Catalytic Indol Synthesis

A Flexible and Catalytic One-Pot Procedure for the Synthesis of Indoles**

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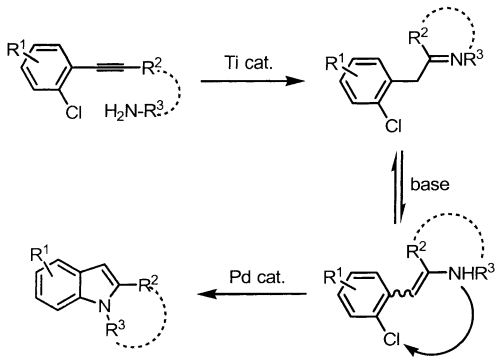
Initiated by improved screening methods, a steadily increasing demand for highly flexible synthetic procedures has evolved during the last couple of years. The major purpose of these synthetic methods is the fast generation of various derivatives of a certain class of substances. In the past, we have repeatedly shown that the titanium-catalyzed hydroamination of alkynes[1] is a versatile tool for the highly flexible synthesis of biologically interesting compounds.[2] Expanding these studies, we now present a highly flexible and catalytic one-pot procedure for the synthesis of indoles[3] employing *ortho*-chloro-substituted 1-phenyl-2-alkyl alkynes or phenyl-(aminoalkyl)alkynes as starting materials.

The general principle of the one-pot procedure is shown in Scheme 1. The major expectation is that under basic conditions, the imines, which are regioselectively formed during



Scheme 1. Outline of a flexible and catalytic one-pot procedure for the synthesis of indoles.

the hydroamination in the presence of the Ti catalyst $[Cp_2TiMe_2]$ ($Cp = C_5H_5$)[4], will be in equilibrium with the corresponding enamines. In addition, an *ortho*-chloro-substituent in the benzene ring, should offer the possibility to convert the enamines into indoles by a Pd-catalyzed N-arylation/cyclization (Buchwald–Hartwig reaction).[5] Since the enamines are removed from the equilibrium during this cyclization step it should be possible to convert the imines completely into indoles. However, to our knowledge, corresponding N-arylations of N-substituted imines under basic conditions in the presence of Pd-catalysts have not been reported.[6]

To investigate the scope of the suggested synthetic strategy, which includes two C–N bond-forming steps, we synthesized a number of *ortho*-chloro-substituted 1-phenyl-2-alkyl alkynes (**1**–**10**, Table 1) by Sonogashira couplings[7] starting from simple 1-chloro-2-iodobenzenes and terminal alkynes.[2c] The alkynes **1**–**10**, which could be isolated in high yields, were then used for the one-pot procedure. For this purpose, the alkynes were first hydroaminated with an arbitrary primary amine in the presence of 5 mol% $[Cp_2TiMe_2]$. Subsequently, 5 mol% $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone, 10 mol% 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, and KO*t*Bu were added directly to the reaction mixture. After heating the resulting mixture to 110 °C, most of the 1,2-, 1,2,5-, and 1,2,6-substituted indoles **11**–**20** could be isolated in good yields [Eq. (1), Table 1]. However, the reaction of **4** and *tert*-butylamine gave the corresponding indole **14** in only 39% yield. This modest result is because the regioselectivity of the $[Cp_2TiMe_2]$-catalyzed hydroamination of 1-phenyl-2-alkenyl alkynes is worse than that of 1-phenyl-2-alkyl alkynes.[2b]

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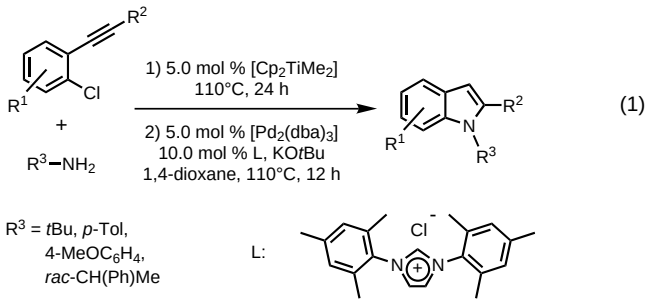
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Dr. Otto Röhm Gedächtnisstiftung, Darmstadt. We further thank Professor E. Winterfeldt for his generous support of our research.

