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Carbocation Catalyzed Bromination of Alkyl Arenes, a Chemoselective *sp³ vs. sp²* C-H functionalization.

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Abstract. The versatility of the trityl cation (TrBF4) as a highly efficient Lewis acid organocatalyst is demonstrated in a light induced benzylic brominaion of alkyl-arenes under mild conditions The reaction was conducted at ambient temperature under common hood light (55 W fluorescent light) with catalyst loadings down to 2.0 mol% using N-bromo succinimide (NBS) as the brominating agent. The protocol is applicable to an extensive number of substrates to give benzyl bromides in good to excellent yields. In contrast to most previously reported strategies, this protocol does not require any radical initiator or extensive heating. For electron-rich alkyl-arenes, the trityl ion catalysed bromination could be easily switched between benzylic sp^3 C-H functionalization and arene sp^2 C-H functionalization by simply alternating the solvent. This chemoselective switch allows for high substrate control and easy preparation of benzyl bromides and bromoarenes, respectively. The chemoselective switch was also applied in a one-pot reaction of 1-methylnaphthalene for direct introduction of both sp^3 C-Br and sp^2 C-Br functionality.

Keywords: Carbocation; Trityl; Bromination; Benzylic; EAS

Introduction

Brominated aromatic compounds, e.g. α-bromoalkyl arenes and bromoarenes, are highly valuable and versatile bulk chemicals in organic synthesis[1] and material science,[2] in particular as benzylation agents,[3] precursors for organometallic reagent[4] not to mention their vast applications in transition metal cross-coupling reactions.[5] α-Bromoalkyl arenes can be directly prepared from its corresponding alkyl arene (*benzylic sp^3 C-H bond functionalization*) using *N*–bromosuccinimide (NBS) in the presences of a radical initiator such as benzoyl peroxide or AIBN in refluxing CCl_4, a classic reaction known as the Wohl−Ziegler reaction.[6] Since its establishment in around 1940 numerous strategies has been reported as improved versions of the original protocol.[7] Despite this, the Wohl–Ziegler bromination generally requires high reaction temperatures and radical initiators and surprisingly small efforts have been made to develop Lewis acid catalyzed protocols, thus allowing for milder reaction conditions.[8] On the other hand, NBS in the presences of Lewis acid is the general choice of reagents for preparation of bromoarenes through electrophilic aromatic substitution (*arene sp^2 C-H bond functionalization*).[9]

This leads to a thorny problem concerning the chemoselectivity between arene *sp^2* C-H and benzylic *sp^3* C-H bond functionaliztion, in particularly for activated and moderately activated arenes and mixture of α-bromoalkyl arenes and bromoarenes are always formed in these cases. Interestingly, Shibatomi *et al.* showed that chemoselectivity between arene *sp^2* C-H and benzylic *sp^3* C-H bond functionaliztion could be controlled by switching between a metal based Lewis acid and a Brønsted acid for a limited number of selected substrates.[10]

Herein we describe a mild and highly chemoselective Lewis acid organocatalyzed protocol for benzylic *sp^3* C-H bromination at room temperature without any observable competing arene *sp^2* C-H bromation even for highly activated aromatic compounds. This reaction is photo-induced by simply using standard hood fluorescent light (55 W F.L.), thus completely avoiding the use of any toxic radical initiator.

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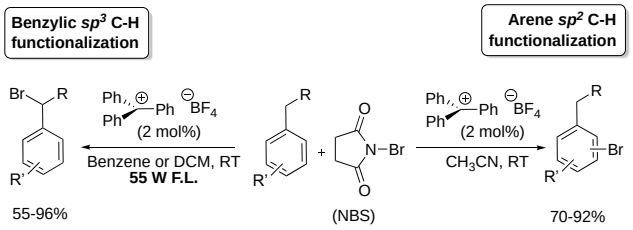


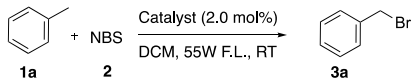
Scheme 1. Chemoselective trityl ion catalyzed sp^3-C vs. sp^2-C bromination of alkyl-arenes.

