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Tandem hydroformylation–hydrazone formation–Fischer indole synthesis: a novel approach to tryptamides†

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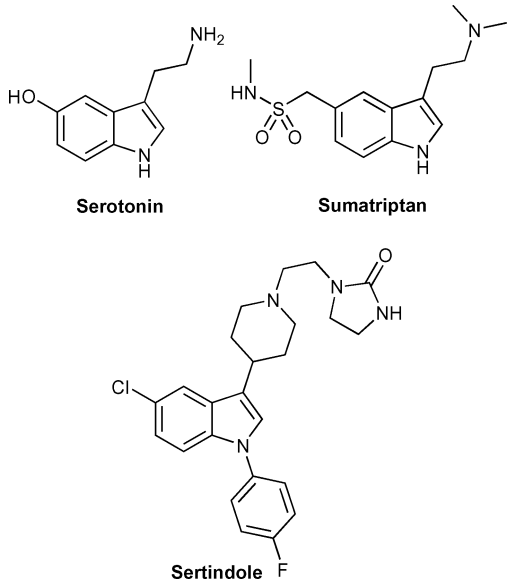
Received 8th March 2005, Accepted 5th May 2005
First published as an Advance Article on the web 20th May 2005

A novel one-pot synthesis of indole systems *via* tandem hydroformylation–hydrazone formation–Fischer indolization starting from allylic amides and aryl hydrazines is described. This tandem procedure directly leads to biologically interesting tryptamides and analogues.

Introduction

In many natural products and biologically active compounds the indole core is a privileged substructure. Tryptamine derivatives in particular are involved in numerous biological processes, *e.g.* melatonin in the control of the circadian rhythm or serotonin in neurological processes. Thus tryptamine and its derivatives are used for the treatment of diverse diseases like migraine (*e.g.* Sumatriptan), depression (*e.g.* D-tryptophan), schizophrenia (*e.g.* Sertindole) and many others (Scheme 1).



Scheme 1

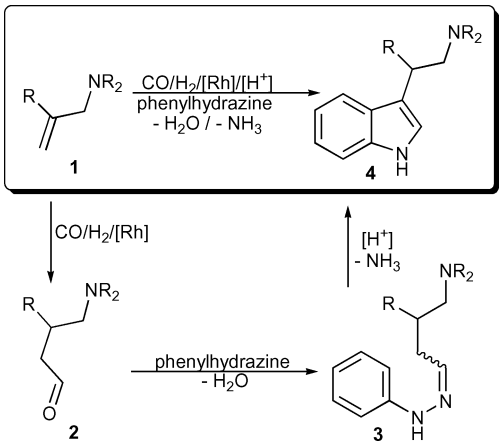
Due to the pharmaceutical relevance of tryptamine and its analogues, numerous syntheses have been reported and the development of new methods is even today a subject of intensive research. Among established methods, the Fischer indole synthesis is the most important method for the synthesis of variably substituted indoles as it is for the synthesis of tryptamine derivatives.[1] In this reaction, carbonyl compounds are condensed with aromatic hydrazines to give aryl hydrazones, which then react in a [3,3]-sigmatropic diaza–Cope type rearrangement mediated by Brønsted or Lewis acids to give indoles. For the synthesis of 3-substituted indoles, aldehydes are used, which leave the 2-position of the indole unsubstituted. But aldehydes undergo side reactions like an aldol reaction or aromatic substitution under the harsh Fischer conditions. Therefore protected aldehydes are often used instead. Thus acetals, aminals, enol ethers as well as bisulfite adducts are deprotected under Fischer indolization conditions and set the carbonyl free *in situ*. In some cases the use of masked carbonyl compounds like in the Japp–Klingemann modification is useful. Here β-ketoesters are reacted with aryl diazonium salts to give aryl hydrazones after cleavage of acetic acid. Fischer indolization of the hydrazones thus obtained gives the indole-2-carboxylic acid ester, which decarboxylates after hydrolysis.[2] In summary the β-ketoesters serve as masked aldehydes. As a matter of fact all these methodologies require a laborious synthesis of the starting carbonyl analogue and, in addition, the cleavage of bonds.

The most atom economic and efficient methodologies are those in which the carbonyl group is formed *via* chain lengthening addition reactions. The hydroformylation of olefins is such a well known and reliable method for the synthesis of aldehydes being used in industrial processes.[3] Surprisingly, only a few examples are described in which hydroformylation has been used to generate the aldehydes required for the synthesis of indoles with sidechains in the 3-position. Thus, hydroformylation of *o*-substituted nitrostyrenes gives indoles in fair yields. Here the olefinic bond is regioselectively hydroformylated and under the same conditions the nitro group is reduced to an aniline which condenses intramolecularly then with the aldehyde to give 3-substituted indoles.[4] This approach can be compared with the Reissert indole synthesis,[5] the Batcho–Leimgruber indole synthesis[6] or the Sugasawa indole synthesis.[7] More recently Selwood *et al.* have used hydroformylation for the synthesis of the migraine drug 4991W93 to control the relative configuration within the final product albeit with poor regioselectivity.[8] Sheldon *et al.* have published the synthesis of melatonin *via* regioselective hydroformylation of *N*-allylacetamide followed by Fischer indole synthesis.[9]

Based on our general interest in tandem hydroformylation sequences,[10] we have recently found that indoles are obtained directly from olefins under hydroformylation conditions, if the hydroformylation is performed in the presence of an aryl hydrazine and a Brønsted acid.[11] This tandem reaction includes three steps: hydroformylation of an olefin **1**, condensation with an aryl hydrazine to an aryl hydrazone **3** and finally Brønsted acid mediated rearrangement and cyclization (Scheme 2). The fact that the aldehydes as well as the hydrazones do not have to be isolated as intermediates in this tandem reaction saves time and resources. Furthermore, the low stationary concentration of reactive intermediates suppresses side reactions and enhances the selectivity of the reaction without an initial protection of the aldehydes. Thus, starting from simple olefins, non-functionalized indoles can be directly obtained in a one-pot

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/ob/b5/b503396a/

DOI: 10.1039/b503396a



Scheme 2 General scheme of the tandem hydroformylation–Fischer indole synthesis.

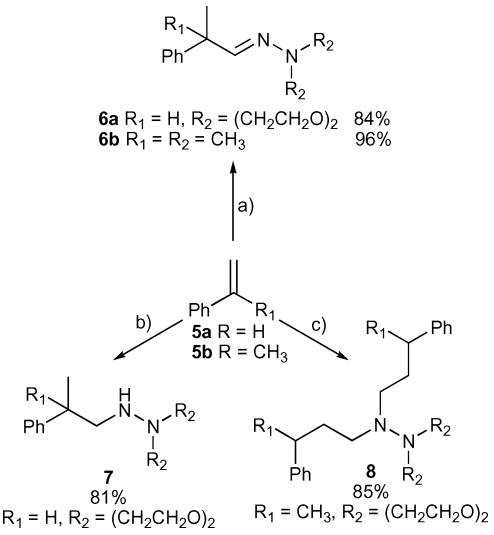
procedure with excellent yields, while the use of functionalized olefins such as allylic alcohols and allylic amines provides direct access to tryptophols and tryptamines. In addition, we have found that benzhydrylidene protected aryl hydrazines obtained from a Buchwald Hartwig amination[12] can directly be used in this tandem procedure giving higher selectivities than the free aryl hydrazines, presumably due to the fact that the protected hydrazines do not form salts with the acid in the chosen unpolar medium. With respect to the high relevance of tryptamine and homotryptamine units, we describe here in full detail our extensive investigations on tandem hydroformylation–Fischer indole synthesis starting from amino olefins and hydrazines. We have developed efficient control of regioselectivity, alternative use of different sources of aryl hydrazines and we give examples for the application of this methodology. Our protocol provides convenient access to branched as well as linear tryptamines.

Results and discussion

To achieve high chemoselectivities for tandem processes, it is important that all individual steps are as selective as possible and that all reagents and reactants required, as well as all intermediates, are compatible and do not affect each other. To ensure this, we started our investigations with optimizations of each step, *e.g.* hydroformylation of amino olefins, hydroformylation in the presence of hydrazines, Fischer indolization of aryl hydrazones and finally the complete tandem hydroformylation–Fischer indole synthesis.

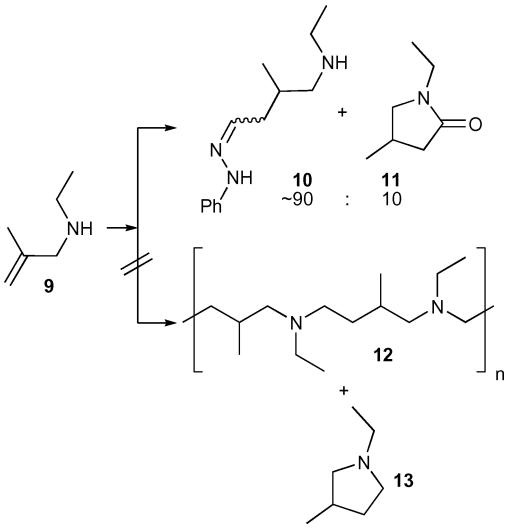
Hydroformylation in the presence of hydrazines

It is well known that hydroformylations can be conducted in the presence of amines. While tertiary amines increase the hydrogenation activity of rhodium based hydroformylation catalysts giving alcohols exclusively,[13] primary and secondary amines condense with aldehydes followed by hydrogenation of the resulting imines or enamines to amines in an overall hydroaminomethylation.[10] It has to be ensured that hydrazines do not behave similarly. Therefore the hydroformylation was conducted in the presence of hydrazines. In fact, hydroformylation of styrene (**5a**) in the presence of *N*,*N*-disubstituted hydrazines gives the hydrazones **6** in excellent yields. No hydrogenation product of the intermediate aldehyde or the hydrazone is observed whereas imines are usually reduced under the harsh hydroformylation conditions. Obviously, the hydrazine does not enhance the hydrogenation activity of the catalyst and rather protects the aldehyde against reduction. Only after prolonged reaction times can the hydrogenated product **7** be selectively obtained as a result of hydroaminomethylation. If α-methylstyrene (**5b**) is used in a two-fold excess, unsymmetrically substituted alkyl hydrazine **8** is obtained as a 2 : 1 adduct (Scheme 3).[14]



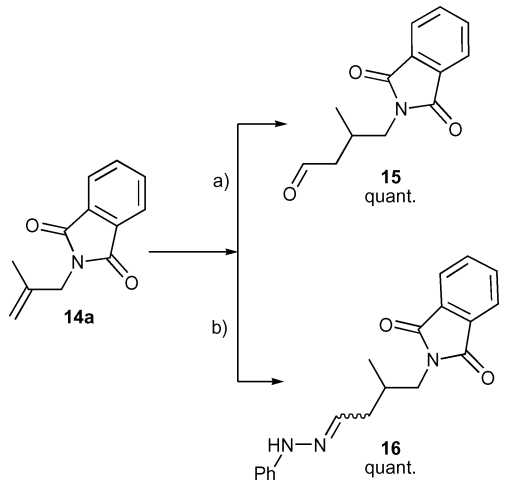
Scheme 3 Reagents and conditions: (a) 1 eq **5a**, 1 eq hydrazine, 1 mol% $[Rh(cod)Cl]_2$, dioxane, 90 bar CO, 20 bar H_2, 18 h, 110 °C; (b) like (a) but 3 days; (c) 2 eq **5b**, 1 eq hydrazine, 1 mol% $[Rh(cod)Cl]_2$, dioxane, 90 bar CO, 20 bar H_2, 5 d, 110 °C.

Using this protocol for the synthesis of tryptamine derivatives, allylic amines have to be used. Since hydroformylation of terminal olefins typically results in a mixture of linear and branched aldehydes, we decided to first investigate disubstituted terminal olefins like *N*-ethyl-*N*-methallylic amine. Such olefins undergo regioselective hydroformylation to linear aldehydes and make the additional use of *n*-directing ligands obsolete. To prevent hydrogenation of the starting olefin we have chosen high carbon monoxide partial pressures to support rate determining carbon monoxide insertion. Hydroformylation of **9** indeed gives the desired aryl hydrazone **10**, but neither inter- nor intramolecular reductive amination products of the aldehyde are observed (Scheme 4). However, approximately 10% of lactam **11** are obtained as a byproduct. Obviously, the rhodium acyl species partially tends to intramolecular nucleophilic addition of the secondary amine and formation of lactam **11** instead of hydrogenolysis to form the aldehyde. This behavior has previously been reported for allylic amines[15] and can be suppressed with an appropriate choice of reaction conditions or protecting groups.