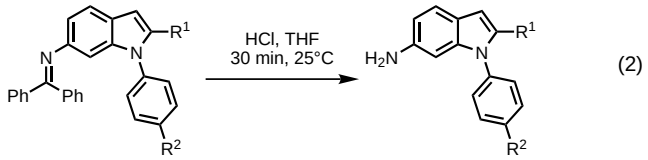
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200351345



(1)

As can be seen from Table 1, methyl and benzyl ethers (entries 2, 5–7, 10), CF_3 groups (entry 8), and diphenylimine groups (entries 9, 10) are functional groups that are tolerated under the reaction conditions. However, from a synthetic point of view the successful transformations of the imine-functionalized alkynes **9** and **10** into the indoles **19** and **20** are especially interesting because these products can be easily converted into the 6-aminoindoles **21** and **22** under acidic conditions [Eq. (2)].[6a]



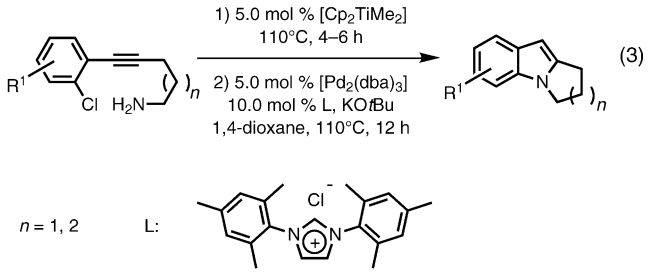
(2)

19 R^1 = *c*Pr, R^2 = Me
20 R^1 = *n*Bu, R^2 = OMe

21 R^1 = *c*Pr, R^2 = Me (86%)
22 R^1 = *n*Bu, R^2 = OMe (85%)

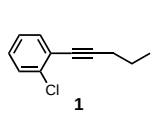
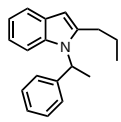
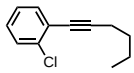
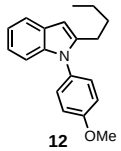
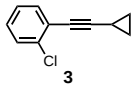
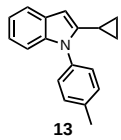
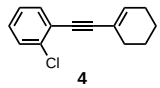
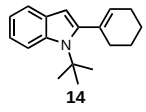
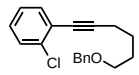
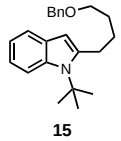
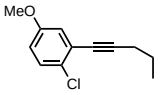
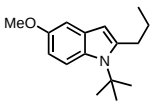
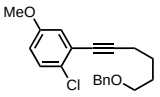
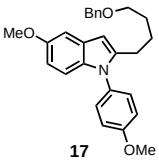
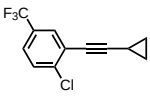
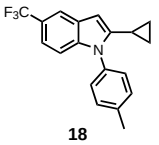
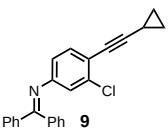
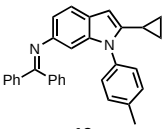
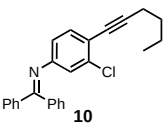
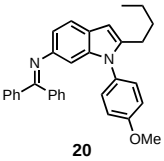
The products **11**, **12**, **17**, and **20** have potentially removable protecting groups at the indole N atom. In addition, the O groups located in the side chains of **15** and **17** offer various possibilities for further synthetic transformations (e.g. cyclization to the carbazole skeleton).

For completeness, we also synthesized some *ortho*-chloro-substituted 1-phenyl-2-(aminoalkyl)alkynes **23**–**30** by Sonogashira couplings[8] and used them as substrates for the described one-pot procedure [Eq. (3), Table 2]. During this study, we recognized that the hydroamination reactions employing **23** and **25**–**30** went to completion within 4–6 h while the sterically demanding δ-aminoalkyne **24** needed 48 h to reach 100 % conversion. However, after the second part of the one-pot procedure (the Pd-catalyzed cyclization reaction) only the piperidine derivatives **31**–**34** could be obtained easily and in reasonable yields (53–77 %, entries 1–4). Starting from the related γ-aminoalkynes **27**–**30**, only **28** could be converted into the corresponding indole **36** (53 % yield). Clearly,



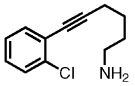
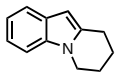
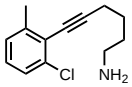
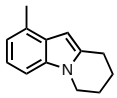
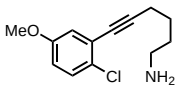
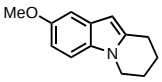
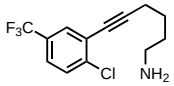
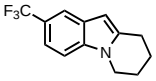
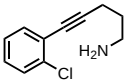
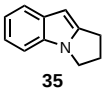
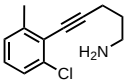
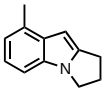
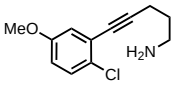
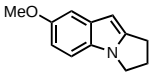
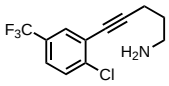
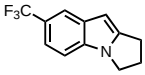
(3)

Table 1: One-pot procedure for the synthesis of indoles from *ortho*-chloro-substituted 1-phenyl-2-alkyl alkynes and primary amines.

