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Lewis Acid Catalyzed Benzylic Bromination

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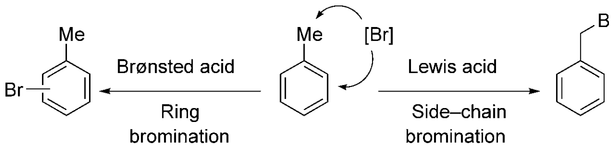
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: The Lewis acid catalyzed bromination of aromatic side chains was achieved efficiently by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromination reagent under mild conditions. Zirconium(IV) chloride showed the highest catalytic activity for this benzylic bromination. It was revealed that the present Lewis acid catalysis proceeds by the radical-generation pathway. In contrast, Brønsted acids promoted aromatic-ring bromination without any benzylic bromination. Monobromination of tetramethylsilane was also demonstrated with zirconium(IV) chloride and DBDMH to provide the desired product in good yield.

Keywords: bromination · Brønsted acids · Lewis acids · radicals · Wohl–Ziegler reaction

Introduction

The bromination of aromatic compounds is a highly useful transformation because the brominated products are widely used in the fields of synthetic organic chemistry and materials science. In particular, recent progress in transition-metal-catalyzed cross-coupling reactions has extended the utility of bromoarenes and benzylic bromides. Although *N*-bromoimides are widely used for both benzylic bromination and electrophilic aromatic-ring bromination, harsh reaction conditions or electron-rich substrates are usually required.[1,2] For example, Wohl–Ziegler bromination, which is one of the most popular methods of obtaining α-brominated alkyl arenes, is usually performed with *N*-bromosuccinimide (NBS) in the presence of a radical initiator at high temperature. Surprisingly little attention has been given to investigating this reaction at lower temperatures.[1] Recently, we reported that zirconium(IV) chloride catalyzes aromatic-ring bromination quite efficiently with NBS as an electrophilic bromination reagent.[1c] In that paper, we also mentioned that the $ZrCl_4$/NBS system promotes Wohl–Ziegler type benzylic bromination of toluene derivatives without bromination on the aromatic ring. Herein, we report an even more efficient Lewis acid catalyzed benzylic bromination under mild conditions, in contrast to Brønsted acid catalyzed aromatic-ring bromination [Eq. (1)].



(1)

Results and Discussion

In the course of our previous studies on Lewis acid catalyzed electrophilic halogenation, we found that zirconium(IV) chloride catalyzes the benzylic bromination of toluene with NBS at room temperature to provide benzylbromide.[1c] Further optimization of the reaction conditions revealed that the use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromination reagent increased the reaction rate dramatically to afford benzylbromide exclusively (Table 1, entries 1–3). Some other metal halides also catalyzed the benzylic bromination selectively (Table 1, entries 4–8). In marked contrast to Lewis acid catalysis, the use of Brønsted acids promoted the ring bromination of toluene to provide a mixture of *o*- and *p*-bromotoluene in excellent yield without the generation of benzylbromide. The

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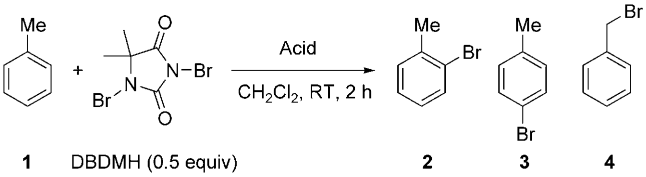
Table 1. Acid-catalyzed bromination of toluene.[a]



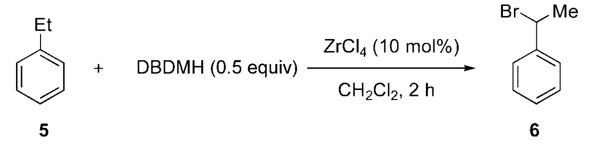
Entry	Acid ([mol %])	Yield [%][b]		
		2	3	4
1	none	0	0	0
2[d]	$ZrCl_4$ (10)	0	0	39
3	$ZrCl_4$ (10)	0	0	86
4	$Zr(O\textit{i}Pr)_4{\cdot}H_2O$ (10)	0	0	32
5	$TiCl_4$ (10)	2	2	71
6	$AlCl_3$ (10)	5	4	70
7	Tf_2NAlCl_2 (10)	1	1	76
8	Cy_2BCl (10)	0	0	71
9	TfOH (50)	49	45	0
10	Tf_2NH (50)	48	46	0
11	$(C_4F_9SO_2)_2NH$ (50)	44	42	0

[a] Reactions were carried out in dichloromethane at room temperature for 2 h with 0.5 equivalent of DBDMH under ambient light unless otherwise noted. [b] Yields determined by GC analysis. [d] 1.0 equivalent of NBS was used instead of DBDMH. Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

use of trifluoromethanesulfonic acid and perfluorinated alkanesulfonimides showed almost the same reactivity and selectivity (Table 1, entries 9–11).

