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Microwave-Assisted Organocatalytic Enantioselective Intramolecular aza-Michael Reaction with α,β-Unsaturated Ketones

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In memory of José Manuel Concellón

Abstract: An organocatalytic enantioselective intramolecular aza-Michael reaction of carbamates bearing conjugated ketones as Michael acceptors is described. By using 9-amino-9-deoxy-*epi*-hydroquinine as the catalyst and pentafluoropropionic acid as a co-catalyst, a series of piperidines, pyrrolidines, and the corresponding benzo-fused derivatives (indolines, isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines) can be obtained in excellent yields and enantioselectivities. In addition, the use of microwave irradiation at 60 °C improves the efficiency of the process giving rise to the final products with comparable yields and enantiomeric excesses. Some mechanistic insights are also considered.

Keywords: aza-Michael reaction · cinchona alkaloids · heterocycles · microwave chemistry · organocatalysis

Introduction

The synthesis of enantiomerically pure compounds plays a pivotal role in medicinal chemistry given that the absolute configuration of many pharmaceutical ingredients has a central importance on their biological activity.[1] During the last decade, together with classical methods based on the use of transition metals and enzymes, organocatalysis has become one of the most exciting and competitive fields in asymmetric catalysis.[2]

The conjugate addition of nitrogen-centered nucleophiles to α,β-unsaturated compounds, the aza-Michael reaction, is one of the simplest and most direct strategies to create C–N bonds and access β-amino carbonyl derivatives. Importantly, the intramolecular version of this reaction allows straightforward access to nitrogen-containing heterocycles. The ubiquitous presence of such heterocycles in biologically active compounds, and their versatility as synthetic intermediates, make them privileged structures; β-amino acids and β-lactams are classic examples.[3]

Unlike Michael additions with carbon nucleophiles, the asymmetric aza-Michael reaction has been explored to a lesser extent, despite being a powerful tool for the synthesis of chiral β-amino carbonyl compounds.[4] Expanding interest in organocatalysis prompted several research groups to study this interesting transformation[5] when faced with the difficulties arising from the amine nature of most of the organocatalysts commonly used. The choice of the amine catalyst and the nitrogen nucleophile is crucial to obtain high levels of enantioselectivity, while avoiding possible competition between them to react with the Michael acceptor. By choosing chiral imidazolidinones as catalysts and *N*-silyloxycarbamates as nucleophiles, MacMillan and co-workers succeeded in the iminium activation of α,β-unsaturated aldehydes for a highly enantioselective aza-Michael reaction.[6] After this work, several examples of organocatalyzed conjugate additions of nitrogen nucleophiles to enals appeared in the literature.[7] However, the participation of enones in the aminocatalyzed aza-Michael reaction remained elusive until three years ago when Deng and co-workers reported a highly enantioselective aza-Michael reaction with α,β-unsaturated ketones catalyzed by a 9-aminoquinine derivative.[8,9] Almost at the same time, Melchiorre and co-workers developed an enantioselective aziridination of enones proceeding through a domino iminium–enamine sequence and catalyzed by a hydroquinine-derived primary amine salt.[7i,10,11] Chiral primary amines have proved to be efficient activators of enones in asymmetric, organocatalyzed conjugate additions. Use of these amines overcomes the difficulties in forming iminium ions between ketones or sterically demanding ac-

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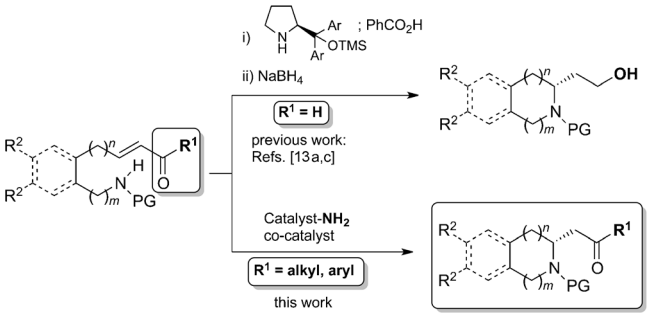
ceptors, and commonly used chiral secondary amine catalysts.[12]