For activated and weakly activated arenes, the chemoselectivity of the bromination could be completely switched from benzylic sp^3 *C-H* functionalization to arene sp^2 *C-H* functionalization simply by changing the solvent of the reaction. In addition, this protocol completely suppresses over-oxidation to give mono-brominated compounds as the sole products.

Results and Discussion

Carbocation catalyzed Benzylic *sp3* C-H functionalization. Recently the trityl cation ($TrBF_4$) has been reported as a novel and highly efficient Lewis acid organocatalyst for various organic transformations.[11] In the course of our previous studies we found that when toluene **1a** and NBS **2** was irradiated by standard hood fluorescent light (55 W F.L.) in the presences of only 2.0 mol% $TrBF_4$ as the catalyst, full conversion was observed within 7 h giving benzyl bromide **3a** in 90% yield. It should be noted that no observable traces of aromatic sp^2 C-H bromination was observed (Table 1, entry 1). The catalyst loading could be even further reduced down to 1.0 mol% without any notable decrease in yield, although the reaction time increased up to 24 h (Table 1, entry 2). Control experiment showed that no reaction occurred in the absence of light or in the absence of catalyst (Table 1, entries 3 and 4). Changing the solvent from DCM to benzene had no effect on the yield, however reaction time increased to 17 h for full conversion (Table 1, entry 5). On the other hand, using the more polar solvent acetonitrile resulted in a drastic decrease of yield (Table 1, entry 6).

Table 1. Optimization of reaction condition for the benzylic bromination.[a]



Entry	Solvent	Catalyst	T (h)	Yield (%)[b]
1	DCM	$TrBF_4$	7	90
2[c]	DCM	$TrBF_4$	24	90
3[d]	DCM	$TrBF_4$	24	trace
4	DCM	-	24	trace
5	Benzene	$TrBF_4$	17	90
6	CH_3CN	$TrBF_4$	17	43
7	DCM	$HBF_4{\cdot}Et_2O$	14	91
8	DCM	$BF_3{\cdot}Et_2O$	15	86
9	DCM	*p*-TsOH	17	90
10	DCM	$AlCl_3$	2	84
11	DCM	(*p*-MeOPh)-$(Ph)_2CBF_4$	21	trace

[a] The catalyst (2.0 mol%) was added to a solution of toluene **1a** (1.0 equiv.) and NBS **2** (1.0 equiv.) in DCM (0.3 M) and irradiated by 55 W F.L. for the indicated time. [b] Determined by ^1H NMR spectroscopy using CH_3NO_2 as the internal standard. [c] 1.0 mol% catalyst was used. [d] The reaction was performed in dark.

In order to evaluate the ability of the trityl ion to catalyze the benzylic bromination, a series of Lewis and Brønsted acids were screened. Interestingly, $HBF_4{\cdot}Et_2O$, $BF_3{\cdot}Et_2O$ and *p*-toluenesulfonic acid all turned out to be competent catalysts for this reaction providing compatible yields to $TrBF_4$ (Table 1, entries 1, 7-9), However, the latter acids all gave a substantially increased reaction times compared to $TrBF_4$. In contrast, $AlCl_3$ gave full conversion of the starting materials in only 2 h, although with the lowest yield of the screened Lewis acids (Table 1, entry 10). The substantially less Lewis acidic mono-*p*-methoxy-susbstituted trityl ion ((4-methoxyphenyl)-diphenylmethylium tetraflouroborate) did not catalyze the bromination under these reaction conditions (Table 1, entry 11).

