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Hydroformylation of 2-Alkynylanilines: Toward an Alternative Methodology for the Synthesis of 3-Substituted Indoles

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A potentially viable route for the synthesis of 3-substituted indoles is presented herein. The methodology is based on a regioselective Rh-catalysed hydroformylation of prepared 2-alkyn-1-ylanilines. The requisite 2-alkynylaniline substrates were prepared in high yields (>85%) using the Pd-catalysed Sonogashira reaction. A catalyst complex that comprises $Rh^{I}(CO)(PPh_3)_3$ and 1,2-bis(diphenylphosphino)ethane as the ligand allowed the quantitative conversions of the alkynyl substrates with selectivities >75% for the desired 3-substituted indoles.

Indoles are ubiquitous in nature and occur in different kinds of plants, animals and marine organisms.[1] The indole backbone represents one of the most important structural motifs in drug discovery, which has been described as a "privileged scaffold"; a term first introduced by Evans and co-workers[2] to define scaffolds that bind many receptors.[3] Indole derivatives have the unique ability to mimic the structure of peptides and to bind reversibly to enzymes,[4] which provides tremendous opportunities to discover new drugs with different modes of action. Indeed, seven indole-containing commercial drugs are in the Top-200 Best Selling Drugs by US Retail Sales in 2012.[5] Given their biological activity and propensity for binding many receptors, the synthesis of substituted indoles has attracted the interest of organic chemists for decades.[6] Present in anti-inflammatory agents,[7] anti-hypersensitive,[8] anti-mural,[9] anti-HIV[10] and anti-migraine[11] drugs, it is no surprise that a profusion of synthetic methods for the indole motif have been developed[6] for the demand upward of 20000 t year^{-1}.[12]

Despite the vast number of synthetic methods available for the formation of the indole backbone, most routes furnish 2-substituted or 2,3-substituted indoles.[6] In contrast, there are relatively few methodologies for the production of 3-substituted indoles[6,13,14] (which include serotonin, sumatriptan, melatonin and tryptophan), and the Fischer indole synthesis (and modifications thereof) remains the most important approach to 3-substituted indoles.[14] However, three potentially viable routes to 3-substituted indoles that involve catalytic hydroformylation have been investigated.[12,15] A particularly attractive approach is that of Dong and Busacca[15a] that involves a tandem Heck–hydroformylation process (Scheme 1). However, the Heck reaction furnished poor yields if electron-rich substrates were employed, which renders the approach less attractive. Notwithstanding the elegance displayed by the intrinsically atom-economic hydroformylation, which allows the functionalisation of unsaturated moieties to valuable aldehydes that can be further manipulated into the approximately 9 million tons of oxo products produced annually,[16] a viable hydroformylation approach towards valuable indoles has not yet been developed.

Previously, Ucciani and Bonfand[15b] transformed *o*-nitrostyrene to 3-methyl indole using a supported Rh-catalysed hydroformylation reaction. However, in addition to the relatively harsh reaction conditions employed (160 °C and 16.0 MPa), no other substrates were evaluated. More recently, Marchetti et al.[12] reported the formation of three 3-(2,2-diethoxyethyl)-1*H*-indoles from the corresponding (*E*)-1-(3,3-diethoxyprop-1-en-1-yl)-2-nitrobenzenes after 168 h at 80 °C using tris(triphenylphosphine)rhodium(I) carbonyl hydride as the catalyst complex. However, in our hands this approach furnished low yields of indole because of catalyst decomposition and indole polymerisation under the long reaction times.

Coupled with our interest in metal-catalysed carbonylation[17] and in the synthesis of indoles,[18] we were attracted to the possibility of a modification of the approach of Dong and Busacca[15a] to obtain 3-substituted indoles that would avoid the use of substrates obtained through the Heck reaction. To this end, a hydroformylation approach based on 2-alkynylanilines, produced through the well-established Pd-catalysed Sonogashira coupling reaction, was envisaged (Scheme 2).

