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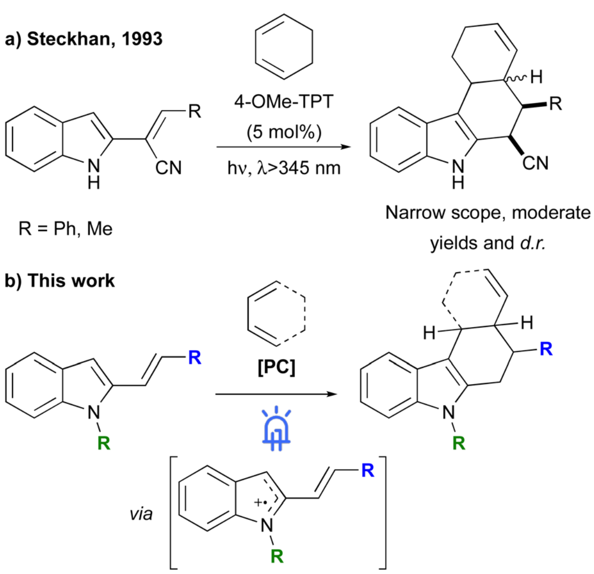
Synthesis of tetrahydrocarbazoles through a radical cation [4+2] cycloaddition reaction of 2-vinylindoles†

Elisa Brambilla,[a] Elisa Moretti,[a] Mirko Magni,[b] Giorgio Abbiati[a] and Valentina Pirovano*[a]

A redox umpolung strategy for the synthesis of complex tetrahydrocarbazoles is reported. The reaction involves a visible light promoted radical cation [4+2] cycloaddition between 2-vinylindoles and conjugated alkenes that proceeds with good yields and diastereoselectivity.

For more than thirty years, 2-vinylindoles have represented an incomparable four-atom building block for the synthesis of polycyclic indole scaffolds, such as carbazoles and tetrahydrocarbazoles, *via* [4+2] cycloaddition reactions.[1] Their easy preparation from commercially available substrates, flexible substitutions on both the indole and vinyl moieties and versatile reactivity in the presence of suitable 2C partners, in fact, have made these substrates an ideal synthon to efficiently build up molecular complexity. Starting from the pioneering works of Pindur, in which tetrahydrocarbazoles were prepared from 2-vinylindoles through thermal Diels–Alder reactions with α,β-unsaturated carbonyl compounds[2] many efforts have been devoted to the development of catalytic [4+2] cycloadditions characterised by broad substrate scope, mild reaction conditions and high levels of stereoselectivity. Examples of [4+2] cycloadditions employing electron-poor alkenes as two carbon units were reported, by our and by other research groups, under Lewis acid[3] and organo-catalysis.[4] Furthermore, we also expanded the applicability of these reactions to other unsaturated systems such as *N*-allenamides[5] and propargylic esters[6] under gold catalysis. However, all reported examples of [4+2] cycloadditions of electron-rich 2-vinylindoles require the use of an electron-poor partner. A strategy to overcome this limitation could be represented by the development of a radical [4+2] cycloaddition reaction.[7] In this case, in fact, the single electron oxidation of the 2-vinylindole would generate its radical cation providing the required difference in electron density for the cycloaddition with neutral alkenes.[8] An example of this reactivity has been reported in 1993 by Steckhan, which studied a radical [4+2] cycloaddition promoted by a triarylpyrylium salt, between 2-vinylindoles bearing a CN group at the α-vinyl position and 1,3-cyclohexadiene (Scheme 1a).[8c] Despite its innovativeness, the substrate scope of this reaction was very limited and the corresponding tetrahydrocarbazoles were obtained with modest yields and diasteroselectivities. For this reason and, considering our research interests in the synthesis of complex indole derivatives through [4+*n*] cycloadditions of 2-vinylindoles, we focused our attention on the development of a radical cation [4+2] cycloaddition between ready-available 2-vinylindoles and conjugated alkenes under visible light photoredox catalytic conditions (Scheme 1b).



Scheme 1 Radical [4+2] cycloaddition reactions.

