ORGANIC LETTERS

2012
Vol. 14, No. 6
1540–1543

High-Pressure Accelerated Asymmetric Organocatalytic Friedel–Crafts Alkylation of Indoles with Enones: Application to Quaternary Stereogenic Centers Construction

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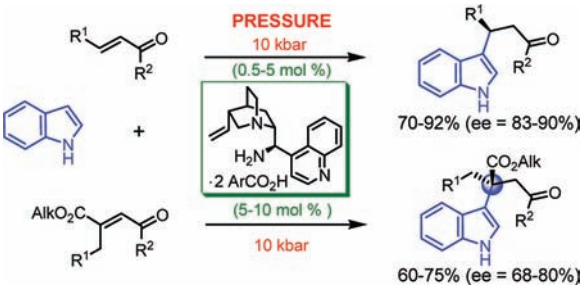
Received February 3, 2012

ABSTRACT



An organocatalytic Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones was found to be efficiently accelerated under high-pressure conditions with a low loading of chiral primary amine salts with good yield and enantioselectivity up to 90%. This approach also allows, for the first time, selected indole derivatives containing quaternary stereogenic centers to be obtained from prochiral β,β-disubstituted enones with an enantioselectivity up to 80%.

Indole-containing motifs are very common in many natural products, bioactive substances, and industrially useful compounds.[1] A large group of such molecules are chiral, so the development of novel, efficient, and environmentally friendly asymmetric synthetic methods remains a very important area of indole chemistry. Of special interest are derivatives with alkyl-type substituents in the C-3 position of indole. Direct functionalization at this position can be realized using Friedel–Crafts (F–C) alkylation,[2] e.g. with α,β-unsaturated carbonyl compounds, very often with generation of a stereogenic center at the benzylic position.

In recent years much attention has been focused on asymmetric F–C reactions catalyzed by simple chiral organic molecules.[3] The iminium activation strategy[4] developed by MacMillan[5] is a very powerful approach for F–C reactions of activated arenes with α,β-unsaturated aldehydes.[3,6] This methodology is also applicable for more difficult F–C reactions with less reactive enones (due to

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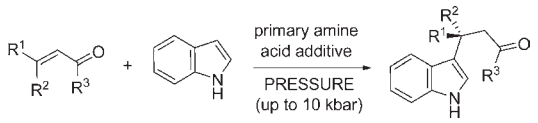
10.1021/ol300274u © 2012 American Chemical Society
Published on Web 03/07/2012

Scheme 1. Friedel–Crafts Reaction of Indole with Enones



steric repulsions).[7] Chen[7b] and Melchiorre[7c] demonstrated that chiral primary amine salts derived from cinchona alkloids are good catalysts for asymmetric F–C alkylation of indoles with enones, although this reaction usually requires a high catalyst concentration (20–30 mol %). The existing literature contains only a few articles concerning asymmetric organocatalytic F–C reactions with α,β-unsaturated ketones catalyzed by chiral amines[7] or Brønsted acids[8] and no information about asymmetric F–C reactions with β,β-disubstituted enones, leading to products with quaternary stereogenic centers.[9]

In our opinion, the reactivity problem of enones in selected organocatalytic reactions can be overcome by applying a high-pressure technique.[10,11] We have recently demonstrated the first example of significant pressure influence on an organocatalytic reaction proceeding via an iminium activation mode.[12] We found that a combination of pressure and bifunctional catalysis with primary amines remarkably accelerate enantioselective conjugate addition of nitroalkanes to sterically congested β,β-disubstituted enones, allowing for the construction of quaternary stereogenic centers with very high enantioselectivity.

Here, we demonstrate the significant influence of pressure on F–C reactions of indoles with enones (Scheme 1) catalyzed by salts of chiral primary amines.[13] This is the first example of pressure influence studies on an organocatalytic F–C reaction proceeding via an iminium activation mode.[14] This technique also allows to synthesize selected indole derivatives containing quaternary stereogenic centers from β,β-disubstituted enones.[9]

As a model reaction for our studies, we chose the alkylation of indole with *E*-benzylidenoacetone (Table 1). This particular reaction was investigated by Chen[7b] and Melchiorre[7c] with primary amines derived from cinchona

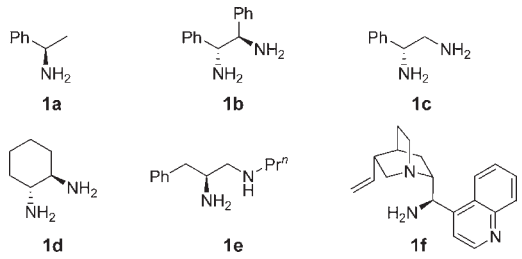


Figure 1. Organocatalysts examined in F–C alkylation.

alkaloids. Chen applied 30 mol % of 9-amino-9-deoxy-*epi*-cinchonine (**1f**, Figure 1) with 2 equiv of TfOH and after 3 days isolated product **3a** with 72% yield and 65% ee. Melchiorre[7c] discovered a more efficient catalytic system based on a primary amine derived from dihydroquinine (20 mol %) and D-*N*-Boc-phenylglycine (40 mol %) as a cocatalyst. After 1 day at 70 °C the product **3a** was isolated with 90% yield and 88% ee.

