JOC The Journal of Organic Chemistry

Freie Universität Berlin

Article

Mild Aliphatic and Benzylic Hydrocarbon C–H Bond Chlorination Using Trichloroisocyanuric Acid (TCCA)

Sascha H. Combe, Abolfazl Hosseini, Alejandro Parra, and Peter R. Schreiner

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02829 • Publication Date (Web): 20 Jan 2017

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Mild Aliphatic and Benzylic Hydrocarbon C–H Bond Chlorination Using Trichloroisocyanuric Acid (TCCA)

Sascha H. Combe,[‡] Abolfazl Hosseini,[‡] Alejandro Parra,[#] and Peter R. Schreiner*[,‡]

[‡]Institute of Organic Chemistry, Justus-Liebig University, Heinrich-Buff-Ring 17, 35392 Giessen, Germany

[#]Departamento de Química Orgánica, Universidad Autónoma de Madrid Cantoblanco, 28049 Madrid, Spain

Keywords: *alkyl chlorides, benzylic chlorides, N-hydroxyphthalimide (NHPI), phthalimido-N-oxyl (PINO), radicals*

ABSTRACT: We present the controlled monochlorination of aliphatic and benzylic hydrocarbons with only *one* equivalent of substrate at 25–30 °C using *N*-hydroxyphthalimide (NHPI) as radical initiator and commercially available trichloroisocyanuric acid (TCCA) as the chlorine source. Catalytic amounts of CBr_4 reduced the reaction times considerably due to the formation of chain-carrying $\bullet CBr_3$ radicals. Benzylic C–H chlorination affords moderate to good yields for arenes carrying electron-withdrawing (50–85%) or weakly electron-donating groups (31–73%); cyclic aliphatic substrates provide low yields (24–38%). The products could be synthesized on gram scale followed by simply purification via distillation. We report the first direct side-chain chlorination of 3-methylbenzoate affording methyl 3-(chloromethyl)benzoate, which is an important building block for the synthesis of vasodilator taprostene.

INTRODUCTION

Benzylic and alkyl chlorides are used for the production of a very large variety and quantity of chemicals.[1] In 1853, Cannizzaro first explored the thermal side-chain chlorination of toluene using elemental chlorine.[2] Sixty years later, BASF published a patent that described the chlorination of *para*-toluenesulfonyl chloride with PCl_5 and Cl_2 under irradiation.[3] The growing significance and ubiquity of these compounds have urged scientists to develop methods with various aliphatic C–H bond chlorination agents including Cl_2,[4] SO_2Cl_2,[5] NaOCl,[6] ^{t}BuOCl,[7] Et_4NCl,[8] benzyltrimethylammonium tetrachloroiodate ($BTMAICl_4$),[9] 1,3-dichloro-5,5-dimethylhydantoin,[10] trichloroisocyanuric acid (TCCA),[11] and NaCl/HCl.[12] These radical-type chlorination reactions often require heating or irradiation, and some chlorination agents are explosive, toxic as well as highly corrosive. The once-common solvent for side-chain chlorination reactions, CCl_4,[11,13] is now forbidden in many countries due to its carcinogenic and ozone depleting nature. Chlorination using elemental chlorine often results in nearly inseparable multiple side-chain chlorinated products. To avoid polychlorination nearly all of the methods mentioned above need a very large excess of substrate or, in many instances, the substrate is used as solvent[4-5,7,11] (Table 1), which represents the major drawback. For that reason the substrates typically are restricted to liquids. An additional drawback especially when using NaOCl or ^{t}BuOCl is the formation of oxygenated products.[6b,7c] Recently Whiting and coworkers invented a visible light nano-Ag/AgCl catalyzed reaction using brine and hydrogen chloride as chlorine source.[12] The crude product NMR spectra also indicated the formation of oxygenated products. There are only very few robust methods for the selective catalytic chlorination of aliphatic C–H bonds.[6a,14] For instance, sodium hypochlorite can be employed as the chlorine source in the presence of a manganese porphyrin catalyst. An L-Mn^{IV}-OCl complex is suggested to transfer a chlorine atom to the substrate, thereby regenerating an Mn^{V}=O complex responsible for hydrogen abstraction.[6a] The substrate scope is limited to aliphatic hydrocarbons and the only example of an aromatic side-chain chlorination is toluene that afforded 38% GC-yield of unisolated benzyl chloride; as the isolation of the pure chlorination products often is as challenging as the reactions themselves (and often is not reported), there still is a considerable need for controlled catalytic and safe chlorination reactions.

In continuation of our previous studies on C–H bond halogenations,[15] we herein report a safe, cheap, atom economic, air and moisture tolerating approach for the side-chain chlorination of a range of arenes and alkanes with yields (of isolated product) of up to 85% at 25–30 °C with *N*-hydroxyphthalimide **1** (NHPI) as radical initiator.