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[a] *Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via G. Venezian 21, 20133, Milano, Italy. E-mail: valentina.pirovano@unimi.it*

[b] *Department of Enviromental Science and Policy, Università degli Studi di Milano, Via Celoria 2, 20133, Milano, Italy*

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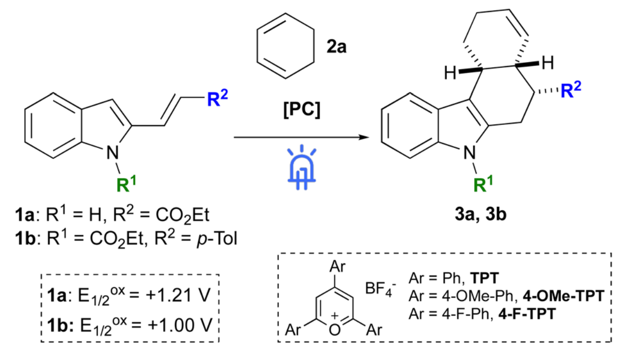
The results that we obtained from the screening of the reaction conditions are summarized in Table 1 (see ESI† for the full screening table). A preliminary electrochemical investigation by cyclic voltammetry was aimed at ranking the selected substrates according to their half-wave potentials of the first oxidation reaction ($E^{\text{ox}}_{1/2}$) to estimate their thermodynamic capability to be oxidized by commonly employed photocatalysts.

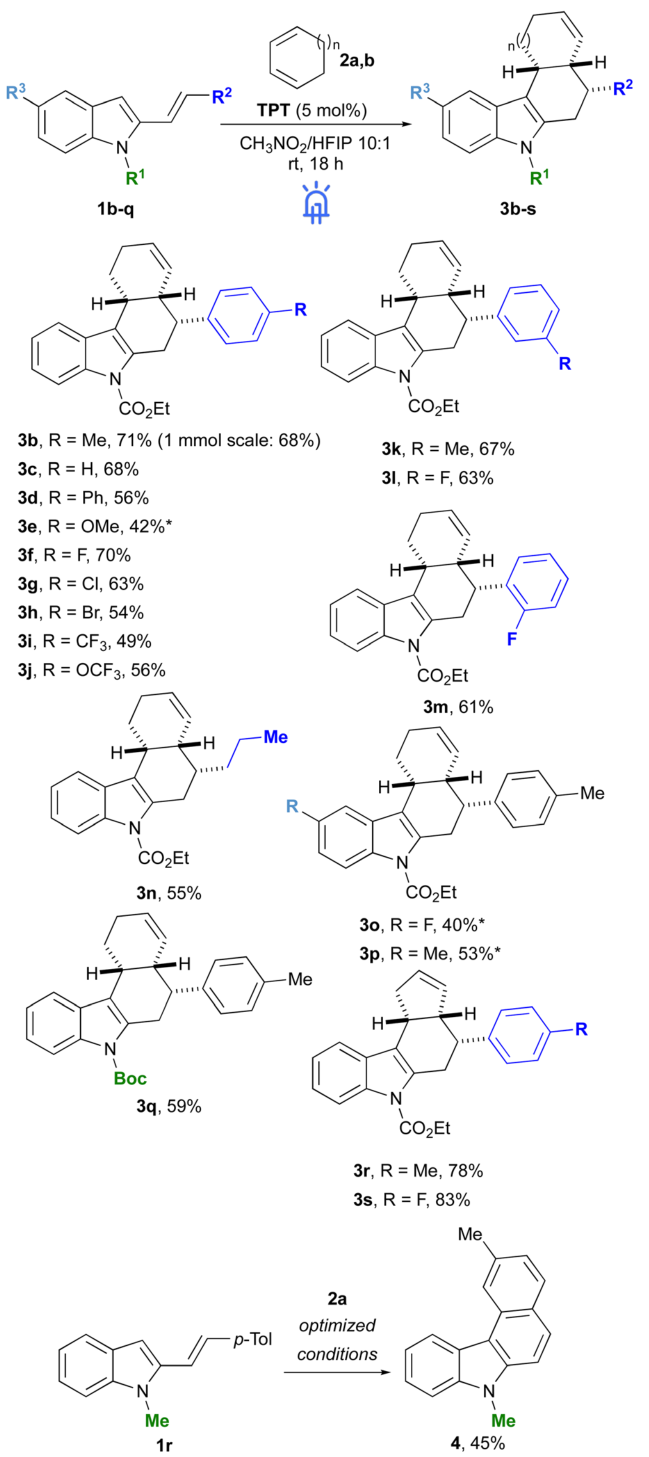
Considering previous reports from Steckhan on radical cycloaddition reactions,[7e,8a,c,d] we verified the activity of pyrylium salts to promote the formation of tetrahydrocarbazoles **3**. Employing 5 mol% of triphenylpyrylium tetrafluoroborate (TPT) as a catalyst we observed a complex mixture of unidentified products when **1a** was used as a substrate. Conversely, vinylindole **1b** afforded tetrahydrocarbazole **3b** in a modest 32% yield and with complete diastereoselectivity (*d.r.* $>$ 20 : 1), (entry 2). Interestingly, despite the modest yield, vinylindole **1b** was completely consumed at the end of the reaction and a series of unidentified side-products were observed in the crude mixture together with **3b**. Furthermore, dimerization of 1,3-CHD or [2+2] cycloaddition products were never detected. Changing the reaction solvent and employing DCE instead of CH_3CN led to a slight increase of the yield (entry 3). Aryl substituted pyrylium salts were then tested in DCE but neither 4-OMe-TPT nor 4-F-TPT led to better results (entries 4–5). An interesting increase of the yield up to 48% was instead observed with CH_3NO_2 as a solvent (entry 6) or when HFIP was added as a co-solvent[9] with DCE (entry 7). The combination of CH_3NO_2 and HFIP (10 : 1, 0.1 M) afforded **3b** in 57% yield (entry 8), while a satisfying 71% yield was finally obtained increasing the equivalents of **2a** up to 4 (entry 9). Having the optimized conditions in hand, we examined the reactivity of vinylindoles

