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2-[(Imidazolylthio)methyl]pyrrolidine as a Trifunctional Organocatalyst for the Highly Asymmetric Michael Addition of Ketones to Nitroolefins

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The direct asymmetric Michael addition of ketones to nitroolefins catalyzed by 2-[(imidazol-2-ylthio)methyl]pyrrolidine, constructed from natural L-proline and imidazolylthio platforms, with salicylic acid as a co-catalyst has been developed to give the products in high yields (up to 95 %) and with excellent enantioselectivities (up to 99 % *ee*). The highly efficient catalytic performance may be attributed to the dual activation of the Michael substrates by the trifunctional organocatalysts and the co-catalyst salicylic acid, leading to the formation of a stable transition state complex through the synergic effect of hydrogen-bonding and electrostatic interactions.

Introduction

Organocatalysis has emerged as an important area of research over the last decade. Compared with biocatalysts and metal catalysts, organocatalysts are usually more stable, more environmentally friendly, more readily available, less expensive and can be applied in less demanding reaction conditions, such as rigorously anhydrous or anaerobic conditions. Therefore much attention has recently been paid to the design and application of organocatalysts[1] with a particular focus on the development of efficient small chiral amine molecules for use in the asymmetric Michael addition of aldehydes or ketones to nitroolefins[2] due to the versatility of the nitro functionality which can be easily transformed into, for example, amine, nitrile oxide, ketone, carboxylic acid, hydrogen.[3] L-Proline[4] and chiral pyrrolidines in which a tertiary amino,[5] pyridyl,[6] pyrrolidinyl,[7] tetrazolyl,[8] diphenyl(silyloxy)methyl,[9] sulfonamido,[10] thiourea functionality[11] and others[12] replace the carboxy group of L-proline have been extensively investigated as organocatalysts for the Michael addition reaction (Figure 1). In this process the pyrrolidine portion is regarded as a unique backbone for the asymmetric catalysis which facilitates enamine- and imine-based transformations of aldehyde or ketone precursors and the configuration of the final Michael adducts is generally controlled by steric hindrance or by hydrogen-bond donors of the substituent groups α to the pyrrolidine nitrogen atom.

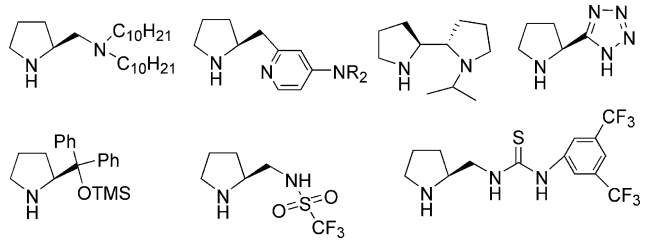
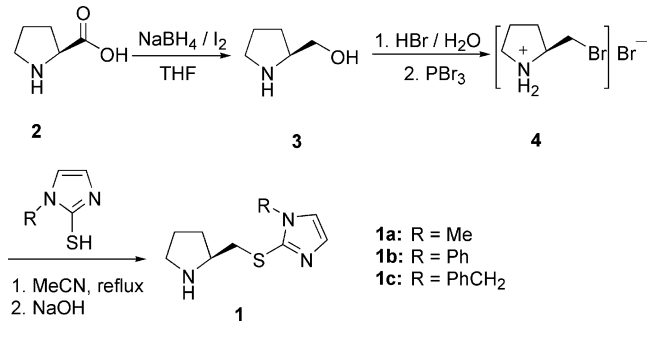


Figure 1. Examples of pyrrolidine-based chiral organocatalysts.

Therefore, as part of a program aimed at developing new organocatalysts, we herein report the behaviour of our novel designed chiral 2-[(imidazol-2-ylthio)methyl]pyrrolidines (Scheme 1) in catalyzing the asymmetric Michael addition of ketones to nitroolefins. We envisioned that the pyrrolidine portion serves as the catalytic site and the imidazole functionality in the pyrrolidine-based diamine motif has the potential to enhance the enantioselectivity, while the thioether moiety, which is found to be a very useful



Scheme 1. Synthesis of (imidazolylthio)methyl-pyrrolidine catalysts **1a**–**c**.

