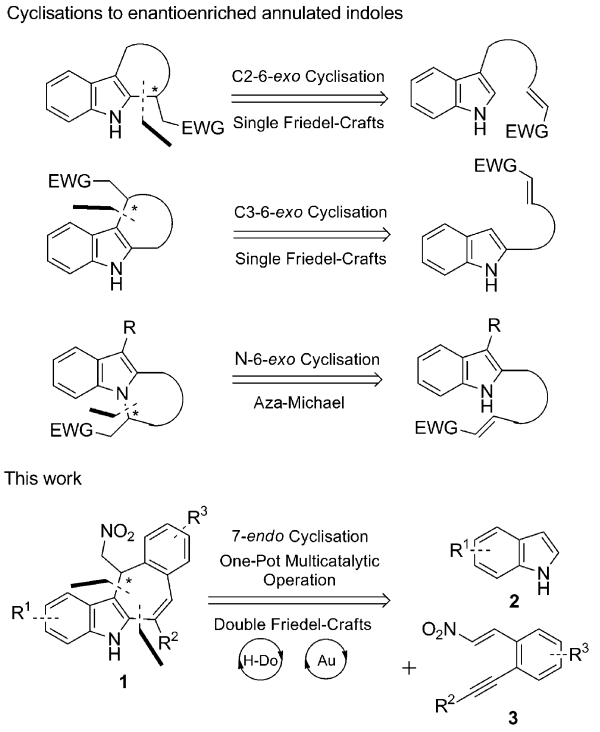
DOI: 10.1002/chem.201102793

Merging Organocatalysis and Gold Catalysis: Enantioselective Synthesis of Tetracyclic Indole Derivatives through a Sequential Double Friedel–Crafts Type Reaction

Charles C. J. Loh, Jan Badorrek, Gerhard Raabe, and Dieter Enders*[a]

Annulated indoles, fused at the C2- and C3-position, are chemically and biologically interesting as key structural motifs in many natural products and as pharmaceutically active substances.[1] Furthermore, annulated, tetracyclic indoles containing a seven-membered ring, such as in **1** (Scheme 1), have shown anticancer activities on leukemia and colon cell lines, as well as antiproliferative activities through DNA intercalation.[2] However, accessing such seven-membered-ring-containing polycycles is synthetically challenging owing to the preferential six-membered-ring formation in the cyclisation step.



Scheme 1. Strategy comparison between current work and known methods.

The reactivities of the indole C3- and C2-position, as well as the indole nitrogen, provide many opportunities to access enantiopure, annulated indole derivatives. This can be achieved, for example, with an intramolecular Friedel–Crafts type reaction[3,4] or an aza-Michael addition of the indolic nitrogen on a suitable acceptor.[5] While reports on the enantioselective synthesis of polycyclic indoles using various catalytic activation modes, especially in the fields of organocatalysis[6] and gold catalysis,[7] are numerous, most of such synthetic strategies required substrates containing a prefunctionalised indole, either on the C3- or the C2-position (Scheme 1).[3,5]

In view of limited precedence for the synthesis of annulated indoles from C3,C2-unsubstituted indoles **2**,[8] we hypothesised that chiral, polycyclic indoles could be accessed enantioselectively through a single-pot tandem operation. To the best of our knowledge, an enantioselective variant of such a transformation is not yet known. Moreover, we envisioned that the recent surge in utilising one-pot, multicatalytic, tandem reactions combining distinct organocatalytic and transition-metal cycles could be used as a viable strategy to obtain enantiopure, annulated indoles.[9–11] This emerging area has also spurred some efforts in utilising indole as a key substrate in enantioselective, sequential reactions.[4k,10d]

In our synthetic planning, we were interested in combining both organocatalysis and gold catalysis, especially the latter to access nonconventional molecular frameworks through domino and rearrangement reactions.[7k] It is worth noting that the pioneering studies on gold catalysis by Echavarren et al.[12] and Zhang et al.,[13a,b] as well as very recent reports,[8d,13c,14] allowed complex functionalisations of indole substrates containing an intramolecular tethered alkyne.

