Heterocycles

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Organocatalyzed CO_2 Trapping Using Alkynyl Indoles**

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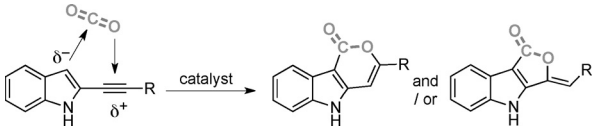
Abstract: *The first organocatalyzed trapping of CO_2 through C–C and C–O bond formation is reported. Alkynyl indoles together with catalytic amounts of an organic base and five equivalents of CO_2 resulted in the formation new heterocyclic structures. These tricyclic indole-containing products were successfully prepared under mild reaction conditions from aromatic, heteroaromatic, and aliphatic alkynyl indoles with complete regioselectivity. Further investigations suggest that C–C bond formation is the initial intermolecular step, followed by lactone-forming C–O bond formation.*

The indole skeleton represents an important structural constituent in a number of natural products displaying a wide variety of biological and pharmaceutical activities.[1] For this reason, the functionalization of indoles has been extensively studied,[2] and its expansion to multicyclic nitrogen-containing structures is relevant for the identification of new biologically active compounds. Because of the growing interest in CO_2 as an attractive C_1 building block in organic synthesis,[3,4] we became interested in exploring whether CO_2 could be employed in the construction of more complex indole-ring-containing molecules.

Few examples have been described in the literature on indole functionalization with CO_2. Among them, Hattori et al. reported the use of dialkylaluminum chloride as a Lewis acid for the direct carboxylation of indoles and pyrroles with CO_2.[5] More recently, Kobayashi and co-workers developed the carboxylation of different indole derivatives, mediated by an excess of *t*BuOLi.[6] However, all of these methodologies, require the stoichiometric use of an air- or moisture-sensitive reagent to ensure efficient carboxylation.[7]

Herein, we describe our results on the highly selective trapping of CO_2 using 2-alkynyl indoles to provide a range of new tricyclic indole structures in good yields. Notably, this transformation is catalyzed by a simple organic base rather than a transition-metal complex displaying complete regioselectivity and efficiency with only five equivalents of CO_2.

Inspired by the carboxylative cyclization of propargylic alcohols and propargylamines,[8] we envisioned the alternative use of a carbon nucleophile, thus resulting in a C–C bond-forming transformation. The C3-position of indole-rings are competent nucleophiles in a number of transformations,[9] while alkynes have been established as good electrophiles under gold catalysis.[10] To this end, 2-alkynyl indoles were selected as potential starting materials for this C–C bond-forming transformation furnishing multicyclic heteroaromatic ring systems with CO_2 fixation (Scheme 1).



Scheme 1. Concept of C–C bond formation by CO_2 trapping with 2-alkynyl indoles.

Initiating the search for a suitable catalyst and reaction conditions, a selection of gold(I) catalysts were screened in combination with different bases.[11] From these results, it became clear that a transition-metal catalyst was not required for this transformation to take place. The exclusive use of 2.0 equivalents of DBU furnished the 6-*endo-dig* cyclization product **2a** in a 73% yield (NMR) after 20 hours at 85°C (Table 1, entry 1). Even if the five-membered lactone arising from a 5-*exo-dig* cyclization could potentially also be formed, a series of NMR experiments (HSQC and HMQC) demonstrated the sole product to be the six-membered ring lactone **2a**, which was later confirmed by X-ray analysis (see the Supporting Information). It is well established that organic nitrogen bases are capable of reacting with CO_2 to form a carbamate adduct.[12] To this end, a range of nitrogen bases were examined as mediators for this reaction, (entries 1–7) and only DBU and TBD proved competent. Notably, strong bases such as a proton sponge (entry 5) and TMG (entry 7) failed to furnish **2a**. Reducing the amount of TBD to 50 mol% revealed that only a catalytic amount is required, thus attaining a near-quantitative yield (NMR) after 20 hours at 100°C (entries 8–10). Switching to MTBD or DBN provided poorer yields (NMR; entries 11 and 12), while the use of *t*BuOLi or the N-heterocyclic carbene IPr was detrimental for the transformation (entries 13 and 14). Using 30 mol% of TBD as catalyst for this transformation led to the isolation of **2a** in a 90% yield (entry 15), thus providing the optimal reaction conditions. Prolonging the reaction time to four days while lowering the catalyst loading

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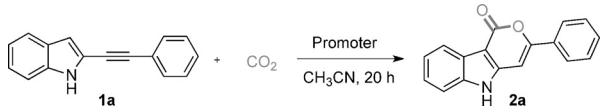
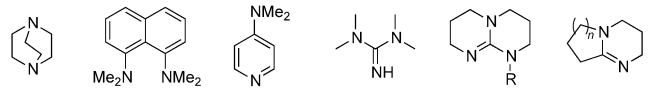
Table 1: Selected entries from the optimization of conditions for the organocatalyzed CO_2 trapping with 2-alkynyl indoles.[a]



