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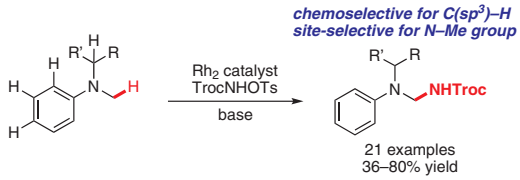
Dirhodium-Catalyzed Chemo- and Site-Selective C–H Amidation of *N*,*N*-Dialkylanilines

Gong Chen
Kenta Arai
Kazuhiro Morisaki
Takeo Kawabata
Yoshihiro Ueda*

Institute for Chemical Research, Kyoto University, Gokasho, Uji, Kyoto 611-0011, Japan
ueda@fos.kuicr.kyoto-u.ac.jp



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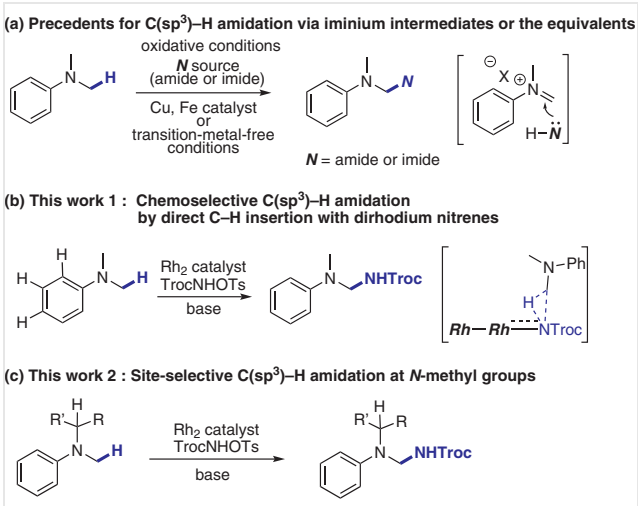
Abstract A method for dirhodium-catalyzed C(sp^3)–H amidation of *N*,*N*-dimethylanilines was developed. Chemoselective C(sp^3)–H amidation of *N*-methyl group proceeded exclusively in the presence of C(sp^2)–H bonds of the electron-rich aromatic ring. Site-selective C(sp^3)–H amidation proceeded exclusively at the *N*-methyl group of *N*-methyl-*N*-alkylaniline derivatives with secondary, tertiary, and benzylic C(sp^3)–H bonds α to a nitrogen atom.

Key words C–H amidation, dirhodium complex, aniline, nitrene, site selectivity



Scheme 1 C(sp^3)–H amidation of *N*,*N*-dialkylanilines. (a) Reported C(sp^3)–H amidation of *N*,*N*-dimethylanilines under oxidative conditions. (b) Dirhodium-catalyzed chemoselective C(sp^3)–H amidation of *N*,*N*-dimethylanilines. (c) Dirhodium-catalyzed site-selective (*N*-methyl-group selective) C(sp^3)–H amidation of *N*-alkyl-*N*-methylanilines (alkyl ≠ methyl).

Development of methods for the construction of C–N bonds is still of great synthetic importance in current synthetic organic chemistry[1] because C–N bonds are ubiquitously involved in functional materials and bioactive molecules.[2] Especially, direct C–N bond formation through C–H bond cleavage represents an attractive and efficient access to such functional molecules.[3] During the past two decades, considerable achievements have been made for C–H amidation of *N*,*N*-dimethylaniline derivatives *via* cross-dehydrogenative coupling between amides and C(sp^3)–H bonds α to a nitrogen atom (Scheme 1a).[4–6] Under these oxidative conditions, C–H amidation proceeds via an iminium intermediate or the equivalent. For example, Fu and co-workers developed Cu-catalyzed C(sp^3)–H amidation of *N*,*N*-dimethylanilines with amides and imides in the presence of *tert*-butyl hydroperoxide as an oxidant.[4a] Fe-catalyzed oxidative protocols[5] as well as transition-metal-free C(sp^3)–H amidation[6,7] have also been developed.