Table 1 Optimisation of the reaction conditions[a]



Entry	1	[PC] (5 mol%)	Solvent	3, (%)[bc]
1	**1a**	TPT	CH_3CN	—[d]
2	**1b**	TPT	CH_3CN	32
3	**1b**	TPT	DCE	42
4	**1b**	4-OMe-TPT	DCE	39
5	**1b**	4-F-TPT	DCE	26
6	**1b**	TPT	CH_3NO_2	48
7	**1b**	TPT	DCE/HFIP (10 : 1)	48
8	**1b**	TPT	CH_3NO_2/HFIP (10 : 1)	57
9[e]	**1b**	TPT	CH_3NO_2/HFIP (10 : 1)	71

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 2 equiv.), catalyst (5 mol%), in the stated solvent (2 ml, 0.1 M) at rt for 18 h under 40 W blue led irradiation ($\lambda_{\max}$ = 440 nm). [b] Isolated yield. [c] *d.r.* $>$ 20 : 1. [d] Degradation of **1a**. [e] 4 equivalents of **2a** were used. ($E^{\text{ox}}_{1/2}$) values *vs.* SCE in CH_3CN.

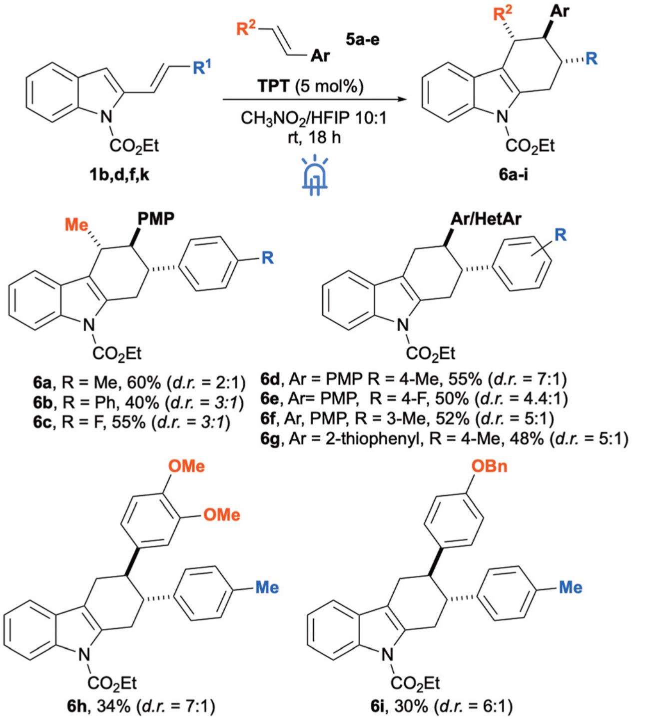


Scheme 2 Scope of the reaction between 2-vinylindoles **1b-r** and 1,3-CHD (**2a**) or cyclopentadiene (**2b**). Reaction conditions: **1b-r** (0.2 mmol), **2a,b** (0.8 mmol), TPT (5 mol%), in CH_3NO_2/HFIP 10 : 1 (2 ml, 0.1 M) at rt for 18 h under 40 W blue led irradiation ($\lambda_{\max}$ = 440 nm). Isolated yields are reported. *d.r.* $>$ 20 : 1. *Reaction time = 48 h.

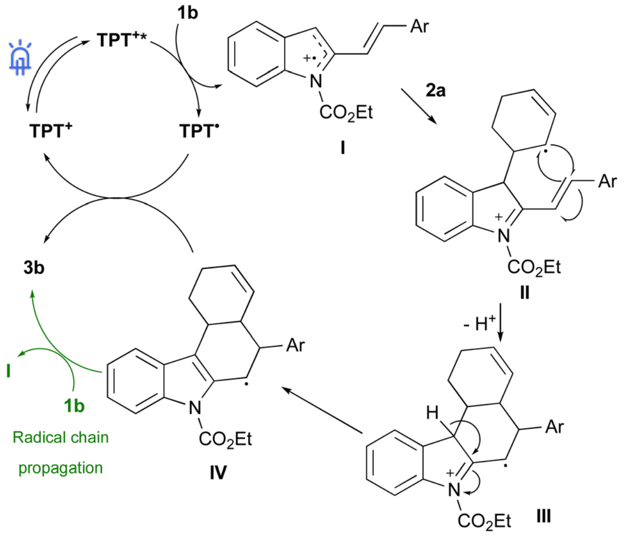
1b-q with 1,3-CHD **2a** (Scheme 2). In all cases, products **3b-q** were formed as single diastereoisomers (*d.r.* > 20 : 1). Modification of the nature of 2-vinylindole was generally well tolerated and applying the optimised reaction conditions we were able to synthesise a library of tetrahydrocarbazoles **3b-q** with good yields. In particular, 4-styryl substituted vinylindoles bearing electron-donating and electron-withdrawing substituents afforded the corresponding products **3d-e** and **3f-j** with yields ranging from 42 to 70%. Notably, 4-OMe substituted 