Application of iridium catalyzed allylic substitution reactions in the synthesis of branched tryptamines and homologues *via* tandem hydroformylation–Fischer indole synthesis†

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Received 29th May 2008, Accepted 30th June 2008
First published as an Advance Article on the web 13th August 2008
DOI: 10.1039/b809143a

Combination of enantioselective allylation reactions with a tandem hydroformylation–Fischer indole synthesis sequence as a highly diversity-oriented strategy for the synthesis of tryptamines and homologues was explored. This modular approach allows the substituents at C3 of the indole core, the type of the amine moiety, and the distance of the amine moiety to the indole core in the final synthetic step to be defined. The starting materials required for the hydroformylation step were synthesized *via* iridium catalyzed enantioselective allylic substitution reactions in high yields and excellent enantioselectivities. The Rh catalyzed hydroformylation step in the presence of phenyl hydrazine, allows the *in situ* formed aldehyde to be trapped as the hydrazone. Subsequent acid catalyzed indolization furnishes the desired indole structures in moderate to good yields.

Introduction

The indole framework is one of the most frequently found structural motifs in natural products and pharmaceutically active compounds.[1] Substituted indoles are referred to as "privileged structures" owing to their binding ability to many different types of receptors.[2] Due to these important properties new methods for indole synthesis and functionalization continue to attract attention.[3] Among indole derivatives, those with a tryptamine scaffold (3-aminoethyl indole) are particularly important compounds and many of these are known as synthetic medicines and physiologically active substances (serotonin, melatonin, psilocin, *etc.*).[4] Serotonin (5-hydroxy tryptamine, 5-HT, Fig. 1) receptor subtypes $5HT_{1B}$ and $5HT_{1D}$ have recently attracted considerable attention as putative targets for novel antimigraine drugs, leading to the development of selective agonists such as sumatriptan (GR43175) and more recently naratriptan, zolmitriptan, rizatriptan, avitriptan, and others (Fig. 1).

However, neither sumatriptan nor related compounds in use significantly distinguish between these two subtypes in their binding activities. In the past few years, it was found that in addition to appropriate substituents at C5 of the indole core, more sophisticated amine moieties have to be attached with varying distances at C3 in order to achieve a discrimination between the subtypes of the serotonin receptor family.[5] From the synthetic chemist's point of view these and additional features such as the occurrence of branching in the α- and β-positions as well as stereochemical issues are important. Recently, the first examples of such branched tryptamines possessing pharmacologically interesting properties have been developed.[6] However, most of the known branched tryptamines are tryptophan derivatives and were synthesized starting from this essential amino acid.

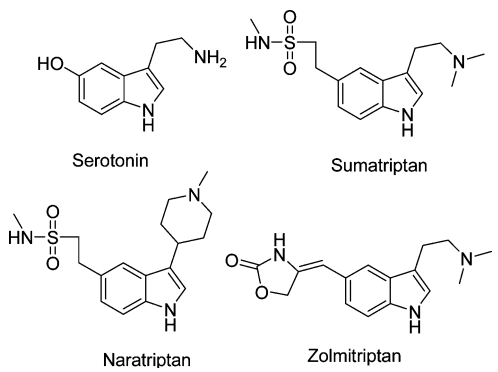
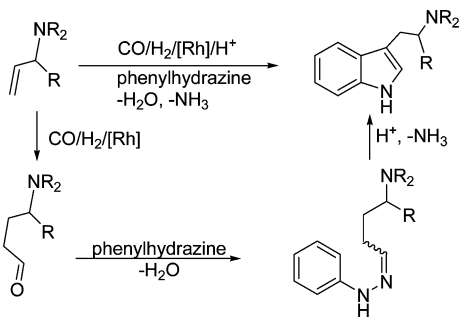


Fig. 1 Recently marketed serotonin receptor agonists.

We have recently reported on the synthesis of various branched tryptamine and tryptamide analogues *via* a tandem hydroformylation–Fischer indole synthesis sequence (Scheme 1).[7]



Scheme 1 General scheme of the tandem hydroformylation–Fischer indole synthesis.

This method involves hydroformylation of allylic amines and amides in the presence of various phenyl hydrazines followed by Brønsted acid catalyzed indolization. In this convergent method

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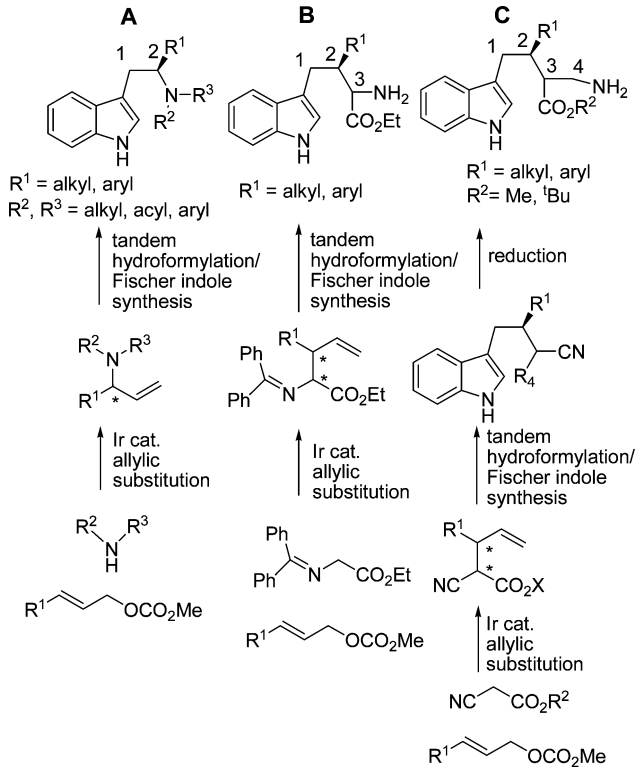
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b809143a

highly functionalized building blocks are assembled in the last synthetic step allowing the introduction of various substituents in all pharmacologically relevant positions of the indole core.