On the other hand, metal-mediated C(sp^3)–H amidation α to a nitrogen atom via nitrene intermediates has been relatively unexplored.[8] Dirhodium nitrene complexes have been known to be representative active species for C–H amidation via a direct C–H insertion process.[3,9] Although significant progress has been made in dirhodium-catalyzed C–H amidation of electron-rich C(sp^3)–H bonds such as tertiary C(sp^3)–H and C(sp^3)–H bonds α to a C–C multiple bond and an oxygen atom, only few examples of amidation of C(sp^3)–H bonds α to a nitrogen atom have been reported. Ito, Sugiyama, and co-workers reported dirhodium-catalyzed C(sp^2)–H amidation of *N*,*N*-dialkylaniline derivatives *ortho* to aniline nitrogen, in which C(sp^3)–H amidation was also observed as a side reaction. (The amidated product was not isolated due to the instability of the aminal structure.)[10] In contrast to the report, we found that the C–H amidation took place chemoselectively at the C(sp^3)–H bond in dirho-

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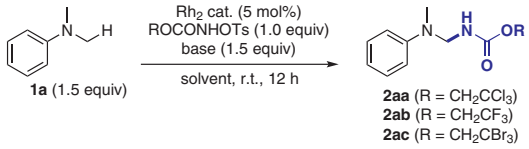
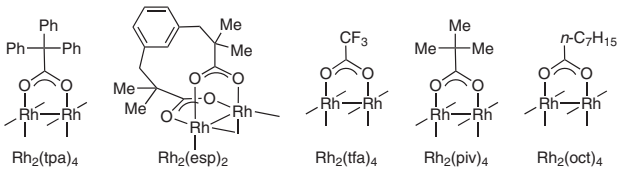
dium-catalyzed reactions of *N*,*N*-dialkylaniline derivatives. Here, we report a general method for dirhodium-catalyzed C(sp^3)–H amidation of *N*,*N*-dimethylanilines using *O*-tosyl-*N*-trichloroethoxycarbonylhydroxylamine (TrocNHOTs)[11] as a nitrene source (Scheme 1b). The C(sp^3)–H amidation takes places chemoselectively in the presence of potentially reactive C(sp^2)–H bonds of the electron-rich aromatic ring. The chemoselectivity shown in Scheme 1b is also in contrast to our previous report that dirhodium-catalyzed C–H amidation of anisole derivatives took place at the aromatic C(sp^2)–H bond.[12] Another salient feature of the present process is site selectivity of the C(sp^3)–H amidation. Control of the site selectivity is still of challenge in C(sp^3)–H amidation of *N*,*N*-dialkylanilines with two different alkyl groups. For example, nonselective C(sp^3)–H amindation of methyl and benzylic C(sp^3)–H bonds α to nitrogen was reported to take place in copper-catalyzed C–H amindation of *N*-benzyl-*N*-methylaniline.[4a,d] On the other hand, under the present conditions, C(sp^3)–H amidation of the *N*-methyl group of various *N*-alkyl-*N*-methylanilines (alkyl ≠ methyl) was observed exclusively even in the presence of potentially reactive benzylic and tertiary C–H bonds α to the nitrogen atom (Scheme 1c).

