

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

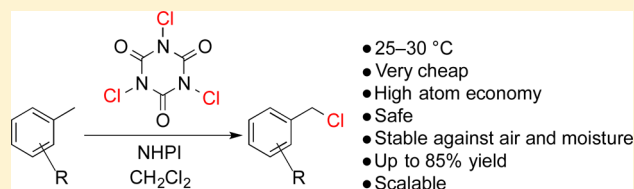
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S Supporting Information

ABSTRACT: We present the controlled monochlorination of aliphatic and benzylic hydrocarbons with only 1 equiv 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 CBr₄ reduced the reaction times considerably due to the formation of chain-carrying ·CBr₃ 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 a gram scale followed by simple 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 *p*-toluenesulfonyl chloride with PCl₅ and Cl₂ 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 Cl₂,⁴ SO₂Cl₂,⁵ NaOCl,⁶ ^tBuOCl,⁷ Et₄NCl,⁸ benzyltrimethylammonium tetrachloroiodate (BTMAICl₄),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, CCl₄,^{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 ^tBuOCl is the formation of oxygenated products.^{6b,7c} Recently, Whiting and co-workers 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.

NHPI serves as a precursor for the phthalimido-*N*-oxyl 2 (PINO) radical (Scheme 1), which abstracts hydrogen atoms from C–H bonds²⁷ 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 catalysts 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 CuCl₂ as the chlorine source.²⁹

Among various chlorinating reagents, TCCA is often used for chlorination^{5d,13a,20} and oxidation reactions³⁰ because it is safe, easy to handle, nontoxic, and a suitable substitute for chlorine

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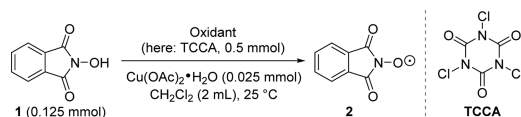
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Table 1. Comparison of Different Chlorination Methods for Some Arenes

