DOI: 10.1002/ejoc.200800841

News from the 80-Year-Old Passerini Variant of the Friedel–Crafts Alkylation of Indole

Giovanni Desimoni,*[a] Giuseppe Faita,[a] Mariella Mella,[a] Marco Toscanini,[a] and Massimo Boiocchi[b]

Keywords: Friedel–Crafts alkylation / Multi-component reactions / Indole / Scandium catalysis / Rearrangements

The multi-component Friedel–Crafts alkylation reaction between indole (**1**), ethyl glyoxylate (**2**) and anilines (**3a–f**) gives, in analogy to the protocol of the old Passerini reaction, the expected ethyl 2-(arylamino)-2-(1*H*-indol-3-yl)acetates **4a–f**. When the reactions are catalysed by 5 mol-% scandium triflate ($Sc^{III}Tf$), however, or when the isolated products **4** are treated under the same conditions, rearrangements involving the arylamino fragments of adducts **4** take place. When the *para* position of **4** is unsubstituted, ethyl 2-(2-aminoaryl)-2-(1*H*-indol-3-yl) acetates **5** are obtained, and their structures were confirmed by the X-ray crystal structure analysis of **5a**. Under milder conditions, $Sc^{III}Tf$ gives more complicated products, deriving from **1**, **2** and **3** in the ratio of 2:2:1, and these converted into **5**. An explanation of the pathway, by which the Passerini adducts **4**, coordinated to scandium, undergo the rearrangements, is proposed.

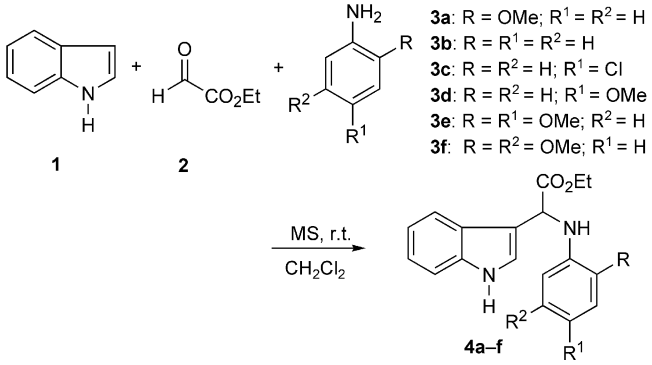
Introduction

Multi-component reactions (MCRs)[1] are the best alternative to the maximization of synthetic efficiency in multistep strategies, and in the last ten years their investigation has become increasingly popular in the syntheses of heterocycles,[2] in the generation of libraries of new drug candidates,[3] and in the creation of several bonds of complex molecules in one operation starting from more than two simple reagents.[4] The most attractive innovation in the field has been the asymmetric version of the MCR, developed either with classical enantioselective catalysts,[5] or through organocatalytic processes.[6] These contemporary investigations occasionally involve venerable reactions, including – in historic order – the Strecker (1850),[7] Hantzsch (1890),[8] Biginelli (1891)[9] and Mannich reactions (1912).[10] Catalytic enantioselective developments have also recently been reported for the Passerini reaction, which in its original version (1921)[11] involved an aldehyde, an acid and an isocyanide reagent.[12] Some years later, Passerini described a further reaction, in which indoles and Schiff bases reacted to give (1*H*-indol-3-yl)benzylanilines.[13] This reaction, which can be regarded as a Friedel–Crafts alkylation, was later studied with catalysis by lanthanide triflate[14] (both in protic and ionic liquid media)[15] and copper triflate.[16] The most relevant current developments are studies on its enantioselective catalytic variant, efficiently achieved with *N*-sulfonyl aldimines first with the [Cu^{II}/bis(oxazoline)] complex,[17] then with chiral phosphoric acid catalysts,[18] and more recently with an organocatalyst.[19] The negative point is sometimes the presence of a bis(indole) addition by-product.[17,18a]

The enantioselective synthesis of indolyl *N*-tosyl α-amino acids was an interesting application of the reaction between *N*-tosylimino esters of ethyl glyoxylate (acting as Schiff bases) and indole catalysed by the [tol-binap/$CuPF_6$] complex.[20] By this route, several new indolyl *N*-aryl α-amino acids have been obtained, either in the absence of any catalyst[21] or in the presence of SmI_2,[22] and finally the reaction was run with indoles, glyoxylate and amines under solvent-free conditions,[23] according to the protocol of an MCR.

Glyoxylate and pyruvate derivatives have been found to be useful reagents for enantioselective reactions catalysed by the lanthanide(III) triflate complexes of (4′*S*,5′*S*)-2,6-bis[5′-phenyl-4′-{[(triisopropylsilyl)oxy]methyl}-1′,3′-oxazolin-2′-yl]pyridine (pybox): Mukaiyama aldol reactions,[24] Diels–Alder/hetero-Diels–Alder cycloadditions,[25] and Friedel–Crafts reactions between a series of substituted indoles and methyl (*E*)-4-aryl-2-oxobut-3-enoates[26] have been usefully performed. The presence of α-aldimino esters among the reagents of the Passerini reaction discussed above suggested testing of the effect of Sc^{III} triflate ($Sc^{III}Tf$) catalysis on the reaction between indole (**1**; Scheme 1), ethyl glyoxylate (**2**) and *o*-anisidine (**3a**: R = OMe), with the *o*-methoxy group of the last reagent suitably placed to coordinate the cation.

[a] Dipartimento di Chimica Organica dell'Università di Pavia, Viale Taramelli 10, 27100 Pavia, Italy
Fax: +39-382-987323
E-mail: desimoni@unipv.it
[b] Centro Grandi Strumenti dell'Università di Pavia, Via Bassi 21, 27100 Pavia, Italy
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. General scheme of the uncatalysed three-component reactions between indole, ethyl glyoxylate and anilines to give the corresponding Passerini adducts.

Results and Discussion

Preliminarily, the reaction was run at ambient temperature in CH_2Cl_2 with molecular sieves (MS, 5 Å). The expected ethyl 2-(1*H*-indol-3-yl)-2-[(2-methoxyphenyl)amino]-acetate (**4a**: R = OMe), the usual Passerini product, was obtained as the sole product in 75% yield (Scheme 1, Table 1, Entry 1).

Table 1. Reactions of indole (**1**), ethyl glyoxylate (**2**) and anilines (**3a–f**) in CH_2Cl_2 at room temperature.

