Cu(II)-Mediated Aminooxygenation of Alkenylimines and Alkenylamidines with TEMPO

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Abstract: A method for the synthesis of oxymethyl dihydropyrroles (pyrrolines) and dihydroimidazoles has been developed via Cu(II)-mediated intramolecular aminooxygenation of alkenylimines and alkenylamidines, respectively, with 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO).

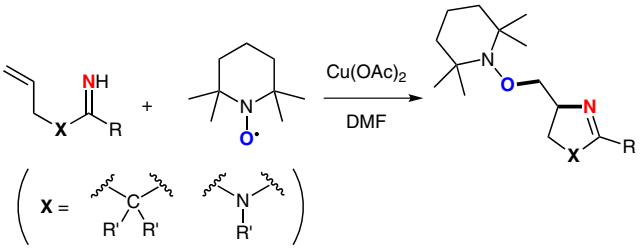
Key words: copper, TEMPO, dihydropyrroles (pyrrolines), dihydroimidazoles

Nitrogen-containing heterocycles (azaheterocycles) are an omnipresent component of numerous natural alkaloids and potent pharmaceutical drugs.[1] Diverse approaches toward azaheterocycle synthesis have been developed so far,[2] while there remains a demand for versatile methodologies to construct azaheterocycles with selective control of substitution patterns from readily accessible starting materials.

We have been interested in the use of readily available carbonitriles as a precursor of N-H imine by the reaction with Grignard reagents followed by proper protonation. It was found that the resulting N-H imines possess a diversity of chemical reactivity towards oxidative C–N bond formation with an intramolecular aryl C–H bond[3] as well as an alkene tether.[4] Moreover, the N-H imines can be served as an intramolecular directing group for copper-catalyzed aerobic C–H oxygenation.[5]

For the case of oxidative C–N bond formation with the intramolecular C=C bond, we recently developed the $PhI(OAc)_2$-mediated aminobromination to provide functionalized cyclic imines, such as bromomethyl dihydropyrroles and dihydroisoquinolines, with a one-pot formation of C–C, C–N, and C–Br bonds.[4] This transformation was carried out by a sequence of nucleophilic addition of Grignard reagents (RMgBr) to alkenyl carbonitriles to form N-H imines and their iminobromination by subsequent treatment with $PhI(OAc)_2$, where the bromine atom of the counteranion of the Grignard reagents was incorporated into the final products without utilizing additional bromine sources.

Inspired by these findings, we have strived to develop the other types of oxidative functionalization of the C=C bond with the transient N-H imine intermediates. Herein, we report the synthesis of oxymethyl dihydropyrroles (pyrrolines) starting from alkenyl carbonitriles and Grignard reagents via Cu(II)-mediated aminooxygenation of the alkene of the resulting NH imine with 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO, Scheme 1). Moreover, application of this strategy to *N*-allylamidines is also presented for the synthesis of oxymethyldihydroimidazoles (Scheme 1).



Scheme 1 Cu(II)-mediated synthesis of azaheterocycles from alkenylimines and alkenylamidines with TEMPO

Chemler has developed an elegant strategy of copper-mediated/-catalyzed aminooxygenation of alkenes with sulfonamide and aniline nitrogens with TEMPO.[6,7] We planned to use an sp^2 imino nitrogen for aminooxygenation of alkenes, which has been unprecedented. Based on this background, suitable reaction conditions were first explored using 2,2,4-trimethylpent-4-enenitrile (**1a**) and *p*-tolylmagnesium bromide (**2a**) as starting materials (Table 1). Addition of *p*-tolylmagnesium bromide (**2a**) to carbonitrile **1a** occurred smoothly in Et_2O at 60 °C (in a sealed tube). After protonation with MeOH,[8] solvent (the reaction was diluted to 0.1 M) and copper salts as well as TEMPO (1.5 equiv) were subsequently added. The desired aminooxygenation proceeded smoothly even at room temperature[9] when the reaction mixture was stirred with one equivalent of $Cu(OAc)_2$ in DMF at room temperature under a N_2 atmosphere, affording oxymethyl pyrroline **3aa** in 68% yield after two hours (Table 1, entry 1), whereas other Cu(II) complexes such as $Cu(OTf)_2$ and $CuCl_2$ were not viable for this transformation (Table 1, entries 2 and 3). A catalytic use of $Cu(OAc)_2$ (10 mol%) in DMF under an O_2 atmosphere provided only a trace amount of **3aa** (Table 1, entry 4). It was found that use of pyridine as a solvent served for enhancement of the catalytic turnover, giving **3aa** in 54% yield with 10 mol% of $Cu(OAc)_2$ (Table 1, entry 5).