#	Starting material ^a	Product	Conditions	Yield [%]
1	toluene	benzyl chloride	SO ₂ Cl ₂ , DBPO, reflux, 0.25 h	80 ^{b,c,5a}
2	toluene	benzyl chloride	SO ₂ Cl ₂ , Pd(PPh ₃) ₄ , reflux, 2–5 h	82 ^{b,c,5b}
3	toluene	benzyl chloride	SO ₂ Cl ₂ , AIBN, reflux, 0.25 h	70 ^{b,c,5c}
4	toluene	benzyl chloride	BTMAICl ₄ , AIBN, reflux, 4–7 h	65 ^{b,c,9}
5	toluene	benzyl chloride	<i>t</i> -BuOCl, AIBN, 40 °C, N ₂ , 4 h	99 ^{b,c,7c}
6	toluene	benzyl chloride	Cl ₃ CSO ₂ Cl, hv, 110 °C, 8 h	80 ^{b,c,16}
7	toluene	benzyl chloride	PCl ₅ , reflux, 40 h	97 ^{b,c,17}
8	toluene	benzyl chloride	TCCA, DBPO, CCl ₄ , 78 °C, 3 h	44 ^{b,c,11}
9	toluene	benzyl chloride	PhICl ₂ , 15 °C, N ₂ , 2 h	84 ^{b,c,18}
10	toluene	benzyl chloride	Et ₃ NCl (0.5 equiv. related to <i>m</i> CPBA), <i>m</i> CPBA, degassed CH ₃ CN, 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 ₂ Cl ₂ , r.t.	38 ^{d,16a}
12	toluene (1 equiv)	benzyl chloride	Et ₃ NCl (10 equiv.), CH ₃ C(O)OOH (4 equiv.), CH ₃ CN, 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 ₂ Cl ₂ , r.t., 1 h	48 ^{d,20}
14	toluene (1 equiv)	benzyl chloride	NaCl/HCl, nano Ag/AgCl (0.09 equiv.), hv, r.t., 5–9 h	40 ^{b,12}
15	toluene (1 equiv)	benzyl chloride	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl ₂ , 25 °C, 22 h	58 ^{b,f}
16	<i>p</i> -xylene	4-methylbenzyl chloride	SO ₂ Cl ₂ , Pd(PPh ₃) ₄ , reflux, 2–5 h	85 ^{b,c,5b}
17	<i>p</i> -xylene	4-methylbenzyl chloride	SO ₂ Cl ₂ , zeolite, (NaX), reflux, 1 h	72 ^{b,c,5d}
18	<i>p</i> -xylene	4-methylbenzyl chloride	Cl ₃ CSO ₂ Cl, DBPO, 70 °C, 2 h	80 ^{b,c,16}
19	<i>p</i> -xylene	4-methylbenzyl chloride	Cl ₂ , reflux, hv, 2 h	84 ^{b,c,21}
20	<i>p</i> -xylene (1 equiv)	4-methylbenzyl chloride	NCS (1 equiv.), DCE, 80 °C, 12–14 h	63 ^{b,d,22}
21	<i>p</i> -xylene (1 equiv)	4-methylbenzyl chloride	[Hmim][NO ₃] (2 equiv.), 37% HCl (1 equiv.), 80 °C, 48 h	10 ^{b,d,23}
22	<i>p</i> -xylene (1 equiv)	4-methylbenzyl chloride	CsCl (1 equiv.), NCS (1 equiv.), powdered glass, 120 W, 102 °C, 4 min	50 ^{d,24}
23	<i>p</i> -xylene (1 equiv)	4-methylbenzyl chloride	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl ₂ , 25 °C, 22 h	31 ^{b,f}
24	3-chlorotoluene	3-chlorobenzyl chloride	SO ₂ Cl ₂ , Pd(PPh ₃) ₄ , reflux, 2–5 h	45 ^{b,c,5b}
25	3-chlorotoluene (1 equiv)	3-chlorobenzyl chloride	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl ₂ , 25 °C, 40 h	55 ^{b,f}
26	4-chlorotoluene	4-chlorobenzyl chloride	SO ₂ Cl ₂ , DBPO, reflux, 0.25 h	70 ^{b,c,5a}
27	4-chlorotoluene	4-chlorobenzyl chloride	SO ₂ Cl ₂ , Pd(PPh ₃) ₄ , reflux, 2–5 h	87 ^{b,c,5b}
28	4-chlorotoluene	4-chlorobenzyl chloride	NaCl/HCl, nano Ag/AgCl (0.09 equiv.), hv, r.t., 5–9 h	27 ^{b,12}
29	4-chlorotoluene (1 equiv)	4-chlorobenzyl chloride	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl 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 ₃ CO ₂ H, 3 h	76 ^{b,25}
31	4-toluic acid methylester (1 equiv)	4-(chloromethyl) benzoic acid methyl ester	K ₂ S ₂ O ₈ (8 equiv.), MeCN/sat. NaCl (v/v = 1/1), 100 °C, 1 h	67 ^{d,26}
32	4-toluic acid methylester (1 equiv)	4-(chloromethyl) benzoic acid methyl ester	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl ₂ , 25 °C, 24 h	85 ^{b,f}
33	4-cyanotoluene	4-(chloromethyl)benzonitrile	SO ₂ Cl ₂ , Pd(PPh ₃) ₄ , reflux, 2–5 h	50 ^{b,c,5b}
34	4-cyanotoluene (1 equiv)	4-(chloromethyl)benzonitrile	TCCA (0.4 equiv.), Cu(OAc) ₂ •H ₂ O (0.02 equiv.), NHPI (0.1 equiv.), CBr ₄ (0.1 equiv.), CH ₂ Cl ₂ , 25 °C, 19 h	59 ^{b,f} (70) ^{b,f,i}

^aUsed as solvent. ^bIsolated. ^cNot isolated. ^dDetermined by GC–MS. ^eYield related to chlorine source. ^fYield related to substrate. ^gYield related to oxidant. ^hConversion; crude mixture isolation, no mass given and therefore no yield calculable. ⁱ2 equiv of substrate.