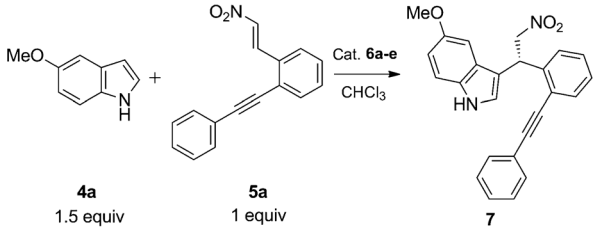
We now wish to report an efficient and highly enantioselective one-pot, multicatalytic, C2/C3-annulation of indoles, giving rise to tetracyclic, seven-membered-ring-containing derivatives **1**. The new protocol utilises the bifunctional *ortho*-alkyne-substituted nitrostyrenes **3** as substrates, allowing two sequential Friedel–Crafts type reactions. The nitroalkene moiety is activated through hydrogen-bonding organocatalysis, to incorporate the stereochemical information in the first Friedel–Crafts reaction,[15] and the alkyne functionality provides access to gold catalysis and its alkynophilicity,[7] to effect the second Friedel–Crafts/ring expansion cascade.

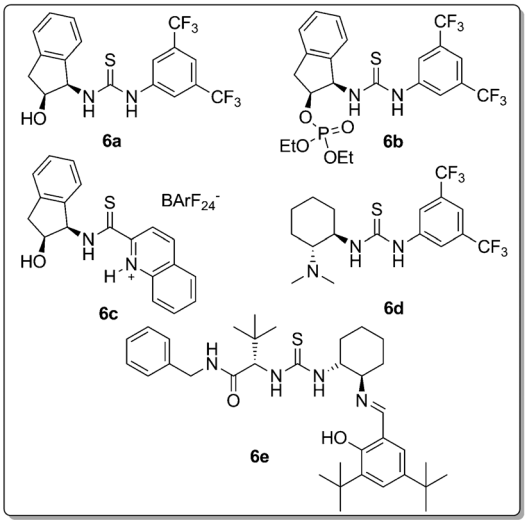
[a] C. C. J. Loh, J. Badorrek, Prof. Dr. G. Raabe, Prof. Dr. D. Enders
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-809-2127
E-mail: enders@rwth-aachen.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102793.

To truncate the practical complexity in achieving the optimal conditions for the sequential reaction, we first tested the protocol as two separate reactions. The sequential process would finally be developed, based on the optimised conditions of each sequential step. First, we screened a series of hydrogen-bonding catalysts for the Friedel–Crafts reaction of methoxyindole **4a** with the *ortho*-alkyne substituted nitrostyrene **5a** (Table 1).

Table 1. Screening of organocatalysts.[a]





	Catalyst	Cat. Loading [%]	*t* [d]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**6a**	20	8	23	48	33
2	**6b**	20	9	23	45	39
3	**6c**	10	1	23	93	89
4	**6c**	10	1	−30	91	95
5	**6d**	20	10	23	55	45
6	**6e**	20	12	23	55	0

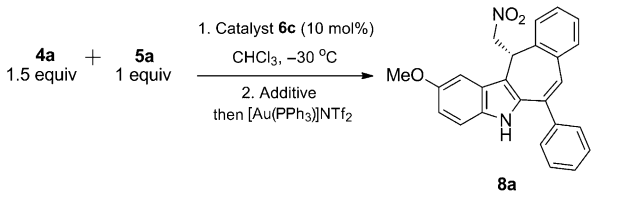
[a] All reactions were conducted on a 0.2 mmol scale of nitroalkene **5a** with indole **4a**. [b] Yields isolated after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

In the series of catalysts tested for the organocatalytic Friedel–Crafts alkylation with **5a**,[16] the thiourea-based organocatalysts **6a**, **6b**, **6d**, and **6e** generally resulted in sluggish reactions at room temperature. Moreover, such catalysts gave only moderate yields with low to moderate enantiomeric excesses. With all the hydrogen-bonding catalysts screened for the organocatalytic first step, catalyst **6c**, developed by Seidel et al.,[16d] provided the best enantioselectivity of up to 95% (Table 1, entry 4). The faster reaction times, excellent yields and high enantioselectivity at −30 °C make this catalyst the optimal choice for our sequential reaction.

