Brominations with Pr_4NBr_9 as a Solid Reagent with High Reactivity and Selectivity

Thorsten M. Beck,[a] Heike Haller,[b] Jan Streuff,*[a] Sebastian Riedel*[b]

[a] Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Alberstr. 21, 79104 Freiburg, Germany
Fax +49(761)2038715; E-mail: jan.streuff@ocbc.uni-freiburg.de

[b] Institut für Anorganische und Analytische Chemie, Albert-Ludwigs-Universität Freiburg, Alberstr. 21, 79104 Freiburg, Germany

Received: 22.10.2013; Accepted after revision: 12.01.2014

Abstract: Tetrapropylammonium nonabromide (Pr_4NBr_9) is introduced as a room-temperature solid reagent for rapid bromination reactions of various substrates. The reagent exhibits reactivity similar to that of elemental bromine, but shows higher selectivity and it is easier and safer to store and to handle.

Key words: alkenes, arenes, bromine, halogenation, nonabromide

Brominated organics are valuable precursors for transition-metal-catalyzed cross-couplings,[1] and numerous other transformations for the synthesis of specialty chemicals and pharmaceutical products.[2] Therefore, reagents for the selective bromination of organic compounds are highly demanded tools for synthetic chemistry. Elemental bromine has been used in the past as a readily available electrophilic bromination reagent, but it is an undesirable chemical to work with because of its disadvantages: high vapor pressure, toxicity, and corrosiveness. Hence, other bromination reagents that are more user-friendly have been developed and used frequently. These include commercially available tribromide salts such as tetrabutylammonium tribromide (**1**),[3] or pyridinium tribromide (**2**),[4] and several variations as ionic liquids such as **3**–**7** [Figure 1 (a)].[5] Commercially available *N*-bromosuccinimide (NBS, **8**)[6] and 1,3-dibromo-5-5-dimethylhydantoin (**9**),[7] hexabromocyclopentadiene (**10**),[8] and 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone (**11**)[9] are non-Br_2-containing Br^+ sources, for example, that have been found useful for brominations of aromatic compounds and α-carbons of activated carbonyls [Figure 1 (b)]. However, since these reagents transfer only one bromine equivalent to the target molecule, a large amount of waste is generated. Although some of these compounds showed a significant increase in chemo- and regioselectivity, elemental bromine remained the most efficient brominating agent. In addition, the reactivity was often much lower than that of Br_2, which in return required longer reaction times or heating of the reaction mixture. A second approach has been the use of bromide salts or hydrogen bromide in combination with strong oxidants to generate the electrophilic bromination reagent in situ. However, this often led to undesired side reactions and in many cases produced a similar amount of waste.[10]

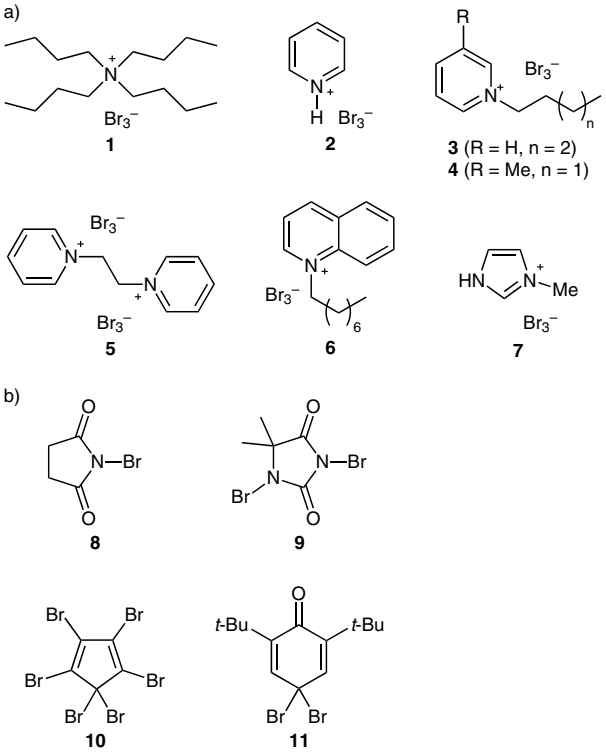


Figure 1 Selected commercial and literature bromination reagents (a) containing a tribromide anion and (b) based on activated Br–X bonds

We herein introduce tetrapropylammonium nonabromide (Pr_4NBr_9, **12**), which we discussed in an earlier communication,[11] as a bromination reagent that overcomes most of the aforementioned limitations (Figure 2). Quaternary ammonium nonabromides and other perbromides have been known in the literature for a long time,[12] and they were, in part, even applied in bromination reactions.[13] However, only recently has further structural evidence of higher polybromides been established,[11,14] and this report represents the first application and study of a solid nonabromide as a bromination agent for organic synthesis. The nonabromide **12** is a dark-red solid that can be handled under air, weighed on a balance, and only slowly releases bromine, which greatly reduces hazards to the user compared to Br_2. It can be conveniently prepared, in large quantities, by neat addition of bromine to tetrapropylammonium bromide, and it could be stored over long periods (at least 3 months) in a closed vessel at 4 °C.