Scheme 1. Formation of PINO (2)

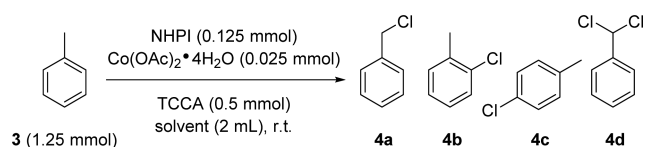


gas.³¹ TCCA was first reported in 1902 by Chattaway and Wadmore and is now produced at a scale of about 10⁶ tons per year; it is mainly used as a disinfectant and in food chemistry.³¹ All chlorine atoms in TCCA are typically utilized, and it generally has a higher solubility than *N*-chlorosuccinimide (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.

Using CH₂Cl₂ as solvent afforded 24% of benzyl chloride 4a after 16 h (Table 2, entry 1). Adding 2 equiv of CH₃OH 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 of 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

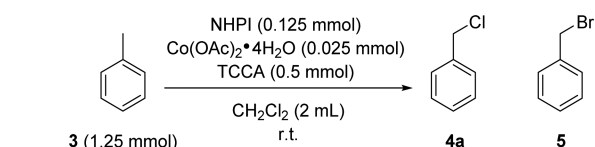
Table 2. Initial Evaluation of Reaction Conditions for the Side-Chain Chlorination of Toluene

no.	time (h)	solvent	conv ^a (%)	4a ^b	4b ^b	4c ^b	4d ^b
1 ^{c,d}	16	CH ₂ Cl ₂	33	73	12	15	
	19		81	41	25	34	
2 ^e	16	AcOH	78	30	51	19	
3 ^e	18	CH ₂ Cl 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			
	40		93	82			18
8 ^g	24	CCl ₄	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					

^aDetermined by GC–MS. ^bGC–MS ratios. ^cTCCA (1.25 mmol). ^dAfter 16 h, MeOH (2.5 mmol) added. ^eTBHP (0.125 mmol) added. ^fAfter 40 h, additional TCCA (0.5 mmol) was added with no further conversion. ^gCo(OAc)₂·4H₂O (0.0125 mmol). ^hCo(OAc)₂·4H₂O (0.0625 mmol). ⁱCo(OAc)₂·4H₂O (0.125 mmol). ^jWithout Co(OAc)₂·4H₂O. ^kNCS (1.25 mmol) instead of TCCA. ^lNCS (0.5 mmol) instead of TCCA.

decomposition.³² In CHCl₃ and 1,2-dichloroethane, the reaction stopped at about 45% (Table 2, entries 5 and 6), even after addition of more TCCA. Somewhat expected and equally unfortunate, the best results were obtained in CCl₄, 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 a 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 ·CCl₃) are involved in the reaction,^{15a–c,33} we performed the reaction in CH₂Cl₂ in the presence of CBr₄. Benzyl radicals can react with CBr₄ to form ·CBr₃ 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 CBr₄ seemed to catalyze the first stage of the reaction (Table 3, entries 1 and 2). Encouraged by these results, we tested catalytic amounts of CBr₄ (Table 3, entries

Table 3. Optimization of Reaction Conditions for the Side-Chain Chlorination of Toluene

no.	time (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	HCBBr ₃ (0.125)		25
	40			45
9	16	HCBBr ₃ (0.188)		28
	40			54
10	16	HCBBr ₃ (0.25)		30
	40			55
11	16	HCBBr ₃ (0.625)		47
	40			63
12	16	HCCl ₃ (0.125)		22
	40			45
13	40	CBr ₄ (0.125)	no NHPI	
	40		NHPI (0.063 mmol)	
15	40	CBr ₄ (0.125)	NHPI (0.25 mmol)	77
	16			TCCA (0.75 mmol)
17	41	CBr ₄ (0.125)	TCCA (1.00 mmol)	24
	16			H ₂ O (0.125 mmol)
19	16	CBr ₄ (0.125)	H ₂ O (0.375 mmol)	1
	40			44
20	18	CBr ₄ (0.125)	18 °C	44
	19		25 °C	74
22	16	CBr ₄ (0.125)	Cu(OAc) ₂ ·H ₂ O (0.025 mmol)	47
	40		Cu(acac) ₂ (0.025 mmol)	75
23	16	CBr ₄ (0.125)		50
	40			62
24	16	CBr ₄ (0.125)	CuCl ₂ (0.025 mmol)	34
	40			79

^aConversion of the starting material to 4a determined by GC–MS.

