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PAPER

Titanium-mediated rearrangement of cyclopropenylmethyl acetates to (*E*)-halodienes†

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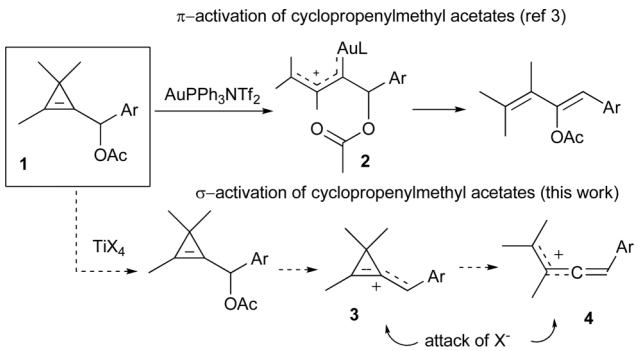
$TiCl_4$ and $TiBr_4$ rapidly transform cyclopropenylmethyl acetates to (*E*)-halodienes *via* ring-opening to allyl-vinyl cations. DFT calculations suggest that the regioselectivity of the halogenation of this cationic intermediate by $[TiX_4OAc]^-$ is under thermodynamic control, while the stereoselectivity is governed by kinetics.

Introduction

The Lewis-acid mediated abstraction of propargylic leaving groups to provide a propargyl cation is a widely investigated method for functionalisation of propargyl alcohol-derived substrates.[1] Cyclopropenylmethyl acetates are an interesting subclass of cyclopropene, which due to the π-rich nature of their double bond bear some resemblance to propargyl alcohol-derived substrates.[2] Indeed, we have previously reported that π-activation of these cyclopropenes with Au(I) catalysts, results in stereoselective rearrangement to (*Z*)-acetoxydienes *via* **2** (Scheme 1).[3] Within this context, we proposed that divergent reactivity by σ-activation with oxaphilic Lewis-acids, such as TiX_4, may be brought about. Acetate abstraction by TiX_4 from cyclopropenes **1** could potentially generate cyclopropenyl cation **3**, which could undergo ring-opening to cation **4**. These two cations can then potentially be intercepted by X^- originating from the TiX_4 to yield halogenated products.[4] As both **3** and **4** can react with X^- at more than one electrophilic site, this proposed reaction raises several chemoselectivity and regioselectivity questions.

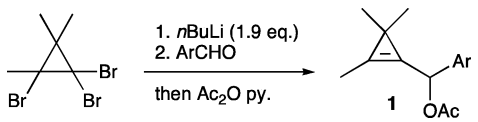
In this paper, we demonstrate that upon treatment with TiX_4, cyclopropenes **1** can be transformed regioselectively and stereoselectively into (*E*)-halo-dienes and use DFT calculations to propose a mechanistic rationale for this reaction.



Scheme 1 Activation of cyclopropenylmethyl acetates with π- and σ-Lewis acidic metals.

Results and discussion

We began our experimental investigations by preparing the required cyclopropenylmethyl acetates from tribromocyclopropanes using the method of Baird *et al.*,[5] followed by acetylation of the resulting alcohols. (Scheme 2). Nitrobenzaldehyde-derived cyclopropene **1a** was chosen as our first substrate as its crystalline nature would enable product identification by X-ray analysis if necessary.



Scheme 2 Synthesis of cyclopropenylmethyl acetates.

To our delight, treatment of *p*-nitrobenzaldehyde-derived cyclopropene **1a** with 1.2 equivalents of $TiCl_4$ at − 78 °C for 5 min resulted in the formation of (*E*)-chlorodiene **5a** in 72% yield (Table 1, entry 1). The stereochemistry of **5a** was unambiguously determined by X-ray crystallography.[6] It is of note that the NMR of the crude reaction mixture did not indicate the presence of

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† Electronic supplementary information (ESI) available: Experimental section, X-ray crystallographic data and NMR spectra. CCDC reference number 737881. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01046d