Our preliminary investigations of the model reaction under 1 bar and 10 kbar at 50 °C with 5 mol % of simple chiral primary amines **1a**–**f** (Figure 1) and benzoic acid as a cocatalyst indicate the strong effect of hydrostatic pressure on the reaction rate (Table 1). In all cases the yield at atmospheric pressure was very low (≤6%), but under 10 kbar benzylidenoacetone conversion exceeds 70%. The best results in terms of yield and enantioselectivity were observed with 9-amino-9-deoxy-*epi*-cinchonine (**1f**) with 2 equiv of BzOH (entry 6, 95% yield and 83% ee at 10 kbar). In contrast, the reaction under atmospheric pressure at 50 °C affords product **3a** with only a 6% yield and comparable enantioselectivity (82% ee).

For further investigations we selected amine **1f** and studied more attentively the influence of pressure (in the 1 bar–10 kbar range) on the reaction course. The results of these investigations with 2 or 5 mol % of catalyst **1f**·2BzOH

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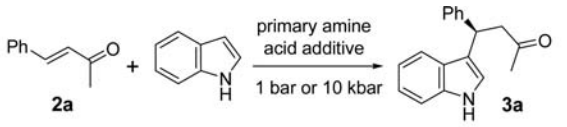
Table 1. Catalyst Screening in the Model Reaction[a]



entry	amine (5 mol %)	benzoic acid (mol %)	yield at 1 bar (%)[b]	10 kbar	
				yield (conv) (%)[b]	ee (%)[c]
1	**1a**	5	3	51 (78)	28 (-)
2	**1b**	10	4	61 (93)	57
3	**1c**	10	3	50 (83)	36
4	**1d**	10	5	33 (77)	52
5	**1e**	10	6	61 (86)	59 (-)
6	**1f**	10	6[d]	**95 (99)**	**83**
7	**1f**	5	3	60 (71)	84

[a] Reaction conditions: **2a** (0.5 mmol, c = 0.5 mol/L), indole (0.6 mmol), amine **1** (5 mol %), benzoic acid (10 or 5 mol %) in toluene (*ca.* 1 mL), 10 kbar, 50 °C, 20 h (or 1 bar, 50 °C, 20 h). [b] Determined by GC analysis with internal standard. [c] Determined by HPLC analysis using Chiralpak AD-H column. [d] 82% ee at 1 bar.

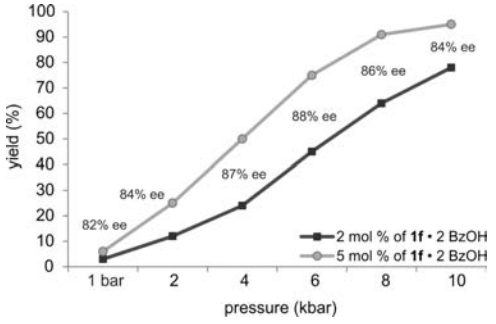


Figure 2. Effect of pressure on the reaction of **2a** with indole.

at 50 °C are shown in Figure 2. Under 6 kbar we observed the highest enantioselectivity (increase from 82 to 88% ee) and yield in the range of 45–75%. Under higher pressure (8–10 kbar) we improved the yield (64–95%) but slightly decreased the enantioselectivity (83–84% ee at 10 kbar).

We also investigated the model reaction with various acid additives and a lower catalyst loading under 10 kbar (Table 2). Use of stronger acids (e.g., salicylic, TCA, and D-*N*-Boc-phenylglycine) increased catalyst activity but resulted in decreased ee (entries 2–4). The reaction can be effectively catalyzed even by 0.5 mol % of **1f** and salicylic acid (1.5 mol %) with a 75% yield and 71% ee (entry 10).[15] The best results in terms of enantioselectivity was obtained with amine **1f** and 2–2.5 equiv of benzoic acid (entries 5 and 6). A higher excess of BzOH increased catalyst activity but slightly decreased enantioselectivity (entries 7–9).

