PERKIN 1 COMMUNICATION

Palladium-catalyzed tandem *C*,*N*-arylation of immobilized enamine for solid phase indole synthesis †

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Intramolecular palladium-catalyzed *N*-arylation of immobilized dehydrohalophenylalaninate was found to proceed smoothly to form indolecarboxylates. The method was successfully combined with the Heck reaction to perform one pot indole synthesis *via* palladium-catalyzed tandem *C*,*N*-arylation reactions.

The palladium-catalyzed amination reaction is one of the most important methods for the preparation of arylamines, amides and carbamates.[1,2] An intramolecular version of the amination has allowed us to synthesize a wide variety of nitrogen-containing heterocyclic compounds.[3] A combination of amination and Heck reactions provides an attractive indole synthesis, for example, the palladium-catalyzed tandem amination–Heck reaction between 1,2-dibromobenzene and enaminone,[4] however further examples are not yet known. Tandem reactions have recently been of interest in the field of organic synthesis,[5] the sequential formation of carbon–carbon and carbon–heteroatom bonds can be accomplished in one synthetic step using a single catalyst. Therefore we have focussed our interest on solid phase indole synthesis[6] using palladium catalyzed tandem *C*,*N*-arylation reactions on a polymer support, as shown in Fig. 1. To date, the application of intramolecular amination in the solid phase chemistry is unprecedented in the literature. Here we report that tandem *C*,*N*-arylation reactions can be successfully applied in solid phase indole synthesis

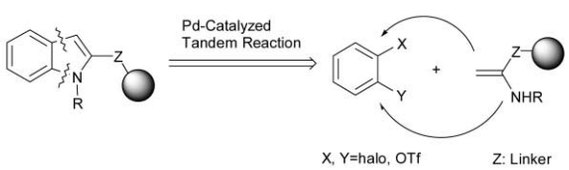
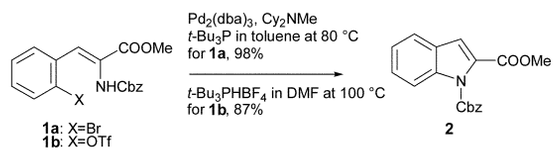


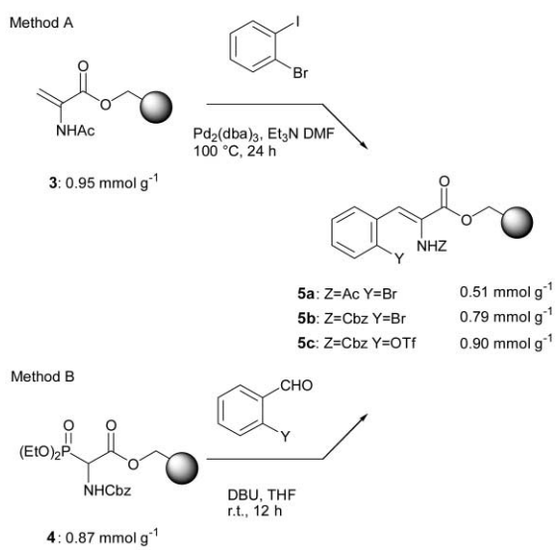
Fig. 1

In solution phase chemistry, Brown has already demonstrated that the intramolecular palladium-catalyzed annulation of dehydroiodophenylalanine can yield *N*-substituted indole-2-carboxylate derivatives.[3d] However, using the reported conditions, our cyclization reactions were not successful and we decided to optimize the catalytic system for the cyclization. We screened phosphine ligands for the intramolecular amination of **1a**,**b**, and *t*-Bu_3P[7] and *t*-Bu_3PHBF_4[8] were found to be the best ligands, as shown in Scheme 1.

On the basis of the above solution-phase results, we investigated the solid phase intramolecular palladium-catalyzed amination reaction. The substrates for the amination reaction, **5a**–**c** were synthesized by the following two methods, as shown in Scheme 2.



Scheme 1



Scheme 2

Method A: the Heck reaction of immobilized *N*-acetyldehydroalanine **3**[9] with 1-bromo-2-iodobenzene was performed under Heck coupling conditions of the regeneratable Michael (REM) resin.[10]

Method B: a rhodium catalyzed insertion reaction of immobilized α-diazophosphonoacetate[6c] with benzyl carbamate gave immobilized *N*-Cbz-α-phosphonylglycine **4** followed by Horner–Emmons reactions with 2-bromobenzaldehyde or 2-formylphenyl trifluoromethanesulfonate were performed. The loading values of **5a**–**c** were estimated by elemental analysis of nitrogen on the polymer beads or from yields after cleavage using Et_3N–MeOH at 50 °C. The values indicated smooth and reasonable progression of the transformation.

