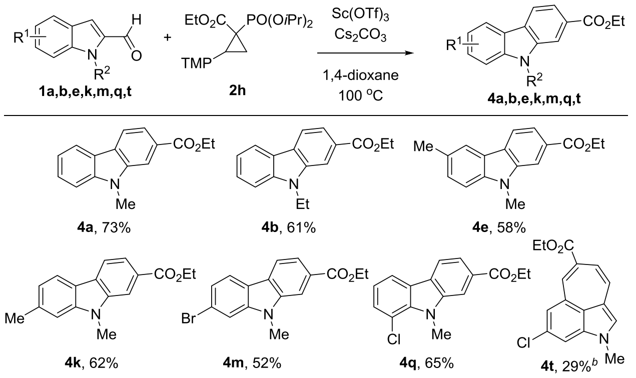
Only minor improvements were observed after a thorough stoichiometry optimization (entry 2). We then focused our attention on the substitution pattern of the cyclopropane. By varying the ester and the phosphonate substituents (entries 3−6), we found the best combination to be **2c** (R^1 = Et, R^2 = *i*Pr). Finally, comparing different aryl substituents (**2f**−**h**, entries 7−9), we observed the highest conversion with **2h** (R^3 = 2,4,6-trimethoxyphenyl).[14] Having optimized the reactants, we attempted to maximize the conversion to **3ah** by increasing the reaction temperature, using 1,4-dioxane as the solvent instead of THF because of its higher boiling point. To our surprise, when the reaction was performed at 80 °C, we isolated carbazole **4a** in 10% yield in addition to the desired dihydrocarbazole **3ah**. A further increase in the temperature to 100 °C selectively afforded **4a** in 73% yield without any traces of **3ah**.

With the optimal conditions in hand, we first focused on the scope of the dihydrocarbazole synthesis (Scheme 2). We began by investigating the influence of indole N1 substituents. Comparing products **3ah**, **3b**, and **3c**, increasing the steric bulk at the indole N1 position appears to negatively affect the yield. Steric effects also appear to play a role with C4 substituents, as **3d** was obtained in only low yield (15%). In contrast, C5-substituted indoles performed well and consistently (always between 60 and 70%), regardless of their electronic nature (**3e**−**3j**). Surprisingly, the 5-methoxy-substituted product **3f** was isolated in somewhat lower yield, whereas the analogous benzyloxy-substituted product **3g** was obtained in 67% yield. A similar trend was observed for C6 substituents (**3k**−**o**). Only the 6-methoxy-substituted product **3l** showed a lower yield, possibly due to some *in situ* demethylation caused by the excess of Lewis acid. Moreover, C7 substituents are also well tolerated, affording the desired dihydrocarbazoles in good yields (**3p**−**3q**). Finally, we also attempted to achieve a (4 + 3) cycloaddition by moving the aldehyde to the C4 position. Delightfully, we observed the formation of the seven-membered product **3r** in excellent yield (92%). Similarly good results were obtained for substituted cyclohepta[*cd*]-indoles **3s**−**u**. This heterocyclic scaffold is present in several alkaloids[15] and is particularly hard to obtain using cascade reactions. Indeed, we found only one other method using DACs and indoles bearing a strong Michael acceptor at the C4 position.[11e]

Intrigued by the formation of carbazole **4a**, we next investigated the generality of the arene elimination. From the initial reaction optimization, we already established that **4a** could be obtained as the sole product in good yield when dioxane was used as the solvent at 100 °C. Gratifyingly, carbazoles **4b**, **4e**, **4k**, **4m**, and **4q** were also obtained in reasonable to good yield using this alternative procedure (Scheme 3). As in the formation of dihydrocarbazoles **3**, substituents on the indole ring did not seem to influence the reaction efficiency, regardless of their position or electronic character. Interestingly, the yields observed for carbazoles **4** are comparable to those for the corresponding dihydrocarbazoles **3**, suggesting that elimination of the trimethoxyphenyl fragment occurs (with high efficiency) after the cyclization. To prove this hypothesis, we heated **3ah** to 100 °C in dioxane in the absence of $Sc(OTf)_3$ and/or $CsCO_3$. In all cases, carbazole **4a** was isolated in quantitative yield, indicating that the aromatization is a purely thermal process.[16]