After establishing the optimal conditions for the trityl ion catalyzed benzylic bromination, we started to investigate the reaction of various aromatic compounds **1a-n** (Table 2). Thus, using the standard reaction conditions benzyl bromide **3a** was isolated in 82% yield from toluene **1a** after work up and flash column. The isolated yield of **3a** is lower compared to the observed ^1H NMR-yield for the same reaction most likely due to the inherent instability generally observed for benzyl bromide derivatives (*cf.* Table 2 and Table 1 entry 1). In addition, *o*- and *p*-bromotoluene **1b-c** and 1-bromo-4-methylnaphthalene **1d** all gave the corresponding benzylbromides **3b-d** in excellent isolated yields (Table 2). Ethylbenzene **1e** gave **3e** in 92% yield. For 4-methyl-ethylbenzene **1f** and diphenylmethane **1g** a clean benzylic bromination occurred and the corresponding benzyl bromide could be observed as the sole product by ^1H NMR on the crude reaction mixtures. Unfortunately, these bromides turned out to be rather unstable and spontaneously hydrolyzed during isolation and purification and was isolated as the corresponding alcohols **3f-3g** in 66% and 71% yield respectively (Table 2). It is worth mentioning that 4-methyl-ethylbenzene was brominated exclusively on the ethyl-group in preference of the methyl-group, which is expected due to the higher stability of the intermediate secondary radical species.

Electron-withdrawing groups, *e.g.* nitro-, ethoxycarbonyl- and cyano-groups were all well tolerated and provided **3h-3j** with excellent yields.

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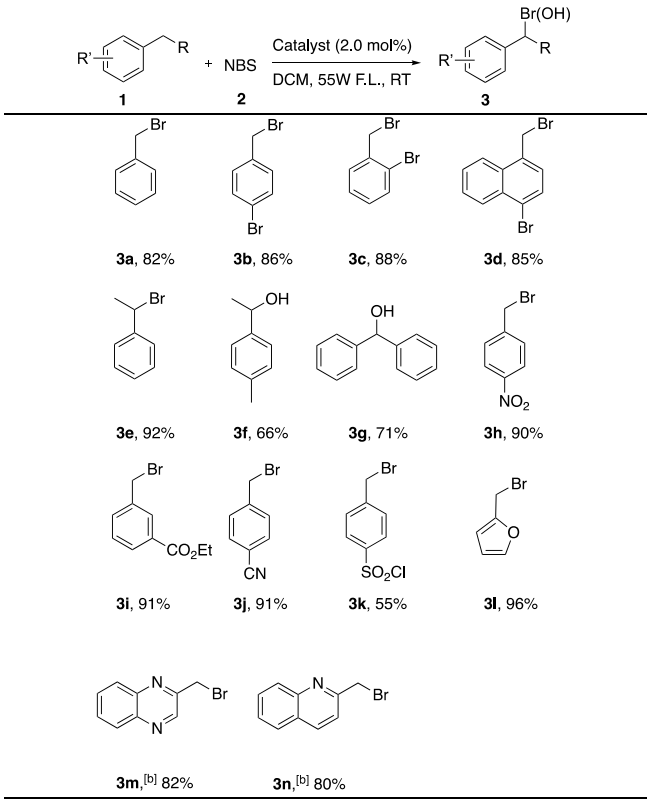
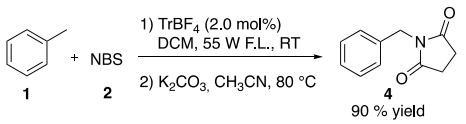
Interestingly, as high as 55% isolated yield was obtained from benzylic bromination of toluenesulfonyl chloride despite the relatively unstable chlorosulfonyl group (Table 2, **3k**). 2-Methylfuran **1l** was selectively brominated at the methyl group to give **3l** in 96% isolated yield (Table 2), in spite of the highly acid sensitive furan moiety and the tendency of electrophilic aromatic bromination often observed for activated furans. The nitrogen containing heterocyclic aromatics, quinoxaline and quinoline **1m-n** turned out to be less reactive and required 20 mol% catalyst loading to achieve acceptable conversions. However, under these conditions they were smoothly brominated at the benzylic position to give **3m-n** in good yields (Table 2).

Table 2. $TrBF_4$ catalyzed benzylic bromination.[a]



[a] $TrBF_4$ (2.0 mol%, 0.25 M in DCM) was added to **1** (1.5 equiv.) and **2** (1.0 equiv.) in DCM (0.3 M) and irradiated by 55 W F.L. [b] 20 mol% of the catalyst was used.