Entry	Reagents[a]	Time	Yield of **4**[b]
1	**1** + **2** + **3a**	15 h	75%
2	**1** + **2** + **3b**	20 h	85%
3	**1** + **2** + **3c**	24 h	75%
4	**1** + **2** + **3d**	24 h	75%
5	**1** + **2** + **3e**	6 h	75%
6	**1** + **2** + **3f**	6 h	54%

[a] In the presence of MS. [b] Isolated yields.

The reaction was then performed under the same conditions at ambient temperature, but in the presence of $Sc^{III}Tf$ (5 mol-%). Again, a single product was obtained in 65% yield, but it was not **4a**. Its molecular mass and spectroscopic data show significant similarities with those of **4a**, the fundamental difference being the ^1H NMR spectrum, since a proton of the anisidine fragment is lacking, and the remaining three protons show that the phenyl ring has a 1,2,4-substitution pattern (Table 2, Entry 1).

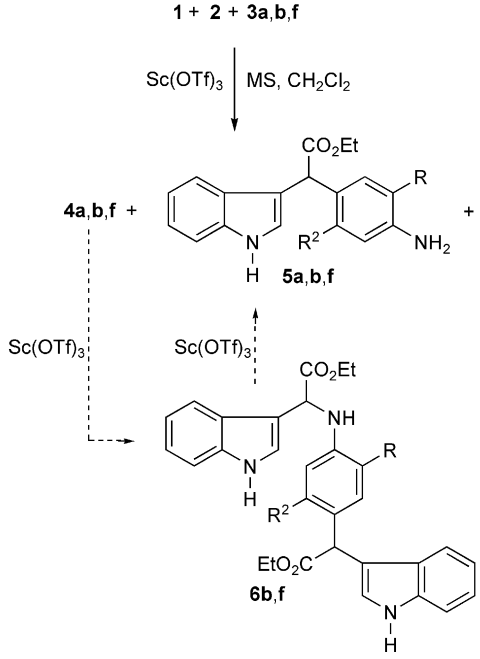
These data suggest a rearrangement involving the 2-methoxyaniline fragment to give ethyl 2-(4-amino-3-methoxyphenyl)-2-(1*H*-indol-3-yl)acetate (**5a**, R = OMe; Scheme 2), the structure of which was confirmed by X-ray analysis (Figure 1). In particular, in the solid state, the **5a** molecule exhibits an extensive hydrogen-bond motif for the particular feature of the NH_2 group of the methoxyaniline fragment.

The formation of the new product occurs in the presence of $Sc^{III}Tf$ at ambient temperature. Are both factors necessary? To test this, the catalysed reaction was run at –50 °C: after 30 min the reaction was complete, and a 92% yield of **4a** was obtained.

Table 2. Reactions between indole (**1**), ethyl glyoxylate (**2**) and anilines (**3a–f**) and those of the Passerini adducts (**4a–f**) with scandium triflate (5 mol-%) in CH_2Cl_2.

Entry	Reagents	Temperature	Time	Yield[a]	Product distribution[b]		
					4	**5**	**6**
1	**1** + **2** + **3a**[c]	room temp.	3 h	65%	–	100%	–
2	**1** + **2** + **3a**[c]	–50 °C	30 min	92%	100%	–	–
3	**4a**	room temp.	1 h	90%	30%	70%	–
4	**1** + **2** + **3b**[c]	–50 °C	8 h	92%	95%	3%	2%
5	**1** + **2** + **3b**[c]	room temp.	8 h	73%	38%	48%	14%
6	**4b**	–20 °C	15 h	82%	30%[d]	15%	55%
7	**4b**	room temp.	15 h	91%	–	86%	14%
8	**1** + **2** + **3d**[c]	–50 °C	10 min	88%	100%	–	–
9	**4d**	room temp.	8 h	75%	35%[d]	–	65%
10	**1** + **2** + **3e**[c]	–50 °C	30 min	98%	100%	–	–
11	**4e**	room temp.	3 h	75%	–	100%	–
12	**4e**	–20 °C	5 h	94%	35%[d]	–	65%
13	**4e**	room temp.	15 min	93%	7%[d]	38%	55%
14	**1** + **2** + **3f**[c]	–50 °C	6 h	35%	100%	–	–
15	**1** + **2** + **3f**[c]	–20 °C	15 min	30%	20%	45%	35%
16	**4f**	room temp.	10 min	95%	–	77%	23%
17	**4f**	room temp.	1 h	95%	–	100%	–

[a] Overall reaction yield. [b] Ratio of the isolated products determined by gravimetric analysis after chromatographic separation. [c] In the presence of MS. [d] % of recovered starting product.



Scheme 2. General scheme for the Sc^{III}-catalysed three-component reaction between indole, ethyl glyoxylate and anilines to give the Passerini adducts and the rearranged products.

Then, a sample of **4a** in CH_2Cl_2 was treated with $Sc^{III}Tf$ (5 mol-%) at ambient temperature: the mixture composition of [**4a**]/[**5a**] obtained after about 1 h was 30:70, and this ratio had not changed after leaving the mixture overnight. The results of all the above reactions are summarized in Table 2 (Entries 2 and 3).

Finally, the MCR was also run at –50 °C in the presence of the [pybox/$Sc^{III}Tf$] complex (5 mol-%) and, after 30 min, **4a** was obtained in quantitative yield, but unfortunately as a racemate.

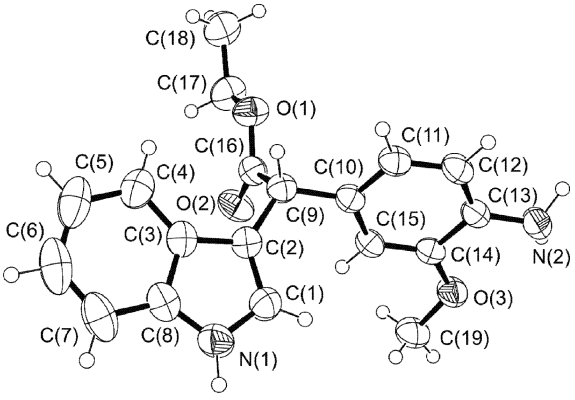


Figure 1. ORTEP view of the crystal structure of **5a** (ellipsoids are drawn at the 50% probability level) labelled with crystallographic atom numbering.

From the reaction involving **3a** as the amine component some pieces of evidence can be pointed out:

(a) In the absence of $Sc^{III}Tf$ the Passerini product **4a** is formed.

(b) The $Sc^{III}Tf$-catalysed reaction gives the rearranged product **5a**, the formation of which depends on the reaction temperature.

(c) At room temperature **4a** rearranges to **5a** in the presence of $Sc^{III}Tf$.