Herein we report use of this methodology developed in our laboratory, combined with efficient enantioselective synthesis of the olefinic starting materials, for the preparation of enantiopure branched tryptamines and homologues. Thus an approach allowing the introduction of substituents other than those obtainable from tryptophan is developed, offering a flexible determination of chain lengths in position C3 of the indole core. Synthetic pathways (**A–C**) as envisaged here are shown on Scheme 2.



Scheme 2 Envisaged pathway for the synthesis of various tryptamine homologues.

Results and discussion

As outlined in Scheme 2 a method was required that allows enantioselective synthesis of all starting materials, such as allylic amines, homoallylic amines and their derivatives. Although a vast number of reactions is available for the enantioselective synthesis of allylic and homoallylic amines, in the last couple of years Ir catalyzed allylic substitutions have emerged as one of the most powerful methods. Ir catalyzed allylic amination was first introduced in 2001 by Takeuchi *et al.*[8] High regioselectivities in allylic aminations of allylic carbonates and acetates were achieved with an Ir–$P(OPh)_3$ catalyst. In 2002 Hartwig *et al.* performed first enantioselective allylic aminations[9] using phosphoramidite type ligands,[10] and achieved excellent regio- and enantioselectivities. Applications of these ligands were further explored by several groups in enantioselective amination, etherification and alkylation reactions.[11]

We envisaged use of Ir catalyzed amination and alkylation reactions of various allylic carbonates for the synthesis of the starting materials required for the indole syntheses. Primary and secondary amines were used for the synthesis of branched allylic amines, while alkylation agents possessing masked or protected amine functionalities in appropriate positions were used for the synthesis of homoallylic amine derivatives and further homologues (Scheme 2).

Synthesis of starting materials

Reactions towards the synthesis of branched allylic amines (Scheme 2, Pathway A) were run using conditions as previously described.[11c] The active catalyst was prepared by stirring $[Ir(cod)Cl]_2$ and phosphoramidite ligands **1**, **2** or **3** (Fig. 2) with propylamine in dry THF at 50 °C for 30 min. After removing the excess of propylamine and THF the solid residue was redissolved in THF to give a stock solution of the active catalyst.

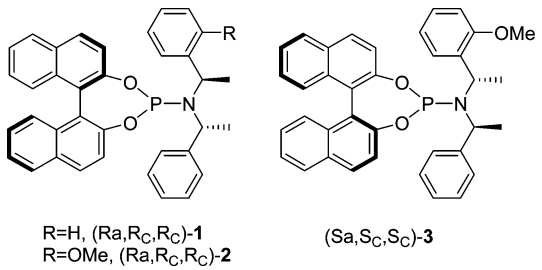
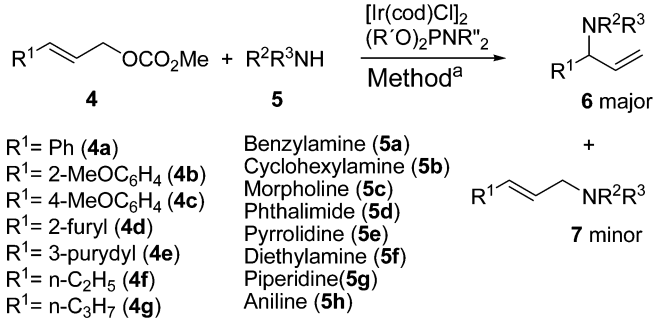


Fig. 2 Phosphoramidite ligands used in this study.

Reaction of cinnamyl carbonate **4a** and benzyl amine **5a** in the presence of 1 mol% of the preformed catalyst prepared from $[Ir(cod)Cl]_2$ and ligand **1** gave product **6a** in 58% yield with 90% ee (Table 1, Entry 1). The catalyst preformed with ligand **2** gave product **6a** in 76% yield with 94% ee (Table 1, Entry 2) while with ligand **3** product **6a** was obtained in comparable yield and enantioselectivity as with ligand **2** but with opposite configuration at the chiral center (Table 1, Entry 3). Since ligand **2** gave better yields and ee's of product **6a** than ligand **1**, reactions with all other substrates were run with this ligand. Good yields and excellent enantioselectivities were obtained in all cases, with allylic carbonates bearing sp^3 as well as sp^2 substituents using both, primary and secondary amines (Table 1). In addition to amines, imides are good nucleophiles for this reaction as well. Phthalimide **5d** in the reaction with cinnamyl carbonate **4a** gave product **6d** in 66% yield with 98% ee (Table 1, Entry 6). The variety of allylic amines thus synthesized (Table 1) demonstrates the versatility of this approach towards starting materials for the tandem hydroformylation–Fischer indole sequence. Aryl and alkyl groups R^1 present in the starting carbonates appear as substituents in the β position of the final tryptamine molecule. As already mentioned introducing these substituents by other methods in the final tryptamine molecule is often a difficult and time consuming process.