Despite its synthetic potential, the enantioselective intramolecular aza-Michael reaction (IMAMR) still represents a challenging task in organic synthesis, because only a few examples have been reported to date. Most of these examples involve the use of chiral secondary amines that can activate α,β-unsaturated aldehydes by iminium ion formation towards the intramolecular attack of either carbamates or amides as nitrogen nucleophiles.[13] In 2007, we described the first highly enantioselective IMAMR of carbamates bearing a remote α,β-unsaturated aldehyde in the presence of a diarylprolinol derivative as the catalyst.[13c] Few other Michael acceptors, aside from α,β-unsaturated aldehydes, have been employed. For example, Bandini and Umani-Ronchi were able to perform an IMAMR of indoles over α,β-unsaturated esters by using an ammonium salt derived from a cinchona alkaloid as the catalyst.[14] To the best of our knowledge, only two examples with α,β-unsaturated ketones have been reported in the literature. Very recently, You and co-workers reported an enantioselective intramolecular Friedel–Crafts-type aza-Michael addition of indoles to conjugated ketones catalyzed by a chiral phosphoric acid.[15] Soon after, Lu and co-workers disclosed an intramolecular conjugate addition of sulfonamides to alkylidene β-ketoesters in the presence of a bifunctional tertiary-amine/thiourea catalyst.[16] However, these two examples are not general, because they concern particular substrates, typically aromatic ketones as Michael acceptors.

As part of our efforts to develop a general and highly selective methodology for an IMAMR,[13a,c,17] herein we report a highly enantioselective IMAMR of carbamates bearing a remote α,β-unsaturated ketone by using chiral primary amines as catalysts (Scheme 1). Starting enones were assembled through a cross-metathesis reaction of the corresponding unsaturated *N*-protected amines with vinyl ketones in the presence of second-generation Hoveyda–Grubbs catalyst [Cl_2(IMes)Ru=CH(*o*-*i*PrOC_6H_4)] (see the Supporting Information).



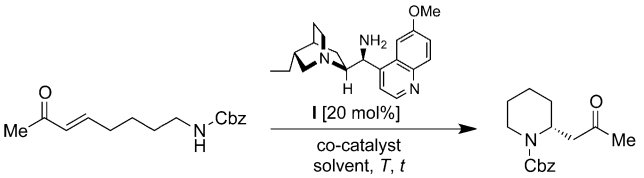
Scheme 1. Organocatalytic asymmetric IMAMR.

Results and Discussion

A model reaction on compound **1a** was used to optimize the reaction conditions and catalysts. First, an array of chiral catalysts, either commercially available or easily prepared in the laboratory, was investigated for the intramolecular conjugate addition of the carbobenzyloxy (Cbz)-protected amine **1a**. Poor enantiomeric excess (*ee*) values were achieved in all cases (see the Supporting Information) except when 9-amino-9-deoxy-*epi*-hydroquinine (**I**) and trifluoroacetic acid as a co-catalyst were used. In this case, the 2-substituted piperidine **2a** was obtained in 88% yield and 91% *ee* (Table 1, entry 1). Consequently, the cinchona alkaloid derivative **I** was chosen as the catalyst for this transformation.

Next, we evaluated the effect of varying the acid co-catalyst, solvent, and temperature in the same model reaction of **1a**. As shown in Table 1, reducing the co-catalyst loading from 40 to 20 mol% was found to be beneficial for both

Table 1. Optimization of the IMAMR conditions (co-catalyst, solvent, temperature and time) for the synthesis of piperidine **2a** by using catalyst **I** (9-amino-9-deoxy-*epi*-hydroquinine).[a]