Scheme 1: Formation of PINO (2)$^{\bullet}$

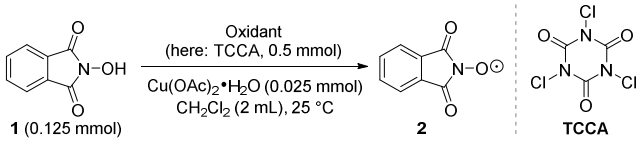


Table 1. Comparison of different chlorination methods for some arenes

#	Starting material[a]	Product	Conditions	Yield [%]
1	toluene	benzyl chloride	SO_2Cl_2, DBPO, reflux, 0.25 h	80[b,e,5a]
2	toluene	benzyl chloride	SO_2Cl_2, $Pd(PPh_3)_4$, reflux, 2–5 h	82[b,e,5b]
3	toluene	benzyl chloride	SO_2Cl_2, AIBN, reflux, 0.25 h	70[b,e,5c]
4	toluene	benzyl chloride	$BTMAICl_4$, AIBN, reflux, 4–7 h	65[b,e,9]
5	toluene	benzyl chloride	*t*-BuOCl, AIBN, 40 °C, N_2, 4 h	99[b,e,7c]
6	toluene	benzyl chloride	Cl_3CSO_2Cl, hν, 110 °C, 8 h	80[b,e,16]
7	toluene	benzyl chloride	PCl_5, reflux, 40 h	97[b,e,17]
8	toluene	benzyl chloride	TCCA, DBPO, CCl_4, 78 °C, 3 h	44[b,e,11]
9	toluene	benzyl chloride	$PhICl_2$, 15 °C, N_2, 2 h	84[b,e,18]
10	toluene	benzyl chloride	Et_4NCl (0.5 equiv. related to *m*CPBA), *m*CPBA, degassed CH_3CN, N_2, r.t. 3 min	11[c,8a]
11	toluene (3 equiv.)	benzyl chloride	NaOCl (0.33 M, pH = 11, 1 equiv.), manganese porphyrin (0.02 equiv.), TBACl (0.04 equiv.), CH_2Cl_2, r.t.	38[c,d,f,6a]
12	toluene (1 equiv.)	benzyl chloride	Et_4NCl (10 equiv.), $CH_3C(O)OOH$ (4 equiv.), CH_3CN, N_2, 22 °C, 8 h	3[d,8b,19]
13	toluene (1 equiv.)	benzyl chloride	KCl (7.5 equiv.), $KHSO_4$ (5 equiv.), CH_2Cl_2, r.t., 1 h	48[c,d,g,20]
14	toluene (1 equiv.)	benzyl chloride	NaCl/HCl, nano Ag/AgCl (0.09 equiv.), hν , r.t., 5–9 h	40[h,12]
15	toluene (1 equiv.)	benzyl chloride	TCCA (0.4 equiv.), $Cu(OAc)_2•H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 22 h	58[b,f]
16	*p*-xylene	4-methylbenzyl chloride	SO_2Cl_2, $Pd(PPh_3)_4$, reflux, 2–5 h	85[b,e,5b]
17	*p*-xylene	4-methylbenzyl chloride	SO_2Cl_2, zeolite, (NaX), reflux, 1 h	72[b,e,5d]
18	*p*-xylene	4-methylbenzyl chloride	Cl_3CSO_2Cl, DBPO, 70 °C, 2 h	80[b,e,16]
19	*p*-xylene	4-methylbenzyl chloride	Cl_2, reflux, hν, 2 h	84[b,e,21]
20	*p*-xylene (1 equiv.)	4-methylbenzyl chloride	NCS (1 equiv.), DCE, 80 °C, 12–14 h	63[b,ed,22]
21	*p*-xylene (1 equiv.)	4-methylbenzyl chloride	$[Hmim][NO_3]$ (2 equiv.), 37% HCl (1 equiv.), 80 °C, 48 h	10[c,d,e,23]
22	*p*-xylene (1 equiv.)	4-methylbenzyl chloride	CsCl (1 equiv.), NCS (1 equiv.), powdered glass, 120 W, 102 °C, 4 min	50[c,d,f,24]
23	*p*-xylene (1 equiv.)	4-methylbenzyl chloride	TCCA (0.4 equiv.), $Cu(OAc)_2•H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 22 h	31[b,f]
24	3-chlorotoluene	3-chlorobenzyl chloride	SO_2Cl_2, $Pd(PPh_3)_4$, reflux, 2–5 h	45[b,e,5b]
25	3-chlorotoluene (1 equiv.)	3-chlorobenzyl chloride	TCCA (0.4 equiv.), $Cu(OAc)_2•H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 40 h	55[b,f]
26	4-chlorotoluene	4-chlorobenzyl chloride	SO_2Cl_2, DBPO, reflux, 0.25 h	70[b,e,5a]
27	4-chlorotoluene	4-chlorobenzyl chloride	SO_2Cl_2, $Pd(PPh_3)_4$, reflux, 2–5 h	87[b,e,5b]
28	4-chlorotoluene	4-chlorobenzyl chloride	NaCl/HCl, nano Ag/AgCl (0.09 equiv.), hν , r.t., 5–9 h	27[h,12]
29	4-chlorotoluene (1 equiv.)	4-chlorobenzyl chloride	TCCA (0.4 equiv.), $Cu(OAc)_2•H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 17 h	73[b,f]
30	4-toluic acid methylester (1 equiv.)	4-(chloromethyl) benzoic acid methyl ester	NCS (2.2 equiv.),DBPO, CH_3CO_2H, 3 h	76[b,f,25]
31	4-toluic acid methylester (1 equiv.)	4-(chloromethyl) benzoic acid methyl ester	$K_2S_2O_8$ (8 equiv.), MeCN/sat. NaCl (v/v = 1/1), 100 °C, 1 h	67[c,d,f,26]

#	Starting material[a]	Product	Conditions	Yield [%]
32	4-toluic acid methylester (1 equiv.)	4-(chloromethyl) benzoic acid methyl ester	TCCA (0.4 equiv.), $Cu(OAc)_2 \cdot H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 24 h	85[b,f]
33	4-cyanotoluene	4-(chloromethyl)benzonitrile	SO_2Cl_2, $Pd(PPh_3)_4$, reflux, 2–5 h	50[b,e,5b]
34	4-cyanotoluene (1 equiv.)	4-(chloromethyl)benzonitrile	TCCA (0.4 equiv.), $Cu(OAc)_2 \cdot H_2O$ (0.02 equiv.), NHPI (0.1 equiv.), CBr_4 (0.1 equiv.), CH_2Cl_2, 25 °C, 19 h	59[b,f](70)[b,f,i]

[a]Used as solvent [b]Isolated. [c]Not isolated. [d]Determined by GC-MS. [e]Yield related to chlorine source. [f]Yield related to substrate. [g]Yield related to oxidant. [h]Conversion; crude mixture isolation, no mass given and therefore no yield calculable. [i]2 equiv. substrate.

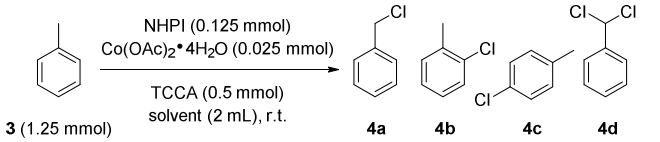
NHPI serves as a precursor for the phthalimido-*N*-oxyl **2** (PINO) radical (Scheme 1), which abstracts hydrogen atoms from C–H bonds[27] and which is widely used in the oxidation of hydrocarbons, C–C as well as C–N couplings.[27] PINO can be generated in the presence of some metal catalyst or a strong oxidant.[15d,28] So far only the Minisci group developed a method for the halogenation of hydrocarbons with NHPI as the catalyst. The reaction proceeds at 100 °C and needs stoichiometric amounts of $CuCl_2$ as the chlorine source.[29]

Among various chlorinating reagents, TCCA is often used for chlorination[5d,13a,20] and oxidation reactions,[30] because it is safe, easy to handle, non-toxic, and a suitable substitute for chlorine gas.[31] TCCA was first reported in 1902 by Chattaway and Wadmore and is now produced at a scale of about 10^6 tons per year; it is mainly used as a disinfectant and in food chemistry.[31] All chlorine atoms in TCCA are typically utilized and it generally has a higher solubility than *N*-chlorosuccinimide (NCS), allowing highly concentrated reaction mixtures and reduction of the volume of organic solvent.