We assume that this sharp contrast between Lewis and Brønsted acid catalysis can be explained by differences in the reaction pathways. Thus, Lewis acids would assist the generation of benzyl radical[3] from DBDMH to promote a Wohl–Ziegler benzylic bromination, whereas Brønsted acids would activate DBDMH by protonation[4] to accelerate Friedel–Crafts type electrophilic ring bromination. To ensure a radical pathway in the course of Lewis acid catalysis, the effect of light was investigated (Table 2). Zirconium(IV) chloride catalyzed the bromination of ethylbenzene under ambient light to afford (1-bromomethyl)benzene (**6**) in 98 % yield (Table 2, entry 1), but the reaction did not proceed in the dark (Table 2, entry 2). Furthermore, irradiation by green laser[5] dramatically accelerated the reaction to afford the desired product even at −78 °C (Table 2, entry 4). These results clearly show that this reaction involves the generation of radical species.

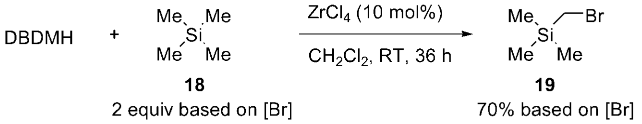
Table 2. Effect of light for benzylic bromination of ethylbenzene.



Conditions	T [°C]	Yield [%]
Ambient light	RT	98
Dark	RT	<5
Ambient light	−78	<5
Green laser	−78	63

Next, the general scope of the reaction was probed by application to a series of alkylated aromatic compounds with zirconium(IV) chloride or trifluoromethanesulfonimide. The results are presented in Table 3. In all examples except for reactions with an electron-rich substrate, Lewis acid catalysis produced benzylic bromination, whereas Brønsted acid catalysis produced ring bromination specifically. In contrast, when the reactions were carried out with electron-rich aromatic substrates, Lewis acid catalysis afforded ring-brominated products as well (Table 3, entries 6–9). Benzylic chlorination of ethylbenzene was performed by using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as a chlorination reagent to afford (1-chloroethyl)benzene (**7**) in good yield (Table 3, entry 2). Substrate **16**, which contains pinacolborate, also underwent benzylic bromination by Lewis acid catalysis to provide the desired benzyl bromide derivative **17** (Table 3, entry 10), whereas the use of Brønsted acid gave a complicated mixture.

Finally, our method was applied to the α bromination of silane.[6] The treatment of tetramethylsilane (**18**) with DBDMH in the presence of 10 mol % of zirconium(IV) chloride successfully afforded bromomethyltrimethylsilane (**19**) in 70 % yield (Scheme 1).



Scheme 1. Lewis acid catalyzed radical bromination of tetramethylsilane.

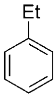
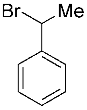
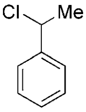
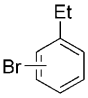
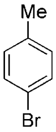
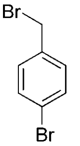
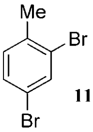
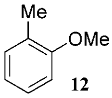
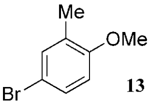
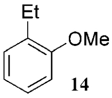
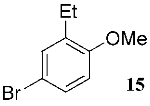
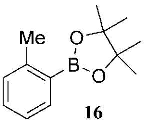
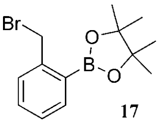
Abstract in Japanese:

ルイス酸触媒を用いたベンジル位臭素化反応が 1,3-ジブロモ-5,5-ジメチルヒダントインを臭素化剤として効率的に達成された。ルイス酸触媒としては塩化ジルコニウムが最も高い活性を示した。本ルイス酸触媒系にはラジカル中間体の生成が関与していることが示唆された。対照的に，ブレンステッド酸触媒を用いたときには芳香環上の臭素化のみが進行した。本ルイス酸触媒系を用いたテトラメチルシランのモノブロモ化もまた円滑に進行した。

Conclusions

We have disclosed the highly effective Lewis acid catalyzed side-chain bromination of aromatic compounds with DBDMH as a bromination reagent. In particular, the use of zirconium(IV) chloride catalyst showed excellent catalytic activity to provide various benzyl bromide derivatives. In contrast to Lewis acid catalysis, Brønsted acid promoted aromatic-ring bromination without any benzylic bromination. Monobromination of tetramethylsilane was also demonstrated with zirconium(IV) chloride and DBDMH. The present

Table 3. Acid-catalyzed halogenation of aromatic compounds.[a]

Entry	Substrate	Acid ([mol %])	t [h]	Product	Yield [%]
1	 **5**	$ZrCl_4$ (10)	2	 **6**	98[b]
2[c]		$ZrCl_4$ (10)	24	 **7**	76[b]
3		Tf_2NH (50)	4	 **8**	93[b] (o/p=1:1.3)
4	 **9**	$ZrCl_4$ (10)	6	 **10**	89[d]
5		Tf_2NH (50)	10	 **11**	45[d]
6	 **12**	$ZrCl_4$ (10)	1	 **13**	99[b]
7		Tf_2NH (50)	1.5		95[b]
8	 **14**	$ZrCl_4$ (10)	1	 **15**	95[d]
9		Tf_2NH (50)	1		90[d]
10	 **16**	$ZrCl_4$ (10)	6	 **17**	84[d]

[a] Reactions were carried out in dichloromethane at room temperature with 0.5 equivalent of DBDMH unless otherwise noted. [b] Yield determined by ^{1}H NMR spectroscopy. [c] 0.5 equivalent of DCDMH was used instead of DBDMH. [d] Yield of isolated product.

bromination system could thus be one of the most powerful methods for Wohl–Ziegler type radical bromination under mild reaction conditions, and it could be a more atom-economical process than that with NBS.