In the separate screening of transition metals to effect the second Friedel–Crafts type reaction, common gold catalysts, such as $[Au(PPh_3)]NTf_2$, $[Au(PPh_3)]SbF_6$ and $[Au(PPh_3)]OTf$, generally led to almost quantitative yields of the cyclised product. Other transition-metal catalysts, such as $PdCl_2$, AgOTf, CuOTf and $InCl_3$, gave no desired products (see Supporting Information for more details). While a wide variety of gold(I) catalysts were effective, $[Au(PPh_3)]NTf_2$ was the catalyst of choice in our sequential reaction development, because gold complexes containing the NTf_2 counterion show greater air and thermal stability compared to other counterions,[17] which makes it more tenable to varying reaction conditions.

With suitable catalysts for both the organo- and gold-catalysed steps in hand, we proceeded with the combination of catalyst **6c** and $[Au(PPh_3)]NTf_2$ in a one-pot tandem sequence. Initial tests without additives yielded only traces of product (Table 2, entry 1). This observation was in line with

Table 2. Additive optimisation of the one-pot sequential reaction.[a]



	$[Au(PPh_3)]NTf_2$ [mol%]	Additive	Yield [%][b]	*ee* [%][c]
1[d]	10	–	–	–
2[d]	10	25% *p*-TSA	40	95
3[e]	10	50% *p*-TSA	50	96
4[e]	10	50% DPP	42	93
5[e]	10	75% *p*-TSA	99	97
6[e]	10	100% *p*-TSA	80	97
7[e]	10	1.5 equiv *t*BuOH	–	–
8[e]	0	75% *p*-TSA	–	–

[a] All reactions were conducted on a 0.2 mmol scale of nitroalkene **5a** with indole **4a**. [b] Yields isolated after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted at room temperature to 40 °C. [e] Reaction was conducted at room temperature to reflux.

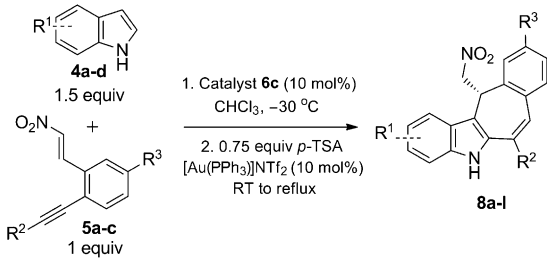
reports from other research groups,[10c,f,g] indicating that a gold catalyst deactivation by the amine-containing **6c** is possible. Hence, a screening was conducted to determine an appropriate additive to regenerate the active Au^I species.[10c,f,g] A series of additives was tested to determine the optimal combination (Table 2). While protic additives, such as *t*BuOH, did not have a measurable effect on the reaction, strong Brønsted acid additives, such as *p*-toluenesulfonic acid hydrate (*p*-TSA) and diphenylphosphate (DPP), showed increased yields for product **8a** with excellent enantioselectivities (Table 2, entries 2–6). The optimised condition was observed, when 0.75 equivalents of *p*-TSA were

used in combination with both catalyst **6c** and [Au(PPh$_3$)]NTf$_2$ (Table 2, entry 5).

To exclude any uncertainty that the gold-catalysed cyclisation might be effected by the presence of *p*-TSA,[18] a control experiment was performed using the exact conditions without [Au(PPh$_3$)]NTf$_2$ (Table 2, Entry 8). This control experiment revealed that no product was detected in the absence of the gold catalyst.