RESULTS AND DISCUSSION

Inspired by this, we chose toluene **3** as model substrate in the presence of TCCA and catalytic amounts of NHPI and cobalt acetate as the radical initiator for our first studies.

Table 2. Initial evaluation of reaction conditions for the side-chain chlorination of toluene



#	*t* [h]	Solvent	Conv. [%][a]	4a[b]	4b[b]	4c[b]	4d[b]
1[c,d]	16	CH_2Cl_2	33	73	12	15	–
	19		81	41	25	34	–
2[c]	16	AcOH	78	30	51	19	–
3[e]	18	CH_2Cl_2	28	86	7	7	–
4	5	MeCN	80	16	36	48	–
5[f]	16	$CHCl_3$	48	98	2	traces	–
	40		46	98	2	traces	–
6	16	1,2-DCE	46	100	–	–	–
	40		35	100	–	–	–
7	16	CCl_4	45	100	–	–	–
8[g]	40	CCl_4	93	82	–	–	18
	24		52	96	–	–	4
	48		91	88	–	–	12
9[h]	24	CCl_4	81	90	–	–	10
	48		89	82	–	–	18
10[i]	24	CCl_4	11	100	–	–	–
	48		51	100	–	–	–
11[j]	46	CCl_4	–	–	–	–	–
12[k]	48	CCl_4	–	–	–	–	–
13[l]	48	CCl_4	–	–	–	–	–

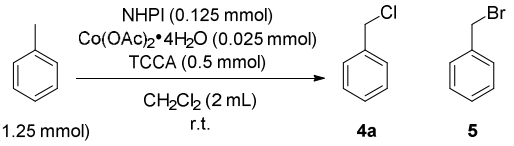
[a]Determined by GC-MS. [b]GC-MS ratios. [c]TCCA (1.25 mmol). [d]After 16 h MeOH (2.5 mmol) added. [e]TBHP (0.125 mmol) added. [f]After 40 h additional TCCA (0.5 mmol) added with no further conversion. [g]$Co(OAc)_2 \cdot 4H_2O$ (0.0125 mmol). [h]$Co(OAc)_2 \cdot 4H_2O$ (0.0625 mmol). [i]$Co(OAc)_2 \cdot 4H_2O$ (0.125 mmol). [j]Without $Co(OAc)_2 \cdot 4H_2O$. [k]NCS (1.25 mmol) instead of TCCA. [l]NCS (0.5 mmol) instead of TCCA.

Using CH_2Cl_2 as solvent afforded 24% of benzyl chloride **4a** after 16 h (Table 2, entry 1). Adding two equivalents of CH_3OH to the reaction or using AcOH as solvent increased the amount of core substitution product (Table 2, entry 2). We found that 0.4 equiv. of TCCA (about 1.2 equiv. Cl•) is enough for the reaction to proceed smoothly. Adding *tert*-butyl hydroperoxide (TBHP) did not accelerate the reaction (Table 2, entry 3). In MeCN mainly **4b** and **4c** were produced (Table 2, entry 4). Increasing the solvent polarity increased the ability of the system for aromatic substitution (Table 2, entry 4), however, the use of DMF or DMSO as solvent led to a violent reaction without formation of products, probably due to reagent decomposition.[32] In $CHCl_3$ and 1,2-dichloroethane the reaction stopped at about 45% (Table 2, entries 5 and 6), even after adding more TCCA. Somewhat expected and equally unfortunate, the best results were obtained in CCl_4, giving mainly benzyl chloride **4a** and some benzal chloride **4d** (entry 7). Variation of the amount of $Co(OAc)_2$ (Table 2, entries 7–10) showed that 2 mol% gave the best results (Table 2, entry 7). Higher concentrations of $Co(OAc)_2$ had an adverse effect on the outcome of the reaction leading to lower conversion even after long reaction times (Table 2, entry 10). The cobalt catalyst is crucial for this reaction and no product formed in the absence of $Co(OAc)_2$ (Table 2, entry 11). The use of NCS only led to quantitative recovery of the starting materials, even at higher dilution (Table 2, entries 12–13). This may

be due to its lower solubility or lower oxidation potential as compared to TCCA.[31]

To support the assumption that catalytically active trihalomethyl radicals (here •CCl_3) are involved in the reaction,[15a-c,33] we performed the reaction in CH_2Cl_2 in the presence of CBr_4. Benzyl radicals can react with CBr_4 to form •CBr_3 radicals and the corresponding bromide. The formation of benzyl bromide **5** confirms our mechanistic suggestion (Table 3, entry 1). Additionally –and somewhat surprisingly–, we observed that CBr_4 seemed to catalyze the first stage of the reaction (Table 3, entries 1–2). Encouraged by these results, we tested catalytic amounts of CBr_4 (Table 3, entries 3–7) and found that with 10 mol% CBr_4 the reaction reached nearly its maximum conversion after 16 h (Table 3, entry 5). Lower and higher CBr_4 loadings (Table 3, entries 3–4 and 6–7) as well as using $HCBr_3$ instead of CBr_4 (Table 3, entries 8–11) or $HCCl_3$ (Table 3, entry 12) gave inferior results. The reaction did not proceed with less than 5 mol% of NHPI (Table 3, entries 13–14). An NHPI loading of 10 mol% (Table 3, entry 5) was sufficient and gave nearly the same result as with higher catalyst loadings (Table 3, entry 15). Even higher TCCA loadings drastically slowed the reaction probably due to decreased solubility (Table 3, entries 16–17), which is in agreement with our first result (Table 2, entry 1). Remarkably, the reaction still proceeds in the presence of water albeit somewhat more slowly (Table 3, entries 18–19). The reaction is temperature dependent and is best performed at ambient temperature (25 °C) (Table 3, entries 20–21).