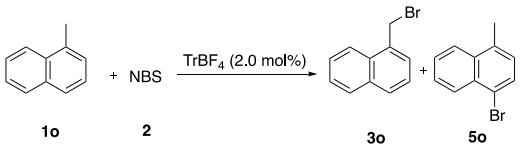
This protocol was also extended into an easy manageable, transition metal free, one-pot benzylic C-H amination where NBS acts both as the oxidating agent and the sources of nitrogen (Scheme 2). Simply, after full conversion of toluene **1a** using the standard reaction conditions (NBS, $TrBF_4$, 55 W F.L., DCM) the solvent was changed to CH_3CN followed by addition of K_2CO_3. Subsequent heating of the resulting reaction mixture at 80 °C for 24 h gave N-benzyl-succinimide **4** in 90% isolated overall yield.[12]



Scheme 2. Direct one-pot oxidative benzylic C-H amination.

Carbocation catalyzed bromination: Benzylic *sp3* vs. aromatic *sp2* C-H functionalization: The substrates screened so far (see Table 2) are moderately activated or deactivated and this protocol showed high selectivity for mono-bromination only at the benzylic position. For more activated aromatic compounds, such as anisol, aniline, etc. chemoselectivity became an issue and electrophilic aromatic substitution started to out-compete benzylic bromination to give mainly bromoarenes. For example, bromination of 1-methylnaphthalene **1o** under the standard reaction conditions (2.0 mol% $TrBF_4$, NBS, 55 W F.L., DCM) gave a 2:98 mixture of 1-(bromomethyl)naphthalene **3o** and 1-bromo-4-methylnaphthalene **5o**, almost complete selectivity for arene sp^2-C bromination (Table 3, entry 1). The benzylic bromination pathway could be completely suppressed by performing the reaction in absence of light, which will prevent radical formation giving **5o** as the single observable product. (Table 3, entry 2). In addition, using the more polar solvent acetonitrile favored the intermediate ionic species involved in the electrophilic aromatic substitution leading to selective formation of **5o** with drastically reduced reaction time (Table 3, entry 3). In fact, absence of light did not affect the selectivity of the reaction in acetonitrile and no percussions to avoid day/hood light were necessary (Table 3, entry 4).

Table 3. Optimization of reaction condition for the chemoselective switch: Benzylic sp^3 vs. aromatic sp^2 C-H functionalization.[a]



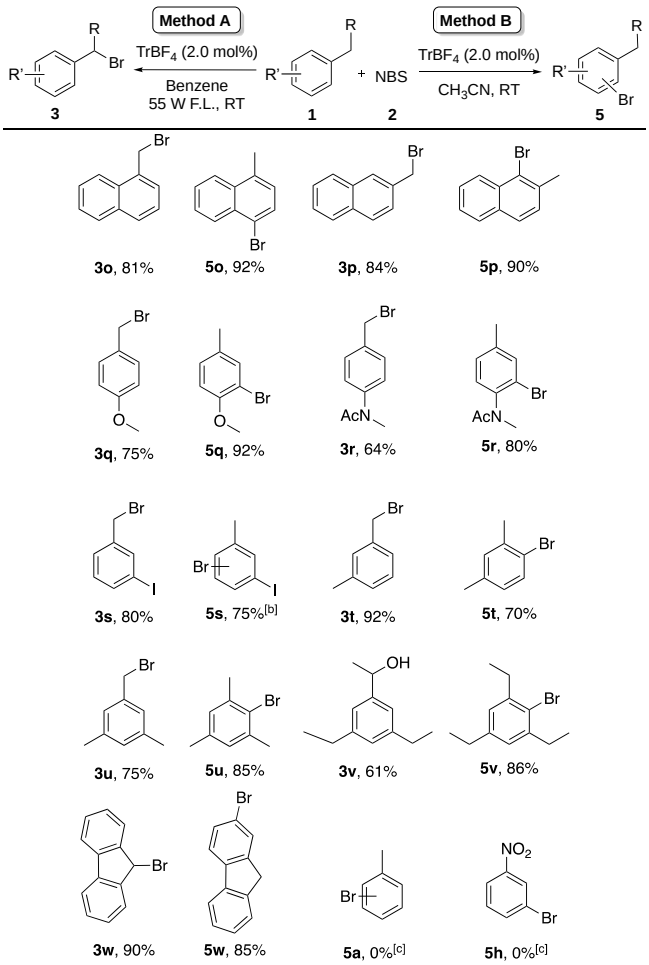
Entry	Solvent	t (h)	Ratio[b] **3o**:**5o**
1	DCM	20	2:98
2[c]	DCM	20	0:100
3	CH_3CN	2	0:100
4[c]	CH_3CN	2	0:100
5	benzene	15	100:0

