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Palladium-Catalyzed Intramolecular Trapping of the Blaise Reaction Intermediate for Tandem One-Pot Synthesis of Indole Derivatives

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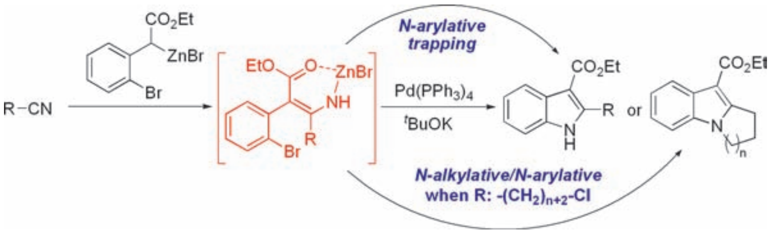
ABSTRACT



Palladium-catalyzed intramolecular N-arylative and N-alkylative/N-arylative trappings of the Blaise reaction intermediates could be a new route to construct the indole moiety in a tandem one-pot manner from nitriles.

Indole is a structural component in a vast number of natural products and biologically relevant compounds.[1] To date, numerous elegant approaches have been continuously developed to generate this unique heterocyclic ring moiety.[2] Most of these approaches rely on anilines or amines as nitrogen sources, and therefore the development of new methods for the synthesis of indoles from simple and readily available nonamino compounds is still a subject of interest. Moreover, methods for metal-catalyzed one-pot construction of N-fused indole moieties are quite limited.[3] We herein report a conceptually distinctive tandem one-pot approach for the construction of indoles and N-fused indole moieties from nitriles, which is based upon Pd-catalyzed intramolecular N-arylative or N-alkylative/N-arylative trappings of the Blaise reaction intermediates (Scheme 1). To the best of our knowledge, this represents the first example of the metal-catalyzed trapping of the Blaise reaction intermediate, a transformation of great synthetic potential.

Because of their undeniable benefits such as atom economy and one-pot operation with maximization of molecular complexicity, the device and implementation

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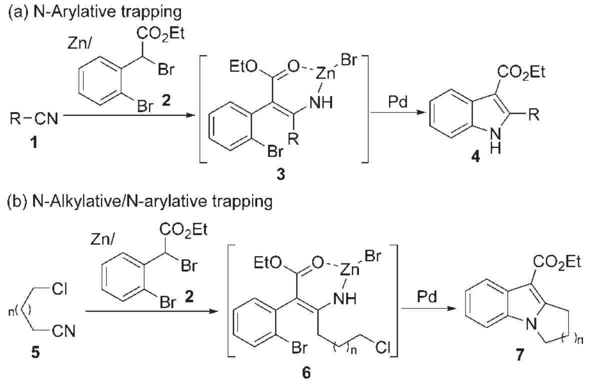
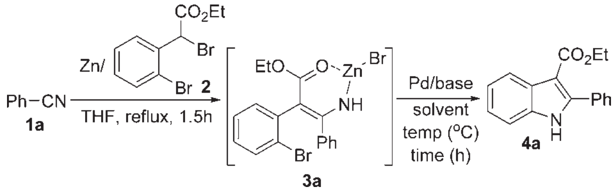
Scheme 1. Pd-Catalyzed Intramolecular Trapping Strategies for Tandem One-Pot Synthesis of (a) Indole and (b) N-Fused Indole Derivatives



of tandem reactions is a challenging facet and has become increasingly important in organic synthesis.[4] Due to the functional group tolerance, the electrophilic trapping of the zinc enolate intermediates is one of the most frequently employed strategies for tandem carbon−carbon bond formation reactions.[5] For example, Krische et al. reported the intramolecular electrophilic trapping of the zinc enolates, generated by Cu-catalyzed conjugate addition of organozinc to enones.[5d] Quite recently, Johnson et al. elegantly developed the double Reformatsky reaction and the tandem Reformatsky/quaternary Claisen condensation, through the electrophilic trapping of zinc enolate intermediates generated by the reaction of Reformatsky reagents with silylglyoxalates.[5e,f] Along these lines, we recently envisioned that the Blaise reaction intermediate, generated by the addition of a Reformatsky reagent to nitriles,[6] could be considered as a reactive aza-isostere of the zinc enolate of β-ketoesters for tandem carbon−carbon and carbon−nitrogen bond forming reactions via electrophilic trapping.[7] In the present work, by taking advantage of the well-developed Pd-catalyzed C−N bond forming process,[8] we became interested in studying the Pd-catalyzed intramolecular trapping of Blaise reaction intermediate **3** to construct the indole moiety **4** (Scheme 1a). In addition, if chemoselective intramolecular N-alkylation proceeded with the intermediate **6** having chloroalkyl appendages, the intramolecular N-alkylative/Pd-catalyzed N-arylative trapping cascade might be possible and provide a new one-pot route to N-fused indoles **7** (Scheme 1b).[9]