SYNTHESIS 2014, 46, 0740–0747
Advanced online publication: 13.02.2014
DOI: 10.1055/s-0033-1340705; Art ID: SS-2013-Z0693-FA

Figure 2 Liquid elemental bromine and solid tetrapropylammonium nonabromide (**12**) at room temperature

The reagent could be crystallized from dichloromethane, but we found that residual solvent then lowered the melting point of the nonabromide to below 23 °C and that purification by crystallization was not necessary. In the following, bromination reactions with Pr_4NBr_9 are described that probe the capabilities of this reagent in terms of reactivity and chemo- and stereoselectivity. Compared to protocols that employ other solid bromination reagents the waste generation was significantly reduced due to the high Br_2/cation ratio (4:1) and the relatively small ammo-

Biographical Sketches

Thorsten M. Beck was born in Heidenheim an der Brenz, Germany, in 1986. He received his Bachelor's degree in chemistry from Albert-Ludwigs-Universität Freiburg in 2010. After that he carried out research internships in the group of Prof. Margaret Brimble at the University of Auckland, New Zealand and in the group of Dr. Streuff in Freiburg. In 2013, he obtained his Master degree from Albert-Ludwigs-Universität Freiburg and is currently working on his Ph.D. studies under the guidance of Prof. Dr. Bernhard Breit.

Heike Haller was born in Villingen, Germany, in 1984. After her studies at the ENSCM, Montpellier, France and the Albert-Ludwigs-Universität Freiburg she obtained her diploma degree in 2010. She is now pursuing her Ph.D. studies at the university of Freiburg and at the Freie Universität Berlin in the field of polyhalides and weakly coordinating cations.

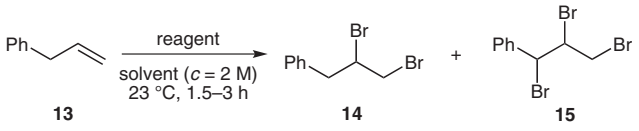
Dr. Jan Streuff was born in Leverkusen, Germany in 1980 and studied chemistry at Rheinische Friedrich-Wilhelms-Universität Bonn. He carried out his Ph.D. research under the guidance of Prof. Kilian Muñiz and received his Ph.D. at the Université Louis Pasteur, Strasbourg in early 2008. Afterwards, he joined the group of Prof. Brian M. Stoltz at the California Institute of Technology as a DAAD postdoctoral fellow. Since 2010 he has been pursuing his independent career at Albert-Ludwigs-Universität Freiburg. He was granted a Liebig-Fellowship of the Fonds der Chemischen Industrie in 2010 and the Thieme Chemistry Journal Award in 2012. His current research focuses on transition-metal-catalyzed redox-umpolung reactions.

Prof. Dr. Sebastian Riedel was born in Groß-Gerau, Germany, in 1975 and trained as a chemistry laboratory technician at Siemens and Degussa in Hanau starting in 1993. He studied chemistry at the Universities of Siegen and Würzburg and obtained his Ph.D. in 2006 under the guidance of Prof. Martin Kaupp, University of Würzburg. He was then a Humboldt postdoctoral fellow in the groups of Prof. Markku Räsänen and Prof. Pekka Pyykkö and afterwards carried out a second postdoctoral stay in the group of Prof. Gary J. Schrobilgen (University of Hamilton, Canada). He recently finished his habilitation supported by a Liebig Fellowship of the Fonds der Chemischen Industrie at Albert-Ludwigs Universität Freiburg and since 2013 he has been full professor of inorganic chemistry at the Freie Universität Berlin. He was awarded the ADUC prize in inorganic chemistry, the International Young Talent Award in Fluorine Chemistry from DuPont, and the Publikationspreis Fluorchemie of the GDCh.

nium cation of the reagent; in this way, a 71% weight content of active bromine was achieved (cf. 33% in Bu_4NBr_3).

In our first investigations allylbenzene (**13**) was examined under varying conditions. We observed rapid consumption of the substrate in presence of 33 mol% Pr_4NBr_9 in dichloromethane at room temperature (23 °C); dibromophenylpropane **14** was isolated in analytically pure form by a simple extraction procedure in 99% yield (Table 1, entry 1). With 25 mol% of the reagent only a maximum yield of 82% was observed (entry 2), which indicated that three of the four coordinated bromine molecules were transferred quickly to the substrate while the fourth reacted rather slowly. In the absence of solvent, a similar result was obtained (entry 3). To confirm this interpretation, the experiment was repeated with tetrabutylammonium tribromide as the reagent. Here, after 1.5 hours reaction time incomplete conversion was observed and a 94% yield of **14** was obtained. In comparison, a similar reaction with bromine yielded 88% of the desired product together with 7% of **15** resulting from overbromination in the benzylic position.

Table 1 Bromination of Allylbenzene with Different Reagents and Varying Conditions

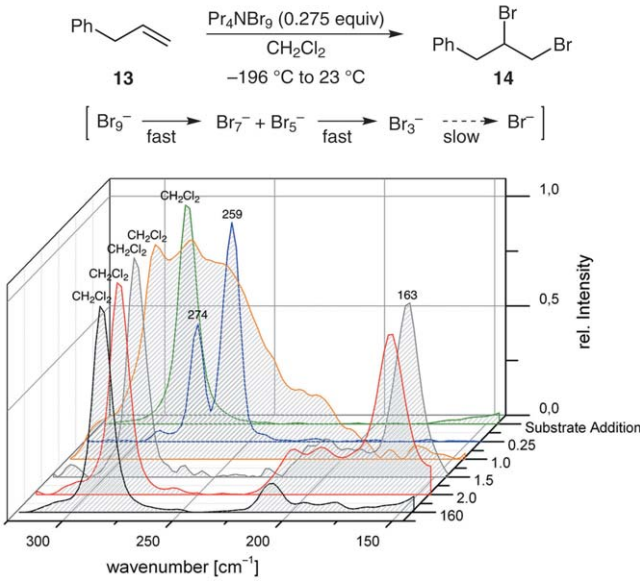


Entry	Reagent	Equiv	Solvent	Yield[a] (%) of **14**
1	Pr_4NBr_9	0.33	CH_2Cl_2	>99
2	Pr_4NBr_9	0.25	CH_2Cl_2	82
3	Pr_4NBr_9	0.25	neat	78
4	Bu_4NBr_3	1.10	CH_2Cl_2	94
5	Br_2	1.05	$CHCl_3$	88 (7% **15**)

[a] Isolated yield.