Starting materials for the synthesis of branched homotryptophans (Scheme 2, Pathway B), were prepared *via* Ir catalyzed allylic alkylation of allylic carbonates with benzophenone glycinate **8**. Ir catalyzed allylic substitutions of symmetric nucleophiles (*e.g.* sodium dimethylmalonate) and 3-substituted allylic alcohol

Table 1 Ir catalyzed allylic aminations of various allylic carbonates **4**, with amines **5**



Entry	R^1	Amine, **5**	L	**6** : **7**[b]	Yield[c], **6** (%)	ee[d] (%)
1	Ph (**4a**)	**5a**	**1**	90 : 10	58 (**6a**)	90 (*R*)
2	Ph (**4a**)	**5a**	**2**	92 : 8	76 (**6a**)	94 (*R*)
3	Ph (**4a**)	**5a**	**3**	96 : 4	75 (**6a**)	97 (*S*)
4	Ph (**4a**)	**5b**	**2**	94 : 6	74 (**6b**)	97
5	Ph (**4a**)	**5c**	**2**	95 : 5	82 (**6c**)	94
6	Ph (**4a**)	**5d**	**2**	98 : 2	66 (**6d**)	98 (*R*)
7	Ph (**4a**)	**5e**	**2**	95 : 5	73 (**6e**)	98
8	2-MeOPh (**4b**)	**5f**	**2**	96 : 4	62 (**6f**)	91
9	4-MeOPh (**4c**)	**5g**	**2**	91 : 9	91 (**6g**)	94
10	2-Furyl (**4d**)	**5c**	**2**	95 : 5	81 (**6h**)	nd[e]
11	3-Pyridyl (**4e**)	**5g**	**2**	96 : 4	85 (**6i**)	99
12	Et (**4f**)	**5a**	**2**	91 : 9	62 (**6j**)	98
13	^{n}Pr (**4g**)	**5a**	**2**	89 : 11	60 (**6k**)	94
14	^{n}Pr (**4g**)	**5h**	**2**	95 : 5	77 (**6l**)	91

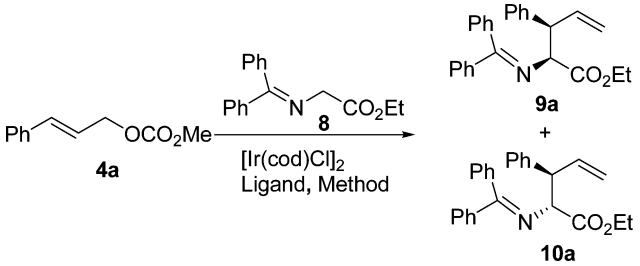
[a] Method: In THF at 25 °C, The ratio of **4** : **5** : "active catalyst" = 100 : 150 : 1. [b] Ratio determined by ^{1}H-NMR of crude reaction mixture. [c] Yield of isolated product. [d] Determined by HPLC on chiral columns. [e] Not determined.

derivatives are very well established reactions.[12] However, the use of unsymmetric nucleophiles is a far more challenging task. Since two new stereogenic centers are formed, not only the regio- and enantio-selectivity have to be controlled, but also the diastereoselectivity has to be taken into account in order to obtain single stereoisomers. In 2003 Takemoto *et al.*[13] published an elegant approach towards β-substituted α-amino acids using Ir catalyzed allylic alkylation of benzophenone protected glycinates as the key step. Binaphthol phosphite type ligands with sulfide linkers were used. It was noted that the diastereoselectivity is influenced by the type of the base and the counter cation used, as well as by the bulk of the ester group of the benzhydrylidene glycinates. Chiral ligands however, showed minor influence on the diastereoselectivity but showed a significant influence on the enantioselectivity of this reaction.

The N-benzhydrylidene group is stable under hydroformylation conditions and hence protects the sensitive amino group during the hydroformylation step. However, under the conditions of subsequent indolization which include reflux in diluted acid this group is cleaved and releases the primary amine in the final molecule (Scheme 2, Pathway B). In order to optimize yields and selectivities of this procedure test substrate **4a** was reacted with benzhydrylidene glycinate **8** in the presence of $[Ir(cod)Cl]_2$ and ligand **6** under various reaction conditions (Table 2). Here Ir catalyzed alkylation reaction in the presence of 20 mol% DABCO for the catalyst activation resulted in complete conversion of the starting carbonate after 16 hours and products **9a** and **10a** were isolated in 87% overall yield (Table 2, Entry 1). While the *anti* isomer **9a** was obtained in slight excess of approximately 3 : 2, both *anti* and *syn* isomers showed excellent ee values of 97 and 95% ee respectively. Notably only 2 mol% of catalyst had to be used to achieve good conversions in reasonable reaction times.

Next, the effect of countercations of the resulting enolate by reaction of **4a** with various bases was explored with results as shown in Table 2. Noteworthy, the countercations had a more significant influence on the diastereoselectivity (**9a** : **10a**) than on the enantioselectivity of **9a**. Preforming the enolate of **8** with LiHMDS at −78 °C gave the expected products with a 4 : 1 ratio of **9a** : **10a**, however with lower ee's as compared to the DABCO method. As expected, ligand **2** gave substantially higher ee values than ligand **1** (Table 2, Entries 2 and 3). Use of KOH as a base, which would generate the potassium enolate, affected a diastereoselectivity in favor of isomer **10a** as the major product. This showed that the diastereoselectivity is controlled by the geometry of the enolate formed (Table 2, Entry 4). Base free allylic substitutions are also well known for palladium catalyzed allylic substitutions using carbonates as substrates.[14] The general mechanism involves coordination of the carbonate to the metal center and subsequent loss of CO_2. Dissociation of the metal bound alkoxide will then normally provide a sufficiently basic species, which will act as base during the reaction. Interestingly, when the catalyst was activated with propylamine[11c] and the excess of this base was thoroughly evaporated even after several days of reaction time no conversion could be observed (Table 2, Entry 5). Use of DABCO in substoichiometric amounts is crucial for the success of this procedure. Besides its role in activating the catalyst DABCO is most probably also taking part in deprotonation of substrate **8** by making it sufficiently nucleophilic for the alkylation

