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Additive-Free Copper-Catalyzed Benzylic $C_{(sp^3)}$–H Carbamation: Simple Preparation of Primary Benzylic Amines

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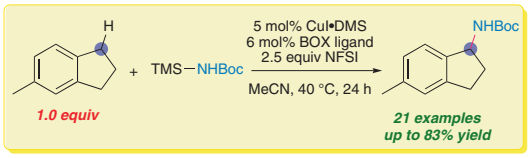

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Abstract A simple and practical method for the synthesis of primary alkylamines by direct functionalization of hydrocarbons is described. The *N*-Boc-protected alkylamines are readily prepared from *tert*-butyl (trimethylsilyl)carbamate and *N*-fluorobenzenesulfonimide in the presence of a Cu(I) catalyst at low catalyst loadings. Advantageously, this process proceeds free of any additive such as auxiliary bases/acids, requires only one equivalent of the substrate, and does not require ligand synthesis. This operationally simple C–H carbamation method shows high site selectivity and good functional-group tolerance, and uses a commercially available Cu precatalyst and oxidant to furnish *N*-Boc protected alkylamines in yields of 16–83%. The products can be simply deprotected under mild acidic conditions to generate primary benzylic amines. This practical method was subsequently used for the synthesis of the active pharmaceutical ingredients cinacalcet and sertraline.

Key words copper catalysis, fluorobenzenesulfonimide, amination, alkylamines, benzylic amines

Because approximately 80% of small-molecule drugs contain at least one nitrogen atom in their structures, the construction of C–N bonds is amongst the most desirable bond-formation reactions.[1] Among amines, primary alkylamines are of great importance in the synthesis of organic molecules as they are prevalent building blocks in natural-product synthesis and medicinal chemistry (Figure 1).[2] Conventional primary alkylamine syntheses require pre-functionalized substrates containing, for example, nitro, azide, or nitrile groups, and generally produce significant amounts of chemical wastes and are less atom economical. Alternatively, reductive amination of carbonyl compounds has been explored thoroughly and many practical procedures have been developed in recent years.[3] On the other hand, direct amination of aliphatic C–H bonds is increasingly explored by synthetic chemists as it targets far less reactive, more abundant C(sp^3)–H bonds.[4–6] Over the past few decades, there have been many reports of direct aliphatic C–H amination and C–H amidation reactions mediated by transition-metal nitrenoids or amides or by hypervalent iodine, or which proceed via radical intermediates.[7–12]

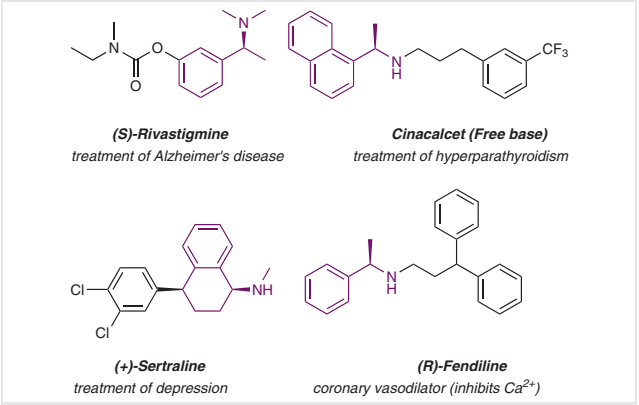

Figure 1 FDA-approved drugs with benzylic amine moieties

There also have been reports of transition-metal-free methods for the construction of C(sp^3)–N bonds through free nitrenes.[13–15] Whereas the direct amination of the C(sp^3)–H bonds has emerged as a promising approach that maximizes atom economy, current state-of-the-art methods typically give N-protected amine products.[7–15] The protected amine products typically require additional manipulations to access the corresponding primary amines. For instance, several research groups have developed methods for the synthesis of alkyl tosylamides (R–NHTs) from the corresponding alkanes by the transfer of an N=$SO_2C_6H_4Me$ moiety through the use of such transition metals as Cu, Rh, or Ag.[16–19] The deprotection of the tosyl group requires harsh conditions [lithium naphthalenide, Na/K alloy on silica, Ni(0)acac/*i*-PrMgCl, Bu_3SnH/AIBN, Mg/Me_3CoLi, or Mg/MeOH] or the use of expensive reductants such as SmI_2