We also attempted to examine the reaction speed for the bromination with Pr_4NBr_9 in comparison with Br_2 and a mixture of Br_2 and Pr_4NBr generated by addition of Br_2 to a solution of the ammonium salt at room temperature.[15,16] However, in all cases complete conversion of allylbenzene (**13**) was observed at 0 °C when the reaction was quenched by addition of thiosulfate after only 10 seconds. This was also the case as well for the bromination of methyl cinnamate (**16**) (>80% conversion with all three reagents).

The reactivity of Pr_4NBr_9 is comparable to elemental bromine, which is a great advantage compared to common Br_3^--based brominating reagents that usually react several magnitudes slower.[15,16] To exclude that **12** is releasing bromine in solution, which then acts as brominating agent, we monitored the reaction of allylbenzene by in situ Raman spectroscopy (Scheme 1). The experiment was started in a low-temperature cuvette[17] at –196 °C in the frozen state in which no free bromine was observed. Then, the sample was layered with allylbenzene and allowed to warm to room temperature. The nonabromide (ν = 259, 274 cm^{-1})[11] quickly decayed into a mixture of Br_9^-, Br_7^- and Br_5^- and then turned into Br_3^- (ν = 163 cm^{-1}) after 90 minutes reaction time.[14b,e] At this point, a small amount of free Br_2 was detected (ν = 313 cm^{-1}).[18] The conversion of the last equivalent of Br_2 (Br_3^- to Br^-) required several hours to complete.



Scheme 1 Reaction of allylbenzene with Pr_4NBr_9 (27.5 mol%) at –196 °C. Bands at 259 cm^{-1} and 274 cm^{-1}: Br_9^- (blue). Bands at t = 1.0 h: Br_9^-, Br_7^- and Br_5^- (orange). Band at 163 cm^{-1} = Br_3^- (grey/red).

We also confirmed the stability of the nonabromide in dichloromethane as solvent by Raman spectroscopy. At room temperature only the nonabromide was present (Figure 3).[19] The room-temperature spectrum of Pr_4NBr_9 in dichloromethane shows a significantly broadened band for Br_9^-, which upon cooling turns into two distinct sharp bands at 259 cm^{-1} and 274 cm^{-1} as shown in Scheme 1.

Due to our observations, we suspect the nonabromide itself to play an important part in the mechanism of the bromination reaction. Regarding the atomic partial charges (see Figure 4) where the bromine atom in position 2 is always positively charged based on natural population analysis (NPA) charges, we suppose a nucleophilic attack of the organic reagent at this position. A detailed investigation of the reaction mechanism is beyond the scope of the present study and will be published elsewhere.

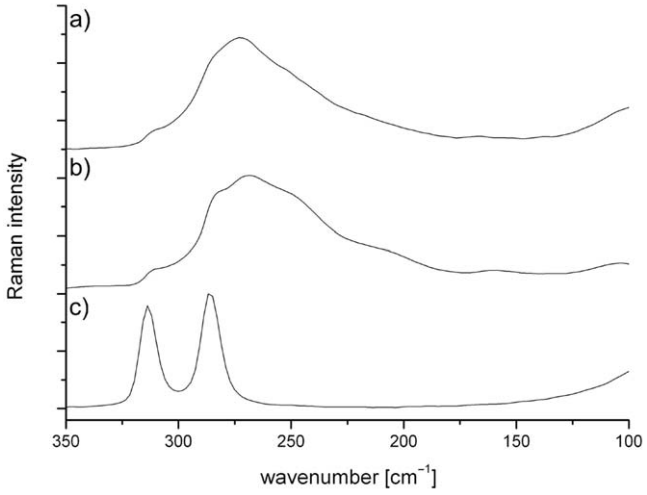
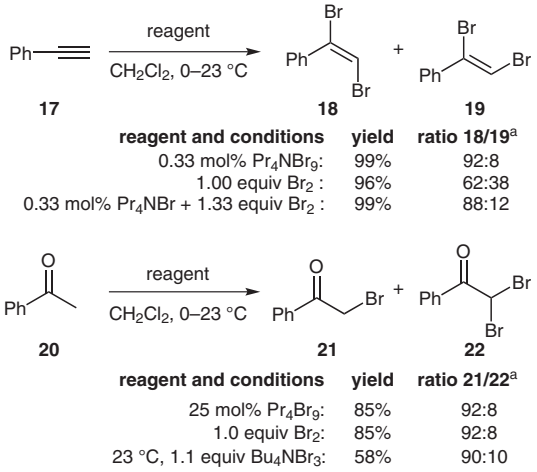


Figure 3 Room-temperature Raman spectra of: (a) Pr_4NBr_9 in CH_2Cl_2, (b) Br_2 added to a solution of Pr_4NBr in CH_2Cl_2, and (c) Br_2 in CH_2Cl_2. The band at 287 cm^{-1} originates from CH_2Cl_2.