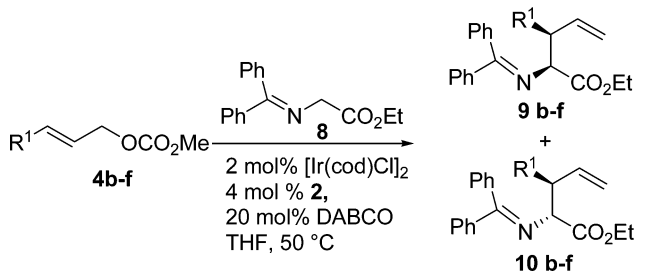
Table 2 Ir catalyzed allylic substitution of **8** and **4a** under various reaction conditions



Entry	Ligand, reaction conditions	Reaction time	Yield, %[a]	Ratio[b]	Ee, %[c]	
			9a + **10a**	**9a** : **10a**	**9a**	**10a**
1	**2**, A	16 h	87	62 : 38	97	95
2	**1**, B	3 h	80	70 : 30	65	62
3	**2**, B	3 h	84	75 : 25	87	nd[d]
4	**2**, C	5 h	65	40 : 60	91	nd[d]
5	**2**, D	7 d	—	—	—	—

Method **A**: In THF at 50 °C, the ratio of **4a** : **8** : [Ir(cod)Cl]$_2$: **2** : DABCO = 100 : 150 : 2 : 4 : 20; Method **B**: In THF at −78 °C to rt, the ratio of **4a** : **8**: [Ir(cod)Cl]$_2$: **1** or **2** : LiHMDS = 100 : 100 : 2 : 4 : 100; Method **C**: In THF at rt, the ratio of **4a** : **8**: [Ir(cod)Cl]$_2$: **2**: KOH = 100 : 100 : 2 : 4 : 100; Method **D**: In THF at 25 °C, the ratio of **4a** : **8** : preformed Ir catalyst was 100 : 100 : 2;[a] Yield of isolated product after column chromatography. [b] Determined by isolation. [c] Determined by HPLC on chiral columns. [d] Not determined.

Table 3 Ir-catalyzed allylic substitution of **4b-4f** with **8**

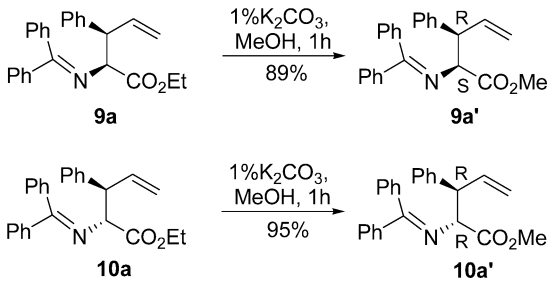


Entry	Substrate	yield, %[a]	ratio[b]	ee, %[c]	
		9 + **10**	**9**: **10**	**9**	**10**
1	2-MeOPh (**4b**)	82	70 : 30	91	nd[d]
2	4-MeOPh (**4c**)	97	56 : 44	94	91
3	2-Furyl (**4d**)	69	60 : 40	95	94
4	3-Pyridyl (**4e**)	72	65 : 35	92	nd[d]
5	n-C_2H_5 (**4f**)	65	75 : 25	nd[d]	nd[d]

[a] Yield of isolated product after column chromatography. [b] Determined by isolation. [c] Determined by HPLC on chiral column. [d] Not determined.

reaction. Due to the good yields and excellent enantioselectivities of both diastereoisomers we adopted the "salt free" conditions with substoichiometric amounts of DABCO as the standard protocol for conversions of various other allylic substrates **4b-4f** (Table 3).

With all substrates used, again good yields and excellent enantioselectivities were achieved. The *anti* isomer was obtained in excess in all cases, although with poor diastereoselectivities. Substrates **4c–4e** with R^1 = *p*-MeO-Ph, furyl or pyridyl group respectively, yielded approximately 60 : 40 ratios of **9** : **10** (Table 3, Entries 2–4) giving both diastereoisomers in enantioselectivities higher than 90%. Substrate **4b** bearing the *o*-MeO-Ph group, however, gave a slightly higher ratio of *anti* : *syn* of 70 : 30 (Table 3, Entry 1) as well as substrate **4f** with an Et group yielding in a 75 : 25 ratio of *anti* : *syn* diastereoisomers with high enantiomeric excesses (Table 3, Entry 5). The absolute configuration of the isolated diastereoisomers **9a** and **10a** was determined by transforming them into methyl esters and by comparing the optical rotations of **9a′** and **10a′** with literature data.[13] Absolute configuration was determined to be as shown in Scheme 3, and configurations of the other substrates were ascribed by analogy.

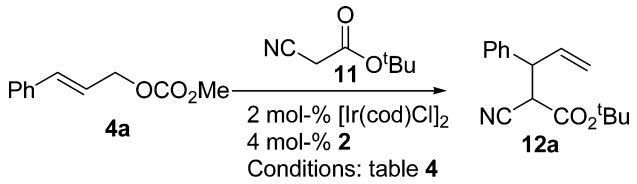


Scheme 3 Determination of absolute configuration.