Having achieved the optimised conditions through the additive screening, we turned our attention to develop the scope of this novel, catalytic, asymmetric synthesis of pharmaceutically interesting tetracyclic indole derivatives (Table 3). In general, this one-pot, sequential, catalytic reaction tolerates a variety of substrates, with varying functionalities on the indole **4**, as well as the alkyne nitrostyrene component **5**. 5-Methyl indole performed excellently in this tandem reaction (Table 3, **8b**, **8f** and **8j**) with yields of over 90%. Other indoles, such as 5-methoxyindole, 7-methylindole and unsubstituted indoles, also gave good to excellent yields.[19]

Table 3. Substrate scope of the methodology.[a,b]



8	R^1	R^2	R^3	t[c] [h]	Yield[d] [%]	*ee*[e] [%]
a	5-OMe	Ph	H	24+19	78	97
b	5-Me	Ph	H	36+30	92	97
c	H	Ph	H	48+38	51	97
d	7-Me	Ph	H	37+31	70	98
e	5-OMe	Ph	F	22+20	67	97
f	5-Me	Ph	F	16+29	96	95
g	H	Ph	F	21+25	81	98
h	7-Me	Ph	F	21+25	78	99
i	5-OMe	3-tolyl	H	18+42	80	97
j	5-Me	3-tolyl	H	27+15	94	98
k	H	3-tolyl	H	25+67	79	97
l	7-Me	3-tolyl	H	25+41	60	98

[a] All reactions were conducted on a 0.8 mmol scale of **5a–c** and indole **4a–d**. [b] Absolute configurations are deduced by analogy to the crystal structure of **8l**. [c] Times for organocatalytic step + gold catalysed cyclisation. [d] Yields isolated after flash column chromatography. [e] Determined by HPLC analysis on a chiral stationary phase.

To ensure the industrial applicability of this novel, multicatalytic protocol, a 4 g scale reaction was conducted to provide convincing evidence of its scalability. This system proceeded smoothly on a multigram scale at significantly lower catalyst loading (3 mol% of **6c** and 5 mol% of [Au(PPh$_3$)]NTf$_2$) with still excellent enantioselectivity (93% *ee*) and yield (93%) comparable to those of the small-scale reaction (Table 3, **8b**). To further understand the role of *p*-TSA in this reaction, two control experiments of the tandem reaction with and without *p*-TSA were performed in $CDCl_3$ and studied by using ^{31}P NMR spectroscopy (see Supporting Information). The NMR studies revealed that only one ^{31}P peak at $\delta = 34.2$ ppm was observed for both control reactions at room temperature, albeit with extremely low product formation for the reaction containing *p*-TSA. This $\delta = 34.2$ ppm resonance is consistent with a separate ^{31}P experiment on a sample containing only catalyst **6c** and [Au(PPh$_3$)]NTf$_2$. A separate experiment on pure [Au(PPh$_3$)]NTf$_2$ showed a ^{31}P resonance at $\delta = 31.8$ ppm. Peaks resonating at $\delta = 46.2$ and 34.2 ppm were observed for both control experiments, when the reactions were heated to reflux. Simultaneous ^{1}H NMR studies on the same reaction mixtures revealed that only the addition of *p*-TSA resulted in product formation.

We believe that the same deactivation effect on the Au^I catalyst is present, regardless of the presence of *p*-TSA. This is exemplified by the downfield shift of the ^{31}P peak to $\delta = 34.2$ ppm at room temperature, which corresponds to the low-reactive adduct formed between Au^I and the organocatalyst **6c**. Upon heating, the new ^{31}P peak, observed at $\delta = 46.2$ ppm, might indicate the formation of covalent Au–C bonds.[20] The role of *p*-TSA seems to be the regeneration of the active Au^I species to re-enter the catalytic cycle; however, apparently this is more effective at elevated temperatures.

The absolute configuration and molecular structure of **8l** was unambiguously determined by X-ray crystallography (Figure 1).[21] This is also consistent in analogy with the absolute configuration reported by Ricci et al. using catalyst **6a**[16a] and double confirmed by comparing the stereochemical outcome with HPLC obtained with both catalysts **6a** and **6c** (Table 1, entries 1 and 4).

