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Gold Catalysis: Alkylideneoxazolines and -oxazoles from Intramolecular Hydroamination of an Alkyne by a Trichloroacetimidate

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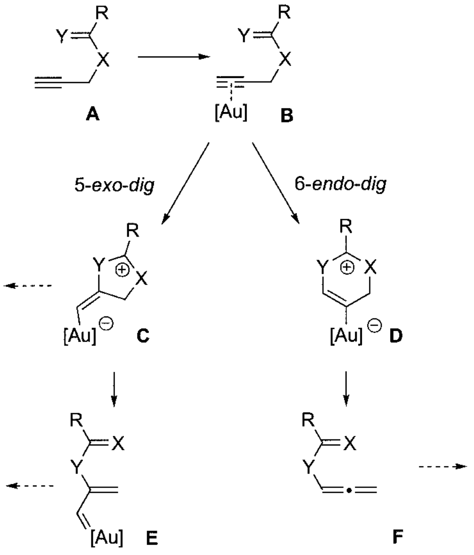
Several propargylic trichloroacetimidates have been prepared and their reactions with gold catalysts studied. Only with the propargyl and the 1-methylpropargyl substituent was a selective cyclization observed; with gold(III) chloride in acetonitrile only the product of a fast hydroamination to 4-methylene-4,5-dihydrooxazoles was obtained, in chloroform the slower subsequent aromatization could not be prevented which delivered the oxazoles after long reaction times. Up to 3333 turnovers could be reached. With gold(I) catalysts in chloroform or dichloromethane selective hydroamination to 4-methylene-4,5-dihydrooxazoles without subsequent aromatization was exclusively observed. The gold(I) catalysts also allowed chemoselective cycloisomerization of *N*-propargylcarboxamides to 5-methylene-4,5-dihydrooxazoles.

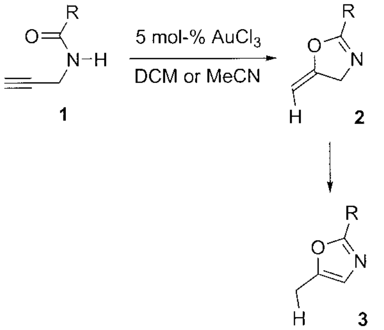
Introduction

In the field of hydroamination[1] soluble gold complexes have recently proven to be active catalysts.[2] Homogeneous gold catalysis has become a very active field;[3] many investigations have explored the reactions of propargylic derivatives of type **A** with ambident allylic nucleophiles as leaving groups, which in principle have the potential to undergo either a 5-*exo*-type cyclization to **C**[4] or a 6-*endo*-type cyclization to **D**[5] (Scheme 1).



Scheme 1. Different reaction patterns of propargylic leaving groups of the allyl-anion type.

With an NH group in intermediate **C** or **D** stabilization by proton-loss is possible;[6] related eliminations have been observed with *tert*-butyl carbonates.[7] In continuation of work on the cycloisomerization of *N*-propargylcarboxamides **1**,[8] which deliver oxazoles **3** by *anti*-oxyauration, proto-deauration to the intermediate **2** and finally isomerization, we have now investigated the reaction of the isomeric amidate groups. In this case, the initial step would be an aminoauration instead of an oxyauration reaction, the product a 4-alkylidene-4,5-dihydrooxazole instead of a 5-alkylidene-4,5-dihydrooxazole (Scheme 2).



Scheme 2. Gold-catalyzed conversion of *N*-propargylcarboxamides **1** to 5-alkylidene-4,5-dihydrooxazoles **2** and oxazoles **3**.