2-vinylindole **1e** gave the worst result despite the prolonged reaction time of 48 h. Substituents in the 3- or 2-position of the aryl group were also tolerated, and the corresponding carbazole derivatives **3k-m** were isolated with satisfactory yields. Interestingly, an alkyl-substituted vinylindole **1n** could be employed in the radical cycloaddition reaction to afford product **3n** in 55% yield. Next, we evaluated the effect of various substituents at the 5-C position of indole scaffolds. In this case the reaction gave the desired products **3o-p**, albeit in lower yields and after a prolonged reaction time (48 h). Finally, a Boc protecting group could be used as an alternative to CO_2Et to prepare Boc-derivative **3q**, while *N*-methyl substituted vinylindole **1r** did not give the expected tetrahydrocarbazole under standard conditions but an intramolecular cyclization product **4** in moderate yield. Variations on 1,3-conjugated diene were more complicated. We tried several cyclic and acyclic substrates, however, only cyclopentadiene (**2b**) reacted with 2-vinylindoles **1b** and **1f** affording the corresponding tetrahydrocarbazoles **3r** and **3s** in 78% and 83% yield, respectively, and as a single diastereoisomer. Conversely, 1,3-cycloheptadiene and 2-(trimethylsiloxy)-1,3-cyclohexadiene gave no reaction under the optimised conditions, while α-terpinene, isoprene and 2,3-dimethyl-1,3-butadiene led to complex mixtures mainly of unreacted **1b** and unidentified side-products. Similarly, not all the tested 2-vinylindoles gave successful results: α-substituted and disubstituted vinylindoles as well as a vinylindole having R^2 = SMe were not reactive or led to a complex mixture of products (see ESI†).