To demonstrate further possible transformations of the tetracyclic indole targets, the nitro group of **8b** was reduced

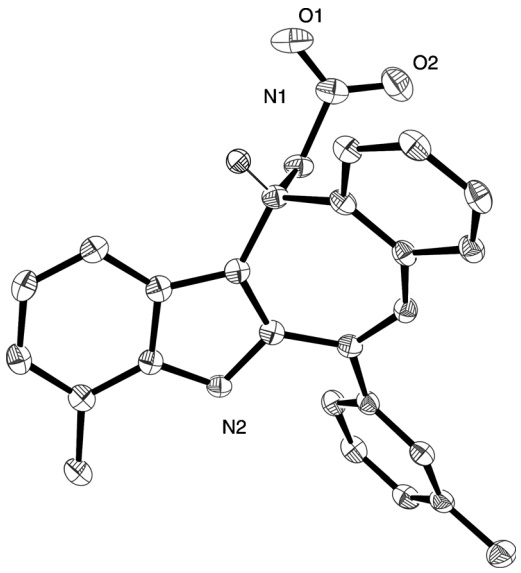
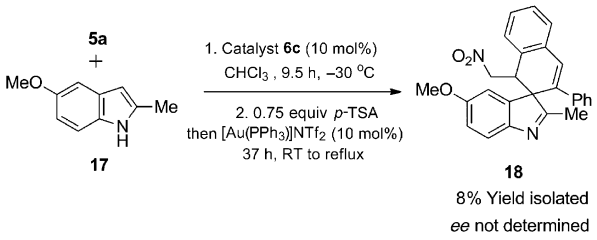


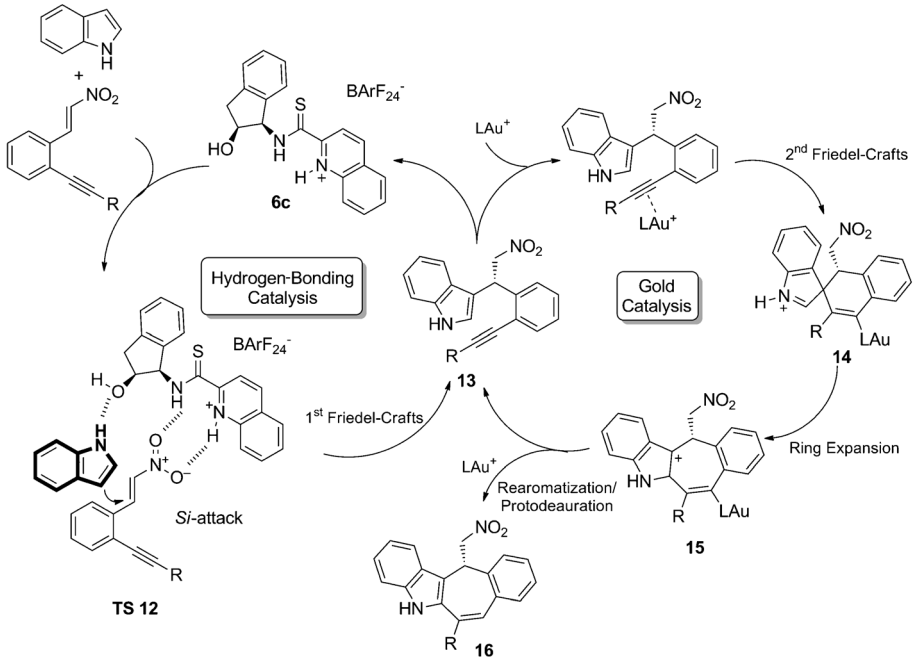
Figure 1. X-ray crystal structure of (*R*)-**8l**.

to the corresponding primary amine (86%), which in turn was converted by acylation into a camphanic amide and a *p*-bromobenzamide in good yields and without racemisation (for details on compounds **9**–**11**, see Supporting Information).

