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Organocatalytic synthesis of α-quaternary amino acid derivatives via aza-Friedel–Crafts alkylation of indoles with simple α-amidoacrylates

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ABSTRACT

The first (organo)catalytic method for regio- and chemoselective aza-Friedel–Crafts (FC) alkylation of indoles and pyrroles with commercially available methyl α-acetamidoacrylates has been discovered. It minimizes/eliminates common competing reactions that occur due to the high and multiatom-nucleophilic character of indole and pyrrole. Diverse quaternary α-amino acids were successfully prepared in good yield and high selectivity using low catalyst loading. The enantioselective variant using BINOL-derived phosphoric acids was also explored with indole providing the desired F–C alkylation product with moderate enantioselectivities.

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1. Introduction

The construction of quaternary stereogenic centers is an ongoing synthetic challenge.[1] In fact, creating these complex fragments rapidly and selectively is a difficult task because of the inherent steric bias encountered in the C–C bond-forming event. Also, the development of efficient chemical and enzymatic methods for the synthesis of unnatural amino acids, in particular quaternary α-amino acids, is highly desirable. Quaternary α-amino acids, also called α,α-disubstituted amino acids, have attracted the interest of organic chemists due to their biological importance. For example, when incorporated into peptides, α,α-disubstituted α-amino acids confer increased stability under physiological conditions and stabilize secondary structure motifs.[2] They also have relevance in natural product total synthesis.[3] Finally, unnatural α-aryl-α-alkyl α-amino acid derivatives have shown strong inhibitory effects on aldose reductases, a potential target for the treatment of various diabetes-related diseases.[4] Although there is now a wide range of methodologies for the synthesis of these compounds,[5] few of these methods are useful for the catalytic synthesis of α-alkyl-α-aryl amino acids.

The catalytic Friedel–Crafts (FC) reaction constitutes an important C–C bond-forming transformation,[6] and several examples with different electrophiles catalyzed by hydrogen donor catalysts, in particular Brønsted acid BINOL-derived phosphoric acids, have been published.[7] Although a variety of electrophilic systems, such as activated trifluoro-carbonyl compounds,[8] α,β-unsaturated carbonyl derivatives,[9] aldimines,[10] and nitroolefins[11] catalyzed by Brønsted acids are available for such purposes, some notable exceptions can be identified, such as α-amidoacrylates. They are poorly reactive with arenes under various conditions but are important building blocks for organic and medicinal research. The potential value of α-amidoacrylates or *N*-acyl-α,β-dehydroamino esters (DHA) in synthetic chemistry is derived mainly from their ready availability and the unique reactivity of their double bonds. The presence of acylamino and ester groups on the same carbon of the double bond facilitates nucleophilic attack at the α position (α-amidoalkylation) after tautomerization to *N*-acyl ketimines,[12] or the β position (Michael-type reactions) giving in both cases α-amino acids that can be readily transformed into a range of different functionalities, or resolved by asymmetric hydrolysis using α-chymotrypsin or carboxypeptidase A.[13] As an extension of our contributions in the field of indolylamino acid synthesis using stoichiometric amounts of transition metal salts,[14] we investigated the more challenging and appealing (organo)catalytic FC alkylation of indoles and pyrroles with α-amidoacrylates. Here, we present the first Brønsted acid catalyzed sequential tautomerization and aminoalkylation of electron-rich arenes with commercially available *N*-acetylated-dehydroalanine methyl ester giving quaternary α-amino acids in good yields (Scheme 1).[15] To the best of our knowledge, no examples of catalytic, regio-, and chemoselective α-amidoalkylation of heteroaromatic compounds with DHA have been previously disclosed.

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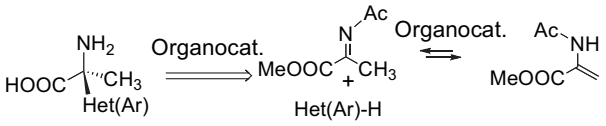


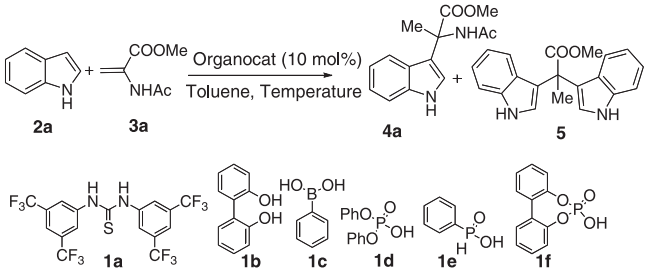
Scheme 1. Organocatalyzed C–C bond formation approach to α-methyl α-hetero (aryl) amino acids via FC alkylation of ketimine.