Scheme 4 Reagents and conditions: 1 eq **9**, 1 eq phenylhydrazine, 0.3 mol% $Rh(acac)(CO)_2$, 50 bar CO, 10 bar H_2, THF, 68 h, 100 °C.

In fact, methallylic phthalimide (**14a**) is regioselectively hydroformylated in quantitative yields to give aldehyde **15** and its hydroformylation in the presence of phenylhydrazine yields the corresponding hydrazone **16** as a mixture of *E*/*Z*-isomers in excellent yields (Scheme 5).



Scheme 5 Reagents and conditions: (a) 1 eq **14a**, 0.3 mol% Rh(acac)-$(CO)_2$, THF, 50 bar CO, 10 bar H_2, 20 h, 100 °C; (b) like (a) but 1 eq phenylhydrazine, 68 h.

Even after three days reaction time at higher temperatures, no hydrogenation of the hydrazone bond can be observed, so that aryl hydrazones seem to be of higher stability against hydrogenation than their alkyl analogues. In addition, the hydrazones obtained from hydroformylation reactions are of high purity. Apparently, hydrazines do not alter the chemoselectivity of the hydroformylation catalysts $[Rh(cod)Cl]_2$ and $Rh(acac)(CO)_2$.

Indolization of aryl hydrazones

Having found conditions for a highly selective synthesis of hydrazones under hydroformylation conditions, we started to optimize the conditions for the Fischer indolization. These must be compatible with the hydroformylation step, which therefore has to be conducted in the same solvent as used for indolization. Furthermore, it is important that the hydroformylation is not hampered by the addition of acids. The latter must be tested in a tandem reaction with fast consumption of starting material and intermediates, since olefins oligomerize and aldehydes undergo aldol reactions in the presence of acids. Therefore, we concentrated on optimizing the Fischer indolization by testing different solvents and acids. The most common systems for Fischer indole synthesis are sulfuric acid in alcohols such as methanol or ethanol. Indeed, there are examples where the hydroformylation of alkenes has been carried out in an alcoholic solution. But here, depending on the reaction conditions, the intermediate rhodium acyl species can be trapped by the alcohol to give esters,[16] or the aldehyde suffers nucleophilic attack by the alcohols to yield acetals.[17] Since acetals are used as protected aldehydes in Fischer indole synthesis, the use of alcohols as solvents in the hydroformylation step is an option and would support the principle of low stationary aldehyde concentrations. To our surprise, hydrazone **16** did not lead to indolization in the presence of 4 wt% sulfuric acid, nor in methanol or ethanol. Only less polar solvents like refluxing THF or toluene, which are also very common in hydroformylation chemistry, gave satisfying conversions.

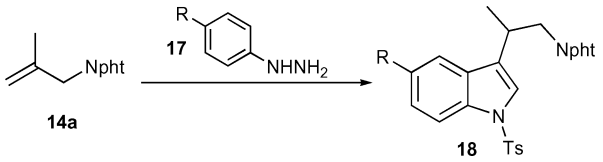
In the next step we tested different acids, turning our attention to commercially available and cheap acids. In order to find small differences in the acids' activity, we used one equivalent of each acid, stopped the reaction after two hours and estimated the conversion by NMR. Our screening contained acids from $p_{Ka} = 5$ to $p_{Ka} = -8$. A good indication for the starting reaction is the precipitation of ammonium salts from the unpolar solvent. Among all acids, sulfuric acid as well as *p*-toluene sulfonic acid (PTSA) showed the best results, leading to full conversion. Obviously the combination of a less polar solvent with at least one equivalent of a strong acid provided a fast and selective conversion of the aryl hydrazones to the desired tryptamines. In particular, the high conversions observed within two hours reaction time were encouraging. Together with a slow hydroformylation step, fast condensation and indolization help to keep the concentrations of aldehyde and hydrazone low, so that they do not undergo intermolecular acid mediated side reactions.

Tandem reaction with methallylic amines

Next, we combined the optimized conditions for each step with a tandem reaction. In fact, tandem hydroformylation–Fischer indolization of methallylic phthalimide (**14a**) with phenylhydrazine (**17a**) in the presence of one equivalent of PTSA gave the desired tryptamine in 60% isolated yield (Table 1). Here the tosylation of the indole nitrogen helped to separate the product from impurities. Obviously, the tandem reaction did not proceed with a selectivity as high as for the single steps. Nevertheless, simple substituents are tolerated, *e.g.* the *tert*-butyl group, which can be found in a number of *in vitro* serotonin receptor antagonists.

If mixing all reagents in less polar solvents like toluene or THF, precipitation is observed, due to protonation of the aryl hydrazine. Therefore solubility problems might be responsible for the decrease in selectivity. An appropriate protection of the basic hydrazine on the other hand must allow the conversion of aldehyde, thus only acid sensitive protecting groups are of interest. Buchwald *et al.* have demonstrated, that benzhydrylidene protected aryl hydrazines in the presence of carbonyl compounds under acidic conditions undergo Fischer indolization in high yields.[18] While the benzophenone hydrazone itself cannot cyclize to form an indole, it can only transcondense with a second carbonyl compound leading to Fischer indolization. Benzhydrylidene protected aryl hydrazines are either obtained from commercially available aryl hydrazines or by palladium catalyzed amination of aryl halides with benzophenone hydrazone. Indeed, the use of protected hydrazines increases the selectivity as well as the yield of the tandem reaction making a consecutive tosylation of the indole nitrogen obsolete. Using this methodology, substituted tryptamines are isolated in up to 83% yield (Table 2). Remarkably, aryl bromides are tolerable although they are known to undergo oxidative addition with rhodium(I) complexes[19] leading to defunctionalization of the aryl bromides. In some cases even without a transition metal catalyst, under conditions of Fischer indolization, bromo substituents are cleaved. On the other hand, bromo substituted indoles are valuable starting materials for further derivatization

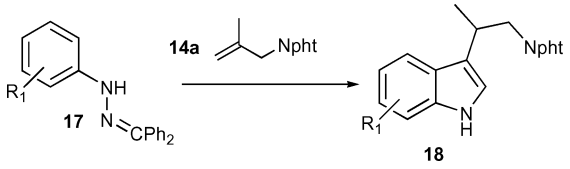
Table 1 Tandem reaction with methallylic amines



Entry	Hydrazine **17**	Yield **18**
1	**17a** (R = H)	60% (**18a**; R = H)
2	**17b** (R = Cl)	53% (**18b**; R = Cl)
3	**17c** (R = *tert*-butyl)	48% (**18c**; R = *tert*-butyl)

Cond.: 1 eq **14a**, 1 eq **17**, 1 mol% $[Rh(cod)Cl]_2$, 50 bar CO, 10 bar H_2, 1 eq PTSA, toluene, 3 d, 100 °C; then 1 eq tosyl chloride, 50 wt% NaOH in water, toluene, 20 h, rt.

Table 2 Use of benzhydrylidene protected hydrazine in the tandem reaction with methallylic amines

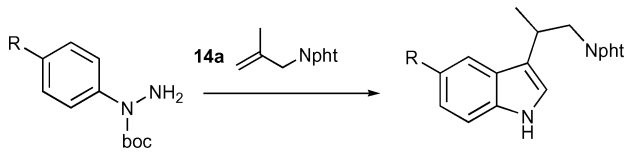


Entry	Hydrazine **17**	Yield **18**
1	**17d** (R_1 = H)	83% (**18d**; R_1 = H)
2	**17e** (R_1 = 4-F)	47% (**18e**; R_1 = 5-F)
3	**17f** (R_1 = 4-Cl)	78% (**18f**; R_1 = 5-Cl)
4	**17g** (R_1 = 4-Br)	50% (**18g**; R_1 = 5-Br)
5	**17h** (R_1 = 2-CH_3)	48% (**18h**; R_1 = 7-CH_3)
6	**17i** (R_1 = 2-Cl)	42% (**18i**; R_1 = 7-Cl)

Cond.: 1 eq **14a**, 1 eq **17**, 1 mol% $[Rh(cod)Cl]_2$, 50 bar CO, 10 bar H_2, 1 eq PTSA, THF, 3 d, 100 °C.

(*e.g.* by palladium catalyzed cross coupling methodologies of 5-bromoindole[20]). Therefore tandem hydroformylation–Fischer indole synthesis offers a convenient pathway to bromo substituted tryptamine derivatives from easily available starting materials.

In 2004, Cho and Lim successfully applied α-boc-aryl hydrazines in Fischer indolization and obtained indoles with very high purities.[21] Therefore we tested **17j** as a substrate for tandem hydroformylation–Fischer indole synthesis. Here the reaction has to be conducted in a stepwise manner with subsequent addition of acid. Since the boc group is stable under hydroformylation conditions, α-boc protected aryl hydrazones can be obtained in quantitative yields. Tandem hydroformylation–Fischer indolization of **17j** gives the pure protected serotonin analogue **18j**[22] in nearly quantitative yields without the need for further purification. A number of different aryl hydrazines, synthesized using Buchwald's optimized conditions of the copper(I) catalyzed *N*-arylation of amides (Goldberg reaction)[23] and the non protected analogues were compared with respect to their reactivity towards tandem hydroformylation–Fischer indole synthesis. Only the *p*-methoxy phenylhydrazine **17j** gives a clearly increased yield (Scheme 6) whereas α-boc-protected phenylhydrazine **17k** gives only 38% of indole **18d**. 4-Bromo substituted α-boc-protected phenylhydrazine **17l** gives 50% of indole **18g**.

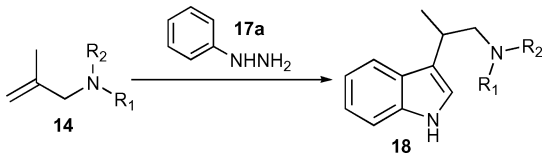


Scheme 6 Reagents and conditions: 1 eq **14a**, 1 eq **17**, 1 mol% $Rh(acac)(CO)_2$, 50 bar CO, 10 bar H_2, THF, 68 h; 120 °C, then 4 wt% H_2SO_4–THF, 2 h, 80 °C.

Stability of different protection groups

For a comparison of the stability of different protecting groups under tandem hydroformylation–Fischer indole synthesis, various methallylic amines were *N*-protected with phthalimide, acetyl, benzoyl, tosyl and ethyloxycarbonyl groups and converted in a stepwise manner. While hydrazone formation under hydroformylation conditions in all cases gave excellent yields, Fischer indolization disclosed differences. The phthalimide has already been proven to be stable under the selected conditions. Also the tosylate and the benzamide gave good yields of the desired tryptamides. The acetyl group, however, gave a slightly decreased yield. Not surprisingly, the boc group is cleaved under Fischer indolization conditions leading to an unselective conversion, but with a simple switch from *tert*-butyloxycarbonyl to an ethyloxycarbonyl group, the protected tryptamine was obtained in 58% yield. Thus all protecting groups chosen are tolerated under the reaction conditions (Table 3).

Table 3 Stability of different protecting groups in the tandem reaction

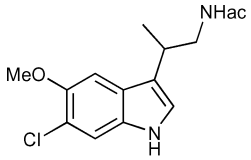


Entry	Olefin **14**	Yield **18**
1	**14b** (R_1 = Et, R_2 = ts)	94% (**18k**)
2	**14c** (R_1 = Et, R_2 = bz)	85% (**18l**)
3	**14d** (R_1 = Et, R_2 = ac)	61% (**18m**)
4	**14e** (R_1 = Et, R_2 = eoc)	58% (**18n**)

Cond.: 1 eq **14**, 1 eq **17a**, 1 mol% $Rh(acac)(CO)_2$, 50 bar CO, 10 bar H_2, THF, 68 h, 120 °C, then 4 wt% H_2SO_4–THF, 2 h, 80 °C.

Application of the hydroformylation–Fischer indolization protocol to the synthesis of sertindole analogues

Having a reliable protocol in hand, we intended to apply the hydroformylation–indolization sequence to the synthesis of pharmacologically active compounds. Scheme 7 illustrates the importance of α-branched tryptamides, which become more and more interesting for pharmaceutical applications. LY 156735, for example, has recently been discovered as a drug against sleep disorders.[24] Above, we have already demonstrated that this substitution pattern in the side chain can be obtained by the use of disubstituted terminal olefins in the tandem hydroformylation–Fischer indole synthesis.