Based on our empirical data, as well as previously reported studies,[7g,12,13,22] a mechanism is proposed to explain this multicatalytic system (Scheme 2). Starting from C3,C2-unsubstituted indoles and *ortho*-alkyne-substituted nitrostyrenes, **6c** serves as a bifunctional organocatalyst, similar to a thiourea catalyst, forming a tight transition state **TS12**, which is stabilised by multiple hydrogen-bonding interactions with the nitroolefin and the N−H of the attacking indole nucleophile. This locks the reacting partners in favouring an indole *Si*-attack and explains the high enantioselectivity and (*R*)-configuration in the first Friedel–Crafts type reaction. Subsequently, the C3-substituted intermediate **13** is activated by the π-acidic $[Au(PPh_3)]NTf_2$, owing to the presence of the auraphilic alkyne. The alkyne activation allows the C3 of indole to undergo a second Friedel–Crafts type reaction in a 6-*endo-dig* fashion, forming a spirocyclic intermediate **14**.[12,13,22] A mechanistic test was conducted by using our protocol on a C2-substituted indole (Scheme 3). Indeed, a small amount of the spirocyclic product **18** was isolated, albeit in low yield, possibly owing to the formation of a highly congested quartenary centre. Nevertheless, the successful isolation of this compound provides a plausible evidence that spirocyclic intermediates, such as **14**, could be involved in the catalytic cycle. With the known character of gold catalysis to engage in nonclassical cationic-type cascades,[7b,l] the intermediate **14** can rearrange through a 1,2-shift



Scheme 3. Indirect mechanistic evidence for the formation of spirocyclic intermediates.



Scheme 2. Proposed mechanism of the sequential organo- and gold-based catalysis.

to effect an expansion from a six- to a seven-membered ring (**15**).[23] The final driving force towards **16** lies in the indole rearomatisation and protodeauration step. It is worth noting that our methodology allows a three-carbon tether between the C3 atom of indole and the alkyne to undergo a seven-membered-ring formation by a formal 7-*endo-dig* cyclisation.[8d] This is in contrast to previous reports, in which an intramolecular Friedel–Crafts attack on a three-carbon, aliphatic tether resulted in six-membered rings, formed by a formal 6-*exo-dig* reaction.[12–14] One possible explanation is that the presence of a fused phenyl group on the tether might stabilise the endocyclic olefin better than an exocyclic one, suggesting that thermodynamic factors could be responsible for the observed regioselectivity.

In conclusion, we have developed a new methodology to access tetracyclic indole derivatives enantioselectively by merging organo- and gold-based catalysis through two sequential Friedel–Crafts type reactions. It is remarkable that this one-pot protocol allows insertion of a stereogenic centre into a highly conjugated, tetracyclic system, without compromising the stereogenic integrity of the dibenzylic position. Moreover, a rare 7-*endo-dig* cyclisation provides deeper insights into gold catalysis on indoles. As some questions regarding the exact dependence of the tethering bridge and the mode of cyclisation remain unsolved, further mechanistic studies are currently ongoing in our laboratories.

Experimental Section

General procedure: Trifluomethanesulfonic acid (7.1 μL, 0.08 mmol, 0.1 equiv) was added under air to a Schlenk tube, containing a solution of **6c** (0.08 mmol, 0.1 equiv) in $CHCl_3$ (4 mL). Then, $NaBArF_{24}$ (0.08 mmol, 0.1 equiv) was added to the reaction mixture, which was

stirred for a further 10 min. The corresponding nitrostyrene alkyne **5a–c** (0.8 mmol, 1 equiv), dissolved in $CHCl_3$ (4 mL), was then added and the reaction mixture was cooled to −30 °C. Indole **4a–d** (1.2 mmol, 1.5 equiv), dissolved in $CHCl_3$ (2 mL), was subsequently added and the reaction was monitored by TLC, until full conversion of the first tandem step was observed. The reaction was warmed to room temperature over 30 min, and *p*-TSA (0.6 mmol, 0.75 equiv) and $[Au(PPh_3)]NTf_2$ (0.08 mmol, 0.1 equiv) were transferred to the reaction mixture sequentially. The reaction mixture was heated under reflux and monitored by TLC, until no further changes were observed. The product was then directly purified by flash column chromatography.