Entry	Promoter (equiv)	*T* [°C]	Yield [%][b]
1	DBU (2.0)	85	73
2	TBD (2.0)	85	>95
3	DMAP (2.0)	85	0
4	DIPEA (2.0)	85	0
5	proton sponge (2.0)	85	0
6	DABCO (2.0)	85	0
7	TMG (2.0)	85	0
8	TBD (0.5)	85	88
9	TBD (0.5)	100	>95
10	TBD (0.2)	100	90
11	MTBD (0.2)	100	60
12	DBN (0.2)	100	50
13	LiO*t*Bu (0.5)	100	0
14	IPr (0.3)	100	0
15	TBD (0.3)	100	93 (90)
16[c]	TBD (0.05)	100	>95

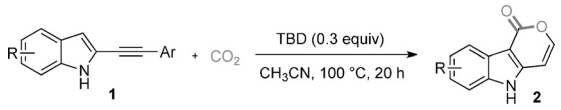


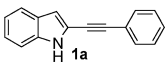
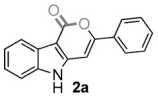
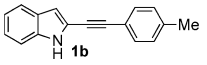
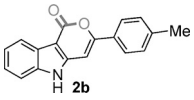
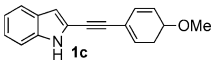
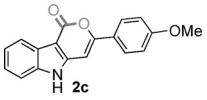
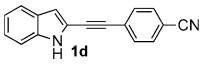
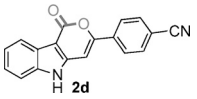
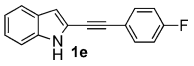
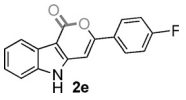
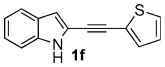
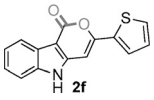
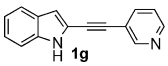
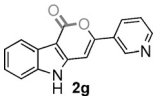
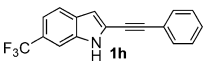
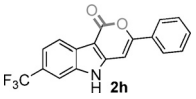
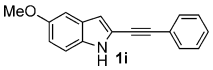
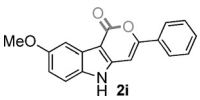
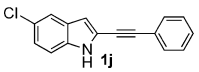
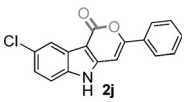
[a] Reaction conditions: **1a** (0.10 mmol) and mediator/catalyst in CH_3CN (0.5 mL), then CO_2 (0.61 mmol). [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Yield of isolated product is shown within parentheses. [c] 4 days. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, MTBD = 1-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TMG = 1,1,3,3-tetramethylguanidine.

to only 5 mol% of TBD similarly ensured complete conversion of **1a** into **2a** (entry 16). Although this was highly pleasing, the reaction conditions from entry 15 were subsequently used because of the faster reaction times.

We then set out to investigate the scope initially, thus focusing on aromatic 2-alkynyl indoles (Table 2). Substrates bearing either electron-donating or electron-withdrawing substituents on the phenyl ring proved reactive with little variation the yields of the isolated products **2b–e** (entries 2–5). Heterocyclic substituents such as thienyl and pyridyl are likewise tolerated, thus furnishing **2f** and **2g** in 69 and 71% yield, respectively (entries 6 and 7). A selection of substrates displaying substituted indole rings was then examined. With the medicinally important and electron-withdrawing trifluoromethyl positioned on C6, **2h** was isolated in 65% yield, whereas the reagent **1i**, displaying a 5-methoxy group, was converted into **2i** in a 71% yield (entries 8 and 9). A chloro substituent in the 5-position is well tolerated, thus allowing post-reaction transformation of **2j** through an array of cross-coupling chemistry (entry 10). To demonstrate the scalability of this transformation, **2j** was prepared on a 5.5 times larger scale with little variation in the yield of the isolated product.

Table 2: Scope of aromatic 2-alkynyl indoles.[a]



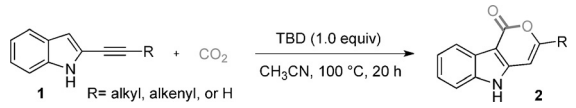
Entry	**1**	**2**	Yield [%][b]
1			90
2			83
3			72
4			79
5			80
6			69
7			71
8			65
9			71
10			79 (83)[c]

[a] Reaction conditions: **1** (0.20 mmol) and TBD (0.06 mmol) in CH_3CN (1.0 mL), then CO_2 (0.61 mmol) for 20 h at 100°C. [b] Yield of isolated product. [c] 1.1 mmol scale applying 2.2 equivalents of CO.

