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From Alcohols to Indoles: A Tandem Ru Catalyzed Hydrogen-Transfer Fischer Indole Synthesis

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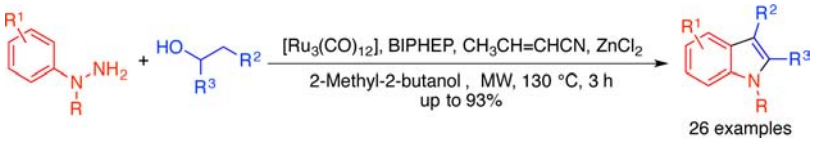
ABSTRACT



In a new version of the Fischer indole synthesis, primary and secondary alcohols have been catalytically oxidized in the presence of phenylhydrazines and protic or Lewis acids to give the corresponding indoles. The overall reaction can be accomplished in one step, and the use of alcohols instead of aldehyes or ketones as starting materials has several advantages in terms of a large selection of reagents, easy handling, and safety of the process.

The indole skeleton is a privileged molecular scaffold in nature and plays a prominent role in drug discovery due to its high receptor binding affinity.[1] Although there are many powerful methodologies for the construction and functionalization of indoles, there is still today a strong demand for a versatile, efficient, and regioselective synthesis of these heterocycles.[2] The Fischer cyclization continues to be one of the most popular approaches to indoles 130 years after its discovery due to its operational simplicity.[3] A potential bothersome restriction of the reaction is the use of enolizable aldehydes that may be unstable toward the acids required in the process, causing side reactions.[4] Consequently, synthetic equivalents such as acetals or imines are often used in place of aldehydes to get in situ generation of the free carbonyl group.[5]

In an effort to improve this well-established reaction, we decided to investigate the possibility of completing the overall Fischer indole synthesis starting from readily

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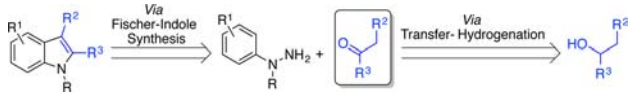
available and inexpensive alcohols, applying a "hydrogen auto-transfer"[6] based protocol (also denoted as "borrowing hydrogen",[7] Scheme 1).

Scheme 1. Protocol for Indole Synthesis Starting from Alcohols and Arylhydrazines



With this approach, sensitive carbonyl compounds could be generated *in situ* with high efficiency and in low concentration starting from alcohols, minimizing both unwanted side reactions and tedious purifications.[8] We report here for the first time that it is possible to directly transform a primary and a secondary alcohol into an indole, in the presence of phenylhydrazine, through a one-pot tandem Ru catalyzed H-transfer Fischer indole synthesis.[9] To study the influence of different parameters such as the nature of the metal, ligands, solvents, and temperature, the reaction between *N*-methyl-*N*-phenylhydrazine **1a** with 1-propanol **2a** was investigated as a model system (Table 1).

Table 1. Synthesis of Indoles: Optimization of the Reaction Conditions[a]

entry	catalyst	solvent	t (°C)	H^+	yield (%)[b]
1	$Pd(PPh_3)_4$	toluene	150	H_2SO_4	–
2	$PdCl_2(PPh_3)_2$	toluene	150	H_2SO_4	–
3	$RhCl(PPh_3)_3$	toluene	150	H_2SO_4	7
4	$RhH(CO)(PPh_3)_3$	toluene	150	H_2SO_4	12
5	$Rh(acac)_3$	toluene	150	H_2SO_4	15
6	$[Cp^*Cl_2Ir]_2$	toluene	150	H_2SO_4	35
7	$[RuCl_2(p\text{-cymene})]_2$	toluene	150	H_2SO_4	18
8	$RuHCl(CO)(PPh_3)_3$	toluene	150	H_2SO_4	15
9	$RuCl_2(PPh_3)_3$	toluene	150	H_2SO_4	11
10	$Ru_3(CO)_{12}$	toluene	150	H_2SO_4	53
11	$Ru_3(CO)_{12}$/BIPHEP	toluene	150	H_2SO_4	77
12	$Ru_3(CO)_{12}$/BIPHEP	toluene	150	H_2SO_4	75[c]
13	$Ru_3(CO)_{12}$/BIPHEP	toluene	150	H_2SO_4	61[d]
14	$Ru_3(CO)_{12}$/BIPHEP	CPME	150	H_2SO_4	69
15	$Ru_3(CO)_{12}$/BIPHEP	dioxane	150	H_2SO_4	65
16	$Ru_3(CO)_{12}$/BIPHEP	TAA[e]	150	H_2SO_4	84
17	$Ru_3(CO)_{12}$/BIPHEP	TAA	150	AcOH	81
18	$Ru_3(CO)_{12}$/BIPHEP	TAA	150	$ZnCl_2$	89
19	$Ru_3(CO)_{12}$/BIPHEP	TAA	150	$ZnCl_2$	86[f]
20	$Ru_3(CO)_{12}$/BIPHEP	TAA	150	$ZnCl_2$	92[g]
21	$Ru_3(CO)_{12}$/BIPHEP	TAA	130	$ZnCl_2$	93[h]
22	$Ru_3(CO)_{12}$/BIPHEP	TAA	170	$ZnCl_2$	90[i]
23	$Ru_3(CO)_{12}$/BIPHEP	TAA	100	$ZnCl_2$	22[j]

[a] Unless otherwise specified, the reactions were carried out in a closed vessel inserted in a preheated oil bath (one-pot reaction): *N*-Methyl-*N*-phenylhydrazine (1.0 mmol), crotononitrile (1.0 mmol), catalyst (5 mol %), ligand (15 mol %), acid additive (1.0 mmol) solvent (2.5 mL), under Ar, 150 °C, overnight. [b] Yields of isolated pure product. [c] The catalyst loading has been reduced to 2 mol % (BIPHEP: 3 mol %). [d] Reaction performed using 1 mol % of catalyst. [e] TAA = 2-methyl-2-butanol (*tert*-amyl alcohol). [f] One-pot, two-step procedure. [g] Reaction performed under microwave dielectric heating (MW) at 150 °C (3 h). [h] MW at 130 °C (3 h). [i] MW at 170 °C (3 h). [j] MW at 100 °C (3 h).

The screening started by examining different Pd, Rh, Ir, and Ru based complexes, which are the most successfully and widely used catalytic systems in the *N*-alkylation of amines by alcohols *via* borrowing hydrogen methodology (Table 1, entries 1–10).[10] Preliminary results showed that the ruthenium carbonyl cluster $[Ru_3(CO)_{12}]$ was the most active catalyst giving 1,3-dimethyl indole in moderate yield after heating reagents **1a** and **2a** in the presence of crotononitrile (as the hydrogen acceptor) at 150 °C in toluene overnight (Table 1, entry 10). The addition of phoshine based ligands improved the yield, and BIPHEP[11] gave the best results in terms of yield and purity of the reaction

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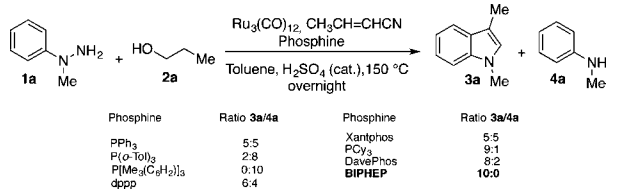
mixture (Scheme 2). It is worthy of note that some phosphines promoted the N−N bond breakage with formation of the aniline and contemporary decrease of the indole yield.[12] The catalyst loading was further reduced to 2 mol % without significantly affecting the yield of **3a** (Table 1, entry 12). Conversely, with 1 mol % $Ru_3(CO)_{12}$, a sharp drop in yield occurred (Table 1, entry 13). Also, no indole ring was obtained in the absence of the metal catalyst.

Scheme 2. Influence of Various Phosphine Ligands on the Indolization Reaction[a]

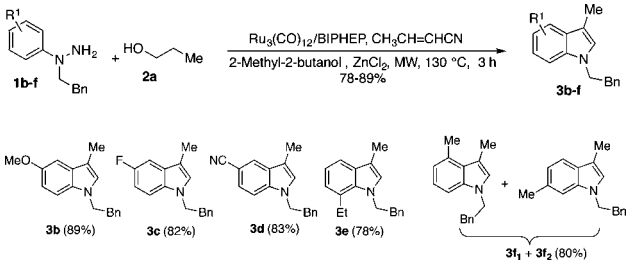


[a] Ratio determined by GC/MS.