Table 3. Optimization of reaction conditions for the side-chain chlorination of toluene



3 (1.25 mmol) **4a** **5**

#	t [h]	Additive [mmol]	Conditions	Conv. [%][a]
1	20	CBr_4 (1.25)	–	53[b]
	43			65
2	17	–	–	31
	42			64
3	16	CBr_4 (0.0125)	–	33
	40			58
4	16	CBr_4 (0.0625)	–	39
	40			63
5	16	CBr_4 (0.125)	–	69
	40			79
6	16	CBr_4 (0.188)	–	47
	40			58
7	16	CBr_4 (0.25)	–	24
	14			49
8	16	$HCBr_3$ (0.125)	–	25
	40			45
9	16	$HCBr_3$ (0.188)	–	28
	40			54
10	16	$HCBr_3$ (0.25)	–	30
	40			55
11	16	$HCBr_3$ (0.625)	–	47
	40			63
12	16	$HCCl_3$ (0.125)	–	22
	40			45
13	40	CBr_4 (0.125)	No NHPI	–
14	40	CBr_4 (0.125)	NHPI (0.063 mmol)	–
15	40	CBr_4 (0.125)	NHPI (0.25 mmol)	77
16	41	CBr_4 (0.125)	TCCA (0.75 mmol)	33
17	41	CBr_4 (0.125)	TCCA (1.00 mmol)	24
18	16	CBr_4 (0.125)	H_2O (0.125 mmol)	16
	40			44
19	16	CBr_4 (0.125)	H_2O (0.375 mmol)	1
	40			37
20	18	CBr_4 (0.125)	18 °C	44
21	19	CBr_4 (0.125)	25 °C	74
22	16	CBr_4 (0.125)	$Cu(OAc)_2$•H_2O (0.025 mmol)	47
	40			75
23	16	CBr_4 (0.125)	$Cu(acac)_2$ (0.025 mmol)	50
	40			62
24	16	CBr_4 (0.125)	$CuCl_2$ (0.025 mmol)	34
	40			79

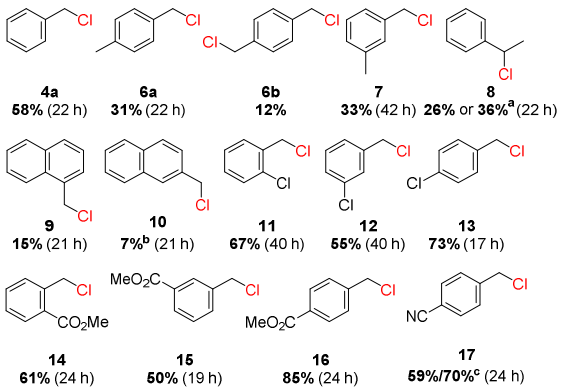
[a]Conversion of the starting material to **4a** determined by GC-MS. [b]Only here **5** was obtained after 20 h in the ratio 10 : 1 (**4a** : **5**) and disappeared over the course of the reaction.

Finally, it is also possible to substitute $Co(OAc)_2$ for less toxic $Cu(OAc)_2$ (Table 3, entry 22).

With the optimized reaction conditions in hand (CBr_4 (0.125 mmol), CH_2Cl_2 (2 mL), $Cu(OAc)_2$•H_2O (0.025 mmol), NHPI (0.125 mmol), substrate (1.25 mmol), TCCA (0.5 mmol), 25 °C, termed P1), the scope and limitations of the reaction were examined (Scheme 2). In general, side-chain chlorination provides moderate to good yields for arenes carrying an electron-withdrawing (50–85%) and a weakly electron-donating group (31–73%); modest to strong electron donating groups favor the S_EAr reaction.[11,30b,34] The stabilization of the resulting substituted tolyl radicals plays an important role concerning the yield, giving the following experimentally observed order: *p* > *o* > *m*, which is consistent with benzyl radical stabilization. Deactivating groups destabilize the radical, hence the substitution at the *meta*-position gives the lowest yield.[35] Electron-withdrawing groups adjacent to the radical also have a destabilizing effect mostly in the proximity to the radical center.[36] Consequently, highest yields are obtained for the *para*-products. Unlike *p*-tolunitrile however for *o*- and *m*-tolunitrile no reaction occurred even when $Co(OAc)_2$ was used instead of $Cu(OAc)_2$. 3-methylpyridine showed only traces of the desired product, while 2-methylpyridine gave less than 5% of the crude chlorinated product (^{1}H NMR). This result is in agreement with the results Jeromin and co-workers, when they examined the side-chain chlorination of *N*-heterocycles using TCCA as chlorine source and DMF as catalyst.[32] When they used radical initiators no increase of the reaction rate was observed – it is believed that the reaction is working similar to that for the α-chlorination

of ketones for these kinds of substrates. In the case of methyl 3-(chloromethyl)benzoate **15** we report the first direct side-chain chlorination. Structure **15** is an important building block in the synthesis of taprostene,[37] a stable prostacyclin analogue used as vasodilator.[38] The chlorination of ethylbenzene gave a 2°/1° selectivity of 10:1. Cumene reacted sluggishly and gave an inseparable reaction mixture of core and side-chain chlorinated products. Adamantane reacted very fast to 1-chloroadamantane **18a** and 2-chloroadamantane **18b** in a 5:1 ratio (GC-MS of crude mixture), which is comparable to Cl-radical mediated adamantane chlorinations.[39] Remarkably, virtually no oxygenated products were obtained for any substrate examined.

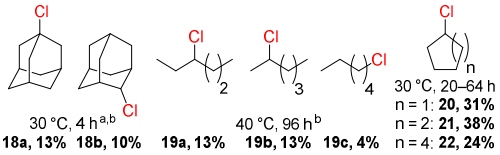
Scheme 2. Substrate scope for the side-chain chlorination of various toluene derivatives; yields of isolated pure products given



Method P1: CBr_4 (0.125 mmol), CH_2Cl_2 (2 mL), $Cu(OAc)_2{\cdot}H_2O$ (0.025 mmol), NHPI (0.125 mmol), substrate (1.25 mmol), TCCA (0.5 mmol), 25 °C. [a]According to P2. [b]Determined by ^{1}H NMR. [c]Substrate (2.5 mmol) used; yield related to TCCA.