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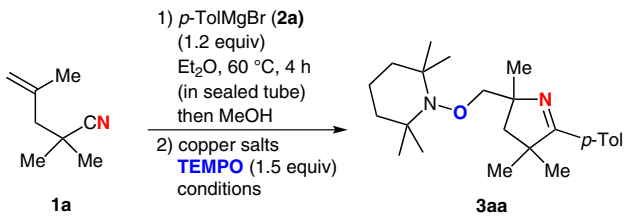
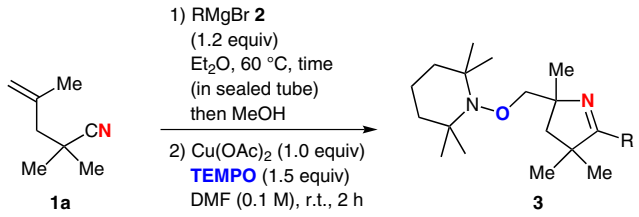
Table 1 Optimization of the Reaction Conditions[a]



Entry	Cu salts (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2$ (1.0)	DMF	r.t.	2	68
2	$Cu(OTf)_2$ (1.0)	DMF	80	18	36
3	$CuCl_2$ (1.0)	DMF	80	5.5	13
4[c]	$Cu(OAc)_2$ (0.1)	DMF	r.t.	18	trace
5[c]	$Cu(OAc)_2$ (0.1)	pyridine	60	18	54

[a] All reactions were conducted using 0.4 mmol of carbonitrile **1a** with 1.2 equiv of *p*-tolylmagnesium bromide **2a** in Et_2O (0.5 mL) at 60 °C (sealed tube) for 4 h followed by addition of MeOH (60 μL), DMF (4 mL), Cu salts, TEMPO (1.5 equiv), and stirring.
[b] Isolated yield.
[c] The reaction was performed under an O_2 atmosphere.

Table 2 Scope of Grignard Reagents[a]