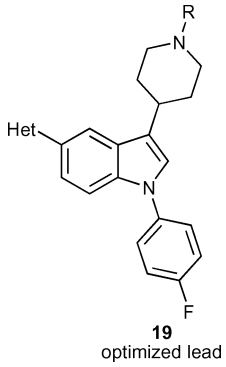


LY 156735

Scheme 7 Recent example of a tryptamide with a branched side-chain.

Besides compounds with linear or branched aliphatic side chains, there are also tryptamine analogues with additional cyclic units, such as 3-piperidyl indoles, which have been recognized as important pharmacophores in the last decade. The most prominent example is *N*-phenylindole sertindole (Scheme 1).

Among the diverse dopamine and serotonin receptors, sertindole blocks the α_1-adrenoceptor predominantly.[25] In 2002, Andersen *et al.* optimized the structure of sertindole and increased selectivity towards the α_1-adrenoceptor by variation of the substituents in the 5-position of the indole and of the piperidyl nitrogen (Scheme 8). In particular, the replacement of the chloro substituent by heterocyclic substituents in **19** helps in increasing this selectivity.[26] In most cases, these substituents can be introduced *via* palladium catalysis starting from the intermediate 5-bromoindole **21**. Tandem hydroformylation–Fischer indole synthesis offers convenient access to intermediate **21** starting from the easily available olefin **20** *via* conversion with commercially available 4-bromo phenylhydrazine **17m** and gives indole **21** in 39% yield. However, in this special case benzhydrylidene protected 4-bromo phenylhydrazine (**17g**) gives no increased yield. Copper catalyzed *N*-arylation with 4-iodo



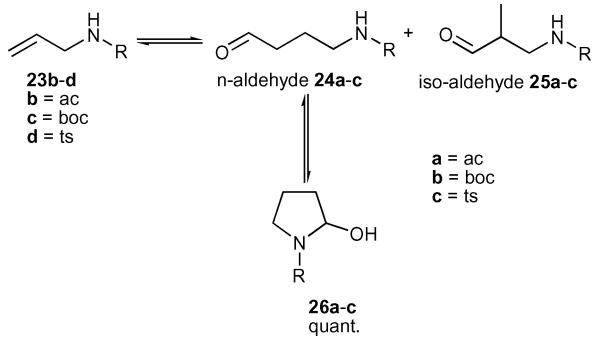
Scheme 8 Optimized lead of the antipsychotic sertindole.

fluoro benzene leads to the intermediate **22**, which is thus conveniently obtainable in only two steps with multiplying the literature reported yield (Scheme 9).[26]

Investigations towards *n*-selective hydroformylation–indolization starting from allylic amines

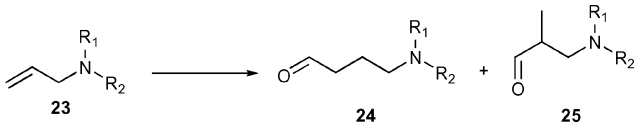
So far we have always used disubstituted terminal olefins leading to indoles with branched chains in the 3-position. Most of the biologically active tryptamines, however, are tryptamines with a non-branched side chain. Here, the hydroformylation–indolization sequence requires monosubstituted olefins. While ligand free hydroformylation of terminal disubstituted olefins regioselectively gives *n*-aldehydes, ligand free hydroformylation of monosubstituted olefins leads to a mixture of *n*- and *iso*-aldehydes. *n*-Selectivity is increased by the use of sterically demanding bidentate ligands such as the biphosphite BIPHEPHOS[27] or the biphosphane XANTPHOS.[28] Both ligands lead to high *n*-selectivities when simple olefins like 1-hexene or 1-octene are used. With functionalized olefins, however, the *n*-selectivity decreases dramatically in our experience. In tandem hydroformylation–Fischer indole synthesis, protected amino olefins have to be used. The nature of the protecting group strongly affects the *n*/*iso*-selectivity. Not only may *N*-donor groups attached to the olefin compete with the catalyst ligand, but also the aryl hydrazines may act as ligands, since amines in general coordinate to the metal centre and influence the performance of the hydroformylation.

For an investigation of the *n*/*iso*-selectivity, allylic phthalimide (**23a**) was hydroformylated with the use of Rh(acac)$(CO)_2$–BIPHEPHOS in a 1 : 4 ratio. Here only a 2 : 1 mixture of *n*-/*iso*-aldehydes was obtained. As an alternative, XANTPHOS was tested, which according to our experience gives higher *n*/*iso*-ratios in the hydroformylation of functionalized olefins. Indeed, the use of Rh–XANTPHOS (1 : 5) gives the *n*-aldehyde with 81% selectivity. Increasing the catalyst–ligand ratio to 1 : 10 results only in a marginal enhancement of the *n*-selectivity (85%) (Table 4, entry 1). To test the influence of the protecting group towards *n*/*iso*-selectivity, several allylic amides with protecting groups were hydroformylated with a Rh(acac)$(CO)_2$–XANTPHOS system (1 : 5) at 70 °C. In contrast to the hydroformylation of disubstituted terminal olefins, a lower carbon monoxide partial pressure was chosen to ensure that CO does not displace XANTPHOS from the catalytically active rhodium complex. Although under these conditions all hydroformylation experiments proceeded with complete olefin conversion, aldehyde could only be detected as the minor product. Instead, 2-hydroxy pyrrolidines (**26**) were formed in nearly quantitative yield *via* intramolecular attack of the primary amide to the carbonyl group. Jackson *et al.* have found similar behavior.[29] Since only the *n*-aldehyde can cyclize, it is removed from the hydroformylation equilibrium shifting the product distribution towards the *n*-aldehyde selectively (Scheme 10).



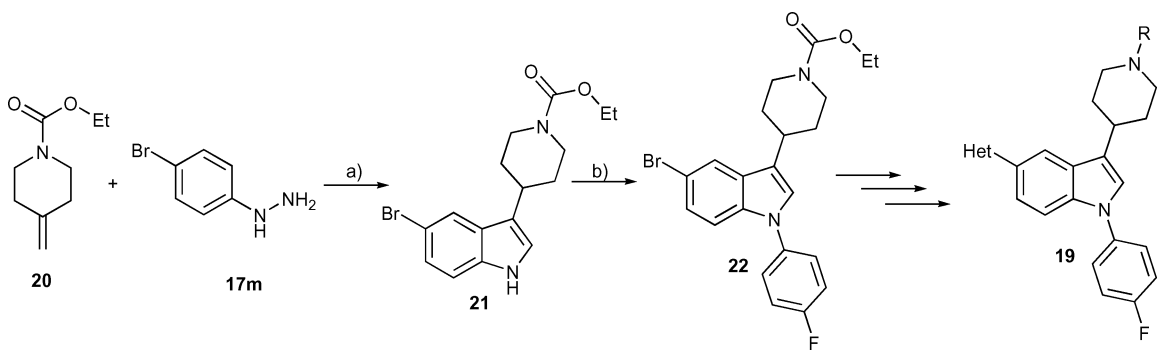
Scheme 10 Reagents and conditions: 1 eq **23**, 0.3 mol% Rh(acac)$(CO)_2$, 1.5 mol% XANTPHOS, 10 bar CO, 10 bar H_2, THF, 20 h, 70 °C.

Table 4 *n*-Selective hydroformylation of allylic amides



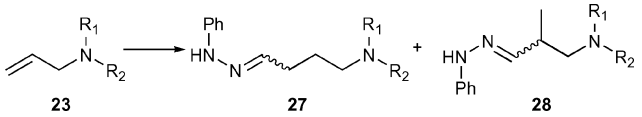
Entry	Olefin **23**	Ligand : [Rh]	**24**–**25**[a,b]	
1	**23a** (R_1 = R_2 = pht)	5 : 1	4 : 1	**24a**–**25a**
		10 : 1	6 : 1	
2	**23e** (R_1 = Et, R_2 = ts)	5 : 1	6 : 1	**24e**–**25e**
		10 : 1	6 : 1	
3	**23f** (R_1 = Et, R_2 = ac)	5 : 1	11 : 1	**24f**–**25f**
		10 : 1	12 : 1	
4	**23g** (R_1 = Et, R_2 = eoc)	5 : 1	13 : 1	**24g**–**25g**
		10 : 1	14 : 1	

Cond.: 1 eq **23**, 0.3 mol% Rh(acac)$(CO)_2$, XANTPHOS (see table), 10 bar CO, 10 bar H_2, THF, 20 h, 70 °C.[a] Determined by ^{1}H-NMR of the crude reaction mixture. [b] Full conversion to the aldehyde.



Scheme 9 Reagents and conditions: (a) 1 eq **20**, 1 eq **17m**, 0.3 mol% Rh(acac)$(CO)_2$, 50 bar CO, 10 bar H_2, THF, 68 h, 120 °C then 4 wt% H_2SO_4–THF, 2 h, 80 °C, 39%. (b) 1 eq **21**, 1.2 eq 4-fluoro-iodobenzene, 2.1 eq $K_3PO_4 \cdot 7H_2O$, 5 mol% copper(I) iodide, 20 mol% *N*,*N*′-dimethylethylendiamine, toluene (1 M), 24 h, 110 °C, 100%.

Table 5 *n*-Selective tandem hydroformylation–condensation of allylic amines



23 **27** **28**

Entry	Olefin **23**	Ligand : [Rh]	**27–28**[a,b]	
1	**23a** ($R_1 = R_2$ = pht)	5 : 1	1 : 1	**27a–28a**
		10 : 1	6 : 1	
2	**23e** (R_1 = Et, R_2 = ts)	5 : 1	3 : 1	**27b–28b**
		10 : 1	6 : 1	
3	**23f** (R_1 = Et, R_2 = ac)	5 : 1	11 : 1	**27c/28c**
		10 : 1	12 : 1	

Cond.: 1 eq **17a**, 1 eq **23**, 0.3 mol% $Rh(acac)(CO)_2$, XANTPHOS (see table), 10 bar CO, 10 bar H_2, THF, 68 h, 70 °C.[a] Determined by ^{1}H-NMR of the crude reaction mixture. [b] Full conversion to the hydrazone.

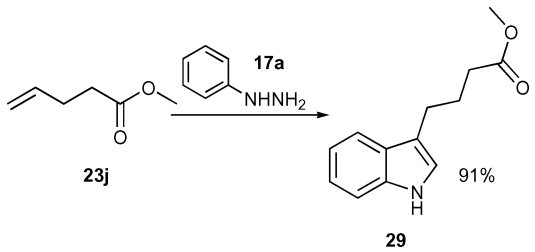
Consequently, by use of secondary allylic amides this consecutive reaction can be suppressed and the *n*-aldehydes are obtained with high yields and selectivities. Among the amides tested, three different types can be recognized. Those containing two carbonyl groups give the lowest *n*/*iso* ratios. Here a precoordination of the catalyst is more probable than in substrates with only one carbonyl group. The allylic acetamide **23f** for example gives an *n*/*iso* ratio of 12 : 1. Ethyloxycarbonyl protected *N*-ethyl allyl amine **23g** gives the highest *n*/*iso* selectivity of approximately 14 : 1 with an optimum of the catalyst ligand ratio at 1 : 10. Higher catalyst ligand ratios gave no further enhancement of the *n*-selectivity in the case of allylic phthalimide.

n-Selective hydroformylation in the presence of phenylhydrazine

In order to study the influence of hydrazines on the *n*/*iso*-selectivity of the rhodium–XANTPHOS catalyst hydroformylation of protected allylic amines, the reactions were conducted in the presence of phenyl. From the results compiled in Table 5, it can be concluded that phenylhydrazines are not competing with the *n*-directing XANTPHOS. Therefore aryl hydrazones are obtained with a high degree of *n*-selectivity starting from protected allylic amines.

Application of *n*-selective hydroformylation–indolization in the synthesis of tryptamides starting from allyl amines

Using the optimized conditions of the tandem hydroformylation–indolization procedure, olefin **23j** gives the methyl ester of the plant growth regulator 3-indole butanoic acid (IBA, **29**) in 91% isolated yield (Scheme 11). Hydrazone formation and indolization proceed smoothly after addition of dilute sulfuric acid.