Usually, such trichloroacetimidates show a different reactivity; the work of Schmidt and Jung has established trichloroacetimidates as coupling reagents,[9] specifically the propargyl trichloroacetimidate has successfully been shown to follow that reaction pattern.[10] But there also exists one

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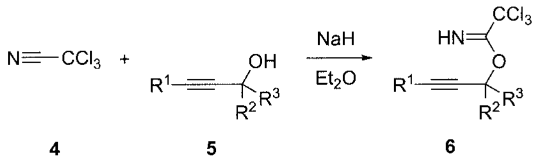
reference, in which such propargyl trichloroacetimidates can be cyclized to the corresponding alkylideneoxazolines in moderate yields in a thermal isomerization process by refluxing in benzene for 48 h.[11]

Results and Discussion

Five different trichloroacetimidates **6a–e** were prepared by the reaction of trichloroacetonitrile **4** with the propargylic alcohols **5a–e** and a catalytic amount of sodium hydride (Scheme 3, Table 1). All the products **6** were insensitive to water; this allowed aqueous workup which significantly simplified the literature procedure[12] and led directly to crude products of sufficient purity for use in gold-catalyzed reactions. Any attempt at purification by column chromatography resulted in a heavy loss of the product (yield of **6a**, for example, was only 23%) without a significant improvement in product purity.



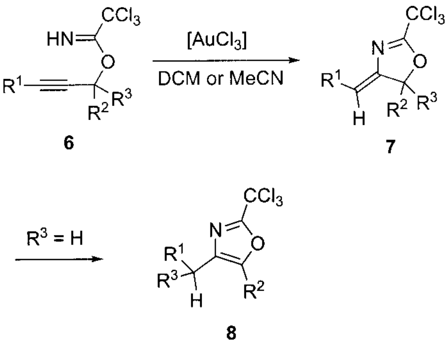
Scheme 3. Synthesis of propargylic trichloroacetimidates **6**.

Table 1. Synthesis of propargylic trichloroacetimidates **6**.

Entry	**5**	**6** (% yield)
1	**5a**: $R^1 = R^2 = R^3 = H$	**6a** (95)
2	**5b**: $R^1 = R^2 = H$; $R^3 = Me$	**6b** (62)
3	**5c**: $R^1 = R^2 = H$; $R^3 = Ph$	**6c** (97)
4	**5d**: $R^1 = H$; $R^2 = R^3 = Me$	**6d** (89)
5	**5e**: $R^1 = R^2 = Me$; $R^3 = H$	**6e** (94)

Treatment of these substrates **6a–e** with gold(III) chloride showed that only **6a** and **6b** reacted selectively. With the benzylic-propargylic leaving group in **6c**, the tertiary propargylic leaving group in **6d** and the internal alkyne in **6e** only a complex product mixture was observed in both chloroform and acetonitrile as solvent.

The selective conversions proceeded via the 4-alkylidene-4,5-dihydrooxazoles **7** to deliver the oxazoles **8** (Scheme 4). For **6a**, after 3 d in $CDCl_3$ a full conversion to **8a** was achieved and an 82% yield obtained. The higher substituted **6b** delivered only 29% of **8b** after the same time.



Scheme 4. Gold-catalyzed isomerization of propargyl trichloroacetimidates to alkylideneoxazolines and -oxazoles.

In the initial step, the hydroamination to **7** (an isomer of **2**) was fast, the subsequent isomerization of **7** to **8** much slower. The time-dependency of the product ratio observed for the conversion of **6a** to **8a** is listed in Table 2. As expected, at higher temperatures the conversion is faster. Entry 4 of Table 2 shows that after only one hour at 56 °C a ratio was obtained similar to the ratio of entry 2 observed after 12 hours.

Table 2. Variation of the **7a/8a** product ratio with reaction time.[a]

Entry	Temp. [°C]	Reaction time	Ratio **6a/7a/8a**
1	20	20 min	0:6:1
2	20	12 h	0:1:1
3	20	72 h	0:0:1
4	56	1 h	0:1:1.2

[a] Using 3 mol-% of $AuCl_3$ in chloroform.

It was also possible to isolate **7a** and **7b** by switching to acetonitrile as solvent; with 3 mol-% $AuCl_3$ in acetonitrile after 25 and 60 min of reaction time and chromatographic workup, 69 and 68% yields of **7a** and **7b** were obtained, respectively. No isomerization of **7** to **8** was observed during chromatographic purification on silica gel. The relatively short reaction times made us curious as to how many turnovers are possible for the obviously very fast transformation of **6** to **7**. Table 3 shows the results observed upon reducing the amount of $AuCl_3$ catalyst in the reaction.