Interestingly, under the same conditions, we did not observe any trace of **4t** but full conversion to **3t** in comparable yield to the previous conditions. Apparently, the energetic barrier of the elimination is higher in this case, possibly due to the lower aromaticity of the seven-membered ring. However, upon additional stirring at 130 °C in toluene for 24 h, we were able to obtain **4t** in modest yield.

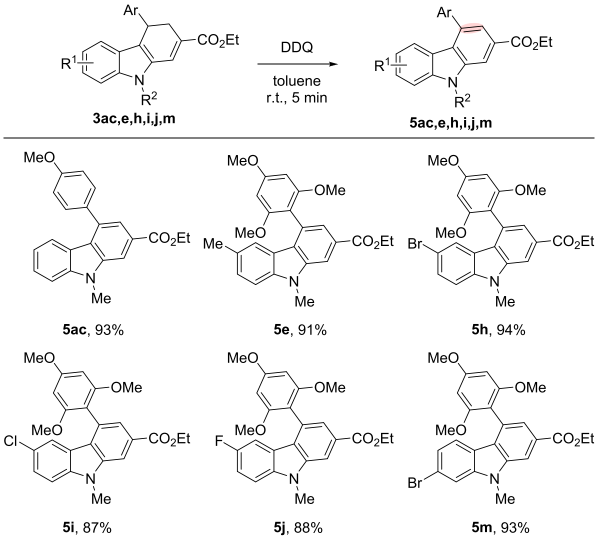
Scheme 3. Scope of the Reaction toward Carbazoles[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Sc(OTf)_3$ (0.6 mmol), and Cs_2CO_3 (0.6 mmol) in 1,4-dioxane (1 mL),100 °C, 24 h. [b]Additional 24 h of reaction time in toluene at 130 °C.

To further expand the scope of accessible carbazoles, we sought to develop a rapid and straightforward method to oxidize the corresponding dihydrocarbazoles. Indeed, by treating a representative group of dihydrocarbazoles **3** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for only 5 min, we were able to obtain six 4-arylcarbazoles (**5**) in excellent yield (Scheme 4).

Scheme 4. Oxidation of Dihydrocarbazoles with DDQ[a]