Table 1. Optimization Study for the Pd-Catalyzed N-Arylative Trapping of the Blaise Intermediate **3a**[a]



entry	Pd/base	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	$Pd(dba)_2$+SPhos/-	THF	65	48	-
2	$Pd(PPh_3)_4$/-	THF	65	48	-
3	$Pd(PPh_3)_4$/-	DMF	120	24	>10
4[d]	$Pd(dba)_2$+SPhos/NaHMDS	toluene	110	48	47
5[e]	$Pd(dba)_2$+XPhos/NaHMDS	toluene	110	48	38
6	$Pd(dba)_2$+SPhos/^{t}BuLi	toluene	110	15	74
7	$Pd(PPh_3)_4$ /NaHMDS	DMF	120	24	31
8	$Pd(PPh_3)_4$ /NaHMDS	DMSO	120	24	60
9	$Pd(PPh_3)_4$ /NaHMDS	toluene	110	24	30
10	$Pd(PPh_3)_4$ /^{t}BuOK	DMF	120	15	84

[a] Conditions: Ethyl (*o*-bromophenyl)-α-bromoacetate (1.3 equiv) was added over 1 h to a solution of **1a** (2.29 mmol) and Zn (2.0 equiv) in THF (0.9 mL) at reflux. After 1.5 h of reflux, the palladium catalyst [$Pd(PPh_3)_4$ (7.4 mol %) or $Pd(dba)_2$ (5 mol %)/ligand (10 mol %)], solvent (THF/solvent = 1/10, v/v), and base (1.3 equiv) were added at room temperature. [b] Isolated yield by column chromatography. [c] SPhos: 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. [d] NaHMDS: Sodium bis(trimethylsilyl)amide. [e] XPhos: 2-Dicyclohexylphosphino-2′,4′.6′-triisopropylbiphenyl.

To investigate the reactivity of the Blaise reaction intermediate under Pd-catalyzed intramolecular coupling conditions, we chose the intermediate **3a**, prepared by the reactions of benzonitrile (**1a**) with a Reformatsky reagent generated in situ from ethyl (*o*-bromophenyl)-α-bromoacetate **2** (Table 1).

Considering the recently disclosed Pd-catalyzed cross-couplings of the Reformatsky reagents with aryl halides

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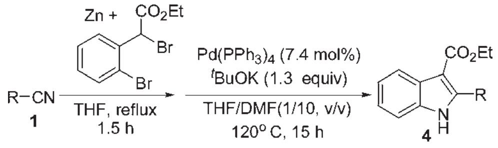
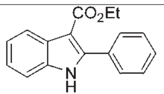
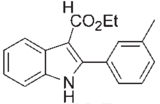
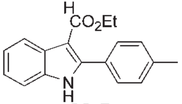
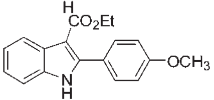
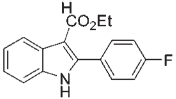
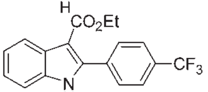
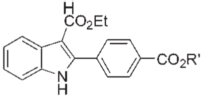
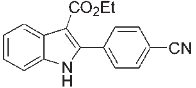
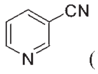
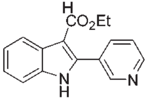
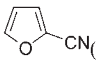
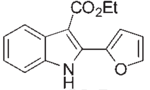
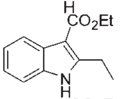
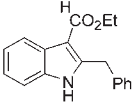
Table 2. Tandem One-Pot Synthesis of Indole Derivatives **4**[a]



entry	1	4	Yield (%)
1	PhCN (**1a**)		**4a** (84)
2	*o*-$CH_3C_6H_4CN$ (**1b**)		**4b** (74)
3	*p*-$CH_3C_6H_4CN$ (**1c**)		**4c** (72)
4	*p*-$CH_3OC_6H_4CN$ (**1d**)		**4d** (84)
5	*p*-FC_6H_4CN (**1e**)		**4e** (51)
6	*p*-$CF_3C_6H_4CN$ (**1f**)		**4f** (72)
7	*p*-$EtO_2CC_6H_4CN$ (**1g**)	 **4g**: R' = Et; **4g'**: R = ^{t}Bu	**4g** (71) **4g'**(6)
8	*p*-CNC_6H_4CN (**1h**)		**4g** (62)
9	 (**1i**)		**4i** (76)
10	(**1j**)		**4j** (64)
11	CH_3CH_2CN (**1k**)		**4k** (58)
12	$PhCH_2CN$ (**1l**)		**4l** (72)