Finally, to demonstrate the scope of the F–C reaction of indole with different simple acyclic *E*-enones and cyclohexenone we applied 9–10 kbar of pressure and 2 mol % of

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Table 2. Optimization of F–C Reaction of Indole with **2a**[a]

entry	**1f** (mol %)	acid (mol %)	temp (°C)	yield at 1 bar (%)[b]	10 kbar	
					yield (conv) (%)[b]	ee (%)[c]
1	5	BzOH (10)	25	< 2	57 (63)	85
2	2	salicylic (4)	25	4	60 (64)	70
3	2	TCA (4)	25	16[d]	59 (66)	56
4	2	Boc-*D*-Phg-OH (4)	50	15[e]	77 (81)	71
5	2	BzOH (4)	50	3 (82)	78 (80)	84
6	2	BzOH (5)	50	-	**88 (89), 85**[f]	**83**
7	2	BzOH (6)	50	-	90 (91)	81
8[f]	2	BzOH (8)	50	5	95 (97)	78
9	1	BzOH (3)	50	-	61 (63)	78
10	0.5	salicylic (1.5)	50	-	74 (75)	71

[a] Reaction conditions: **2a** (c = 0.5 mol/L, 0.5–2 mmol scale), indole (1.2 equiv) in toluene, 10 kbar, 50 °C, 20 h (or 1 bar, 50 °C, 20 h). [b] Determined by GC analysis. [c] Determined by HPLC analysis using AD-H column. [d] 66% ee at 1 bar. [e] 91% ee at 1 bar. [f] Isolated yield.

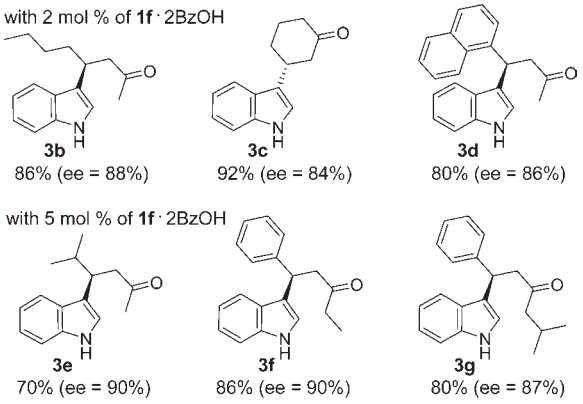


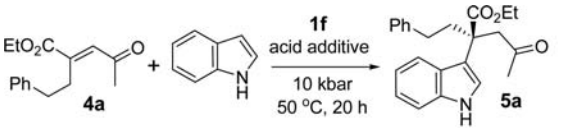
Figure 3. Products of high pressure reaction of indole with simple enones catalyzed by **1f**·2BzOH (isolated yield given).

1f with 2–2.5 equiv of benzoic acid (Figure 3; see products **3b–d**). For more hindered acyclic enones with isopropyl in the β-position and ethyl or isobutyl connected to the carbonyl group we increased the catalyst loading to 5 mol % (products **3e–g**). By comparison, product **3f** was obtained with a 56% yield and 20 mol % of Melchiorre catalyst after 3 days at 70 °C.[7c] Under high-pressure conditions and 5 mol % of **1f**·2BzOH we obtained the product **3f** in 86% yield and 90% ee.

In this project special attention was focused on reactions of indole with various β,β-disubstituted enones, enabling the generation of quaternary stereogenic centers.[9,16] For preliminary studies we chose the reaction of indole with enone *E*-**4a** containing an alkyl and electron-withdrawing group in the β-positions (Table 3). Application of 10 mol % of **1f** and 20 mol % of benzoic acid resulted in a modest

(16) To the best of our knowledge, only one example of an intramolecular organocatalytic F–C reaction of pyrroles with β,β-disubstituted enals has been reported in the literature: Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163.

Table 3. Model F−C Reaction of Indole with β,β-Disubstituted Enone **4a**: Construction of Quaternary Stereogenic Center[a]



entry	amine **1f** (mol %)	acid (20 mol %)	pressure (bar)	yield (conv) (%)[b]	ee (%)[c]
1	10	BzOH	10 000	34 (51)	73
2	10	salicylic	10 000	78 (88), 75[d]	72
3	10	Boc-*D*-Phg-OH	10 000	54 (69)	76
4[e]	10	TCA	10 000	71 (90)	19
5	10	salicylic	1	< 3	-
6	10	salicylic	6 000	45 (57)	74
7	10	salicylic	8 000	62 (70)	75
8	5	salicylic (10)	10 000	69 (79)	66
9	10	salicylic (15)	10 000	55 (70)	74
10	10	salicylic (30)	10 000	87 (97)	61
11[f]	10	salicylic	10 000	48 (75)	44 (-)

[a] Reaction conditions: **4a** (0.3 mmol, c = 0.5 mol/L), indole (0.45 mmol), **1f** (10 mol %), acid (20 mol %) in toluene (*ca.* 0.5 mL), 10 kbar, 50 °C, 20 h. [b] Determined by GC analysis with internal standard. [c] Determined by HPLC analysis using IA column. [d] Isolated yield. [e] 10% yield and 45% ee at 1 bar (50 °C, 20 h); in other cases yield ≤5%. [f] *Z*-isomer of **4a** was used.