Scheme 11 Reagents and conditions: 1 eq **17a**, 1 eq **23j**, 0.3 mol% $Rh(acac)(CO)_2$, 3 mol% XANTPHOS, 10 bar CO, 10 bar H_2, 68 h, 70 °C. (b) 4 wt% H_2SO_4–THF, 2 h, 80 °C.

If allylic amides and homoallylic amides are subjected to the same conditions, tryptamines and homotryptamines are obtained in good yields. All protecting groups are tolerated and as expected from the results described above, strong electron withdrawing protecting groups give the best yields (Table 6).

It is noteworthy that the tandem hydroformylation–Fischer indole synthesis of **23h** gives tosylated homotryptamine **30f** in good yields. Application of α-boc protected *p*-methoxy phenylhydrazine **17j** yields the 5-methoxy tryptamine **30c** in excellent yields. Here, no further purification is required.

Conclusions

With the tandem hydroformylation–Fischer indole synthesis, we have developed a new tandem sequence, which gives fast and convenient access to pharmacologically interesting tryptamides, respectively primary and secondary tryptamines and homotryptamines, starting from protected aryl hydrazines as well as allylic and homoallylic amines. The fact that intermediates do not have to be isolated or purified clearly saves time and resources. Regioselectivity of the tandem reaction can effectively be controlled with the use of the biphosphane ligand XANTPHOS. Finally we have given several examples for the application of this new tandem sequence towards the synthesis of the serotonin analogues **18j** and **30c**, the methylester of the plant growth regulator IBA (**29**) and of **22**, a valuable intermediate in the synthesis of sertindole analogues.

Experimental

Materials

All reagents and solvents were dried and purified before use by the usual procedures. $Rh(acac)(CO)_2$ and Xantphos were purchased. $[Rh(cod)Cl]_2$[30] and Biphephos[31] were prepared according to published methods. All aromatic hydrazines were purchased excluding protected hydrazines. *N*-Allyl, *N*-ethylamides (**23e–23g**) were synthesized by allylation of the corresponding secondary amides. All *N*-ethylamides were prepared by the reaction of ethylamine with the corresponding acid chloride in the presence of triethylamine and DMAP. All other protected allylic amines (**14b–14e, 23b–23d**) were synthesized by the reaction of the corresponding allylic amines with the corresponding acid chlorides in the presence of triethylamine and DMAP. 2-(2-Methylallyl)isoindoline-1,3-dione (**14a**) and 2-allyl-isoindole-1,3-dione (**23a**) were synthesized according to published methods.[31] Benzhydrylidene protected aryl hydrazines[18,11a] and *N*-Boc aryl hydrazines[23] were prepared according to published methods.

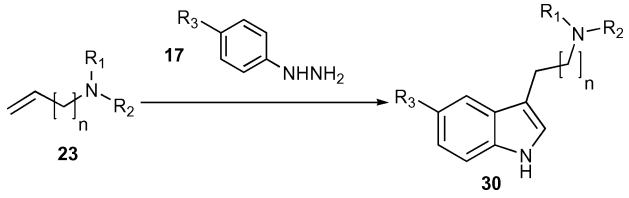
General methods

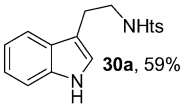
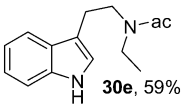
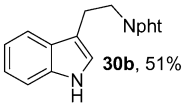
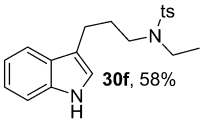
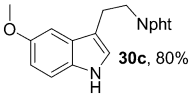
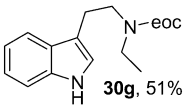
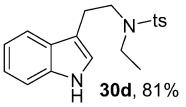
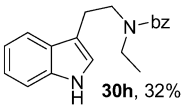
^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker Advance DRX 400 spectrometer or a Bruker Advance DRX 500 spectrometer using $CHCl_3$ or CH_2Cl_2 as internal standards. All samples were dissolved in $CDCl_3$. IR spectra were measured on a Nicolet Impact 400D FT-IR spectrometer. Column chromatography was carried out on 70–230 mesh silica gel (Macherey–Nagel; silicagel 60). Elemental analyses were performed on a Leco CHNS-932. High resolution mass analyses were performed on a Jeol JMS-SX 102A.

General procedure for the tandem hydroformylation–Fischer indole synthesis followed by tosylation of the crude product

A typical procedure is described. 2-(2-Methylallyl)isoindoline-1,3-dione (0.66 g, 3.3 mmol), phenylhydrazine (0.36 g, 3.3 mmol), $[Rh(cod)Cl]_2$ (16 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.63 g, 3.3 mmol) are dissolved in anhydrous toluene (12 ml), placed in an autoclave and pressurized with 10 bar H_2 and 50 bar CO. After stirring for 3 days at 120 °C, the mixture is poured into a suspension of tetrabutylammonium hydrogensulfate (0.1 g) in toluene (15 ml) and NaOH (10 g, 50 wt% in water). Tosyl chloride (0.69 g, 3.6 mmol) in toluene (15 ml) are dropped into the mixture over 10 minutes. After stirring for 1 hour, the layers are separated and the organic layer is extracted 3 times with ethyl acetate. The solvent is

Table 6 *n*-Selective tandem hydroformylation–Fischer indole synthesis towards non-branched tryptamides



Entry	Olefin **23**	Hydrazine **17**	Yield **30**	Entry	Olefin **23**	Hydrazine **17**	Yield **30**
1	**23c** ($n = 1$, $R_1 = H$, $R_2 =$ ts)	**17a**	 **30a**, 59%	5	**23f** ($n = 1$, $R_1 =$ Et, $R_2 =$ ac)	**17a**	 **30e**, 59%
2	**23a** ($n = 1$, $R_1 = R_2 =$ pht)	**17a**	 **30b**, 51%	6	**23h** ($n = 2$, $R_1 =$ Et, $R_2 =$ ts)	**17a**	 **30f**, 58%
3	**23a** ($n = 1$, $R_1 = R_2 =$ pht)	**17j**	 **30c**, 80%	7	**23g** ($n = 1$, $R_1 =$ Et, $R_2 =$ eoc)	**17a**	 **30g**, 51%
4	**23e** ($n = 1$, $R_1 =$ Et, $R_2 =$ ts)	**17a**	 **30d**, 81%	8	**23i** ($n = 1$, $R_1 =$ Et, $R_2 =$ bz)	**17a**	 **30h**, 32%

Cond.: (a) 1 eq **17**, 1 eq **23**, 0.3 mol% $Rh(acac)(CO)_2$, 3 mol% XANTPHOS, 10 bar CO, 10 bar H_2, 68 h, 70 °C. (b) 4 wt% H_2SO_4–THF, 2 h, 80 °C.

evaporated and the residue is purified by flash chromatography on silica to give 2-{2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (0.91 g, 60%).

2-{2-[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (18a). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.24$ (d, 3H, $J = 7.0$ Hz, CH_3), 2.16 (s, 3H, CH_3), 3.43 (m, 1H, CH), 3.64 (dd, 1H, $J = 8.9$ Hz, $J = 13.8$ Hz, C*H*H), 3.88 (dd, 1H, $J = 6.1$ Hz, $J = 13.8$ Hz, C*H*H), 7.03 (d, 1H, $J = 8.3$ Hz, CH), 7.09–7.22 (2H, 2 x CH), 7.38 (s, 1H, CH), 7.56–7.68 (8H, 8 x CH), 7.84 (d, 1H, $J = 8.3$ Hz, CH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 17.7$ (CH_3), 21.3 (CH_3), 29.9 (CH), 43.4 (CH_2), 113.5 (CH), 119.7 (CH), 122.2 (2 x CH), 123.0 (2 x CH), 124.6 (CH), 124.7 (C), 126.6 (2 x CH), 127.7 (CH), 129.6 (2 x CH), 130.0 (C), 131.7 (C), 133.8 (2 x CH), 135.0 (2 x C), 144.6 (C), 168.2 (2 x C, C not observed. IR: ν [cm^{-1}] = 2966 (s), 2933 (s), 1770 (vs), 1718 (vs), 1398 (vs), 1184 (vs), 1132 (vs), 717 (vs), 671 (vs). MS (EI, 70 eV): m/z (%) = 458 (M^+, 22), 298 (100), 200 (25), 160 (51), 155 (60), 106 (31), 91 (91). HRMS found M^+ 458.1314, $C_{26}H_{22}N_2O_4S$ requires M^+, 458.1300.

2-{2-[5-Chloro-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (18b). The general procedure is followed with 2-(2-methylallyl)isoindoline-1,3-dione (1.3 g, 6.5 mmol), 4-chloro-phenylhydrazine (0.92 g, 6.5 mmol), $[Rh(cod)Cl]_2$ (32 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (1.23 g, 6.5 mmol) to give 2-{2-[5-chloro-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (0.82 g, 53%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.37$ (d, 3H, $J = 7.0$ Hz, CH_3), 2.35 (s, 3H, CH_3), 3.52 (m, 1H, CH), 3.78 (dd, 1H, $J = 8.6$ Hz, $J = 13.6$ Hz, C*H*H), 3.98 (dd, 1H, $J = 6.4$ Hz, $J = 13.6$ Hz, CH*H*), 7.21 (d, 1H, $J = 8.2$ Hz, CH), 7.26 (d, 1H, $J = 8.7$ Hz, CH), 7.52 (s, 1H, CH), 7.69 (s, 1H, CH), 7.73–7.75 (4H, 4 x CH), 7.83–7.88 (4H, 4 x CH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 17.9$ (CH_3), 21.5 (CH_3), 29.9 (CH), 43.5 (CH_2), 114.7 (CH), 119.5 (CH), 123.3 (2 x CH), 124.3 (C), 125.0 (CH), 126.7 (2 x CH), 129.0 (CH), 129.1 (C), 129.9 (2 x CH), 131.4 (C), 131.8 (C), 133.5 (C), 134.0 (2 x CH), 145.0 (2 x C), 168.3 (2 x C), C not observed. HRMS found $[M + H]^+$, 493.0979, $C_{26}H_{21}ClN_2O_4S$ requires $[M + H]^+$, 493.0958.

2-{2-[5-*tert*-Butyl-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (18c). The general procedure is followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.27 g, 1.3 mmol), 4-*tert*-butyl-phenylhydrazine (0.22 g, 1.3 mmol), $Rh(acac)(CO)_2$ (14 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.25 g, 1.3 mmol) to give 2-{2-[5-*tert*-butyl-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-propyl}-isoindole-1,3-dione (0.32 g, 48%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.20$ (s, 9H, 3 x CH_3), 1.26 (d, 3H, $J = 6.8$ Hz, CH_3), 2.15 (s, 3H, CH_3), 3.44 (m, 1H, CH_3), 3.64 (dd, 1H, $J = 8.5$ Hz, $J = 13.5$ Hz, C*H*H), 3.86 (dd, 1H, $J = 6.2$ Hz, $J = 13.5$ Hz, CH*H*), 7.03 (d, 2H, $J = 8.6$ Hz, 2 x CH), 7.23 (d, 1H, $J = 8.8$ Hz, CH), 7.54 (s, 1H, CH), 7.53–7.55 (2H, 2 x CH), 7.62–7.67 (4H, CH), 7.66 (d, 2H, $J = 8.6$ Hz, 2 x CH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 17.7$ (CH_3), 21.3 (CH_3), 26.7 (C), 29.7 (CH), 31.5 (3 x CH_3), 43.6 (CH_2), 112.9 (CH), 115.6 (CH), 122.1 (CH), 122.6 (CH) 123.0 (2 x CH), 124.9 (C), 126.6 (2 x CH), 129.6 (2 x CH), 129.9 (C), 131.7 (2 x C), 133.0 (C), 133.8 (2 x CH), 135.2 (C), 144.4 (C), 146.1 (C), 168.5 (2 x C). IR: ν [cm^{-1}] = 2962 (s), 2870 (m), 1772 (s), 1713 (vs), 1398 (vs), 1398 (vs), 1369 (vs), 1173 (vs). HRMS found M^+, 514.1946, $C_{30}H_{30}SN_2O_4$ requires M^+, 514.1926.

