

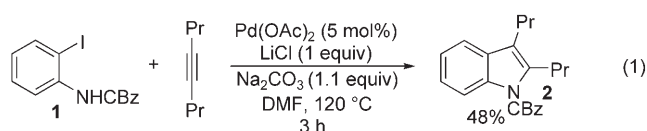
One-Pot Multicomponent Synthesis of Indoles from 2-Iodobenzoic Acid**

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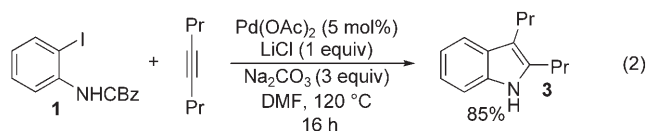
Considerable attention has been devoted to the synthesis of indole scaffolds because of their prominence as a motif in a wide variety of bioactive natural products and pharmaceutical compounds.^[1] The seminal work of Fischer and Jourdan^[2] has been followed by numerous other approaches to prepare this useful framework.^[3] Recently, the palladium-catalyzed annulation of 2-iodoanilines or anilides with internal alkynes or carbonyl compounds has emerged as one of the most powerful synthetic methods to access the indole skeleton.^[4] However, drawbacks such as the high cost and the low stability of 2-iodoanilines are still associated with this process.^[5] To overcome this problem, a one-pot strategy could be envisioned.^[6] Not only would such a process eliminate the need for isolation of the potentially unstable 2-iodoanilines, but also it would decrease the amount of chemical waste generated.^[7] Furthermore, it has been shown that the overall yields for one-pot procedures are higher than those of step-by-step processes.^[8] Synergistic effects between reactions are also likely, and it is possible that a by-product from a reaction could become a reagent in a subsequent reaction. Herein we report a novel multicomponent process that allows the transformation of readily available 2-iodobenzoic acid into indole derivatives by a one-pot Curtius rearrangement/palladium-catalyzed indolization process (Scheme 1). In this strategy the 2-iodoaniline intermediate is not isolated, and moreover one of the by-products of the Curtius rearrange-

ment becomes an essential reagent for the next step of the transformation.

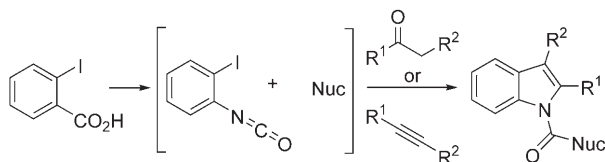
There are few reported examples of an intermolecular palladium-catalyzed indolization with alkynes in which a carbamate substrate is used.^[9] Initially the annulation reaction of benzyl 2-iodophenylcarbamate (**1**) and 4-octyne was investigated. By using the optimized reaction conditions of palladium acetate, one equivalent of lithium chloride, and sodium carbonate, the carbobenzoxy (CBz) protected indole **2** was isolated in 48% yield after three hours [Eq. (1)].^[10] This



moderate yield was a consequence of cleavage of the CBz-protecting group and indeed, a longer reaction time of 16 hours and an excess of base led to the exclusive formation of the unprotected indole **3** in an excellent yield [Eq. (2)].^[11] No indolization reaction occurred in the absence of lithium chloride, however an excess of the salt led to low yields.^[10]



We then investigated the formation of indole **3** using a one-pot Curtius-indolization process starting from 2-iodobenzoic acid (Table 1). This substrate was treated under the standard Curtius reaction conditions recently reported by our research group which allows the direct conversion of aromatic carboxylic acids into carbamates and ureas.^[12] The CBz-protected aniline intermediate **1** was not isolated, but directly subjected to the palladium-catalyzed indolization reaction



Scheme 1. One-pot multicomponent synthesis of indoles from 2-iodobenzoic acid. Nuc = nucleophile.

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Table 1: One-pot Curtius rearrangement/palladium-catalyzed indolization starting from 2-iodobenzoic acid and 4-octyne.

Entry	LiCl	Base [equiv]	Alkyne [equiv]	Yield [%]
1	yes	K ₂ CO ₃ (5.0)	5.0	29
2	no	Na ₂ CO ₃ (1.5)	1.5	71
3	no	K ₂ CO ₃ (1.5)	1.5	73
4	no	Cs ₂ CO ₃ (1.5)	1.5	40
5	no	Na₂CO₃ (3.0)	3.0	84
6	no	K ₂ CO ₃ (3.0)	3.0	73

conditions. A disappointing 29% yield of the desired indole **3** was observed when the standard reaction conditions for indolization (including one equivalent of lithium chloride) were used (Table 1, entry 1). It has been shown previously that an excess of a chloride salt is detrimental for palladium-catalyzed heteroannulations.^[4f] An equivalent of sodium chloride is generated in situ as a by-product after the Curtius rearrangement, thus remained in the reaction mixture and led to a low yield.

Significantly lower yields (67%) were observed for the indolization reaction in the presence of one equivalent of lithium chloride or one equivalent of sodium chloride, which are considerably less soluble than the in situ generated species.^[10] Conversely, when no lithium chloride was added, the reaction with 1.5 equivalents of both potassium carbonate and alkyne resulted in the yield of **3** improving to 73% (Table 1, entry 3). A real synergy was observed between the two reactions (namely the Curtius rearrangement and the indolization processes), as one by-product of the first step became a reagent in the second step. To our knowledge this is one of the few examples of such a synergistic effect in a one-pot strategy. After optimization, three equivalents of sodium carbonate proved to be the best base and gave **3** in 84% yield (compare Table 1, entry 5 to entries 2–4 and 6). This yield is comparable to that obtained for the individual indolization step [see Eq. (2)], which clearly illustrates that one-pot processes lead to higher yields than step-by-step procedures.