1a **2a**

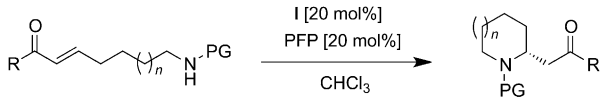
	Co-catalyst [mol%][b]	Solvent	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	TFA (40)	$CHCl_3$	25	15	88	91
2	TFA (20)	$CHCl_3$	25	15	91	95
3	TFA (10)	$CHCl_3$	25	15	48	91
4	TFA (20)	$CHCl_3$	10	24	80	97
5	TFA (20)	$CHCl_3$	4	24	71	95
6	TFA (20)	THF	25	15	78	97
7	TFA (20)	Et_2O	25	8	72	97
8	TFA (20)	DCM	25	15	88	93
9	TFA (20)	toluene	25	15	91	84
10	TFA (20)	*i*PrOH	25	24	90	47
11	NCLP (40)	$CHCl_3$	25	72	48	87
12	CSA (20)	$CHCl_3$	25	24	60	69
13	BTFMBA (40)	$CHCl_3$	25	48	85	85
14	*p*-NBA (40)	$CHCl_3$	25	15	76	80
15	PFP (20)	$CHCl_3$	25	15	93	96
16	DNBS (20)	$CHCl_3$	25	72	64	52
17[e]	TFA (20)	$CHCl_3$	80	0.5	91	90
18[e]	TFA (20)	$CHCl_3$	60	1	93	95
19[e]	PFP (20)	$CHCl_3$	60	1	94	95
20[e]	TFA (20)	THF	60	1	60	90

[a] Reactions were carried out with **1a** (0.07 mmol) and catalyst **I** (20 mol%) in the specified solvent (0.1 M), time and temperature. [b] TFA = trifluoroacetic acid, NCLP = *N*-Cbz-L-phenylalanine, CSA = (+)-10-camphorsulfonic acid, BTFMBA = 3,5-bis(trifluoromethyl)benzoic acid, *p*-NBA = 4-nitrobenzoic acid, PFP = pentafluoropropionic acid, DNBS = 2,4-dinitrobenzenesulfonic acid. [c] Yields are of isolated compounds after flash chromatography. [d] Determined by HPLC on a chiral stationary phase (Chiracel OD-H); see Supporting Information for details. [e] Heating by means of microwave irradiation.

yield and enantioselectivity (Table 1, entry 1 versus 2), whereas a further decrease to 10 mol% led to a considerable drop in the yield (48%) of the product albeit maintaining a good *ee* (91%) (Table 1, entry 3). Lowering the temperature resulted in a slight rise in enantioselectivity (97% *ee* at 10°C), but a bigger decrease in yield (80%) (Table 1, entries 4 and 5).[18] Excellent asymmetric induction was observed when the reaction was carried out in THF, diethyl ether, and also dichloromethane (Table 1, entries 6–8), whereas the use of toluene and 2-propanol led to a significant drop in the *ee* values (Table 1, entries 9 and 10). In all these cases yields were lower than that of the reaction performed in chloroform. The co-catalyst required in the reaction was also evaluated.[19] Among different acid additives screened (Table 1, entries 11–16), pentafluoropropionic acid (PFP) was the best and afforded the desired product in 93% yield and 96% *ee* (Table 1, entry 15). The use of a chiral co-catalyst, such as *N*-Cbz-L-phenylalanine, had a negative effect on both the enantioselectivity and the yield of the reaction (Table 1, entry 11). Finally, we studied the reaction under microwave irradiation.[20] This type of activation has been described recently in different types of organocatalyzed asymmetric reactions with the aim of shortening reaction times and catalyst loadings.[21] We found that microwave irradiation had a positive effect on the reaction time and retained very good yields and selectivities. When the reaction was performed in chloroform at 80°C, a 90% *ee* and a 91% yield were achieved in only 30 min (Table 1, entry 17). Extending the reaction time to one hour allowed us to obtain excellent levels of enantioselectivity and excellent yields at 60°C in the presence of either TFA or PFP as co-catalysts (Table 1, entries 18 and 19). However, the reaction in THF was less efficient both in yield and selectivity relative to the results obtained at room temperature (Table 1, entry 20 versus 6). To the best of our knowledge this is the first report of a microwave accelerating effect in a Michael-type reaction catalyzed by a cinchona alkaloid derivative.