General procedure for the tandem hydroformylation–Fischer indole synthesis using benzhydrylidene protected aryl hydrazines

A typical procedure is described. 2-(2-Methylallyl)isoindoline-1,3-dione (1.32 mg, 6.6 mmol), *N*-benzhydrylidene-*N*′-phenyl-hydrazine (1.79 g, 6.60 mmol), $[Rh(cod)Cl]_2$ (32 mg, 1 mol% and *p*-toluenesulfonic acid monohydrate (1.25 g, 6.60 mmol) are

dissolved in anhydrous THF (11 g, 10 wt% olefin), placed in an autoclave and pressurized with 10 bar H_2 and 50 bar CO. After stirring for 3 days at 100 °C, the mixture is filtered through an alumina pad and the solvent is evaporated to get 3.16 g of crude product. 1.06 g of the crude product are purified by flash chromatography on silica to give 2-[2-(1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.56 g, 83%).

2-[2-(1*H*-Indol-3-yl)-propyl]-isoindole-1,3-dione (18d). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.44$ (d, 3H, $J = 7.0$ Hz, CH_3), 3.73 (m, 1H, CH), 3.87 (dd, 1H, $J = 9.0$ Hz, $J = 13.3$ Hz, CH_2), 4.09 (dd, 1H, $J = 6.3$ Hz, $J = 13.3$ Hz, CH_2), 7.13–7.24 (3H, 3 x CH), 7.37 (d, 1H, $J = 8.0$ Hz, CH), 7.70–7.87 (5H, 5 x CH), 8.31 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta =$ 18.4 (CH_3), 30.0 (CH), 44.5 (CH_2), 111.1 (CH), 118.3 (C), 119.1 (CH), 119.2 (CH), 120.6 (CH), 121.9 (2 x CH), 123.0 (2 x CH), 126.7 (C), 131.9 (C), 133.8 (CH), 136.2 (2 x C), 168.6 (2 x C). IR: ν [cm^{-1}] = 3406 (s), 2962 (m), 2931 (m), 1770 (vs), 1712 (vs), 1398 (vs), 1034 (s), 714 (vs). HRMS found M^+, 304.1219, $C_{19}H_{16}N_2O_2$ requires M^+, 304.1212.

2-[2-(5-Fluoro-1*H*-indol-3-yl)propyl]-isoindole-1,3-dione (18e). The general procedure is followed with 2-(2-methylallyl)-isoindoline-1,3-dione (0.62 g, 3.1 mmol), *N*-benzhydrylidene-*N*′-(4-fluorophenyl)-hydrazine (0.90 g, 3.1 mmol), Rh(acac)-$(CO)_2$ (8 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.59 g, 3.1 mmol) to give 2-[2-(5-fluoro-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.47 g, 47%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.37$ (d, 3H, $J = 7.0$ Hz, CH_3), 3.59 (m, 1H, $J = 7.0$ Hz, CH), 3.79 (dd, 1H, $J = 8.7$ Hz, $J = 13.5$ Hz, CHH), 3.97 (dd, 1H, $J = 6.7$ Hz, $J = 13.5$ Hz, CHH), 6.88 (dd, 1H, $J = 9.0$ Hz, $J = 9.0$ Hz, CH), 7.13 (s, 1H, CH), 7.23 (dd, 1H, $J = 9.0$ Hz, $J = 9.0$ Hz, CH), 7.41 (d, 1H, $J = 9.7$ Hz, CH), 7.67–7.69 (2H, 2 x CH), 7.78–7.80 (2H, 2 x CH), 8.10 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 18.4$ (CH_3), 30.0 (CH), 44.4 (CH_2), 104.1 (d, 1C, $J_{C-F} = 23$ Hz, CH), 110.3 (d, 1C, $J_{C-F} = 25$ Hz, CH), 111.7 (d, 1C, $J_{C-F} = 10$ Hz, CH), 116.2 (C), 118.7 (C), 122.3 (CH), 123.1 (2 x CH), 132.0 (2 x C), 133.9 (2 x CH), 157.7 (d, 1C, $J_{C-F} = 234$ Hz, C), 168.6 (2 x C). IR: ν [cm^{-1}] = 3392 (m), 2964 (w), 2933 (w), 1770 (w), 1708 (vs), 1486 (s), 1398 (vs), 1153 (m), 1033 (m). HRMS found M^+, 323.1145, $C_{19}H_{15}FN_2O_2$ requires M^+, 323.1118. Elementary analysis found C 70.38%, H 5.02%, N 8.30%, $C_{19}H_{15}FN_2O_2$ requires C 70.80%, H 4.69%, N 8.69%.

2-[2-(5-Chloro-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (18f). The general procedure is followed with 2-(2-methylallyl)-isoindoline-1,3-dione (0.92 g, 4.6 mmol), *N*-benzhydrylidene-*N*′-(4-chlorophenyl)-hydrazine (1.40 g, 4.6 mmol), $[Rh(cod)Cl]_2$ (22 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.87 g, 4.6 mmol) to give 2-[2-(5-chloro-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.58 g, 78%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.41$ (d, 3H, $J = 7.0$ Hz, CH_3), 3.63 (m, 1H, CH), 3.80 (dd, 1H, $J = 8.3$ Hz, $J = 13.6$ Hz, C*H*H), 4.00 (dd, 1H, $J =$ 6.8 Hz, $J = 13.6$ Hz, CH*H*), 7.09 (d, 1H, $J = 8.2$ Hz, CH), 7.14 (s, 1H, CH), 7.24 (m, 1H, CH), 7.69–7.72 (3H, 3 x CH), 7.81–7.83 (2H, 2 x CH), 8.31 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 18.4$ (CH_3), 29.9 (CH), 44.5 (CH_2), 112.12 (CH), 118.24 (C), 118.5 (CH), 122.0 (CH), 122.2 (CH), 123.1 (2 x CH), 125.0 (C), 128.0 (C), 131.8 (C), 133.9 (2 x CH), 134.5 (2 x C), 168.6 (2 x C). IR: ν [cm^{-1}] = 3383 (m), 2964 (w), 2360 (w), 1765 (s), 1705 (vs), 1466 (s), 1429 (s), 1398 (vs), 1032 (s), 717 (s). HRMS found M^+, 338.0802, $C_{19}H_{15}N_2O_2Cl$ requires M^+, 338.0822. Elementary analysis found C 66.90%, H 4.35%, N 8.10%, $C_{19}H_{15}N_2O_2Cl$ requires C 67.36%, H 4.46%, N 8.27%.

2-[2-(5-Bromo-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (18g). The general procedure is followed with 2-(2-methylallyl)-isoindoline-1,3-dione (0.79 g, 3.9 mmol), *N*-benzhydrylidene-*N*′-(4-bromophenyl)-hydrazine (1.38 g, 3.9 mmol), $[Rh(cod)Cl]_2$ (19 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.74 g, 3.9 mmol) to give 2-[2-(5-bromo-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.74 g, 50%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.36$ (d, 3H, $J = 6.9$ Hz, CH_3), 3.58 (m, 1H, CH), 3.79 (dd, 1H, $J = 8.7$ Hz, $J = 13.8$ Hz, C*H*H), 3.94 (dd, 1H, $J = 6.2$ Hz, $J = 13.8$ Hz, CH*H*), 7.08–7.16 (3H, 3 x CH), 7.65–7.81 (5H, 5 x CH), 8.27 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta =$ 18.4 (CH_3), 29.8 (CH), 44.5 (CH_2), 112.6 (CH), 112.6 (C), 118.2 (C), 121.6 (CH), 121.8 (CH), 123.1 (2 x CH), 124.8 (CH), 128.6 (C), 131.8 (C), 133.9 (2 x CH), 134.8 (2 x C), 168.5 (2 x C). IR: ν [cm^{-1}] = 3377 (s), 1770 (s), 1716 (vs), 1466 (s), 1433 (s), 1398 (vs), 1354 (s), 1034 (s), 795 (s), 715 (vs). HRMS found M^+, 382.0280, $C_{19}H_{15}BrN_2O_2$ requires M, 382.0317. Elementary analysis found C 59.75%, H 3.95%, N 7.35%, $C_{19}H_{15}BrN_2O_2$ requires C 59.55%, H 3.95%, N 7.31%.

2-[2-(7-Methyl-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (18h). The general procedure is followed with 2-(2-methylallyl)-isoindoline-1,3-dione (0.95 g, 4.7 mmol), *N*-benzhydrylidene-*N*′-*o*-tolyl-hydrazine (1.35 g, 4.7 mmol), $[Rh(cod)Cl]_2$ (23 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.90 g, 4.7 mmol) to give 2-[2-(7-methyl-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.72 g, 48%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.38$ (d, 3H, $J = 7.0$ Hz, CH_3), 2.45 (s, 3H, CH_3), 3.68 (m, 1H, CH), 3.81 (dd, 1H, $J = 8.9$ Hz, $J = 13.7$ Hz, C*H*H), 4.05 (dd, 1H, $J = 6.4$ Hz, $J = 13.7$ Hz, CH*H*), 6.96–7.11 (3H, 3 x CH), 7.66–7.82 (5H, 5 x CH), 8.07 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 16.5$ (CH_3), 18.5 (CH_3), 30.2 (CH), 44.5 (CH_2), 116.9 (CH), 118.9 (C), 119.6 (CH), 120.2 (CH), 120.3 (C), 122.5 (CH), 123.1 (2 x CH), 126.3 (C), 132.0 (C), 133.8 (2 x CH), 135.8 (2 x C), 168.6 (2 x C). IR: ν [cm^{-1}] = 3402 (s), 1770 (s), 1716 (vs), 1466 (s), 1458 (s), 1433 (s), 1398 (vs), 1034 (s), 714 (vs). HRMS found M^+, 318.1395, $C_{20}H_{18}N_2O_2$ require M^+, 318.1368. Elementary analysis found C 75.30%, H 5.80%, N 8.20%, $C_{20}H_{18}N_2O_2$ requires C 75.45%, H 5.70%, N 8.80%.

2-[2-(7-Chloro-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (18i). The general procedure is followed with 2-(2-methylallyl)-isoindoline-1,3-dione (0.93 g, 4.6 mmol), *N*-benzhydrylidene-*N*′-(2-chlorophenyl)-hydrazine (1.41 g, 4.6 mmol), $[Rh(cod)Cl]_2$ (23 mg, 1 mol%) and *p*-toluenesulfonic acid monohydrate (0.87 g, 4.6 mmol) to give 2-[2-(7-chloro-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (0.21 g, 42%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) $\delta = 1.38$ (d, 3H, $J = 7.0$ Hz, CH_3), 3.63 (m, 1H, CH), 3.80 (dd, 1H, $J = 8.8$ Hz, $J = 13.8$ Hz, C*H*H), 4.00 (dd, 1H, $J = 6.5$ Hz, $J = 13.8$ Hz, CH*H*), 7.00 (dd, 1H, $J = 7.8$ Hz, CH), 7.15 (s, 1H CH), 7.65–7.70 (4H, 4 x CH), 7.78–7.82 (2H, 2 x CH), 8.38 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 18.4$ (CH_3), 30.2 (CH), 44.4 (CH_2), 116.5 (C), 117.8 (CH), 119.5 (C), 120.1 (CH), 121.3 (2 x CH), 123.1 (2 x CH), 128.3 (C), 131.9 (2 x C), 133.5 (C), 133.9 (2 x CH), 168.6 (2 x C). IR: ν [cm^{-1}] = 3381(m), 1765 (m), 1705 (vs), 1398 (m), 1032 (m), 893 (m), 717 (m). HRMS found M^+, 338.0844, $C_{19}H_{15}ClN_2O_2$ requires M, 338.0822. Elementary analysis found C 67.43%, H 4.07%, N 8.10%, $C_{19}H_{15}ClN_2O_2$ requires C 67.36%, H 4.46%, N 8.27%.

General procedure for the tandem hydroformylation–Fischer indole synthesis with subsequent addition of acid

A typical procedure is described. 2-(2-Methylallyl)isoindoline-1,3-dione (301 mg, 1.50 mmol), α-Boc-1-(4-methoxyphenyl)-hydrazine (356 mg, 1.50 mmol) and Rh(acac)$(CO)_2$ (1.16 mg, 0.03 mol%) are dissolved in anhydrous THF (2.71 g, 10 wt% olefin), placed in an autoclave and pressurized with 10 bar H_2 and 50 bar CO. After stirring for 3 days at 120 °C, the mixture is poured into sulfuric acid (15 ml, 4 wt% in THF) and the resulting mixture is stirred for an additional 2 h under reflux. Ammonia (10 ml, 30 wt% in water) is added and the mixture is extracted 3 times with ethyl acetate. The solvent is evaporated and the residue is chromatographed (ethyl acetate, cyclohexane, silica) to give 2-[2-(5-methoxy-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (462 mg, 95%).