The formation of doubly chlorinated products can be diminished to traces or even avoided by reducing the reaction time and by using two equivalents of the substrate. Doubling the amount of the substrate also increased the product yield as exemplified with *p*-tolunitrile. We also investigated the C–H bond chlorination of cyclic and acyclic alkanes on gram scale (Scheme 3). As bromocyclohexane was obtained with CBr_4 as catalyst it had to be omitted. A reason for this observation may lie in the differences of the bond dissociation energies of the products. The bond dissociation energy (BDE) difference for the RCH_2–Br bond in benzyl bromide (BDE = 63 kcal mol^{-1})[40] and bromoethane (BDE = 72 kcal mol^{-1})[40] is about 9 kcal mol^{-1}. This energy difference seems to allow homolytic cleavage of benzyl bromide (Table 3, entry 1). 2-Bromopropane has a BDE about 74 kcal mol^{-1},[40] i.e., bromocyclohexane is stable under the reaction conditions. Cyclic substrates with various ring sizes (Scheme 3) were chlorinated in low yields (24–38%) and could be purified by simple distillation. As expected, the chlorination of *n*-hexane gave a mixture of three regioisomers, preferentially 3-chlorohexane **19a** and 2-chlorohexane **19b** (3:3:1, ^{1}H NMR).

Scheme 3. Chlorination of hydrocarbons on gram scale; yields of isolated pure products given

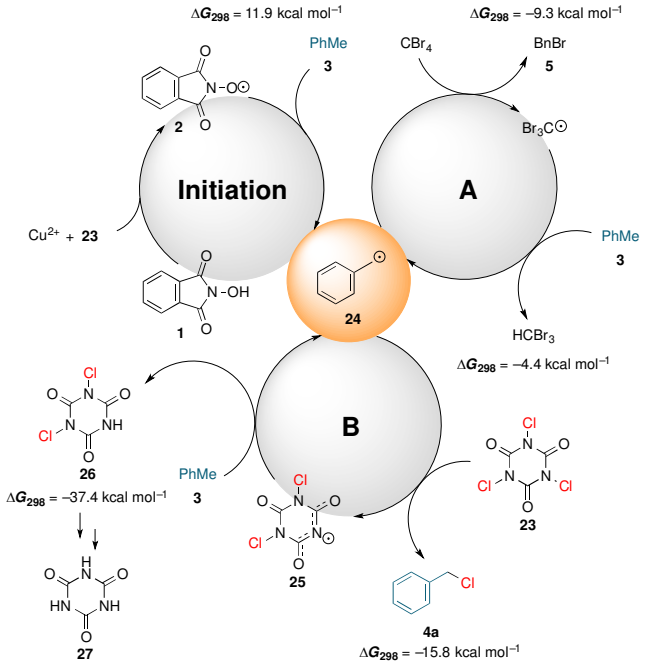


Method P2: CH_2Cl_2 (90 mL), $Cu(OAc)_2{\cdot}H_2O$ (1.16 mmol), NHPI (5.80 mmol), substrate (58.0 mmol), TCCA (23.2 mmol). [a]According to P1; without CBr_4. [b]Determined by ^{1}H NMR.

Based on the results presented here, literature reports, and our computations at the M06-2X/cc-pVTZ and B3LYP–D3/6–31G(d,p) level of theory (see SI for computational details), we propose a mechanism as shown in Scheme 4.

$Cu(OAc)_2$ and TCCA (**23**) generate the PINO radical (**2**)[41] that abstracts an H• radical from **3** to form the corresponding benzyl radical (**24**) in an endergonic step (ΔG_{298} = 11.9 kcal mol^{-1}) (**Initiation**). The chain length of NHPI is *one* (Table S1), which means that NHPI serves only as radical initiator. Radical **24** subsequently reacts with **23** to form product **4a** as well as **25** (ΔG_{298} = −15.8 kcal mol^{-1}). Radical **25** is also able to abstract an H• radical from **3** (ΔG_{298} = −37.4 kcal mol^{-1}) and forms **26**; the latter reacts further until all chlorine is consumed and cyanuric acid (**27**) precipitates from the reaction mixture as a white solid (catalytic cycle **B**).[11] The computed reaction enthalpies for the hydrogen abstraction from **3** with dichloroisocyanuric acid radical **25**, monochlorisocyanuric acid radical, cyanuric acid radical (ΔG_{298} = −26.1 to −27.6 kcal mol^{-1}) and $\cdot CBr_3$ radical (ΔG_{298} = −4.4 kcal mol^{-1}) show an overall highly exergonic process. The formation and precipitation of **27** is suggested to be the driving force of the reaction.

Scheme 4. Suggested mechanism for the side-chain chlorination of toluene



CBr_4 catalyzes the reaction considerably (Table 3, entry 5) due to the favored formation of $\bullet CBr_3$ radicals (ΔG_{298} = –9.3 kcal mol^{-1}). When all PINO is consumed trihalomethyl radicals carry on the chain reaction (Table S2). Even if one equivalent of **24** is used to produce $\bullet CBr_3$ radicals, homolytic cleavage of **5** (Table 3, entry 1) as well as C–H abstraction of **3** by a $\bullet CBr_3$ radical gives overall two equivalents of **24** (catalytic cycle **A**).

In summary, we report a powerful method for the catalytic chlorination of benzylic and aliphatic hydrocarbon C–H bonds using TCCA as a cheap and efficient chlorine source. The metal catalyst $Co(OAc)_2$[41] that is often employed for the generation of the hydrogen-abstracting PINO radical, could be replaced by less toxic $Cu(OAc)_2$. Our present approach has the advantage of being mild, safe, cheap, scalable, and that it allows a controlled monochlorination with only *one* equivalent of substrate. A full elucidation of the reaction mechanism is now under investigation.

EXPERIMENTAL SECTION

General Information: All chemicals were purchased in reagent grade or better quality and used without further purification; $Cu(OAc)_2 \cdot H_2O$ >99%, $Co(OAc)_2 \cdot 4H_2O$ >98%, NHPI >99% (TCI), TCCA ≤100%. All solvents were distilled before usage with exception of 1,2-dichloroethane. All boiling points were measured with a precision thermometer of Amarell (up to 250 °C). Analytical thin-layer chromatography (TLC) was performed on SIL G UV_{254} with a fluorescence indicator. Visualization of the TLC plate was performed by UV (254 nm), 5% phosphomolybdic acid in CH_3CH_2OH or permanganate stain. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). ^1H and ^{13}C spectra were measured at 25 °C with 200 MHz and 400 MHz spectrometers, using TMS or the solvent peak ($CHCl_3$: 7.26 ppm; 77.16 ppm) as the internal standard. Reaction progress was monitored by GC-MS analyses with a Quadrupol-MS (EI) and a GC equipped with a fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 90–250 °C (10 °C/min heating rate), injector and transfer line 250 °C.