We commenced our studies on C–H amidation with *N*,*N*-dimethylaniline (**1a**) as a substrate in the presence of various dirhodium catalysts, *O*-tosyl-*N*-trihaloethoxycarbonylhydroxylamines as nitrene sources, and bases (Table 1). According to the previously optimized conditions for C–H amination of anisole derivatives[12] and organosilanes,[13] **1a** (1.5 equiv) was treated with TrocNHOTs in the presence of $Rh_2(tpa)_4$ and K_2CO_3 in chlorobenzene at room temperature to give no C–H-amidated products (entry 1). Use of $Rh_2(esp)_2$[9e] in place of $Rh_2(tpa)_4$ gave the desired C(sp^3)–H-amidated product **2aa** in 39% yield (entry 2). Further catalyst screening revealed that $Rh_2(oct)_4$ promoted the C(sp^3)–H amidation most effectively to give **2aa** in 46% yield (entry 6 vs 1–5). We assume that lack of the catalytic activity of $Rh_2(tpa)_4$ in the C–H amidation seems to be due to inactivation by stronger and irreversible coordination of **1a** to Rh of $Rh_2(tpa)_4$, while coordination of **1a** to Rh of $Rh_2(oct)_4$ appears to be weaker and reversible (for association energies of **1a** with $Rh_2(tpa)_4$ and $Rh_2(OAc)_4$, see Scheme S1 in the Supporting Information). This behavior could also be observed by the color change of the reaction solution. While the color of the solution of coordination-free dirhodium complexes is usually green, it changes to pink by coordination of **1a** to Rh. The color of the solution of **1a** and $Rh_2(tpa)_4$ was light pink, indicative of formation of inactive Rh complexes. On the other hand, the color of the solutions of **1a** and $Rh_2(OAc)_4$ or $Rh_2(oct)_4$ was purple, which may suggest weak and reversible coordination of **1a** to Rh. Use of other nitrene sources with trifluoroethyl and tribromoethyl groups provided C(sp^3)–H amidated product **2ab** and **2ac**, respectively, in the comparable yields (entries 7 and 8). By solvent screening, CH_2Cl_2 and toluene were found most suitable for the purpose (entries 9–15). It is worthy to note that benzylic methyl C(sp^3)–H bonds of toluene were totally inactive for amidation, even when toluene was used as a solvent (entry 15). Use of bases such as Li_2CO_3, Na_2CO_3, Cs_2CO_3, or Rb_2CO_3 did not improve the yield of the amidation reaction (entry 15 vs 16–20). Finally, the yield of amidation was improved by use of 10 equivalents of the substrate to afford the desired **2aa** in 79% yield (entry 21).

Table 1 Optimization of the Conditions for C–H Amidation of *N*,*N*-Dimethylaniline (**1a**)