[a] The $TrBF_4$ (2.0 mol%, 0.25 M in DCM) was added to a solution of 1-methylnaphthalene **1o** (1.2 equiv.) and NBS (1.0 equiv.) in the indicated solvent (0.3 M) and irradiated by 55 W F.L. [b] Determined by ^1H NMR using CH_3NO_2 as internal standard after completed reaction. [c] The reaction was performed in dark.

On the other hand, we reasoned that selective benzylic sp^3-C bromination should be possible through

trityl ion catalysis also for activated arenes. Thus, we thought to take advantage of this in order to develop an easily available chemoselective switch between the two reaction modes. Gratifyingly, by simply changing the solvent of the reaction from DCM to the more nonpolar benzene, electrophilic aromatic substitution was completely suppressed and 1-(bromomethyl)-naphthalene **3o** was obtained as the sole product (Table 3, entry 5). With these optimized conditions in hand, 1- and 2-methyInaphthalenes **1o** and **1p** was brominated in benzene to give the benzylic bromination product 1- and 2-(bromomethyl)-naphthalene **3o** and **3p** in high yields (Table 4). The analogous reactions in acetonitrile resulted in complete switch in chemoselectivity and bromonaphthalenes **5o** and **5p** was isolated in 92% and 90% isolated yields, respectively (Table 4).

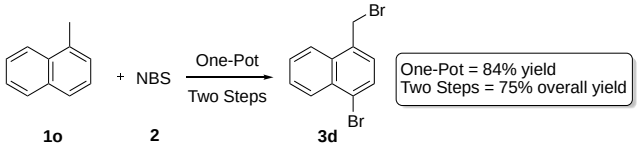
Table 4. Selected substrates for the chemoselective switch: Benzylic sp^3 vs. aromatic sp^2 C-H functionalization.[a]



[a] Method A: $TrBF_4$ (2.0 mol%, 0.25 M in DCM) was added to **1a** (1.5 equiv.) and **2** (1.0 equiv.) in benzene (0.3 M). Method B: $TrBF_4$ (2.0 mol%, 0.25 M in DCM) was added to **1a** (1.2 equiv.) and **2** (1.0 equiv.) in CH_3CN (0.3 M). [b] 1.5 eq. of **1s** was used. [c] No reaction, starting material was recovered.

In the same manner, the highly activated arenes *p*-methylanisol **1q** and *N*-methyl-*N*-(*p*-tolyl)acetamide **1r** could be chemoselectively brominated in benzene and acetonitrile to give benzyl bromides **3q-r** and bromobenzenes **5q-r**, respectively, in moderate to excellent yields (Table 4). Furthermore, the $TrBF_4$ catalyzed benzylic bromination of *m*-iodotoluene **1s**, *m*-xylene **1t** and mesitylene **1u** in benzene gave **3s-u** as single products in moderate to excellent yield (Table 4). For the analogous reactions of **1s-u** in acetonitrile (Table 4) a complete switch in selectivity to aromatic substitution was observed to give the corresponding bromobenzene derivatives **5s-u** in high yields (Table 4). As for the reaction of compound **1f-g** (*c.f.* Table 2), the benzylic bromination product of 1,3,5-triethylbenzene **1v** was isolated as the corresponding alcohol **3v** after flash column in 61% yield due to the instability of the secondary bromide (Table 4). Bromination of 1,3,5-triethylbenzene **1v** in acetonitrile smoothly gave bromobenzene **5v** in high yield (Table 4). Finally, fluorene was brominated in benzene (Conditon A) and acetonitrile (Conditon B) to give the benzylic bromination product **3w** and bromoarene **5w**, respectively, in high yields (Table 4). As expected, less electron rich aromatics such as toluene **1a** and 4-nitro-toluene **1h**, which could be efficiently brominated in the benzylic position (*cf.* Table 3), was completely unreacted under the aromatic *sp2* C-H functionalization reaction conditions and non of product **5a** and **5h** could be isolated (Table 4).