Once reaction conditions had been optimized, we extended this methodology to other carbamates bearing a remote α,β-unsaturated ketone. For the optimized conditions we choose catalyst **I** in the presence of PFP as co-catalyst. Reactions were carried out in chloroform both at room temperature and under microwave irradiation at 60°C. The results are summarized in Table 2. We found that the nitrogen protecting group (*tert*-butoxycarbonyl (Boc) or Cbz) had no influence on the selectivity or the yield of the final product **2a**/**2b** (Table 1, entry 15 versus Table 2, entry 1). The process was highly efficient for both propyl- and pentyl-substituted ketones **1c** and **1d**, and afforded products **2c** and **2d**, respectively, in 98% *ee* and excellent yields (Table 2, entries 2 and 3). When the starting substrate was an aromatic ketone (**1e**, R = Ph), longer reaction times were needed to obtain an acceptable yield, although the enantioselectivity was very good (93% *ee*) (Table 2, entry 4). The formation of a five-membered ring was less efficient in terms of yield and selectivity; the corresponding pyrrolidine **2f** was obtained in 80% yield and 82% *ee* (Table 2, entry 5). When this reaction was performed at 60°C under microwave irradiation, comparable results of yield and enantioselectivity were achieved. (Table 2, entries 6–10).

Table 2. Substrate scope of the organocatalytic IMAMR. Synthesis of 2-substituted piperidines and pyrrolidines.[a]



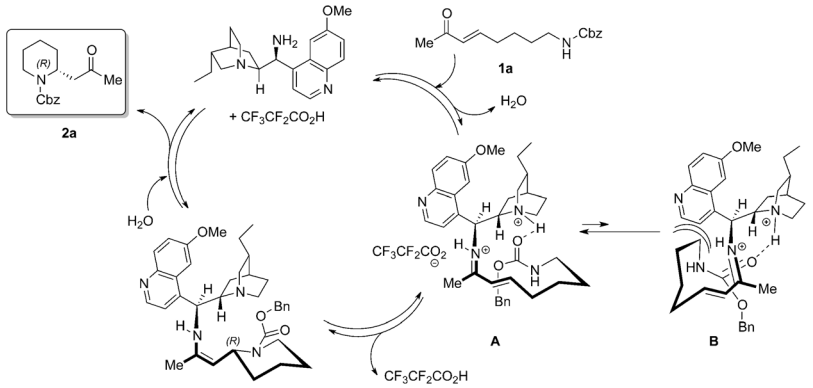
1 **2**

	n	**1**	PG	R	*T* [°C]	*t* [h]	**2**	Yield [%][b]	*ee* [%][c]
1	1	**1b**	Boc	Me	25	15	**2b**	92	93
2	1	**1c**	Cbz	*n*Pr	25	15	**2c**	95	98
3	1	**1d**	Cbz	*n*Pn	25	15	**2d**	92	98
4	1	**1e**	Cbz	Ph	25	240	**2e**	58	93
5	0	**1f**	Cbz	Me	25	24	**2f**	80	82
6[d]	1	**1b**	Boc	Me	60	1	**2b**	97	90
7[d]	1	**1c**	Cbz	*n*Pr	60	1	**2c**	94	96
8[d]	1	**1d**	Cbz	*n*Pn	60	1	**2d**	89	97
9[d]	1	**1e**	Cbz	Ph	60	4	**2e**	75	84
10[d]	0	**1f**	Cbz	Me	60	1	**2f**	85	79

[a] Reactions were carried out with **1** (0.15 mmol), catalyst **I** (20 mol%) and pentafluoropropionic acid (PFP) (20 mol%) in chloroform (0.1 M). [b] Yields are of isolated compounds after flash chromatography. [c] Determined by HPLC on a chiral stationary phase (Chiracel OD-H); see the Supporting Information for details. [d] Heating by means of microwave irradiation.