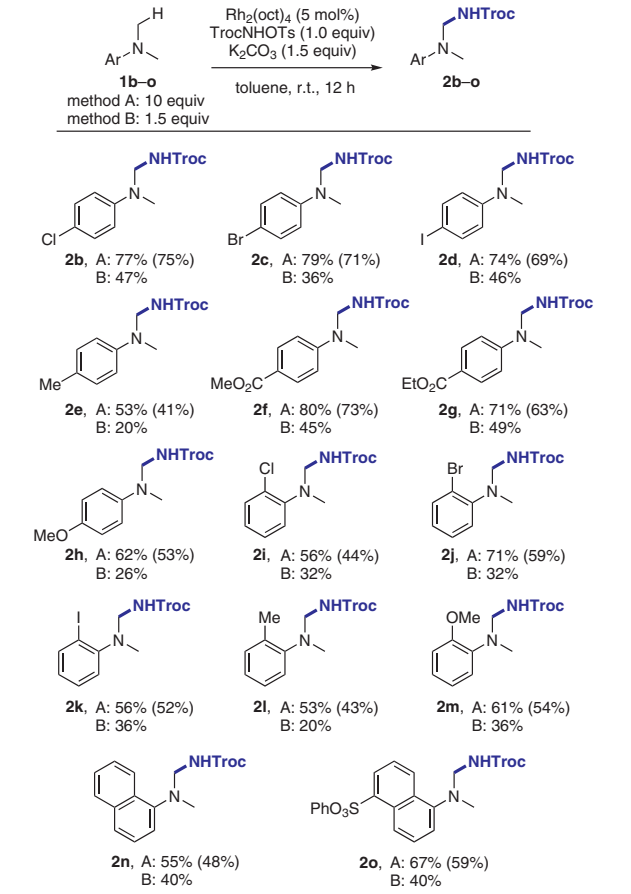


Entry	Catalyst	R	Solvent	Base	Yield of **2a** (%)[a]
1	$Rh_2(tpa)_4$	CH_2CCl_3	PhCl	K_2CO_3	0
2	$Rh_2(esp)_2$	CH_2CCl_3	PhCl	K_2CO_3	39
3	$Rh_2(OAc)_4$	CH_2CCl_3	PhCl	K_2CO_3	42
4	$Rh_2(tfa)_4$	CH_2CCl_3	PhCl	K_2CO_3	36
5	$Rh_2(piv)_4$	CH_2CCl_3	PhCl	K_2CO_3	40
6	$Rh_2(oct)_4$	CH_2CCl_3	PhCl	K_2CO_3	46
7	$Rh_2(oct)_4$	CH_2CF_3	PhCl	K_2CO_3	39
8	$Rh_2(oct)_4$	CH_2CBr_3	PhCl	K_2CO_3	43
9	$Rh_2(oct)_4$	CH_2CCl_3	EtOAc	K_2CO_3	40
10	$Rh_2(oct)_4$	CH_2CCl_3	CH_2Cl_2	K_2CO_3	60
11	$Rh_2(oct)_4$	CH_2CCl_3	$CHCl_3$	K_2CO_3	49
12	$Rh_2(oct)_4$	CH_2CCl_3	PhH	K_2CO_3	51
13	$Rh_2(oct)_4$	CH_2CCl_3	PhF	K_2CO_3	52
14	$Rh_2(oct)_4$	CH_2CCl_3	$PhCF_3$	K_2CO_3	48
15	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	K_2CO_3	60
16	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	Li_2CO_3	44
17	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	Na_2CO_3	30
18	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	Cs_2CO_3	41
19	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	Rb_2CO_3	54
20	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	KOAc	40
21[b]	$Rh_2(oct)_4$	CH_2CCl_3	PhMe	K_2CO_3	79

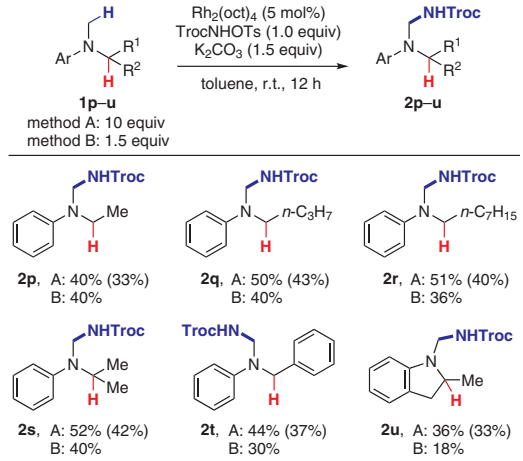


[a] Determined by crude ^1H NMR analysis, using 1,3-dinitrobenzene as internal standard.
[b] Run with 10 equiv of **1a**.

Substrate scope was then investigated with various *N*,*N*-dimethylarylamines under the optimized conditions for the C–H amidation (Table 1, entry 21; Scheme 2). Substrates **1b**, **1c**, and **1d** with chloro, bromo, and iodo groups, respectively, at C(4) successfully gave the amidated products **2b**, **2c**, and **2d**, respectively, in good yields. On the same treatment, 4,*N*,*N*-trimethylaniline (**1e**) gave **2e** as a single regioisomer with the benzylic methyl C(sp^3)–H bonds remained intact. Either an electron-withdrawing or electron-donating group at C(4) did not affect the efficiency of the C(sp^3)–H amidation reaction (**2f**–**h**). The present procedure for C(sp^3)–H amidation was found applicable to aniline derivatives **1i**–**m** with various substituents at the C(2). Compound **1o** with a dansyl group, a widely used fluorescent group,[14] also underwent selective amidation of the C(sp^3)–H bond α to the nitrogen atom. With all the 15 *N*-methylaniline derivatives examined, chemoselective C(sp^3)–H amidation was observed exclusively in the presence of aromatic C(sp^2)–H bonds. In all cases, TrocNHOTs was almost completely consumed and the formation of $TrocNH_2$ was observed, which indicated partial decomposition of the aminating agent under the reaction conditions.[11b,15,16c]

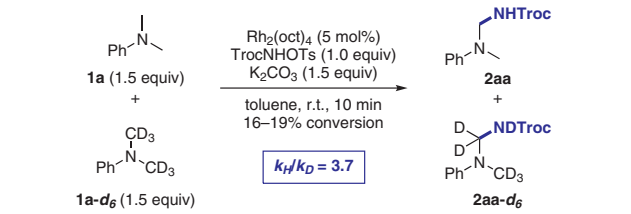


Scheme 2 Chemoselective C(sp^3)–H amidation of *N*,*N*-dimethylarylamines. The yields were determined by crude ^{1}H NMR analysis, using 1,3-dinitrobenzene as internal standard; isolated yields are given in parentheses.