No side-products were observed. With 0.2 mol-% $AuCl_3$ the conversion was slower than with 3 mol-% $AuCl_3$, but after 5 d a full conversion to **8a** could still be achieved. By using as little as 0.01 mol-% of $AuCl_3$, no more conversion was observed after 24 h. Nevertheless, the ratio of 2:1 for **6a/7a** represents a 33% yield of **7a**, which overall gives an impressive turnover number of 3333. In most of the examples of gold-catalyzed hydroamination, turnovers of be-

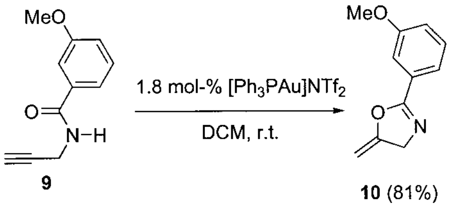
Table 3. Variation of the **6a/7a/8a** ratio with reaction time and amount of catalyst.

3 mol-% $AuCl_3$ in $CHCl_3$		0.2 mol-% $AuCl_3$ in $CHCl_3$		0.01 mol-% $AuCl_3$ in $CHCl_3$	
Reaction time	**6a/7a/8a**	Reaction time	**6a/7a/8a**	Reaction time	**6a/7a/8a**
20 min	0:6:1	20 min	1:2:0	20 min	5:1:0
12 h	0:1:1	12 h	1:5.5:0	24 h	2:1:0
72 h	0:0:1	120 h	0:0:1	72 h	2:1:0

tween 20 and 100 have been reported;[2] only in one example using neat substrates were values similar to ours reached.[2f]

Tests with the Schmidbaur–Bayler salt [(Mes$_3$PAu)$_2$Cl]-BF$_4$, a gold(I) catalyst,[13] and substrate **6a** showed only a slow reaction; after three days at room temperature in chloroform a maximum conversion of 71% to **7a** was obtained. A change to Gagosz's gold(I) catalyst, [Ph$_3$PAu]NTf$_2$,[14] gave a highly selective reaction; with 1 mol-% of the catalyst in dichloromethane a quantitative yield of **7a** was obtained from **6a** after 2 h at room temperature.

Based on the success of these gold(I) catalysts, we returned to the reactions of the *N*-propargylcarboxamides. Indeed, the reaction of substrate **9** with [Ph$_3$PAu]NTf$_2$ delivered exclusively 5-methylene-4,5-dihydrooxazole **10** (Scheme 5), which was completely stable under the reaction conditions and could be isolated by column chromatography. The aromatization observed in the AuCl$_3$-catalyzed reactions[8] was not observed at all.



Scheme 5. Chemoselective gold(I)-catalyzed isomerization of *N*-propargylcarboxamide **9** to 5-methylene-4,5-dihydrooxazole **10**.

Conclusions

The gold-catalyzed cycloisomerization of propargyl trichloroacetimidates can be a highly efficient process, but is strongly dependent on the substituents. The cyclization step is much faster than the subsequent aromatization, the latter being only observed with gold(III) but not gold(I) catalysts. This chemoselectivity of the gold(I) catalysts can be extended to the reactions of *N*-propargylcarboxamides.

Experimental Section

General Procedure for the Synthesis of the Propargylic Trichloroacetimidates 6: NaH (0.1 equiv.) was suspended in absolute diethyl ether (2 mL per mmol propargylic alcohol) and propargylic alcohol (1 equiv.) dissolved in diethyl ether (1 mL per mmol propargylic alcohol) was added. After the reaction time *t*1, the reaction mixture was cooled to 0 °C and trichloroacetonitrile (1.05 equiv.) was added. After the reaction time *t*2, distilled water (2 mL per mmol propargylic alcohol) was added with vigorous stirring and the solution was extracted three times with dichloromethane (2 mmol per mmol propargylic alcohol). After drying with MgSO$_4$ the solvent was evaporated in vacuo (Table 4).