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functionality in coordination compounds, supramolecular chemistry and nanomaterials, should benefit the formation of a stable enamine- or imine-based transition state during the catalytic cycle through electrostatic interactions.

Results and Discussion

The novel designed trifunctional catalysts **1a**–**c** were readily synthesized by etherification of 1-substituted 2-mercaptoimidazole with (*S*)-(+)-2-(bromomethyl)pyrrolidine hydrobromide (**4**) in refluxing MeCN, followed by neutralization with NaOH (Scheme 1). The key precursor **4** was prepared according to our previous work from commercially available L-proline by reduction with $NaBH_4/I_2$, a neutralization step and bromination with PBr_3.[13] NMR, IR and HRMS analysis results were in full accordance with their molecular structures, and the X-ray crystallographic analysis result of *N*-(*p*-tolylsulfonyl)-**1a**, which was obtained by treatment of **1a** with *p*-toluenesulfonyl chloride, further confirmed their relative configurations as described above (Figure 2).[14]

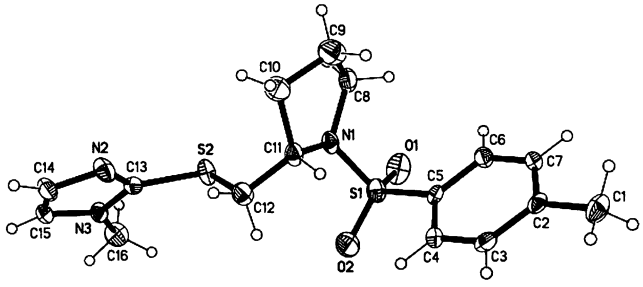
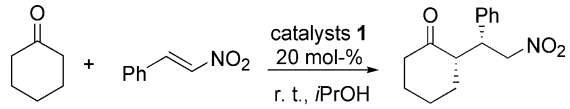


Figure 2. X-ray crystal structure of *N*-(*p*-tolylsulfonyl)-**1a**.

To investigate the catalytic performance of **1**, the Michael addition reaction of β-nitrostyrene (**6**) and 2 equiv. of cyclohexanone (**5**) was initially carried out in *i*PrOH at room temperature in the presence of 20 mol-% of the catalysts. As can be seen from the results summarized in Table 1, the reaction was slow when treated with **1** alone without co-catalysts, affording the Michael adduct **7** in low yields of less than 28% after 156 h (entries 1–3), because a powdery and insoluble solid side-product was formed which might be the polymerization product of **6**.[5b] To our delight, the addition of hydrobromic acid as co-catalyst increased dramatically the catalytic activity to provide 70–78% yields and a high level of diastereo- and enantioselectivity after 72 h (entries 4–6). After screening various co-catalysts of various acids, including HBF_4, HPF_6, TFA, TsOH (entries 7–18), salicylic acid was found to be the co-catalyst of choice for **1a**, which afforded **7** within 20 h in a high yield of 95% with excellent diastereo- and enantioselectivity of 97:3 and 99% *ee*, respectively (entry 17). This observation highlights the importance of the use of an acid co-catalyst with the pyrrolidine-based diamine motif.[5–7] In addition, one feature that seems to be favourable for the carboxylic acid co-catalysts is an adjacent hydrogen-bond donor (entries 16–18).

Table 1. Performance of catalysts **1** and acid co-catalysts in the asymmetric Michael addition of cyclohexanone (**5**) to β-nitrostyrene (**6**) in *i*PrOH at room temperature.[a]