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in toxic solvents such as HMPA or DMPU, which ultimately makes these methods less practical and less atom economical.[20–26] Recently, the groups of Buchwald, Hu, Kramer, and Warren have each developed Pd- or Cu-catalyzed reactions that generate an alkylated benzophenone imine (H–N=CPh$_2$) that can be deprotected to furnish the free amine under mild conditions.[27–31] The work of the groups of Buchwald[27] and Hu[28] did not involve benzylic substrates despite their prevalence in synthetic organic and medicinal chemistry.

Kramer developed a facile route to α-substituted, primary benzylimines through a cross-dehydrogenative coupling method catalyzed by a CuI/1,10-phenanthroline system.[29] The method is simple and the reaction proceeds under low catalyst loadings, but requires high substrate loadings (10 equiv) and long reaction periods (48 h). More recently, Kramer's group reported a dehydrogenative C–N bond formation by the combined use of a chiral Cu catalyst with a photocatalytic reaction between limiting amounts of an R–H substrate and NH$_2$Boc (Boc = *tert*-butyloxycarbonyl); this proceeds with high yields and high enantioselectivities (Figure 2A).[30] The Warren group developed a similar method that uses a copper(I) β-diketiminate catalyst, but they focused mainly on the mechanism of this transformation. The major drawback of their methods was the formation of the azine Ph$_2$C=N–N=CPh$_2$ as the main byproduct, which significantly increases the nonproductive consumption of the benzophenone imine (Figure 2B).[31] More recently, the Comito group reported a versatile hypervalent iodine(III)-mediated C–H imination under blue LED light and heating (75 °C) conditions to form primary and secondary amines after a mild deprotection (Figure 2C).[32] Although practical for both benzylic and nonbenzylic substrates, the biggest drawback of the method was the use of large excess of the substrates (60–120 equiv), which makes the methodology less atom economical and less energy efficient (use of both light and heat), as shown in Figure 2C.

In light of the above considerations, we sought a C–N coupling protocol that would combine operational simplicity with the use of an Earth-abundant catalyst to access primary amines using only one equivalent of the R–H substrate. In 2020, the group of Landis reported a Cu-catalyzed carbamation of benzylic C–H bonds by using *N*-fluorobenzenesulfonimide (NFSI) or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA; Selectfluor) as the oxidant and ethyl carbamate (urethane) as source of the nitrogen functional group (Figure 2D).[33] Although the Landais system was found to be highly efficient for the synthesis of ethyl carbamates (*N*-Cbz or *N*-Troc) derivatives, it failed to deliver *N*-Boc-protected carbamates, the only example reported giving low yields (16–22%). Because the Boc group is possibly one of the most desirable protecting groups in organic synthesis, we sought to develop a method that delivers Boc-protected amines through Cu catalysis.

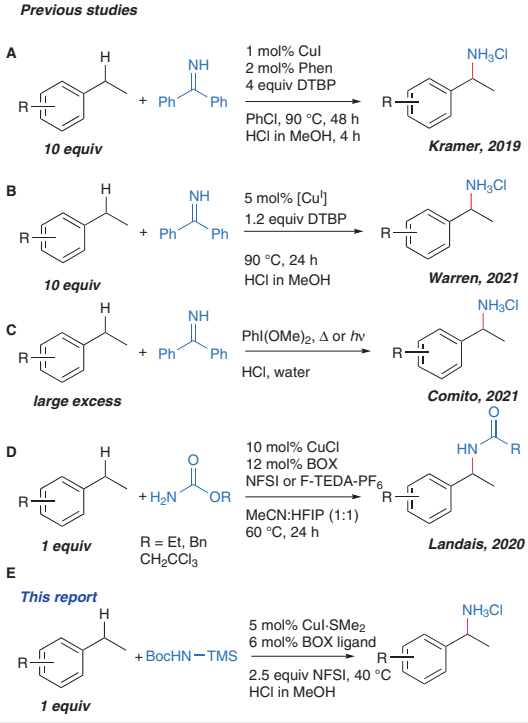


Figure 2 Benzylic C–H amination for the preparation of primary amines

Here, we address the challenge of synthesizing primary amines[34] by developing an Earth-abundant Cu-catalyzed oxidative amination of benzylic C–H bonds to convert chemical feedstocks into amine pharmacophores. To this end, we developed a benzylic C(sp^3)–H carbamation under Cu(I)/BOX ligand catalysis, and we used TMSNHBoc as the aminating reagent and NFSI as the terminal oxidant (Figure 2E). Unlike diaryl imines, which are moisture sensitive, TMSNHBoc is a bench-stable white solid with a shelf life of more than three months, and which can be easily prepared by a one-step reaction between TMSCl and *tert*-butyl carbamate (BocNH$_2$) on a decagram scale with >99% purity (^{1}H NMR) and in nearly quantitative yield. The substrate scope in this report mainly focuses on cheap and widely available alkylarene feedstocks that could provide facile access to primary amine building blocks through simple and mild deprotection of the Boc group. It is noteworthy that although the current method is similar to that reported Landais,[33] there are some improvements that make our method worthwhile. For instance, in the aforementioned report, Landis's method requires hexafluoroisopropanol (HFIP) (in a 1:1 mixture with MeCN), which markedly increases the cost of the synthesis. Furthermore, their system works at higher temperatures and requires greater catalyst loadings. Also, their method gave rise to only one example of an *N*-Boc-protected benzylic amine in a modest yield. Considering the relevance of the Boc protecting group in organic

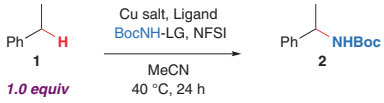
synthesis in comparison with ethyl carbamates (*N*-Cbz or *N*-Troc), this makes the current method a good complement to the previously reported method.

By considering the recent Cu(I)/NFSI catalyst systems that have been explored in recent years,[35–37] we started our screening efforts to identify optimal conditions for benzylic C–H carbamation to form R–NHBoc compounds that could be further deprotected under mild and simple conditions to give primary amines. In the beginning, we selected $BocNH_2$ as the carbamate source, due to its low price and wide commercial availability. After optimization, we focused on *tert*-butyl (trimethylsilyl)carbamate (TMSNHBoc), due to the high affinity of the TMS group for fluoride, in an attempt to increase the driving force for NHBoc transfer to the copper(II) center. Ethylbenzene was selected as the benzylic substrate due to its low price ($116/2.5 L) and ready availability. Summarized optimization data is presented in Table 1, with additional details provided in the Supporting Information (SI). We continued by examining commonly used copper sources and ligands. $CuI{\cdot}SMe_2$ was chosen due to its higher solubility, along with the bulky $^{t\text{Bu}}$BOX ligand (BOX = bis-oxazoline) **L1**, with NFSI as the terminal oxidant. Screening the source of copper showed that CuCl, $CuBr{\cdot}SMe_2$, and CuOAc all afforded the desired product (yield 14–8%); however, $CuI{\cdot}SMe_2$ gave the highest yield (36%). Cu(I) halide salts in general provided much better yields, whereas Cu(II) salts, such as $Cu(OAc)_2$ and $Cu(OTf)_2$, gave much lower yields.

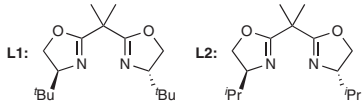
Next, we screened a wide range of ligands (bipyridines, phenanthrolines, and BOX ligands) and found that the BOX ligand **L1** gave the desired product in high yields (up to 69%). Testing the reaction without a ligand highlighted the importance of an ancillary ligand, as no product was detected by GC/MS analysis. Increasing the ligand loading decreased the formation of the desired product and diminished the yields to as low as 6% (see SI). The formation of the product with ligands **L1** and **L2** exclusively (SI) can be rationalized in terms of the steric properties of these ligands, which hinders any double ligation that could result in deactivation of the catalyst. A final improvement in yield was achieved by using acetonitrile as the solvent. Other solvents such as acetone, ethyl acetate, or fluorobenzene did not ensure homogeneity of the reaction mixture, and lower yields were observed with those solvents; therefore, MeCN was kept as the reaction solvent.