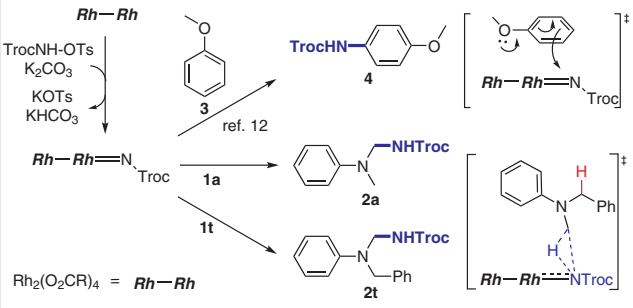


Scheme 3 Site selectivity of C(sp^3)–H amidation of *N*-alkyl-*N*-methylaniline derivatives. The yields were determined by crude ^{1}H NMR analysis, using 1,3-dinitrobenzene as internal standard; isolated yields are given in parentheses.

Site selectivity of the C–H amidation was investigated using several aniline derivatives with *N*-alkyl-*N*-methyl groups (alkyl ≠ methyl, Scheme 3). Treatment of *N*-ethyl-*N*-methylaniline (**1p**) by the present protocol provided the *N*-methyl-amidated product **2p** as a single regioisomer. Potential reactivity of the *N*-ethyl group toward the C–H amidation might be missed because of the instability of the C–H amidation product generated at the *N*-ethyl group if any.[8b,10] However, this concern seems not to be the case because *N*-methylaniline, a dealkylated product supposed to be obtained by decomposition of the aminal generated at the *N*-ethyl group, was not obtained. Thus, amidation of **1p** took place site-selectively at the primary C(sp^3)–H bond adjacent to the nitrogen atom. Similarly, C(sp^3)–H amidation of substrate **1q** and **1r** with an *n*-butyl and an *n*-octyl group provided *N*-methyl-amidated products **2q** and **2r**, respectively, as the single regioisomers. Notably, substrates **2s** and **2t** with tertiary and benzylic C(sp^3)–H bonds α to the nitrogen atom underwent amidation at the primary C(sp^3)–H bond selectively, to give **2s** and **2t**, respectively. The present method was also applicable to *N*-methyl-selective C–H amidation of indoline derivative **1u** with an electronically reactive tertiary C(sp^3)–H bond adjacent to a nitrogen atom. When slight excess amounts (1.5 equivalents) of the substrates were employed, decrease in the yields of the desired products was observed in most cases, while products **2p**, **2q**, and **2s** were obtained in comparable yields with those obtained by the original procedure using 10 equivalents of substrates (Scheme 2 and 3).



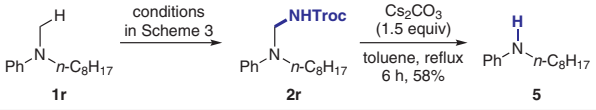
Scheme 4 Determination of a kinetic isotope effect (KIE) by competitive reaction between **1a** and **1a-*d*$_6$**