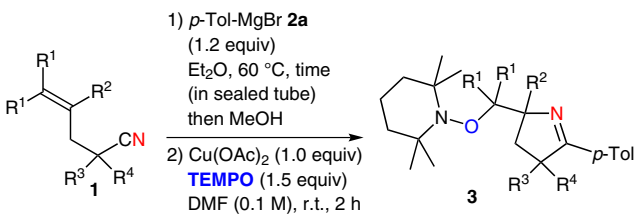


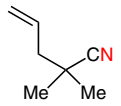
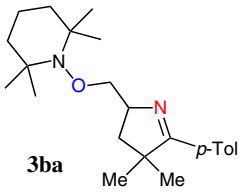
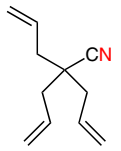
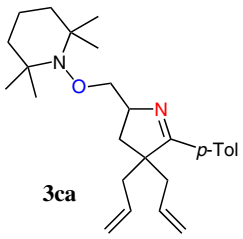
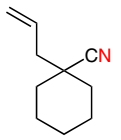
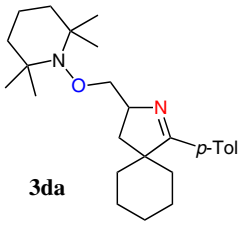
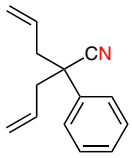
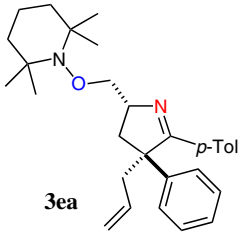
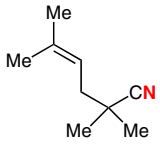
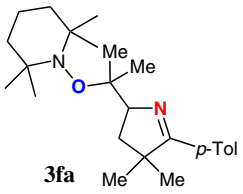
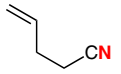
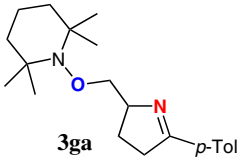
Entry	Grignard reagents **2**	Time (h)	Yield of **3** (%)[b]
1	4-$MeOC_6H_4MgBr$ (**2b**)	3.5	**3ab** 49
2	4-$PhOC_6H_4MgBr$ (**2c**)	24	**3ac** 69
3	2-MeC_6H_4MgBr (**2d**)	9	**3ad** 58
4	2-naphthylMgBr (**2e**)	7	**3ae** 58
5	4-ClC_6H_4MgBr (**2f**)	44	**3af** 51
6	2-thienylMgBr (**2g**)	18	**3ag** 42

[a] All reactions were conducted using 0.4 mmol of carbonitrile **1a** with 1.2 equiv of Grignard reagents **2** in Et_2O (0.5 mL) at 60 °C (sealed tube) for 4 h followed by addition of MeOH (60 μL), DMF (4 mL), $Cu(OAc)_2$ (1.0 equiv), TEMPO (1.5 equiv), and stirring at r.t.
[b] Isolated yields.

By using one equivalent of $Cu(OAc)_2$ (Table 1, entry 1), the generality for the synthesis of oxymethyl dihydropyrroles **3** was investigated by employing a range of alkenyl carbonitriles **1** and Grignard reagents **2**. The reactions of **1a** with various Grignard reagents **2** were summarized in Table 2. The reactions proceeded with electron-rich aryl Grignard reagents **2b** and **2c** (Table 2, entries 1 and 2) as well as sterically hindered *o*-tolyl and 2-naphthyl

Table 3 Scope of Carbonitriles[a]

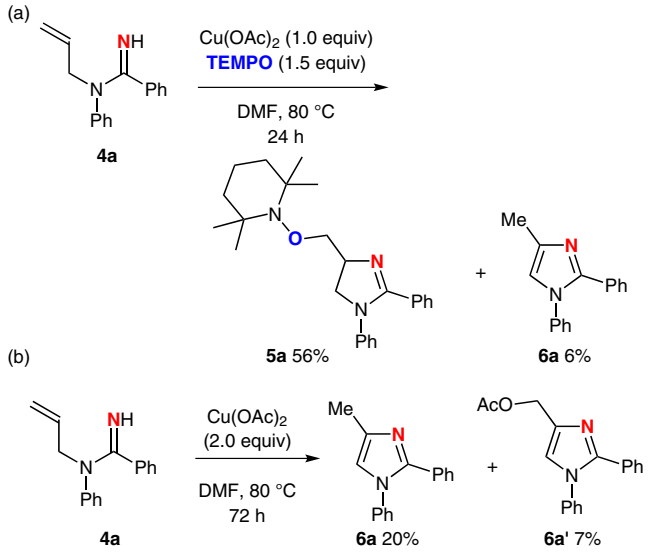


Entry	Carbonitriles **1**	Pyrrolines **3**	Yield (%)[b]
1	 **1b**	 **3ba**	56
2	 **1c**	 **3ca**	51
3	 **1d**	 **3da**	51
4	 **1e**	 **3ea**	59% (*trans*/*cis* = 3:1)[c]
5	 **1f**	 **3fa**	54
6	 **1g**	 **3ga**	23

[a] All reactions were conducted using 0.4 mmol of carbonitrile **1** with 1.2 equiv of *p*-tolylmagnesium bromide **2a** in Et_2O (0.5 mL) at 60 °C (sealed tube) for 4 h followed by addition of MeOH (60 μL), DMF (4 mL), $Cu(OAc)_2$ (1.0 equiv), TEMPO (1.5 equiv), and stirring at r.t.
[b] Isolated yields.
[c] The stereochemistry was determined by NOE measurements.