	NPA charge at atom		
anion	1	2	3
$[Br_9]^-$	–0.70107	**0.60976**	–0.14449
$[Br_7]^-$	–0.69818	**0.08955**	–0.19016
$[Br_5]^-$	–0.65345	**0.12778**	–0.30106
$[Br_3]^-$	–0.58547	**0.17093**	–0.58547

Figure 4 NPA charges of $[Br_9]^-$, $[Br_7]^-$, $[Br_5]^-$, and $[Br_3]^-$ at BP86/def2-TZVPP//SCS-MP2/def2-TZVPP level

We also examined the reactivity of Pr_4NBr_9 towards alkynes on the example of phenylacetylene (**17**) (Scheme 2). Here, 33 mol% of the reagent (1.33 Br_2 equivalents) resulted in quantitative, chemoselective, and stereoselective conversion into the 1,2-dibrominated *E*-styrene (**18**/**19** 92:8). The bromination with bromine itself gave only a *E*/*Z* mixture of 62:38, which may be caused by the partial formation of a cationic intermediate in this case.[20] In a third experiment, a solution of tetrapropylammonium monobromide and the substrate was treated with 1.33 equivalents of bromine and a slightly lower stereoselectivity (*E*/*Z* 88:12) compared to preformed **12** was observed. This positive effect of added bromide salts to bromination reactions was observed and discussed earlier by others,[20] but in our case we can attribute this to the presence of Br_9^-. The nonabromide is also a reagent suitable for the selective monobromination of ketones. For example, we treated acetophenone (**20**) with the nonabromide (25 mol%) at 0 °C and received the desired monobromide **21** in 85% yield together with only a small amount of the dibromide **22** (7.5%) (Scheme 2, bottom). Here, an excess of the bromination reagent had to be avoided to prevent overbromination, because all four bromine molecules present in the nonabromide were transferred rapidly to the substrate. The reaction with tetrabutylammonium tribromide resulted in incomplete conversion and the selectivity was slightly lower than with **12** or Br_2 (90:10).



Scheme 2 Brominations of phenylacetylene and acetophenone: [a] Determined by ^{1}H NMR of the crude reaction mixture

To further determine the scope of the reagent, we employed Pr_4NBr_9 in the bromination of several other substrates on a 2-mmol scale. The results are summarized in Table 2 including the reaction times to achieve complete conversion. The bromination of other alkenes such as dec-1-ene (**23**) or Michael acceptor systems like chalcone **25** and methyl cinnamate (**16**) proceeded smoothly in 94–99% yield within 1–10 minutes depending on the electronic nature of the alkene (entries 2–4). The *anti*/*syn* ratio was excellent and only chalcone led to the formation of a minor amount of the *syn* diastereomer.

Table 2 Summary of Bromination Reactions with Pr_4NBr_9 (**12**)[a]

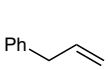
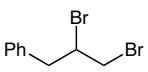
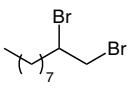
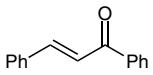
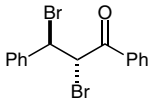
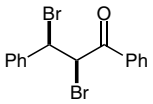
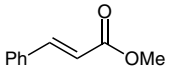
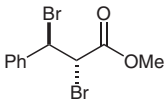
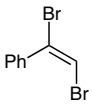
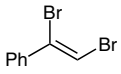
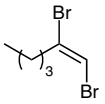
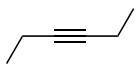
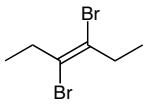
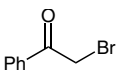
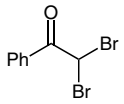
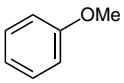
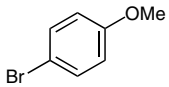
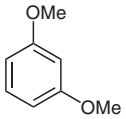
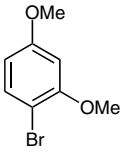
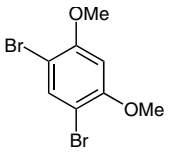
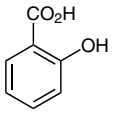
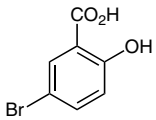
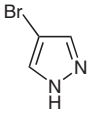
Entry	Substrate	Products	Product ratio	Equiv Pr_4NBr_9	T (°C)	Time (min)	Yield[b] (%)
1			–	0.33	0–23	<1	99
	13	**14**					
2			–	0.33	0–23	<1	99
	23	**24**					

Table 2 Summary of Bromination Reactions with Pr_4NBr_9 (**12**)[a] (continued)

Entry	Substrate	Products		Product ratio	Equiv Pr_4NBr_9	T (°C)	Time (min)	Yield[b] (%)
3				94:6	0.33	0–23	5	94
	25	**26**	**27**					
4				–	0.33	0–23	10	99
	16	**28**						
5				92:8	0.33	0–23	<1	99[c]
	17	**18**	**19**					
6				–	0.33	0–23	<1	92
	29	**30**						
7				–	0.33	0–23	<1	88
	31	**32**						
8				92:8	0.25	0–23	15	85
	20	**21**	**22**					
9				–	0.33	0–23	5	99
	33	**34**						
10a 10b				75:25 0:100	0.25 0.66	0 0–23	5 1	85[c] 99
	35	**36**	**37**					
11				–	0.33	23	30[d]	95
	38	**39**						
12				–	0.33	0–23	10	99
	40	**41**						

[a] For detailed reaction conditions, see the experimental section.
[b] Yield of isolated major product.
[c] Combined yield.
[d] In comparison, the reaction of salicylic acid was significantly slower due to its low solubility in CH_2Cl_2.