(d) The $Sc^{III}Tf$ catalysis in the presence of pybox does not induce enantioselectivity.

Two questions deserve attention: (i) Because the rearrangement from **4a** to **5a** involves the *o*-anisidine residue of the Passerini adduct, is this behaviour specific for **4a** or can it be expected for products with different aniline residues? (ii) What is the mechanism of this new rearrangement?

The next reaction was carried out with **1**, **2** and aniline **3b** (R = H), the Passerini adduct of which (**4b**) had been reported in the literature previously.[21,23] Compound **4b**, obtained in 85% yield under uncatalysed conditions (Table 1, Entry 2), was dissolved in CH_2Cl_2, and $Sc^{III}Tf$ (5 mol-%) was added at –50 °C. After 2 d, together with a 60% yield of unreacted **4b**, a new product was obtained. The spectroscopic and mass data support a structure derived from **1**, **2** and **3b** in a 2:2:1 ratio, with the phenyl ring originating from **3b** being *para*-disubstituted.

From these data, **6b** is ethyl 2-({4-[(ethoxycarbonyl)(1*H*-indol-3-yl)methyl]phenyl}amino)-2-(1*H*-indol-3-yl)acetate. When **4b** was treated with $Sc^{III}Tf$ at –20 °C for 15 h, **6b** was obtained as the major product (45%) together with unreacted **4b** (25% yield), whereas **5b** was isolated in 12% yield. This last product became the major one (78%) when the reaction was run at ambient temperature, and the yield of **6b** was only 13% (Table 2, Entries 6 and 7; Scheme 2). To test the possible relationship between **5b** and **6b**, this latter adduct was allowed to stand with $Sc^{III}Tf$ at ambient temperature overnight, and **5b** was obtained in 30% yield.

The reaction between **1**, **2** and **3b** was also run in the presence of $Sc^{III}Tf$ (5 mol-%) both at –50 °C and at ambient temperature, and **4b**, **5b** and **6b** were obtained in different yields (Table 2, Entries 4 and 5).

To explore further possibilities of the rearrangement, the reactions of **1** and **2** with **3c**–**f** were run first under uncatalysed conditions, and excellent yields of the normal Passerini products **4c**–**f** were obtained (Table 1, Entries 4–6). The same reactions were then performed in the presence of $Sc^{III}Tf$ as catalyst, and the results are reported in Table 2 (Entries 8, 10 and 14).

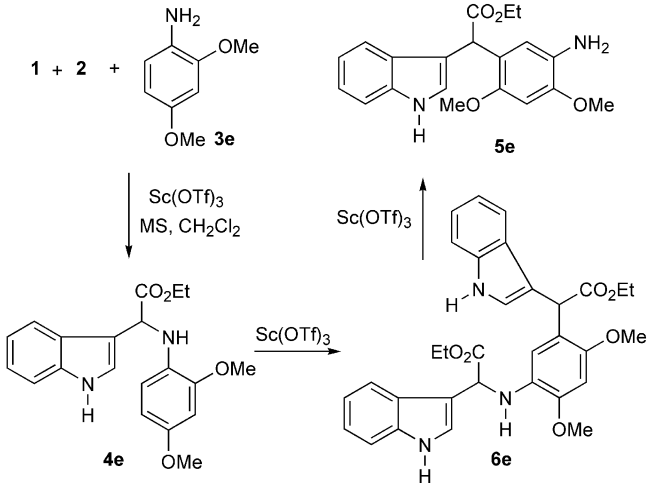
The catalysed reaction of **1**, **2** and **3c** gave unsatisfactory results because only decomposition products were obtained, together with variable amounts of **4c**. The same disappointing result was obtained when **4c** was allowed to react with $Sc^{III}Tf$, with no significant amount of rearranged product being obtained.

The reaction of **1**, **2** and **3d** in the presence of $Sc^{III}Tf$ at –50 °C gave **4d** as the sole product (Table 2, Entry 8), whereas at higher temperature only decomposition products were observed. When ethyl 2-(1*H*-indol-3-yl)-2-[(4-methoxyphenyl)amino]acetate (**4d**) was treated with $Sc^{III}Tf$ at ambient temperature, **6d** was obtained in 50% yield after 24 h, together with unreacted **4d** (26%; Table 2, Entry 9); its ^1H and ^{13}C NMR spectra suggest that it derives from **1**, **2** and **3d** in the ratio of 2:2:1 and consists of at least two diastereoisomers. Since any attempt to transform **6d** into the analogous derivative of **5** by treatment with $Sc^{III}Tf$ either failed (at –50 °C) or only gave decomposition products (at higher temperatures), it is difficult to give it a definite structure.

The reaction between **1**, **2** and **3e** at ambient temperature, either in the absence of catalyst or at –50 °C with $Sc^{III}Tf$, gave ethyl 2-[(2,4-dimethoxyphenyl)amino]-2-(1*H*-indol-3-yl)acetate (**4e**) in 75% and 98% yields, respectively (Table 1, Entry 5 and Table 2, Entry 10). When **4e** was treated with $Sc^{III}Tf$, after 3 h at ambient temperature, ethyl 2-(5-amino-2,4-dimethoxyphenyl)-2-(1*H*-indol-3-yl)acetate (**5e**) was obtained in 75% yield (Table 2, Entry 11); its structure (Scheme 3) is easily derived from the presence of two aromatic protons as singlets in the ^1H NMR spectrum.

When the above reaction was run at –20 °C, after a few minutes a new product (**6e**) had begun to form at the expense of **4e**, which correspondingly tended to disappear. The optimum conditions (Table 2, Entry 12) maximizing its formation (61% yield), without any **5e**, were reached after 5 h. The ^1H and ^{13}C NMR spectra strongly suggest that two different diastereoisomers are formed, deriving from **1**, **2** and **3e** in the ratio of 2:2:1. The evidence that **6e** is the intermediate between **4e** and **5e** could be obtained by treatment of **4e** with $Sc^{III}Tf$ at ambient temperature, stopping the reaction after 15 min (Table 2, Entry 13), before the reaction begins to behave as in Entry 11. Chromatographic separation gave, besides a small amount of **4e**, a good yield of **5e**, and again **6e**, the structure of which is therefore ethyl 2-({5-[(ethoxycarbonyl)(1*H*-indol-3-yl)methyl]-2,4-dimethoxyphenyl}amino)-2-(1*H*-indol-3-yl)acetate.

The reaction between **1**, **2** and **3f** at ambient temperature, either in the absence of any catalyst or at –50 °C in the presence of $Sc^{III}Tf$, gave ethyl 2-[(2,5-dimethoxyphenyl)-



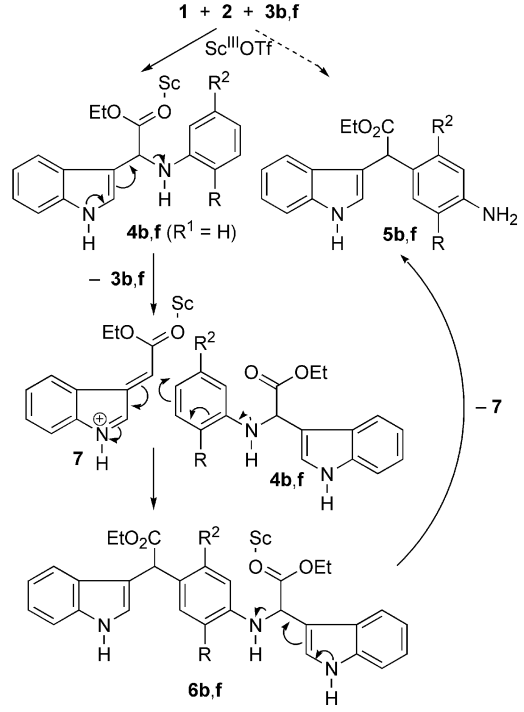
Scheme 3. General scheme of the Sc^{III}-catalysed three-component reaction between indole, ethyl glyoxylate and 2,4-dimethoxyaniline to give the Passerini adducts and the rearranged products.

amino]-2-(1*H*-indol-3-yl)acetate (**4f**) in 54% and 35% yields, respectively (Table 1, Entry 6 and Table 2, Entry 14). When **4f** was treated with $Sc^{III}Tf$ at ambient temperature, ethyl 2-(4-amino-2,5-dimethoxyphenyl)-2-(1*H*-indol-3-yl)-acetate (**5f**) was obtained in 95% yield after 2 h (Table 2, Entry 16), its structure being easily derivable from the presence of two aromatic protons as singlets in its ^1H NMR spectrum. If the same reaction was interrupted after 10 min (Table 2, Entry 17), the new product **6f** (disappearing after prolonged treatment with $Sc^{III}Tf$) was also obtained together with **5f**, which could be separated by column chromatography (Scheme 2). The ^1H and ^{13}C NMR spectra allow it to be determined that **6f** is ethyl 2-({4-[(ethoxycarbonyl)(1*H*-indol-3-yl)methyl]-2,4-dimethoxyphenyl}-amino)-2-(1*H*-indol-3-yl)acetate, as a pair of diastereoisomers. The products **5f** and **6f**, together with **4f**, were obtained from **1**, **2** and **3f** at –20 °C (Table 2, Entry 15) in the presence of $Sc^{III}Tf$, again following first an MCR, and then a cascade of reactions involving **6f** to give **5f**.

Conclusions

The efforts to induce enantioselective catalysis of Passerini MCRs between indole, ethyl glyoxylate and anilines through the use of a [pybox/$Sc^{III}Tf$] complex were unsuccessful, but the attempt has allowed the discovery of new Sc^{III}-catalysed rearrangements of the above reaction products **4a**, **4b** and **4d**–**f** (either formed "in situ" from the MCR, or isolated beforehand), in which the arylamino groups migrate to give **5a**, **5b**, **5e** and **5f**. These unusual conversions occur through the intermediates **6** (isolated in many experiments), which develop during the courses of the reactions at the expense of **4**, and disappear when products **5** are formed. To understand the mechanism of the rearrangements of **4** to **5**, the role of **6**, even if not always isolated and sometimes difficult to obtain at a high level of purity, is therefore crucial.

Scheme 4 depicts a plausible pathway: the Passerini adducts **4**, coordinated to scandium, undergo elimination of the corresponding aniline to generate the Sc^{III}-coordinated ethyl 2-(1*H*-indol-3-yl)acetate (**7**). This reactive electrophile attacks what is available in the environment, which could be a second indole to give a bis(indolyl)methane derivative,[15a] or a second molecule of **4** (if this is suitably activated, as in the majority of the examples described) at the most nucleophilic site, which in **4b** and **4f** (when R^1 = H, as reported in Scheme 4) is the *para* position, giving rise to the isolated intermediates **6b** and **6f**. It is noteworthy that, with the *para* position of the (2,4-dimethoxyphenyl)amino group of **4e** occupied by a methoxy group, the preferred position involved in the rearrangement is not the 6-position, *ortho* to the amino group, but the 5-position, which seems to benefit from combined *ortho*/*para* activation induced by two methoxy groups, thus giving **6e** (Scheme 3).



Scheme 4. Proposed mechanism for the Sc^{III}-catalysed rearrangements from **4b** and **4f** to **5b** and **5f**.

Intermediates **6** again coordinate to scandium and undergo the elimination of **5b**, **5e** or **5f** (the products of the rearrangement), giving rise again to **7**, which goes on in the catalytic cycle. Obviously, the expulsion of the anilines not only sometimes gives the observed coloured decomposition products, but it may interfere in the catalytic cycle, competing in the coordination of scandium and sometimes preventing the complete rearrangement of **4**, as $Sc^{III}Tf$ is 5 mol-% of the reagents.

In conclusion, lanthanides are efficient catalysts of the reactions between indole and imines, but whereas dysprosium and ytterbium triflate simply increase the reaction rates,[15a,15b] scandium triflate is found to catalyse a new re-

arrangement that, starting from the products of an old MCR between indole and the imine precursors, gives rise to a new class of indole derivatives.

Experimental Section

General: Melting points were determined by the capillary method and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. IR spectra were registered with a Perkin–Elmer RX I spectrophotometer. Separation and purification of the products was carried out by column chromatography on Merck silica gel 60 (230–400 mesh).

Materials: Dichloromethane was the hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately. Other solvents were purified by standard procedures. Scandium triflate, indole, ethyl glyoxylate and all anilines **3a**–**f** were commercially available Aldrich reagents; powdered molecular sieves (5 Å) were Aldrich reagents heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer.

General Procedure for the Reactions between Indole (1), Ethyl Glyoxylate (2) and Anilines 3a–f: MS (0.10–0.15 g) were added to a solution of indole (**1**, 0.234 g, 2 mmol), ethyl glyoxylate (**2**, 0.41 mL solution 50% in toluene, 2 mmol) and one of the arylamines **3a**–**f** (2 mmol) in CH_2Cl_2 (5.0 mL), and stirring at ambient temperature was continued for the time reported in Table 1, after which nearly all reagents had disappeared. Column chromatography with the eluent reported in each specific description gave **4a**–**f** with the yields reported in Table 1.

Ethyl 2-(1*H*-Indol-3-yl)-2-[(2-methoxyphenyl)amino]acetate (4a): Eluent cyclohexane/ethyl acetate (80:20), white crystals, m.p. 104–105 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.24 (br. s, 1 H, NH), 7.90 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, indole 4-H), 7.36 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, indole 7-H), 7.28–7.18 (m, 2 H, indole 5-H and 6-H), 7.21 (s, 1 H, indole 2-H), 6.87–6.59 (m, 4 H, aromatic protons), 5.44 (s, 1 H, CH acetate), 5.4 (br. s, 1 H, NH), 4.30 (m, 1 H, CH*H* ethyl), 4.18 (m, 1 H, C*H*H ethyl), 3.87 (s, 3 H, methoxy), 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 146.6, 136.1, 136.0, 125.4, 122.7, 121.9, 120.6, 119.4, 119.1, 116.9, 112.0, 110.9, 110.1, 109.2, 61.0, 54.9, 53.7, 13.7 ppm. IR (Nujol): $\tilde{\nu}$ = 3405 (NH), 3374 (NH), 1717 (C=O) cm^{-1}. $C_{19}H_{20}N_2O_3$ (324.4): calcd. C 70.35, H 6.21, N 8.64; found C 70.42, H 6.28, N 8.81.

Ethyl 2-(1*H*-Indol-3-yl)-2-(phenylamino)acetate (4b): Eluent cyclohexane/ethyl acetate (85:15), white crystals, m.p. 94–95 °C from ethyl acetate/hexane (ref.[21,23] slightly yellow oil). ^{1}H and ^{13}C NMR ($CDCl_3$) data are identical to those reported in the literature.[21] IR (Nujol): $\tilde{\nu}$ = 3422 (NH), 3346 (NH), 1705 (C=O) cm^{-1}.

Ethyl 2-[(4-Chlorophenyl)amino]-2-(1*H*-indol-3-yl)acetate (4c): Eluent cyclohexane/ethyl acetate (85:215), white crystals, m.p. 90–91 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.27 (br. s, 1 H, NH), 7.87 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, indole 4-H), 7.37 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, indole 7-H), 7.31–7.12 (m, 2 H, indole 5-H and 6-H), 7.20 (s, 1 H, indole 2-H), 6.59 (pseudo-d, 4 H, aromatic protons), 5.40 (s, 1 H, CH acetate), 4.86 (br. s, 1 H, NH), 4.34 (m, 1 H, CH*H* ethyl), 4.18 (m, 1 H, C*H*H ethyl), 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0, 144.6, 136.0, 131.5, 128.6, 125.2, 122.7, 122.2, 119.7, 119.0, 114.5, 114.1, 111.5, 111.1, 61.3, 53.9, 53.7, 13.7 ppm. IR (Nujol): $\tilde{\nu}$ = 3419 (NH), 3350 (NH), 1706 (C=O) cm^{-1}. $C_{18}H_{17}ClN_2O_2$ (328.8): calcd. C 65.75, H 5.21, N 8.52; found C 65.87, H 5.08, N 8.69.

Ethyl 2-(1*H*-Indol-3-yl)-2-[(4-methoxyphenyl)amino]acetate (4d): Eluent cyclohexane/ethyl acetate (70:30), light cream-coloured crystals, m.p. 66–67 °C from ethyl acetate/hexane (ref.[21] slightly yellow oil). ^{1}H and ^{13}C NMR ($CDCl_3$) data are identical to those reported in the literature.[21] IR (Nujol): $\tilde{\nu}$ = 3396 (NH), 3376 (NH), 1726 (C=O) cm^{-1}.

Ethyl 2-[(2,4-Dimethoxyphenyl)amino]-2-(1*H*-indol-3-yl)acetate (4e): Eluent cyclohexane/ethyl acetate (70:30), white crystals, m.p. 114–115 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.23 (br. s, 1 H, NH), 7.88 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, indole 4-H), 7.37 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, indole 7-H), 7.28–7.18 (m, 2 H, indole 5-H and 6-H), 7.24 (s, 1 H, indole 2-H), 6.51 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 6-H aromatic proton), 6.49 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 3-H aromatic proton), 6.35 (dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 2.6 Hz, 1 H, 5-H aromatic proton), 5.37 (s, 1 H, CH acetate), 5.0 (br. s, 1 H, NH), 4.28 (m, 1 H, CH*H* ethyl), 4.16 (m, 1 H, C*H*H ethyl), 3.84 (s, 3 H, methoxy), 3.75 (s, 3 H, methoxy), 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.3, 151.9, 147.8, 136.0, 130.4, 125.6, 122.6, 121.9, 119.4, 119.2, 112.4, 110.8, 110.6, 103.1, 98.8, 60.9, 55.2, 55.0, 54.4, 13.7 ppm. IR (Nujol): $\tilde{\nu}$ = 3434 (NH), 3347 (NH), 1708 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.59, H 6.30, N 8.01.

Ethyl 2-[(2,5-Dimethoxyphenyl)amino]-2-(1*H*-indol-3-yl)acetate (4f): Eluent cyclohexane/ethyl acetate (80:20), white crystals, m.p. 105 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.18 (br. s, 1 H, NH), 7.86 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, indole 4-H), 7.39 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, indole 7-H), 7.28–7.15 (m, 2 H, indole 5-H and 6-H), 7.28 (s, 1 H, indole 2-H), 6.69 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 3-H aromatic proton), 6.20 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 6-H aromatic proton), 6.35 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 2.6 Hz, 1 H, 4-H aromatic proton), 5.37 (s, 1 H, CH acetate), 5.4 (br. s, 1 H, NH), 4.29 (m, 1 H, CH*H* ethyl), 4.16 (m, 1 H, C*H*H ethyl), 3.82 (s, 3 H, methoxy), 3.70 (s, 3 H, methoxy), 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.3, 154.4, 141.7, 137.5, 136.3, 125.8, 123.0, 122.4, 119.9, 119.6, 112.5, 111.2, 110.0, 99.4, 98.7, 61.4, 55.9, 55.3, 53.9, 14.0 ppm. IR (Nujol): $\tilde{\nu}$ = 3430 (NH), 3344 (NH), 1723 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.65, H 6.20, N 7.79.

General Procedure for the Sc^{III}Tf-Catalysed Reactions Between Indole (1), Ethyl Glyoxylate (2) and Anilines 3a–f: MS (0.07–0.10 g) were added to a solution of indole (**1**, 0.117 g, 1 mmol), ethyl glyoxylate (**2**, 0.204 mL 50% solution in toluene, 1 mmol) and one of the arylamines **3a**–**f** (1 mmol) in CH_2Cl_2 (1.5 mL). The mixture, in a rubber-sealed vial, was cooled to the temperature reported in Table 2, Sc^{III}Tf (0.025 g, 0.05 mmol) was then added, and stirring was continued for the time reported in Table 2, after which nearly all reagents had disappeared. The reaction was quenched with water, the mixture was extracted with CH_2Cl_2, the organic layer was dried, and the residue was column-chromatographed. When **4** was the sole reaction product, the conditions were those reported above in each specific product. For the reaction described in Table 2, Entry 1, **5a** was separated with cyclohexane/ethyl acetate (70:30) as eluent, whereas for the reactions described in Entries 4 and 5, compounds **4b**, **6b** and **5b** were eluted in that order on a column (60 cm × 1.5 cm), and the eluent used was cyclohexane/ethyl acetate (70:30).

General Procedure for the Sc^{III}Tf-Catalysed Reactions of the Passerini Products 4a, 4b, 4d–f: Sc^{III}Tf (0.005 g, 0.01 mmol) was added to a CH_2Cl_2 (1.0 mL) solution of compound **4** (0.2 mmol) in a rubber-sealed vial cooled to the temperature reported in Table 2, and

stirring was continued for the time reported. The reaction was quenched with water, the mixture was extracted with CH_2Cl_2, the organic layer was dried, and the residue was column-chromatographed to separate the different products with the eluents reported below in the specific description of each product.

Ethyl 2-(4-Amino-3-methoxyphenyl)-2-(1*H*-indol-3-yl)acetate (5a): Eluent cyclohexane/ethyl acetate (70:30), white crystals, m.p. 105 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.16 (br. s, 1 H, NH), 7.51 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, indole 4-H), 7.34 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, indole 7-H), 7.20 (dt, $^3J_{H,H}$ = 7.1, $^4J_{H,H}$ = 1.0 Hz, 1 H, indole proton), 7.14 (d, $^3J_{H,H}$ = 2.3 Hz, 1 H, indole 2-H), 7.09 (dt, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.0 Hz, 1 H, indole proton), 6.93 (d, $^4J_{H,H}$ = 1.7 Hz, 1 H, 2-H aromatic proton), 6.88 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.7 Hz, 1 H, 6-H aromatic proton), 6.67 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 5-H aromatic proton), 5.16 (s, 1 H, CH acetate), 4.24 (m, 2 H, OCH_2), 3.80 (s, 3 H, methoxy), 3.7 (br. s, 2 H, NH_2), 1.29 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.4, 147.2, 136.2, 135.1, 128.6, 126.6, 123.0, 122.0, 120.9, 119.5, 119.0, 114.7, 114.4, 111.1, 110.6, 60.9, 55.4, 48.6, 14.2 ppm. IR (Nujol): $\tilde{\nu}$ = 3404, 3332 (NH_2), 3179 (NH), 1710 (C=O) cm^{-1}. $C_{19}H_{20}N_2O_3$ (324.4): calcd. C 70.35, H 6.21, N 8.64; found C 70.53, H 6.18, N 8.77.

Ethyl 2-(4-Aminophenyl)-2-(1*H*-indol-3-yl)acetate (5b): For the reaction described in Table 2, Entry 6, **4b**, **6b** and **5b** were eluted in that order on a column (60 cm × 1.5 cm), and the eluent used was cyclohexane/ethyl acetate (70:30). White crystals, m.p. 123–124 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.11 (br. s, 1 H, NH), 7.48 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, indole 4-H), 7.36 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, indole 7-H), 7.23 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 2-H and 6-H aromatic protons), 7.19 (d, $^3J_{H,H}$ = 2.3 Hz, 1 H, indole 2-H), 7.18 (dt, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 1.0 Hz, 1 H, indole 6-H), 7.08 (dt, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 0.9 Hz, 1 H, indole 5-H), 6.65 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 3-H and 5-H aromatic protons), 5.15 (s, 1 H, CH acetate), 4.23 (m, 2 H, OCH_2), 3.6 (br. s, 2 H, NH_2), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.9, 144.9, 135.8, 128.8, 128.2, 126.2, 122.5, 121.7, 119.1, 118.6, 114.7, 113.9, 110.6, 60.4, 55.4, 47.7, 13.7 ppm. IR (Nujol): $\tilde{\nu}$ = 3402, 3330 (NH_2), 3171 (NH), 1724 (C=O) cm^{-1}. $C_{18}H_{18}N_2O_2$ (294.4): calcd. C 73.45, H 6.16, N 9.52; found C 73.68, H 6.28, N 9.43.

Ethyl 2-({4-[(Ethoxycarbonyl)(1*H*-indol-3-yl)methyl]phenyl}amino)-2-(1*H*-indol-3-yl)acetate (6b): White crystals, m.p. 81–83 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.19 (br. s, 1 H, NH), 8.08 (br. s, 1 H, NH), 7.84 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, indole 4-H), 7.49 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, indole 4-H), 7.32 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, indole 7-H), 7.29 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, indole 7-H), 7.22 (d, 2 H, 2-H and 6-H aromatic protons), 7.24–7.05 (m, 6 H, indole protons), 6.59 (d, 2 H, 3-H and 5-H aromatic protons), 5.37 (s, 1 H, CH acetate), 5.14 (s, 1 H, CH acetate), 4.79 (br. s, 1 H, NH), 4.21 (m, 4 H, 2 × OCH_2),1.26 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3 ethyl), 1.22 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.1, 172.1, 145.2, 136.0, 135.8, 128.8, 127.5, 126.1, 125.2, 122.72, 122.69, 121.9, 121.6, 119.4, 119.02, 118.99, 118.6, 113.8, 112.9, 111.8, 110.9, 110.7, 61.1, 60.5, 53.8, 47.7, 13.7, 13.8 ppm. IR (Nujol): $\tilde{\nu}$ = 3406 (NH), 1720 (C=O) cm^{-1}. $C_{30}H_{29}N_3O_4$ (495.6): calcd. C 72.71, H 5.90, N 8.48; found C 72.58, H 6.03, N 8.61.