As a proof of concept, this chemoselective switch was developed into a selective one-pot dibromination of the aromatic and benzylic positions in 1-methylnaphthalene **1o** using 2 equivalents of NBS and 2 mol% $TrBF_4$ (Scheme 3). The one-pot sequence was initiated with arene brominiation using acetonitrile as the solvent. After full conversion of 1-methylnaphthalene **1o**, the solvent was simply changed to benzene and the reaction was allowed to continue for an additional 16 h (Scheme 3). Under these conditions the dibrominated product **3d** was isolated in 84% yield, which can be compared to the notable lower yield obtained for the more tedious two-step procedure (Scheme 3).



Scheme 3. One-pot vs. two-step dibromination of 1-methylnaphthalene. One-pot: 1) $TrBF_4$ (2.0 mol%, 0.25 M in DCM), NBS (2.0 equiv.), 55 W F.L., CH_3CN. 2) Benzene, 55 W F.L. Two-step: 1) $TrBF_4$ (2.0 mol%, 0.25 M in DCM), NBS (1.0 equiv.), 55 W F.L., CH_3CN. 2) $TrBF_4$ (2.0 mol%, 0.25 M in DCM), NBS (1.0 equiv.), benzene, 55 W F.L.

Mechanistic considerations: Lewis acid activation of NBS by $AlCl_3$, $FeCl_3$, $ZrCl_4$ among others have been previously reported to catalyze electrophilic aromatic bromination.[8c,13] The activation mode in these cases involves metal coordination to the carbonyl oxygen in NBS thereby making the bromine atom more

electrophilic. In an attempt to verify such a coordination of the trityl ion, $TrBF_4$ and NBS was mixed in 1:1 ratio in CD_2Cl_2. A smal changes in ^{1}H-NMR shifts from 2.959 to 2.962 MHz could be observed for the CH_2-groups on succinimide. The signals corresponding to the trityl ion did not change shift upon addition of succinimide witch is suggesting a weak coordination. Furthermore, investigation of the IR-absorption band of NBS with mixtures of $TrBF_4$ and NBS reveled a shift in the absorption band from 1695 cm^{-1} to 1700 cm^{-1} even at such low catalyst loadings as 2.0 mol% (Figure 1). Such an increase in absorption frequency is consistent with a more electron deficient carbonyl carbon supporting activation of NBS through trityl ion coordination.

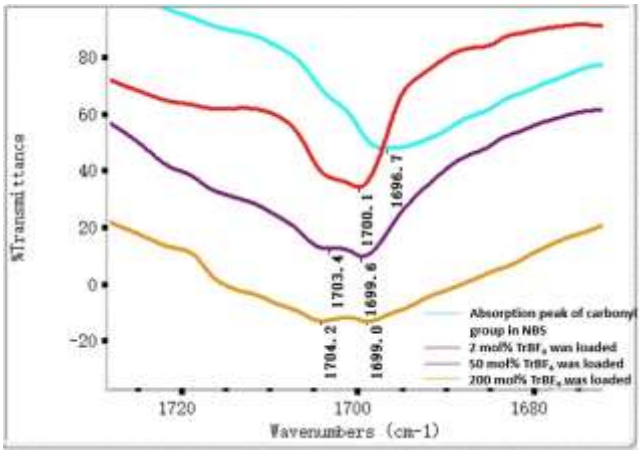


Figure 1. IR absorption of a) blue line: NBS (100%), b) red line: NBS/ $TRBF_4$ (50:1), c) purple line: NBS/ $TRBF_4$ (2:1), d) yellow line: NBS/ $TRBF_4$ (1:2).