General procedure for the chlorination (P1): In a 5 mL reaction vessel $Cu(OAc)_2 \cdot H_2O$ (5.00 mg, 0.025 mmol, 0.02 equiv.), *N*-hydroxyphthalimide (20.4 mg, 0.125 mmol, 0.1 equiv.), CBr_4 (41.5 mg, 0.125 mmol, 0.1 equiv.) was diluted in CH_2Cl_2 (2 mL) and stirred for 0.5 min at 25 °C. Subsequently TCCA (116 mg, 0.500 mmol, 0.4 equiv.) and the substrate (1.25 mmol, 1.0 equiv.) was added and the vessel was sealed. After an additional stirring for 17–22 h at 25 °C, the reaction mixture was diluted with sat. brine (10 mL), extracted with CH_2Cl_2 (3x10 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure for the chlorination on gram scale without CBr_4 (P2): In a 250 mL reaction vessel $Cu(OAc)_2 \cdot H_2O$ (0.232 g, 1.16 mmol, 0.02 equiv.), *N*-hydroxyphthalimide (0.946 g, 5.80 mmol, 0.1 equiv.) was diluted in CH_2Cl_2 (95 mL) and stirred for 0.5 min at 25 °C. Subsequently TCCA (5.39 g, 23.2 mmol, 0.4 equiv.) and the substrate (58.0 mmol, 1.0 equiv.) was added and the vessel was sealed. After an additional stirring for 20–96 h at 25–30 °C, the reaction mixture was diluted with sat. brine (100 mL), extracted with CH_2Cl_2 (3x80 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Benzyl chloride (4a):[42] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 9:1) to give the chloride **4a** (91.9 mg, 0.726 mmol, 58% as a colorless liquid, R_f = 0.48; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 5 H), 4.60 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 128.9, 128.7, 128.6, 46.4 ppm.

4-methylbenzyl chloride (6a):[43] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 19:1) to give the chloride **6a** (54.9 mg, 0.390 mmol, 31%) as a colorless liquid, R_f = 0.51; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, 2 H, J = 8.1 Hz), 7.18 (d, 2 H, J = 7.8 Hz), 4.58 (s, 2 H), 2.37 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 134.7, 129.6, 128.7, 46.4, 21.3 ppm.

1,4-Bis(chloromethyl)benzene (6b):[44] According to (P1). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 19:1) to give the chloride 6b (26.6 mg, 0.152 mmol, 12%) as a colorless solid, R_f = 0.35; m.p. 98–99 °C (Lit. 98 °C)[45]; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 4 H), 4.59 (s, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 129.1, 45.8 ppm.

3-methylbenzyl chloride (7):[42] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 19:1) to give the chloride **7** (58.4 mg, 0.415 mmol, 33%) as a colorless liquid, R_f = 0.48; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.13 (m, 4 H), 4.57 (s, 2 H), 2.37 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 137.5, 129.5, 129.3, 128.8, 125.8, 46.5, 21.5 ppm.

1-chloro-1-phenylethane (8):[46] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, pentane) to give the chloride **8** (45.9 mg,0.327 mmol, 26%) as a colorless liquid, R_f = 0.29; According to (**P2**). The residue was purified by distillation after 18 h to give a mixture of (2-chloroethyl)benzene (403 mg, 2.87 mmol, 5%) and **8** (2.97 g, 21.1 mmol, 36%) as a colorless liquid, bp = 60 °C (10 mbar); yield determined by ^{1}H-NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.26 (m, 5 H), 5.10 (q, 1 H, *J* = 6.8 Hz), 1.86 (d, 3 H, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 128.8, 128.4, 126.6, 58.9, 26.7 ppm.

1-(chloromethyl)naphthalene (9):[42] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 19:1) to give the chloride **9** (34 mg, 0.192 mmol, 15%) as a light brownish viscous oil, R_f = 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.14 (m, 1 H), 7.91–7.84 (m, 2 H), 7.63–7.58 (m, 1 H), 7.56–7.51 (m, 2 H), 7.46–7.41 (m, 1 H), 5.07 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.1, 133.2, 131.3, 129.9, 129.0, 127.8, 126.9, 126.3, 125.4, 123.8, 44.7 ppm.

2-chlorobenzyl chloride (11):[42] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 12:1) to give the chloride **11** (136 mg, 0.842 mmol, 67%) as a colorless liquid, R_f = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 1 H), 7.42–7.37 (m, 1 H), 7.30–7.24 (m, 2 H), 4.70 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 134.2, 131.0, 130.1, 130.0, 127.3, 43.7 ppm.

3-chlorobenzyl chloride (12):[46b] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 12:1) to give the chloride **12** (110 mg, 0.684 mmol, 55%) as a colorless liquid, R_f = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (bs, 1 H), 7.31–7.27 (m, 3 H), 4.55 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 134.7, 130.1, 128.9, 128.7, 126.8, 45.4 ppm.

4-chlorobenzyl chloride (13):[42] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 20:1) to give the chloride **13** (147 mg, 0.912 mmol, 73%) as a colorless solid, R_f = 0.37; m.p. 28–29 °C (Lit. 28 °C)[47]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 4 H), 4.55 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1, 134.5, 130.1, 129.1, 45.5 ppm.

Methyl 2-(chloromethyl)benzoate (14):[48] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 9:1) to give the chloride **14** (141 mg, 0.764 mmol, 61%) as a colorless liquid, R_f = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (d, 1 H, *J* = 7.8 Hz), 7.57–7.49 (m, 2 H), 7.43–7.37 (m, 1 H), 5.05 (s, 2 H), 3.93 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 138.9, 132.7, 131.2, 131.0, 129.2, 128.5, 52.4, 44.6 ppm.