Table 4. Details for the preparation of propargylic trichloroacetimidates **6**.

Propargylic alcohol (mmol)	*t*1 [min]	*t*2 [min]	Product (yield: g, %)
5a (73.0)	10	60	**6a** (13.9, 95)
5b (10.9)	60	60	**6b** (1.45, 62)
5c (14.6)	20	180	**6c** (3.88, 96)
5d (14.6)	10	60	**6d** (2.97, 89)
5e (7.30)	20	60	**6e** (1.57, 94)

Prop-2-ynyl 2,2,2-Trichloroacetimidate (6a):[10] R_f (PE/EA = 3:1) = 0.51. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.55 (t, ^4J = 2.4 Hz, 1 H), 4.90 (d, ^4J = 2.4 Hz, 2 H), 8.50 (s, 1 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 56.58, 75.78, 77.05, 90.69, 161.73 ppm.

1-Methylprop-2-ynyl 2,2,2-Trichloroacetimidate (6b):[12] R_f (PE/EA = 3:1) = 0.63. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.58 (d, ^3J = 6.7 Hz, 3 H), 2.46 (d, ^4J = 2.1 Hz, 1 H), 5.48 (dq, ^3J = 6.7, ^4J = 2.1 Hz, 1 H), 8.42 (s, 1 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 20.95, 65.08, 73.75, 81.50, 91.24, 161.57 ppm.

1-Phenylprop-2-ynyl 2,2,2-Trichloroacetimidate (6c): R_f (PE/EA = 3:1) = 0.76; m.p. 37 °C. IR (neat): $\tilde{\nu}$ = 3343, 3260, 3033, 2122, 1762, 1660, 1492, 1459, 1331, 1288, 1260, 1195, 1064, 1007, 970, 929, 899, 854, 825, 783, 745, 711, 689, 672, 645, 618 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.73 (d, ^4J = 2.2 Hz, 1 H), 6.56 (d, ^4J = 2.2 Hz, 1 H), 7.34–7.47 (m, 3 H), 7.56–7.64 (m, 2 H), 8.59 (s, 1 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 70.06 (d), 76.29 (d), 79.66 (s), 91.08 (s), 127.53 (d, 2C), 128.81 (d, 2C), 129.29 (d), 136.09 (s), 161.39 (s) ppm. MS [EI(+)]: *m*/*z* (%) = 275 (0.3) [M]$^+$, 240 (20), 204 (38), 130 (58), 115 (100). $C_{11}H_8Cl_3NO$ (276.55): calcd. C 47.77, H 2.92, N 5.06; found C 47.69, H 2.99, N 5.04. A crystal structure analysis of this compound was carried out.[15]

1,1-Dimethylprop-2-ynyl 2,2,2-Trichloroacetimidate (6d):[16] ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 1.81 (s, 6 H), 2.61 (s, 1 H), 8.56 (s, 1 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 28.70 (2C), 73.43, 75.50, 84.02, 92.11, 159.98 ppm.

1-Methylbut-2-ynyl 2,2,2-Trichloroacetimidate (6e): R_f (PE/EA = 3:1) = 0.65. IR (neat): $\tilde{\nu}$ = 1664, 1325, 1283, 1074, 1051, 994, 875, 795 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.58 (d, ^3J = 6.7 Hz, 3 H), 1.85 (d, ^4J = 2.1 Hz, 3 H), 5.41–5.57 (m, 1 H), 8.39 (s, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 3.83 (q), 21.38 (q), 65.99 (d), 77.02 (s), 82.07 (s), 91.50 (s), 161.70 (s) ppm.

General Procedure for the Gold-Catalyzed Conversion of 6 to 8: The substrate **6** (1 equiv.) was dissolved in CDCl$_3$ (2 mL per mmol of substrate) and AuCl$_3$ (3 mol-%, 10 wt.-% solution in CD$_3$CN) was added. After 3 d the product was purified by chromatography on silica gel (Table 5).