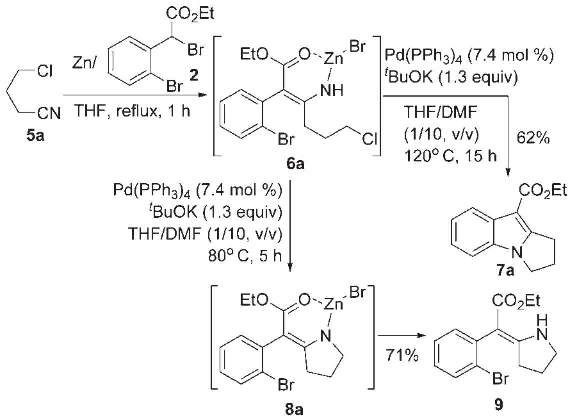
[a] Conditions: Ethyl (*o*-bromophenyl)-α-bromoacetate (1.3 equiv) was added over 1 h to a solution of nitrile **1** (2.29 mmol) and Zn (2.0 equiv) in THF (0.9 mL) at reflux. After 1.5 h of reflux, $Pd(PPh_3)_4$ (7.4 mol %), DMF (9.0 mL), and ^{t}BuOK (1.3 equiv) were added at room temperature, and the reaction mixture was heated to 120 °C for 15 h.

under base-free conditions,[10] we initially anticipated that the nucleophilic nature of the intermediate **3a** would make it possible to conduct the Pd-catalyzed intramolecular N-arylation in the absence of base. However, the tandem reactions did not proceed at all at THF reflux temperature in the presence of $Pd(dba)_2$/Sphos or $Pd(PPh_3)_4$ as the catalyst (entries 1 and 2, Table 1). When the reaction temperature was increased to 120 °C by heating in THF/DMF (1/10, v/v), the intramolecular N-arylation of **3a** proceeded but afforded **4a** in less than 10% yield (entry 3, Table 1). These results suggest that the nucleophilicity of the Blaise reaction intermediate **3a** may not be sufficient for the intramolecular transmetalation of the Pd^{2+} species, formed by oxidative addition of the *o*-bromide with Pd(0). Although the reaction efficiencies were substantially increased by addition of base and alteration of either the Pd source or the solvent, the yields were not sufficiently high (entries 4−9, Table 1). Gratifyingly, it was found that the N-arylative trapping of **3a** was effective in the presence of $Pd(PPhh_3)_4$ (7.4 mol %) and ^{t}BuOK (1.3 equiv) in THF/DMF (1/10, v/v) and afforded the corresponding indole **4a** in 84% yield (entry 10, Table 1).

Under the optimized conditions, various aromatic nitriles **1a**−**1h** with electron-donating and -withdrawing substitutents (entries 1−8, Table 2), heteroaromatic nitriles **1i** and **1j** (entries 9 and 10, Table 2), and aliphatic nitriles **1k** and **1l** (entries 11 and 12, Table 2) can be converted into the corresponding indoles **4a**−**4l** in a one-pot manner. Although 4-fluorobenzonitrile and propionitrile were converted to the corresponding indoles **4e** and **4k** in slightly diminished yields, the electronic nature of the substituents on the aromatic nitriles did not significantly influence the reactivity. The *p*-ethyl ester substituted benzonitrile **1g** afforded the mixture of indoles **4g** (71%) and **4g′** (ca. 6%) formed by ester exchange with ^{t}BuOK (entry 7, Table 2). One of the nitriles of terephthalonitrile **1h** can be transformed into the indole ring to afford **4g** in 62% yield (entry 8, Table 2).