Methyl 3-(chloromethyl)benzoate (15):[37] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 9:1) to give the chloride **15** (115 mg, 0.625 mmol, 50%) as a colorless liquid, R_f = 0.10; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.99 (d, 1 H, *J* = 7.8 Hz), 7.58 (d, 1 H, *J* = 7.6 Hz), 7.43 (t, 1 H, *J* = 7.7 Hz), 4.61 (s, 2 H), 3.92 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 138.0, 133.1, 130.8, 129.8, 129.6, 129.0, 52.3, 45.6 ppm.

Methyl 4-(chloromethyl)benzoate (16):[49] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 9:1) to give the chloride **16** (196 mg, 1.06 mmol, 85%) as a colorless solid, R_f = 0.12; m.p. 36–37 °C (Lit. 38–39 °C)[49]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, 2 H, *J* = 8.2 Hz), 7.46 (d, 2 H, *J* = 8.2 Hz), 4.61 (s, 2 H), 3.92 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 142.4, 130.3, 130.2, 128.6, 52.4, 45.5 ppm.

4-(chloromethyl)benzonitrile (17):[50] According to (**P1**). The residue was purified by column chromatography (silica gel, 2 x 27 cm column, hexane/Et_2O 4:1) to give the chloride **17** (112 mg, 0.741 mmol, 59%)/(160 mg, 1.06 mmol, 70%)[51] as a colorless solid, R_f = 0.22; m.p, 80–81 °C (Lit. 81 °C)[52]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 2 H), 7.51 (d, 2 H, *J* = 8.3 Hz), 4.60 (s, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 132.7, 129.3, 118.5, 112.4, 45.0 ppm.

Chlorocyclopentane (20):[42] According to (**P2**). The residue was purified by distillation. However **20** formed an azeotrope with CH_2Cl_2 (60 °C), hence remaining CH_2Cl_2 was removed under reduced pressure (25 mbar) while the flask was cooled with an ice bath to give the chloro compound **20** (1.86 g, 17.7 mmol, 31%) as a colorless liquid, ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43–4.33 (m, 1 H), 2.05–1.81 (m, 6 H), 1.73–1.58 (m, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 62.3, 37.2, 23.1 ppm.

Chlorocyclohexane (21):[42] According to (**P2**). The residue was purified by distillation to give the chloro compound **21** (2.60 g, 22.2 mmol, 38%) as a colorless liquid, bp = 39 °C (25 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05–3.97 (m, 1 H), 2.11–2.02 (m, 2 H), 1.84–1.74 (m, 2 H), 1.72–1.60 (m, 2 H), 1.58–1.48 (m, 1 H), 1.42–1.24 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.5, 36.9, 25.3, 25.0 ppm.

Chlorocyclooctane (22):[53] According to (**P2**). The residue was purified by distillation to give the chloro compound **22** (2.01 g, 13.8 mmol, 24%) as a colorless liquid, bp = 80 °C (10 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (sept, 1 H), 2.16–2.06 (m, 2 H), 2.05–1.91 (m, 2 H), 1.83–1.68 (m, 2 H), 1.65–1.42 (m, 8 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.7, 35.3, 27.6, 25.1, 23.7 ppm.

ASSOCIATED CONTENT

Supporting Information. Spectra of all compounds, computations and procedure, Cartesian coordinates and absolute energies of all optimized structures "This material is available free of charge via the Internet at http://pubs.acs.org."

AUTHOR INFORMATION

Corresponding Author

*prs@org.chemie.uni-giessen.de

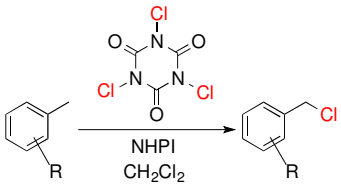
ACKNOWLEDGMENT

This work was supported by the Justus-Liebig University.