As a continuation, we searched for alternative 2C partners to expand the scope of the cycloaddition reaction with 2-vinylindoles and, among all the possibilities, styrenes were selected because of their wide use in radical cycloadditions (albeit as oxidable species)[7i–l,10] (Scheme 3). Vinylindoles **1b**, **1d** and **1f** smoothly reacted under the optimised conditions with 2 equivalents of *trans*-anethole (**5a**) affording the corresponding tetrahydrocarbazoles **6a-c** with moderate yields and *d.r.* ranging from 2 : 1 for **6a** up to 3 : 1 for **6b** and **6c**. 4-Methoxystyrene (**5b**) could also be employed and yielded carbazoles **6d-f** when reacted with the corresponding 4- or 3-arylsubstituted vinylindoles **1b**, **1f** and **1k**, while 2-vinylthiophene (**5c**) gave **6g** by its reaction with **1b**. Interestingly, in this case, the yields were still moderate but *d.r.* increased up to 7 : 1 for product **6d**. Other styrenes such as 3,4-dimethoxy or benzyloxy derivatives **5d-e** were also tested and led to the formation of products **6h** and **6i** even if in lower yields.

Considering the observed reactivity and previous mechanistic investigations on radical cation cycloaddition reactions,[11] including transformations on indole derivatives,[8,12] the mechanism that we propose for the synthesis of tetrahydrocarbazoles **3** is reported in Scheme 4. Single electron oxidation, promoted by the excited state of the triphenylpyrylium tetrafluoroborate (TPT^{+}; $E_{1/2}$ = TPT^{+*}/$TPT^{\bullet}$ = 2.28 V *vs.* SCE)[13] leads to the formation of indoxyl radical cation **I** (**1b**, $E^{\text{ox}}_{1/2}$ = 1.00 V *vs.* SCE). Radical attack of the C3 position of indole on 1,3-CHD (**2a**, $E^{\text{ox}}_{1/2}$ = 1.54 V *vs.* SCE)[14] gives radical intermediate **II**, which cyclises on exocyclic double bond to afford **III**. Aromatisation of the indole core to **IV**, followed by single



Scheme 3 Scope of the reaction with styrenes **5a-e**. Reaction conditions: **1b,d,f,k** (0.2 mmol), **5a-e** (0.4 mmol), TPT (5 mol%), in CH_3NO_2/HFIP 10 : 1 (2 ml, 0.1 M) at rt C for 18 h under 40 W blue led irradiation (λ_{max} = 440 nm). Isolated yields are reported.



Scheme 4 Hypothesised reaction mechanism.

electron reduction finally leads to product **3b**. Considering this last step, reduction of **IV** to **3b** might be promoted by the photocatalyst (TPT$^{\bullet}$) with concurrent regeneration of the active species (TPT^{+}), or, as for analogous transformations,[15] might likely proceed through a radical chain propagation mechanism that involves the oxidation of a second equivalent of **1b** to **I**. We believe that a similar mechanism could also be invoked for the reaction of 2-vinylindoles with styrenes. A comparison between the oxidation potentials of **1b** (1.00 V *vs.* SCE) and *trans*-anethole or 4-methoxy styrene (1.24 V and 1.29 V *vs.* SCE, respectively)[14,16] suggests the preferential oxidation of **1b** to **I** rather than the formation of a styryl radical cation from **5**. Finally, a difference in the reactivity of **1a** and **1b** could be explained by cyclic voltammetry studies. Despite being both oxidisable by the catalyst (**1a**, $E_{1/2}^{\mathrm{ox}} = 1.21$ V *vs.* SCE), CV revealed different voltammetric patterns that thus imply a different reactivity (see ESI† for detailed description).

In conclusion we have designed a radical cation [4+2] cycloaddition of 2-vinylindoles promoted by an organic photoredox catalyst. The single electron oxidation of these substrates to the corresponding indoxyl radical cations allows for their reaction with otherwise unreactive conjugated alkenes. Therefore, through a redox umpolung strategy we were able to efficiently synthesise a new series of tetrahydrocarbazoles.

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Conflicts of interest

There are no conflicts to declare.

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