Scheme 5 Possible reaction paths depending on the substrates

To get insights into the reaction mechanism, the kinetic isotope effect (KIE) of the reaction was measured (Scheme 4). The KIE value was determined by the competitive reaction of a 1:1 mixture of **1a** and **1a-*d*$_6$** to be k_H/k_D = 3.7. This result indicated that the C–H bond cleavage is involved in the product-determining step. Possible reaction paths and our hypothetical understanding for chemo- and site selectivity of dirhodium-catalyzed C–H amidation depending on the substrates are described in Scheme 5. A dirhodium nitrene complex is assumed to be generated from the dirhodium tetracarboxylate complex, TrocNHOTs, and K_2CO_3 according to the previous reports.[11,16] The nitrene species was expected to be inserted into the C(sp^3)–H bond α to the nitrogen atom of **1a** in a concerted asynchronous manner, including a hydride-transfer process assisted by effective donation of the lone-pair electron of the neighboring nitrogen atom. On the other hand, dirhodium-catalyzed C–H amidation of anisole (**3**) took place at the aromatic *para*-C(sp^2)–H bond even in the presence of C(sp^3)–H bonds α to the oxygen atom.[12] The difference in chemoselectivity could be ascribed to the difference in the electronegativity between nitrogen and oxygen. The partial positive charge developed in the transition state of C(sp^3)–H amidation of the *N*-methyl group in **1a** would be stabilized by the adjacent nitrogen lone pair. On the other hand, such stabilization may not to be effectively operative in the reaction of anisole because of the stronger negative inductive effect of oxygen than nitrogen. As the result, electrophilic aromatic substitution of the electron-rich aromatic ring of **3** would take place at the *para* position distal from the oxygen atom to selectively provide C(sp^2)–H-amidated product **4**. In the C(sp^3)–H amidation of *N*-benzyl-*N*-methylaniline (**1t**), steric effect would be dominant to control the site selectivity. The dirhodium nitrene species are expected to be selectively inserted into the sterically more accessible primary C(sp^3)–H bond adjacent to the nitrogen atom rather than the electronically more favorable secondary benzylic C(sp^3)–H bonds. Similar site selectivity was also observed in β-silicon-effect-promoted C(sp^3)–H amidation of organosilicon compounds with dirhodium nitrene species.[13]

An application to two-step demethylation of the *N*-methyl aniline derivative **1r** was demonstrated (Scheme 6). Treatment of **2r** obtained by C(sp^3)–H amidation of **1r** with Cs_2CO_3 in toluene under reflux conditions afforded the desired N-demethylated product of **1r**, phenyloctylamine (**5**), in 58% yield. While N-demethylation reaction seems to be one of the valuable structural modifications of natural products and drug candidates,[17] the methods for N-demethylation have been quite limited. The present method is assumed to be potentially useful for the application to late-stage functionalization of bioactive molecules containing aromatic *N*-methyl group.[18]



Scheme 6 Two-step demethylation of *N*-methyl-*N*-octylaniline (**1r**)

In summary, we have developed a general method for the C(sp^3)–H amidation of various *N*-methyl-*N*-alkylaniline derivatives catalyzed by dirhodium complexes.[19] A primary C(sp^3)–H bond of the *N*-methyl group was selectively converted into the C–N bond in the presence of the secondary, tertiary, and benzylic C(sp^3)–H bonds α to a nitrogen atom. The protocol was successfully applied to a two-step demethylation process of a *N*-methylaniline derivative. Further studies on mechanistic analysis and late-stage functionalization of complex molecules of biological interests are currently underway.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1334-6450.

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(19) **General Procedure for Dirhodium-Catalyzed C(sp^3)–H Amidation of *N*,*N*-Dialkylanilines**

To a suspension of *N*,*N*-dialkylanilines (0.5 mmol, 10 equiv), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv), and K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv) in toluene (0.25 mL) were added $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv) at room temperature. After being stirred for 12 h, the reaction was quenched by addition of water and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated. The yields of the aminated product **2** were determined by ^{1}H NMR analysis using 1,3-dinitrobenzene as internal standard. The residue was purified by preparative TLC purification to afford the aminated product **2**.

Trichloroethyl{[methyl(phenyl)amino]methyl}carbamate (2aa)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): δ = 7.29–7.25 (m, 2 H), 6.84–6.81 (m, 3 H), 5.41 (br s, 1 H), 4.91 (d, *J* = 6.0 Hz, 2 H), 4.73 (s, 2 H), 3.01 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 147.7 129.6, 118.7, 113.6, 95.5, 74.6, 59.6, 37.8. IR (neat): 3326, 2952, 1722, 1598, 1499, 1367, 1220, 1132, 1041, 817, 750 cm^{-1}. HRMS-ESI$^+$: *m/z* calcd for $C_{11}H_{13}Cl_3N_2O_2$ [M + H]$^+$: 311.0115; found: 311.0115.