REFERENCES

(1) Beilstein, F.; Geitner, P. *Liebigs Ann. Chem.* **1866**, *139*, 331.
(2) (a) Cannizzaro, M. S. *Compt. Rend.* **1855**, *41*, 517; (b) Darmstaedter, L.; du Bois-Reymond, R.; Schaefer, C. *Handbuch zur Geschichte der Naturwissenschaften und der Technik*; 2. Aufl. 1908. Softcover reprint of the original 2nd ed. 1908 ed.; Springer, 1908.
(3) Friedländer DRP 234913, 1913.
(4) (a) Qinghua, C.; Kongfu, L. CN103787874 A, 2014; (b) Ding, L.; Tang, J.; Cui, M.; Bo, C.; Chen, X.; Qiao, X. *Ind. Eng. Chem. Res.* **2011**, *50*, 11143.
(5) (a) Kharasch, M. S.; Brown, H. C. *J. Am. Chem. Soc.* **1939**, *61*, 2142; (b) Matsumoto, H.; Nakano, T.; Kato, M.; Nagai, Y. *Chem. Lett.* **1978**, *7*, 223; (c) Ford, M. C.; Waters, W. A. *J. Chem. Soc.* **1951**, 1851; (d) Delaude, L.; Laszlo, P. *J. Org. Chem.* **1990**, *55*, 5260; (e) Kurdyukov, A. M. *Russ. J. Appl. Chem.* **2007**, *80*, 1566.
(6) (a) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847; (b) Querci, C.; Strologo, S.; Ricci, M. *Tetrahedron Lett.* **1990**, *31*, 6577.
(7) (a) Clark Jr., B. F. *Chcm. News* **1931**; (b) Kenner, J. *Nature* **1945**, *156*, 369; (c) Walling, C.; Jacknow, B. B. *J. Am. Chem. Soc.* **1960**, *82*, 6108.
(8) (a) Kojima, T.; Matsuo, H.; Matsuda, Y. *Chem. Lett.* **1998**, *27*, 1085; (b) He, Y.; Goldsmith, C. R. *Synlett* **2010**, *2010*, 1377.
(9) Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Tanaka, T.; Fujisaki, S. *Tetrahedron Lett.* **1988**, *29*, 5783.
(10) Zhang, Y.; Yamamoto, H.; Shibatomi, K. US20080275253, 2008.
(11) Juenge, E. C.; Beal, D. A.; Duncan, W. P. *J. Org. Chem.* **1970**, *35*, 719.
(12) Liu, S.; Zhang, Q.; Li, H.; Yang, Y.; Tian, X.; Whiting, A. *Chem. Eur. J.* **2015**, *21*, 9671.
(13) (a) Tanemura, K.; Suzuki, T.; Nishida, Y.; Horaguchi, T. *Tetrahedron* **2010**, *66*, 2881; (b) Tanemura, K.; Suzuki, T.; Nishida, Y.; Horaguchi, T. *Tetrahedron Lett.* **2008**, *49*, 6419.
(14) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 696.
(15) (a) Schreiner, P. R.; Lauenstein, O.; Kolomitsyn, I. V.; Nadi, S.; Fokin, A. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 1895; (b) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Fokin, A. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2786; (c) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Gunchenko, P. A.; Kolomitsin, I. V.; Wittkopp, A.; Feder, G.; Fokin, A. A. *Chem. Eur. J.* **2001**, *7*, 4996; (d) Zhuk, T. S.; Gunchenko, P. A.; Korovai, Y. Y.; Schreiner, P. R.; Fokin, A. A. *Theor. Exp. Chem.* **2008**, *44*, 48.
(16) Huyser, E. S.; Giddings, B. *J. Org. Chem.* **1962**, *27*, 3391.
(17) Kimbrough Jr., R. D.; Bramlett, R. N. *J. Org. Chem.* **1969**, *34*, 3655.
(18) Banks, D. F.; Huyser, E. S.; Kleinberg, J. *J. Org. Chem.* **1964**, *29*, 3692.
(19) Goldsmith, C. R.; Coates, C. M.; Hagan, K.; Mitchell, C. A. *J. Mol. Catal. A: Chem.* **2011**, *335*, 24.
(20) Çimen, Y.; Akyuz, S.; Türk, H. *New J. Chem.* **2015**, *39*, 3894.
(21) Xie, G.; Zheng, Q.; Huang, C.; Chen, Y. *Synth. Commun.* **2003**, *33*, 1103.
(22) Thirumamagal, B. T. S.; Narayanasamy, S.; Venkatesan, R. *Synth. Commun.* **2008**, *38*, 2820.
(23) Chiappe, C.; Leandri, E.; Tebano, M. *Green Chem.* **2006**, *8*, 742.
(24) Bucos, M.; Villalonga-Barber, C.; Micha-Screttas, M.; Steele, B. R.; Screttas, C. G.; Heropoulos, G. A. *Tetrahedron* **2010**, *66*, 2061.
(25) Pathi, S. L.; Kankan, R. N.; Puppala, R. 2008MU02726, 2008.
(26) Gu, L.; Lu, T.; Zhang, M.; Tou, L.; Zhang, Y. *Adv. Synth. Catal.* **2013**, *355*, 1077.
(27) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800.
(28) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520.
(29) Minisci, F.; Porta, O.; Recupero, F.; Gambarotti, C.; Paganelli, R.; Pedulli, G. F.; Fontana, F. *Tetrahedron Lett.* **2004**, *45*, 1607.
(30) (a) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999; (b) Hubbard, A.; Okazaki, T.; Laali, K. K. *Australian Journal of Chemistry* **2007**, *60*, 923; (c) Jing, Y.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 4932; (d) Mishra, A. K.; Nagarajaiah, H.; Moorthy, J. N. *Eur. J. Org. Chem.* **2015**, *2015*, 2733.
(31) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.
(32) Jeromin, G. E.; Orth, W.; Rapp, B.; Weiß, W. *Chem. Ber.* **1987**, *120*, 649.
(33) Fokin, A. A.; Lauenstein, O.; Gunchenko, P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842.
(34) Maraš, N.; Kočevar, M. *Monatsh. Chem.* **2015**, *146*, 697.
(35) (a) Naidu, V. R.; Ni, S.; Franzén, J. *ChemCatChem* **2015**, *7*, 1896; (b) Gronert, S.; Keeffe, J. R. *J. Phys. Org. Chem.* **2013**, *26*, 1023.
(36) Nonhebel, D. C.; Walton, J. C. *Free-radical Chemistry*; Cambridge University Press, 1974.
(37) Bergman, N. A.; Halvarsson, T. *J. Org. Chem.* **1988**, *53*, 2548.
(38) (a) Virgolini, I.; Fitscha, P.; O'Grady, J.; Barth, H.; Sinzinger, H. *Prostaglandins Leukot. Essent. Fatty Acids* **1989**, *38*, 31; (b) Virgolini, I.; Fitscha, P.; Sinzinger, H.; Barth, H. *Eur. J. Clin. Pharmacol.* **1990**, *38*, 347.
(39) Smith, G. W.; Williams, H. D. *J. Org. Chem.* **1961**, *26*, 2207.
(40) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.
(41) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.
(42) (4a) SDBS No. 1724; (7) SDBS No. 6157; (9) SDBS No. 5939; (11) SDBS No. 1585; (13) SDBS No. 3551; (20) SDBS No. 4784; (21) SDBS No. 2131, Spectral Database for Organic Compounds, accessed 2017-01-03.
(43) Alonso, F.; Barba, I.; Yus, M. *Tetrahedron* **1990**, *46*, 2069.
(44) Tong, Y.-Y.; Wang, R.; Xu, N.; Du, F.-S.; Li, Z.-C. *J. Polym. Sci. Pol. Chem.* **2009**, *47*, 4494.
(45) Richter, R.; Tucker, B. *J. Org. Chem.* **1983**, *48*, 2625.
(46) (a) Parham, W. E.; Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 4804; (b) Ding, R.; He, Y.; Wang, X.; Xu, J.; Chen, Y.; Feng, M.; Qi, C. *Molecules* **2011**, *16*, 5665.
(47) Fuchs, R. *J. Am. Chem. Soc.* **1957**, *79*, 6531.
(48) Hori, M.; Kataoka, T.; Shimizu, H.; Tsutsumi, K. *J. Org. Chem.* **1987**, *52*, 1397.
(49) Newman, S. G.; Bryan, C. S.; Perez, D.; Lautens, M. *Synthesis* **2011**, *2011*, 342.
(50) Metzger, A.; Argyo, C.; Knochel, P. *Synthesis* **2010**, *2010*, 882.
(51) Substrate (2.5 mmol); yield related to TCCA.
(52) Baker, J. W.; Brieux, J. A. L.; Saunders, D. G. *J. Chem. Soc.* **1956**, 404.
(53) Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1979**, *101*, 3240.

For Table of Contents Only



- 25–30 °C
- Very cheap
- High atom economy
- Safe
- Stable against air and moisture
- Up to 85% yield
- Scalable