A variety of oxidants were also screened, including Selectfluor (F-TEDA), Selectfluor II, NFSI, *N*-fluoropyridinium (NFPY), *N*-fluorocollidinium tetrafluoroborate, and iodosylbenzene (PhIO). We found that only Selectfluor and NFSI were efficient reagents for this transformation, and the latter was found to be much more efficient in most cases. Initial chiral gas-chromatographic studies showed no enantioselectivity toward the desired product, although the chiral bis(oxazoline) ligand **L1** was used. Although we did not pursue thorough mechanistic studies, this observation is in agreement with a radical–polar crossover pathway involving a benzylic carbocation intermediate (SI; Figure S1B).

Table 1 Effect of Selected Reaction Parameter on the Yield of the Cu-Catalyzed C(sp^3)–N Bond Formation[a]

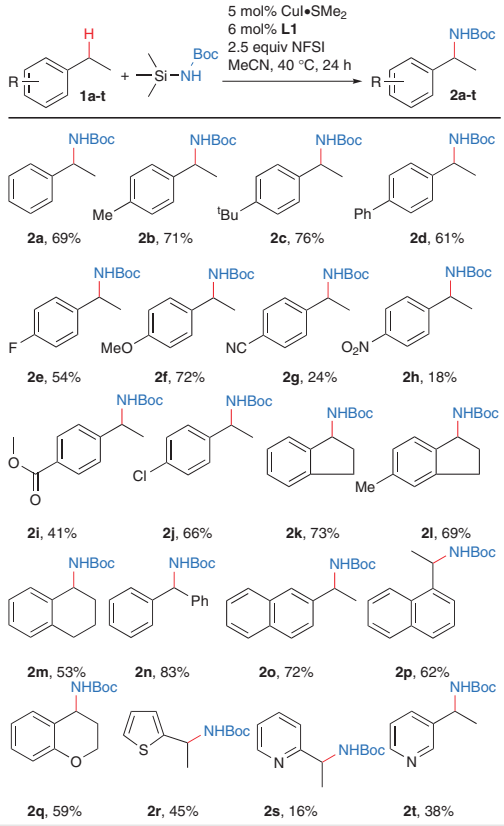


Entry	Cu salt (mol %)	Ligand (mol%)	NFSI (equiv)	LG[b] (equiv)	Yield[c] (%)
1	CuCl (10)	**L1** (12)	2	TMS (2)	11
2	$CuBr{\cdot}SMe_2$ (10)	**L1** (12)	2	TMS (2)	19
3	$CuI{\cdot}SMe_2$ (10)	**L1** (12)	2	TMS (2)	41
4	CuOAc (10)	**L1** (12)	2	TMS (2)	29
5	$Cu(OAc)_2$ (10)	**L1** (12)	2	TMS (2)	12
6	$Cu(MeCN)_4BF_4$ (10)	**L1** (12)	2	TMS (2)	trace
7	$Cu(MeCN)_4PF_6$ (10)	**L1** (12)	2	TMS (2)	trace
8	$CuI{\cdot}SMe_2$ (20)	**L1** (12)	2	TMS (2)	16
9	$CuI{\cdot}SMe_2$ (5)	**L2** (6)	2	TMS (2)	57
10	$CuI{\cdot}SMe_2$ (2.5)	**L1** (6)	2	TMS (2)	26
11	$CuI{\cdot}SMe_2$ (5)	**L1** (6)	2	TMS (2)	67
12	$CuI{\cdot}SMe_2$ (5)	**L1** (6)	2.5	TMS (2)	69
13	$CuI{\cdot}SMe_2$ (10)	**L1** (12)	2	H (2)	21



[a] Reaction conditions: ethylbenzene (0.25 mmol, 1.0 equiv), TMSNHBoc (0.5 mmol, 2.0 equiv), NFSI (0.75 mmol, 2.5 equiv), ligand (6 mol%), CuI•SMe2 (5 mol%), MeCN (2.0 mL), sealed tube.
[b] LG = leaving group.
[c] Isolated yield.