Although several olefins can be used as a hydrogen acceptor, crotononitrile was preferred as a hydrogen scavenger on the basis of volatility of the alkene and its hydrogenated product. At least 1.0 equiv of crotononitrile was required for good results.[13] Next, the influence of different solvents on the reaction efficiency was checked, observing that 2-methyl-2-butanol and toluene gave the best results in terms of yield and purity (Table 1 entries 11 and 16). After these optimizations, a variety of acidic catalysts were investigated (Table 1, entries 17−18), and $ZnCl_2$ was found to be superior and of general applicability. To these optimized reaction conditions, microwave dielectric heating was applied finding that the reaction worked well heating the reagents at 130 °C for 3 h in 2-methyl-2-butanol (93% see Table 1, entry 21). With microwaves, a temperature increase had no appreciable effects on the reaction yields, while reducing the temperature or shortening the reaction time reduced the amounts of **3a** obtained (Table 1, entries 22 and 23). Based on these results, the reaction conditions described in entry 21 were chosen as optimal.

Having developed a reliable method for the catalytic synthesis of indoles from alcohols and arylhydrazines, the reaction scope and limitations of the protocol were investigated. In order to evaluate the influence of substituents on the aromatic ring, the reaction of 1-propanol with various commercially available aryl hydrazines was explored (Scheme 3).

Scheme 3. Effect of Substituent on the Phenylhydrazine Ring



These conditions allowed aryl functionalized indole derivatives to be prepared in high yields. In general, both electron-donating and -withdrawing groups, irrespective of the position on the aryl ring, were tolerated and had no significant impact on the yield, allowing the preparation of different functionalized indoles (**3b**−**3f** in Scheme 3). As expected, a *meta* substituted phenylhydrazine led to an approximately equimolar mixture of both regioisomers $\mathbf{3f_1}$ and $\mathbf{3f_2}$ in 80% overall yield (Scheme 3).[14]

Encouraged by these results, the reaction of several arylhydrazines with an array of commercially available primary alcohols (C2−C3 indole fragment) was investigated (Scheme 4). No remarkable variations in terms of yields and purities of the corresponding indoles were observed using a primary alcohol higher than 1-propanol (Scheme 4, indoles **3g**−**3i**). Good yields were also achieved using benzyl alcohols and other aliphatic alcohols containing an aryl ring (Scheme 4, indoles **3j**−**3l**). The use of the unsubstituted phenylhydrazines was also possible providing NH-free indoles, albeit in moderate yields (Scheme 4, indoles **3m**−**3o**). Secondary alcohols have also been used to introduce additional substituents at both C-2 and C-3 of the indole ring. Reaction of *N*-methyl-phenylhydrazine with various commercially available symmetrical aliphatic and cyclic secondary alcohols was carried out in the presence of the Ru catalyst and $ZnCl_2$. All of the substrates were transformed into the corresponding 2,3-dialkylindoles in good yields (Scheme 4, indoles **3p** and **3v**). 2-Hydroxyalkanes exclusively gave the indole[15] derived by cyclization on the more highly substituted side of the corresponding hydrazones (Scheme 4, indoles **3r** and **3s**). Conversely, other unsymmetrical secondary alcohols led to the corresponding indoles as a 65/35 mixture of two regioisomers[16] (Scheme 4, indoles $\mathbf{3t_1}$ and $\mathbf{3t_2}$). This protocol was also applicable to a variety of alcohols bearing an additional functional group on the aliphatic chain, and indoles **3u**−**3z** were obtained in moderate to good yields (Scheme 4).

The present method was mild enough to tolerate a wide variety of common functional groups on starting materials,

(11) (a) BIPHEP = 2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl. (b) dppp = 1,3-Bis(diphenylphosphino)propane. (c) Xantphos = 4,5-Bis-(diphenylphosphino)-9,9-dimethylxanthene. (d) Davephos = 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl.

(12) The N−N bond breaking of arylhydrazine may occur, as a side reaction, when the alcohol oxidation is slowed down by different factors producing the anilines as byproducts. However, this behavior is minimized using the $[Ru_3(CO)_{12}]$/BIPHEP catalyst.