The implementation of the proposed methodology, amongst others, required the regioselective hydroformylation of the alkyne substrate. Although the hydroformylation of alkenes is well documented,[12,15,19] the hydroformylation of alkynes has received less attention, despite the atom-economic benefits for the production of synthetically versatile enals.[19] The relevant literature, particularly with regards to the hydroformylation of aryl alkynes provides little information on the factors that determine the outcome of the reaction. Therefore, we initiated our studies by establishing the parameters (which included the Rh^{I} source, ligand architecture, temperature, pressure, CO/H_2 ratio and Rh/ligand ratio).[20] Optimal branch selectivity (75%) was obtained if the bidentate ligand bis(diphenylphosphino)ethane (dppe; **1**) was used as the ligand under the conditions described in Scheme 3. The only other products of

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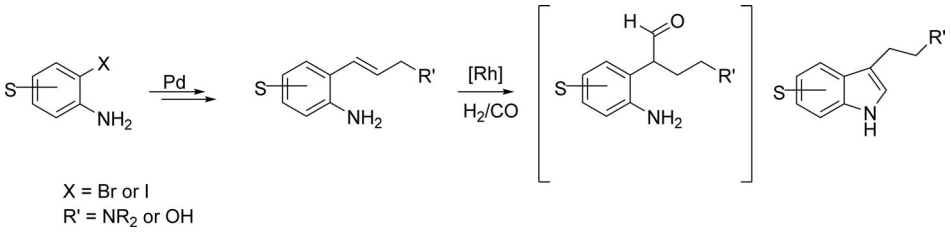
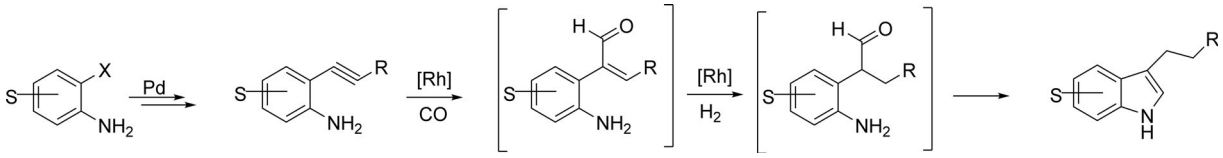
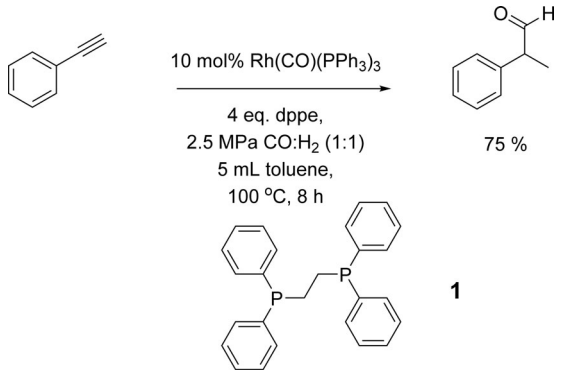


Scheme 1. Tandem Heck-hydroformylation of 2-alkenyl anilines.[15a]



Scheme 2. Proposed route to 3-substituted indoles.



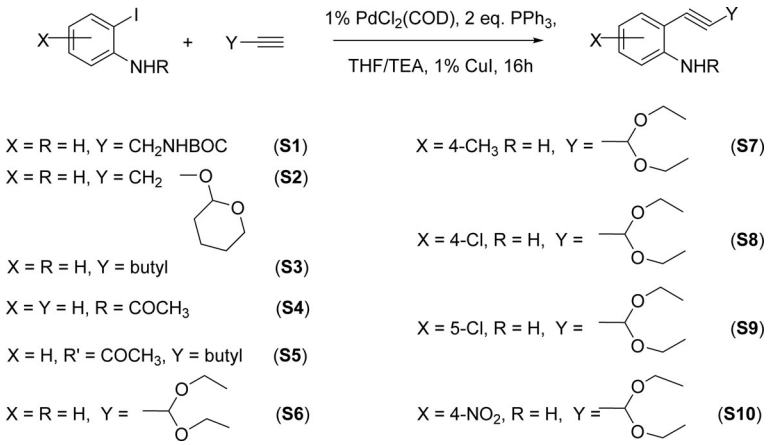
Scheme 3. Hydroformylation of phenylacetylene.

the reaction were the corresponding linear aldehydes, saturated and unsaturated. Interestingly, the unsaturated branched aldehyde was not detected under any of the conditions employed.[20]

Although exclusive selectivity for the branched aldehyde product could not be obtained in the case of phenylacetylene, it is well known[21] that the substrate may have an influence on the selectivity of the reaction. This was demonstrated beautifully with the hydroformylation of 2-ethynylaniline under the optimised conditions to furnish skatole in an 83% isolated yield.