Thus, the role of the trityl ion in the electrophilic aromatic substitution is rather straightforward and is believed to involve Lewis acid activation of NBS making it a more potent electrophile (Figure 2). It should also be mentioned that no adduct formation between the NBS derived byproduct succinimide and the trity ion was observed under the benzylic sp^3 or aromatic sp^2 C-H functionalization reaction conditions, despite the nucleophilic potential of succinimid.

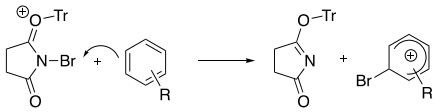
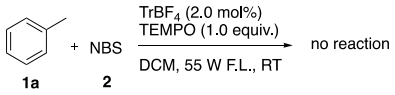


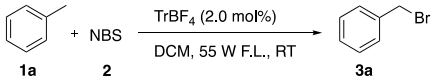
Figure 2. Trityl ion catalyzed EAS process.

On the other hand, the benzylic bromination (Wohl–Ziegler reaction) involves a radical chain reaction that usually requires a radical initiator (AIBN) or UV-light to generate atomic bromine. In this case the exact role of the trityl ion catalyst is not obvious. As previously shown, essentially no background reaction occurs in the absence of catalyst (Table 1, entry 1). Furthermore, no reaction occurs in the absence of daylight (Table 1, entry 4) or in the present of a radical inhibitor, which supports a radical chain reaction (Scheme 4).



Scheme 4. Radical quenching control experiment.

The time course of the trityl ion catalyzed benzylic bromination of toluene shows a relatively slow initial conversion of NBS to succinimide. After 4 h and approximately 40 % conversion of NBS, an increase in reaction rate was observed to give full conversion after 6 h (Figure 3). Such a pronounced induction period is characteristic for a free radical reaction.



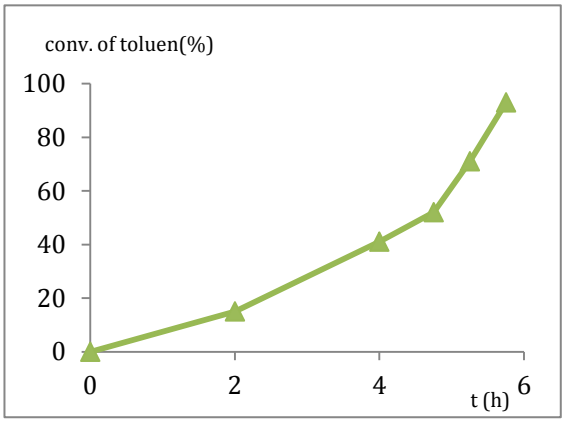


Figure 3. Reaction profile for the trityl ion catalyzed benzylic bromination of toluene with NBS. Reaction conditions: $TrBF_4$ (2.0 mol%, 0.25 M in DCM) was added to a solution of toluene **1a** (1.0 equiv.) and NBS (1.0 equiv.) in DCM (0.3 M) and irradiated by 55 W F.L.

Based on the fact that both the trityl ion and light is needed for the radical benzylic bromination to proceed, it could be suggested that the role of the trityl ion is to assist in the generation of bromine from HBr and NBS by further activation of NBS towards nucleophilic attack of bromide (Figure 4).[14]

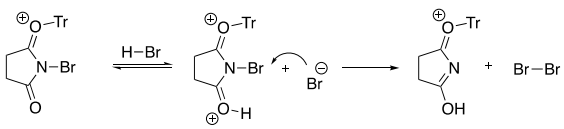


Figure 4. Proposed trityl ion catalyzed bromine formation.