Palladium-catalyzed intramolecular amination of immobilized substrates was performed using similar reaction conditions as the solution phase procedure. Thus, immobilized intermediates **5a**–**c** were heated at 80–100 °C in the presence of $Pd_2(dba)_3$, ligand and Cy_2NMe in toluene or DME.[11] This was followed by the transesterification of polymer-bound indolecarboxylate using MeONa in MeOH–THF, and methyl indole-2-carboxylate **6**[12] was obtained in good to moderate yields (Scheme 3).

Next, we investigated the tandem *C*,*N*-arylation reactions for one-pot indole synthesis using the immobilized intermediate **3** (Scheme 4). In our approach, the initial step involves Heck

† Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/p1/b2/b206378f/

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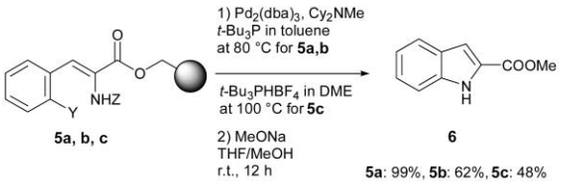
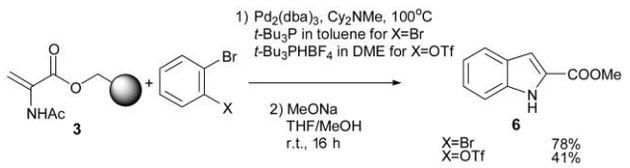


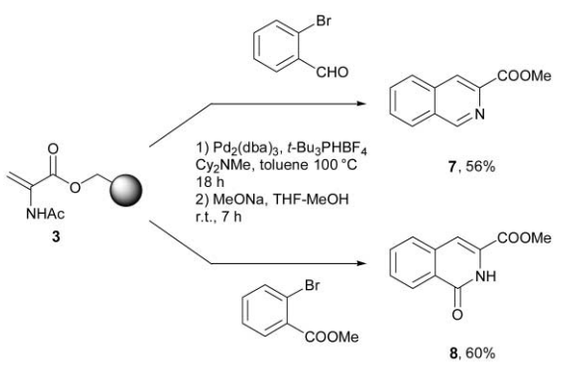
Scheme 3



Scheme 4

coupling followed by the amination reaction to yield a polymer-bound indole. It was found that 1,2-dibromobenzene works better than 1-bromo-2-iodobenzene for the tandem reaction, and the reaction at 100 °C led to indolecarboxylate in good yields after transesterification. Aryl triflates§ were also used as substrates, however further modification of reaction conditions seems to be necessary.

As an extension of the Heck reaction of the immobilized dehydroalanate, we examined isoquinoline synthesis. The Heck reactions of immobilized *N*-acetyldehydroalanine with 2-bromobenzaldehyde or methyl 2-bromobenzoate followed by transesterification gave isoquinoline-3-carboxylates **7**[13] or **8**[14] in moderate yield (Scheme 5).[15]



Scheme 5

In summary, the first solid phase intramolecular amination reaction for the synthesis of indolecarboxylate was achieved in high yield in the presence of palladium catalyst. The palladium catalyzed tandem *C*,*N*-arylation also provides a new one-pot method for solid phase indole synthesis. Further investigation on the scope and limitations towards synthesis of diverse heterocyclic libraries is currently under way.

Acknowledgements

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Notes and references

§ The IUPAC name for triflate is trifluoromethanesulfonate.

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15 *Typical experimental procedure*: To a mixture of resin **3** (300 mg, 0.285 mmol, 0.95 mmol g^{-1}), 1,2-dibromobenzene (0.051 ml, 0.428 mmol) tris(dibenzylideneacetone)dipalladium(o)·$CHCl_3$ (39 mg, 0.043 mmol) and *N,N*-dicyclohexyl-*N*-methylamine (Cy_2NMe) (0.18 ml, 0.855 mmol) in toluene (3 ml) was added 0.5 M toluene solution of tri-*tert*-butylphosphine (0.34 ml, 0.17 mmol) and the mixture was heated at 100 °C for 24 h. The resin was collected by filtration and washed with DMF (×3), DMF–H_2O = 1 : 1 (×3), DMF (×3), THF (×3), MeOH (×3) and the resin was dried under reduced pressure at 40 °C. The above resin and NaOMe (15 mg, 0.285 mmol) in THF (3 ml) and MeOH (1.5 ml) were agitated at room temperature for 16 h. The resin was separated by filtration and washed with ethyl acetate, the filtrate was washed with saturated aqueous NH_4Cl, water and brine, dried over Na_2SO_4 and evaporated to afford the crude product. The crude product was purified by chromatography on silica gel using hexane–ethyl acetate (4 : 1) to afford 39 mg (78%) of **6** as a colorless solid.