The absolute configuration of the newly created stereocenter was determined to be *R* by comparing the optical rotation values of compounds **2a**–**2d** and **2f** with those reported in the literature (see the Supporting Information).[22] Identical stereochemical outcomes were assumed for all other substrates. It is worth noting that piperidines **2a** and **2b** are direct precursors of the alkaloid pelletierine[22a–d,23] requiring only removal of the nitrogen protecting group. Likewise, starting from compounds **2c** and **2d**, several members of the tetraponerine[22e,f,24] family could be synthesized in a straightforward manner. Additionally, the reduction of the Cbz group in **2f** would lead to the skeleton of the pyrrolidine alkaloid hygrine.[22g,25]

The mechanism commonly invoked to rationalize the organocatalytic conjugate additions of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds involves activation of the Michael acceptor by the catalyst through the formation of an iminium ion, thereby facilitating the intramolecular addition of the nucleophile to the β-carbon. We propose a possible mechanism that accounts for the *R* stereochemical assignment mentioned above. First, the primary amine catalyst would react with the enone **1a** to form an iminium intermediate under the acid conditions. Indeed, no reaction took place in the absence of acid.[19] Simultaneously, the quinuclidine nitrogen would be protonated and a hydrogen-bond interaction would be established with the carbamate carbonyl oxygen. In this conformation, the attack of the nitrogen nucleophile would take place onto the *Re* face of the less sterically constrained (*E*)-iminium transition state **A** to furnish the aza-Michael product (*R*)-**2a** after hydrolysis (Scheme 2).[26]



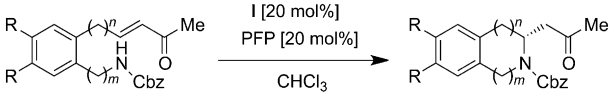
Scheme 2. Plausible mechanistic pathway and transition state of the intramolecular aza-Michael reaction.

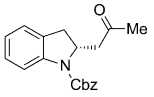
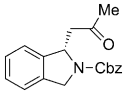
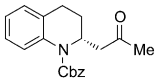
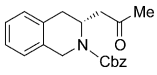
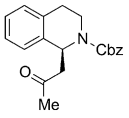
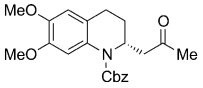
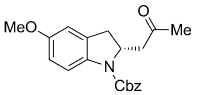
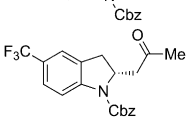
The extension of this protocol to the synthesis of several benzo-fused heterocycles was examined next. The optimal conditions for the IMAMR were applied to conveniently functionalized aniline and benzylamine substrates **3** to obtain enantiomerically enriched indolines, isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines. The pyrrolidine benzo-fused products **4a** and **4b** were obtained in excellent yields and *ee* values either at room temperature or under microwave heating at 60 °C (Table 3, entries 1 and 2). Even better results were achieved in the preparation of two tetrahydroisoquinolines **4d** and **4e** (Table 3, entries 4 and 5). The synthesis of the tetrahydroquinoline derivative **4c** proceeded with lower enantioselectivity (88 and 86 % *ee* at room temperature and 60 °C, respectively; Table 3, entry 3). However, this *ee* value, as well as the yield of the aza-Michael product, improved when two methoxy groups were attached to the benzene ring (Table 3, entry 6). This is probably due to the enhanced nitrogen nucleophilicity making the conjugate addition faster, thus avoiding alternative reaction pathways promoted by protons liberated during the process (Brønsted acid catalysis). This nonselective process would compete with iminium activation by the organocatalyst and decrease the enantioselectivity of the overall reaction. This effect was proved by comparing the results achieved in the synthesis of indolines **4g** and **4h**, with an electron-donating and an electron-withdrawing group, respectively. Although **4g** was obtained in good yield and enantioselectivity (Table 3, entry 7), the aza-Michael addition on compound **3h** bearing a trifluoromethyl moiety was less efficient (Table 3, entry 8). Both at room temperature and under microwave heating, these reactions proceeded in lower yield, and significantly diminished *ee*, possibly due to electronic issues related to the nitrogen nucleophilicity, as indicated above.