In contrast, moving the chloro substituent to the C4-position of the indole ring was detrimental for the transformation (results not shown).

With aliphatic 2-alkynyl indoles, the loading of TBD had to be increased to 1.0 equivalents as these substrates proved less reactive (Table 3). Simple linear and cyclic aliphatic chains were tolerated equally well, thus providing **2l** and **2m** in 82% yields (entries 1 and 2). Similarly, with the more sterically encumbered secondary α-alkynyl carbon atom presented by **1n** and **1o**, good results were obtained. The products **2n** and **2o**, displaying a cyclopropyl and a cyclohexyl, respectively, were isolated in the corresponding yields of 86 and 83%, with no observation of cyclopropane opening (entries 3 and 4). The presence of a silyl- or acetal-protected alcohol had little effect on the efficiency of the reaction as **2p** and **2q** were isolated in 75 and 80% yield, respectively

Table 3: Scope of aliphatic 2-alkynyl indoles.[a]



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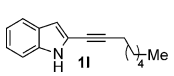
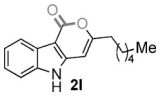
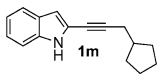
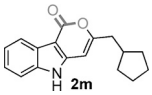
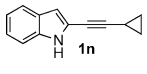
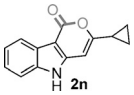
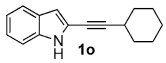
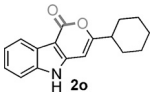
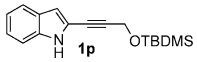
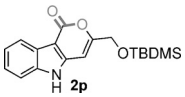
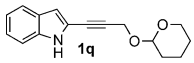
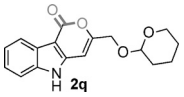
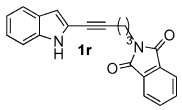
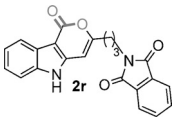
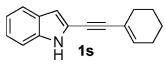
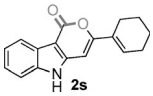
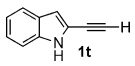
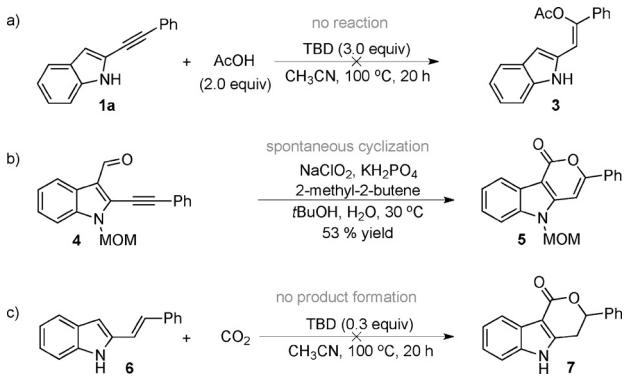
1			82
2			82
3			86
4			83
5			75
6			80
7			68
8			74
9			53[c]

[a] Reaction conditions: **1** (0.20 mmol) and TBD (0.06 mmol) in CH_3CN (1.0 mL), then CO_2 (0.61 mmol) for 20 h at 100 °C. [b] Yield of isolated product. [c] TBD (0.60 mmol) at 70 °C. TBDMS = *tert*-butyldimethylsilyl.

(entries 5 and 6). In contrast, a phthalimido-protected amine retarded product formation slightly, thus furnishing a 68% yield of **2r** (entry 7). Using an enyne indole secured a good yield of the isolated **2s** (entry 8). Finally, with a terminal alkynyl indole, the product appeared to decompose at 100 °C and consequently a reaction temperature of 70 °C combined with 3.0 equivalents of TBD were required to generate **2t** in an acceptable yield of 53% (entry 9). Attempts to employ other alkyne-substituted electron-rich aryl and heteroaryl ring systems for this transformation were unsuccessful in our hands.[13]

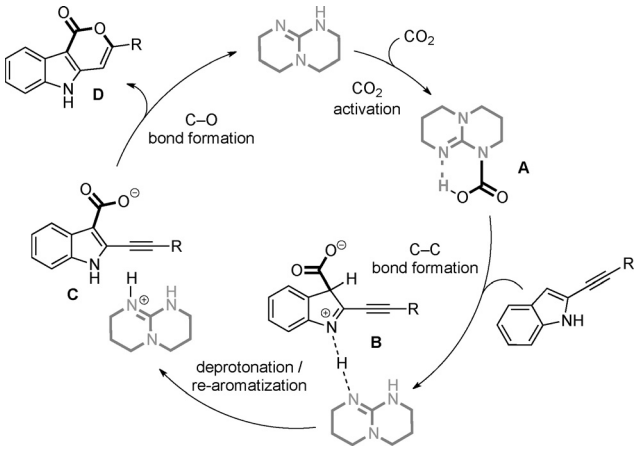
Having developed an efficient organocatalytic method for the functionalization of indoles, a small investigation of the mechanism of this transformation was undertaken (Scheme 2). The formation of a zwitterionic adduct upon treatment of TBD with CO_2 has been well established,[12d] and we speculated that this adduct was central in the mechanism. However, the observed results during the optimization could merely be a case of TBD being a strong base and an acyl-