2. Results and discussion

The initial evaluation of the proposed FC alkylation was performed with indole (**2a**),[16] methyl α-acetamidoacrylate (**3a**), and several classes of established hydrogen-bonding catalysts in toluene (Table 1).

The newly designed reaction did not proceed in the absence of catalyst. Stirring the two reagents at room temperature or refluxing in toluene for almost three days resulted in no detectable quantities of the desired product **4a** (entries 1 and 2). While thiourea **1a** and diol **1b** did not induce FC alkylation (entries 3 and 4), stronger acids, such as trifluoromethanesulfonic acid (TfOH) and 2,4-dinitrobenzenesulfonic acid (DNSA) did indeed provide the desired alkylation adduct, albeit in low yields (entries 5–8). Under these strongly acidic conditions, the symmetrical bisindolylmethane derivative **5** was the major product.[17] Most likely, this product was obtained by elimination of acetamide and reaction with a second equivalent of indole via highly electrophilic alkylideneindoleninium ions. In addition, bisindolyl product **5** predominated upon using other Brønsted acids and it was the only product obtained when trifluoromethanesulfonimide (Tf_2NH) was used (entries 9–10). Elimination of acetamide occurred to a lesser extent when the reaction was performed at lower temperature and increasing amounts of *N*-acetyl-α,β-didehydroalanine methyl ester was used. The desired product was obtained in poor yields when phenyl boronic acid (**1c**) or diphenyl phosphate (**1d**) were used as the catalysts (entries 11 and 12). Phenyl phosphinic acid[18] (**1e**) could also promote this reaction but with low conversion (entry 13). A large screen of Brønsted acids (**1**) identified phosphoric acid **1f** as the best catalyst (entry 16). Lowering the temperature made the reaction sluggish, but favorably suppressed the side reaction. Higher conversion of **4a** was achieved by the prolonged reaction time with **1f** (5 mol %).[19] Importantly, preliminary studies have revealed that water, generated in the initial condensation step, has a deleterious impact on both iminium formation and the FC alkylation step. Therefore, the introduction of Na_2SO_4 was found to be critical to achieve useful reaction rates and selectivities. In general, the presence of molecular sieves is detrimental to the reaction, which resulted in sharp decrease in reaction rate and yield. The effect of other solvents, such as 1,2-dichloroethane, acetonitrile, ethyl acetate, and methyl *tert*-butyl ether also was examined under the conditions shown but always lower yield or no reaction was observed. Having established the optimal conditions for hydrogen bond catalysis, we next examined the scope of the indole component in this unprecedented organocatalytic alkylation. As shown in Table 2, various substituted indole derivatives **2a**–**o** were successfully coupled. Use of 5-halogenated indole derivatives afforded the products in good yields. However, in the case of 5-chloroindole (**2c**), the yield was slightly lower (entry 3) as compared to the 5-fluoro- or 5-bromo-substituted indoles (68% and 63%, respectively, entries 2 and 4). Electron-rich indoles also reacted readily. 5-Methoxy- and 5-methyl-indole furnished the desired products in good yields (entries 10 and 11). Worthy of note is that the use of 3-methyl-substitued indole[20] provided clean formation

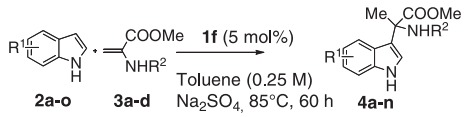
Table 1
Identification of an efficient catalyst **1** and reaction conditions for the FC aminoalkylation of indole (**2a**) with DHA (**3a**)



Entry[a]	Catalyst	Time (h)	Temp(°C)	Conversion[b]	Yield **4a** (%)[c]
1	—	60	25	—	—
2	—	60	110	—	—
3	**1a**	60	110	—	—
4	**1b**	60	110	—	—
5	TfOH[d]	2	110	>90	9
6	TfOH[d]	4	70	>90	7
7	TfOH[d]	16	RT	—	—
8	DNSA[e]	2	110	>90	13
9	Tf_2NH[f]	2	110	>90	Traces
10	Tf_2NH[f]	2	79	>90	Traces
11	**1c**	16	110	>90	27
12	**1d**	16	110	>90	31
13	**1e**	16	110	<50	21
14	**1f**	16	110	>90	38
15	**1f**	60	85	>90	47
16[g]	**1f**	60	85	>90	72
17[h]	**1f**	60	85	>90	22

[a] Reaction conditions: **2a** (0.6 mmol), **3a** (0.66 mmol), Na_2SO_4 (1.06 mmol), and **1** (0.06 mmol) in toluene (0.25 M).
[b] Determined by HPLC-MS.
[c] Yield after flash chromatography.
[d] TfOH=trifluoromethanesulfonic acid.
[e] DNSA=2,4-dinitrobenzenesulfonic acid.
[f] Tf_2NH=trifluoromethanesulfonimide.
[g] Using 5 mol % of catalyst.
[h] Reaction carried out without Na_2SO_4.