In summary, Ir catalyzed asymmetric allylic alkylation of benzhydrylidene glycinate **8** and various allyl carbonates using phosphoramidite type ligand **2** yielded excellent ee values of both diastereoisomers. These highly valuable starting materials were obtained in high yields although moderate selectivities were achieved which is due to the sterically undemanding ester group of benzhydrylidene glycinate **8** applied.

For the synthesis of olefins required for preparation of longer chain tryptophan analogues, cyanoacetates were used as nucleophiles in the Ir catalyzed alkylation reaction. The nitrile group of cyanoacetates was used as a masked amine functionality (Scheme 2, Pathway C). Since stereodifferentiation of the enantiotopic faces of the allyl–metal complex coordinated by chiral ligand is highly independent of the nucleophiles employed,[13] we expected to obtain similar enantioselectivities with the cyanoacetates as were observed with benzhydrylidene

Table 4 Ir catalyzed allylic substitution of 11 and **4a** under various reaction conditions



Entry	Base, conditions	Time	dr[a]	Yield, %[b] **12a**
1	LiHMDS, THF, –78 °C to rt	3 h	62 : 38	65
2	Solid KOH, THF, rt	6 h	43 : 57	62
3	Solid NaOH, THF, rt	3 h	45 : 55	60
4	DABCO, THF, 50 °C	18 h	57 : 43	76
5	Preformed active catalyst	5 days	52 : 48	42

[a] Diastereomeric ratio (dr) determined by ^{1}H-NMR of the crude reaction mixture. [b] Yield of isolated product after column chromatography.

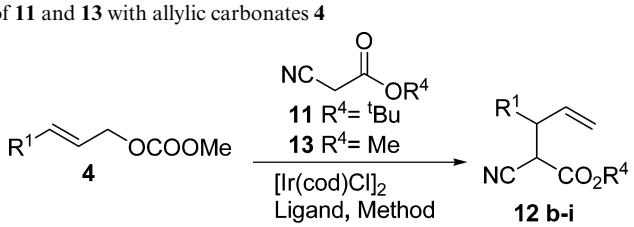
glycinates. Since there are no precedents for Ir catalyzed allylic alkylations with cyanoacetates as nucleophiles reported in the literature, optimization of the reaction conditions was required. We focussed on allylic alkylations using *tert*-butyl cyanoacetate as nucleophile hoping that the sterically more demanding *tert*-butyl group of **11** would both increase the diastereoselectivity and ease the separation of the diastereomers (Table 4). Allylic carbonate **4a** was chosen as test substrate. Salt free conditions involving the use of 20 mol% of DABCO as well as kinetic and thermodynamic conditions as in the case of benzhydrylidene glycinate **8** were tested (Table 4). In all cases good yields were obtained but diastereoselectivities were rather poor even though a bulky ester group was used. Only approximately 1 : 1 ratios were obtained in all cases, since the reaction showed small dependence on the bases and reaction conditions applied. The poor diastereoselectivities may be due to epimerization under the reaction conditions since methylene protons of cyanoacetates are more acidic than those of benzhydrylidene glycinates. Abstraction of the methylene proton and subsequent reprotonation would presumably produce a mixture close to 1 : 1 for both diastereoisomers. This assumption was supported by the fact that in this case, under base free conditions using the preactivated catalyst (by using the propyl amine activation method) the reaction proceeds with moderate yields, even after prolonged reaction time of 5 days (Table 4, Entry 5). In contrast to the benzhydrylidene glycinates the methoxide released is obviously sufficiently basic to deprotonate **11** and make it more susceptible to the alkylation reaction. Unfortunately we were not able to separate the diastereoisomers in all cases and consequently the ee values of *syn* and *anti* isomers could not be determined.

Despite these shortcomings some mentionable observations were made. Thus, the use of an external base dramatically decreases the reaction time, especially notable in this context were the reactions employing NaOH and LiHMDS as bases. Here full conversion was reached within 3 hours. Carbonates were used as substrates and in no case could hydrolysis of the substrate to the corresponding alcohol be observed.

Next allylic alkylations of various carbonates **4** applying cyanoacetates **11** and **13** as nucleophiles and using DABCO as a base were investigated. Although showing somewhat slower reaction rates as compared to other bases this protocol gave the best yields in the test reactions. Several experiments were set up first utilizing **13** as the nucleophile (Table 5, Entries 1–5). All reactions gave a ratio of approximately 1 : 1 for the stereoisomers in moderate to good yields.

Next attention was turned to cyanoacetate **11** bearing the bulky *t*-Bu ester group (Table 5, entries 6–9). Here all products were obtained in moderate to good yields. Disappointingly, regardless of substrate used only slightly improved diastereoselectivities were observed as compared to the methyl ester. Reactions with this nucleophile showed that the benzhydrylidene protecting group and its steric demand seems to be vital for obtaining significant diastereomeric inductions. Due to its sp hybridisation the resulting shape of the nitrile group is especially small and might be unsuitable for this kind of diastereoselectivity control. In a reaction with the *ortho*-methoxy substituted cinnamyl carbonate **4b** (Table 5, Entry 7) a slightly enhanced diastereoselectivity of 70 : 30 was observed. To test whether DABCO as the base

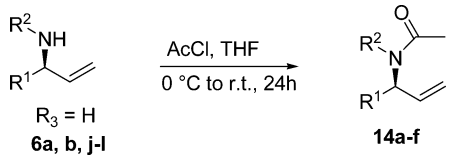
Table 5 Ir-catalyzed allylic alkylation of **11** and **13** with allylic carbonates **4**