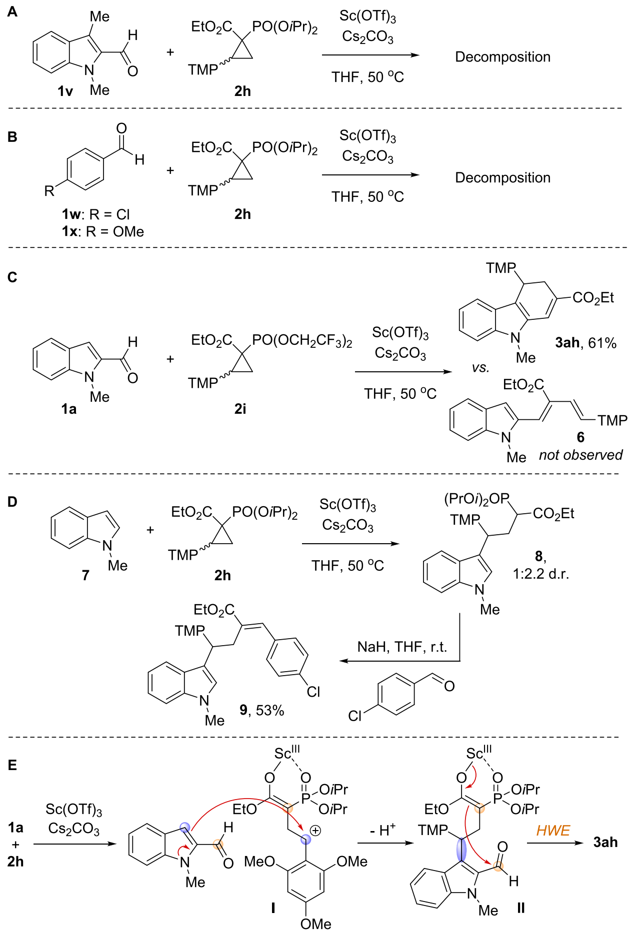


[a]Reaction conditions: **3** (0.10 mmol), DDQ (0.11 mmol) in toluene (0.5 mL), 0 °C, 5 min.

Finally, we focused our attention on the mechanism of the (3 + 3) cycloaddition, notably on establishing the order of events. We previously observed that C4 substituents significantly decreased the yield (**3d**), probably due to steric effects, suggesting that the alkylation step should takes place prior to the HWE olefination, contrary to what we observed with vinylcyclopropanes in palladium-catalyzed (4 + 3) cycloadditions.[13] Moreover, because electron density at the

C3 position is a crucial factor for the cyclization, it is not surprising that indole-4-carboxaldehydes (**3r**−**3u**) performed better than indole-2-carboxaldehydes (**3ah**−**3q**). Indeed, in the former case, the C3 position is more electron-rich than that in the latter (due to inductive and resonance effects). To gain further support for the proposed mechanism, we performed the reaction with the C3 methyl-substituted indolecarboxaldehyde **1v** (Scheme 5A). As expected, no reaction was observed, most likely due to steric hindrance. Similarly, substituted benzaldehydes **1w** and **1x** (Scheme 5B) did not afford styrene derivatives, demonstrating that the intermolecular HWE step does not take place under these conditions. In both cases, decomposition was observed when the temperature was increased to 100 °C. A key experiment involved the use of cyclopropane **2i** and aldehyde **1** (Scheme 5C). Given the *Z* selectivity of the Still−Gennari olefination, the linear product **6** would be expected if the olefination occurred first. However, dihydrocarbazole **3ah** was obtained in 61% yield, nearly identical to the analogous reaction with cyclopropane **2h** (68%), suggesting that the olefination occurs only after the alkylation. Finally, when *N*-methylindole (**7**, which does not contain an aldehyde moiety) was used, the linear product **8** was obtained (Scheme 5D), providing additional evidence that the reaction is initiated by the alkylation. Because of purification issues, crude **8** was directly reacted with 4-chlorobenzaldehyde, affording **9** in 42% yield over two steps. On the basis of these observations, we postulate the following mechanism: After activation of the DAC **2h**, the resulting benzylic cation **I** is attacked by the C3 position of **1a**. The formed intermediate **II** then undergoes intramolecular HWE olefination to give **3a** (Scheme 5E).

Scheme 5. Mechanistic Investigation



In conclusion, we report formal (3 + 3) and (3 + 4) cycloadditions of 2- or 4-indolecarboxaldehydes and phosphonate-functionalized DACs, affording a wide range of dihydrocarbazoles or cyclohepta[*cd*]indoles, respectively. A slight modification to the reaction conditions provided selective access to the corresponding fully aromatic carbazoles and cyclohepta[*cd*]indoles by thermal loss of the electron-rich aryl substituent. The investigation of the mechanism revealed that the alkylation step precedes the olefination, in contrast with our previous findings with vinylcyclopropanes under palladium catalysis.[13]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02795.

Experimental details and characterization data and ^{1}H and ^{13}C NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**−**i**, **3aa**−**ah**, **3b**−**u**, **4a**,**b**,**e**,**k**,**m**,**q**,**t**, **5a**,**c**,**e**,-**h**,**i**,**j**,**m**, and **9** (ZIP)

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Notes

The authors declare no competing financial interest.

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