Entry	Alkyne	Product	Yield [%][a]
1	 **1**	 **11**	65[b]
2	 **2**	 **12**	78
3	 **3**	 **13**	77
4	 **4**	 **14**	39
5	 **5**	 **15**	70
6	 **6**	 **16**	65
7	 **7**	 **17**	81
8	 **8**	 **18**	68
9	 **9**	 **19**	75
10	 **10**	 **20**	64

[a] Reaction conditions: 1) alkyne (2.0 mmol), amine (2.0 mmol), $[Cp_2TiMe_2]$ (0.48 mol L^{-1} in toluene, 0.1 mmol, 5.0 mol %), 110 °C, 24 h; 2) $[Pd_2(dba)_3]$ (0.1 mmol, 5.0 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (0.2 mmol, 10.0 mol %), KO*t*Bu (3.0 mmol), 1,4-dioxane, 110 °C, 12 h. [b] 10.0 mol % $[Cp_2TiMe_2]$ and amine (3.0 mmol) were used.

Table 2: One-pot procedure for the synthesis of indoles from *ortho*-chloro-substituted 1-phenyl-2-(aminoalkyl)alkynes.

Entry	Aminoalkyne	Product	Yield [%][a]
1	 **23**	 **31**	68
2	 **24**	 **32**	53[b]
3	 **25**	 **33**	75
4	 **26**	 **34**	77
5	 **27**	 **35**	–[c]
6	 **28**	 **36**	53
7	 **29**	 **37**	–[c]
8	 **30**	 **38**	–[c]

[a] Reaction conditions: 1) aminoalkyne (1.0 mmol), [Cp_2TiMe_2] (0.48 mol L^{-1} in toluene, 0.05 mmol, 5.0 mol%), 110°C, 4–6 h; 2) [$Pd_2(dba)_3$] (0.05 mmol, 5.0 mol%), 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride (0.1 mmol, 10.0 mol%), KO*t*Bu (1.5 mmol), 1,4-dioxane, 110°C, 12 h. [b] The reaction time of the hydroamination step was 48 h. [c] After a successful hydroamination reaction, no cyclization product could be isolated.

cyclization reactions that result in the formation of two annulated five-membered rings are disfavored by the increased ring-strain. However, the reasonable results obtained with substrates **24** and **28** prove that our one-pot procedure can also be applied successfully for the synthesis of 4-substituted indoles (**32**, **36**).

In summary, we have shown that a clever combination of a [Cp_2TiMe_2]-catalyzed hydroamination of alkynes with a Pd-catalyzed N-arylation of imines results in a new and general method for the synthesis of indoles, in which two new C–N bonds are formed during the one-pot procedure. Since the starting materials employed are easily accessible from 1-chloro-2-iodobenzenes and terminal alkynes by Sonogashira coupling reactions this procedure offers a great deal of synthetic flexibility.

Experimental Section

A Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with amine (2.0 mmol), alkyne (2.0 mmol), and a solution of [Cp_2TiMe_2] (0.21 mL, 0.48 M in toluene, 0.1 mmol, 5.0 mol%). The mixture was heated under argon to 110°C for 24 h (thin-layer chromatography (TLC) monitoring). After the resulting brown liquid had cooled to room temperature, [$Pd_2(dba)_3$] (92 mg, 0.1 mmol, 5.0 mol%), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (68 mg, 0.2 mmol, 10.0 mol%), KO*t*Bu (337 mg, 3.0 mmol), and 1,4-dioxane (5.0 mL) were added. The mixture was heated to 110°C for further 12 h (TLC monitoring) and then filtered through SiO_2. After the SiO_2 had been washed with CH_2Cl_2, the organic layer was concentrated under vacuum. The residue was purified by flash chromatography (SiO_2).

Received: March 6, 2003 [Z51345]

Keywords: alkynes · homogeneous catalysis · hydroamination · palladium · titanium

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