5 **6** **7**

Entry	Catalyst	Co-catalyst	Time [h]	% Yield[b]	*dr*[c] (*syn*/*anti*)	*ee*[d] (%)
1	**1a**	–	156	28	88:12	84
2	**1b**	–	156	4	n.d.[e]	n.d.[e]
3	**1c**	–	156	10	n.d.[e]	n.d.[e]
4	**1a**	HBr	72	78	98:2	91
5	**1b**	HBr	72	70	92:8	85
6	**1c**	HBr	72	72	93:7	83
7	**1a**	HBF_4	72	4	n.d.[e]	n.d.[e]
8	**1a**	HPF_6	72	13	95:5	91
9	**1a**	CH_3SO_3H	72	44	93:7	93
10	**1a**	CH_3COOH	72	56	96:4	92
11	**1a**	$ClCH_2COOH$	72	67	92:8	91
12	**1a**	CF_3COOH	28	72	99:1	92
13	**1a**	$CH_3(CH_2)_5COOH$	96	58	92:8	87
14	**1a**	$HOOCCH_2COOH$	96	81	97:3	91
15	**1a**	*p*-$CH_3C_6H_4SO_3H$	72	80	95:5	85
16	**1a**	PhCOOH	40	90	97:3	74
17	**1a**	*o*-OH-C_6H_4COOH	20	95	97:3	99
18	**1a**	*m*-OH-C_6H_4COOH	96	37	96:4	90

[a] All reactions were conducted in *i*PrOH (2 mL) using **5** (1 mmol) and **6** (0.5 mmol) in the presence of 20 mol-% of the catalysts. [b] Isolated yield. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis with a CD detector (Daicel Chiralpak AS-H, hexane/*i*PrOH = 95:5). [e] n.d. = not determined.

The Michael addition reaction catalyzed by **1a** with the co-catalyst salicylic acid in various solvents at room temperature was next probed. As shown in Table 2, in weak and non-polar solvents such as hexane, Et_2O and CH_2Cl_2, the reactions were sluggish with 62–70% yields after 156 h, although good enantioselectivities (85–89% *ee*) were observed (entries 1–3). However, in THF and DMSO the Michael reaction proceeded relatively smoothly to give 80–91% yields with a high enantioselectivity of 91% after 60–72 h (entries 4 and 5). Among the conventional organic solvents investigated, the greatest enhancement was recorded with *i*PrOH, affording 95% yield and 99% *ee* within 20 h (entry 6). The reaction in H_2O was very slow due to the poor solubility of β-nitrostyrene (entry 7). At the same time, the use of ionic liquids such as [BMIm]BF_4 and [BMIm]PF_6 gave enantioselectivities of 86 and 72% and 70 and 65% yields after 156 h, respectively (entries 8 and 9). In addition, the reaction proceeded readily under solvent-free conditions and 95% yield with 91% *ee* could be obtained within 12 h (entry 10). Therefore, *i*PrOH was chosen for further reactions.

After optimization of the reaction conditions, the asymmetric Michael additions of diverse unmodified ketones to a variety of nitroolefins promoted by **1a**/salicylic acid were conducted in *i*PrOH at room temperature. As shown in Table 3, cyclohexanone reacted readily with various sty-

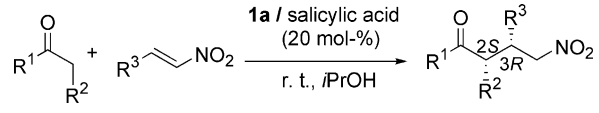
Table 2. Solvent effects on the asymmetric Michael addition of cyclohexanone (**5**) to β-nitrostyrene (**6**) catalyzed by **1a**/salicylic acid.[a]

Entry	Solvent	Time [h]	% Yield[b]	*dr*[c] (*syn*/*anti*)	*ee* (%)[d]
1	hexane	156	70	92:8	88
2	Et_2O	156	65	92:8	85
3	CH_2Cl_2	156	62	93:7	89
4	THF	60	91	92:8	91
5	DMSO	72	80	94:6	91
6	*i*PrOH	20	95	97:3	99
7	H_2O	156	20	90:10	85
8	[BMIm]BF_4	156	70	92:8	86
9	[BMIm]PF_6	156	65	85:15	72
10	neat[e]	12	95	94:6	91

[a] Unless otherwise noted, all reactions were conducted in solvent (2 mL) using **5** (1 mmol) and **6** (0.5 mmol) with 20 mol-% of **1a**/salicylic acid at room temperature. [b] Isolated yield. [c] Determined by GC–MS. [d] Determined by chiral HPLC analysis with a CD detector (Daicel Chiralpak AS-H, hexane/*i*PrOH = 95:5). [e] Cyclohexanone (2 mL) was used.