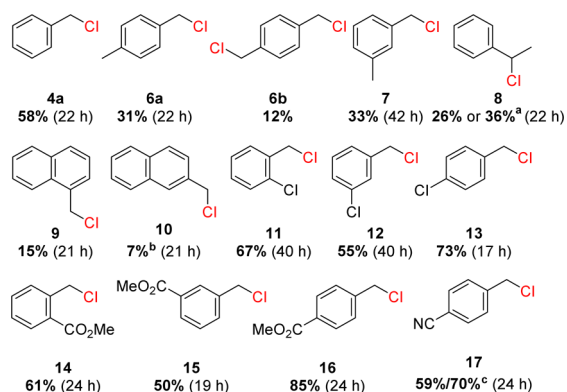
^bOnly here, 5 was obtained after 20 h in a 10:1 (4a/5) ratio and disappeared over the course of the reaction.

3–7) and found that with 10 mol% of CBr₄ the reaction reached nearly its maximum conversion after 16 h (Table 3, entry 5). Lower and higher CBr₄ loadings (Table 3, entries 3, 4 and 6, 7) as well as using HCBBr₃ instead of CBr₄ (Table 3, entries 8–11) or HCCl₃ (Table 3, entry 12) gave inferior results. The reaction did not proceed with less than 5 mol% of NHPI (Table 3, entries 13 and 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 and 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 and 19). The reaction is best performed at ambient temperature (25 °C) (Table 3, entries 20 and 21). Finally, it is also possible to substitute $\text{Co}(\text{OAc})_2$ for less toxic $\text{Cu}(\text{OAc})_2$ (Table 3, entry 22).

With the optimized reaction conditions in hand (CBr_4 (0.125 mmol), CH_2Cl_2 (2 mL), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (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

Scheme 2. Substrate Scope for the Side-Chain Chlorination of Various Toluene Derivatives; Yields of Isolated Pure Products Given*



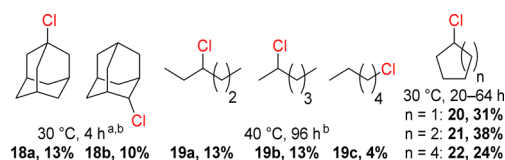
*Method P1: CBr_4 (0.125 mmol), CH_2Cl_2 (2 mL), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.025 mmol), NHPI (0.125 mmol), substrate (1.25 mmol), TCCA (0.5 mmol), 25 °C. ^aAccording to P2. ^bDetermined by ^1H NMR. ^cSubstrate (2.5 mmol) used; yield related to TCCA.

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 $\text{S}_{\text{E}}\text{Ar}$ reaction.^{11,30b,34} The stabilization of the resulting substituted tolyl radicals plays an important role concerning the yield, giving the experimentally observed order *para* > *ortho* > *meta*, 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, the highest yields are obtained for the *para* products. Unlike *p*-tolunitrile, however, for *o*- and *m*-tolunitrile no reaction occurred even when $\text{Co}(\text{OAc})_2$ was used instead of $\text{Cu}(\text{OAc})_2$. 3-Methylpyridine showed only traces of the desired product, while 2-methylpyridine gave less than 5% of the crude chlorinated product (^1H NMR). This result is in agreement with the results Jeromin and co-workers obtained, 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 a 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 give 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.

The formation of doubly chlorinated products can be diminished to traces or even avoided by reducing the reaction time and by using 2 equiv 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). Since bromocyclohexane was obtained with CBr_4

Scheme 3. Chlorination of Hydrocarbons on Gram Scale; Yields of Isolated Pure Products Given*



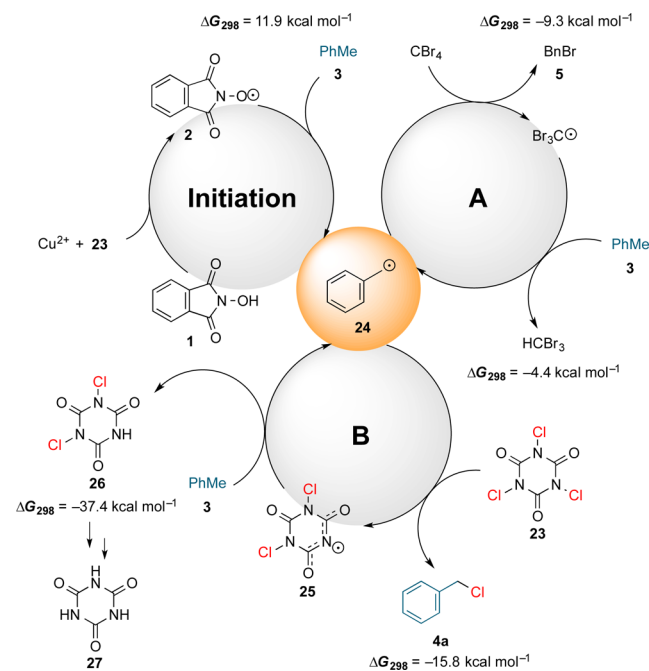
*Method P2: CH_2Cl_2 (90 mL), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.16 mmol), NHPI (5.80 mmol), substrate (58.0 mmol), TCCA (23.2 mmol). ^aAccording to P1; without CBr_4 . ^bDetermined by ^1H NMR.

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 $\text{RCH}_2\text{–Br}$ bond in benzyl bromide ($\text{BDE} = 63 \text{ kcal mol}^{-1}$)⁴⁰ and bromoethane ($\text{BDE} = 72 \text{ kcal mol}^{-1}$)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, ^1H 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 the SI for computational details), we propose a mechanism as shown in Scheme 4.

$\text{Cu}(\text{OAc})_2$ 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 ($\Delta G_{298} = 11.9 \text{ kcal mol}^{-1}$) (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 ($\Delta G_{298} = -15.8 \text{ kcal mol}^{-1}$). Radical 25 is also able to abstract an H· radical from 3 ($\Delta G_{298} = -37.4 \text{ kcal mol}^{-1}$) 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, monochloroisocyanuric acid radical, cyanuric acid radical ($\Delta G_{298} = -26.1$ to $-27.6 \text{ kcal mol}^{-1}$), and $\cdot\text{CBr}_3$ radical ($\Delta G_{298} = -4.4 \text{ kcal}$

Scheme 4. Suggested Mechanism for the Side-Chain Chlorination of Toluene; Computations at the B3LYP-D3/6-31G(d,p) level of theory (ΔG_{298K})



mol^{-1}) show an overall highly exergonic process. The formation and precipitation of **27** is suggested to be the driving force of the reaction.

CBr_4 catalyzes the reaction considerably (Table 3, entry 5) due to the favored formation of $\cdot\text{CBr}_3$ radicals ($\Delta G_{298} = -9.3 \text{ kcal mol}^{-1}$). When all PINO is consumed, trihalomethyl radicals carry on the chain reaction (Table S2). Even if 1 equiv of **24** is used to produce $\cdot\text{CBr}_3$ radicals, homolytic cleavage of **5** (Table 3, entry 1) as well as C–H abstraction of **3** by a $\cdot\text{CBr}_3$ radical gives overall 2 equiv 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 $\text{Co}(\text{OAc})_2$ ⁴¹ that is often employed for the generation of the hydrogen-abstrating PINO radical could be replaced by less toxic $\text{Cu}(\text{OAc})_2$. Our present approach has the advantage of being mild, safe, cheap, and scalable and allows a controlled monochlorination with only 1 equiv 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: $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O} > 99\%$, $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O} > 98\%$, NHPI $> 99\%$ (TCI), TCCA $\leq 100\%$. All solvents were distilled before use with the 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 UV₂₅₄ with a fluorescence indicator. Visualization of the TLC plate was performed by UV (254 nm), 5% phosphomolybdic acid in $\text{CH}_3\text{CH}_2\text{OH}$, or permanganate stain. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). ¹H and ¹³C spectra were measured at 25 °C with 200 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 \times 0.250 mm, 0.25 μm DB–SMS 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, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (5.00 mg, 0.025 mmol, 0.02 equiv), *N*-hydroxyphthalimide (20.4 mg, 0.125 mmol, 0.1 equiv), and CBr_4 (41.5 mg, 0.125 mmol, 0.1 equiv) were 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) were added, and the vessel was sealed. After additional stirring for 17–22 h at 25 °C, the reaction mixture was diluted with satd brine (10 mL), extracted with CH_2Cl_2 (3 \times 10 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, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.232 g, 1.16 mmol, 0.02 equiv) and *N*-hydroxyphthalimide (0.946 g, 5.80 mmol, 0.1 equiv) were 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) were added, and the vessel was sealed. After additional stirring for 20–96 h at 25–30 °C, the reaction mixture was diluted with satd brine (100 mL), extracted with CH_2Cl_2 (3 \times 80 mL), dried over MgSO_4 , and concentrated under reduced pressure.