Conclusion

In conclusion, we have developed a photo-induced trityl ion catalyzed benzylic bromination that operates under mild reaction conditions with low catalyst loading avoiding the use of toxic radical initiators. This protocol is applicable both on electron-deficient and electron-rich alkyl-arenes to give α-bromoalkyl arenes in good to excellent yields without any traces of over-oxidation to dibrominated compounds. In addition, for activated and weakly activated arenes we show that the trityl ion is an efficient Lewis acid catalyst for activation of NBS towards electrophilic aromatic substitution. This allowed for the development of a chemoselective switch between benzylic sp^3 C-H functionalization and arene sp^2 C-H functionalization by simply changing the solvent of the reaction

Experimental Section

General: All reactions are preformed in pre-dried solvents under nitrogen atmosphere. TrBF4 was dissolved in DCM (0.25 M) and used as a stock solution (for further details see supporting information).

General procedure for the preparation of benzyl bromides 3: Synthesis of 1-(Bromomethyl)naphthalene 3o. $TrBF_4$ (24 µl, $[TrBF4]_{DCM}$ = 0.25 M) was added to a solution of 1-methyl naphthalene **1o** (64.0 mg, 0.45 mmol) and *N*-bromosuccinimide **2** (53.4 mg, 0.30 mmol) in benzene (1.0 ml). The resulting mixture was exposed to standard hood fluorescent light (55 W F.L.) and stirred until full conversion of **2** was observed (determined by ^{1}H NMR on the crude reaction mixture). The reaction was quenched by adding a drop of water. The solvent was removed under vacuum and the residue was purified by flash chromatography to give 1-(bromomethyl)naphthalene **3o** as a colorless oil (53.7 mg, 81%). Spectral data were in accordance with those previously reported.[15]

General procedure for the preparation of aryl bromides 5: Synthesis of 1-Bromo-4-methylnaphthalene 5o. $TrBF_4$ (24 µl, $[TrBF4]_{DCM}$ = 0.25 M) was added to a solution of 1-methyl naphthalene **1o** (51.2 mg, 0.36 mmol) and *N*-bromosuccinimide **2** (53.4 mg, 0.30 mmol) in CH_3CN (1.0 ml). The resulting mixture was stirred until full conversion of **2** was observed (determined by ^{1}H NMR on the crude reaction mixture). The reaction was quenched by adding a drop of water. The solvent was removed under vacuum and the residue was purified by flash chromatography to give 1-Bromo-4-methylnaphthalene **5o** as a colorless oil (61.0 mg, 92%). Spectral data were in accordance with those previously reported.[16]

One-pot synthesis of N-(benzyl)succinimide 4: $TrBF_4$ (2 mol%, 24 µl, $[TrBF_4]_{DCM}$ = 0.25 M) was added to a solution of toluene **1a** (48 µL, 0.45 mmol) and *N*-bromosuccinimide **2** (53.4 mg, 0.30 mmol) in DCM (1 ml). The reaction was stirred at RT for 6 h before the solvent was removed under vacuum. The crude mixture was redissolved in CH_3CN (1 ml) and K_2CO_3 (82.9 mg, 0.6 mmol) was added. The resulting mixture was heated at 80 °C for 24 h. The residue was purified by flash chromatography (PE/EA = 1/1) to give *N*-(benzyl)succinimide **4** as a white solid (51 mg, 90%). Spectral data were in accordance with those previously reported.[17]

One-pot synthesis of 1-bromo-4-(bromomethyl)naphthalene 3d: $TrBF_4$ (2 mol%, 24 µl, $[TrBF_4]_{DCM}$ = 0.25 M) was added to 1-methylnaphthalene **1o** (99.5 mg, 0.45 mmol) and *N*-bromosuccinimide **2** (53.4 mg, 0.90 mmol) in CH_3CN (1 ml). The reaction was stirred for 2 h before the solvent was removed under vacuum. The crude mixture was redissolved in benzene (1 ml) stirred at RT for an additional 16 h. One drop of water was added to quench the reaction. The residue was purified by flash chromatography to afford **3d** as a white solid (75.6 mg, 84%). Spectral data were in accordance with those previously reported.[18]

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