Entry	R^1	R^4	Method	Time/h	dr ratio[a]	Yield[b] (%), **12**
1	Ph (**4a**)	Me	A	16	50 : 50	65 (**12b**)
2	4-MeO-Ph (**4c**)	Me	A	12	50 : 50	70 (**12c**)
3	2-Furyl (**4d**)	Me	A	3	55 : 45	47 (**12d**)
4	3-Pyridyl (**4e**)	Me	A	45	50 : 50	50 (**12e**)
5	H (**4h**)	Me	A	48	—	27 (**12f**)
6	H (**4h**)	tBu	A	48	—	47 (**12g**)
7	2-MeO-Ph (**4b**)	tBu	A	20	70 : 30	70 (**12h**)
8	2-MeO-Ph (**4b**)	tBu	D	6 days	68 : 32	35 (**12h**)
9	3-Pyridyl (**4e**)	tBu	A	48	52 : 48	60 (**12i**)

Method **A**: In THF at 50 °C, the ratio of **4a** : **8**: $[Ir(cod)Cl]_2$: **2**: DABCO = 100 : 150 : 2 : 4 : 20; Method **D**: In THF at 25 °C, the ratio of **4a** : **8**: preformed Ir catalyst was 100: 100: 2.[a] Determined by ^{1}H-NMR of crude reaction mixture. [b] Yield of isolated product after column chromatography.

Table 6 Protection of primary amines prior to hydroformylation



Entry	Substrate Label	R^1	R^2	Yield, %[a]
1	**6a**	Ph	Bn	88 (*R*) (**14a**)
2	**6a**	Ph	Bn	85 (*S*) (**14a**)
3	**6b**	Ph	Cy	92 (**14b**)
4	**6j**	Et	Bn	75 (**14c**)
5	**6k**	^{n}Pr	Bn	78 (**14d**)
6	**6l**	^{n}Pr	Ph	76 (**14e**)

[a] Yield of isolated product after column chromatography.

is responsible for this result the catalyst preformed without an external base was used. Here the same diastereoselectivity was observed; albeit in this case the reaction rate and yield were lower (Table 5, Entry 8). Obviously DABCO is not solely controlling the diastereoselectivity. In addition a substrate control of the diastereoselectivity might be apparent. Most probably due to the steric compression caused by the methoxy substituent of the substrate one of the regioisomeric enolates (*E* or *Z*) of **13** is reacting faster with **4b**. Since diastereoisomers could not be separated in any case we decided to use the unseparated mixtures of diastereoisomers for hydroformylation–Fischer indolization reactions and try to separate both diastereomers in the later stages of the synthesis.

Syntheses of indoles

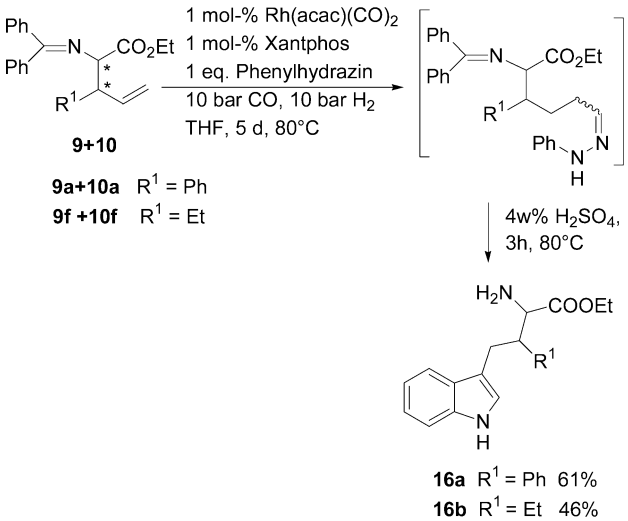
Under hydroformylation conditions primary and secondary allylic amines may undergo intramolecular "hydroaminomethylation" reaction.[15] Hence, use of protected tertiary amines in the tandem hydroformylation–Fischer indolization sequence is required. Therefore the secondary amines obtained from the Ir catalyzed allylic amination reaction with primary amines were protected with the acetyl group. Here in all cases good yields of acetylation products were obtained (Table 6).

The acetyl group is stable under hydroformylation conditions and is often desirable in potentially bioactive molecules as it is increasing lipophilicity of parent molecules. The starting amines were submitted to the hydroformylation–Fischer indole synthesis reaction. An optimized stepwise procedure as previously described involving tandem hydroformylation–hydrazone formation was used.[7] Here 1 mol% of $Rh(acac)(CO)_2$ and 10 mol% of *n*-directing ligand XANTPHOS under 10/10 bar $CO–H_2$ pressure in THF at 80 °C for 3 days with subsequent indolization in 4 wt% H_2SO_4 were applied. The results are summarized in Table 7.

While the allylic aminations proceed with high enantiomeric excesses, the stereocenter may epimerize during tandem hydroformylation–Fischer indolization *via* reversible double bond isomerization either caused by the transition metal catalyst or the acid. The tryptamines obtained from enantiomerically pure allylic amines, however, reveal complete retention of enantiopurity (Table 7, Entries 1, 2, 4 and 6). In all cases hydroformylation led to complete conversion of the olefin to the aldehyde. Subsequent indolizations in 4 wt% H_2SO_4 gave moderate to good yields in all cases except for entry 10 where the protic acid led to a precipitation of pyridinium salts of the hydrazone formed. As an alternative, indolization in the presence of 4 eq. of $ZnCl_2$ in refluxing toluene for 12 h gave 41% yield of the product. Allylic amides in general gave slightly higher yields of products than tertiary amines. This is probably due to the lowered basicity of the side chain nitrogen in the amides, which eases isolation of the product and prevents tailing and stacking on SiO_2 columns (Table 7, Entries 1, 2, 3, 5, 12, 13).