Table 2
Phosphoric acid **1f** catalyzed FC alkylation of indoles (**2a**–**q**) and DHA (**3a**–**d**)



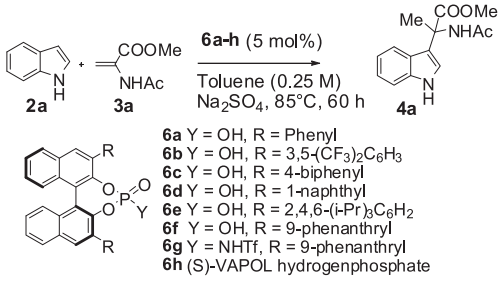
Entry[a]	R^1	R^2	Yield (%)[b]	Product
1	H (**2a**)	Ac (**3a**)	63	**4a**
2	5-F (**2b**)	Ac (**3a**)	68	**4b**
3	5-Cl (**2c**)	Ac (**3a**)	47	**4c**
4	5-Br (**2d**)	Ac (**3a**)	63	**4d**
5	4-Br (**2e**)	Ac (**3a**)	58	**4e**
6	5-NO_2 (**2f**)	Ac (**3a**)	76	**4f**
7	5-CN (**2g**)	Ac (**3a**)	68	**4g**
8	5-COOMe (**2h**)	Ac (**3a**)	65	**4h**
9	5-B(pin) (**2i**)	Ac (**3a**)	54	**4i**
10	5-OMe (**2j**)	Ac (**3a**)	76	**4j**
11	5-Me (**2k**)	Ac (**3a**)	57	**4k**
12	2-Me (**2l**)	Ac (**3a**)	60	**4l**
13	3-Me (**2m**)	Ac (**3a**)	31[c]	**4m**
14	6-OMe (**2n**)	Ac (**3a**)	43	**4n**
15	H (**2o**)[d]	Ac (**3a**)	NR[e]	—
16	H (**2a**)	Bz (**3b**)	NR[e]	—
17	H (**2a**)	Cbz (**3c**)	NR[e]	—
18	H (**2a**)	Ac(**3d**)[f]	NR[e]	—
19	(**2p**)[g]	Ac (**3a**)	35	**4p**
20	(**2q**)[h]	Ac (**3a**)	33	**4q**

[a] Reaction conditions: **2** (0.6 mmol), **3** (0.66 mmol), **1** (0.03 mmol), and Na_2SO_4 (1.06 mmol) in toluene (0.25 M) at 85 °C for 60 h.
[b] Yield after flash chromatography.
[c] Formation of methyl 2-acetamido-2-(3-methyl-1*H*-indol-2-yl)propanoate.
[d] *N*-methyl indole.
[e] No reaction.
[f] *N*-methyl acetamidoacrylate.
[g] *N*-Me-pyrrole.
[h] Dihydroindole.

of the alkylated product in the 2-position (entry 13), with no troublesome reaction or indole annulations with dearomatization of the indole nucleus. On the other hand, the electrophilic alkylation of indole derivatives was initially selective (at the C3 position) and then the C2-isomer was formed from 1,2-migration of the C3-isomer. The results listed in (Table 2 entries 6–9) represent one of the strong points of this methodology. In fact, electron-poor indoles are generally recognized as FC-reluctant.[21] On the contrary, the present phosphoric acid catalyzed methodology allowed electron-deficient indoles to be readily transformed into the corresponding α-methyl-α-indolylamino acids in moderate to good yields.[22] *N*-methylindole (**2o**) proved to be inert under optimal reaction conditions (entry 15), in accordance with findings by others[15c] regarding the existence of a key N–H of the indole to interact with the phosphoric acid in the present FC-alkylation methodology. Finally, we tried other *N*-acylamido acrylates in the reaction to evaluate their reactivity. Other amino protecting groups, such as benzoyl (**3b**) or benzyloxycarbonyl (**3c**) failed to provide the desired product (entries 16 and 17). In addition, the N–H group of the amide seems to be crucial for the reactivity, since tertiary *N*-methylated **3d** did not react.[15c] Also, we investigated other suitable substrates for the present phosphoric acid catalyzed FC alkylation methodology with DHA to give α,α-disubstituted α-amino esters.

Several heteroarenes and electron-rich benzene derivatives were tested with DHA **3a**, but only the more reactive *N*-Me-pyrrole (**2p**) and dihydroindole (**2q**) were suitable substrates in this reaction (see Experimental section and Supplementary data). Less activated arenes like dimethoxybenzene and trimethoxybenzene as well as different furans, such as methylfurane and methoxyfurane did not afford the desired coupling products.[23] Our success in the organocatalytic reactions of indoles with dehydroamino acids by sequential tautomerization–alkylation prompted us to extend this methodology to catalytic asymmetric reactions (Table 3). A series of chiral phosphoric acids (**6a**–**h**) with different substituents at the 3,3′-positions of the binaphthyl ring were prepared and tested in the reaction of indole (**2a**) and *N*-acetylated-dehydroalanine methyl ester (**3a**). Although there are several reported examples of BINOL-phosphoric acid catalyzed enantioselective alkylations of indoles with aldimines[10] and one very recent example with the more reactive trifluoromethyl ketimines,[24] only moderate to good enantiomeric excess values have been obtained. The sterically congested phosphoric acid catalysts were found to be crucial for achieving enantioselectivity, with the catalyst **6f** bearing bulky 9-phenanthryl at the 3,3′-positions being the most enantioselective (entry 7). With the more acidic *N*-triflyl phosphoramide derivative **6g**, the yield of the FC product was only moderate (19%) due to hydrolysis of the enamide substrate and increasing formation of bisindolyl derivatives. However, it represents the first example of catalyzed asymmetric FC alkylation of this class on unreactive pyruvate-derived ketimine substrates. The low reactivity of ketimines, which often exist as a mixture of *E* and *Z* isomers, and the difficulty in differentiating the two substituents on the prochiral ketimine carbon are the main obstacles that make the development of a catalytic asymmetric addition of simple ketimines formidably challenging.[25] To date, a non-stereocontrolled catalytic FC reaction of simple ketimines has yet to be reported. *E*/*Z* relative stability of the imine substrate is an important factor for deciding the stereochemical outcome of the reaction, since reaction with the *Z* conformer yields the opposite enantiomer with respect to the *E* conformer. The little difference in steric effect between methyl and carboxymethyl groups (A-values of 1.7 and 1.3, respectively) do not allow the predominant formation of one imine conformer over the other. *E*/*Z* isomerization of imines would be a slow process if it were to occur via a planar inversion.[26] However, as the first step of the reaction is tautomerization of the acyl enamine to the *N*-acyl imine, both *E* and *Z* imine conformers can be readily obtained. This, combined with the relatively high temperature needed to have good reaction conversion, does not allow energy differences among the different diastereomeric transition states.

Table 3
Chiral Brønsted acid catalyzed asymmetric FC reaction of **2a** and **3a**



Entry[a]	Catalyst	Yield (%)[b]	er[c]
1	**6a**	57	58:42
2	**6b**	56	72:28
3	**6c**	52	68:32
4	**6d**	60	77:23
5	**6e**	77	73:27
6	**6f**	64	78:22
7[d]	**6f**	20	83:17
8	**6g**	19	64:36
9[e]	**6g**	NR[f]	—
10	**6h**	NR[f]	—

[a] Reaction conditions: **2a** (0.6 mmol), **3a** (0.66 mmol), **6** (0.03 mmol), and Na_2SO_4 (1.06 mmol) in toluene (0.25 M) at 85 °C for 60 h.
[b] Yield after flash chromatography.
[c] Determined by chiral HPLC on a Chiralpak AD-H column.
[d] Reaction was run at 60 °C.
[e] Reaction was run at rt.
[f] No reaction.

3. Conclusion

We have disclosed the first Brønsted acid catalyzed direct FC-type addition reaction between indoles and pyrroles with DHA where phosphoric acids were proven to be highly effective at catalyzing this transformation. High levels of reaction efficiency and perfect regio- and chemselectivity on both arenes and DHA were obtained. The effects of the nature of the substituents both on the indoles and on the DHA components were analyzed. Outstanding compatibility of the functional groups OMe, Br, Cl, CN, B(pinacolate), COOMe, and NO_2 is noteworthy. In addition, this methodology might employ easily available chiral catalysts and provides enantioenriched α-quaternary amino acids. We speculate that the moderate enantioselectivity can be attributed to the low intrinsic electrophilicity of ketimines, combined with the small steric difference between the two groups flanking the azacarbonyl moiety. Therefore, we conclude that a novel, operationally simple, metal-free process and, moreover, catalytic method for the synthesis of enantioenriched α-quaternary amino acids has been established. Our current investigations are focused on expansion of the general scope and synthetic applications for obtaining bioactive molecules by this new methodology.

4. Experimental section

4.1. General experimental procedure

All reactions were performed in round-bottom flasks. Column chromatography purifications were performed in flash conditions using 230–400 mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}), that

were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM).

4.2. Structural analysis

Instrumentation: ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200/50 MHz on spectrometer. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). ESI-MS spectra were taken on an LC-MS instrument. Only base peaks (100%) are given. High-performance liquid chromatography was carried out using following apparatus: only base peaks (100%) are given. Enantiomeric excesses were determined on an HPLC instrument (chiracel AD-H column; mobile phase hexane/*i*-PrOH 9:1, flux 1.0 mL min^{-1}, λ=287 nm). Infrared spectra were obtained on an FTIR spectrometer, absorbances are reported in cm^{-1}. Melting points were determined on capillary melting point apparatus. The optical rotation analysis was performed using a polarimeter with a sodium lamp (λ=589 nm, D-line); $[\alpha]_D^{20}$ value is reported in 10^{-1} dec cm^2 g^{-1}; concentration (c) is in g per 100 mL. Elemental analyses were within ±0.4 of the theoretical values (C,H,N).

4.3. General procedure for the Friedel–Crafts alkylation

In a dry, argon-flushed Schlenk tube, the appropriate arenes **2a**–**q** (0.6 mmol), methyl 2-acetamidoacrylate (**3a**) (95 mg, 0.66 mmol), 1,1′-biphenyl-2,2′-diyl hydrogen phosphate **1f** (7.5 mg, 0.03 mmol, 5 mol %), and Na_2SO_4 (150 mg, 1.06 mmol) were dissolved in dry toluene (2.4 mL, 0.25 M). The solution was stirred at 85 °C for 60 h. The reaction mixture was directly transferred onto a column and purified by flash chromatography on silica gel (gradient from ethyl acetate/cyclohexane 1:1 to ethyl acetate) affording desired compounds **4a**–**q**.

*4.3.1. Methyl 2-acetamido-2-(1H-indol-3-yl)propanoate (**4a**).* White solid by crystallization with ethyl acetate/hexane; yield 63%. Mp: 197–198 °C (lit. mp 199–202 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ.2.03 (s, 3H), 2.13(s, 3H), 3.70 (s, 3H), 6.74 (br s, 1H), 7.11–7.25 (m, 3H), 7.37 (d, 1H, J=7.5 Hz), 7.79 (d, 1H, J=7.5 Hz), 8.62 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.5, 169.3, 136.7124.5, 123.3, 122.2, 120.0, 119.9, 115.2, 111.8, 58.7, 52.9, 23.7, 22.3. The chemical-physical data are in agreement with those reported in the literature.[14]

*4.3.2. Methyl 2-acetamido-2-(5-fluoro-1H-indol-3-yl)propanoate (**4b**).* Off-white solid; yield 68%; mp: 158–160 °C; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 220 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3375, 1730, 1652; ^{1}H NMR (200 MHz, acetone-d_6): δ 1.99 (s, 6H), 3.59 (s, 3H), 6.93 (ddd, 1H, J_1=J_2=9.0 Hz, J_3=2.5 Hz), 7.40 (dd, 1H, J_1=9 Hz, J_2=5 Hz) 7.49 (s, 1H) 7.56 (dd, 2H, J_1=11, J_2=2.5 Hz), 10.46 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 172.3, 169.1, 157.2 (d, J=230 Hz), 133.8, 125.3 (d, J=10 Hz), 115.4 (d, J=5 Hz), 112.4 (d, J=10 Hz), 109.7 (d, J=26 Hz), 106.5, 105.8 (d, J=26 Hz), 58.0, 51.4, 22.2, 22.0; Anal. Calcd for $C_{14}H_{15}FN_2O_3$ (278.11): C, 60.42; H, 5.43; N, 10.07. Found: C, 60.39; H, 5.23; N, 10.04.

*4.3.3. Methyl 2-acetamido-2-(5-chloro-1H-indol-3-yl)propanoate (**4c**).* Off-white amorphous solid; yield 47%; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 236 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3365, 2950, 1728, 1655; ^{1}H NMR (200 MHz, acetone-d_6): δ 1.99 (s, 3H), 2.00 (s, 3H), 3.60 (s, 3H), 7.11 (dd, 1H, J_1=9 Hz, J_2=2 Hz), 7.42 (d, 1H, J=9 Hz), 7.49–7.50 (m, 1H), 7.66 (br s, 1H), 7.89 (d, 1H, J=2 Hz), 10.60 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 172.3, 169.0, 135.7, 126.1, 125.2, 124.3, 121.6, 120.5, 115.1, 112.9, 58.0, 51.4, 22.3, 22.0; Anal. Calcd for $C_{14}H_{15}ClN_2O_3$ (294.08): C, 57.05; H, 5.13; N, 9.50. Found: C, 57.36; H, 5.08; N, 9.51.

*4.3.4. Methyl 2-acetamido-2-(5-bromo-1H-indol-3-yl)propanoate (**4d**).* Orange solid by crystallization with ethyl acetate/hexane; yield 63%; mp: 217–218 °C ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.09 (s, 3H), 3.68 (s, 3H), 6.96–6.98 (br m, 2H), 7.11 (dd, 1H, J_1=0.5 Hz, J_2=8.5 Hz) 7.21 (dd, 1H, J_1=2 Hz, J_2=8.5 Hz), 7.78 (d, 1H, J_1=2 Hz), 8.98 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 169.4, 135.3, 126.2, 124.9, 124.7, 121.9, 114.4, 113.2, 113.1, 58.4, 53.2, 24.0, 22.3. The chemical-physical data are in agreement with those reported in the literature.[14]

*4.3.5. Methyl 2-acetamido-2-(4-bromo-1H-indol-3-yl)propanoate (**4e**).* White solid; yield 58%; mp: 262–263 °C; TLC (ethyl acetate), R_f: 0.3 (UV, CAM). MS (ESI): 280 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3360, 1730; ^{1}H NMR (200 MHz, acetone-d_6): δ 1.89 (s, 3H), 2.13 (s, 3H), 3.69 (s, 3H), 6.99 (t, 1H, J=8 Hz), 7.26 (dd, 1H, J_1=8 Hz, J_2=2 Hz), 7.38 (br s, 1H), 7.42–7.47 (m, 2H), 10.59 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 174.9, 167.4, 126.6126.4124.4122.2, 115.9, 112.5, 111.3, 111.2, 58.3, 52.1, 24.8, 23.1; Anal. Calcd for $C_{14}H_{15}BrN_2O_3$ (338.03): C, 49.57; H, 4.46; N, 8.26. Found: C, 49.17; H, 4.2; N, 8.57.

*4.3.6. Methyl 2-acetamido-2-(5-nitro-1H-indol-3-yl)propanoate (**4f**).* Yellow solid; yield 76%; mp: 244–246 °C; TLC (ethyl acetate), R_f: 0.3 (UV, CAM). MS (ESI): 247 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3370, 1723; ^{1}H NMR (200 MHz, acetone-d_6): δ 2.00 (s, 3H), 2.03 (s, 3H), 3.63 (s, 3H), 7.59 (d, 1H, J=9.0 Hz), 7.70 (d, 1H, J=2.5 Hz), 7.87 (br s, 1H), 8.04 (dd, 1H, J_1=9.0 Hz, J_2=2.0 Hz), 8.92 (d, 1H, J=2 Hz), 11.02 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 172.3, 169.1, 141.3, 140.2, 127.3, 124.4, 118.4, 118.0, 116.8, 111.9, 58.0, 51.6, 22.6, 22.0; Anal. Calcd for $C_{14}H_{15}N_3O_5$ (305.1): C, 55.08; H, 4.95; N, 13.76. Found: C, 54.87; H, 5.28; N, 14.38.

*4.3.7. Methyl 2-acetamido-2-(5-cyano-1H-indol-3-yl)propanoate (**4g**).* Off-white solid; yield 68%; mp: 214–216 °C; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 328 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3360, 2951, 1723, 1651; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 6H), 3.67 (s, 3H), 6.99 (d, 1H, J=2.5 Hz), 7.09 (d, 1H, J=8.5 Hz), 7.25 (d, 2H, J=1.5 Hz), 7.95 (s. 1H), 9.67 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 169.4, 138.4, 126.0, 124.7, 124.6, 124.1, 120.8, 115.3, 112.5, 102.5, 58.2, 53.5, 24.2, 22.3; Anal. Calcd for $C_{15}H_{15}N_3O_3$ (285.11): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.46; H, 5.58; N, 14.47.

*4.3.8. Methyl 3-(2-acetamido-1-methoxy-1-oxopropan-2-yl)-1H-indole-5-carboxylate (**4h**).* White solid by crystallization with ethyl acetate; yield 65%; mp: 198–200 °C; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 260 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3385, 1720; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.88 (s, 3H), 1.89 (s, 3H), 3.53 (s, 3H), 3.86 (s, 3H), 7.45 (d, 1H, J=9 Hz), 7.52 (s, 1H), 7.73 (d, 1H, J=9 Hz), 8.50 (br s, 1H), 8.53 (s, 1H), 11.53 (br s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 172.8, 169.6, 167.8, 139.9, 125.9, 124.8, 124.3, 122.6, 120.9, 116.5, 112.0, 58.1, 52.3, 52.2, 23.8, 22.9; Anal. Calcd for $C_{16}H_{18}N_2O_5$ (318.32): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.17; H, 5.4; N, 8.9.

*4.3.9. Methyl 2-acetamido-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3 yl)propanoate (**4i**).* Off-white solid; yield 54%; mp: 212–213 °C; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 227 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3364, 2952, 1725, 1653; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 12H), 2.01 (s, 3H), 2.10 (s, 3H), 3.68 (s, 3H), 6.89 (d, 1H, J=4 Hz), 6.94 (s, 1H), 7.32 (d, 1H, J=10 Hz), 7.63 (d, 1H, J=8 Hz), 8.22 (s, 1H), 9.13 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.8, 169.7, 138.8, 128.2, 127.3, 124.3, 123.6, 115.3, 111.3, 83.5, 58.8, 52.9, 24.9, 23.7, 22.7; Anal. Calcd

for $C_{20}H_{27}BN_2O_5$ (386.20): C, 62.19; H, 7.05; N, 7.25. Found: C, 62.49; H, 7.25; N, 7.15.

*4.3.10. Methyl 2-acetamido-2-(5-methoxy-1H-indol-3-yl)propanoate (**4j**).* Brown amorphous solid; yield 76%; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.3 (UV, CAM). MS (ESI): 232 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3411, 3004, 2360, 2342, 1716; ^1H NMR (200 MHz, acetone-d_6): δ 2.95 (s, 3H), 2.96 (s, 3H), 4.5 (s, 3H), 4.76 (s, 3H), 7.74 (dd, 1H, J_1=2 Hz, J_2=10 Hz), 8.25 (dd, 1H, J_1=2 Hz, J_2=10 Hz), 8.32 (dd, 2H, J_1=2 Hz, J_2=6 Hz), 8.5 (br s, 1H), 11.2 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 172.4, 169.1, 153.7, 132.3, 125.4, 123.8, 114.8, 112.1, 111.7, 103.0, 58.2, 54.9, 51.3, 22.3, 22.1; Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.13): C, 62.06; H, 6.25; N, 9.65. Found: C, 61.66; H, 6.43; N, 9.41.

*4.3.11. Methyl 2-acetamido-2-(5-methyl-1H-indol-3-yl)propanoate (**4k**).* Orange amorphous solid; yield 57%; TLC (cyclohexane/ethyl acetate 4:6), R_f: 0.3 (UV, CAM). MS (ESI): 216 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3364, 2952, 1725, 1653; ^1H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.11 (s, 3H), 2.48 (s, 3H), 3.69 (s, 3H), 6.75 (br s, 1H), 7.02–7.06 (m, 2H), 7.23 (s, 1H), 7.55 (s, 1H), 8.73 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 173.5, 169.4, 135.1, 129.2, 124.7, 123.8, 123.4, 119.4, 114.5, 111.5, 58.7, 52.9, 23.7, 22.3, 21.7. δ; Anal. Calcd for for $C_{15}H_{18}N_2O_3$ (274.13): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.44; H, 6.79; N, 10.61.

*4.3.12. Methyl 2-acetamido-2-(2-methyl-1H-indol-3-yl)propanoate (**4l**).* Brown solid by crystallization with ethyl acetate/hexane; yield 60%; mp: 190–191 °C; TLC (cyclohexane/ethyl acetate 2:8), R_f: 0.4 (UV, CAM). MS (ESI): 216 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3380, 2924, 1701, 1655; ^1H NMR (200 MHz, acetone-d_6): δ 1.96 (s, 3H), 2.05 (under solvent peak acetone-d_6, 3H), 2.44 (s, 3H), 3.66 (s, 3H), 6.95–7.03 (m, 2H), 7.27 (dd, 1H, J_1=1.5 Hz, J_2=7 Hz), 7.46 (br s, 1H), 7.48 (d, 1H, J=7 Hz), 10.09 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 173.3, 169.1, 135.2, 131.9, 126.8, 124.0, 120.5, 119.8, 118.8, 110.5, 59.4, 51.5, 23.5, 22.3, 12.8; Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.13): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.35; H, 6.83; N, 10.6.

*4.3.13. Methyl 2-acetamido-2-(3-methyl-1H-indol-2-yl)propanoate (**4m**).* Off-white solid by crystallization with ethyl acetate; yield 31%; mp: 176–177 °C; TLC (cyclohexane/ethyl acetate 1:1), R_f: 0.3 (UV, CAM). MS (ESI): 216 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3370, 1710, 1672; ^1H NMR (200 MHz, acetone-d_6): δ 1.96 (s, 6H), 2.30 (s, 3H), 3.67 (s, 3H), 6.95–7.12 (m, 2H), 7.3 (d, 1H, J=8 Hz), 7.5 (d, 1H, J=8 Hz), 7.78 (br s, 1H), 10.1 (br s, 1H); ^{13}C NMR (50 MHz, acetone-d_6): δ 171.9, 168.9, 135.1, 132.2, 129.5, 121.5, 118.6, 118.0, 111.0, 107.4, 58.7, 52.0, 22.4, 22.1, 8.6; Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.13): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.67; H, 6.38; N, 10.16.