Grignard reagents **2d** and **2e** (Table 2, entries 3 and 4), giving oxymethyl pyrrolines **3** in moderate to good yields. Introduction of 4-chlorophenyl and 2-thienyl groups could be possible (Table 2, entries 5 and 6), while no desired product was observed from alkyl Grignard reagents probably due to the instability of the resulting N-H imine intermediates.

The effects of substituents on the alkenyl carbonitriles **1** were examined using *p*-tolylmagnesium bromide (**2a**, Table 3). Dimethyl- and 2,2-diallyl-4-pentenenitriles **1b** and **1c** could be utilized to access 4,4-disubstituted dihydropyrroles (Table 3, entries 1 and 2). A 2-azaspiro[4.5]dec-1-ene structure **3da** was efficiently constructed from 1-allylcyclohexanecarbonitrile (**1d**, Table 3, entry 3). The reaction of 2-allyl-2-phenyl-4-pentenenitrile (**1e**) resulted in a *trans*/*cis* mixture of **3ea** in 59% yield, where *trans*-**3ea** was a major product (3:1 ratio; Table 3, entry 4). From 5,5-dimethyl derivative **1f**, only 5-*exo*-cyclization was observed exclusively (Table 3, entry 5). The reaction of 4-pentenenitrile (**1g**) also proceeded to give dihydropyrrole **4ga** while the yield was low (23%; Table 3, entry 6).

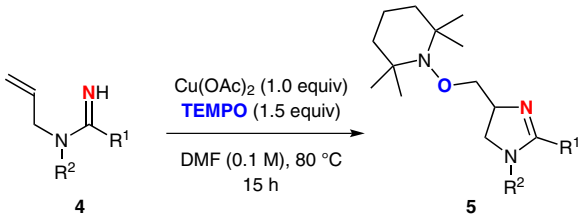


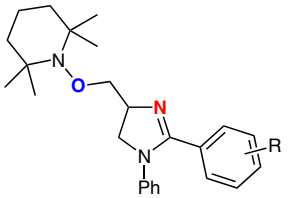
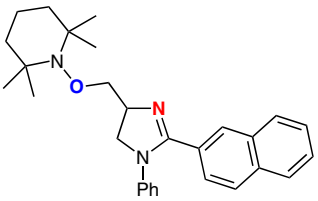
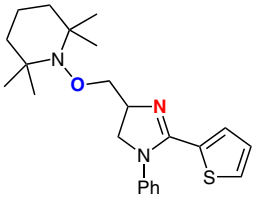
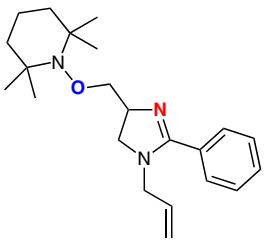
Scheme 2 Reactions of *N*-allylamidine **4a**

Having developed this $Cu(OAc)_2$-mediated oxyamination of alkenylimines with TEMPO, we next examined the reactivity of *N*-allylamidine **4a** towards the intramolecular aminooxygenation under the present reaction conditions.[10] It is noted that amidines could easily be prepared by addition reactions of amines to the corresponding carbonitriles or imidate salts and generally stable to handle.[11] Treatment of *N*-allylamidine **4a** with one equivalent of $Cu(OAc)_2$ and 1.5 equivalents of TEMPO in DMF at 80 °C (for 24 h) afforded the aminooxygenation products, dihydroimidazoles **5a** in 56% yield along with the formation of 4-methylimidazole **6a** in 6% yield (Scheme 2, a). On the other hand, the reaction of amidine **4a** with two equivalents of $Cu(OAc)_2$ in the absence of TEMPO was very sluggish, giving 4-methylimidazole **6a** and 4-acetoxymethylimidazole **6a′** in 20% and 7% yields, respectively, after three days (Scheme 2, b). These results indicated that TEMPO might play an important role to facilitate the N–C bond forming (cyclization) process.[12,13] Examination of the substrate scope revealed that several dihydroimidazoles could be prepared in good to moderate yields through the present aminooxygenation strategy (Table 4).