Interestingly, in all cases the yields and reaction times surpassed those previously observed with other reagents.[21–24] Terminal and internal alkynes **29** and **31** were rapidly brominated in a similar fashion and a superior stereoselectivity was observed towards the *trans*-dibromoolefin as discussed above for phenylacetylene (**17**) (entries 5–7). Aromatic compounds such as anisole (**33**) and the more electron-rich resorcin dimethyl ether (**35**) were investigated (entries 9 and 10). The bromination of anisole proceeded in five minutes in quantitative yield and with complete selectivity in favor of the *para*-brominated arene **34**. In a report on this reaction with *N*-bromosuccinimide (**8**), a common reagent for selective electrophilic aromatic brominations, the reaction time was 18 hours.[25] *N*-Bromosuccinimide was also reported to be superior in terms of selectivity in the reaction with **35**, but again the bromination was reported to take 18 hours to complete.[25] In our hands the reactions employing either Pr_4NBr_9 or Br_2 were significantly faster (entry 10) and with controlled addition of the reagent at 0 °C moderate selectivity towards the monobromination product was achieved (Br_2: 76% yield, 79:21 product ratio, 2.5 h). With an excess of **12**, quantitative conversion into the dibromoarene **37** took place within one minute reaction time. Salicylic acid (**38**) on the other hand was smoothly transformed in a quantitative fashion, but the reaction required 30 minutes to complete due to the low solubility of the substrate (entry 11). Other reagents like tribromide containing ionic liquids or *N*-bromosuccinimide were reported to be slower or required irradiation and heat or strong acid additives.[5e,26,27] Finally, pyrazole (**40**) was selectively brominated in quantitative yield in the 4-position within 10 minutes (entry 12).

In conclusion, readily available tetrapropylammonium nonabromide (**12**) is an effective brominating agent for various substrate classes. This nonabromide is more reactive than for example Bu_4NBr_3, with a reactivity similar to that of elemental bromine. In several cases, however, better chemo- and stereoselectivity was observed than with bromine itself. It is known that the addition of salt additives such as Pr_4NBr can have a similar selectivity-enhancing effect in reactions with Br_2 and we demonstrated that under our conditions Pr_4NBr_9 is formed. The advantages of tetrapropylammonium nonabromide are its high active bromine content, its selectivity and reactivity, and the fact that it is a solid reagent, which can be weighed at the balance and safely stored for long periods. In this way, once the reagent has been prepared, the handling of elemental bromine can be avoided.

All substrates and products are known in the literature and matched the ^{1}H NMR data reported. All bromination reactions were carried out without an inert gas atmosphere and using dry glassware unless stated otherwise. EtOAc (technical quality) was purified by distillation with a rotary evaporator. CH_2Cl_2 (p.a., Aldrich) was used as received. Br_2 was purchased from Merck. Pr_4NBr was purchased from Aldrich. Acetophenone (Aldrich) was distilled before use. All other chemicals were purchased from Aldrich and used without further purification. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or MnO_4^- staining. FT-Raman spectra were recorded on a Bruker Vertex 70 spectrophotometer equipped with a RAM II module using a liquid N_2 cooled Ge detector. ^{1}H NMR spectra were recorded on a Varian Mercury 300 HFCP (300 MHz) spectrometer and referenced to $CDCl_3$ (δ = 7.26).

Synthesis of Pr_4NBr_9

This procedure can be also used for the in situ preparation of Pr_4NBr_9. A flame-dried, argon-backfilled Schlenk tube equipped with a magnetic stir bar and a rubber septum was charged with Pr_4NBr (532.5 mg, 2.0 mmol, 1 equiv) followed by slow addition of Br_2 (430.4 μL, 8.4 mmol, 4.2 equiv). The mixture was stirred for 30 min and became a homogeneous dark-red liquid. Stirring was ceased and the reaction vessel was cooled to 4 °C for ca. 10 min after which the mixture became solid and remained solid after rewarming to r.t.; yield: 1.79 g (99%). Raman analysis of the reagent prepared this way showed that Pr_4NBr_9 was the only species present in the solid. The reagent was transferred to a screw-cap vial and remained stable for several weeks as long as the vial was correctly sealed. Under reduced pressure the compound released bromine and decayed to the tribromide.

Brominations with Pr_4NBr_9; General Procedure A

A round-bottom flask equipped with a magnetic stir bar and a rubber septum was charged with Pr_4NBr_9 (0.66 mmol, 0.33 mol%) and CH_2Cl_2 (1 mL). The homogeneous solution was stirred and cooled to 0 °C if not described otherwise (partial precipitation of the nonabromide can occur at this point). The substrate (2.0 mmol, 1.0 equiv) was added and the reaction allowed to warm to 23 °C (attention: exothermic reaction!) After the reported reaction time the dark-red color of the nonabromide had vanished and TLC control showed completion of the reaction. The reaction was quenched by addition of sat. aq $Na_2S_2O_3$ (2 mL) and transferred to a separation funnel. H_2O was added (15 mL) followed by extraction with Et_2O (4 × 20 mL) if not described otherwise. The organic layers were combined, washed with H_2O (4 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude product.