Scheme 2. Mechanistic insight into this CO_2 trapping reaction with 2-alkynyl indoles.

transfer reagent. To this end, conducting the reaction with a combination of the equally strong base TMG and employing DMAP as an acyl-transfer reagent resulted in no conversion of starting material (results not shown).[11] Next, in an attempt to demonstrate whether electrophilic or nucleophilic attack onto the 2-alkynyl indole is the initial step, the transformation was carried out with a carboxylic acid in place of CO_2 (Scheme 2a). The nucleophilicity of the carboxylate should mimic that of the TBD–CO_2 adduct and provide **3** if nucleophilic attack onto the alkyne is indeed the initial step. However, after 20 hours at 100 °C, only the starting material **1a** could be detected in the reaction mixture. In contrast, the aldehyde **4** and its transformation into the carboxylic acid by a Pinnick oxidation, resulted in spontaneous cyclization and isolation of **5** in a 53% yield (Scheme 2b). Consequently, we believe that C–C bond-forming electrophilic attack of TBD coordinated CO_2 into the 2-alkynyl indole is the intermolecular step for the transformation.

While this reaction works well for 2-alkynyl indoles requiring a 6-*endo*-*dig* cyclization of the carboxylate onto the alkyne, we speculated β-indole styrenes would be competent substrates. Subjecting **6** to the optimized reaction conditions, however, only provided a complex product mixture with none of the desired product **7** being observed



Scheme 3. Proposed mechanism for this C–C and C–O bond-forming organocatalyzed CO_2 trapping using 2-alkynyl indoles.

(Scheme 2c). This outcome is attributed to poor orbital overlap in the required 6-*endo-trig* cyclization.[14]

With these results in hand the following mechanism is proposed (Scheme 3). After formation of the TBD-CO_2 adduct **A**, the C–C bond is formed by nucleophilic attack of the indole C3-position onto the TBD–CO_2 adduct to afford the intermediate **B**. Alternatively, the nucleophilic attack may take place directly onto CO_2, with no prior coordination to TBD.[8a] Subsequent re-aromatization by deprotonation furnishes the carboxylate **C**, which is setup for the favorable 6-*endo-dig* cyclization, the providing the lactone **D** and regenerating the TBD catalyst.

To conclude, we have developed a new methodology, thus allowing the formation of a C–C bond between CO_2 and an indole derivative leading to tricyclic indole-containing ring systems with the use of TBD as an organocatalyst. Good results have been obtained with aromatic, heteroaromatic, and aliphatic alkynyl indoles in terms of both yields and selectivities. This simple and user-friendly transformation only requires 5 equivalents of CO_2 along with as low as 5 mol% of TBD to give efficient turnover of aromatic alkynyl indoles. Thus, this method provides easy access to a range of novel polycyclic heteroaromatic compounds with potentially interesting biological properties. Further exploitation of these results for development of other CO_2 fixation reactions, as well as mechanistic investigations are ongoing.

Experimental Section

General procedure for carboxylative cyclization of alkynyl indoles with CO_2: 2-Alkynyl indole (**1**, 0.20 mmol, 1.0 equiv) and TBD followed by CH_3CN (1.0 mL) were added to a 10 mL vial in an argon-filled glove box. The vial was sealed with a screw cap, a 2 mm stabilizing PTFE disc and a 2 mm PTFE-lined silicone disc, and transferred outside the glovebox. By syringe, 15 mL CO_2 was injected into the vial through the septum. The reaction was stirred for 20 h at 100 °C. The reaction mixture was allowed to cool to room temperature. In some cases, the products were purified by direct filtration and washed with acetone several times. In other cases, the reaction mixture was concentrated in vacuo, before the crude oil was purified by flash chromatography.

Keywords: carbon dioxide · heterocycles · lactones · organocatalysis · synthetic methods

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[13] Two additional substrates 2-(phenylethynyl)benzo[*b*]thiophene and *N*-methyl-3-(phenylethynyl)aniline were examined.

[14] A *m*/*z* of 262.0875 corresponding to 3-carboxylation of the indole, could be observed in HRMS in negative mode. Attempts to isolate and characterize this product were unsuccessful.

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