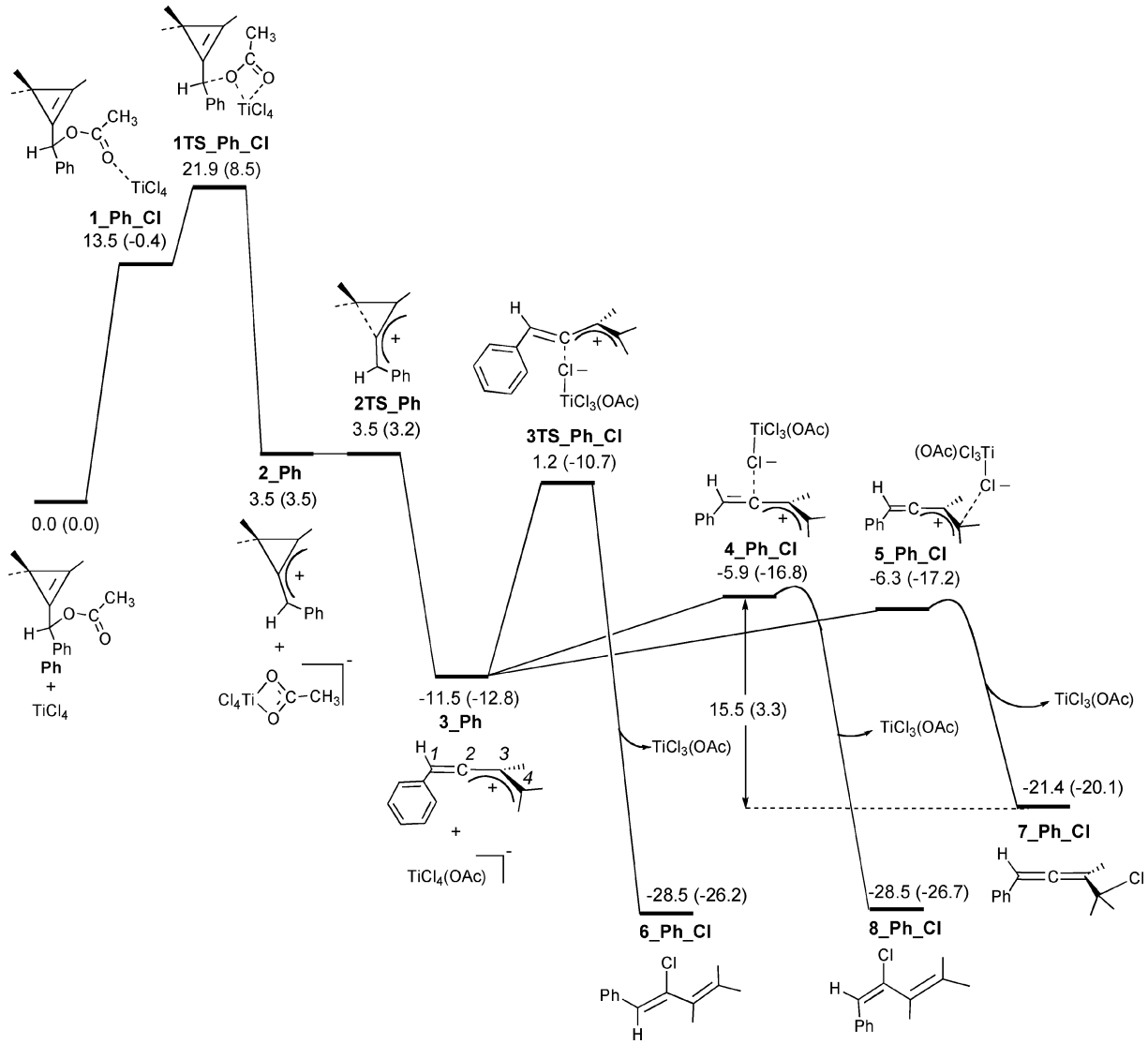
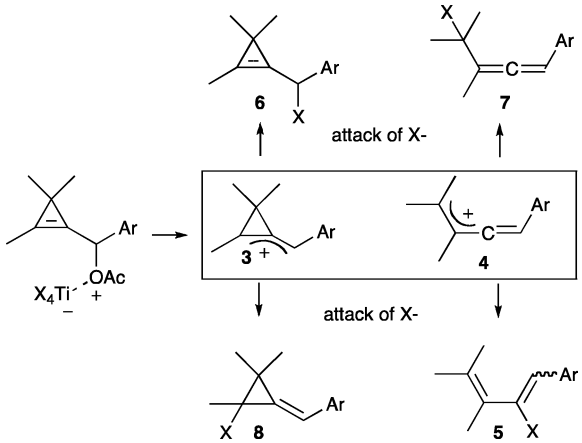