To our delight, these reaction conditions could be applied to the N-alkylative/N-arylative trapping reactions. Thus, under the same reaction conditions, the tandem reaction of the Blaise reaction intermediate **6a**, formed from 4-chlorobutyronitrile **5a**, afforded the N-fused indole **7a** in 62% yield (Scheme 2). When the tandem reaction of **6a** was carried out at a lower temperature (80 °C), only the N-alkylated product **9** was isolated in 71% yield. These

Scheme 2. Pd-Catalyzed N-Alkylative/N-Arylative Trapping of the Blaise Reaction Intermdiate **6a**



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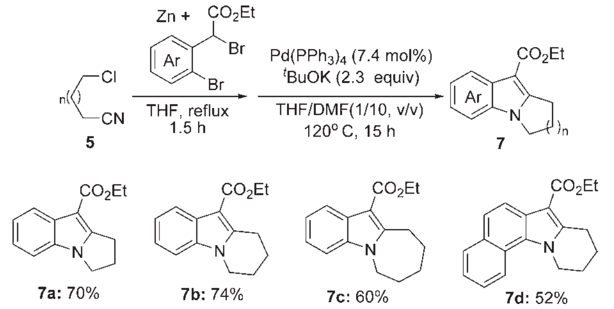
results suggested that the intramolecular N-alkylative trapping reaction of **6a** proceeded prior to the N-arylation with high chemoselectivity to generate **8a**, which has enough nucleophilicity for the intramolecular transmetalation of the oxidative addition adduct, Ar−Pd(II)−Br complex, to afford **7a**.

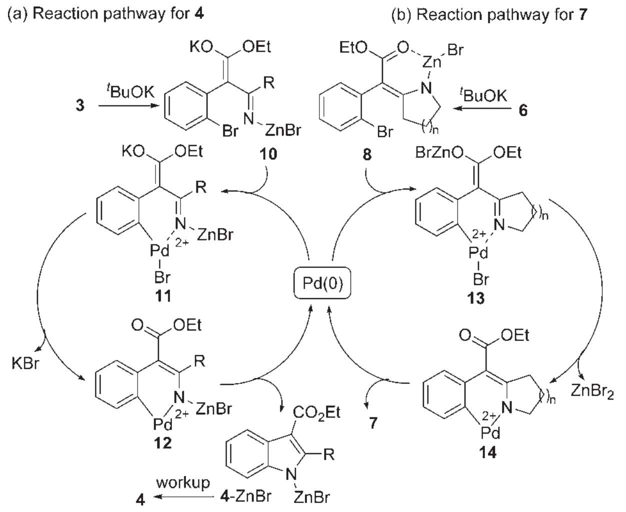
Scheme 3. Tandem One-Pot Synthesis of N-Fused Indoles **7**



Addition of one more equivalent of base increased the yield of **7a** to 70% (Scheme 3). Through the N-alkylative/N-arylative trapping reactions, the 6- and 7-membered N-fused indoles **7b** (74%) and **7c** (60%) could also be synthesized efficiently starting from the corresponding 5-chloropentanenitrile **5b** (n = 2) and 6-chlorohexanenitrile **5c** (n = 3). By using the Reformatsky reagent, generated from ethyl (1-bromonaphthalene-2-yl)-α-bromoacetate, the tetrahydrobenzopyrridoindole **7d** was synthesized from **5b** in 52% yield .

The possible reaction pathways for the formation of indoles **4** and N-fused indoles **7** are depicted in Scheme 4. Deprotonation of the acidic N−H of **3** could generate the iminoenolate **10**, which could oxidatively add to Pd(0) affording the arylpalladium(II) bromide complex **11**. Intramolecular transmetalation, followed by reductive elimination of the resulting Aryl−Pd(II)−N complex **12**, could regenerate Pd(0) for the next catalytic cycle, as well as the zinc bromide complex of indole **4-ZnBr**, which can then be converted to indole **4** after workup (Scheme 4a). For the formation of N-fused indoles **7**, the intramolecular N-alkylation of the Blaise reaction intermediate **6** may proceed first in the presence of base to form **8** having enough nucleophilicity for the intramolecular transmetalation of

Scheme 4. Possible Reaction Pathways for Indole **4** and N-Fused Indole **7**



13 to form **14**. Reductive elimination afforded the N-fused indole **7** (Scheme 4b).

In summary, we have developed a novel tandem one-pot method for the synthesis of indoles and N-fused indoles from readily available nitriles and Reformatsky reagents through the Pd-catalyzed intramolecular N-arylative and N-alkylative/N-arylative trappings of the Blaise reaction intermediates. This result has provided a platform for future studies probing applications of the Blaise reaction intermediate as a functionalized organozinc nucleophile for metal-catalyzed bond forming reactions.

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Supporting Information Available. Experimental details and spectral data of **4a**−**4l**, **7a**−**7d**, **8a** and their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.