Experimental Section

General

All reactions were carried out in flame-dried glassware under argon atmosphere and stirred by magnetic stirrer bars. Flash column chromatography for the isolation of products was performed according to the method of Still with silica gel 60 (230–400 mesh) supplied by E. Merck. All reactions were carried out with anhydrous dichloromethane, which was dried with an M BRAUN solvent-purification system (A2 Alumina). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm (tetramethylsilane: $\delta = 0.00$ ppm for ^{1}H; residual chloroform: $\delta = 77.0$ ppm for ^{13}C).

Materials

All starting compounds were purchased from Aldrich or Boron Molecular, Inc. and used without further purification. All acid catalysts were purchased from Aldrich or Strem and also used without further purification. Zirconium(IV) chloride, aluminum(III) chloride, and bistrifluoromethanesulfonimide were handled in a glove box. All products were characterized by the comparison of their ^{1}H NMR spectra with those of commercially available authentic samples. The green laser pointer (wavelength 532 nm, max output power <5 mW) used in Table 2 was purchased from Leadlight Technology, Inc.

Syntheses

Typical procedure for Tables 1 and 3: A solution of toluene (**1**; 0.5 mmol) and DBDMH (0.25 mmol) in dichloromethane (2 mL) was added to a suspension of zirconium(IV) chloride (0.05 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred for 2 h at room temperature under ambient light. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with diethyl ether. The organic layer was subjected to GC analysis with 1,2-dichlorobenzene as an internal standard. The yield of benzylbromide (**4**) was determined to be 86%.

17: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.0 Hz, 1H), 7.42–7.37 (m, 2H), 7.30–7.26 (m, 1H), 4.92 (s, 2H), 1.37 ppm (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.2, 136.4, 131.3, 130.4, 127.6, 83.8, 33.9, 24.8 ppm.

Reaction procedure for Table 2: Reactions were carried out with ethylbenzene (**5**; 0.5 mmol) as substrate by a procedure similar to that used for Table 1. Yields of (1-bromoethyl)benzene (**6**) were determined by ^{1}H NMR spectroscopic analysis of the crude mixture. The reaction vessel was covered with aluminum foil when the reaction was carried out in the dark. A laser pointer was placed on the top of the reaction vessel, and the entire piece of equipment was covered with aluminum foil when the reaction was carried out under irradiation with green laser.

Reaction procedure for Scheme 1: Tetramethylsilane (**18**; 4 mmol) and DBDMH (1 mmol) were added to a suspension of zirconium(IV) chloride (0.1 mmol) in dichloromethane (4 mL) at room temperature. The mixture was stirred for 36 h at room temperature under ambient light. The yield of bromomethyltrimethylsilane (**19**) was determined by ^{1}H NMR spectroscopic analysis of the reaction mixture to be 70% (1.4 mmol, based on $^1/_2$ DBDMH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 2H), 0.14 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.2, −2.5 ppm.

Acknowledgements

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[1] Selected recent examples for benzylic halogenation with *N*-haloimide: a) H. Togo, T. Hirai, *Synlett* **2003**, 702–704; b) T. Yamane, H. Mitsudera, T. Shundoh, *Tetrahedron Lett.* **2004**, *45*, 69–73; c) Y. Zhang, K. Shibatomi, H. Yamamoto, *Synlett* **2005**, 2837–2842; d) A. Podgorsek, S. Stavber, M. Zupan, J. Iskra, *Tetrahedron Lett.* **2006**, *47*, 1097–1099; e) G. A. Heropoulos, G. Cravotto, C. G. Screttas, B. R. Steele, *Tetrahedron Lett.* **2007**, *48*, 3247–3250, and references therein.

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[3] Otera, Fukuzumi, and co-workers reported that the Mukaiyama–Michael reaction is initiated by one-electron transfer from silyl ketene acetal to Lewis acid. A similar electron transfer might occur in our reaction to generate zirconium radical as an important intermediate; see: J. Otera, Y. Fujita, N. Sakuta, M. Fujita, S. Fukuzumi, *J. Org. Chem.* **1996**, *61*, 2951–2962.

[4] Prakash and Olah showed that ground-state destabilization by the multiple protonation of *N*-haloimide is the driving force for electrophilic ring halogenation from DFT calculations; see reference [2a].

[5] A commercially available green laser pointer was used for irradiation; see Experimental Section.

[6] α Brominations of tetralkyl silanes, except for the benzylic or allylic position, reported so far: a) T. Fuchikami, I. Ojima, *J. