Organocatalytic Aza-Friedel–Crafts/Lactonization Domino Reaction of Naphthols and Phenols with 2-Acetamidoacrylate to Naphtho- and Benzofuranones Bearing a Quaternary Center at the C3 Position

Francesca Bartoccini, Michele Mari, Michele Retini, Silvia Bartolucci and Giovanni Piersanti*

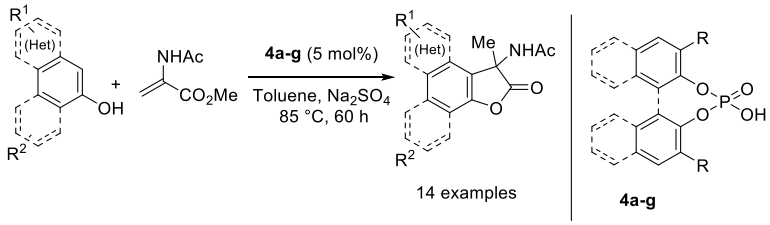
Department of Biomolecular Sciences, University of Urbino "Carlo Bo", P.zza Rinascimento 6, 61029 Urbino, PU, Italy.

Corresponding Author:

E-mail: giovanni.piersanti@uniurb.it

Web site: http://www.people.uniurb.it/GiovanniPiersanti/

TABLE OF CONTENTS/ABSTRACTGRAPHIC



ABSTRACT

N-Acetyl ketimine generated from methyl 2-acetamidoacrylate was explored to develop an unprecedented domino aza-Friedel–Crafts/lactonization reaction with naphthols and phenols (including 5-hydroxyindoles). This novel method requires a catalyst loading of only 5 mol% of a phosphoric acid catalyst and provides a new series of 3-NHAc-naphtho- and benzofuranone derivatives bearing tetra-substituted stereogenic centers in moderate-to-good yields. The enantioselective variant using BINOL-derived phosphoric acids was also explored with 1-naphthol, providing the desired product with moderate enantioselectivities (up to 99:1 following recrystallization).

The structural motifs of 3,3-disubstituted benzo- and naphthofuranone are common in a variety of medicinally effective natural products.[1] They are also found as synthetic intermediates of valuable biologically active compounds that possess interesting cytotoxic and pharmacological properties[2] as well as in functionalized compounds with applications in materials, supramolecular, and polymer chemistry.[3] Many of these structures feature a chiral quaternary stereocenter at the C3 position of the heterocyclic ring (Figure 1).[4] In spite of all these interesting properties, limited strategies for the preparation of these compounds have been investigated thus far.[4c-f] Hence, the development of a new alternative methodology for the synthesis of diversely structured benzo- and naphthofuranones is urgently required.

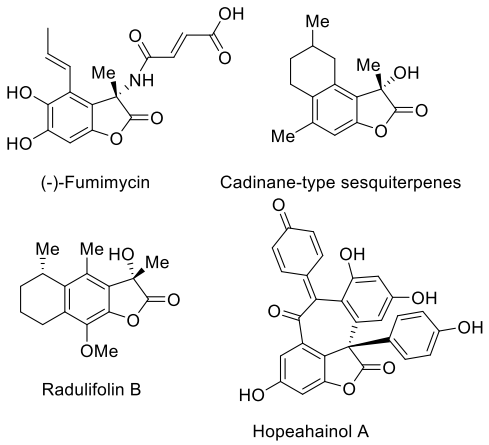


Figure 1. Representative Natural Products.

Dehydroalanine (Dha) is a unique and versatile noncanonical, yet naturally occurring, α,β-unsaturated amino acid endowed with peculiar structural properties and various reactivity profiles due to the presence of both an α,β-unsaturated ester functionality and an enamide moiety on the same carbon of the double bond.[5] Because of the multiple functionalities of Dha, several electrophilic addition reactions onto the enamide moiety[6] as well as various Michael additions[7] and cycloadditions[8] across the α,β-unsaturated carbonyl system have been demonstrated, proving its function as an important precursor to a variety of novel α-amino acids and modified peptides.[9] Compared to the well-known nucleophilic conjugate addition chemistry of Dha, the 1,2-nucleophilic addition reactions engaging the enamide moiety have received less attention, although it is known that enamides can also be considered as masked imines and be converted to iminium ion electrophiles in the presence of Brønsted acids and react with nucleophiles, i.e. aza-Friedel–Crafts reactions.[10]

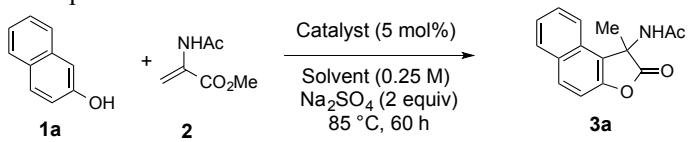
In this context, in which an α-carboxyl-substituted enamide such as methyl 2-acetamidoacrylate, a Dha commercially available is used, only nitrogen-containing arenes such as indoles and pyrroles have been targeted, leading to quaternary α-amino acid-centered indoles and pyrroles by (enantio)selective aza-Friedel–Crafts reactions.[11] On the contrary, fully carbon-based aromatic compounds have faced less success, mainly due to intrinsic challenges such as a lower nucleophilicity and regioselectivity issues. However, in the realm of catalytic aza-Friedel–Crafts reactions, naphthol and phenol derivatives used as the donor are facing growing attention,[12] resulting in the direct preparation of densely functionalized and biologically important chiral compounds.

Herein, we report a new organocatalytic aza-Friedel–Crafts/lactonization domino reaction between naphthols and ketimines derived from *N*-protected dehydroamino esters to provide 3,3-disubstituted naphthofuranones. In addition to the domino aza-Friedel–Crafts lactonization, the domino reaction of naphthols and ketimines as well as the corresponding reaction with phenols to give benzofuranone are described. To the best of our knowledge, the aza-Friedel–Crafts reaction between dehydroalanine derivatives and naphthol/phenol has not been reported previously.

First, we investigated the reaction between 2-naphthol (**1a**) and methyl 2-acetamidoacrylate (**2**) using the same reaction conditions as described for indole,[11a] which included modestly acidic diphenyl phosphate (DPP) as the Brønsted acid (5 mol%) and Na_2SO_4 in toluene at 85 °C (Table 1, entry 1). The initial trials allowed us to achieve the formation of the target lactone through an aza-Friedel–Crafts/lactonization reaction (i.e., **3a**), in a good overall yield after a reasonable reaction time, though the conversion was not complete, whereas the Friedel–Crafts product and *O*-alkylation products were not isolated. Neither the replacement of Na_2SO_4 with 4 Å molecular sieves (Table 1, entry 2) nor starting with a slight excess of 2-naphthol (Table 1, entry 3) provided a better result. Polar solvents generally gave a

lower conversion and yield (Table 1, entries 4 and 5), and toluene was found to be the best solvent for this reaction. Decreasing the amount of catalyst to 1 mol% caused a marked decrease in the product yield (Table 1, entry 6). No reaction was observed in the absence of catalyst (Table 1, entry 10). Finally, when PPA was replaced by TsOH, H_3BO_3, AcOH, or any other Brønsted acid catalyst, the product yield was decreased to 0–11% (Table 1, entries 7-9). The reaction was also performed at a scale of 1 mmol under standard conditions. Compared with the small-scale reaction (Table 1, entry 11), this 1-mmol-scale reaction afforded the corresponding product **3a** in a nearly maintained good yield of 60%.

Table 1. Optimization of the Reaction Conditions for aza-Friedel–Crafts/lactonization



1a **2** **3a**

Entry	Catalyst	Solvent	Yield[b]
1	DPP	Toluene	64
2[c]	DPP	Toluene	21
3[d]	DPP	Toluene	48
4[e]	DPP	Toluene	13
5	DPP	DMF	29
6	DPP	CH_3CN	37
7	TsOH	Toluene	7
8	H_3BO_3	Toluene	NR
9	AcOH	Toluene	11
10	/	Toluene	NR
11[f]	DPP	Toluene	60

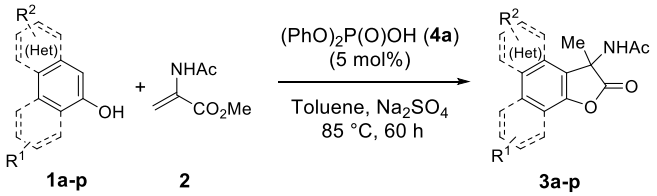
[a]*Reaction conditions:* **1a** (0.6 mmol), **2** (0.66 mmol), catalyst (0.03 mmol), Na_2SO_4 (1.2 mmol), and solvent (0.25 M), 85 °C, 60 h. [b]Isolated yield. [c]Molecular sieves 4 Å (300 mg) instead of Na_2SO_4. [d]**1a** (0.66 mmol), **2** (0.6 mmol). [e]Catalyst (1 mol%). [f]The reaction was carried out on a scale of 1 mmol. NR, no reaction.

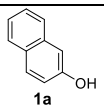
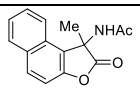
The optimal reaction conditions (Table 2, entry 1) were then applied to various 2-naphthols, 1-naphthols, and phenols to evaluate the scope and limitations of this unprecedented aza-Friedel–Crafts/lactonization reaction. As illustrated in Table 2, the reaction could be accomplished with good generality. 2-Naphthols with electron-donating groups or electron-withdrawing groups all provided the desired products in decent-to-good yields. (Table 2, entries 2 and 3). In order to expand the reaction scope and the diversity of this procedure as well as further functionalization, we decided to test dihydroxynaphthalene derivatives. It is worthwhile to note that when 2,7-dihydroxynaphthalene (**1d**) was subjected to this procedure instead of 2-naphthol, the reaction proceeded smoothly, and the corresponding naphthofuran-2(1H)-one (**3d**) was obtained in 67% yield (Table 2, entry 4). The scope of the reaction was further examined under the same conditions by using more hindered naphthol derivatives such as 8-iodo-2-hydroxynaphthalene (**1e**) and 8-NHBoc-2-hydroxynaphthalene (**1f**) as the substrates; however, no reaction occured with **1e** whereas **1f** yielded an unknown product, along with recovered starting material and the expected products were not obtained (Table 2, entries 5 and 6). 1-Naphthol (**1g**) and substituted 1-naphthol on either the first or second aromatic ring (**1h-j**) also exhibited good reactivity with Dha under the same reaction conditions, affording the corresponding lactones **3g–j** in decent yields (Table 2, entries 7–10). Hydroxyindoles can be regarded as naphthol analogs. Therefore, based on this concept, the

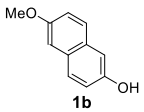
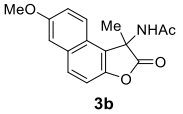
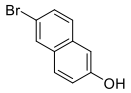
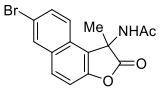
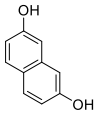
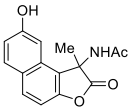
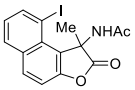
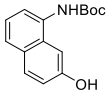
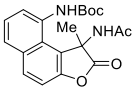
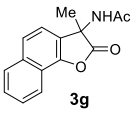
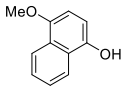
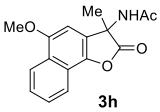
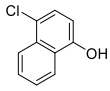
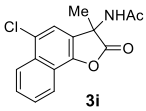
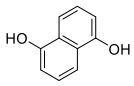
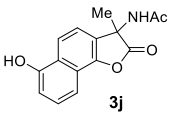
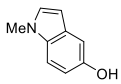
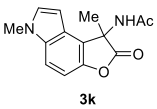
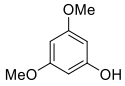
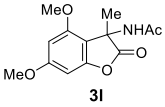
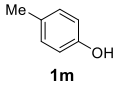
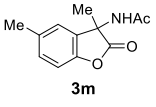
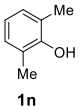
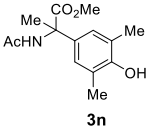
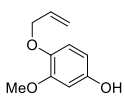
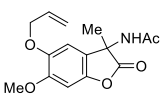
direct functionalization of the generally less-reactive indole benzene ring could be achieved even by using C2- and C3-unsubstituted hydroxyindoles as the nucleophiles.[13] However, the C3 position is still the dominant reaction site for the functionalization of free-(NH) 5-hydroxyindole with **2** under the above reaction conditions, and 3,3-bis(indolyl)propanoate was the only product obtained.[14] On the contrary, when 5-hydroxyindole with methyl substituent at the indole nitrogen (**1k)** was tested, the alkylation in the carbocyclic ring of indole is recovered and the lacton **3k** was isolated in good yield (Table 2, entry 11). These results are in accordance with findings by others[15] regarding the existence of a key interaction between the N-H of the indole with the phosphoric acid in Friedel–Crafts alkylation reaction. Finally, we tried to replace *N*-Ac by *N*-Boc or *N*-Cbz. However, these derivatives are very unstable and decomposed quickly under the reaction conditions. Hence, it can be concluded that the scope of naphthols was very good, but the scope of dehydroalanines was rather poor.

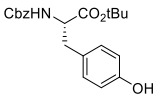
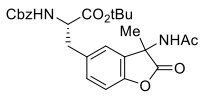
Encouraged by the above successful alkylation/lactonization of 1-naphthols and 2-naphthols with methyl 2-acetamidoacrylate, to extend the scope of our findings, we further evaluated phenols as the aza-Friedel–Crafts donor to deliver the 3-NHAc-benzofuranone core bearing a quaternary center at the C3 position. The optimized conditions were evaluated using phenols **1l-o**, which were decorated on the aromatic ring with various substituents with different electronic and steric properties. In almost all cases, the desired product was successfully formed in moderate yield. With the strongly electron-donating group **1l** (Table 2, entry 12) or the weakly activating alkyl substituent **1m** (Table 2, entry 13), the corresponding 3-amidolactones were formed smoothly in yields (up to 45%) and reaction times comparable to the reference substrate (i.e., **3a**). Unsubstituted phenol as well as 3-chlorophenol were inert for this reaction, with no product formation. Conversely, substitution with two alkyl groups in the *ortho* positions (**1n**) dramatically diminished the overall reactivity and led to the slow formation of only the uncyclized intermediate/Friedel–Crafts alkylation in the *para* position (Table 2, entry 14). The obtained aza-Friedel–Crafts adducts are versatile intermediates that can be readily converted to other chiral building blocks and natural products. For example, the lactone **3o** (Table 2, entry 15) can be considered an advanced intermediate for the synthesis of the antibiotic agent fumimycin.[16] Diversification of drug molecules or natural products to create analogs for screening or repurposing is now an established and vital strategy for medicinal chemists.[17] Toward this end and to demonstrate the late-stage diversification of existing biologically active architectures, we successfully performed the reaction with (L)-(benzyloxy)carbonyltyrosine-*t*-butyl ester (**1p**). The tyrosine derivative **3p** was obtained selectively but as a 1:1 mixture of diastereomers, as confirmed by NMR analysis although the diastereomers were not separated (Table 2, entry 16). We also tested other phenolic natural products such as tyrosol and estradiol but only acetylation of the alcoholic hydroxyl groups was observed.

Table 2. Evaluation of Substrate Scope



Entry[a]	Substrate	Product	Yield (%)[b]
1	 1a	 3a	64

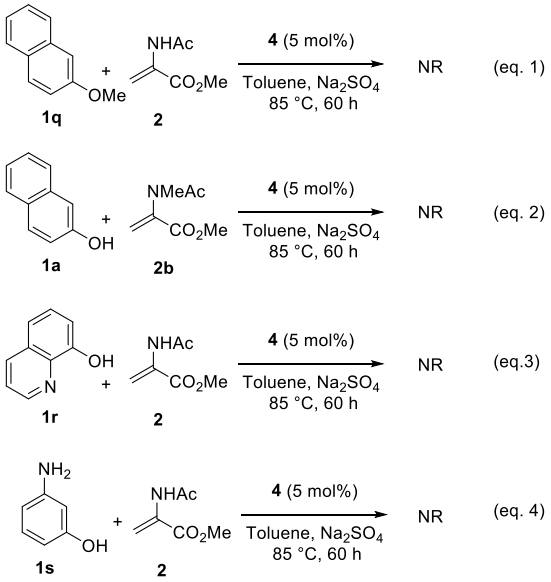
2	 **1b**	 **3b**	51
3	 **1c**	 **3c**	49
4	 **1d**	 **3d**	67
5	 **1e**	 **3e**	NR
6	 **1f**	 **3f**	-
7	 **1g**	 **3g**	44
8	 **1h**	 **3h**	65
9	 **1i**	 **3i**	46
10	 **1j**	 **3j**	42
11	 **1k**	 **3k**	49
12	 **1l**	 **3l**	33
13	 **1m**	 **3m**	45
14	 **1n**	 **3n**	35
15	 **1o**	 **3o**	40

16   14

1p 3p

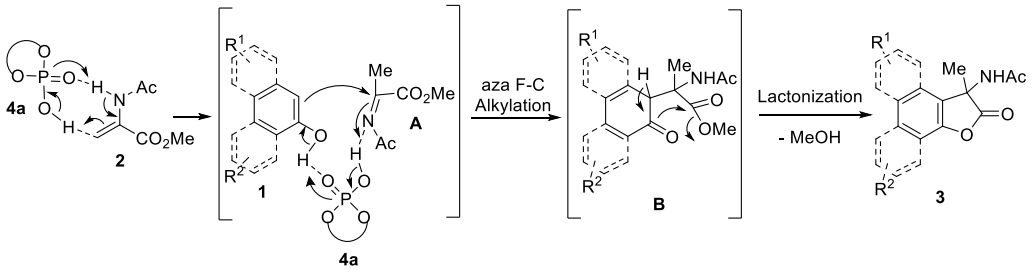
[a]*Reaction conditions:* **1a–p** (0.6 mmol), **2** (0.66 mmol), **4a** (0.03 mmol), Na_2SO_4 (1.2 mmol), and toluene (0.25 M), 85 °C, 60 h. [b]Isolated yield.

In order to gain some insights into the activation mode of catalyst **4a** to substrates **1a** and **2**, we performed some control experiments (Scheme 1). When 2-methoxynaphthalene (**1q**) or *N*-methyl-protected acetamidoacrylate (**2b**) was utilized as a substrate for this reaction under the standard conditions (eq. 1–2), no reaction (NR) occurred, indicating that the OH group of naphthol and the NH group of acetamidoacrylate play a crucial role in controlling the reactivity (and forming *N*-acetylimine) via the formation of hydrogen bonds with the catalyst **4a**. In addition, the basic compounds 8-hydroxyquinoline (**1r**) and 3-aminophenol[18] (**1s**) failed to participate in the reaction with *N*-methyl acetamidoacrylate **2** (eq. 3–4), implying that the OH group on the catalyst also plays an important role in the reaction via tautomer generation and a hydrogen-bonding interaction with the substrate.



Scheme 1. Control Experiments

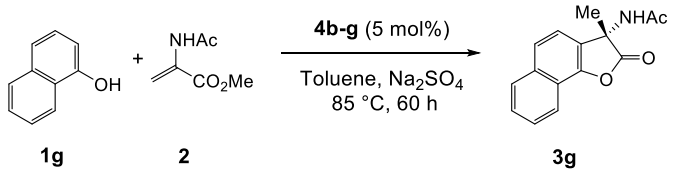
Based on the experimental results, a possible reaction pathway was suggested to explain the observed chemistry of this Brønsted acid-catalyzed domino aza-Friedel–Crafts/lactonization reaction of naphthol/phenol with methyl 2-acetamidoacrylate (**2**) (Scheme 2). As exemplified by the formation of product, the active *N*-acetylimine **A** would be generated from methyl 2-acetamidoacrylate (**2**) via tautomerization under the catalysis of **4a**. In the transition state, **4a** is proposed to activate *N*-acetylimine **A** and naphthol **1** simultaneously via hydrogen-bonding interactions (dual activation). Then, *N*-acetylimine **A** is directly trapped by the *ortho* position of phenol/naphthol **1**, leading to the formation of a transient intermediate **B** by an aza-Friedel–Crafts reaction. Finally, the observed product **3** would be formed after aromatization of intermediate **B** and intramolecular lactonization. Not surprisingly, these results can be partially rationalized by the bifunctional structure of the phosphoric acids acting both as a Brønsted acid (tautomerization to *N*-acylimine; the electrophilicity of which is heightened) and involved in the activation of protic nucleophiles (naphthol), resulting in highly organized transition states and high levels of stereocontrol with BINOL-derived phosphoric acids.

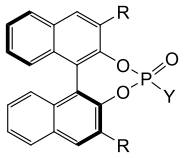


Scheme 2. Proposal Dual Activation for the Aza-Friedel–Crafts/Lactonization of Naphthols and Phenols with 2-Acetamidoacrylate

Finally, a series of chiral phosphoric acids (**4b–g**) with different substituents at the 3,3-positions of the binaphthyl ring were prepared and tested in the reaction of 1-naphthol (**1g**) and *N*-acetylated dehydroalanine methyl ester (**2**). Although there are some reported examples of organocatalytic enantioselective aza-Friedel–Crafts reactions of phenolic compounds with ketimines,[19] only moderate-to-scarce enantiomeric excess values have been obtained (Table 3), presumably due to the low reactivity of ketimines and more difficult control of facial selectivity. However, **3g** could be enantioenriched to er 99:1 by one single recrystallisation (Table 3, entry 1). This study represents the first example of catalyzed asymmetric Friedel–Crafts alkylation of this class on unreactive pyruvate-derived ketimine substrates with naphthol.

Table 3. Chiral Brønsted Acid Catalyzed Asymmetric Aza-Friedel–Crafts/Lactonization Domino Reaction of 1-Naphthol





(*S*)-**4**

b: Y = OH, R = 1-naphthyl
c: Y = OH, R = 9-phenanthryl
d: Y = OH, R = 2,4,6-(i-Pr)$_3$C$_6$H$_2$
e: Y = OH, R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
f: (S)-VAPOL hydrogenphosphate
g: Y = NHTf, R = 9-phenanthryl

Entry[a]	Catalyst	Yield (%)[b]	er[c,d]
1	**4b**	48	82:18 (99:1)[e]
2	**4c**	52	84:16
3	**4d**	7	68:32
4	**4e**	39	51:49
5	**4f**	4	53:47
6	**4g**	20	50:50

[a]*Reaction conditions:* **1g** (0.6 mmol), **2** (0.66 mmol), **4b–g** (0.03 mmol), Na_2SO_4 (1.2 mmol), and toluene (0.25 M), 85 °C, 60 h. [b]Isolated yield. [c]Determined by chiral HPLC on a Chiralpak OD-H column. [d]The absolute configuration was determined relatively by comparison of polarimetry data with related molecules of known stereochemistry[20]. [e] In the mother liquor by recrystallisation with *i*Pr$_2$O/acetone 7:1, Crystals were racemic.

In conclusion, we have successfully developed a domino aza-Friedel–Crafts/lactonization reaction of readily available phenols and naphthols with aliphatic ketimines generated *in situ* from methyl 2-acetamidoacrylate under the influence of a phosphoric acid catalyst. This reaction is a rare example of the Friedel–Crafts reaction involving ketimines possessing alkyl substituents and is also an attractive method for the synthesis of 3-NHAc-benzofuran-2-ones and naphthofuranone derivatives that have a quaternary stereogenic center at the C3 position. This atom-economical and environmentally friendly procedure uses an inexpensive nonmetal catalyst with low loadings and establishes a new type of Friedel–Crafts alkylation between naphthols/phenols with electron-rich alkenes. Applications of this methodology to other reactions and natural products synthesis are currently under investigation in our laboratory.

Experimental section

General Methods. All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash chromatography conditions using 230-400 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (Silica Gel 60 F254). ^{1}H NMR and ^{13}C NMR spectra were recorded on 200 or 400 spectrometer, using $CDCl_3$, DMSO-d_6 and CD_3OD as solvent. 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). IR spectra were obtained on FT-IR spectrometer, absorbance are reported in cm^{-1}. Melting points were determined on capillary melting point apparatus and are uncorrected. Enantiomeric excesses were determined on a HPLC instrument (chiral column OD-H; mobile phase *n*-hexane/ *i*PrOH 85:15, flow 1.0 mL min-1, λ = 220 nm). Optical rotation analysis are performed using a Perkin-Elmer 241 polarimeter using a sodium lamp (λ 589 nm, D-line); $[\alpha]_D^{20}$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g for 100 mL. HRMS analysis was performed using a Q-TOF microTM mass spectrometer.

Starting Materials. Naphthalen-2-ol (**1a**), 6-methoxynaphthalen-2-ol (**1b**), 6-bromonaphthalen-2-ol (**1c**), naphthalene-2,7-diol (**1d**), naphthalen-1-ol (**1g**), 4-methoxynaphthalen-1-ol (**1h**), 4-chloronaphthalen-1-ol (**1i**), naphthalene-1,5-diol (**1j**), 3,5-dimethoxyphenol (**1l**), *p*-cresol (**1m**), 2,6-dimethylphenol (**1n**), methyl 2-acetamidoacrylate (**2**), diphenyl phosphate (**4a**) and (S)-VAPOL hydrogenphosphate (**4f**) are commercially available. 8-iodonaphthalen-2-ol (**1e**),[21] *tert*-butyl (7-hydroxynaphthalen-1-yl)carbamate (**1f**),[21] 1-methyl-1*H*-indol-5-ol (**1k**),[22] 4-(allyloxy)-3-methoxyphenol (**1o**),[16b] *tert*-butyl ((benzyloxy)carbonyl)-L-tyrosinate (**1p**),[23] **4b**,[24] **4c**,[25] **4d**,[26] **4e**[27] and **4g**[25] are synthetized as reported in literature.

General procedures for Aza-Friedel–Crafts/Lactonization of Naphthols and Phenols with 2-Acetamidoacrylate. A vial was charged with the appropriate naphthol or phenol derivatives (**1a-p**) (0.6 mmol), methyl 2-acetamidoacrylate (**2**) (94 mg, 0.66 mmol), Na_2SO_4 (170 mg, 1.2 mmol), the appropriate phosphoric acid (0.03 mmol) and toluene (2.4 mL). The vial was immersed in a preheated (85 °C) oil bath and stirred at this temperature for 60 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography.

*N-(1-Methyl-2-oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)acetamide (**3a**).* The title compound was prepared according to the general procedure using naphthalen-2-ol (**1a**) (86 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3a** (98 mg, 64%) as white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.88 (s, 3H), 7.34-7.58 (m, 4H), 7.82-7.92 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 21.9, 23.2, 58.0, 111.8, 120.8, 121.5, 124.6, 127.7, 128.3, 129.7, 130.7, 131.3, 150.7, 170.0, 176.8. IR (film): 3372, 3056, 1811, 1652 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_3$ $(M + H)^+$ 256.0968; Found 256.0980.

*N-(7-Methoxy-1-methyl-2-oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)acetamide (**3b**).* The title compound was prepared according to the general procedure using 6-methoxynaphthalen-2-ol (**1b**) (104 mg, 0.6 mmol) and methyl 2-

acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ EtOAc 6:4 to cyclohexane/ EtOAc 1:1) to give **3b** (87 mg, 51%) as beige solid. ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 3H), 1.81 (s, 3H), 3.86 (s, 3H) 7.28 (dd, J_1 = 9.0 and J_2 = 2.5 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.43 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 9.35 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.8, 23.5, 55.7, 57.6, 108.4, 112.3, 120.7, 122.4, 123.3, 123.6, 129.1, 132.6, 148.8, 156.6, 169.3, 176.8. m.p. 131-135 °C. IR (film): 3258, 1820, 1648 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_4$ $(M + H)^+$ 286.1074; Found 286.1052.

*N-(7-Bromo-1-methyl-2-oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)acetamide (**3c**).* The title compound was prepared according to the general procedure using 6-bromonaphthalen-2-ol (**1c**) (133 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3c** (98 mg, 49%) as white solid. ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 3H), 1.81 (s, 3H), 7.52-7.99 (m, 4H), 8.30 (s, 1H), 9.41(br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.7, 23.2, 57.4, 113.3, 118.0 122.4, 124.0, 126.8, 130.0, 131.0, 131.8, 132.4, 150.8, 169.5, 176.5. m.p. 242-245 °C. IR (film): 3291, 1815, 1648 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{13}BrNO_3$ $(M + H)^+$ 334.0073; Found 334.0088.

*N-(8-hydroxy-1-methyl-2-oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)acetamide (**3d**).* The title compound was prepared according to the general procedure using naphthalene-2,7-diol (**1d**) (96 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 2:8) to give **3d** (109 mg, 67%) as pink solid. ^{1}H NMR (DMSO-d_6): δ 1.69 (s, 3H), 1.83 (s, 3H), 7.05–7.07 (m, 1H), 7.18–7.20 (m, 2H), 7.79–7.83 (m, 2H), 9.33 (br s, 1H), 9.97 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.9, 22.9, 57.5, 103.7, 108.5, 117.6, 120.0, 125.9, 130.2, 130.4, 131.5, 150.8, 157.1, 169.3, 177.1. m.p. > 250 °C. IR (film): 3265, 1816, 1656 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_4$ $(M + H)^+$ 272.0917; Found 272.0945.

*N-(3-Methyl-2-oxo-2,3-dihydronaphtho[1,2-b]furan-3-yl)acetamide (**3g**).* The title compound was prepared according to the general procedure using naphthalen-1-ol (**1g**) (86 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3g** (67 mg, 44%) as white solid. ^{1}H NMR (DMSO-d_6) δ 1.61 (s, 3H), 1.83 (s, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.58-7.67 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.97-8.01 (m, 2H), 9.20 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 21.9, 23.8, 57.4, 119.4, 120.0, 120.9, 124.5, 125.2, 127.2, 127.4, 128.8, 134.2, 148.2, 169.6, 176.7. m.p. 240-241 °C. IR (film): 3371, 1813, 1650 cm^{-1}. $[\alpha]^{20}_D$: -162 (c 1.647 in MeOH) (Determinated in the mother liquor after recrystallisation with *i*Pr$_2$O/acetone 7:1 of product obtained using **4b** as catalyst). HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_3$ $(M + H)^+$ 256.0968; Found 256.0997.

*N-(5-Methoxy-3-methyl-2-oxo-2,3-dihydronaphtho[1,2-b]furan-3-yl)acetamide (**3h**).* The title compound was prepared according to the general procedure using 4-methoxynaphthalen-1-ol (**1h**) (104 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ acetone 8:2 to cyclohexane/ acetone 6:4) to give **3h** (111 mg, 65%) as off-white solid. ^{1}H NMR (DMSO-d_6): δ 1.60 (s, 3H), 1.84 (s, 3H), 3.98 (s, 3H), 6.83 (s, 1H), 7.53-7.70 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 9.04 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 22.0, 23.8, 56.5, 58.0, 98.6, 120.2, 120.8, 122.8, 124.8, 125.4, 126.5, 127.9, 141.7, 152.7, 169.5, 177.0. m.p. 226-230 °C. IR (film): 3312, 1809, 1660 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_4$ $(M + H)^+$ 286.1074; Found 286.1075.

*N-(5-Chloro-3-methyl-2-oxo-2,3-dihydronaphtho[1,2-b]furan-3-yl)acetamide (**3i**).* The title compound was prepared according to the general procedure using 4-chloronaphthalen-1-ol (**1i**) (107 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ acetone 8:2 to cyclohexane/ acetone 7:3) to give **3i** (80 mg, 46%) as orange solid. ^{1}H NMR (DMSO-d_6): δ 1.63 (s, 3H), 1.84 (s, 3H), 7.63 (s, 1H) 7.74-7.79 (m, 2H), 8.05-8.24 (m, 2H), 9.18 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.9, 23.4, 57.6, 120.4,

120.6, 121.8, 124.9, 125.5, 126.3, 128.4, 128.9, 130.6, 147.7, 169.8, 176.1. m.p. 236-238 °C. IR (film): 3262, 1816, 1656 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{12}ClNNaO_3$ $(M + Na)^+$ 312.0398; Found 312.0374.

N-(6-hydroxy-3-methyl-2-oxo-2,3-dihydronaphtho[1,2-b]furan-3-yl)acetamide (**3j**). The title compound was prepared according to the general procedure using naphthalene-2,7-diol (**1j**) (96 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 4:6) to give **3j** (68 mg, 42%) as brown solid. ^{1}H NMR (DMSO-d_6): δ 1.59 (s, 3H), 1.82 (s, 3H), 6.94 (dd, J = 7.0 and 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.38 – 7.45 (m, 2H), 7.96 (d, J = 8.5 Hz, 1H), 9.16 (br s, 1H), 10.4 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.9, 23.8, 57.5, 109.4, 111.4, 118.3, 118.8, 120.8, 125.4, 125.7, 128.1, 148.2, 154.1, 169.5, 176.8. m.p. > 250 °C. IR (film): 3268, 1821, 1659 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_4$ $(M + H)^+$ 272.0917; Found 272.0925.

*N-(1,6-dimethyl-2-oxo-1,6-dihydro-2H-furo[3,2-e]indol-1-yl)acetamide (**3k**).* The title compound was prepared according to the general procedure using 1-methyl-1*H*-indol-5-ol (**1k**) (88 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3k** (76 mg, 49%) as beige solid. ^{1}H NMR (DMSO-d_6): δ 1.60 (s, 3H), 1.78 (s, 3H), 3.79 (s, 3H), 6.41 (d, J = 3.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 3.0 Hz, 1H), 9.15 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.8, 23.2, 33.2, 57.2, 96.8, 104.8, 110.3, 119.4, 122.7, 132.6, 134.8, 146.2, 169.1, 177.2. m.p. > 250 °C. IR (film): 3274, 1811, 1633 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{15}N_2O_3$ $(M + H)^+$ 259.1077; Found 259.1065.

*N-(4,6-Dimethoxy-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)acetamide (**3l**).* The title compound was prepared according to the general procedure using 3,5-dimethoxyphenol (**1l**) (92 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3l** (52 mg, 33%) as beige solid. ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H), 1.96 (s, 3H), 3.80 (s, 6H) 6.19 (d, J = 2.0 Hz, 1H), 6.22 (br s, 1H), 6.34 (d, J = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 55.5, 55.7, 56.4, 89.5, 94.7, 107.5, 154.8, 156.2, 162.2, 169.1, 175.7. m.p. 195-197 °C. IR (film): 3292, 1805, 1644 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_5$ $(M + H)^+$ 266.1023; Found 266.1049.

*N-(3,5-dimethyl-2-oxo-2,3-dihydrobenzofuran-3-yl)acetamide (**3m**).* The title compound was prepared according to the general procedure using *p*-cresol (**1m**) (65 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3m** (59 mg, 45%) as orange oil. ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 3H), 1.93 (s, 3H), 2.34 (s, 3H), 6.94 (bs, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.1, 22.0, 24.1, 57.0, 110.6, 122.7, 129.6, 130.0, 134.0, 151.0, 169.5, 176.3. IR (film): 3285, 1813, 1658 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{14}NO_3$ $(M + H)^+$ 220.0968; Found 220.0946.

*Methyl 2-acetamido-2-(4-hydroxy-3,5-dimethylphenyl)propanoate (**3n**).* The title compound was prepared according to the general procedure using 2,6-dimethylphenol (**1n**) (122 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ EtOAc 6:4 to cyclohexane/ EtOAc 1:1) to give **3n** (56 mg, 35%) as white solid. ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 3H), 1.87 (s, 3H), 2.16 (s, 6H), 3.52 (s, 3H), 6.99 (s, 2H), 8.21 (br s, 1H), 8.26 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 17.3, 23.0, 24.0, 52.3, 61.0, 124.2, 126.4, 131.1, 153.3, 169.6, 173.2. m.p. 207-209 °C. IR (film): 3386, 1714, 1660 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_4$ $(M + H)^+$ 266.1387; Found 266.1384.

*N-(5-(allyloxy)-6-methoxy-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-yl)acetamide (**3o**).*[16a] The title compound was prepared according to the general procedure using 4-(allyloxy)-3-methoxyphenol (**1o**) (108 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ EtOAc 8:2 to cyclohexane/ EtOAc 4:6) to give **3o** (70 mg, 40%) as white solid. ^{1}H NMR (DMSO-d_6): δ 1.47 (s, 3H), 1.80 (s, 3H), 3.79 (s, 3H), 4.50 (d, J = 5.5 Hz, 1H), 5.24 (dd, J = 10.5 and 1.5 Hz, 1H), 5.38 (dd, J = 17.5 and 1.5 Hz, 1H), 5.99 -

6.06 (m, 1H), 6.85 (s, 1H), 6.94 (s, 1H), 8.94 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 22.0, 24.1, 56.6, 56.9, 70.5, 97.1, 109.2, 117.9, 121.2, 134.4, 145.1, 147.2, 150.7, 169.3, 177.0. m.p. 182-184 °C. IR (film): 3276, 1721, 1648 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{18}NO_5$ $(M + H)^+$ 292.1179; Found 292.1205.

*tert-butyl (2S)-3-(3-acetamido-3-methyl-2-oxo-2,3-dihydrobenzofuran-5-yl)-2-(((benzyloxy)carbonyl)amino)propanoate (**3p**).* The title compound was prepared according to the general procedure using *tert*-butyl ((benzyloxy)carbonyl)-L-tyrosinate (**1p**) (223 mg, 0.6 mmol) and methyl 2-acetamidoacrylate (**2**). The product was purified by flash chromatography (gradient from cyclohexane/ EtOAc 7:3 to cyclohexane/ EtOAc 4:6) to give **3p** (40 mg, 14%) as colorless oil. ^{1}H NMR (CD_3OD): δ 1.39 (s, 9H), 1.40 (s, 9H), 1.51 (s, 3H), 1.52 (s, 3H), 1.88 (s, 3H), 1.89 (s, 3H), 2.89–2.95 (m, 2H), 3.04–3.10 (m, 2H), 4.28–4.33 (m, 2H), 5.03 (s, 2H), 5.04 (s, 2H), 6.99–7.03 (m, 2H), 7.13–7.21 (m, 4H), 7.28–7.31 (m, 10H). ^{13}C NMR (CD_3OD): δ 18.6, 21.0, 21.1, 25.3, 35.3, 35.4, 54.4, 54.7, 55.1, 64.6, 64.7, 80.0, 80.1, 108.4, 108.5, 121.2, 121.4, 125.7, 125.9, 126.0, 126.1, 126.5, 128.6, 128.7, 128.8, 131.8, 132.0, 135.2, 135.3, 150.4, 155.4, 169.3, 169.5, 169.6, 174.8. IR (film): 3363, 1721, 1697 cm^{-1}. HRMS (ESI) m/z calcd for $C_{26}H_{31}N_2O_7$ $(M + H)^+$ 483.2126; Found 483.2139.

Procedure for 1 mmol scale synthesis of compound 3a. A vial was charged with naphthalen-2-ol (**1a**) (144 mg, 1 mmol), methyl 2-acetamidoacrylate (**2**) (172 mg, 1.2 mmol), Na_2SO_4 (284 mg, 2 mmol), diphenyl phosphate (**4a**) (12.5 mg, 0.05 mmol) and toluene (4 mL). The vial was immersed in a preheated (85 °C) oil bath and stirred at this temperature for 60 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give **3a** (153 mg, 60%). The chemical-physical data are in accordance as reported above.

Supporting Information.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and HPLC traces of **3g**.

References

(1) For Benzofuranones, see: (a) Ge, H.-M.; Zhu, C.-H.; Shi, D.-H.; Zhang, L.-D.; Xie, D.-Q.; Ng, J. S. W.; Tan, R.-X. Hopeahainol A: an acetylcholinesterase inhibitor from Hopea hainanensis. *Chem. Eur. J.* **2008**, *14*, 376–381. (b) Wada, S.; Hitomi, T.; Tokuda, H.; Tanaka, R. Anti-Tumor-Initiating Effects of Spiro-biflavonoids from *Abies sachalinensis*. *Chem. Biodiversity* **2010**, *7*, 2303–2308. (c) Fedorova, T. E.; Ivanova, S. Z.; Fedorov, S. V.; Babkin, V. A. Larisinol, a new spirobiflavonoid from *Larix gmelinii* bark. *Chem. Nat. Compd.* **2007**, *43*, 208–209. (d) Piacente, S.; Montoro, P.; Oleszek, W.; Pizza, C. *Yucca schidigera* Bark: Phenolic Constituents and Antioxidant Activity. *J. Nat. Prod.* **2004**, *67*, 882–885. (e) Bassarello, C.; Bifulco, G.; Montoro, P.; Skhirtladze, A.; Kemertelidze, E.; Pizza, C.; Piacente, S. Gloriosaols A and B, two novel phenolics from Yucca gloriosa: structural characterization and configurational assignment by a combined NMR-quantum mechanical strategy. *Tetrahedron* **2007**, *63*, 148–154. (f) Sontag, B.; Rüth, M.; Spiteller, P.; Arnold, N.; Steglich, W.; Reichert, M.; Bringmann, G. Chromogenic Meroterpenoids from the Mushrooms *Russula ochroleuca* and *R. viscida*. *Eur. J. Org. Chem.* **2006**, 1023–1033. (g) Kwon, Y.-J.; Sohn, M.-J.; Zheng, C.-J.; Kim, W.-G. Fumimycin: A Peptide Deformylase Inhibitor with an Unusual Skeleton Produced by Aspergillus fumisynnematus. *Org. Lett.* **2007**, *9*, 2449–2451. For Naphthofuranones, see: (h) Srivastava, V.; Negi, A. S.; Kumar, J. K.; Faridi,U.; Sisodia, B. S.; Darokar, M. P.; Luqman, S.; Khanuja, S. P. S. Synthesis of 1-(3′,4′,5′-trimethoxy) phenyl naphtho[2,1b]furan as a novel anticancer agent. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 911−914. (i) Ho, L.-K.; Don, M.-J.; Chen, H.-C.; Yeh, S.-F.; Chen, J.-M. Inhibition of Hepatitis B Surface Antigen Secretion on Human Hepatoma Cells. Components from *Rubia cordifolia*. *J. Nat. Prod.* **1996**, *59*, 330−333. (j) Son, J. K.; Jung, S. J.;

Jung, J. H.; Fang, Z.; Lee, C. S.; Seo, C. S.; Moon, D. C.; Min, B. S.; Kim, M. R.; Woo, M. H. Anticancer constituents from the roots of Rubia cordifolia L. *Chem. Pharm. Bull.* **2008**, *56*, 213−216.

(2) (a) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. The synthesis of a natural product family: from debromoisolaurinterol to the aplysins. *Tetrahedron* **2001**, *57*, 791–804. (b) Chandrashekhar, C.H.; Latha, K. P.; Vagdevi, H. M.; Vaidya, V. P. Synthesis and antimicrobial activity of chalcones of naphtho[2,1- b]furan condensed with barbituric acid. *Der. Pharma Chem.* **2011**, *3*, 329−333. (c) Lardic, M.; Patry, C.; Duflos, M.; Guillon, J.; Massip, S.; Cruzalegui, F.; Edmonds, T.; Giraudet, S.; Marini, L.; Leonce, S. Synthesis and primary cytotoxicity evaluation of arylmethylenenaphthofuranones derivatives. *J. Enz. Inhib. Med. Chem.* **2006**, *21*, 313−325. (d) Tseng, C.-H.; Lin, C.-S.; Shih, P.-K.; Tsao, L.-T.; Wang, J.-P.; Cheng, C.-M.; Tzeng, C.-C.; Chen, Y.-L. Furo[3′,2′:3,4]naphtho[1,2-d]imidazole derivatives as potential inhibitors of inflammatory factors in sepsis. *Bioorg. Med. Chem.* **2009**, *17*, 6773−6779. (e) Shashikala Devi, K.; Ramaiah, M.; Vanita, G. K.; Veena, K.; Vaidya, V. P. Synthesis and analgesic activity of triazolothiadiazoles and triazolothiadiazines encompassing 3–nitronaphtho[2,1-b]furan. *J. Chem. Pharm. Res.* **2011**, *3*, 445−451. (f) Adediran, S. A.; Vabaret, D.; Drouillat, B.; Pratt, R. F.; Wakselman, M. The synthesis and evaluation of benzofuranones as β-Lactamase substrates. *Bioorg. Med. Chem.* **2001**, *9*, 1175–1183; (g) Panisheva, E. K.; Alekseeva, L. M.; Evstratova, M. I.; Kiselev, S. S.; Granik, V. G. Synthesis of N-substituted aminomethylene-benzofuran-2-ones. *Pharm. Chem. J.* **2007**, *41*, 549–553.

(3) (a) Laver, H. S.; Nesvadba, P. Benzofuranones as heat stabilizers for powder coatings. Eur. Pat. Appl. 857765, 1998. (b) Frenette, M.; MacLean, P. D.; Barclay, R. C.; Scaiano, J. C. Radically Different Antioxidants: Thermally Generated Carbon-Centered Radicals as Chain-Breaking Antioxidants. *J. Am. Chem. Soc.* **2006**, *128*, 16432–16433. (c) Li, Y.; Lampkins, A. J.; Baker, M. B.; Sumpter, B. G.; Huang, J.; Abboud, K. A.; Castellano, R. K. Benzotrifuranone: Synthesis, Structure, and Access to Polycyclic Heteroaromatics. *Org. Lett.* **2009**, *11*, 4314–4317.

(4) For general reviews on the importance of Quaternary Stereocenters see: (a) Vetica, F.; Marcia de Figueiredo, R.; Orsini, M.; Tofani, D.; Gasperi T. Recent Advances in Organocatalytic Cascade Reactions toward the Formation of Quaternary Stereocenters. *Synthesis*, **2015**, *47*, 2139–2184. (b) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz B.M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740–751. (c) Heileman, M. J.; Moore, H. W. Generation and intramolecular cyclization of (2-ethenylphenyl)bisketenes. Synthesis of benzofuranones. *Tetrahedron Lett.* **1998**, *39*, 3643–3646. (d) Vetica, F.; Marcia de Figueiredo, R.; Cupioli, E.; Gambacorta, A.; Loreto, M. A.; Micelia, M.; Gasperi, T. First asymmetric organocatalyzed domino Friedel–Crafts/lactonization reaction in the enantioselective synthesis of the GABAB receptor modulator (S)-BHFF. *Tetrahedron Lett.* **2016**, *57*, 750–753. (e) Vetica, F.; Pelosi, A.; Gambacorta, A.; Loreto, M.A.; Miceli, M.; Gasperi T. Catalytic Friedel–Crafts/Lactonization Domino Reaction: Facile Access to 3-Hydroxybenzofuran-2-one Scaffold. *Eur. J. Org. Chem.* **2014**, 1899–1906. (f) Zhu, C.-L.; Zhang, F.-G.; Meng, W.; Nie, J.; Cahard, D.; Ma, J.-A. Enantioselective base-free electrophilic amination of benzofuran-2(3*H*)-ones: catalysis by binol-derived P-spiro quaternary phosphonium salts. *Angew. Chem. Int. Ed.* **2011**, *50*, 5869–5872. (g) Salami-Ranjbaran, E.; Khosropour, A. R.; Mohammadpoor-Baltork, I. A domino approach for the synthesis of naphtho[2,1-b]furan-2(1*H*)-ones from azlactones. *Tetrahedron* **2014,** *70*, 9268–9273.

(5) (a) Kotha, S.; Bandarugattu, V. B.; Krishna, N. G. Diversity-oriented approach to unusual amino acid derivatives and heterocycles via methyl 2-acetamidoacrylate and its congeners. *Tetrahedron*, **2014**, *70*, 5361–5384. (b) Kazmaier, U.; Synthesis and Chemistry of α,β-Didehydroamino Acids, Amino Acids, Peptides and Proteins in Organic Chemistry, Building Blocks, Catalysis and Coupling Chemistry,. Hughes, A. B., Eds.; Wiley-VCH: Weinheim, Germany, 2009, Vol. 2, Chapter 1, pp. 3–18;

(6) (a) Love, A. L.; Olsen, R. K. Orientation in electrophilic addition reactions to 2-acetamidoacrylic acid derivatives. *J. Org. Chem.*, **1972**, *37*, 3431–3433. (b) Berry, J. M.; Doyle, P. M.; Young, D. W. An interesting dichotomy in the cyclisation of exocyclic enamines with protected dehydroamino acids leading to different β-turn templates. *Tetrahedron Lett.* **2002**, *43*, 8963–8966. (c) Richards, K. D.: Kolar, A. J.; Srinivasan, A.; Stephenson, R. W.; Olsen, R. K. The reaction of dialkylcopper lithium reagents with 3-halo-2-acylaminoacrylic acids. *J. Org. Chem.* **1976**, *41*, 3674–3677. (d) Durow, A. C.; Butts, C.; Willis, C. L. Stereochemical Assignments of the Chlorinated Residues in Victorin C. *Synthesis* **2009,** *17*, 2954–2962. (e) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. Regioselective Synthesis of Substituted Pyrroles: Efficient Palladium-Catalyzed Cyclization of Internal Alkynes and 2-Amino-3-iodoacrylate Derivatives. *Org. Lett.* **2006**, *8*, 5837–5840. (f) Kohn, H.; Sawhney, K. N.; Bardel, P.; Robertson, D. W.; Leander, J. D. Synthesis and anticonvulsant activities of .alpha.-heterocyclic .alpha.-acetamido-*N*-benzylacetamide derivatives. *J. Med. Chem.* **1993**, *36*, 3350–3360. For the reviews of enamides on their nucleophilicity, see: (g) Carbery, D. R. Enamides: valuable organic substrates. *Org. Biomol. Chem.*, **2008**, *6*, 3455–3460. (h) Gopalaiah, K.; Kagan, H. B. Use of Nonfunctionalized Enamides and Enecarbamates in Asymmetric Synthesis. *Chem. Rev.* **2011**, *111*, 4599–4657. (i) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. Catalytic Enantioselective Formation of C−C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. *Chem. Rev.* **2011**, *111*, 2626–2704.

(7) With heteroatoms: (a) Montserrat, P.; Roser, P. $FeCl_3$-catalyzed conjugate addition of secondary amines, imidazole and pyrazole to methyl 2-acetamidoacrylate. Preparation of *β*-dialkylamino-αalanine and *β*-(*N*-heteroaryi)-α-alanine derivatives. *Tetrahedron* **1995**, *51*, 8355–8362. (b) Boschin, G.; Scaglioni, L.; Arnoldi, A. Optimization of the Synthesis of the Cross-Linked Amino Acid Ornithinoalanine and Nuclear Magnetic Resonance Characterization of Lysinoalanine and Ornithinoalanine. *J. Agric. Food Chem.* **1999**, *47*, 939–944. (c) Lin, Y. A.; Boutureira, O.; Lercher, L.; Bhushan, B.; Paton, R. S.; Davis, B. G. Rapid Cross-Metathesis for Reversible Protein Modifications via Chemical Access to Se-Allyl-selenocysteine in Proteins. *J. Am. Chem. Soc.* **2013**, *135*, 12156–12159. (d) Bartoccini, F.; Bartolucci, S.; Lucarini. S.; Piersanti, G. Synthesis of Boron- and Silicon-Containing Amino Acids through Copper-Catalysed Conjugate Additions to Dehydroalanine Derivatives. *Eur. J. Org. Chem.* **2015**, 3352–3360. (e) Obara, N.; Watanabe, T.; Asakawa, T.; Kan, T.; Tanaka, T. Efficient Synthesis of 3-Amino-1,5-benzodiazepine-2-one Derivatives. *Synlett* **2017**, *28*, 1183–1186. With arenes: (f) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini S.; Piersanti; G. Switchable Reactivity of Acylated *α*,*β*-Dehydroamino Ester in the Friedel−Crafts Alkylation of Indoles by Changing the Lewis Acid. *J. Org. Chem.* **2008**, *73*, 5654–5657. (g) Bartolucci, S.; Bartoccini, F.; Righi, M.; Piersanti. G. Direct, Regioselective, and Chemoselective Preparation of Novel Boronated Tryptophans by Friedel–Crafts Alkylation. *Org. Lett.* **2012**, *14*, 600–603. (h) De Marco, R.; Cavina, L.; Greco, A.; Gentilucci, L. Easy preparation of dehydroalanine building blocks equipped with oxazolidin-2-one chiral auxiliaries, and applications to the stereoselective synthesis of substituted tryptophans *Amino Acids* **2014**, *46*, 2823–2839. (i) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. Enantioselective Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts Conjugate Addition/Asymmetric Protonation Reaction. *J. Am. Chem. Soc.* **2012**, *134*, 5131–5137.

(8) (a) Zhao, M.-N.; Yu, L.; Hui, R.-R.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Iron-Catalyzed Dehydrogenative [4 + 2] Cycloaddition of Tertiary Anilines and Enamides for the Synthesis of Tetrahydroquinolines with Amido-Substituted Quaternary Carbon Centers. *ACS Catalysis* **2016**, *6*, 3473–3477. (b) Lucarini, S.; Bartoccini, F.; Battistoni, F.; Diamantini, G.; Piersanti, G.; Righi, M.; Spadoni G. A Novel One-Pot Approach of Hexahydropyrrolo[2,3-b]indole Nucleus by a cascade addition/cyclization strategy: Synthesis of (±)-Esermethole. *Org. Lett.* **2010**, *12*, 3844–3847. (c) Repka, L. M.; Ni, J.; Reisman, S. E. Enantioselective Synthesis of Pyrroloindolines by a Formal [3 + 2] Cycloaddition

Reaction. *J. Am. Chem. Soc.* **2010**, *132*, 14418–14420. (d) Rossi, E.; Pirovano, V.; Negrato, M.; Abbiati, G.; Dell'Acqua, M. Synthesis of constrained analogues of tryptophan. *Beilstein J. Org. Chem.* **2015**, *11*, 1997–2006.

(9) (a) Schmidt, U.; Öhler, E. Optical Induction During Biomimetic Formation of Cysteine. *Angew. Chem. Int. Ed.* **1976**, *15*, 42. (b) Zhu, Y.; van der Donk, W. A. Convergent Synthesis of Peptide Conjugates Using Dehydroalanines for Chemoselective Ligations. *Org. Lett.* **2001**, *3*, 1189–1192. (c) Galonic, D. P.; Van Der Donk, W. A.; Gin, D. Y.; Oligosaccharide-peptide ligation of glycosyl thiolates with dehydropeptides: synthesis of S-linked mucin-related glycopeptide conjugates. *Chem. Eur. J.* **2003**, *9*, 5997–6006. (d) Chalker, J. M.; Gunnoo, S. B.; Boutureira, O.; Gerstberger, S. C.; Fernández-González, M.; Bernardes, G. J. L.; Griffin, L.; Hailu, H.; Schofield C. J.; Davis, B. G. Methods for converting cysteine to dehydroalanine on peptides and proteins. *Chem. Sci.* **2011**, *2*, 1666–1676. (e) Freedy, A. M.; Matos, M. J.; Boutureira, O.; Corzana, F.; Guerreiro, A.; Akkapeddi, P.; Somovilla, V. J.; Rodrigues, T.; Nicholls, K.; Xie, B.; Jimenez-Oses, G.; Brindle, K. M.; Neves A. A.; Bernardes, G. J. L. Chemoselective Installation of Amine Bonds on Proteins through Aza-Michael Ligation. *J. Am. Chem. Soc.* **2017**, *139*, 18365–18375. (f) Aronoff, M. R.; Gold, B.; Raines, R. T. 1,3-Dipolar Cycloadditions of Diazo Compounds in the Presence of Azides. *Org. Lett.* **2016**, *18*, 1538–1541. (g) Wright, T. H.; Bower, B. J.; Chalker, J. M.; Bernardes, G. J. L.; Wiewiora, R.; Ng, W. L.; Raj, R.; Faulkner, S.; Vallee, M. R. J.; Phanumartwiwath, A.; Coleman, O. D.; Thezenas, M. L.; Khan, M.; Galan, S. R. G.; Lercher, L.; Schombs, M. W.; Gerstberger, S.; Palm-Espling, M. E.; Baldwin, A. J.; Kessler, B. M.; Claridge, T. D. W.; Mohammed, S.; Davis, B. G. Posttranslational mutagenesis: A chemical strategy for exploring protein side-chain diversity. *Science* **2016**, *354*, 597. (h) Yang, A.; Ha, S.; Ahn, J.; Kim, R.; Kim, S.; Lee, Y.; Kim, J.; Söll, D.; Lee, H.Y.; Park, H.S. A chemical biology route to site-specific authentic protein modifications. *Science* **2016**, *354*, 623–626. (i) Key, H. M.; Miller, S. J. Site- and Stereoselective Chemical Editing of Thiostrepton by Rh-Catalyzed Conjugate Arylation: New Analogues and Collateral Enantioselective Synthesis of Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 15460–15466.

(10) (a) Terada, M.; Sorimachi, K. Enantioselective Friedel−Crafts Reaction of Electron-Rich Alkenes Catalyzed by Chiral Brønsted Acid. *J. Am. Chem. Soc.* **2007**, *129*, 292–293. (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. Chiral Brønsted acid catalyzed enantioselective Friedel-Crafts reaction of indoles and alpha-aryl enamides: construction of quaternary carbon atoms. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565–5567. (c) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. Highly enantioselective organocatalytic formation of a quaternary carbon center via chiral Brønsted acid catalyzed self-coupling of enamides. *Chem. Commun.* **2008**, 4637–4639. (d) Hermeke, J.; Toy, P. H. Phosphonium ion tagged chiral phosphoric acids and their application in Friedel–Crafts reactions of indoles. *Tetrahedron,* **2011**, *67*, 4103–4109. (e) Wu, K.; Zhuo, M.-H.; Sha, D.; Fan, Y.-S.; An, D.; Jiang, Y.-J.; Zhang, S. H_8-BINOL chiral imidodiphosphoric acid catalyzed highly enantioselective aza-Friedel–Crafts reactions of pyrroles and enamides/imines. *Chem. Commun.* **2015**, *51*, 8054–8057.

(11) (a) Righi, M.; Bartoccini, F.; Lucarini S.; Piersanti, G. Organocatalytic synthesis of α-quaternary amino acid derivatives via aza-Friedel–Crafts alkylation of indoles with simple α-amidoacrylates. *Tetrahedron* **2011**, *67*, 7923–7928. (b) Lucarini, S.; Mari, M.; Piersanti, G.; Spadoni, G. Organocatalyzed coupling of indoles with dehydroalanine esters: synthesis of bis(indolyl)propanoates and indolacrylates. *RSC Adv.* **2013,** *3*, 19135–19143. (c) de la Hoz, A.; Diaz-Ortiz, A.; Victoria Gomez, M.; Antonio Mayoral, J.; Moreno, A.; Sanchez-Migallon, A. M.; Vazquez, E. Preparation of α- and β-substituted alanine derivatives by α-amidoalkylation or Michael addition reactions under heterogeneous catalysis assisted by microwave irradiation. *Tetrahedron* **2001**, *57*, 5421–5428. (d) Pirovano, V.; Facoetti, D.; Dell'Acqua, M.; Della Fontana, E.; Abbiati, G.; Rossi, E. Gold(I) or Silver Catalyzed Synthesis of α-Indolylacrylates. *Org. Lett.* **2013**, *15*, 3812–3815. (e) For an earlier report, using a Lewis-acid-promoted stoichiometric

Friedel–Crafts reaction, see: Royo, E.; López, P.; Cativiela, C. Application of a new methodology for the synthesis of α-methyl-α-arylglycines using methyl acetamidoacrylate as an α-methylglycine cation equivalent. ARKIVOC **2005**, *vi)*, 46-61.

(12) A review on enantioselective Friedel–Crafts reactions of naphthols: (a) Montesinos-Magraner, M. ; Vila, C.; Blay, G.; Pedro, J. R. Catalytic Enantioselective Friedel–Crafts Reactions of Naphthols and Electron-Rich Phenols. *Synthesis* **2016**, *48*, 2151–2164. Selected examples of aza-Friedel –Crafts reaction of naphthols: (b) Niu, L. F.; Xin, Y.-C.; Wang, R.-L.; Jiang, F.; Xu, P.-F.; Hui, X.-P. Asymmetric Aza-Friedel-Crafts Reaction of 2-Naphthol with Tosylimines Catalyzed by a Dinuclear Zinc Complex. *Synlett* **2010**, 765–768. (c) Chauhan, P.; Chimni, S. S. Asymmetric Organocatalytic Aza-Friedel–Crafts Reaction of Naphthols with N-Sulfonyl Imines. *Eur. J. Org. Chem.* **2011**, 1636-1640. (d) Liu, G.; Zhang, S.; Li, H.; Zhang, T.; Wang, W. Organocatalytic Enantioselective Friedel−Crafts Reactions of 1-Naphthols with Aldimines. *Org. Lett.* **2011**, *13*, 828–831. (e) Takizawa, S.; Hirata, S.; Murai, K.; Fujioka, H.; Sasai, H. C_3-Symmetric chiral trisimidazoline-catalyzed Friedel–Crafts (FC)-type reaction. *Org. Biomol. Chem.* **2014**, *12*, 5827–5830. (f) Montesinos-Magraner, M.; Cantln, R.; Villa, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Organocatalytic enantioselective aza-Friedel–Crafts reaction of 2-naphthols with benzoxathiazine 2,2-dioxides. *RSC Adv.* **2015**, *5*, 60101–60105. (g) Kumari, P.; Barik, S.; Khan, N. H.; Ganguly, B.; Kureshy, R. I.; Abdi, S. H. R., Bajaj, H. C. The origin for highly enantioselective induction of 1-naphthol to isatin-derived *N*-Boc ketimines catalyzed by quinine thiourea catalyst: an experimental and computational study. *RSC Adv.* **2015**, *5*, 69493–69501. (h) Kaya, U.; Chauhan, P.; Mahajan, S.; Deckers, K.; Valkonen, A.; Rissanen, K.; Enders D. Squaramide-Catalyzed Asymmetric aza-Friedel-Crafts/N,O-Acetalization Domino Reactions Between 2-Naphthols and Pyrazolinone Ketimines. *Angew. Chem. In. Ed.* **2017,** *56*, 15358–15362. (i) Weber, M.; Weber, M.; Kleine-Boymann, M. "Phenol" in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, **2004**, pp. 503–519.

(13) (a) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans. *Angew. Chem. Int. Ed.* **2015**, *54*, 8203–8207. (b) Montesinos-Magraner, M.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Hydroxy-Directed Enantioselective Hydroxyalkylation in the Carbocyclic Ring of Indoles. *Org. Lett.*, **2017**, *19*, 1546–1549. (c) Xiao, M.; Xu, D.; Liang, W.; Wu, W.; Chan, A. S. C.; Zhao, J. Organocatalytic Enantioselective Friedel–Crafts Alkylation/Lactonization Reaction of Hydroxyindoles with Methyleneoxindoles. *Adv. Synth. Catal.* **2018**, *360*, 917–924 (d) Vila, C.; Rostoll-Berenguer, J.; Sánchez-García, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Enantioselective Synthesis of 2-Amino-1,1-diarylalkanes Bearing a Carbocyclic Ring Substituted Indole through Asymmetric Catalytic Reaction of Hydroxyindoles with Nitroalkenes. *J. Org. Chem.* **2018**, *83*, 6397–6407.

(14) Methyl 2,2-bis(5-hydroxy-1*H*-indol-3-yl)propanoate: ^{1}H NMR (CD_3OD): δ 2.02 (s, 3H), 3.66 (s, 3H), 6.63 (dd, J = 8.5 and 2.5 Hz, 2H), 6.80 (d, J = 2.5 Hz, 2H), 6.92 (s, 2H), 7.16 (d, J = 8.5 Hz, 2H), ^{13}C NMR (CD_3OD) δ 24.8, 46.0, 51.0, 104.8, 110.7, 111.2, 117.1, 123.7, 126.6, 132.2, 149.3, 176.8.

(15) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. Chiral Brønsted Acid Catalyzed Enantioselective Friedel–Crafts Reaction of Indoles and α-Aryl Enamides: Construction of Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565–5567.

(16) (a) Zhou, Z.-W.; Li, W.-C.; Hu, Y.; Wang, B.; Ren, G.; Feng, L.-H. Synthesis of the intermediate for fumimycin: a natural peptide deformylase inhibitor. *Res. Chem. Intermed.* **2013**, *39*, 3049–3054. (b) Gross, P.J.; Bräse, S. The Total Synthesis of (±)-Fumimycin. *Chem. Eur. J.* **2010**, *16*, 12660–12667. (c) Zhou, Z.; Hu, Y.; Wang, B.; He, X.; Ren, G.; Feng, L. A Concise Synthesis of (±)-Methoxyfumimycin Ethyl Ester *J. Chem. Res.* **2014**, *38*, 378– 380.

(17) Wencel-Delord, J.; Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of

functional molecules. *Nat. Chem.* **2013**, *5*, 369–375.

(18) A small amount of aza-Michael adduct was formed. Methyl 2-acetamido-3-((3-hydroxyphenyl)amino)propanoate: ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.46 – 3.64 (m, 2H), 3.78 (s, 3H), 4.80 (dd, *J* = 12.5 and 5.0 Hz, 1H), 6.17 – 6.27 (m, 3H), 6.50 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.28 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 23.1, 45.6, 52.7, 52.9, 99.9, 105.4, 105.7, 130.3, 148.9, 157.3, 170.9, 171.6.

(19) (a) Zhou, D.; Huang, Z.; Yu, X.; Wang, Y.; Li, J.; Wang, W.; Xie, H. A Quinine-Squaramide Catalyzed Enantioselective Aza-Friedel–Crafts Reaction of Cyclic Trifluoromethyl Ketimines with Naphthols and Electron-Rich Phenols. *Org Lett.* **2015**, *17*, 5554–5557; (b) Montesinos-Magraner, M.; Vila, C.; Canton, R.; Blay, G.; Fernandez, I.; Munoz, M. C.; Pedro, J. R. Organocatalytic asymmetric addition of naphthols and electron-rich phenols to isatin-derived ketimines: highly enantioselective construction of tetrasubstituted stereocenters. *Angew. Chem., Int. Ed.* **2015**, *54*, 6320–6324. (c) Montesinos-Magraner, M.; Vila, C.; Rendón-Patiño, A.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Organocatalytic Enantioselective Friedel–Crafts Aminoalkylation of Indoles in the Carbocyclic Ring. *ACS Catal.* **2016**, *6*, 2689–2693.

(20) Li, G.; Sun, W.; Li, J.; Jia, F.; Hong, L.; Wang, R. Organocatalytic enantioselective formal arylation of azlactones using quinones as the aromatic partner. *Chem. Commun.* **2015**, *51*, 11280–11282.

(21) Di Iorio, N.; Filippini, G.; Mazzanti, A.; Righi, P.; Bencivenni, G. Controlling the C(sp3)-C(sp2) Axial Conformation in the Enantioselective Friedel-Crafts-Type Alkylation of β-Naphthols with Inden-1-ones. *Org. Lett.* **2017**, *19*, 6692–6695.

(22) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. Indolynes as Electrophilic Indole Surrogates: Fundamental Reactivity and Synthetic Applications. *Org. Lett.* **2009**, *11*, 1007–1010.

(23) Palmer, F. N.; Lach, F.; Poriel, C.; Pepper, A. G.; Bagley, M. C.; Slawinb, A. M. Z.; Moody, C. J. The diazo route to diazonamide A: studies on the tyrosine-derived fragment. *Org. Biomol. Chem.* **2005**, *3*, 3805–3811.

(24) Hatano, M.; Ikeno, T.; Matsamura, T.; Torii, S.; Ishihara, K. Chiral Lithium Salts of Phosphoric Acids as Lewis Acid–Base Conjugate Catalysts for the Enantioselective Cyanosilylation of Ketones. *Adv. Synth. Catal.* **2008**, *350*, 1776–1780.

(25) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. Synthesis and structural aspects of N-triflylphosphoramides and their calcium salts--highly acidic and effective Brønsted acids. *Chem. Eur. J.* **2010**, *16*, 13116–13126.

(26) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. Synthesis of TRIP and Analysis of Phosphate Salt Impurities. *Synlett.* **2010**, 2189–2192.

(27) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. Chiral Brønsted Acid-catalyzed Enantioselective Hydrophosphonylation of Imines: Asymmeteric Synthesis of α-Amino Phosphonates *Org. Lett*. **2005**, *7*, 2583–2585.