Expanding on the results obtained with ethylbenzene, we evaluated the carbamation of other benzylic R–H substrates (Scheme 1). Reactions of various *para*-substituted ethylbenzenes [*p*-Me, *p*-*t*-Bu, *p*-Ph, *p*-F, *p*-OMe, *p*-CN, *p*-NO_2, *p*-Cl, and *p*-C(O)OMe] gave products **2b–j** in low to good yields (18–76%). Substrates with electron-deficient rings bearing a cyano or nitro group gave poor yields (**2g** and **2h**), whereas electron-rich ethylarenes (**2b**, **2c**, and **2f**) generally gave high yields, further supporting a radical–polar crossover pathway involving a benzylic carbocation intermediate. Note that no double functionalization was observed with this method. Also, methylarenes did not give noticeable yields under this protocol, like other methodologies involving Cu/NFSI.[37,38]



Scheme 1 Scope of alkylarene benzylic C–H carbamation. Yields after column chromatography are reported.

The common pharmacophore indane underwent carbamation in 73% yield (**2k**), and 5-methyl-2,3-dihydro-1*H*-indene and tetralin afforded **2l** and **2m**, respectively, in good yields of 53 and 69%, . Diphenylmethane underwent carbamation to give product **2n** in 83% yield, and ethylnaphthalenes gave high yields (62–72%) of the corresponding carbamate products **2o** and **2p**. Heterocycles also underwent carbamation by this method with acceptable yields. For instance, 2- and 3-ethylpyridines gave the carbamated products **2s** and **2t**, respectively, in yields of 16 and 38%, and 2-ethylthiophene gave **2r** in a modest yield of 45% (**2r**). Chromane, another common pharmaceutical core, gave product **2q** in a moderate yield of 59%. It is worth noting that 2-ethylfuran did not give the desired product, although several attempts were made with various combinations of solvent, temperature, and ligand. We assume that ring opening of the furan might be a possible explanation, although we did not pursue an analysis of the outcome of that reaction. Other ethylarenes, such as 3-ethyl-1*H*-indole and 7-ethyl-1*H*-indole, and complex substrates, such as dextromethorphan hydrobromide, mestranol, and dehydroabietylamine, were also examined, but our method failed to deliver the desired benzylic carbamate products (SI; Figure S1).

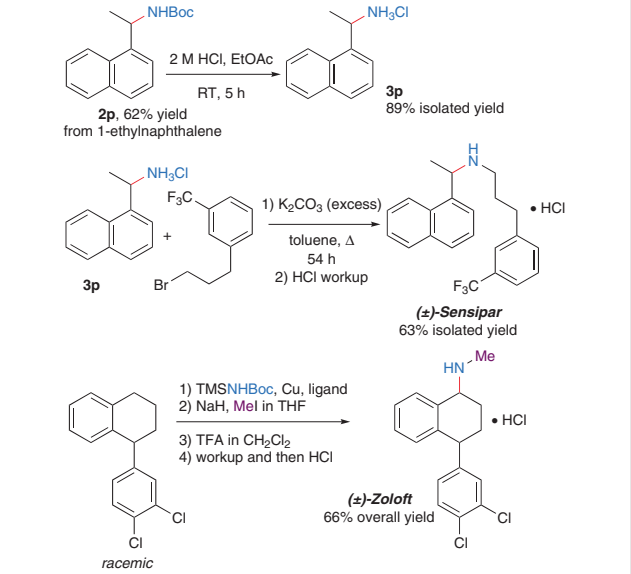
As mentioned in the introduction to this report, current C–H amination methods generate tosyl, nosyl, or Troc-protected (tosyl = *p*-$MeC_6H_4SO_2$; nosyl = *p*-$O_2NC_6H_4SO_2$, or Troc = $Cl_3CCH_2OSO_2$) amines, deprotection of which is notoriously difficult and requires separate laborious, time-consuming, and hazardous deprotection steps.[39] In some cases, toxic and carcinogenic solvents such as benzene or chlorinated solvents are required, making these methods less attractive from a process standpoint. On the other hand, our method provides Boc-protected amines that can be deprotected in a one-pot procedure requiring mildly acidic conditions (2 M HCl in ethyl acetate; see SI) instead of the use of excess amount of harsh and expensive reducing agents such as SmI_2, Li/NH_3, Na/naphthalene, Bu_3SnH/AIBN, or Cu/Zn. Moreover, our method uses Cu, a base metal, as a catalyst that is much cheaper than Ag, Rh, or other noble metals, and does not require a large excess of the R–H substrate.

The relevance of this C–H carbamation protocol for medicinal chemistry was investigated through the synthesis of the racemic cinacalcet (Sensipar), used for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease, as presented in Scheme 2. The reaction was conducted with 1 mmol of 1-ethylnaphthalene by the developed protocol to give **2p** as a starting material for this synthesis. We then deprotected the carbamation product (2 M HCl in EtOAc)[40] and used the primary ammonium salt, without any further purification, for the second step, to give racemic cinacalcet in 63% yield (see SI for details). We then attempted to synthesize racemic sertraline (Zoloft), an antidepressant of the selective serotonin reuptake inhibitor class. Carbamation of racemic 1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene,[41] followed by deprotection (2 M HCl in EtOAc) and methylation resulted in overall 66% yield of sertraline as a mixture of diastereomers (see SI for details).

The results described herein demonstrate that an operationally simple Cu-based catalyst system composed of commercially available components permits site-selective benzylic C–H carbamation.[42] A combination of good yields, broad functional-group compatibility, and high benzylic site selectivity makes this method an attractive green alternative to existing protocols for the incorporation of primary amines into pharmaceutical and agrochemical building blocks. The relevance to medicinal chemistry was demonstrated by short syntheses of the racemates of Sensipar and Zoloft hydrochloride salts.

Conflict of Interest

The authors declare no conflict of interest.



Scheme 2 Syntheses of the hydrochloride salts of (±)-Sensipar and (±)-Zoloft by using our method

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2170-2630.

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(43) **Copper-Catalyzed Benzylic C–H Carbamation; General Procedure** On the benchtop, a disposable 4 mL glass vial equipped with a Teflon-coated stirrer bar was charged with TMSNHBoc (0.5 mmol, 95 mg, 2 equiv) and NFSI (0.75 mmol, 236.5 mg, 2.5 equiv). Solid R–H substrates (0.25 mmol, 1 equiv) were weighed and added to the vial. The vial was then sealed with a PTFE-lined pierceable cap. BOX (**L1**; 0.015 mmol, 4.5 mg, 6 mol%) was weighed into a second vial equipped with a Teflon stirrer bar. Both vials were then transferred to a purged glovebox under an atmosphere of dry N_2. In the glovebox, CuI·Me_2S (0.018 mmol, 4.5 mg, 5 mol%) was weighed into the vial containing the BOX ligand, and MeCN (2.0 mL) and the R–H substrate (if liquid) were added. The mixture was then stirred for 30 min under N_2 to form a dull-purple Cu catalyst solution. This was then added to the vial containing the other reaction components, and the mixture was stirred at 40 °C for 24 h.

(44) ***tert*-Butyl (5-Methyl-2,3-dihydro-1*H*-inden-1-yl)carbamate (2l)** Prepared by the general procedure, with purification by flash column chromatography (silica gel, 0–20% gradient EtOAc–hexanes) to give a white solid; yield: 53 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 11.0 Hz, 2 H), 5.13 (q, *J* = 7.8 Hz, 1 H), 4.78 (d, *J* = 8.8 Hz, 1 H), 2.90 (ddd, *J* = 16.0, 8.8, 3.9 Hz, 1 H), 2.78 (dt, *J* = 16.1, 8.1 Hz, 1 H), 2.62–2.44 (m, 1 H), 2.33 (s, 3 H), 1.85–1.71 (m, 1 H), 1.49 (s, 9 H). ^{13}C NMR (121 MHz, $CDCl_3$): δ = 155.8, 143.5, 140.8, 137.7, 127.6, 125.5, 123.9, 79.4, 55.8, 34.6, 30.1, 28.7, 21.4. GC/MS (EI): *m*/*z* = 247.1. HRMS (TOF-ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}NO_2$: 248.1651; found: 248.1657.