Conclusion

In conclusion, a general protocol for a highly enantioselective organocatalytic IMAMR has been developed. The combination of 9-amino-9-deoxy-*epi*-hydroquinine and pentafluoropropionic acid is an efficient catalytic system for the intramolecular conjugate addition of carbamates to α,β-unsaturated ketones as Michael acceptors. We were able to obtain 2-substituted piperidines, pyrrolidines, and several benzo-fused nitrogen heterocycles with excellent yields and enantioselectivities. Interestingly, the cyclization step under microwave irradiation led to comparable results in terms of yield and *ee* to those obtained at room temperature. This is, as far as we know, the first report of a microwave accelerating effect in a Michael-type reaction catalyzed by a cinchona alkaloid derivative.

Table 3. Substrate scope of the organocatalytic IMAMR. Synthesis of benzo-fused heterocycles.[a]



	4		Yield [%][b,d]	*ee* [%][c,d]	Yield [%][b,e]	*ee* [%][c,e]
1		**4a**	90	93	83	91
2		**4b**	96	93	91	92
3		**4c**	80	88	93	86
4		**4d**	97	97	95	97
5		**4e**	94	98	91	96
6		**4f**	95	91	92	87
7		**4g**	85	92	81	90
8		**4h**	71	68	68	63

[a] Reactions were carried out with 0.15 mmol of starting substrate, 20 mol % of catalyst **I** and pentafluoropropionic acid (PFP) (20 mol %) in chloroform (0.1 M). [b] All yields are of isolated compounds after flash chromatography. [c] Enantiomeric excesses were determined by HPLC on a chiral stationary phase (Chiracel OD-H); see the Supporting Information for details. [d] At room temperature for 20 h. [e] Microwave irradiation at 60 °C for 1 h.

Experimental Section

General procedure for the preparation of N-protected amines 1 and 3: The corresponding conjugated ketone (3.0 equiv) and Hoveyda–Grubbs second-generation catalyst (5 mol%) were added to a solution of *N*-protected amine (1.0 equiv) in CH_2Cl_2 (0.1 M) under nitrogen atmosphere. The resulting solution was stirred for 12 h at room temperature before the solvent was removed and the crude mixture purified by flash chromatography with hexanes and ethyl acetate as eluents.

(*E*)-8-Benzyloxycarbonylamino-3-octen-2-one (1a): By means of the general procedure described above, **1a** (212 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-5-hexenamine as a pale yellow oil in 90% yield after flash chromatography with hexanes/ethyl acetate 3:1 as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.53 (m, 4H), 2.15–2.26 (m, 2H), 2.21 (s, 3H), 3.15–3.21 (m, 2H), 4.94 (brs, 1H), 5.07 (s, 2H), 6.04 (d, J = 16.2 Hz, 1H), 6.70–6.80 (m, 1H), 7.28–7.35 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.0 (CH_2), 26.8 (CH_3), 29.4 (CH_2), 31.9 (CH_2), 40.6 (CH_2), 66.5 (CH_2), 128.0 (CH), 128.2 (CH), 128.4 (CH), 131.4 (CH) 136.5 (C), 147.6 (CH), 156.3 (C), 198.6 ppm (C); HRMS (EI): *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521 [M^+]; found: 275.1519.

(*E*)-5-(2-Benzyloxycarbonylamino)phenyl-3-penten-2-one (3a): By means of the general procedure described above, **3a** (210 mg) was obtained from methyl vinyl ketone and *N*-benzyloxycarbonyl-2-allylaniline as a pale brown solid in 91% yield after flash chromatography with hexanes/ethyl acetate 3:1 as eluent. M.p. 47–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.40 (d, J = 6.3 Hz, 2H), 5.07 (s, 2H), 5.88 (dt, J = 15.9, 1.4 Hz, 1H), 6.55 (brs, 1H), 6.71–6.81 (m, 1H), 7.03 (d, J = 4.1 Hz, 2H), 7.15–7.28 (m, 6H), 7.56 ppm (d, J = 7.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.0 (CH_3), 34.4 (CH_2), 67.0 (CH_2), 125.4 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 130.1 (CH), 131.9 (CH), 135.4 (C), 135.9 (C), 136.5 (C), 144.6 (CH), 154.0 (C), 198.0 ppm (C); HRMS (EI): *m/z* calcd for $C_{19}H_{19}NO_3$: 309.1365 [M^+]; found: 309.1363.

