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Hydroamination/Heck reaction sequence for a highly regioselective one-pot synthesis of indoles using 2-chloroaniline†

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Received (in Cambridge, UK) 29th July 2004, Accepted 17th September 2004
First published as an Advance Article on the web 27th October 2004

A one-pot indole synthesis consisting of a highly regioselective $TiCl_4$-catalyzed hydroamination and a 5-*endo* Heck cyclization starting from 2-chloroaniline is described, using an *in-situ* generated, sterically hindered imidazol-2-ylidene palladium complex.

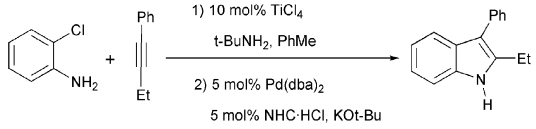
The prevalence of indoles in natural products and biologically active compounds has led to continued strong interest in practical syntheses of the indole scaffold.[1] In addition to classical approaches, such as the Fischer-indole synthesis, palladium-catalyzed annulation[2] and cyclization[3] reactions have proven useful tools for the preparation of indole derivatives. While the former approach has been extensively employed, its limitation to the use of aryl iodides constitutes a significant drawback. Particularly the annulation of aryl-substituted alkynes by 2-iodoaniline affords, according to Larock, unclean reactions, yielding a multitude of products.[4]

The hydroamination reaction, the addition of amines onto carbon–carbon multiple bonds, provides an efficient access to substituted amines from inexpensive feedstocks.[5] Within a number of protocols for the intermolecular hydroamination of alkynes, titanium-based transformations have gained considerable interest recently, due to low cost and low toxicity as well as good functional group tolerance of the catalysts.[6] We have developed user-friendly $TiCl_4$-catalyzed intermolecular hydroamination reactions of alkynes[7] and norbornene.[8] During these studies we found that *ortho*-halide substituents on aniline derivatives were tolerated by the catalyst. The enamine derived from 2-bromoaniline and tolane was subsequently used for the synthesis of 2,3-diphenylindole *via* a less common 5-*endo* Heck-reaction.[9,7] This encouraging preliminary result prompted us to develop a more convenient protocol for the synthesis of the indole framework, starting from readily available aryl chlorides[10] (Scheme 1). Herein, we present a regioselective one-pot synthesis of indole derivatives, which starts from inexpensive 2-chloroaniline and unsymmetrically substituted alkynes.[11]

To optimize the catalytic performance and to study the regioselectivity, we chose the conversion of unsymmetrically substituted 1-phenyl-1-butyne with 2-chloroaniline (Scheme 2, Table 1). 5 mol% of a palladium species derived from mesityl-substituted imidazol-2-ylidene provided 2-ethyl-3-phenylindole in a yield of only 37%, albeit with excellent regioselectivity (entry 1). A direct heteroannulation was not viable using this palladium catalyst. It is noteworthy, that the regioselectivity is complementary to the one obtained through Larock's annulation reaction employing unsymmetrically substituted alkynes.[4] Consequently, the reactivities of complexes generated from representative N-heterocyclic carbene ligands[12] were probed.[13] Changing the electronic properties of the carbene to an imidazolin-2-ylidene backbone gave rise to a less active catalytic system (entry 2). The use of the bidentate ligand precursor **3** did not lead to any product formation (entry 3). However, the sterically more hindered 2,6-diisopropylphenyl-substituted ligand generated from **4**[14] proved to be more efficient (entry 4). The use of $Pd(OAc)_2$ gave results comparable to the ones obtained with $Pd(dba)_2$ (entry 5).

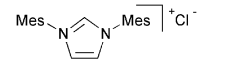
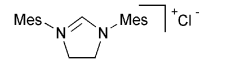
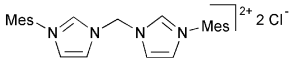
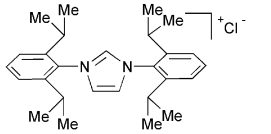
Differently substituted alkynes were subjected to the reaction conditions using 2-chloroaniline (Scheme 3, Table 2).‡ Importantly, the hydroamination of unsymmetrically substituted aryl-alkyl alkynes led again with good to excellent regioselectivity to the corresponding enamines.[15] Enamines generated from aryl-substituted alkynes were efficiently converted applying our improved palladium catalyst. A variety of functional groups, such as MeO-, F-, CF_3- and Cl-substituents, was tolerated in *para*, *meta*- or *ortho*-position of the aromatic substituent by the two catalytic systems.

In summary, we developed a regioselective one-pot indole synthesis based on a user-friendly $TiCl_4$-catalyzed hydroamination reaction of alkynes with 2-chloroaniline. Efficient catalysis for the 5-*endo* Heck reaction was achieved using sterically hindered

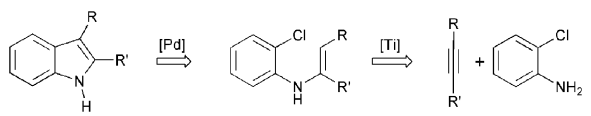


Scheme 2 Regioselective indole synthesis starting from 2-chloroaniline.