Fig. 1 The DFT energy profile for the reaction of cyclopropenylmethyl acetate **1b** with $TiCl_4$. The relative free energies and potential energies (in parentheses) are given in kcal mol^{-1}.[9]

any of the (*Z*)-isomer. Short reaction times were particularly important as much lower yields were obtained if the reaction was left longer than 5–10 min at – 78 °C. These lower yields are presumably a result of product decomposition under the strongly Lewis-acidic conditions. A deep purple colour was also noted upon the addition of $TiCl_4$, pointing towards the formation of a carbocation intermediate.[6]

To test the substrate scope of the reaction, a range of cyclopropenylmethyl acetates with varying Ar groups were subjected to the same reaction conditions and in all cases high yields and complete (*E*)-selectivity was observed (Table 1, entries 1–7). The only exception was the *p*-tolylaldehyde derived cyclopropene **5c**, which gave the resulting diene in only 36% yield. We were delighted to find that $TiBr_4$ could also initiate the transformation of cyclopropenes **1a–f** to (*E*)-bromodienes **5h–k** (entries 8–11, Table 1).[7]

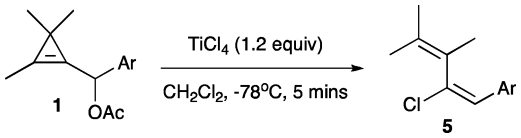
Given the four possible regioisomeric products outlined in Scheme 3, it is remarkable that the reaction is both completely regio- *and* stereoselective for (*E*)-halodienes **5**. In order to explain



Scheme 3 Possible reaction pathways for interception of cations **3** and **4**.

the high selectivity observed in the reaction we turned our attention to computational studies (Fig. 1).

Table 1 TiX_4 mediated synthesis of halodienes **5**



Entry	Substrate	TiX_4	Ar	Product	Yield%[a]
1	**1a**	$TiCl_4$	*p*-Nitrophenyl	**5a**	72
2	**1b**	$TiCl_4$	Phenyl	**5b**	84
3	**1c**	$TiCl_4$	*p*-Tolyl	**5c**	36
4	**1d**	$TiCl_4$	*o*-Chlorophenyl	**5d**	84
5	**1e**	$TiCl_4$	*o*-Bromophenyl	**5e**	89
6	**1f**	$TiCl_4$	*p*-Fluorophenyl	**5f**	72
7	**1a**	$TiBr_4$	*p*-Nitrophenyl	**5g**	68
8	**1b**	$TiBr_4$	Phenyl	**5h**	70
9	**1d**	$TiBr_4$	*o*-Chlorophenyl	**5i**	79
10	**1e**	$TiBr_4$	*o*-Bromophenyl	**5j**	70
11	**1f**	$TiBr_4$	*p*-Fluorophenyl	**5k**	68

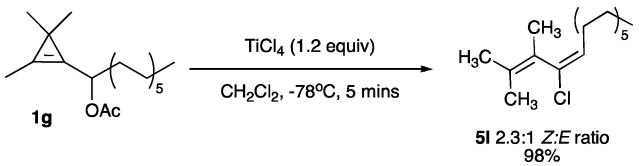
[a] Isolated yield following chromatography.

We surmised that the first step in the reaction would be coordination of $TiCl_4$ to the acetate **Ph**. Based on this, our DFT calculations predicted that the adduct **1_Ph_Cl** is formed and subsequently undergoes acetate abstraction *via* **1TS_Ph_Cl** give **2_Ph** and $TiCl_4(OAc)^-$. This relatively low energy transition state (21.9[8] (8.5) kcal mol^{-1}) represents the rate-determining step in the reaction and provides an indication of why the reaction is so facile at low temperature.[9] Barrierless ring-opening to allyl-vinyl cation **3_Ph** then occurs through **2TS_Ph**. This remarkably facile transformation is due to the associated relief of ring-strain and as such, allyl vinyl cation **3_Ph** should be considered the only reactive intermediate in the reaction. Indeed, there are examples of simple cyclopropenes undergoing ring-opening reactions by metal salts, such as MgX_2,[10a] $Fe(acac)_3$[10b] NaI[10c] and Au(I)[10d–f].