In summary, an expedient method for the synthesis of oxymethyl dihydropyrroles (pyrrolines)[14] and oxymethyldihydroimidazoles was developed by the Cu(II)-mediated reactions of alkenylimines derivatives with TEMPO.[15–17] Further investigation of the scope, detailed mechanisms, and synthetic applications of the present strategy to other azaheterocycles is currently under way.

Table 4 Synthesis of Dihydroimidazoles[a,b]



Entry	Dihydroimidazoles		Yield (%)
1		**5a** R = H **5b** R = 2-Me **5c** R = 4-Cl	56 77 54
2		**5d**	43
3		**5e**	66
4		**5f**	47

[a] All reactions were conducted using 0.5 mmol of *N*-allylamidines **4** with $Cu(OAc)_2$ (1.0 equiv) and TEMPO (1.5 equiv) in DMF at 80 °C.
[b] Isolated yields were noted above with more than 90% purity of **5**.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) For the copper-mediated diamination of alkenes in similar manner to the oxyamination, see: Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 6365.

(8) Pickard, P. L.; Tolbert, T. L. *J. Org. Chem.* **1961**, *26*, 4886.

(9) The copper-catalyzed/-mediated aminooxygenation with sulfonamide and TEMPO generally needed high temperature (110–130 °C), see ref. 6.

(10) Zhang and Zhu reported copper-catalyzed aerobic reactions of *N*-allyl amidines that afforded formylimidazoles via aminooxygenation of the alkene, see: Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 5678.

(11) (a) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463. (b) Caron, S.; Wei, L.; Douville, J.; Ghosh, A. *J. Org. Chem.* **2010**, *75*, 945; and references cited therein.

(12) The reactions might be initiated by aminocupration of putative copper iminyl species onto alkene followed by conversion of the resulting organocopper species into the C–O bond with TEMPO. For a review on synthetic applications of TEMPO, see: Vogler, T.; Studer, A. *Synthesis* **2008**, 1979.

(13) Recent literature precedents have shown that Cu(II) species and TEMPO make a Cu(III)–TEMPO complex that works as an ionic electrophile, see: (a) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5927. (b) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012. (c) Michel, C.; Belanzoni, P.; Gamez, P.; Reedjik, J.; Baerends, E. J. *Inorg. Chem.* **2009**, *48*, 11909. (d) It could also be proposed that the resulting Cu(III)–TEMPO complex induces electrophilic cyclization of the imino sp^2 nitrogen with the intramolecular alkene.

(14) There have been reported some biologically active natural alkaloids such as broussonetine and nectrisine bearing oxymethyl dihydropyrrole or pyrrolidine structures, see: (a) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org Chem.* **2008**, 2929. (b) Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, *44*, 7649.

(15) We have tried oxidative and reductive cleavage of the O–N bond of **3aa** (using MCPBA and Zn/MeOH–aq NH_4Cl conditions, respectively), while only decomposed complex mixtures were obtained.

(16) **General Procedure for the Synthesis of 2,2,6,6-Tetramethyl-1-[(2,4,4-trimethyl-5-*p*-tolyl-3,4-dihydro-2*H*-pyrrol-2-yl)methoxy]piperidine (3aa)**

To a 10 mL Schlenk tube with a Teflon valve was added carbonitrile **1a** (48.2 mg, 0.39 mmol) in Et_2O (0.4 mL) and *p*-tolylmagnesium bromide (**2a**, 0.53 mL, 0.47 mmol, 0.88 M in Et_2O) was added slowly. The reaction was then heated at 60 °C under sealed conditions for 4 h. The mixture was quenched with distilled MeOH (60 μL) at 0 °C, and DMF (4 mL), $Cu(OAc)_2$ (72.2 mg, 0.40 mmol), and TEMPO (91.7 mg, 0.59 mmol) were added immediately. The mixture was further stirred at r.t. for 2 h under an inert atmosphere. The reaction was quenched with ammonium buffer solution (pH 9) and extracted three times with Et_2O. The organic phase was then washed with H_2O and brine and dried over $MgSO_4$. The solvent was evaporated to give a crude mixture, which was purified by flash column chromatography (hexane–EtOAc = 95:5) to provide **3aa** (98.7 mg, 0.27 mmol) in 68% yield.