Table 1 Influence of the carbene ligand

Entry	Ligand precursor		Yield[a] (%)
1		**1**	37
2		**2**	20
3		**3**	—
4		**4**	57
5			54[b]

[a] Reaction Conditions: Isolated Yields; 2.00 mmol 2-chloroaniline, 2.00 mmol 1-phenyl-1-butyne, 0.20 mmol $TiCl_4$, 1.20 mmol t-$BuNH_2$, 2.5 mL PhMe, 20 h; 3.00 mmol KOt-Bu, 0.10 mmol $Pd(dba)_2$, 0.10 mmol NHC·HCl, 24 h; Mes = 2,4,6-$Me_3C_6H_2$. [b] 5 mol% $Pd(OAc)_2$ instead of $Pd(dba)_2$.

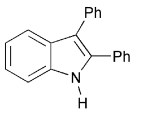
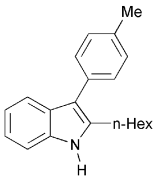
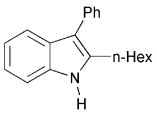
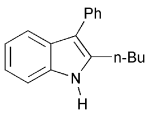
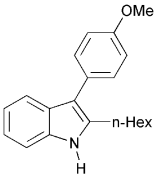
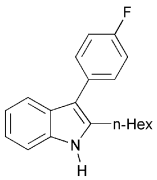
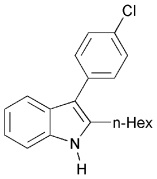
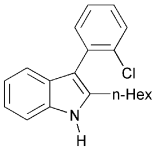
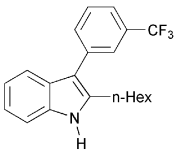
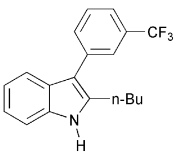


Scheme 1 Retrosynthetic analysis for one-pot indole synthesis.

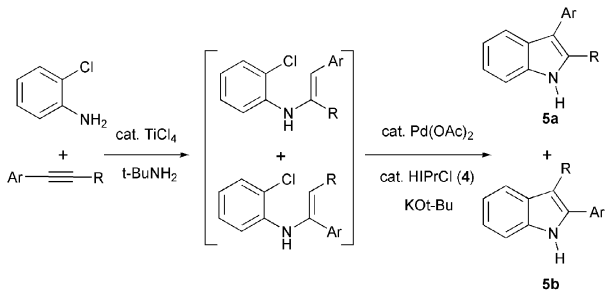
† Electronic supplementary information (ESI) available: details of the synthesis of compounds in Table 1 and 2 including analytical and spectroscopic data for new compounds. See http://www.rsc.org/suppdata/cc/b4/b411571f/

DOI: 10.1039/b411571f

Table 2 One-pot indole synthesis starting from 2-chloroaniline

Entry	Ar	R	Major product	Isolated yield (%)[a]	**5a/5b**[b]
1	Ph	Ph		76[c]	—
2	4-MeC_6H_4	n-Hex		81[d]	89/11
3	Ph	n-Hex		81[d]	92/8
4	Ph	n-Bu		81[d]	92/8
5	4-$MeOC_6H_4$	n-Hex		66	>99/<1
6	4-FC_6H_4	n-Hex		74[e]	>99/<1
7	4-ClC_6H_4	n-Hex		67[f]	>99/<1
8	2-ClC_6H_4	n-Hex		46[f]	>99/<1
9	3-$(CF_3)C_6H_4$	n-Hex		82[e]	97/3
10	3-$(CF_3)C_6H_4$	n-Bu		84[e]	97/3

[a] Reaction conditions: 1.50 mmol 2-chloroaniline, 1.50 mmol alkyne, 0.30 mmol $TiCl_4$, 1.80 mmol t-$BuNH_2$, 2 mL PhMe, 20 h; 0.15 mmol $Pd(OAc)_2$, 0.15 mmol **4**, 4.50 mmol KOt-Bu, 20 h. [b] By GC-analysis. [c] 10 mol% $TiCl_4$. [d] Isolated with up to 8% of a regioisomer, formed *via* Heck reaction of the tautomeric enamine. [e] Isolated with up to 5% of a regioisomer. [f] Using 2-bromoaniline.



Scheme 3 Indole synthesis starting from 2-chloroaniline.

carbene precursor **4**. The regioselectivity is complementary to Larock's annulation of alkynes by 2-iodoaniline derivatives.

Support by the Ludwig-Maximilians-Universität, and Professor P. Knochel is gratefully acknowledged. We thank the DFG for financial support (Emmy Noether-Programm).

Notes and references

‡ Representative procedure: $TiCl_4$ (0.05 mL, 0.47 mmol) was added to a solution of t-$BuNH_2$ (0.30 mL, 2.86 mmol), 2-chloroaniline (610 mg, 4.76 mmol), and tolan (1.02 g, 5.70 mmol) in toluene (5 mL) and the resulting mixture was stirred for 20 h at 105 °C. The solvent was partially removed and $Pd(OAc)_2$ (106 mg, 0.48 mmol), **4** (202 mg, 0.48 mmol), and KOt–Bu (1.60 g, 14.0 mmol) were added and the mixture was stirred at 105 °C for 24 h. CH_2Cl_2 (75 mL) and aqueous HCl (2N, 50 mL) were added to the cold suspension. The separated aqueous phase was washed with CH_2Cl_2 (2 × 75 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). Drying with $MgSO_4$ and purification by column chromatography (silica gel, n-pentane/Et_2O 20/1 → 10/1 → 4/1) yielded 2,3-diphenylindole (974 mg, 76%) as an off-white solid.

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15 The connectivity of the regioisomers was confirmed *via* hydrolysis of the hydroamination products and isolation of the corresponding ketones.