Brominations with Pr_4NBr_9 by Controlled Addition of the Reagent; General Procedure B

A 0.66 M Pr_4NBr_9 in CH_2Cl_2 solution was prepared as described in General Procedure A. A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with CH_2Cl_2 (1 mL) and the desired substrate (2 mmol). This solution was cooled to 0 °C and the Pr_4NBr_9 solution (0.75 mL, 25 mol%) was added dropwise. The mixture was allowed to warm to r.t. and stirred for the reported time. Then the reaction was quenched and worked up as described in General Procedure A.

Experimental Procedure for Raman Measurements

In a low-temperature cuvette a solution of Pr_4NBr_9 (115 mg, 0.127 mmol, 0.275 equiv) in CH_2Cl_2 (0.25 mL) was frozen at –196 °C and layered with allylbenzene (61 μL, 0.46 mmol, 1.0 equiv) on top of the solid. Then, the cuvette was placed in a Raman spectrometer and continuous recording of the spectra began (10 scans for each spectrum). The mixture was slowly allowed to warm to r.t. The spectra recorded after 0.25, 1.0, 1.5, 2.0, and 160 h are shown in Scheme 1.

(2,3-Dibromopropyl)benzene (14)[28]

Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a colorless oil; yield: 553 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.15 (dd, *J* = 7.8, 14.5 Hz, 1 H), 3.53 (dd, *J* = 4.7, 14.4 Hz, 1 H), 3.65 (dd, *J* = 8.9, 10.4 Hz, 1 H), 3.84 (dd, *J* = 4.2, 10.5 Hz, 1 H), 4.38 (dddd, *J* = 4.2, 4.8, 7.8, 8.9 Hz, 1 H), 7.28–7.40 (m, 5 H).

(*E*)-(1,2-Dibromovinyl)benzene (18)[29,30]

Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O to-

gether with a small amount of the *Z*-isomer (*E*/*Z* 11:1) as a colorless oil; yield: 519 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 1 H, *E*), 7.08 (s, 0.09 H, *Z*), 7.35–7.44 (m, 3.3 H, *E* and *Z*), 7.51–7.55 (m, 2.2 H, *E* and *Z*).

2-Bromo-1-phenylethan-1-one (21)[31]
Following general procedure B, the reaction was quenched after 15 min. The crude product was isolated after extraction with Et_2O–H_2O; crude yield: 383 mg; containing mono/dibromoacetophenone 11:1 (93%) and remaining acetophenone (5%) (NMR). Crystallization (heptane–Et_2O) afforded **21** (338 mg, 85%) as a colorless needles that matched literature data.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45 (s, 2 H), 7.48 (dddd, *J* = 1.4, 2.0, 7.4, 7.8 Hz, 2 H), 7.60 (tt, *J* = 1.3, 7.4 Hz, 1 H), 7.95–8.00 (m, 2 H).

1,2-Dibromodecane (24)[28]
Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a colorless oil; yield: 594 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.18–1.46 (m, 11 H), 1.50–1.62 (m, 1 H), 1.78 (dddd, *J* = 4.7, 9.0, 9.8, 14.5 Hz, 1 H), 2.13 (dddd, *J* = 3.3, 5.8, 10.0, 14.5 Hz, 1 H), 3.63 (dd, *J* = 10.1, 9.9 Hz, 1 H), 3.85 (dd, *J* = 4.4, 10.2 Hz, 1 H), 4.16 (dddd, *J* = 3.33, 4.4, 9.1, 9.6 Hz, 1 H).

***anti*-2,3-Dibromo-1,3-diphenylpropan-1-one (26)**[30]
Following general procedure A, the reaction was quenched after 5 min. Extraction with Et_2O–H_2O gave **26** and **27**; crude yield: 730 mg (99%); ratio **26**/**27** 15:1. After crystallization (Et_2O–CH_2Cl_2), **26** was isolated as a white solid; yield: 691 mg (94%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.66 (d, *J* = 11.3 Hz, 1 H), 5.84 (d, *J* = 11.3 Hz, 1 H), 7.35–7.47 (m, 3 H), 7.51–7.59 (m, 4 H), 7.67 (tt, *J* = 1.3, 7.4 Hz, 1 H), 8.09–8.14 (m, 2 H).

Methyl *anti*-2,3-Dibromo-3-phenylpropanoate (28)[30]
Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a white solid; yield: 643 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 4.86 (d, *J* = 11.7 Hz, 1 H), 5.36 (d, *J* = 11.7 Hz, 1 H), 7.35–7.43 (m, 5 H).

(*E*)-1,2-Dibromohex-1-ene (30)[32]
Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a colorless oil; yield: 445 mg (92%); data matched that in the literature. Evaporation of solvent at the rotavapor was carried out at 23 °C due to the slightly volatile nature of the product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.36 (qt, *J* = 7.2, 7.6 Hz, 2 H), 1.56 (tt, *J* = 7.2, 7.8 Hz, 2 H), 2.61 (t. *J* = 7.3 Hz, 2 H), 6.40 (s, 1 H).

(*E*)-3,4-Dibromohex-3-ene (32)[33]
Following general procedure A, the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a colorless oil; yield: 425 mg (88%); data matched that in the literature. Evaporation of solvent at the rotavapor was carried out at 23 °C due to the slightly volatile nature of the product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.4 Hz, 3 H), 2.67 (q, *J* = 7.4 Hz, 2 H).

1-Bromo-4-methoxybenzene (34)[34]
Following general procedure A, the reaction was quenched after 5 min. The product was isolated after extraction with Et_2O–H_2O as a colorless oil; yield: 374 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 6.79 (d, *J* = 9.1 Hz, 2 H), 7.38 (d, *J* = 9.1 Hz, 2 H).