In summary the combination of iridium catalyzed enantioselective allylic amination and tandem hydroformylation–Fischer indole synthesis reported here, in contrast to other methods, gives fast access to β-branched tryptamines which cannot easily be derived from tryptophan and therefore allows access to a new class of tryptamine derivatives for biological screenings.

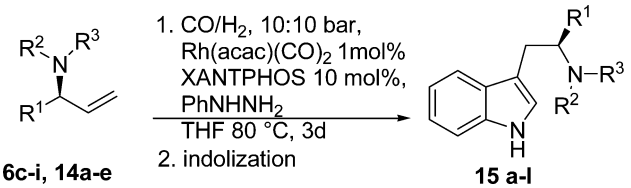
For the synthesis of branched homotryptophans (Scheme 2, Pathway B) *via* tandem hydroformylation–Fischer indole synthesis the same conditions were applied as for the synthesis of branched tryptamines. Since it turned out to be difficult to separate sufficient amounts of diastereoisomers for indole synthesis, as a proof of principle a diastereomeric mixture of homoallylic amines **9a** and **10a** was submitted to the standard stepwise procedure. After 3 days of reaction time, however, the olefin was only partially hydroformylated as determined by ^{1}H-NMR of the crude reaction mixture which resulted in only 22% yield of the desired indole **16a**. In order to obtain full conversion of the olefin the reaction time was prolonged to 5 days leaving other variables the same. This led to full conversion of the olefin. The ratio of branched : linear aldehydes as determined by the ^{1}H-NMR of the crude reaction mixture was 95 : 5, and subsequent addition of acid to the reaction mixture led to indolization of the hydrazones and cleavage of the benzophenone protecting group yielding in β-branched homotryptophans with primary amine groups. The product was isolated in 61% yield as a mixture of diastereoisomers (Scheme 4).



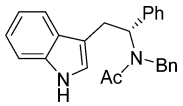
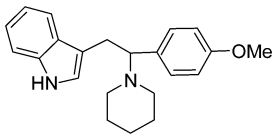
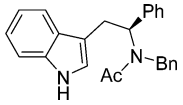
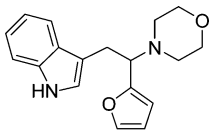
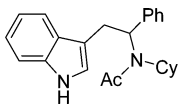
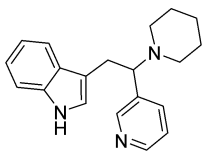
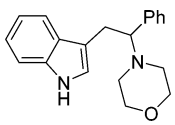
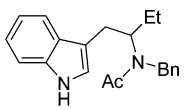
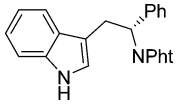
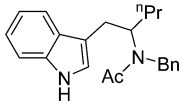
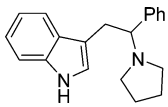
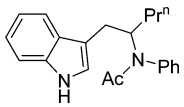
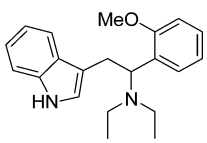
Scheme 4 Synthesis of branched homotryptophans from allyl glycinates (**9+10**) **a**,**f**.

A diastereomeric mixture of olefins **9f** and **10f** was submitted to the same conditions. The ratio of branched and linear aldehydes

Table 7 Tandem hydroformylation–Fischer indole synthesis of various allylic amines



6c-i, 14a-e → **15 a-l**

Entry	Substrate	Product	Yield,[a] ee%[b]	Entry	Substrate	Product	Yield[a]
1	**14a**, R^1 = Ph, R^2 = Ac, R^3 = Bn		62%, (*R*) 92% ee ((+)-**15a**)	8	**6g**, R^1 = 4-MeO-Ph, $R^2 = R^3$ = piperidine		50%, ((–)-**15g**)
2	**14a**, R^1 = Ph, R^2 = Ac, R^3 = Bn		65%, (*S*) 97% ee ((–)-**15a**)	9	**6h**, R^1 = 2-furyl, $R^2 = R^3$ = morpholine		56% (**15h**)
3	**14b**, R^1 = Ph, R^2 = Ac, R^3 = Cy		45%, ((+)-**15b**)	10	**6i**, R^1 = 3-pyridyl, $R^2 = R^3$ = piperidine		41% (**15i**)[c]
4	**6c**, R^1 = Ph, $R^2 = R^3$ = morpholine		52%, 97% ee ((–)-**15c**)	11	**14c**, R^1 = Et, R^2 = Ac, R^3 = Bn		59% (**15j**)
5	**6d**, R^1 = Ph, $R^2 = R^3$ = pht		67%, (*R*) ((+)-**15d**)	12	**14d**, R^1 = ^{n}Pr, R^2 = Ac, R^3 = Bn		76%, 91% ee ((+)-**15k**)
6	**6e**, R^1 = Ph, $R^2 = R^3$ = pyrrolidine		47%, 98%ee ((–)-**15e**)	13	**14e**, R^1 = ^{n}Pr, R^2 = Ac, R^3 = Ph		66%, ((–)-**15l**)
7	**6f**, R^1 = 2-MeO-Ph, $R^2 = R^3$ = Et		33%, ((–)-**15f**)				