General procedure for the organocatalytic IMAMR reaction at room temperature (A) and under microwave irradiation (B): Preparation of 2-substituted nitrogen heterocycles **2** and **4**. A) In a 10 mL round bottomed flask, α,β-unsaturated ketones (**1** or **3**) (1.0 equiv) were dissolved in chloroform (0.1 M). A mixture of catalyst **I** (20 mol%) and pentafluoropropionic acid (PFP) (20 mol%, added from a freshly prepared stock solution in chloroform) was added and the resulting solution was stirred at room temperature. After 12–96 h, the crude reaction mixture was subjected to flash chromatography on silica gel by using mixtures of *n*-hexanes and ethyl acetate as eluents to afford the corresponding heterocycles **2** and **4**. The enantiomeric ratios were determined by means of HPLC analysis with a Chiracel OD-H column (25 cm × 0.46 cm). B) The corresponding α,β-unsaturated ketones (**1** or **3**) (1.0 equiv) were dissolved in chloroform (0.1 M) in a microwave vial and then catalyst **I** (20 mol%) and PFP (20 mol%, added from a freshly prepared stock solution in $CHCl_3$) were added successively. The vial was sealed and the corresponding solution was heated under microwave irradiation at 60 °C for 1–4 h. After this time, the crude reaction mixture was purified by means of flash chromatography on silica gel by using the appropriate eluent.

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)piperidine (2a): By means of the general procedure described above, **2a** (38 mg) was obtained as a colorless oil from **1a** in 93% yield and 96% *ee* at room temperature [94% yield (39 mg) and 95% *ee* at 60 °C under microwave irradiation]. The spectroscopic data are in agreement with those previously reported in the literature.[22b] The *ee* values were determined by means of HPLC analysis by using a Chiracel OD-H column (hexane: isopropanol 95:5). Flow rate = 1.0 mL min^{-1}, t_{major} = 14.1 min, t_{minor} = 14.8 min; $[\alpha]_D^{25}$ = +11.6 (c = 1.0 in $CHCl_3$); [lit. $[\alpha]_D^{25}$ = +10.2 (c = 2.5 in $CHCl_3$)].[22b]

(2*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)indoline (4a): By means of the general procedure described above, **4a** (42 mg) was obtained as colorless oil from **3a** in 90% yield and 93% *ee* at room temperature [83% yield (38 mg) and 91% *ee* at 60 °C under microwave irradiation]. The *ee* values were determined by means of HPLC analysis by using a Chiracel OD-H column (hexane:isopropanol 95:5). Flow rate = 1.0 mL min^{-1}, t_{major} = 19.4 min, t_{minor} = 15.8 min; $[\alpha]_D^{25}$ = +82.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.61–2.73 (m, 2H), 3.00–3.04 (m, 1H), 3.45 (dd, J = 16.6, 9.6 Hz, 1H), 4.83–4.89 (m, 1H), 5.29 (s, 2H), 6.94–6.99 (m, 1H), 7.12–7.17 (m, 2H), 7.33–7.41 (m, 5H), 7.70–7.81 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.4 (CH_3), 34.5 (CH_2), 48.2 (CH_2), 55.6 (CH) 67.3 (CH_2), 115.4 (CH), 123.1 (CH), 125.1 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (C), 136.1 (C), 136.7 (C), 161.0 (C), 206.7 ppm (C); IR (film): $\tilde{\nu}$ = 3489, 2884, 1707, 1600, 1482, 1402, 1128, 751 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{19}H_{19}NO_3$: 309.1365 [M^+]; found: 309.1369.

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