Keywords: gold · indoles · multicatalysis · one-pot reaction · organocatalysis

[1] a) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–48; b) A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances*, 4th ed., Thieme Medical Publishers, New York, **2001**; c) J. Sundberg in *Comprehensive Heterocyclic Chemistry, Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, pp. 313–376; d) A. Joule in *Indole and its Derivatives in Science of Synthesis, Vol. 10*, 5th ed., (Ed.: E. J. Thomas), Thieme, Stuttgart, **2000**, chapter 10.13; e) H. J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427.

[2] a) B. Joseph, V. Chapellier, J.-Y. Mérour, S. Léonce, *Heterocycles* **1998**, *48*, 1423–1430; b) B. Joseph, D. Alagille, J.-Y. Mérour, S. Léonce, *Chem. Pharm. Bull. (Tokyo)* **2000**, *48*, 1872–1876.

[3] For general reviews on Friedel–Crafts reactions of indoles, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560–566; *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; b) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903–2915; c) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; d) S. L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; e) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.

[4] For examples of intramolecular Friedel–Crafts reactions to form annulated indoles, see: a) H. Yamada, T. Kawate; M. Matsumizu, A. Nishida, K. Yamaguchi, M. Nakagawa, *J. Org. Chem.* **1998**, *63*, 6348–6354; M. Matsumizu, A. Nishida, K. Yamaguchi, M. Nakagawa, *J. Org. Chem.* **1998**, *63*, 6348–6354; b) M. Agnusdei, M. Bandini, A. Melloni, A. Umani-Ronchi, *J. Org. Chem.* **2003**, *68*, 7126–7129; c) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; d) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087; e) X. Han, R. A. Widenhoefer, *Org. Lett.* **2006**, *8*, 3801–3804; f) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405; g) M. J. Wanner, R. N. S. Van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629–7631; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485–7487; h) D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 745–748; i) N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. von Gelder, J. H. van Maarseveen, H. Hiemsra, *J. Org. Chem.* **2008**, *73*, 6405–6408; j) H. Huang, R. Peters, *Angew. Chem.* **2009**, *121*, 612–615; *Angew. Chem. Int. Ed.* **2009**, *48*, 604–606; k) Q. Cai, Z. A. Zhao, S. L. You *Angew. Chem.* **2009**, *121, 7564–7567; Angew. Chem. Int. Ed.* **2009**, 48, 7428–7431; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428–7431; l) M. Bandini, A. Eichholzer *Angew. Chem.* **2009**, *121, 9697–9701; Angew. Chem. Int. Ed.* **2009**, 48, 9533–9537; *Angew. Chem. Int. Ed.* **2009**, *48*, 9533–9537; m) J. W. Zhang, Q. Cai, X. X. Shi, W. Zhang, S. L. You, *Synlett* **2011**, 1239–1242.

[5] For selected examples of intramolecular aza-Michael reactions to form annulated indoles, see: a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282–3285; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238–3241; b) Q. Cai, C. Zheng, S. L. You, *Angew. Chem.* **2010**, *122*, 8848–8851; *Angew. Chem. Int. Ed.* **2010**, *49*, 8666–8669.

[6] For selected general reviews on organocatalysis, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; b) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; c) special issue on organocatalysis: B. List, *Chem. Rev.* **2007**, *107*, 5413–5415; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; e) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; f) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1587; g) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; h) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; i) C. F. Barbas, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; j) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870; k) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; l) K. A. Jørgensen, S. Bertelsen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; m) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614; n) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178.

[7] For selected general reviews on gold catalysis, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; d) J. Muzart, *Tetrahedron* **2008**, *64*, 5815–5849; e) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; g) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; h) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; i) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917–4938; j) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; k) S. F. Kirsch, *Synthesis* **2008**, 3183–3204; l) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; m) N. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; n) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609–619; o) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; p) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358–1367; q) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009.

[8] For examples of indoles as double nucleophiles, see: a) B. Bajtos, M. Yu, H. Zhao, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634; b) J. Barluenga, E. Tudela, A. Ballesteros, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 2096–2097; c) A. C. Silvanus, S. J. Heffernan, D. J. Liptrot, G. Kociok-Köhn, B. L. Andrews, D. R. Carbery, *Org. Lett.* **2009**, *11*, 1175–1178; d) Y. Lu, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 1517–1522; e) Y. Lian, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 440–441; f) M. C. Haibach, I. Deb, C. K. De, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 2100–2103.