Table 5. Details for the preparation of oxazoles **8**.

Substrate (mmol)	Column	Product (yield: mg, %)
6a (1.63)	PE/EA, 50:1	**8a** (268, 82)
6b (2.19)	PE/EA, 100:1	**8b** (136, 29)

4-Methyl-2-(trichloromethyl)oxazole (8a): R_f (PE/EA, 10:1) = 0.49. IR (film): $\tilde{\nu}$ = 2961, 2929, 2360, 1770, 1733, 1596, 1544, 1455, 1385, 1324, 1269, 1100, 999, 961, 855, 814, 781, 698 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.18 (d, ^3J = 1.3 Hz, 3 H), 7.43 (q, ^3J = 1.3 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 11.67 (q), 85.67 (s), 137.04 (d), 138.06 (s), 158.67 (s) ppm. MS [EI(+)]: *m*/*z* (%) = 199 (16) [M]$^+$, 170 (23), 166 (65), 164 (100), 138 (13), 136 (20), 100 (10), 42 (22). HRMS (70 eV): calcd. for $C_{18}H_{18}O_2$ [M]: 198.9358; found 198.9351.

4,5-Dimethyl-2-(trichloromethyl)oxazole (8b): R_f (PE/EA = 10:1) = 0.41. IR (film): $\tilde{\nu}$ = 2971, 2931, 2591, 2472, 2359, 2324, 1262, 2150, 1995, 1982, 1638, 1542, 1436, 1297, 1021, 860, 818, 668, 657, 633, 606 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.15 (q, ^5J = 0.9 Hz, 3 H), 2.33 (q, ^5J = 0,9 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, CDCl$_3$): δ = 10.37 (q), 11.27 (q), 132.46 (s), 146.97 (s), 156.38 (s) ppm. MS

[EI(+)]: *m*/*z* (%) = 213 (11) $[M]^+$, 180 (35), 178 (56), 43 (17), 28 (21), 18 (100). HRMS (70 eV): calcd. 212.9515; found 212.9516.

Synthesis of the Intermediates 7: The starting material **6** (1 equiv.) was dissolved in CH_3CN and $AuCl_3$ (3 mol-%, 10 wt.-% solution in CD_3CN) was added. After the reaction time *t* the product was purified by chromatography on silica gel (Table 6).

Table 6. Details for the preparation of 4-alkylidene-4,5-dihydrooxazoles **7**.

Substrate (mmol)	*t* [min]	Column	Product (yield: mg, %)
6a (2.49)	25	PE/EE, 50:1	**7a** (344, 69)
6b (1.65)	60	PE/EE, 100:1	**7b** (241, 68)

4-Methylene-2-(trichloromethyl)-4,5-dihydrooxazole (7a): R_f (PE/EA = 10:1) = 0.44. IR (film): $\tilde{\nu}$ = 3160, 3137, 3052, 2952, 2878, 2848, 2812, 1776, 1742, 1712, 1650, 1606, 1450, 1409, 1343, 1270, 1235, 1204, 1042, 1004, 957, 943, 877, 824, 793, 683, 660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.88 (dt, ^4J = 2.8, ^2J = 1.5 Hz, 1 H), 5.25 (pseudo-t, J = 3.1 Hz, 2 H), 5.40 (dt, ^4J = 3.37, ^2J = 1.54 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl3): δ = 74.55 (t), 102.23 (t), 153.44 (s), 168.73 (s) ppm. MS [EI(+)]: *m*/*z* (%) = 199 (16) $[M]^+$, 170 (18), 166 (64), 164 (100), 138 (12), 136 (20),100 (11), 42 (17). HRMS (70 eV): calcd. 198.9358; found 198.9346.