Ethyl 2-(5-Amino-2,4-dimethoxyphenyl)-2-(1*H*-indol-3-yl)acetate (5e): For the reaction described in Table 2, Entry 13, **4e**, **6e** and **5e** were eluted in that order with cyclohexane/ethyl acetate (68:32) as eluent. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.21 (br. s, 1 H, NH), 7.55 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, indole 4-H), 7.35 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, indole 7-H), 7.19 (dt, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, indole proton), 7.14 (d, $^3J_{H,H}$ = 2.4 Hz, 1 H, indole 2-H), 7.08 (dt, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 0.9 Hz, 1 H, indole proton), 6.60 (s, 1 H, 6-H aromatic proton), 6.52 (s, 1 H, 3-H aromatic proton), 5.52 (s, 1 H, CH acetate), 4.20 (m, 2 H, OCH_2), 3.86 (s, 6 H, 2 × methoxy), 3.5 (br. s, 2 H, NH_2), 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.6 149.9, 147.0, 136.2, 129.2, 126.9, 123.1, 122.0, 119.7, 119.5, 119.3, 116.3, 113.4, 111.0, 96.9, 60.7, 56.8, 55.6, 41.4, 14.2 ppm. IR (Nujol): $\tilde{\nu}$ = 3406, 3370 (NH_2), 3180 (NH), 1719 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.95, H 6.38, N 7.77.

Ethyl 2-({5-[(Ethoxycarbonyl)(1*H*-indol-3-yl)methyl]-2,4-dimethoxyphenyl}amino)-2-(1*H*-indol-3-yl)acetate (6e): Pale yellow oil (when one stereoisomer makes up at least 80% of the mixture, the product becomes a solid with m.p. 83–85 °C). ^{1}H NMR ($CDCl_3$): δ = 7.8 (8.06) (br. s + br. s, 1 H, NH), 7.58 (7.7) (br. s + br. s, 1 H, NH), 7.74 (7.69) [d, $^3J_{H,H}$ = 7.8 (7.7) Hz, 1 H, indole 4-H], 7.40 (7.50) [d, $^3J_{H,H}$ = 7.8 (7.7) Hz, 1 H, indole 4-H], 7.4–7.0 (m, 3 H, remaining indole protons), 6.66 (6.91) [d + d, $^4J_{H,H}$ = 2.4 (2.4) Hz, 1 H, indole 2-H], 6.49 (6.73) [d + d, $^4J_{H,H}$ = 2.4 (2.4) Hz, 1 H, indole 2-H], 6.49 (6,52) (s + s, 1 H, 6-H aromatic proton), 6.42 (6.36) (s + s, 1 H, 3-H aromatic proton), 5.46 (5.44) (s + s, 1 H, CH acetate), 5.14 (5.06) (s + s, 1 H, CH acetate), 4.05–4.25 (m, 4 H, 2 × OCH_2), 3.86 (3.85) (s + s, 3 H, methoxy), 3.81 (3.83) (s + s, 3 H, methoxy), 1.26 (1.18) (t + t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl), 1.17 (1.03) (t + t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR [pair of diastereoisomers (the signal of the second stereoisomer, when detectable, is reported in parentheses), 75 MHz, $CDCl_3$, 25 °C, TMS]: δ = 173.6 (173.8), 172.2 (172.3), 149.0 (149.2), 147.0, 136.27 (136.32), 135.9 (136.0), 130.14 (130.06), 126.9, 125.6 (125.9), 123.8 (123.4), 123.3 (123.4), 121.7 (121.9), 121.6 (121.8), 119.7 (119.8), 119.5 (119.6), 119.2 (119.3), 119.1 (119.2), 119.0 (118.9), 113.2 (112.8), 113.1 (112.5), 112.2 (112.7), 111.0, 110.9 (111.0), 96.8 (96.6), 61.3 (61.1), 60.62 (60.55), 57.0 (56.8), 55.7 (55.6), 54.6 (54.5), 40.9 (41.5), 15.0 (14.1), 14.0 (13.8) ppm. IR (Nujol): $\tilde{\nu}$ = 3404 (NH), 1720 (C=O) cm^{-1}.

Ethyl 2-(4-Amino-2,5-dimethoxyphenyl)-2-(1*H*-indol-3-yl)acetate (5f): Eluent cyclohexane/ethyl acetate (75:25), light cream-coloured crystals m.p. 81–83 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.15 (br. s, 1 H, NH), 7.58 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, indole 4-H), 7.35 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, indole 7-H), 7.19 (dt, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.1 Hz, 1 H, indole proton), 7.13 (d, $^3J_{H,H}$ = 2.4 Hz, 1 H, indole 2-H), 7.09 (dt, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.1 Hz, 1 H, indole proton), 6.76 (s, 1 H, 6-H aromatic proton), 6.39 (s, 1 H, 3-H aromatic proton), 5.54 (s, 1 H, CH acetate), 4.20 (m, 2 H, OCH_2), 3.81 (s, 3 H, methoxy), 3.7 (br. s, 2 H, NH_2), 3.62 (s, 3 H, methoxy), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3 ethyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.8 151.3, 141.1, 136.2, 135.8, 126.8, 123.0, 122.0, 119.4, 116.5, 113.8, 112.5, 111.0, 99.6, 60.7, 56.3, 56.1, 41.5, 14.2 ppm. IR (Nujol): $\tilde{\nu}$ = 3464, 3376 (NH_2), 3160 (NH), 1711 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.68, H 6.31, N 8.02.

Ethyl 2-({4-[(Ethoxycarbonyl)(1*H*-indol-3-yl)methyl]-2,4-dimethoxyphenyl}amino)-2-(1*H*-indol-3-yl)acetate (6f): For the reaction described in Table 2, Entry 15, **6f**, and **5f** were eluted in that order with cyclohexane/ethyl acetate (68:32) as eluent. Pale yellow oils. ^{1}H NMR [pair of diastereoisomers (the signal of the second stereoisomer, when detectable, is reported in parentheses), 300 MHz, $CDCl_3$, 25 °C, TMS]: δ = 8.20 (br. s, 1 H, NH), 8.07 (br. s, 1 H, NH), 7.86 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, indole 4-H), 7.56 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, indole 4-H), 7.40–7.05 (m, 8 H, indole protons), 6.76