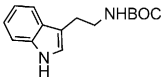
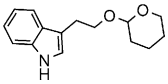
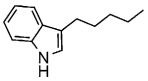
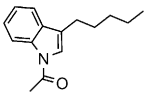
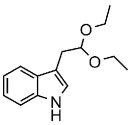
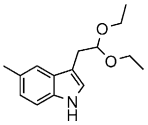
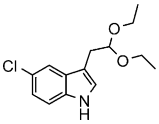
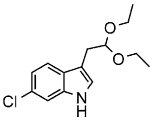
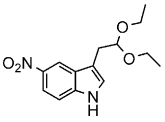
Although the effective synthesis of skatole by the hydroformylation of 2-ethynylaniline was gratifying, our stated objective was to develop an alternative general method to generate 3-substituted indoles, which includes those that can be transformed readily to valuable pharmaceutical derivatives. To explore this possibility, an array of 2-(alkyn-1-yl)anilines were subjected to the hydroformylation reaction (Table 1). The substrates were prepared through the Pd-catalysed Sonogashira[22] coupling reaction (Scheme 4; the experimental procedure is included in the Supporting Information).

Notably, substrates **S1**–**S10** were all isolated in yields >85%; a significant benefit over the Heck reaction used by Dong and Busacca.[15a]



Scheme 4. Pd-catalysed Sonogashira coupling of 2-iodoanilines with various alkynes.

Table 1. The hydroformylation of various phenyl-substituted 2-(alkyn-1-yl)anilines.[a]

	Substrate	Product		Yield [%][b]
	2-ethynyl aniline		skatole	83
1	**S1**		**I1**	28[c]
2	**S2**		**I2**	78[d]
3	**S3**		**I3**	71
4	**S4**		**I4**	92
5	**S5**		**I5**	84[e]
6	**S6**		**I6**	87
7	**S7**		**I7**	84
8	**S8**		**I8**	80
9	**S9**		**I9**	79
10	**S10**		**I10**	75

[a] Reaction conditions: 10 mol% $RhH(CO)(PPh_3)_3$, Rh/dppe = 1:4, CO/H_2 (1:1, 2.5 MPa), 0.2 g substrate, 5 mL toluene, 100 °C, 8 h. [b] Hydroformylation product, isolated yield. [c] The other major product was the corresponding quinoline that arises from the cyclisation of the linear aldehyde. [d] The corresponding unprotected alcohol and O-acetylated derivatives furnished the 3-indoles in poor yields (< 10%).[20] [e] Isolated as **I3**.

The results show the envisaged hydroformylation of 2-alkyn-1-ylanilines as a viable alternative methodology for the synthesis of 3-substituted indoles. Furthermore, the resulting indoles may be prepared without the need to protect the indole nitrogen atom. The most impressive results were obtained using the easily manipulated 3,3-diethoxy acetal side chain, which allowed for extremely high branch selectivity and furnished the desired indoles in yields > 70%. The origin of this high regioselectivity is unclear but could involve a combination of steric, electronic[23] and donor-atom effects. The distinct advantage of this acetal functional group is the well-established reactions that allow further manipulation of the aldehyde functionality to other relevant pharmacophores.[15b]

In summary, we have demonstrated a simple two-step process with significant potential for the production of pharmacologically important 3-substituted indoles based on the hydroformylation of 2-(alkyn-1-yl)anilines. The high yields and mild reaction conditions are advantageous. Furthermore, the resulting phenyl-substituted indoles are valuable intermediates for further derivatisation.

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Keywords: alkynes · hydroformylation · regioselectivity · rhodium · synthesis design

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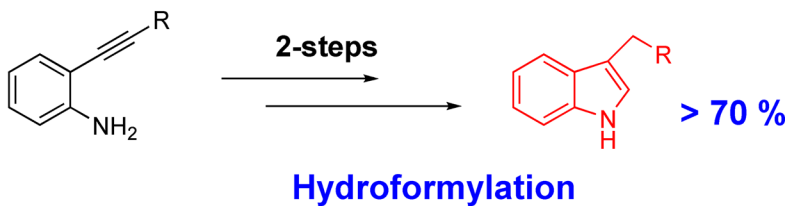

Valley of the indoles: Practical methodologies for the production of 3-substituted indoles are scarce; most often based on the Fischer indole synthesis. The method presented herein furnishes 3-substituted indoles in high yields by the regioselective Rh^{I}-catalyzed hydroformylation of 2-alkynylanilines.

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