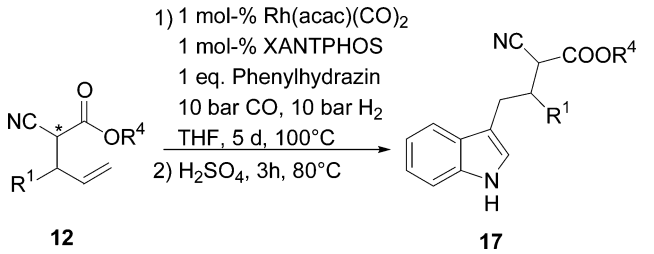
All indolizations are performed in 4 wt% H_2SO_4 under reflux for 2 h unless otherwise stated.[a] Isolated yield after column chromatography. [b] Determined by the analysis on chiral HPLC columns, ee not determined unless otherwise stated. [c] Indolization performed with 4 eq. of $ZnCl_2$ in toluene.

was 94 : 6 as determined by ^{1}H-NMR of the crude reaction mixture. After indolization of the hydrazone, product **16b** was isolated in 46% yield as a mixture of diastereoisomers. An attempted hydroformylation–Fischer indolization sequence with $ZnCl_2$,[16] which should preserve the benzhydrylidene group and yield in a tertiary tryptophan was unsuccessful. After 24 hours at reflux temperature with 4 equiv. of $ZnCl_2$ in toluene only the intermediate hydrazone was quantitatively recovered.

In summary, Ir catalyzed allylic alkylations of benzhydrylidene glycinate **8** furnishes a valuable building block for the synthesis of homotryptophans *via* the hydroformylation–Fischer indolization sequence. Moderate yields of the desired primary homotryptophans are obtained after indolization which proceeded in parallel with deprotection of primary amine functionality in the presence of Brønsted acid.

Hydroformylation of homoallylic nitriles towards synthesis of homotryptophan homologues (Scheme 2, Pathway C) proved to be difficult. Initial test reactions using standard conditions for hydroformylation of homoallylic amines with allylic cyanoacetate **12a** did not yield the desired indole. Therefore all individual steps of the reaction were tested separately. Performing the reaction in the absence of phenylhydrazine with the same substrate under the

Table 8 Synthesis of indoles from homoallylnitriles **12**



12 **17**

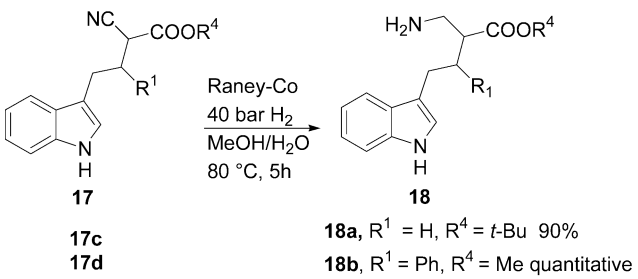
Entry	R^1	R^2	Yield %,[a] **17**
1	Ph	^{t}Bu	60 (**17a**)
2	2-MeO-Ph	^{t}Bu	37 (**17b**)
3	H	^{t}Bu	57 (**17c**)
4	Ph	Me	39 (**17d**)
5	4-MeO-Ph	Me	66 (**17e**)

[a] Yield of isolated product after column chromatography.

same conditions revealed that only 20% of olefin was converted under these conditions as determined by ^{1}H-NMR of crude reaction mixture. Increase of the reaction temperature to 100 °C after 5 days yielded in a complete conversion of the olefin **12a**. Hydrazone formation was then carried out under atmospheric pressure at room temperature within 2 h reaction time. After indolization under standard conditions the desired indole **17a** was isolated in 60% yield. Control experiments demonstrated that conversion of the olefin is the decisive factor for a successful conversion. After the new conditions were established other substrates were submitted to these conditions. Table 8 summarizes for indoles thus synthesized, all being obtained in moderate to good yields as mixtures of diastereoisomers.

It is noteworthy to mention that hydroformylation conditions as well as subsequent acidic indolization conditions did not have any influence on the diastereomeric ratio of the products obtained. For reduction of the nitrile group different conditions using metal hydrides (*i.e.* $LiAlH_4$ and $NaBH_4$) were tested but in all cases complex mixtures of products were observed.

Catalytic hydrogenation, however, using Raney-Co as a catalyst in stoichiometric amounts, under 40 bar pressure of H_2 furnishes excellent yields of the desired product possessing primary amino functionality (Scheme 5).



Scheme 5 Reduction of nitrile functionality in indoles **17c**,**d**.

Conclusions

In summary, combination of enantioselective Ir catalyzed allylation chemistry and tandem hydroformylation–Fischer indolization is an efficient and highly diversity-oriented strategy for the synthesis of tryptamines and homologues. Stereocenters close to the olefinic bond are tolerated and do not epimerize, leading to enantiomerically pure β-branched tryptamines.

The number of required steps is reduced to a minimum, since simple functional group transformations (*e.g.*, hydrogenations, homologization, reduction, oxidation, protection) are not required. This modular approach is remarkable since substituents at C3, the type of the amine moiety, and the distance from the amine moiety to the indole core are predefined by the starting material and assembled in the final synthetic step. Therefore, this approach can be used as a valuable tool for the synthesis of highly diverse substance libraries.

Acknowledgements

The authors wish to thank Professor Dr Bernd Plietker, Stuttgart for help with chiral HPLC measurements.

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