Benzyl Chloride (4a).⁴² Following P1, the residue was purified by column chromatography (silica gel, 2 \times 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): $\delta = 7.41\text{--}7.30$ (m, 5 H), 4.60 (s, 2 H). ¹³C NMR (100 MHz, CDCl_3): $\delta = 137.6, 128.9, 128.7, 128.6, 46.4$.

4-Methylbenzyl Chloride (6a).⁴³ Following P1, the residue was purified by column chromatography (silica gel, 2 \times 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): $\delta = 7.29$ (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). ¹³C NMR (100 MHz, CDCl_3): $\delta = 138.4, 134.7, 129.6, 128.7, 46.4, 21.3$.

1,4-Bis(chloromethyl)benzene (6b).⁴⁴ Following P1, the residue was purified by column chromatography (silica gel, 2 \times 27 cm column, hexane/ Et_2O 19:1) to give the chloride **6b** (26.6 mg, 0.152 mmol, 12%) as a colorless solid, $R_f = 0.35$. Mp: 98–99 °C (lit.⁴⁵ mp 98 °C). ¹H NMR (400 MHz, CDCl_3): $\delta = 7.39$ (s, 4 H), 4.59 (s, 4 H). ¹³C NMR (100 MHz, CDCl_3): $\delta = 137.8, 129.1, 45.8$.

3-Methylbenzyl Chloride (7).⁴² Following P1, the residue was purified by column chromatography (silica gel, 2 \times 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): $\delta = 7.27\text{--}7.13$ (m, 4 H), 4.57 (s, 2 H), 2.37 (s, 3 H). ¹³C NMR (100 MHz, CDCl_3): $\delta = 138.6, 137.5, 129.5, 129.3, 128.8, 125.8, 46.5, 21.5$.

1-Chloro-1-phenylethane (8).⁴⁶ Following P1, the residue was purified by column chromatography (silica gel, 2 \times 27 cm column, pentane) to give the chloride **8** (45.9 mg, 0.327 mmol, 26%) as a colorless liquid, $R_f = 0.29$. Following 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 ¹H NMR. ¹H NMR (400 MHz, CDCl_3): $\delta = 7.44\text{--}7.26$ (m, 5 H), 5.10 (q, 1 H, $J = 6.8$ Hz), 1.86 (d, 3 H, $J = 6.8$ Hz). ¹³C NMR (100 MHz, CDCl_3): $\delta = 143.0, 128.8, 128.4, 126.6, 58.9, 26.7$.

1-(Chloromethyl)naphthalene (9).⁴² Following P1, the residue was purified by column chromatography (silica gel, 2 \times 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. $R_f = 0.18$. ¹H NMR (400 MHz, CDCl_3): $\delta = 8.17\text{--}8.14$ (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). ¹³C NMR (100 MHz, CDCl_3): $\delta = 134.1, 133.2, 131.3, 129.9, 129.0, 127.8, 126.9, 126.3, 125.4, 123.8, 44.7$.

2-Chlorobenzyl Chloride (11).⁴² Following P1, the residue was purified by column chromatography (silica gel, 2 \times 27 cm column, hexane/ Et_2O 12:1) to give the chloride **11** (136 mg, 0.842 mmol,

67%) as a colorless liquid. $R_f = 0.48$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.48\text{--}7.44$ (m, 1 H), $7.42\text{--}7.37$ (m, 1 H), $7.30\text{--}7.24$ (m, 2 H), 4.70 (s, 2 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 135.2, 134.2, 131.0, 130.1, 130.0, 127.3, 43.7$.