Analytical Data

Colorless oil. IR (NaCl): 2968, 2932, 2870, 1609, 1468, 1360, 1312, 1244, 1132, 1070, 1053, 752, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (3 H, s), 1.13 (3 H, s), 1.20 (3 H, s), 1.24 (3 H, s), 1.32 (3 H, s), 1.36 (3 H, s), 1.44 (3 H, s), 1.27–1.51 (6 H, m), 1.68 (1 H, d, *J* = 12.8 Hz), 2.34 (1 H, d, *J* = 12.8 Hz), 2.36 (3 H, s), 3.79 (1 H, d, *J* = 8.4 Hz), 3.89 (1 H, d, *J* = 8.4 Hz), 7.16 (2 H, d, *J* = 8.2 Hz), 7.60 (2 H, d, *J* = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 18.6, 18.9, 19.6, 25.0, 26.3, 28.0, 31.4, 31.5, 38.0, 47.4, 50.0, 58.3, 70.5, 81.0, 126.3, 127.0, 130.6, 137.2, 175.8. ESI-HRMS: *m/z* calcd for $C_{24}H_{39}N_2O$ $[M + H]^+$: 371.3062; found: 371.3053.

(17) **General Procedure for the Synthesis of 1-[(1,2-Diphenyl-4,5-dihydro-1*H*-imidazol-4-yl)methoxy]-2,2,6,6-tetramethylpiperidine (5a)**

To a 25 mL Schlenk tube was added amidine **4a** (136.7 mg, 0.58 mmol), $Cu(OAc)_2$ (113.0 mg, 0.62 mmol), and TEMPO (135.5 mg, 0.87 mmol) in DMF (6.0 mL). The reaction was then heated at 80 °C for 24 h. The reaction was quenched with ammonium buffer solution (pH 9) at r.t. It was then extracted three times with EtOAc. The organic phase was then washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed in vacuo, affording crude residue, which was purified by flash column chromatography (hexane–EtOAc = 80:20, gradually 20% EtOAc increment every time after 50 mL eluent, until 100% EtOAc was reached) to provide **5a** (126.8 mg, 0.33 mmol) in 56% yield (94% purity).

Analytical Data

Yellow oil. IR (NaCl): 2932, 1614, 1595, 1574, 1495, 1470, 1385, 1360, 1300, 1283, 1134, 1051, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (3 H, s), 1.08 (3 H, s), 1.17 (3 H, s), 1.24 (3 H, s), 1.42–1.49 (6 H, m), 3.95–3.98 (2 H, m), 4.05–4.08 (1 H, m), 4.22 (1 H, dd, *J* = 9.4, 9.9 Hz), 4.33–4.43 (1 H, m), 6.79 (2 H, d, *J* = 8.1 Hz), 6.96 (1 H, dd, *J* = 7.1, 7.4 Hz), 7.15 (2 H, dd, *J* = 7.6, 7.8 Hz), 7.25–7.29 (2 H, m), 7.35 (1 H, dd, *J* = 7.1, 7.4 Hz), 7.51 (2 H, d, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 19.9, 20.1, 33.1, 33.3, 39.6, 56.7, 60.0, 63.5, 78.6, 122.6, 123.1, 128.1, 128.2, 128.6, 128.7, 129.8, 131.3, 143.1. ESI-HRMS: *m/z* calcd for $C_{25}H_{34}N_3O$ $[M + H]^+$: 392.2702; found: 392.2701.