2-[2-(5-Methoxy-1*H*-indol-3-yl)-propyl]-isoindole-1,3-dione (18j). ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ = 1.38 (d, 3H, J = 7.0 Hz, CH_3), 3.60 (m, 1H, J = 7.0 Hz, CH), 3.78 (dd, 1H, J = 9.0 Hz, J = 13.6 Hz, C*H*H), 3.85 (s, 3H, CH_3), 4.01 (dd, 1H, J = 6.2 Hz, J = 13.6 Hz, CH*H*), 6.79 (d, 1H, J = 8.7 Hz, CH), 7.07 (s, 1H, CH), 7.19 (d, 1H, J = 8.7 Hz, CH), 7.27 (s, 1H, CH), 7.66 (d, 2H, J = 5.4 Hz, 2 x CH), 7.78 (d, 2H, J = 5.4 Hz, 2 x CH), 8.26 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) δ = 18.2 (CH_3), 30.0 (CH), 44.5 (CH_2), 55.7 (CH_3), 100.6 (CH), 111.9 (CH), 112.3 (CH), 118.1 (C), 121.3 (CH), 123.0 (2 x CH), 127.2 (C), 131.3 (C), 131.9 (2 x C), 133.8 (2 x CH), 153.8 (C), 168.6 (2 x C). IR: ν [cm^{-1}] = 3399 (m), 1770 (m), 1700 (vs), 1484 (s), 1428 (m), 1398 (s), 1376 (m), 1216 (s), 1157 (m), 1037 (s), 713 (s). HRMS found [M]$^+$ 334.1299, $C_{20}H_{18}N_2O_3$ requires [M]$^+$ 334.1318. Elementary analysis found C 71.64%, H 5.38%, N 8.11%, $C_{20}H_{18}N_2O_3$ requires C 71.84%, H 5.43%, N 8.38%.

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (18k).** The general procedure is followed with *N*-ethyl-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide (0.71 g, 2.8 mmol), phenylhydrazine (0.30 g, 2.8 mmol) and Rh(acac)$(CO)_2$ (2.2 mg, 0.3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (0.94 g, 94%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ = 1.11 (t, 3H, J = 7.3 Hz, CH_3), 1.50 (d, 3H, J = 6.5 Hz, CH_3), 2.43 (s, 3H, CH_3), 3.29 (q, 2H, J = 7.3 Hz, CH_2), 3.40–3.47 (3H, CH_2, CH), 7.07 (s, 1H, CH), 7.15 (dd, 1H, J = 7.0 Hz, J = 8.1 Hz, CH), 7.22 (dd, 1H, J = 7.0 Hz, J = 8.1 Hz, CH), 7.28 (d, 2H, J = 8.0 Hz, 2 x CH), 7.40 (d, 1H, J = 8.1 Hz, CH), 7.68 (d, 1H, J = 8.1 Hz, CH), 7.72 (d, 2H, J = 8.0 Hz, 2 x CH), 8.46 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) δ = 13.6 (CH_3), 18.2 (CH_3), 21.3 (CH_3), 30.2 (CH), 43.3 (CH_2), 54.0 (CH_2), 111.3 (CH), 118.2 (C), 118.6 (CH), 119.0 (CH), 121.0 (CH), 121.7 (CH), 126.4 (C), 127.0 (2 x CH), 129.5 (2 x CH), 136.3 (C), 136.9 (C), 142.9 (C). IR: ν [cm^{-1}] = 3398 (s), 2972 (s), 2931 (s), 1599 (s), 1456 (s), 1329 (s), 1153 (m), 741 (m). HRMS found [M]$^+$ 356.1584, $C_{20}H_{24}N_2O_2S$ requires [M]$^+$ 356.1558.

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-benzamide (18l).** The general procedure is followed with *N*-ethyl-*N*-(2-methylallyl)-benzamide (0.66 g, 3.3 mmol), phenylhydrazine (0.35 g, 3.3 mmol) and Rh(acac)$(CO)_2$ (2.5 mg, 0.3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-benzamide (0.82 g, 85%). ^{1}H-NMR: ($C_2D_2Cl_4$, 400 MHz, 80 °C) δ = 1.06–1.20 (3H, CH_3), 1.43 (d, 3H, J = 6.5 Hz, CH_3), 3.30–3.79 (5H, 2 x CH_2, CH), 7.00 (s, 1H, CH), 7.10 (dd, 1H, J = 7.5 Hz, J = 7.3 Hz, CH), 7.20 (t, 1H, J = 8.0 Hz, J = 7.0 Hz), 7.27–7.29 (2H, 2 x CH), 7.35–7.53 (5H, 5 x CH), 8.21 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) δ = 13.5, 12.5 (CH_3), 18.8, 17.8 (CH_3), 28.9, 30.4 (CH), 44.0, 39.9 (CH_2), 50.6, 54.7 (CH_2), 111.3, 114.9 (CH), 118.4, 117.1 (C), 118.7, 118.3 (CH), 120.8, 121.0 (CH), 121.3 (CH), 126.1, 126.5 (2 x CH), 126.8 (C), 128.2, 128.7 (2 x CH), 128.9, 129.0 (CH), 136.3 (C), 137.1, 136.9 (C), 171.9 (C). IR: ν [cm^{-1}] = 3188 (s), 2972 (s), 2931 (s), 1633 (s), 1456 (s), 1381 (s), 1105 (m), 739 (s).

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-acetamide (18m).** The general procedure is followed with *N*-ethyl-*N*-(2-methylallyl)-acetamide (0.58 g, 4.1 mmol), phenylhydrazine (0.44 g, 4.1 mmol) and Rh(acac)$(CO)_2$ (3.2 mg, 0.3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-propyl]-acetamide (0.61 g, 61%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ = 1.01, 1.10 (t, 3H, J = 7.1 Hz, CH_3), 1.33, 1.41 (d, 3H, J = 6.9 Hz, CH_3), 2.06, 1.95 (s, 3H, CH_3), 2.97–3.12 (2H, CH_2), 3.36–3.55 (2H, CH_2), 3.71–3.75 (1H, CH), 6.98, 6.95 (s, 1H, CH), 7.08, 7.03 (d, 1H, J = 8.0 Hz, CH), 7.15, 7.11 (d, 1H, J = 8.0 Hz, CH), 7.32, 7.34 (d, 1H, J = 8.0 Hz, CH), 7.66, 7.57 (d, 1H, J = 8.0 Hz, CH), 8.81, 9.01 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) δ = 13.5, 12.5 (CH_3), 18.6, 18.1 (CH_3), 21.4, 21.6 (CH_3), 29.2, 30.9 (CH), 43.7, 40.7 (CH_2), 51.9, 54.7 (CH_2), 111.2, 111.5 (CH), 118.8, 118.5 (CH), 119.0, 117.7 (C), 119.1, 119.4 (CH), 121.0, 120.6 (CH), 121.5, 121.7 (CH), 126.9, 126.2 (C), 136.5, 136.3 (C), 170.6, 170.5 (C). IR: ν [cm^{-1}] = 3271 (s), 2970 (s), 2931 (s), 1631 (s), 1458 (s), 1379 (s), 1033 (m), 742 (s). HRMS found [M + H]$^+$ 245.1682, $C_{15}H_{20}N_2O$ requires [M + H]$^+$ 245.1654.

Ethyl-[2-(1*H*-indol-3-yl)-propyl]-carbamic acid ethyl ester (18n). The general procedure is followed with ethyl-(2-methylallyl)-carbamic acid ethyl ester (0.62 g, 3.6 mmol), phenylhydrazine (0.39 g, 3.6 mmol) and Rh(acac)$(CO)_2$ (2.8 mg, 0.3 mol%) to give ethyl-[2-(1*H*-indol-3-yl)-propyl]-carbamic acid ethyl ester (0.58 g, 58%). ^{1}H-NMR: ($CDCl_3$, 400 MHz) δ = 1.03–1.13 (3H, CH_3), 1.28 (t, 3H, J = 7.1 Hz, CH_3), 1.39 (bs, 3H, CH_3), 3.23–3.72 (5H, 2 x CH_2, CH), 4.15–4.20 (2H, CH_2), 7.01, 6.98 (s, 1H, CH), 7.12 (dd, 1H, J = 7.3 Hz, J = 7.3 Hz, CH), 7.19 (dd, 1H, J = 7.3 Hz, J = 7.7 Hz, CH), 7.35 (d, 1H, J = 7.7 Hz, CH), 7.69 (bs, 1H, CH), 8.38 (bs, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) δ = 12.9, 13.4 (CH_3), 14.6 (CH_3), 18.4, 18.1 (CH_3), 29.9, 30.7 (CH), 42.3, 42.8 (CH_2), 52.9, 53.5 (CH_2), 61.0 (CH_2), 110.6 (C), 111.3, 111.2 (CH), 119.0 (2 x CH), 119.2 (C), 120.6 (CH), 121.8 (CH), 136.5 (C), 154.7 (C). IR: ν [cm^{-1}] = 3315 (vs), 2973 (s), 2886 (s), 1683 (vs), 1484 (s), 1380 (m), 1172 (s), 1074 (m), 771 (m). HRMS found [M]$^+$ 274.1652, $C_{16}H_{22}N_2O_2$ requires [M]$^+$ 274.1682.

Ethyl 4-(5-bromo-1*H*-indol-3-yl)piperidine-1-carboxylate (21). The general procedure is followed with ethyl 4-methylenepiperidine-1-carboxylate (1.75 g, 10.3 mmol), 4-bromophenylhydrazine (1.93 g, 10.3 mmol) and Rh(acac)$(CO)_2$ (11 mg, 0.3 mol%) to give ethyl 4-(5-bromo-1*H*-indol-3-yl)piperidine-1-carboxylate (1.93 g, 39%).^{1}H-NMR: ($CDCl_3$, 500 MHz) δ = 1.29 (t, 3H, J = 7.2 Hz, CH_3), 1.63 (q, 2H, J = 11.7 Hz, CH_2), 2.00 (d, 2H, J = 13.7 Hz, CH_2), 2.92 (t, 3H, J = 11.7 Hz, CH_2), 4.17 (q, 2H, J = 7.2 Hz, CH_2), 4.28 (bs, 2H, CH_2), 6.92 (s, 1H, CH), 7.20 (d, 1H, J = 8.5 Hz, CH), 7.25 (d, 1H, J = 8.5 Hz, CH), 7.73 (s, 1H, CH), 8.56 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) δ = 14.7 (CH_3), 32.6 (2 x CH_2), 33.4 (CH), 44.4 (2 x CH_2), 61.3 (CH_2), 112.3 (C), 112.7 (CH), 120.2 (C), 121.0 (CH), 121.4 (CH), 124.6 (CH), 128.2 (C), 135.0 (C), 155.6 (C).

Ethyl 4-(5-bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)piperidine-1-carboxylate (22). Copper(I) iodide (5.35 mg, 5 mol%), *N*,*N*′-dimethylethylenediamine (20.2 mg, 20 mol%), potassium phosphate heptahydrate (399 mg, 1.18 mmol), 4-fluoro-iodobenzene (150 mg, 0.67 mmol) and **24** (197 mg, 0.56 mmol) are dissolved in toluene (1 M). After stirring for 24 h at 110 °C, the mixture is poured into ethyl acetate and filtered through a pad of silica. The solvent is removed to give ethyl 4-(5-bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl)piperidine-1-carboxylate (250 mg, 100%) without further purification. ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ = 1.28 (t, 3H, J = 7.2 Hz, CH_3), 1.67 (q, 2H, J = 9.7 Hz, CH_2), 2.04 (d, 2H, J = 13.7 Hz, CH_2), 2.97 (q, 3H, J = 12.0 Hz, CH_2, CH), 4.16 (q, 2H, J = 7.2 Hz, CH_2), 4.30 (bs, 2H, CH_2), 7.03 (s, 1H, CH), 7.17 (dd, 2H, J = 8.6 Hz, J = 9.0 Hz, 2 x CH), 7.27 (bs, 2H, 2 x CH), 7.37 (dd, 2H, J = 8.6, J = 9.0 Hz, 2 x CH), 7.78 (s, 1H, CH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) δ = 14.6 (CH_3), 32.5 (2 x CH_2), 33.3 (CH), 44.3 (2 x CH_2), 61.1 (CH_2), 111.8 (CH), 113.01 (C), 116.4 (d, 2C, J = 23 Hz, 2 x CH), 121.3 (C), 124.8 (CH), 125.3 (CH), 125.9 (d, 2C, J = 10 Hz, 2 x CH), 129.3 (C), 135.1 (d, 1C, J = 36 Hz, C), 155.5 (C), 161.0 (d, 1C, J = 248 Hz, C). IR: ν [cm^{-1}] = 2929 (m), 2850 (m), 1693 (vs), 1511 (vs), 1457 (vs), 1442 (s), 1382 (m), 1213 (vs), 1120 (s), 840 (s), 788 (s). HRMS found [M]$^+$ 444.0864, $C_{22}H_{22}BrFN_2O_2$ requires [M]$^+$ 444.0849.