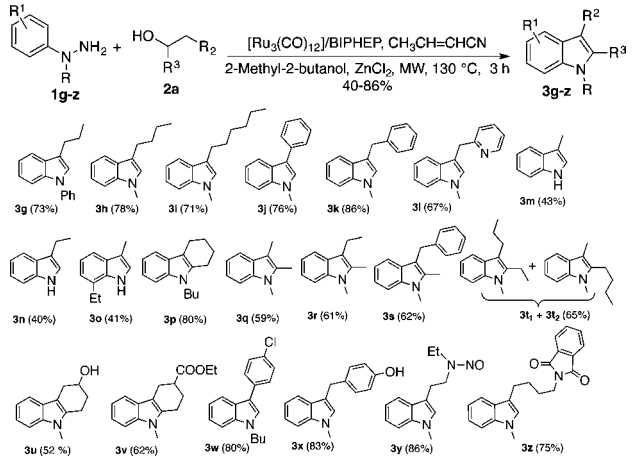
(13) Control experiments indicated that no reaction occurred without the hydrogen acceptor.

(14) The regioisomer ratio (6/4) of indoles $\mathbf{3f_1}$ and $\mathbf{3f_2}$ was determined by ^{1}H NMR.

(15) Indoles **3r** and **3s** were prepared starting from 2-pentanol and 4-phenyl-2-butanol respectively.

(16) Indoles $\mathbf{3t_1}$ and $\mathbf{3t_2}$ were prepared starting from 3-heptanol. The regioisomer ratio was determined by ^{1}H NMR.

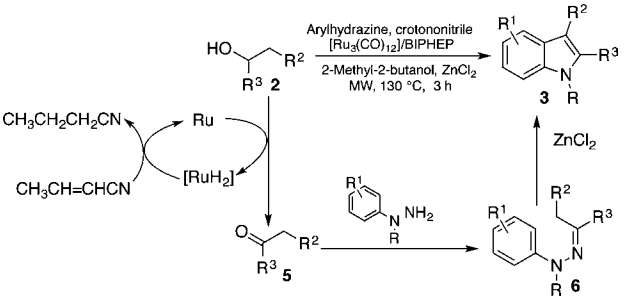
Scheme 4. Different Indoles Prepared from Arylhydrazines and Alcohols[a]



[a] Reaction conditions: *N*-substituted-*N*-arylhydrazine (1.0 mmol), crotononitrile (1.0 mmol), $[Ru_3(CO)_{12}]$ (2 mol %), BIPHEP ligand (3 mol %), $ZnCl_2$ (1 equiv), 2-methyl-2-butanol (2.5 mL), under Ar, MW 130 °C, 3 h. Yields of isolated products after column chromatography.

which may be subsequently subjected to further processing in order to increase the molecular diversity of final products. Inspired by previously published mechanisms,[7] the most probable reaction pathway for the conversion of aryl hydrazines and alcohols into indoles is outlined in Scheme 5. We believe that the reactions may proceed *via* an initial oxidation of alcohol **2** into the corresponding carbonyl compound **5** by formal transfer of a hydrogen molecule to crotononitrile with concomitant regeneration of the catalyst. The *in situ* generated carbonyl compound **5**, in the presence of arylhydrazine, is immediately converted into the corresponding hydrazone **6**.[17] The subsequent acid catalyzed aromatic [3 + 3] sigmatropic rearrangement gives access to the desired indole ring **3** (Scheme 5).

Scheme 5. Mechanistic Proposals for the Catalyzed Synthesis of Indoles



In summary, we developed a simple, convenient, and efficient method for the preparation of indole derivatives combining the classical Fischer indole synthesis with the innovative hydrogen autotransfer technology. The most remarkable advantages in using alcohols in the place of aldehydes or ketones as starting material are the easy handling, the lower toxicity, the higher stability, and the large selection of commercially available alcohols to be employed in the reaction.[18] The ability to easily incorporate on the indole ring a further element of molecular diversity, which may be subsequently modified, makes this synthetic protocol particularly attractive for increasing the molecular complexity. In addition, microwave irradiation significantly increases the reaction rate enhancing the final indole yields.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) The hydrazone intermediate was isolated in the reaction performed without the presence of the acid catalyst.

(18) Although suffering from the use of phenylhydrazines, this reaction has the advantage of the use of a Ru catalyst (2 mol %), and it could be considered a valid alternative to the recently developed Pd catalyzed (5–10 mol %) Fischer type indole synthesis based on anilines. (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230–7233. (b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298–7303. (c) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220–9222.