At this point it is important to note that calculations showed that dissociation of $TiCl_4(OAc)^-$ to generate Cl^- is an endergonic process (7.3 kcal mol^{-1}) with an energy barrier of approximately 17.5 kcal mol^{-1}. As such, it is probable that it is $TiCl_4(OAc)^-$ rather than free Cl^- that undergoes direct attack on **3_Ph**. We can now consider the regioselectivity of the reaction in order to explain why the formation of diene **5** is favored over allene **7**.

All attempts to locate the transition states for the formation of **8_Ph_Cl** and **7_Ph_Cl** were unsuccessful and led to adducts **4_Ph_Cl** and **5_Ph_Cl**, respectively. This indicates that the potential energy surface with respect to attack of $TiCl_4(OAc)^-$ on **3_Ph** should be very flat and that transformation into **8_Ph_Cl** and **7_Ph_Cl** should occur with roughly equal propensity. This result suggests that the regioselectivity of the reaction is not determined by kinetic factors and we will demonstrate below that the thermodynamic factors are responsible for the observed regioselectivity of halogenation. From Fig. 1, we can see that both the reactions **3_Ph** + $[TiCl_4(OAc)]^-$ → **8_Ph_Cl** + $TiCl_3(OAc)$ and **3_Ph** + $[TiCl_4(OAc)]^-$ → **7_Ph_Cl** + $TiCl_3(OAc)$ are thermodynamically favourable, although the formation of diene **8_Ph_Cl** is more exothermic than formation of allene **7_Ph_Cl**. The low exergonicity for the reaction of **4_Ph** + $[TiCl_4(OAc)]^-$ → **7_Ph_Cl** + $TiCl_3(OAc)$ (9.9 kcal mol^{-1}) suggests that the attack at carbon 4 is reversible (Fig. 1). In such a case, $TiCl_3(OAc)$ can readily abstract the chloride from allene **7_Ph_Cl** and regenerate the more stable diene **8_Ph_Cl** with an activation barrier of about 15.5[11] (3.3) kcal mol^{-1} (Fig. 1). Therefore, it can be seen that diene **8_Ph_Cl** represents a thermodynamic well in the reaction and is obtained as the only product due to the reversibility of allene **7_Ph_Cl** formation at low temperature. Repeating the calculations with $TiBr_4$ resulted in a similar outcome. These calculations gave a Gibbs free energy for **7_Ph_Br** of – 21.3 kcal/mol, which is about 7.3 kcal mol^{-1} less stable than **8_Ph_Br**. Also, the energy difference between **3_Ph**/$[TiBr_4(OAc)]^-$ and **7_Ph_Br**/$TiBr_3(OAc)$ is still small at 6.2 kcal mol^{-1}, which again supports the reversibility of the reaction **3_Ph** + $[TiBr_4(OAc)]^-$ → **7_Ph_Br** + $TiBr_3(OAc)$.

To explain the stereochemical outcome of the reaction it is important to remember that the sterically encumbered $[TiCl_4(OAc)]^-$ is the species that delivers a chlorine to the allyl-vinyl cation **3_Ph**. Delivery of chloride to the same face as the phenyl ring is effectively blocked by an unfavorable steric interaction between the in-plane Ph group and the incoming $[TiCl_4(OAc)]^-$. For this unfavorable attack it was possible to locate the transition state **3TS_Ph_Cl**, which is about 6 kcal mol^{-1} higher than for attack *trans* to phenyl. This significant energy difference explains the complete stereoselectivity observed experimentally. In support of this proposal is the lowered stereoselectivity observed upon treatment of dodecylaldehyde-derived cyclopropene **1g** with $TiCl_4$ (Scheme 4). This reduced stereoselectivity fits in with our proposal above and can be ascribed to the lowered steric demand of an alkyl group compared to an aryl group. This lowered steric demand is reflected in the earlier transition state **3TS_Et_Cl**: the Ti–Cl^1 bond in **3TS_Et_Cl** is ~0.041 Å shorter than that in **3TS_Ph_Cl**; the Cl^1–C^2 bond in **3TS_Et_Cl** is ~0.114 Å longer than that in **3TS_Ph_Cl** and the C^1–C^2–C^3 bond angle in **3TS_Et_Cl** is less bent than in **3TS_Ph_Cl**. This earlier nature of the transition state **3TS_Et_Cl** results in a ~4.2 kcal mol^{-1} stabilization on the potential energy surface compared to **3TS_Ph_Cl**. As a result, the reaction affording (*Z*)-chlorodiene **5l** becomes viable under the reaction conditions and this leads to the lack of stereoselectivity observed experimentally.