rene-type nitroolefins with high enantioselectivity (87–99% *ee*, entries 1–9). The O- and S-heteroaromatic nitroolefins could also be used as acceptors, giving the corresponding Michael adducts in 85 and 90% yields with 78 and 92% *ee*, respectively (entries 10 and 11). Cyclopentanone worked well to give the desired adduct with an excellent enantioselectivity of 95% (entry 12). Tetrahydropyran-4-one and tetrahydrothiopyran-4-one were suitable substrates as donors as well, providing the products in yields of 90–91%

Table 3. Asymmetric Michael addition of ketones to nitroolefins in *i*PrOH catalyzed by **1a**/salicylic acid.[a]

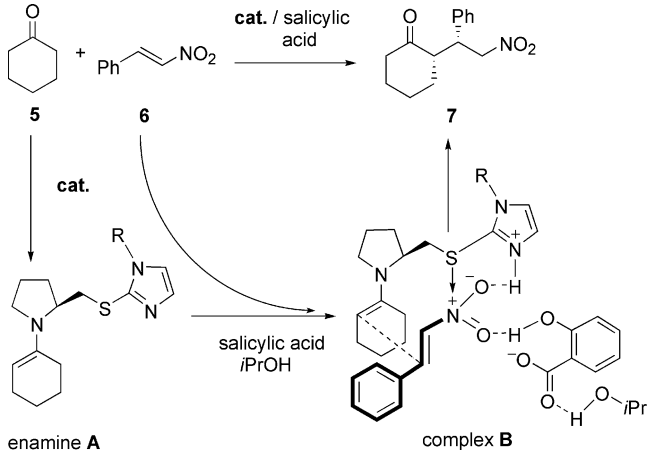


Entry	Adduct R^1–R^2	R^3	% Yield[b]	*dr*[c] (*syn*/*anti*)	*ee*[d] (%)
1	–$(CH_2)_4$–	*o*-$MeOC_6H_4$	94	91:9	94
2	–$(CH_2)_4$–	*p*-$MeOC_6H_4$	89	94:6	99
3	–$(CH_2)_4$–	*p*-MeC_6H_4	92	97:3	99
4	–$(CH_2)_4$–	*p*-ClC_6H_4	92	92:8	87
5	–$(CH_2)_4$–	*o*-BrC_6H_4	95	92:8	95
6	–$(CH_2)_4$–	*m*-BrC_6H_4	83	87:13	96
7	–$(CH_2)_4$–	*p*-$CF_3C_6H_4$	86	93:7	95
8	–$(CH_2)_4$–	*o*-$NO_2C_6H_4$	85	80:20	89
9	–$(CH_2)_4$–	2-naphthyl	91	98:2	96
10	–$(CH_2)_4$–	2-furanyl	85	85:15	78
11	–$(CH_2)_4$–	2-thienyl	90	86:14	92
12	–$(CH_2)_3$–	Ph	88	83:17	95
13	–$CH_2CH_2OCH_2$–	Ph	90	98:2	99
14	–$CH_2CH_2SCH_2$–	Ph	91	87:13	88
15	CH_3 *i*Pr	Ph	50	–	63
16	CH_3 H	Ph	82	–	56
17[e]	H *i*Pr	Ph	85	80:20	63

[a] All reactions were conducted in *i*PrOH (2 mL) using ketones (1 mmol) and nitroolefins (0.5 mmol) with 20 mol-% of **1a**/salicylic acid. [b] Isolated yield. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis with a CD detector. [e] The product with the 2*R*,3*S* configuration was observed which resulted from a *Si*-face attack on the aldehyde-derived enamine.[10b]

and enantioselectivities of 88–99% (entries 13 and 14). Linear ketones and isovaleraldehyde also provided the desired adducts in moderate enantioselectivities (entries 15–17).

On the basis of the experimental results described above and Seebach and Pieraccini's enamine-based reaction mechanism,[15] a stereochemical model was developed to account for the high enantioselectivity of this Michael addition reaction. As shown in Scheme 2, multiple interactions between nitrostyrene (**6**), salicylic acid and the enamine **A**, formed from the catalyst **1a** and cyclohexanone (**5**), occur to afford the complex **B** through two synergic effects: 1) the electrostatic attractions of the electrophilic nitro nitrogen of **6** and the thioether functional group[16] and 2) hydrogen-bonding between the nitro oxygen of **6**, the hydroxy group of the salicylic acid and the protonated imidazole moiety of the enamine **A**. Moreover, the solvent of *i*PrOH may participate in an additional hydrogen-bonding interaction with the carboxy group of salicylic acid which results in the stabilization of carboxy anion of salicylic acid. Consequently, this complex **B** may impose a strong directing effect with the enamine **A** attacking the activated nitrostyrene (**6**) from the *Re* face to predominately give the Michael adduct **7**, which is consistent with experimental results.