The above one-pot process is also compatible with aryl-substituted alkynes (Table 2, entry 1) and affords the corresponding indoles in good yield. Unsymmetrical alkynes gave

the corresponding indole **5** and **6** with complete regiocontrol in 56% and 82% yields, respectively (Table 2, entries 2 and 3). Aldehydes and ketones could also be used as coupling partners by using 1,4-diazabicyclo[2.2.2]octane (DABCO) instead of the carbonate base.^[4f] Under these modified reaction conditions, 2-iodobenzoic acid was converted into 3-benzylindole (**7**) in 50% yield using hydrocinnamaldehyde (Table 2, entry 4). A benzyl ether was also tolerated, producing indole **8** in 53% yield (Table 2, entry 6), and when cyclohexanone was employed, the tetrahydrocarbazole **9** was recovered in 56% yield.^[13]

The preparation of indole *N*-carboxamide derivatives,^[1,14] which are important pharmacophores, typically proceeds through the acylation of indoles.^[15] No intermolecular heteroannulation has so far been reported with aromatic ureas.^[7] Thus, we investigated a novel one-pot urea synthesis by using palladium-catalyzed heteroannulation with internal alkynes, to produce 2,3-disubstituted indole-carboxamide derivatives (Table 3). Treatment of 2-iodobenzoic acid with phenyl chloroformate and sodium azide, followed by addition of an amine led to the formation of the corresponding urea

Table 3: Synthesis of indole *N*-carboxamides from 2-iodobenzoic acid by a one-pot Curtius rearrangement/palladium-catalyzed indolization process.

Entry	Product	Yield [%] ^[a]
1		64
2		68
3		54
4		62
5		59
6		39

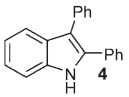
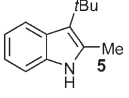
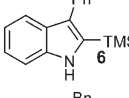
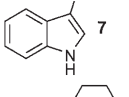
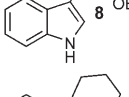
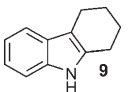
[a] Yields of isolated products. NMP = *N*-methyl-2-pyrrolidinone.

Table 2: Synthesis of indoles from 2-iodobenzoic acid by a one-pot Curtius rearrangement/palladium-catalyzed indolization process.



$\xrightarrow[2. \text{Pd}(\text{OAc})_2, \text{base, coupling agent}]{1. \text{NaN}_3, \text{CBzCl}, t\text{BuONa} (15 \text{ mol}\%), \text{DMF}, 75^\circ\text{C}, 5 \text{ h}}$



Entry	Coupling agent Base	Product	Yield [%] ^[a]
1	Ph≡Ph Na ₂ CO ₃	 4	77
2	Me≡ <i>t</i> Bu Na ₂ CO ₃	 5	56
3	Ph≡TMS Na ₂ CO ₃	 6	82
4	PhCH ₂ CHO DABCO	 7	50
5	BnOCH ₂ CH ₂ CHO DABCO	 8	53
6	 DABCO	 9	56

[a] Yields of isolated products. TMS = trimethylsilyl, Bn = benzyl.

intermediate. Without isolation, the intermediate was directly engaged in palladium-catalyzed indolization with diphenylpropyne or 4-octyne to give indole-carboxamides. The cyclic amines morpholine, piperidine, and pyrrolidine produced indoles **10–13** in 54–68% yield (Table 3, entries 1–4), whereas a substituted acyclic amine produced indole **14** in 59% yield (Table 3, entry 5). A moderate yield of indole **15** was obtained with phenylethylamine (Table 3, entry 6).

In conclusion, we have developed a novel one-pot Curtius rearrangement/palladium-catalyzed indolization process that allows the direct synthesis of 2,3-disubstituted and 3-substituted indoles starting from readily available 2-iodobenzoic acid. A synergistic effect between the two reactions of the process was observed, with a by-product of the first reaction serving as a reagent in the second synthetic step. In addition, the use of a one-pot procedure leads to higher yields while generating less by-products and chemical residues. This multicomponent process was also used to synthesize the first indole *N*-carboxamide derivatives through a heteroannulation procedure.

Experimental Section

Typical procedure: Benzyl chloroformate (150 μ L, 1.10 mmol) was added to a solution of sodium azide (0.110 g, 1.70 mmol), sodium *tert*-butoxide (14.4 g, 0.15 mmol), and 2-iodobenzoic acid (0.248 g, 1.0 mmol) in *N,N*-dimethylformamide (DMF, 5.0 mL) at 25°C. The resulting mixture was then stirred at 75°C for 5 h and then cooled to room temperature. Pd(OAc)₂ (11.2 mg, 0.05 mmol), the base (Na₂CO₃ for alkynes or DABCO for carbonyl compounds (3 mmol)), and the alkyne (3 mmol) or the carbonyl compound (3 mmol for ketones and 0.90 mmol for aldehydes) were then added and the mixture was heated at 120°C for 16 h. The reaction mixture was then cooled to room temperature and then filtered through celite, which was washed with EtOAc (100 mL). The resulting organic layer was washed with saturated NH₄Cl (2 $\times$ 40 mL) and brine (40 mL). The organic layer was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

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