*4.3.14. Methyl 2-acetamido-2-(6-methoxy-1H-indol-3-yl)propanoate (**4n**).* Orange solid; yield 43%; TLC (cyclohexane/ethyl acetate 4:6), mp: 175–176 °C; R_f: 0.3 (UV, CAM). MS (ESI): 232 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3365, 2950, 1720, 1656; ^1H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.10 (s, 3H), 3.69 (s, 3H), 3.82 (s, 3H), 6.72 (br s, 1H), 6.76–6.82 (m, 2H), 6.98 (d, 1H, J=2.5 Hz), 7.65 (d, 1H, J=9.5 Hz), 8.55 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.5, 169.4, 156.4, 137.6, 122.0, 120.5, 118.8, 115.1, 110.1, 94.8, 58.6, 55.6, 52.9, 23.7, 22.2; Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.13): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.27; H, 6.43; N, 9.93.

*4.3.15. Methyl 2,2-di(1H-indol-3-yl)propanoate (**5**).* By-product **5** was isolated as white solid by crystallization with methanol; yield 35%; mp: 201–203 °C (lit. mp: 88 °C) TLC (cyclohexane/ethyl acetate 8:2), R_f: 0.3 (UV, CAM): MS (ESI): 260 $[M+H-COOCH_3]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.69 (s, 3H), 6.97 (d, 2H, J=2.5 Hz), 7.03 (ddd, 2H, J_1=7 Hz, J_2=1 Hz), 7.19 (ddd, 2H, J_1=7 Hz, J_2=1 Hz), 7.38 (d, 2H, J=8 Hz), 7.53 (d, 2H, J=8 Hz), 8.02 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.9, 136.8, 126.0, 122.9, 121.8, 121.2, 119.3, 119.1, 111.2, 52.2, 46.2, 25.9. The chemical-physical data are in agreement with those reported in the literature.[17]

*4.3.16. Methyl 2-acetamido-2-(1-methyl-1H-pyrrol-2-yl)propanoate (**4p**).* Yellow solid by crystallization with hexane; yield 35%; mp: 176–177 °C; TLC (cyclohexane/ethyl acetate 3:7), R_f: 0.3 (UV, CAM). MS (ESI): 166 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 3260, 2951, 1739, 1655; ^1H NMR (200 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.05 (s, 3H), 3.55 (s, 3H) 3.76 (s, 3H), 6.08 (dd, 1H, J_1=4 Hz, J_2=3 Hz), 6.28 (dd, 1H, J_1=4 Hz, J_2=2 Hz), 6.54 (dd, 1H, J_1=3 Hz, J_2=2 Hz), 6.72 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.6, 168.5, 129.7, 124.5, 109.5, 106.8, 58.3, 53.4, 24.0, 23.2; Anal. Calcd for $C_{11}H_{16}N_2O_3$ (224.12): C, 58.91; H, 7.19; N, 12.49. Found: C, 58.58; H, 7.45; N, 12.26.

*4.3.17. Methyl 2-acetamido-2-(4,7-dihydro-1H-indol-2-yl)propanoate (**4q**).* Colorless oil; 33 yield %; TLC (ethyl acetate), R_f: 0.3 (UV, CAM). MS (ESI): 204 $[M+H-COOCH_3]^+$; IR (film, cm^{-1}): 325, 2950, 1745, 1650; ^1H NMR (200 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.01 (s, 3H), 3.79 (s, 3H), 5.85 (d, 2H, J=3.5 Hz), 5.94 (s, 1H, J=2.5 Hz), 6.25 (br s, 1H), 8.89 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.9, 170.4, 129.6, 125.6, 125.3, 122.8, 113.3, 104.9, 57.8, 53.2, 24.7, 23.9, 23.4, 22.4; Anal. Calcd for $C_{14}H_{18}N_2O_3$ (262.13): C, 64.10; H, 6.92; N, 10.68. Found: 63.9C; H, 6.57; N, 10.35.

4.4. General procedure for the asymmetric Friedel–Crafts alkylation

In a dry, argon-flushed Schlenk tube, **2a** (0.6 mmol), methyl 2-acetamidoacrylate (**3a**) (95 mg, 0.66 mmol), the appropriate chiral Brønsted acid **6a–h** (7.5 mg, 0.03 mmol, 5 mol %) and Na_2SO_4 (150 mg, 1.06 mmol) were dissolved in dry toluene (2.4 mL, 0.25 M). The solution was stirred at 85 °C for 60 h. The reaction mixture was directly transferred onto a column and purified by flash chromatography on silica gel (gradient from ethyl acetate/cyclohexane 1:1 to ethyl acetate) affording desired compound **4a** as a mixture of enantiomers. Enantiomeric excesses were determined by HPLC, major product t_R=21.5 min and minor product t_R=17.1 min. Optical rotation was measured for compound **4a** using chiral Brønsted acid **6f**; $[\alpha]_D^{20}$ +3.4 (0.89, ee=66).

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Supplementary data

^1H NMR and ^{13}C NMR spectra for all compounds and HPLC traces for chiral compounds are reported in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.039.

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