Scheme 4 Reaction of dodecylaldehyde-derived **1g** with $TiCl_4$.

The $[TiCl_4(OAc)]^-$, which acts as the chloride shuttle in the reaction has an approximately octahedral structure as illustrated in Fig. 2. It is interesting to note that there are two chlorines that can potentially be transferred to the cationic intermediate. However, calculations revealed that a chlorine *trans* to chlorine is more nucleophilic than the chlorine *trans* to oxygen.

For example, this more nucleophilic chloride preferentially adopts **3TS_Et_Cl**, which is about 2 kcal mol^{-1} lower in energy than **3′TS_Et_Cl** (Fig. 2). The higher nucleophilicity of the chlorine *trans* to chlorine is supported by a longer Ti–Cl bond length and a greater partial negative charge on Cl of $[TiCl_4OAc]^-$. This results in **3TS_Et_Cl** being an earlier transition state than **3′TS_Et_Cl**; for **3TS_Et_Cl** the angle C^1–C^2–C^3 is larger and the Cl–C^2 bond length is longer (Fig. 2). We believe that these

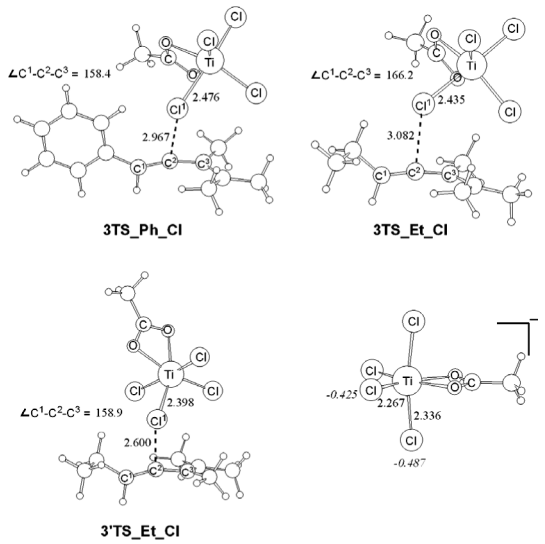


Fig. 2 B3LYP-optimized structures for **3TS_Ph_Cl**, **3TS_Et_Cl**, **3′TS_Et_Cl** and $[TiCl_4(OAc)]^-$. Selected structure parameters are given in Å and °. Muliken atomic charges for selected atoms of $[TiCl_4OAc]^-$ are given in italics.

observations could have potentially important implications for the design of titanium based catalysts.

Conclusions

In conclusion, we have developed a stereoselective synthesis of (*E*)-2-chloro-1,3-dienes and (*E*)-2-bromo-1,3-dienes and accounted for the mechanism of the reaction using DFT calculations. These calculations show that TiX_4-mediated ring-opening is extremely facile and that the regioselectivity of the subsequent halogenation operates under thermodynamic control while the stereoselectivity of halide addition is kinetically controlled. It should be noted that dienes of this type have not received much attention due to a surprising scarcity of methods for their preparation.[12] Only recently have Barluenga and coworkers reported an elegant and simple synthesis of 2-chloro-1,3-dienes by selective Suzuki coupling of 1,1-dichloroethylene.[13] Work is currently underway on further developing the reactivity of cyclopropenylmethyl acetate-derived allyl-vinyl cations.