Scheme 2. Plausible reaction mechanism for the Michael addition of cyclohexanone (**5**) to nitrostyrene (**6**) with **1a**/salicylic acid.

Conclusions

In summary, trifunctional organocatalysts based on 2-[(imidazol-2-ylthio)methyl]pyrrolidines **1** have been designed and readily synthesized from commercially available L-proline. The catalytic system of compound **1a** and salicylic acid in *i*PrOH demonstrated high yields (83–95%) and good enantioselectivities (78–99% *ee*) in the Michael addition of unmodified cyclohexanones to various aromatic nitroolefins. The key to the highly efficient catalytic performance might be the dual activation of the Michael substrates by the organocatalyst **1a** and the co-catalyst salicylic acid which leads to the formation of complex **B** through the synergic effect of hydrogen-bonding and electrostatic in-

teractions in the enamine-based mechanism. Further investigations on the application of these trifunctional catalysts in asymmetric organocatalysis are currently in progress and results will be reported in due course.

Experimental Section

General: All the starting chemicals were commercial products (Aldrich or J&K Chemica) of analytical grade. Organic solvents were dried and purified before use by the usual methods. ^1H and ^{13}C NMR spectra were recorded with a Varian NMR spectrometer. Chemical shifts are given in δ relative to tetramethylsilane (TMS). Coupling constants J are given in Hz. IR spectra were obtained with a Bruker EQUINOX 55 spectrometer. Electrospray ionization (ESI) mass spectrometry was performed with a Finnigan LCQ Advantage spectrometer. ESI-HRMS spectra were obtained with a Bruker APEX III FTICR mass spectrometer. GC-MS experiments were performed with an Agilent 6890N GC system equipped with a 5973N mass-selective detector. HPLC experiments were carried out using a JASCO LC-2000 Plus system consisting of MD and CD detectors.

Synthesis and Characterization of 2-[(Imidazol-2-ylthio)methyl]pyrrolidine Catalysts 1: (*S*)-(+)-2-(Bromomethyl)pyrrolidine hydrobromide (**4**) was prepared, in accord with our previous work, from commercially available L-proline by reduction with $NaBH_4/I_2$, a neutralization step and bromination with PBr_3.[13] Then a mixture of the 1-substituted 2-mercaptoimidazole (10 mmol) and (*S*)-(+)-2-(bromomethyl)pyrrolidine hydrobromide (**4**) (2.45 g, 10 mmol) in MeCN (30 mL) was heated with stirring at 80 °C for 8 h. After completion, the solvent was removed by distillation and the residue was recrystallized from EtOH and then neutralized by NaOH to pH 12. After extraction with CH_2Cl_2 (3 × 10 mL), the solvent was removed to afford **1**.

3-Methyl-2-[(2*S*)-(pyrrolidin-2-yl)methylthio]-3*H*-imidazol-1-ium Bromide (Hydrobromide Salt of 1a): ^1H NMR (400 MHz, [D$_6$]-DMSO, 25 °C): δ = 1.68–1.77 (m, 1 H), 1.83–1.98 (m, 2 H), 2.07–2.16 (m, 1 H), 3.19–3.22 (m, 2 H), 3.35–3.42 (m, 2 H), 3.61 (s, 3 H), 3.81–3.84 (m, 1 H), 7.01 (d, J = 1.6 Hz, 1 H), 7.33 (d, J = 1.6 Hz, 1 H), 9.36 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO, 25 °C): δ = 23.4, 29.2, 33.2, 34.4, 44.6, 59.1, 123.6, 127.9, 139.7 ppm. IR (KBr): $\tilde{\nu}$ = 3418, 3107, 2953, 2748, 1631, 1461, 687 cm^{-1}. ESI-MS: m/z = 198 [M – Br]$^+$, 79 and 81 [Br]$^-$. HRMS (ESI+): calcd. for $[C_9H_{16}N_3S]^+$ 198.1059; found 198.1056.