General procedure for the regioselective tandem hydroformylation–Fischer indole synthesis

A typical procedure is described. Methyl pent-4-enoate (263 mg, 2.30 mmol), phenylhydrazine (249 mg, 2.30 mmol), Rh(acac)$(CO)_2$ (1.78 mg, 0.3 mol%) and Xantphos (40.0 mg, 3 mol%) are dissolved in anhydrous THF (2.36 g, 10 wt% olefin), placed in an autoclave and pressurized with 10 bar H_2 and 10 bar

CO. After stirring for 3 days at 70 °C, the mixture is poured into sulfuric acid (15 ml, 4 wt% in THF) and the resulting mixture is stirred for an additional 2 h under reflux. Ammonia (10 ml, 30 wt% in water) is added and the mixture is extracted 3 times with ethyl acetate. The solvent is evaporated and the residue is chromatographed (ethyl acetate–cyclohexane, silica) to give methyl 4-(1*H*-indol-3-yl)butanoate (455 mg, 91%).

Methyl 4-(1*H*-indol-3-yl)butanoate (29). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 2.06$ (m, 2H, $J = 7.5$ Hz, CH_2), 2.40 (t, 2H, $J = 7.5$ Hz, CH_2), 2.82 (t, 2H, $J = 7.5$ Hz, CH_2), 3.67 (s, 3H, CH_3), 6.97 (s, 1H, CH), 7.12 (dd, 1H, $J = 7.1$ Hz, $J = 7.8$ Hz, CH), 7.19 (dd, 1H, $J = 7.1$ Hz, $J = 7.8$ Hz, CH), 7.34 (d, 1H, $J = 7.8$ Hz, CH), 7.62 (d, 1H, $J = 7.8$ Hz, CH), 8.12 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 24.4$ (CH_2), 25.3 (CH_2), 33.6 (CH_2), 51.4 (CH_3), 111.0 (CH), 115.4 (C), 118.8 (CH), 119.1 (CH), 121.5 (CH), 121.8 (CH), 127.4 (C), 136.3 (C), 174.2 (C). NMR data fits with literature.[32]

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (30a).** The general procedure is followed with *N*-allyl-4-methyl-benzenesulfonamide (336 mg, 1.59 mmol), phenylhydrazine (172 mg, 1.59 mmol), Rh(acac)$(CO)_2$ (1.23 mg, 0.30 mol%) and Xantphos (28 mg, 3 mol%) to give *N*-[2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (295 mg, 59%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 2.39$ (s, 3H, CH_3), 2.90 (t, 2H, $J = 6.7$ Hz, CH_2), 3.25 (dt, 2H, $J = 6.0$ Hz, $J = 6.7$ Hz, CH_2), 4.71 (t, 1H, $J = 6.0$ Hz, NH), 6.94 (s, 1H, CH), 7.05 (dd, 1H, $J = 7.6$ Hz, $J = 7.7$ Hz, CH), 7.17 (dd, 1H, $J = 7.6$ Hz, $J = 8.0$ Hz, CH), 7.20 (d, 2H, $J = 8.2$ Hz, 2 x CH), 7.32 (d, 1H, $J = 7.7$ Hz, CH), 7.40 (d, 1H, $J = 7.6$ Hz, CH), 7.64 (d, 2H, $J = 8.2$ Hz, 2 x CH), 8.17 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 21.4$ (CH_3), 25.4 (CH_2), 43.0 (CH_2), 111.3 (CH), 111.4 (C), 118.4 (CH), 119.4 (CH), 122.1 (CH), 122.6 (CH), 126.8 (C), 126.9 (2 x CH), 129.6 (2 x CH), 136.3 (C), 136.7 (C), 143.3 (C). NMR data fits with literature.[33]

2-[2-(1*H*-Indol-3-yl)-ethyl]-isoindole-1,3-dione (30b). The general procedure is followed with 2-allyl-isoindole-1,3-dione (322 mg, 1.72 mmol), phenylhydrazine (186 mg, 1.72 mmol), Rh(acac)$(CO)_2$ (0.13 mg, 0.30 mol%) and Xantphos (29.9 mg, 3 mol%) to give 2-[2-(1*H*-indol-3-yl)-ethyl]-isoindole-1,3-dione (255 mg, 51%). The product was obtained as *n*/*iso*-isomers. Analytical data were obtained from the mixture. *n*-Regioisomer: ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 3.17$ (dd, 2H, $J = 7.5$ Hz, $J = 8.1$ Hz, CH_2), 4.02 (dd, 2H, $J = 7.5$ Hz, $J = 8.1$ Hz, CH_2), 7.08 (s, 1H, CH), 7.13 (dd, 1H, $J = 7.3$ Hz, $J = 8.1$ Hz, CH), 7.19 (dd, 1H, $J = 7.3$ Hz, $J = 8.1$ Hz, CH), 7.34 (d, 1H, $J = 8.1$ Hz, CH), 7.50 (d, 1H, $J = 7.0$ Hz, CH), 7.75 (d, 1H, $J = 7.3$ Hz, CH), 7.66 (d, 2H, $J = 5.5$ Hz, 2 x CH), 8.11 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 24.4$ (CH_2), 38.5 (CH_2), 111.1 (CH), 112.9 (C), 118.8 (CH), 119.4 (CH), 122.0 (CH), 123.1 (2 x CH), 127.3 (2 x C), 132.4 (C), 133.6 (2 x CH), 136.2 (2 x C), 168.3 (2 x C). Characteristic data for the *iso*-regioisomer (structure confirmed with 1D-NOESY): ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 2.44$ (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 7.07 (dd, 1H, $J = 7.0$ Hz, $J = 7.0$ Hz, CH), 7.15 (dd, 1H, $J = 7.0$ Hz, $J = 7.0$ Hz, CH), 7.28 (d, 1H, $J = 7.0$ Hz, CH), 7.50 (d, 1H, $J = 7.0$ Hz, CH), 7.66 (d, 2H, $J = 5.5$ Hz, 2 x CH), 7.8 (d, 2H, $J = 5.5$ Hz, 2 x CH), 8.56 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) $\delta = 8.3$ (CH_3), 32.6 (CH_2), 110.1 (C), 110.8 (CH), 119.0 (CH), 119.2 (CH), 122.5 (CH), 123.4 (2 x CH), 128.2 (C), 128.9 (C), 131.9 (2 x C), 134.1 (2 x CH), 135.6 (C), 168.4 (2 x C). HRMS found $[M]^+$ 290.1068, $C_{18}H_{14}N_2O_2$ requires $[M]^+$ 290.1055.

2-[2-(5-Methoxy-1*H*-indol-3-yl)-ethyl]-isoindole-1,3-dione (30c). The general procedure is followed with 2-allyl-isoindole-1,3-dione (292 mg, 1.56 mmol), α-Boc-1-(4-methoxyphenyl)-hydrazine (372 mg, 1.56 mmol), Rh(acac)$(CO)_2$ (0.12 mg, 0.30 mol%) and Xantphos (27.1 mg, 3 mol%) to give 2-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-isoindole-1,3-dione (400 mg, 80%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 3.11$ (t, 2H, $J = 7.8$ Hz, CH_2), 3.85 (s, 3H, CH_3), 3.98 (t, 2H, $J = 7.8$ Hz, CH_2), 6.82 (d, 1H, $J = 8.8$ Hz, CH), 7.06 (s, 1H, CH), 7.16 (s, 1H, CH), 7.21 (d, 1H, $J = 8.8$ Hz, CH), 7.69 (d, 2H, $J = 5.5$ Hz, 2 x CH), 7.81 (d, 2H, $J = 5.5$ Hz, 2 x CH), 8.04 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 24.5$ (CH_2), 38.4 (CH_2), 55.8 (CH_3), 100.3 (CH), 119.1 (CH), 112.1 (C), 112.5 (CH), 122.8 (CH), 123.1 (2 x CH), 127.8 (C), 131.3 (C), 132.2 (2 x C), 133.8 (2 x CH), 156.1 (C), 168.4 (2 x C). Elementary analysis found C 70.82%, H 5.12%, N 8.41%, $C_{19}H_{16}N_2O_3$ requires C 71.24%, H 5.03%, N 8.74%. NMR data fits with literature.[34]

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (30d).** The general procedure is followed with *N*-allyl-*N*-ethyl-4-methyl-benzenesulfonamide (349 mg, 1.46 mmol), phenylhydrazine (158 mg, 1.46 mmol), Rh(acac)$(CO)_2$ (1.13 mg, 0.30 mol%) and Xantphos (25 mg, 3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (405 mg, 81%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.14$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.38 (s, 3H, CH_3), 3.03 (dd, 2H, $J = 7.7$ Hz, $J = 8.3$ Hz, CH_2), 3.29 (q, 2H, $J = 7.2$ Hz, CH_2), 3.41 (dd, 2H, $J = 7.7$ Hz, $J = 8.3$ Hz, CH_2), 7.01 (s, 1H, CH), 7.10 (dd, 1H, $J = 7.5$ Hz, $J = 8.0$ Hz, CH), 7.16 (dd, 1H, $J = 7.5$ Hz, $J = 8.2$ Hz, CH), 7.24 (d, 2H, $J = 8.2$ Hz, 2 x CH), 7.35 (d, 1H, $J = 8.2$ Hz, CH), 7.57 (d, 1H, $J = 8.0$ Hz, CH), 7.69 (d, 2H, $J = 8.2$ Hz, 2 x CH), 8.41 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 14.8$ (CH_3), 21.3 (CH_3), 25.4 (CH_2), 43.0 (CH_2), 48.1 (CH_2), 111.3 (CH), 112.1 (C), 118.3 (CH), 119.1 (CH), 121.7 (CH), 122.2 (CH), 127.0 (2 x CH), 129.5 (2 x CH), 129.6 (C), 136.9 (C), 142.9 (C). IR: ν [cm^{-1}] = 3399 (s), 2954 (s), 2923 (vs), 2856 (s), 1455 (vs), 1332 (s), 1153 (s). HRMS found $[M]^+$ 342.1415, $C_{19}H_{22}N_2O_2S$ requires $[M]^+$ 342.1402.