(6.74) (s + s, 1 H, 3-H aromatic proton), 6.250 (6.245) (s + s, 1 H, 6-H aromatic proton), 5.52 (s, 1 H, CH acetate), 5.39 (s, 1 H, CH acetate), 5.3 (br. s, 1 H, NH), 4.22 (m, 4 H, $2\times OCH_2$), 3.70 (3.69) (s + s, 3 H, methoxy), 3.63 (3.61) (s + s, 3 H, methoxy), 1.255, 1.245, (1.240, 1.299) (t + t + t + t, $^3J_{H,H}$ = 7.5 Hz, 6 H, $2\times CH_3$ ethyl) ppm. ^{13}C NMR [pair of diastereoisomers (the signal of the second stereoisomer, when detectable, is reported in parentheses), 75 MHz, $CDCl_3$, 25 °C, TMS]: δ = 173.4, 172.0, 151, 140.7 (140.6), 136.01 (135.98), 135.88, 135.80 (135.77), 126.5, 125.4, 122.6, 122.5, 122.0, 121.6, 119.5, 119.0, 118.9, 114.6 (114.5), 113.71 (113.65), 112.23 (112.17) 111.1, 110.8, 110.5, 95.86 (95.78), 61.0, 60.2, 55.02 (55.95), 55.89 (55.55), 53.8, 40.97 (40.88), 13.75, 13.69 ppm. IR (Nujol): $\tilde{\nu}$ = 3404 (NH), 1718 (C=O) cm^{-1}.

X-ray Crystallographic Study: Diffraction data for a crystal of **5a** were collected with a Bruker-Axs Smart-Apex CCD-based diffractometer, working with graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å). Crystal data for **5a**: $C_{19}H_{20}N_2O_3$; M_r = 324.37; T = 293 K; crystal dimensions $0.50\times0.45\times0.05$ mm; triclinic; $P\bar{1}$ (No. 2); a = 8.9027(6), b = 9.5400(7), c = 11.4684(8) Å; α = 70.058(1), β = 70.685(1), γ = 86.011(1)°; V = 863.06(10) Å^3; Z = 2; $\rho_{calcd.}$ = 1.248; $F(000)$ = 344; μ = 0.085 mm^{-1}; $2\theta_{max}$ = 60°; 16719 measured reflections; 5060 independent reflections (R_{int} = 0.022); 3751 strong reflections [$I_o > 2\sigma(I_o)$]; 228 refined parameters; R_1 = 0.0533 (strong data) and 0.0691 (all data); wR_2 = 0.1439 (strong data) and 0.1561 (all data); GOF = 1.040; 0.33 and –0.17 max. and min. residual electron density. Data reduction (including intensity integration, background, Lorentz and polarization corrections) was performed with the SAINT software.[27] Absorption effects were empirically evaluated by use of the SADABS software,[28] and absorption correction was applied to the data (min./max. transmission factors were 0.891/0.993). The crystal structure was solved by direct methods (SIR97)[29] and refined by full-matrix, least-squares procedures on F^2 with use of all reflections (SHELXL97).[30] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were placed at calculated positions with the appropriate AFIX instructions and refined with a riding model; H atoms bonded to N atoms were located in the ΔF map and refined with restraint of the N–H distance to 0.96 ± 0.01 Å. CCDC-693250 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of products obtained from thermal and Sc^{III}-catalysed reactions.

Acknowledgments

This work was supported by the Ministero Istruzione Università Ricerca (MIUR) and the University of Pavia.

[1] *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.
[2] For a recent review see: D. M. D'Souza, J. J. Miller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108.
[3] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329.
[4] A. J. von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, *Chem. Eur. J.* **2003**, *9*, 4286–4294.
[5] D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.
[6] G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700.
[7] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27.
[8] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.
[9] P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962–2967; P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
[10] C. Mannich, W. Krosche, *Arch. Pharm.* **1912**, *250*, 647–667.
[11] M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126–129.
[12] P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231–4233; S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2008**, *47*, 388–391.
[13] M. Passerini, M. Bonciani, *Gazz. Chim. Ital.* **1933**, *63*, 138–144; M. Passerini, F. Albani, *Gazz. Chim. Ital.* **1935**, *65*, 933–938.
[14] a) D. A. Evans, K. R. Fandrick, H. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942–8943; b) D. A. Evans, H. Song, K. R. Fandrick, *Org. Lett.* **2006**, *8*, 3351–3354; c) D. A. Evans, K. R. Fandrick, H. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041.
[15] a) W. Xie, K. M. Blomfield, Y. Jin, N. Y. Dolney, P. G. Wang, *Synlett* **1999**, 498–500; b) X. Mi, S. Luo, J. He, J. P. Cheng, *Tetrahedron Lett.* **2004**, *45*, 4567–4570.
[16] J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 629–633.
[17] Y. X. Jia, J. H. Xie, H. F. Duan, L. X. Wang, Q. L. Zhou, *Org. Lett.* **2006**, *8*, 1621–1624.
[18] a) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609–2611; b) Q. Kang, Z. A. Zhao, S. L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485; c) M. Terada, S. Yokoyama, K. Sorimachi, D. Uraguchi, *Adv. Synth. Catal.* **2007**, *349*, 1863–1867; d) Q. Kang, X. J. Zheng, S. L. You, *Chem. Eur. J.* **2008**, *14*, 3539–3542.
[19] Y. Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
[20] M. Johannsen, *Chem. Commun.* **1999**, 2233–2234.
[21] B. Jiang, Z. G. Huang, *Synthesis* **2005**, 2198–2204.
[22] M. Soueidan, J. Collin, R. Gil, *Tetrahedron Lett.* **2006**, *47*, 5467–5470.
[23] J. L. Zhao, L. Liu, H. B. Zhang, Y. C. Wu, D. Wang, Y. J. Chen, *Synlett* **2006**, 96–100.
[24] G. Desimoni, G. Faita, F. Piccinini, M. Toscanini, *Eur. J. Org. Chem.* **2006**, 5228–5230.
[25] G. Desimoni, G. Faita, M. Mella, F. Piccinini, M. Toscanini, *Eur. J. Org. Chem.* **2007**, 1529–1534; G. Desimoni, G. Faita, M. Toscanini, M. Baiocchi, *Chem. Eur. J.* **2007**, *13*, 9478–9485.
[26] G. Desimoni, G. Faita, M. Toscanini, M. Baiocchi, *Chem. Eur. J.* **2008**, *14*, 3630–3636.
[27] *SAINT-NT, Software Reference Manual*, version 6, Bruker AXS, Inc., Madison, Wisconsin, USA, **2003**.
[28] G. M. Sheldrick, *SADABS, Siemens Area Detector Absorption Correction Program*, University of Göttingen, Germany, **1996**.
[29] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
[30] G. M. Sheldrick, *SHELX97, Programs for Crystal Structure Analysis*, University of Göttingen, Germany, **1997**.

Received: September 2, 2008
Published Online: November 12, 2008