3-Phenyl-2-[(2*S*)-(pyrrolidin-2-yl)methylthio]-3*H*-imidazol-1-ium Bromide (Hydrobromide Salt of 1b): ^1H NMR (400 MHz, [D$_6$]-DMSO, 25 °C): δ = 1.69–1.76 (m, 1 H), 1.84–1.98 (m, 2 H), 2.06–2.14 (m, 1 H), 3.16–3.26 (m, 2 H), 3.39–3.51 (m, 2 H), 3.86–3.92 (m, 1 H), 7.17 (d, J = 1.6 Hz, 1 H), 7.47–7.53 (m, 3 H), 7.55–7.60 (m, 3 H), 9.27 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 23.5, 29.4, 34.5, 44.9, 58.8, 123.3, 125.2, 128.5, 129.1, 129.5, 136.5, 140.5 ppm. IR (KBr): $\tilde{\nu}$ = 3427, 3086, 2961, 2722, 1593, 1498, 1478, 1344, 767, 695 cm^{-1}. MS (ESI): m/z = 260 [M – Br]$^+$. HRMS (ESI+): calcd. for $[C_{14}H_{18}N_3S]^+$ 260.1216; found 260.1221.

3-Benzyl-2-[(2*S*)-(pyrrolidin-2-yl)methylthio]-3*H*-imidazol-1-ium Bromide (Hydrobromide Salt of 1c): ^1H NMR (400 MHz, [D$_6$]-DMSO, 25 °C): δ = 1.68–1.76 (m, 1 H), 1.83–1.98 (m, 2 H), 2.06–2.12 (m, 1 H), 3.18–3.24 (m, 2 H), 3.34 (s, 2 H), 3.35–3.49 (m, 2 H), 3.87–3.91 (m, 1 H), 7.17 (d, J = 1.6 Hz, 1 H), 7.46–7.53 (m, 3 H), 7.56–7.60 (m, 1 H), 9.20 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 23.6, 29.4, 35.2, 45.0, 49.6, 59.3, 123.2, 127.3, 127.9, 128.8, 128.9, 136.9, 140.2 ppm. IR (KBr): $\tilde{\nu}$ = 3388, 3029, 2928, 2708, 1604, 1496, 1454, 1358, 715, 693 cm^{-1}. MS (ESI): m/z = 274 [M – Br]$^+$. HRMS (ESI+): calcd. for $[C_{15}H_{20}N_3S]^+$ 274.1372; found 274.1380.

Typical Experimental Procedure for the Asymmetric Michael Addition of Ketones to Nitroolefins: Cyclohexanone (**5**) (98 mg, 1 mmol) was added to a solution of nitrostyrene (**6**) (74.5 mg, 0.5 mmol), catalyst **1a** (19.7 mg, 0.1 mmol) and salicylic acid (13.8 mg, 0.1 mmol) in *i*PrOH (2 mL). The mixture was stirred at room temperature until completion of the reaction (by GC monitoring) H_2O was added to the reaction mixture to give an infusible substance. After filtration the residue was dissolved in ethyl acetate and purified by preparative TLC (hexane/$CHCl_3$ = 4:1) to afford the Michael adduct **7** (117.3 mg, 95%). The *ee* of the product was determined by chiral HPLC analysis with a CD detector [(Daicel Chiralpak AS-H, hexane/*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 14.28 (minor), 20.84 min (major)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19–2.72 (m, 9 H, cycl), 3.75 (ddd, J = 10, 10, 4.8 Hz, 1 H), 4.63 (dd, J = 12.4, 10 Hz, 1 H), 4.95 (dd, J = 12.4, 4.8 Hz, 1 H), 7.16–7.34 (m, 5 H) ppm. MS (EI): m/z (%) = 55 (30), 77 (12), 91 (63), 104 (34), 115 (25), 141 (15), 157 (13), 171 (100), 183 (21), 200 (60), 247 (1).

Acknowledgments

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