1-Bromo-2,4-dimethoxybenzene (36)[10m]
Following general procedure B and the reaction was stirred at 0 °C for 5 min followed by addition of sat. aq $Na_2S_2O_3$. The product was obtained after extraction with Et_2O–H_2O together with 1,5-dibromo-2,4-dimethoxybenzene (ratio 3.0:1 as determined by ^{1}H NMR); combined yield: 403 mg (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 3.87 (s, 3 H), 6.39 (dd, *J* = 2.7, 8.7 Hz, 1 H), 6.49 (d, *J* = 2.7 Hz, 1 H), 7.41 (d, *J* = 8.7 Hz, 1 H).

1,5-Dibromo-2,4-dimethoxybenzene (37)[35]
Following general procedure A but with 66 mol% of Pr_4NBr_9 and the reaction was quenched after 1 min. The product was isolated after extraction with Et_2O–H_2O as a white solid; yield: 591 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 6.48 (s, 1 H), 7.65 (s, 1 H).

5-Bromo-2-hydroxybenzoic Acid (39)[27]
Following general procedure A, the reaction was quenched after 30 min. The crude product after extraction with EtOAc–H_2O contained **39** together with a small amount of unreacted salicylic acid. Crystallization (CH_2Cl_2) gave pure **39** as white needles; yield: 412 g (95%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.9 (d, *J* = 8.9 Hz, 1 H), 7.60 (dd, *J* = 2.5, 8.9 Hz, 1 H), 8.03 (d, *J* = 2.5 Hz, 1 H), 10.29 (s, 1 OH).

4-Bromopyrazole (41)[36]
Following general procedure A. After 10 min the mixture became solid. Additional CH_2Cl_2 (1 mL) was added followed by addition of sat. aq $Na_2S_2O_3$ with stirring. The product was isolated after extraction with EtOAc–H_2O as a white solid; yield: 293 mg (99%); data matched that in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 2 H), 11.80 (br, 1 NH).

Quantum-Chemical Calculations
Calculations of the NPA charges were performed at BP86/def2-TZVPP//SCS-MP2/def2-TZVPP level.[37–43] All calculations were done with the Turbomole V6.2[44] program package and the analytical gradient methods implemented therein. Structures were fully optimized at SCS-MP2 level. Minima on the potential energy surface were characterized by harmonic vibrational frequency analyses, using numerical second derivatives based on energies and analytical gradients. For the NBO analysis single points were calculated at BP86/def2-TZVPP level.[45]

Acknowledgment

The authors wish to acknowledge the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.
(2) *Comprehensive Organic Transformations*, 2nd ed.; Larock, R. C., Ed.; Wiley-VCH: Weinheim, **1999**.