3-Chlorobenzyl Chloride (12).^{46b} Following P1, the residue was purified by column chromatography (silica gel, 2×27 cm column, hexane/ Et_2O 12:1) to give the chloride 12 (110 mg, 0.684 mmol, 55%) as a colorless liquid. $R_f = 0.46$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.40$ (bs, 1 H), $7.31\text{--}7.27$ (m, 3 H), 4.55 (s, 2 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 139.4, 134.7, 130.1, 128.9, 128.7, 126.8, 45.4$.

4-Chlorobenzyl Chloride (13).⁴² Following P1, the residue was purified by column chromatography (silica gel, 2×27 cm column, hexane/ Et_2O 20:1) to give the chloride 13 (147 mg, 0.912 mmol, 73%) as a colorless solid. $R_f = 0.37$. Mp: $28\text{--}29$ °C (lit.⁴⁷ mp 28 °C). $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.36\text{--}7.30$ (m, 4 H), 4.55 (s, 2 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 136.1, 134.5, 130.1, 129.1, 45.5$.

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

Methyl 3-(Chloromethyl)benzoate (15).³⁷ Following P1, the residue was purified by column chromatography (silica gel, 2×27 cm column, hexane/ Et_2O 9:1) to give the chloride 15 (115 mg, 0.625 mmol, 50%) as a colorless liquid. $R_f = 0.10$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 8.06$ (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). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 166.6, 138.0, 133.1, 130.8, 129.8, 129.6, 129.0, 52.3, 45.6$.

Methyl 4-(Chloromethyl)benzoate (16).⁴⁹ Following P1, the residue was purified by column chromatography (silica gel, 2×27 cm column, hexane/ Et_2O 9:1) to give the chloride 16 (196 mg, 1.06 mmol, 85%) as a colorless solid. $R_f = 0.12$. Mp: $36\text{--}37$ °C (lit.⁴⁹ mp $38\text{--}39$ °C). $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 8.03$ (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). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 166.7, 142.4, 130.3, 130.2, 128.6, 52.4, 45.5$.

4-(Chloromethyl)benzotrile (17).⁵⁰ Following P1, the residue was purified by column chromatography (silica gel, 2×27 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. $R_f = 0.22$. Mp: $80\text{--}81$ °C (lit.⁵² mp 81 °C). $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.69\text{--}7.64$ (m, 2 H), 7.51 (d, 2 H, $J = 8.3$ Hz), 4.60 (s, 2 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 142.5, 132.7, 129.3, 118.5, 112.4, 45.0$.

Chlorocyclopentane (20).⁴² Following P2, the residue was purified by distillation. However, 20 formed an azeotrope with CH_2Cl_2 (60 °C), and hence, the 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. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.43\text{--}4.33$ (m, 1 H), $2.05\text{--}1.81$ (m, 6 H), $1.73\text{--}1.58$ (m, 2 H). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): $\delta = 62.3, 37.2, 23.1$.

Chlorocyclohexane (21).⁴² Following 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). $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.05\text{--}3.97$ (m, 1 H), $2.11\text{--}2.02$ (m, 2 H), $1.84\text{--}1.74$ (m, 2 H), $1.72\text{--}1.60$ (m, 2 H), $1.58\text{--}1.48$ (m, 1 H), $1.42\text{--}1.24$ (m, 3 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 60.5, 36.9, 25.3, 25.0$.

Chlorocyclooctane (22).⁵³ Following 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); $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.23$ (sept, 1 H), $2.16\text{--}2.06$ (m, 2 H), $2.05\text{--}1.91$ (m, 2 H), $1.83\text{--}1.68$ (m, 2 H), $1.65\text{--}1.42$ (m, 8 H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 63.7, 35.3, 27.6, 25.1, 23.7$.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02829.

Spectra of all compounds, computations and procedures, Cartesian coordinates and absolute energies of all optimized structures (PDF)

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Notes

The authors declare no competing financial interest.

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