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-acetamide (30e).** The general procedure is followed with *N*-allyl-*N*-ethyl-4-acetamide (276 mg, 2.17 mmol), phenylhydrazine (235 mg, 2.17 mmol), Rh(acac)$(CO)_2$ (1.68 mg, 0.30 mol%) and Xantphos (18.8 mg, 3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-acetamide (295 mg, 59%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.16$, 1.13 (t, 3H, $J = 7.0$ Hz, CH_2), 1.92, 2.13 (s, 3H, CH_3), 3.00, 3.03 (t, 2H, $J = 7.3$ Hz, CH_2), 3.45, 3.23 (q, 3H, $J = 7.0$ Hz, CH_2), 3.53, 3.63 (t, 2H, $J = 7.3$ Hz, CH_2), 6.98, 6.95 (s, 1H, CH), 7.12–7.21 (2H, 2 x CH), 7.33, 7.35 (d, 1H, $J = 8.0$ Hz, CH), 7.56, 7.65 (d, 1H, $J = 7.7$ Hz, CH), 8.67, 8.86 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 14.0$, 12.9 (CH_3), 21.4, 21.3 (CH_3), 24.8, 23.6 (CH_2), 40.4, 43.9 (CH_2), 46.5, 48.9 (CH_2), 111.5, 111.2 (CH), 113.0, 111.7 (C), 118.0, 118.6 (CH), 119.1, 119.3 (CH), 121.7, 121.9 (CH), 122.4, 122.0 (CH), 127.0, 127.4 (C), 136.3 (C), 170.4, 170.2 (C). NMR data fits with literature.[35]

***N*-Ethyl-*N*-[3-(1*H*-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (30f).** The general procedure is followed with *N*-but-3-enyl-*N*-ethyl-4-methyl-benzenesulfonamide (355 mg, 1.40 mmol), phenylhydrazine (152 mg, 1.40 mmol), Rh(acac)$(CO)_2$ (1.09 mg, 0.30 mol%) and Xantphos (12.2 mg, 3 mol%) to give *N*-ethyl-*N*-[3-(1*H*-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (290 mg, 58%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.09$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.94 (m, 2H, $J = 7.5$ Hz, CH_2), 2.39 (s, 3H, CH_3), 2.76 (t, 2H, $J = 7.5$ Hz, CH_2), 3.20–3.24 (4H, 2 x CH_2), 7.00 (s, 1H, CH), 7.10 (dd, 1H, $J = 7.5$ Hz, $J = 7.5$ Hz, CH), 7.18 (dd, 1H, $J = 7.2$ Hz, $J = 8.0$ Hz, CH), 7.23 (d, 2H, $J = 8.1$ Hz, 2 x CH), 7.35 (d, 1H, $J = 8.0$ Hz, CH), 7.53 (d, 1H, $J = 8.0$ Hz, CH), 7.65 (d, 2H, $J = 8.1$ Hz, 2 x CH), 8.14 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 14.0$ (CH_3), 21.4 (CH_3), 22.1 (CH_2), 28.7 (CH_2), 42.6 (CH_2), 47.2 (CH_2), 111.1 (CH), 115.1 (C), 118.6 (CH), 119.0 (CH), 121.5 (CH), 121.8 (CH), 127.0 (2 x CH), 127.3 (C), 129.5 (2 x CH), 136.3 (C), 137.0 (C), 142.9 (C). IR: ν [cm^{-1}] = 3403 (s), 2935 (s), 1455 (vs), 1336 (vs), 1305 (vs), 1184 (s), 1155 (vs), 1089 (vs), 742 (vs), 715 (s), 551 (s). HRMS found $[M]^+$ 356.1569, $C_{20}H_{24}N_2O_2S$ requires $[M]^+$ 356.1558.

Ethyl-[2-(1*H*-indol-3-yl)-ethyl]-carbamic acid ethyl ester (30g). The general procedure is followed with allyl-ethyl-carbamic acid ethyl ester (302 mg, 1.92 mmol), phenylhydrazine (208 mg, 1.92 mmol), $Rh(acac)(CO)_2$ (1.49 mg, 0.30 mol%) and Xantphos (33.3 mg, 3 mol%) to give ethyl-[2-(1*H*-indol-3-yl)-ethyl]-carbamic acid ethyl ester (255 mg, 51%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.12$ (bs, 3H, CH_3), 1.27 (bs, 3H, CH_3), 3.01 (bs, 2H, CH_2), 3.32, 3.27 (2 x bs, 2H, CH_2), 3.53 (bs, 2H, CH_2), 4.14, 4.16 (2 x bs, 2H, CH_2), 6.99 (s, 1H, CH), 7.13 (dd, 1H, $J = 7.2$ Hz, $J = 7.2$ Hz, CH), 7.19 (dd, 1H, $J = 7.7$ Hz, $J = 7.2$ Hz, CH), 7.35 (d, 1H, $J = 7.7$ Hz, CH), 7.65 (bs, 1H, CH), 8.27 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 13.4$, 13.9 (CH_3), 14.7 (CH_3), 24.9, 24.3 (CH_2), 26.9 (CH_2), 42.3 (CH_2), 47.3, 48.1 (CH_2), 61.0 (CH_3), 111.1 (CH), 113.2 (C), 118.7 (CH), 119.2 (CH), 121.9 (2 x CH), 127.4 (C), 136.3 (C), 156.3 (C). IR: ν [cm^{-1}] = 3318 (vs), 2977 (vs), 1697 (vs), 1486 (vs), 1280 (vs), 1193 (vs), 1095 (s), 1012 (s), 742 (s). HRMS found $[M]^+$ 260.1490, $C_{15}H_{20}N_2O_2$ requires $[M]^+$ 260.1525.

***N*-Ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-benzamide (30h).** The general procedure is followed with *N*-allyl-*N*-ethylbenzamide (324 mg, 1.71 mmol), phenylhydrazine (185 mg, 1.71 mmol), $Rh(acac)(CO)_2$ (1.32 mg, 0.30 mol%) and Xantphos (29.7 mg, 3 mol%) to give *N*-ethyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-benzamide (160 mg, 32%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) $\delta = 1.27$ (bs, 3H, CH_3), 2.94, 3.19 (2 x bs, 2H, CH_2), 3.20, 3.51 (2 x bs, 2H, CH_2), 3.67, 3.81 (2 x bs, 2H, CH_2), 6.83–7.78 (10H, 10 x CH), 8.24 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) $\delta = 25.0$, 23.4 (CH_2), 44.3, 39.9 (CH_2), 45.6, 49.3 (CH_2), 111.2 (CH), 118.8 (CH), 119.3 (CH), 126.3 (2 x CH), 126.3 (2 x CH), 128.4 (2 x CH), 129.1, 129.0 (CH), 137.1, 136.2 (C). IR: ν [cm^{-1}] = 3181 (s), 2929 (s), 1606 (vs), 1596 (vs), 1467 (m), 1455 (s), 1319 (m), 748 (s). HRMS found $[M]^+$ 292.1539, $C_{19}H_{20}N_2O$ requires $[M]^+$ 292.1575.

Acknowledgements

The authors thank Degussa AG, Düsseldorf and Bayer AG, Leverkusen for donation of chemicals.

References

1 (*a*) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045; (*b*) E. Fischer and F. Jourdan, *Chem. Ber.*, 1883, **16**, 2241; (*c*) E. Fischer and O. Hess, *Chem. Ber.*, 1884, **17**, 559; (*d*) B. Robinson, *The Fischer Indole Synthesis*, John Wiley & Sons, Chichester, 1982; (*e*) I. I. Grandberg, *Zh. Org. Khim.*, 1983, **19**, 2439–2452.

2 For recent examples see: T. Heinrich, H. Böttcher, R. Gericke, G. D. Bartoszyk, S. Anzali, C. A. Seyfried, H. E. Greiner and C. van Amsterdam, *J. Med. Chem.*, 2004, **47**, 4684–4692.

3 M. Beller, B. Cornils, C. D. Frohning and C. W. Kohlpaintner, *J. Mol. Catal. A: Chem.*, 1995, **104**, 17.

4 E. Ucciani and A. Bonfand, *J. Chem. Soc., Chem. Commun.*, 1981, 82.

5 J. G. Cannon, *J. Med. Chem.*, 1981, **24**, 238.

6 J. Siu, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2004, **2**, 160–167.

7 A. W. Douglas, *Tetrahedron Lett.*, 1994, **35**, 6807.

8 K. S. Jandu, V. Barrett, M. Brockwell, D. Cambridge, D. R. Farrant, C. Foster, H. Giles, R. C. Glen, A. P. Hill, H. Hobbs, A. Honey, G. R. Martin, J. Salmon, D. Smith, P. Wollard and D. L. Selwood, *J. Med. Chem.*, 2001, **44**, 681–693.

9 G. Verspui, G. Elbertse, F. A. Sheldon, M. A. P. J. Hacking and R. A. Sheldon, *Chem. Commun.*, 2000, 1363.

10 (*a*) L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt and P. Eilbracht, *Chem. Rev.*, 1999, **99**, 3329; (*b*) A. M. Schmidt, P. Eilbracht, in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn., 2004, pp. 57-111.

11 (*a*) P. Köhling, A. M. Schmidt and P. Eilbracht, *Org. Lett.*, 2003, **5**(18), 3213–3216; (*b*) Beller *et al.* have isolated hydrazones from the hydroformylation of olefins in the presence of hydrazines. In addition, the authors report that tandem hydroformylation–indolization can be performed with Lewis acids such as $ZnCl_2$ instead of Brønsted acids. See: M. Ahmed, R. Jackstell, A. M. Seayad, H. Klein and M. Beller, *Tetrahedron Lett.*, 2004, **45**(4), 869–873 for further details.

12 G. D. Cuny and S. L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 2066–2068.

13 (*a*) K. Kaneda, M. Yasumura, M. Hiraki, T. Imanaka and S. Teransihi, *Chem. Lett.*, 1981, 1763; (*b*) K. Kaneda, T. Imanaka and S. Teranishi, *Chem. Lett.*, 1983, 1465.

14 T. Rische, PhD Thesis, 1999.

15 K. Wittmann, W. Wisniewski, R. Mynott, W. Leitner, C. L. Kranemann, T. Rische, P. Eilbracht, S. Kluwer, J. M. Ernsting and C. J. Elsevier, *Chem.–Eur. J.*, 2001, **7**, 4584–4589.

16 K. Hakkaku, Y. Sakakibara, JP2000143587, 2000.

17 (*a*) H. W. Bohnen and B. Cornils, *Adv. Catal.*, 2002, **47**, 1–64; (*b*) B. Cornils, *J. Mol. Catal. A: Chem.*, 1999, **143**, 1–10; (*c*) M. Beller, B. Cornils, C. D. Frohning and C. W. Kohlpaintner, *J. Mol. Catal. A: Chem.*, 1995, **104**, 17–85; (*d*) B. Cornils, W. A. Herrmann and C. W. Kohlpaintner, *Angew. Chem.*, 1994, **106**, 2219, (*Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2144); (*e*) B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds*, VCH, Weinheim, 1996; (*f*) *Rhodium Catalyzed Hydroformylation*, ed. P. W. N. M. van Leeuwen and C. Claver, Kluwer Academic Publishers, Dordrecht, 2000.

18 (*a*) S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 6621–6622; (*b*) S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **121**, 10251–10263.

19 T. Ishiyama and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**(48), 12043–12044.

20 P. Blatcher, M. Carter, R. Hornby, M. R. Owen, WO 9509166, 1995.

21 Y. K. Lim and C. G. Cho, *Tetrahedron Lett.*, 2004, **45**, 1857–1859.

22 R. E. Kenton, S. D. Dudlettes and A. T. Shulgin, *Biol. Psychiatry*, 1980, **15**, 349–352.

23 M. Wolter, A. Klapars and S. Buchwald, *Org. Lett.*, 2001, **3**, 3803–3805.

24 M. E. Flaugh, *Eur. Pat. Appl.*, EP 655243 A2, 1995.

25 J. Arnt and T. Skarsfeldt, *Neuropsychopharmacology*, 1998, **18**, 2539–2544.

26 T. Balle, J. Perregaard, M. T. Ramirez, A. K. Larsen, K. K. Søby, T. Liljefors and K. Andersen, *J. Med. Chem.*, 2003, **46**, 265–283.

27 E. Billig, A. G. Abatjoglou, D. R. Bryant, US4769498A, 1988.

28 R. P. J. Bronger, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Organometallics*, 2003, **22**, 5358–5369.

29 (*a*) E. Teoh, E. M. Campi and W. R. Jackson, *Chem. Commun.*, 2002, 978–979; (*b*) E. Teoh, E. M. Campi, W. R. Jackson and A. Robinson, *New J. Chem.*, 2003, **27**, 387–394.

30 G. Giordano and R. Crabtree, *Inorg. Chem.*, 1979, **19**, 218–219.

31 G. Delogu, G. Faedda and S. Gladiali, *J. Organomet. Chem.*, 1984, **268**, 167–174.

32 J. Perregaard, E. K. Moltzen, E. Meier and C. Sanchez, *J. Med. Chem.*, 1995, **11**, 1998–2008.

33 A. Onistschenko and H. Stamm, *Chem. Ber.*, 1989, **122**, 2397–2398.

34 I. A. Petrunin, L. Vinograd, N. M. Przhiyalgovskaya and N. N. Suvorov, *Chem. Heterocycl. Compd.*, 1987, **8**, 839–842.

35 O. S. Povalyaeva, L. N. Kurkovskaya, M. M. Vigdorchik and N. N. Suvorov, *J. Org. Chem. (USSR)*, 1987, **6**, 1171–1179.