(3) (a) Buckles, R. E.; Popov, A. I.; Zelezny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* **1951**, *73*, 4525. (b) Buckles, R. E.; Harris, L. *J. Am. Chem. Soc.* **1957**, *79*, 886.
(4) (a) Trowbridge, P. F.; Diehl, O. C. *J. Am. Chem. Soc.* **1897**, *19*, 558. (b) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417. (c) Merker, P. C.; Vona, J. A. *J. Chem. Educ.* **1949**, *26*, 613.
(5) (a) Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett.* **2001**, *3*, 1061. (b) Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536. (c) Salazar, J.; Dorta, R. *Synlett* **2004**, 1318. (d) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267. (e) Borikar, S. P.; Daniel, T.; Paul, V. *Tetrahedron Lett.* **2009**, *50*, 1007.
(6) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271.
(7) (a) Eguchi, H.; Kawaguchi, H.; Yoshinaga, S.; Nishida, A.; Nishiguchi, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1918. (b) Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1997**, *38*, 4415.
(8) Magen, S.; Oren, J.; Fuchs, B. *Tetrahedron Lett.* **1984**, *25*, 3369.
(9) (a) Omura, K. *J. Org. Chem.* **1996**, *61*, 2006. (b) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.
(10) For example, see: (a) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127. (b) Kim, E.-H.; Koo, B.-S.; Song, C.-E.; Lee, K.-J. *Synth. Commun.* **2001**, *31*, 3627. (c) Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, *57*, 7417. (d) Narender, N.; Mohan, K. V. V. K.; Kulkarni, S. J.; Raghavan, K. V. *J. Chem. Res.* **2003**, 597. (e) Zhang, G.; Liu, R.; Xu, Q.; Ma, L.; Liang, X. *Adv. Synth. Catal.* **2006**, *348*, 862. (f) Terent'ev, A. O.; Khodykin, S. V.; Krylov, I. B.; Ogibin, Y. N.; Nikishin, G. I. *Synthesis* **2006**, 1087. (g) Tajik, H.; Mohammadpoor-Baltork, I.; Albadi, J. *Synth. Commun.* **2007**, *37*, 323. (h) Das, B.; Srinivas, Y.; Sudhakar, C.; Damodar, K.; Narender, R. *Synth. Commun.* **2008**, *39*, 220. (i) Firouzabadi, H.; Iranpoor, N.; Kazemi, S. *Can. J. Chem.* **2009**, *87*, 1675. (j) Kumar, M. A.; Rohitha, C. N.; Kulkarni, S. J.; Narender, N. *Synthesis* **2010**, 1629. (k) Macharla, A. K.; Nappunni, R. C.; Marri, M. R.; Peraka, S.; Nama, N. *Tetrahedron Lett.* **2012**, *53*, 191. (l) Yousefi-Seyf, J.; Tajeian, K.; Kolvari, E.; Koukabi, N.; Khazaei, A.; Zolfigol, M. A. *Bull. Korean Chem. Soc.* **2012**, *33*, 2619. (m) Prebil, R.; Laali, K. K.; Stavber, S. *Org. Lett.* **2013**, *15*, 2108.
(11) Haller, H.; Ellwanger, M.; Higelin, A.; Riedel, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11528.
(12) Chattaway, F. D.; Hoyle, G. *J. Chem. Soc., Trans.* **1923**, *123*, 654.
(13) Farkas, L.; Schächter, O. *J. Am. Chem. Soc.* **1949**, *71*, 2252.
(14) (a) Strømme, K. O. *Acta Chem. Scand.* **1959**, *13*, 2089. (b) Kalina, D. W.; Lyding, J. W.; Ratajack, M. T.; Kannewurf, C. R.; Marks, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 7854. (c) Cunningham, C. W.; Burns, G. R.; McKee, V. *Inorg. Chim. Acta* **1990**, *167*, 135. (d) Robertson, K. N.; Bakshi, P. K.; Cameron, T. S.; Knop, O. *Z. Anorg. Allg. Chem.* **1997**, *623*, 104. (e) Chen, X.; Rickard, M. A.; Hull, J. W. Jr.; Zheng, C.; Leugers, A.; Simoncic, P. *Inorg. Chem.* **2010**, *49*, 8684. (f) Wolff, M.; Meyer, J.; Feldmann, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 4970. (g) Wolff, M.; Okrut, A.; Feldmann, C. *Inorg. Chem.* **2011**, *50*, 11683. (h) Vitske, V.; Herrmann, H.; Enders, M.; Kaifer, E.; Himmel, H.-J. *Chem. Eur. J.* **2012**, *18*, 14108. (i) Haller, H.; Schröder, J.; Riedel, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 4937. (j) Haller, H.; Hog, M.; Scholz, F.; Scherer, H.; Krossing, I.; Riedel, S. *Z. Naturforsch.* **2013**, 68b, 1103. (k) Haller, H.; Ellwanger, M.; Higelin, A.; Riedel, S. *Z. Anorg. Allg. Chem.* **2012**, *638*, 553.
(15) (a) Bellucci, G.; Bianchini, R.; Ambrosetti, R.; Ingrosso, G. *J. Org. Chem.* **1985**, *50*, 3313. (b) Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* **1986**, *51*, 4224. (c) Bellucci, G.; Chiappe, C.; Moro, G. L. *J. Org. Chem.* **1997**, *62*, 3176.
(16) Ruasse, M.-F.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* **1991**, *113*, 3440.
(17) See the Supporting Information.
(18) Put, J.; Maes, G.; Huyskens, P.; Zeegers-Huyskens, T. *Spectrochim. Acta* **1981**, 37A, 699.
(19) Trace amounts of Br_2 originating from the small excess of Br_2 used in the preparation became visible upon dissolving the material in CH_2Cl_2. However, this was removed by crystallization and the resulting nonabromide material showed identical bromination performance.
(20) Pincock, J. A.; Yates, K. *Can. J. Chem.* **1970**, *48*, 3332.
(21) Weber, F. G. *Tetrahedron* **1969**, *25*, 4283.
(22) Berthelot, J.; Benammar, Y.; Lange, C. *Tetrahedron Lett.* **1991**, *32*, 4135.
(23) Tanaka, K.; Shiraishi, R.; Toda, F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3069.
(24) Ma, X.; Li, W.; Li, X.; Tao, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *Chem. Commun.* **2012**, *48*, 5352.
(25) Zysman-Colman, E.; Arias, K.; Siegel, J. S. *Can. J. Chem.* **2009**, *87*, 440.
(26) Chhattise, P. K.; Ramaswamy, A. V.; Waghmode, S. B. *Tetrahedron Lett.* **2008**, *49*, 189.
(27) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504.
(28) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron Lett.* **2010**, *51*, 340.
(29) Liu, J.; Li, W.; Wang, C.; Li, Y.; Li, Z. *Tetrahedron Lett.* **2011**, *52*, 4320.
(30) Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561.
(31) (a) Choi, H. Y.; Chi, D. Y. *Org. Lett.* **2003**, *5*, 411. (b) See also supporting information in: Streuff, J.; Feurer, M.; Bichovski, P.; Frey, G.; Gellrich, U. *Angew. Chem. Int. Ed.* **2012**, *51*, 8661.
(32) Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron* **1998**, *54*, 1021.
(33) Hanson, K.; Roskop, L.; Djurovich, P. I.; Zahariev, F.; Gordon, M. S.; Thompson, M. E. *J. Am. Chem. Soc.* **2010**, *132*, 16247.
(34) Li, B.; Gao, L.; Bian, F.; Yu, W. *Tetrahedron Lett.* **2013**, *54*, 1063.
(35) Pahari, P.; Rohr, J. *J. Org. Chem.* **2009**, *74*, 2750.
(36) Graczyk, P. P.; Dimopoulos, P.; Bhatia, P. G.; Farthing, C. N.; Khan, A. WO 2008,095,944, **2008**.
(37) Dirac, P. A. M. *Proc. R. Soc. London, Ser. A* **1929**, *123*, 714.
(38) Slater, J. C. *Phys. Rev.* **1951**, *81*, 385.
(39) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
(40) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
(41) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822.
(42) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.
(43) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095.
(44) Turbomole 6.3 ed., a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, Karlsruhe, **2011**, available from http://www.turbomole.com.
(45) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.