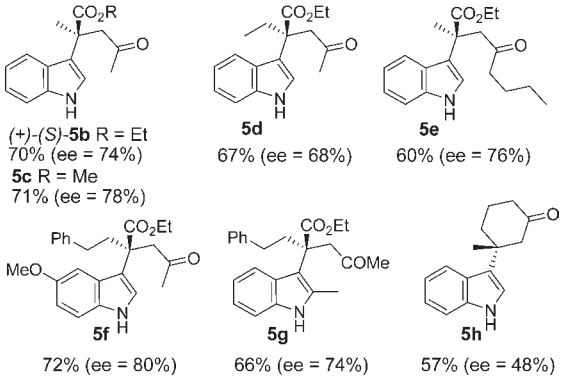
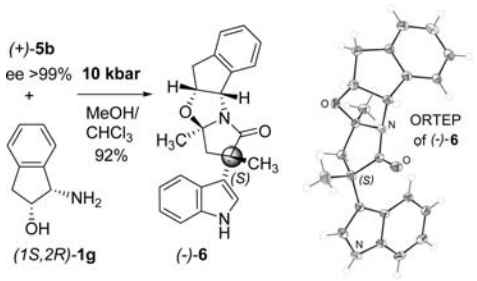


Figure 4. Products of high-pressure organocatalytic indole alkylation with β,β-disubstituted enones (isolated yield given).

yield and promising enantioselectivity (entry 1). A considerably better yield and a similar level of enantioselectivity (~75% ee) were observed with slightly stronger acids, e.g. salicylic or Boc-D-Phg-OH (entries 2 and 3). By comparison, the yield under atmospheric pressure and 50 °C with the same catalytic systems did not exceed 5%. Combining stronger acids and high pressure resulted in a drop in enantioselectivity (e.g., 19% ee with TCA, entry 4). To summarize, the most promising results in terms of yield and enantioselectivity were observed with salicylic acid under 10 kbar (entry 2). The use of isomeric *Z*-**4a** enone resulted in the opposite direction of asymmetric induction and in a moderate yield and ee (entry 11).

The F−C reaction was also tested with other β,β-disubstituted enones and indole in the presence of 10 mol %

Scheme 2. Determination of Absolute Configuration



of **1f** and 20−25 mol % of salicylic acid (or 25 mol % of BzOH for **5g** and **5h**). Combining the high-pressure technique and aminocatalysis works well with various *E*-enones having an alkyl and a carboalkoxy group in the β-position with enantioselectivities up to 80% (Figure 4). The reaction is also possible with β,β-dialkyl substituted enones but with low enantioselectivity. Acceptable yields and moderate enantiomeric excesses were obtained with cyclic 3-methylcyclohexenone (see product **5h**).

Products **5a**−**f** are crystalline, and simple crystallization can improve their optical purity (e.g., for **5b** 96% ee and *ca.* 50% yield after single crystallization; recrystallization ee > 99%). We found that high pressure accelerates Meyers' lactamization of (+)-**5b** with *cis*-aminoindanol **1g** to provide diastereomerically pure compound **6** (Scheme 2). Based on X-ray crystallographic analysis of **6** we assigned the absolute configuration of products **5a**−**g** obtained in the F−C reaction with catalyst **1f**.

In conclusion, we have demonstrated that hydrostatic pressure has a significant effect on the rate of organocatalytic Friedel−Crafts alkylation of indoles with enones proceeding via an iminium activation mode. The reaction with simple enones is effectively catalyzed under 8−10 kbar by 0.5−5 mol % of chiral primary amines derived from cinchona alkaloids and weak acid cocatalysts with good enantioselectivity (83−90%). Such a catalytic system is almost nonactive under atmospheric pressure. We have also presented for the first time promising results of the organocatalytic F−C reaction with prochiral sterically hindered β,β-disubstituted enones, which under high pressure allows for the formation of indole derivatives containing all-carbon quaternary stereogenic centers with good yields and 48−80% enantioselectivity.

Acknowledgment. We are grateful to the Polish National Science Centre (Grant No. N N204 145740) and the Foundation for Polish Science for financial support. Many thanks to Professor Janusz Jurczak (University of Warsaw and Polish Academy of Sciences) for his help and encouragement.

Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.