Experimental

Computational details

Gaussian 09[14] was used to fully optimize all the structures reported in this paper at the B3LYP level of density functional theory.[15] The 6-311G(d) basis set was chosen to describe titanium.[16] The 6-31G(d) basis set was used for other atoms. This basis set combination will be referred to as BS1. Frequency calculations were carried out at the same level of theory as for structural optimization. To further refine the energies obtained from the B3LYP/BS1 calculations, we carried out single point energy calculations for all the structures with the larger 6-311+G(2d,p) basis set (BS2). The solvation energies were calculated using BS2 on gas phase optimized geometries with the CPCM solvation model[17] using dichloromethane as a solvent. To estimate the corresponding Gibbs free energies in solvent (ΔG), entropy corrections were calculated at the B3LYP/BS1 level and added to the solvent potential energies. We have used the solvent energies throughout the paper unless otherwise stated.

Materials and methods

Unless otherwise stated all reactions were carried out under an argon or nitrogen atmosphere in flame-dried glassware. Reactions were monitored by TLC using glass-backed silica gel XHL plates (purchased from Sorbtech with UV 254, thickness 250 μm) or by GC and GC/MS on an Agilent 7890 (FID detector and HP-5 column 30 m × 0.32 mm 0.25 μm, part number: 19091j-413) and Varian 3900/Saturn 2100T (ion-trap mass-selective detector and, FactorFour capillary column VF-5ms, 30 m × 0.25 μm, Part number: cp8944), respectively. Compounds were purified using flash column chromatography with Sorbtech silica gel or by radial chromatography with a Chromatotron®. Chromatography plates employed on the Chromatotron® were 1 mm or 2 mm prepared from a mixture of calcium sulfate hemihydrate and Aldrich Silica gel (TLC standard grade, without binder, with fluorescent indicator). NMR spectra were recorded on a BrukerAvance DRX-400 (400 MHz) in $CDCl_3$ unless otherwise noted. $CDCl_3$ was stored over K_2CO_3 or 4 Å molecular sieves and was purchased from Acros. Melting points are uncorrected and measure on a Thomas Hoover Unimelt capillary melting point apparatus. IR spectra were recorded on a Thermo electron corporation Nicolet 380 FT-IR as films on NaCl plates (liquids) or in a NaCl solution cells (solids). Accurate mass measurements were recorded at the University of California, Riverside High Resolution Mass Spectrometry Facility and at the University of California, Irvine. X-ray analyses were carried out at the W.M. Keck Foundation Center for Molecular Structure in California State University, Fullerton. *n*BuLi was purchased from Strem and titrated against diphenylacetic acid prior to use. Other reagents were commercially available and used without further purification.

Typical procedure for preparation of (*E*)-chlorodienes

The cyclopropenyl acetate (0.17 mmol, 1.0 equiv.) was weighed into a flame-dried flask purged with argon and CH_2Cl_2 (3.4 ml) added. The solution was then cooled to −78 °C with a dry-ice acetone bath and $TiCl_4$ (0.17 ml of a 1.0 M solution in CH_2Cl_2) added dropwise. After 5 min the reaction was quenched by the addition of MeOH–H_2O (5 ml of a 1 : 1 mixture) and allowed to warm to room temperature. The organic layer was separated and the aqueous extracted with CH_2Cl_2 (2 × 5 ml). The combined organics were dried ($MgSO_4$) and evaporated to dryness. Purification on SiO_2 (pentane on a Chromatotron®) yielded the pure diene **3e**.

(*E*)-1-chloro-2-(2-chloro-3,4-dimethylpenta-1,3-dienyl)benzene 3e was obtained as a clear yellow oil (72 mg, 84%). IR 1650, 1623, 1468, 1440, 1374, 1148, 1129, 1052, 1035, 946, 929, 806, 749 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 1H), 7.26–7.24 (m, 1H), 7.25–7.11 (m, 2H), 6.90 (s, 1H), 1.91–1.90 (m, 3H), 1.65 (d, J = 8.0, 1.0 Hz, 3H), 1.52–1.51 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.1, 133.6, 133.1, 128.7, 128.4, 126.4, 125.1, 125.0, 115.5, 21.6, 20.0, 17.0. HRMS-CI (m/z): $(M + H)^+$ calcd for $C_{13}H_{14}Cl_2$, 240.0473; found 240.0466.

Acknowledgements

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