5-Methyl-4-methylene-2-(trichloromethyl)-4,5-dihydrooxazole (7b): R_f (PE/EA; 10:1) = 0.39. IR (film): $\tilde{\nu}$ = 3148, 3051, 2928, 1769, 1734, 1602, 1444, 1409, 1345, 1306, 1261, 1245, 1203, 1031, 998, 894, 811, 790, 753 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.58 (d, ^3J = 6.5 Hz, 3 H), 4.78 (dd, ^4J = 2.5, ^2J = 1.5 Hz, 1 H), 5.36 (dd, ^4J = 3.1, ^2J = 1.5 Hz, 1 H), 5.47 (ddq, ^3J = 6.5, ^4J = 3.1, ^4J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.50 (q), 83.49 (d), 101.96 (t), 158.64 (s), 167.09 (s) ppm.

Synthesis of 9: Propargylamine (815 mg, 14.5 mmol) and triethylamine (1.47 g, 14.5 mmol) were dissolved in dichloromethane (15 mL) and 3-methoxybenzoyl chloride (2.48 g, 14.5 mmol) was added. DMAP (10 mol%) was then added. The reaction was monitored by TLC; after consumption of the starting material distilled water (5 mL) and dichloromethane (5 mL) were added to the flask. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 mL). Any remaining amine was removed from the combined organic layers with a saturated sodium hydrogen carbonate solution (2 × 20 mL), then the organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The crude material (2.67 g, 97%) was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to yield **9** (2.19 g, 80%) as a colourless solid. M.p. 74 °C; R_f (petroleum ether/ethyl acetate, 1:1) = 0.36. IR (neat): $\tilde{\nu}$ = 3341, 3248, 1636, 1589, 1536, 1487, 1468, 1449, 1301, 1241, 1038, 873, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (td, J = 2.5, 1.3 Hz, 1 H), 7.32 (q, J = 7.7 Hz, 1 H), 7.28 (dd, J = 2.5, 1.3 Hz, 1 H), 7.08 (dd, J = 2.5, 1.3 Hz, 1 H), 6.39 (s, 1 H), 4.28 (dd, J = 5.1, 2.5 Hz, 2 H), 3.87 (s, 3 H), 2.31 (t, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 167 (s), 159.9 (s), 135.2 (s), 129.7 (d), 118.7 (d), 118.1 (d), 112.4 (d), 79.4 (s), 71.9 (d), 55.5 (q), 29.8 (t) ppm. MS (70 eV): *m*/*z* (%) = 189 (69) $[M]^+$, 135 (100), 107 (44), 92 (24), 77 (32). $C_{11}H_{11}NO_2$ (189.21): calcd. C 69.83, H 5.86, N 7.40; found C 69.83, H 5.88, N 7.43.

Gold-Catalyzed Conversion of 9 to 10: Compound **9** (52.9 mg, 0.28 mmol) was dissolved in $CDCl_3$ and $[Ph_3PAuNTf_2]$ (5 mg, 5.73 µmol) was added. The reaction was monitored by ^1H NMR spectroscopy. After the consumption of the starting material, the crude product showed traces of impurities and was purify by column chromatography on silica gel (petroleum ether/ethyl acetate, 3.5:1) to yield **10** (43 mg, 81%) as a colourless oil. R_f (petroleum ether/ethyl acetate, 3.5:1) = 0.25. IR (neat): $\tilde{\nu}$ = 1649, 1601, 1464, 1325, 1265, 1226, 1041, 631 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.56 (dt, J = 7.9, 1.26 Hz, 1 H), 7.50 (m, 1 H), 7.34 (t, J = 7.9 Hz, 1 H), 7.05 (ddd, J = 8.2, 2.7, 1.0 Hz, 1 H), 4.81 (dd, J = 5.5, 2.8 Hz, 1 H), 4.65 (t, J = 2.8 Hz, 2 H), 4.36 (dd, J = 5.5, 2.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 163.7 (s), 159.6 (s), 158.8 (s), 129.6 (d), 127.9 (s), 120.5 (d), 118.7 (d), 112.3 (d), 83.9 (t), 57.7 (t), 55.5 (q) ppm. $C_{11}H_{11}NO_2$ (189.21): calcd. C 69.83, H 5.86, N 7.40; found C 69.54, H 5.72, N 7.33.

Acknowledgments

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