[9] For highlights and reviews on the combination of organocatalysts and transition-metal catalysts, see: a) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2008**, *120*, 5787–5789; *Angew. Chem. Int. Ed.* **2008**, *47*, 5703–5705; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755; c) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3025; d) A. S. K. Hashmi, C. Hubbert, *Angew. Chem.* **2010**, *122*, 1026–1028; *Angew. Chem. Int. Ed.* **2010**, *49*, 1010–1012; e) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350–9365; f) N. T. Patil, *Angew. Chem.* **2011**, *123*, 1797–1799; *Angew. Chem. Int. Ed.* **2011**, *50*, 1759–1761.

[10] For selected examples combining organocatalysis and gold catalysis in a one-pot reaction, see: a) A. S. K. Hashmi, M. Wölfle, J. H. Teles, W. Frey, *Synlett* **2007**, 1747–1752; b) J. T. Binder, B. Crone, T. T. Haug, H. Menz, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 1025–1028; c) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem.* **2009**, *121*, 9085–9088; *Angew. Chem. Int. Ed.* **2009**, *48*, 8923–8926; d) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797; e) Z.-Y. Han, H. Xiao, X. H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183; f) D. Monge, K. L. Jensen, P. T. Franke, L. Lykke, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 9478–9484; g) T. Zweifel, D. Höllmann, B. Prüger, M. Nielsen, K. A. Jørgensen, *Tetrahedron: Asymmetry* **2010**, *21*, 1624–1629; h) K. L. Jensen, P. T. Franke, C. Arróniz, S. Kobbelgaard, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 1750–1753.

[11] For highlights and reviews on one-pot reactions under multicatalytic conditions, see: a) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312; b) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422–434; c) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem.* **2011**, *123*, 3685–3687; *Angew. Chem. Int. Ed.* **2011**, *50*, 3605–3607; d) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642–8660; *Angew. Chem. Int. Ed.* **2011**, *50*, 1580–1583.
[12] a) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123–1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358–1373; c) C. Ferrer, A. Escribano-Cuesta, A. M. Echavarren, *Tetrahedron* **2009**, *65*, 9015–9020.
[13] a) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; b) G. Zhang, V. J. Catalano, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 11358–11359; c) G. Cera, P. Crispino, M. Monari, M. Bandini, *Chem. Commun.* **2011**, *47*, 7803–7805.
[14] Y. Liu, W. Xu, X. Wang, *Org. Lett.* **2010**, *12*, 1448–1451.
[15] For general reviews on hydrogen-bonding catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*,1520–1543; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; f) M. Kotke, P. R. Schreiner in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 141–352; g) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601; h) K. Etzenbach-Effers, A. Berkessel, *Top. Curr. Chem.* **2009**, *291*, 1; i) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678–20685.
[16] For previous studies of indole Friedel–Crafts reactions with nitroolefins, see: a) R. P. Herrera, V. Sgarzani, L. Bernadi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734–6737; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579; b) W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 2566–2571; c) E. M. Fleming, T. McCabe, S. J. Connon, *Tetrahedron Lett.* **2006**, *47*, 7037–7042; d) M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 16464–16465; e) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080–4082; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016–4018; f) E. Marqués-López, A. Alcaine, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2011**, 3700–3705.
[17] a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136; b) L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704–4707; c) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.
[18] A. S. K. Hashmi, *Catal. Today* **2007**, *122*, 211–214.
[19] A bromide atom on the R^1 position and a cyclopentyl substituent as R^2 gave diminished yields in this methodology.
[20] T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513.
[21] CCDC-838179 (**81**) 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; see the Supporting Information for details.
[22] C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155–3164.
[23] For a review on Au-catalysed 1,2-alkyl shifts, see: B. Crone, S. F. Kirsch, *Chem. Eur. J.* **2008**, *14*, 3514–3522.

Received: September 7, 2011
Published online: October 24, 2011

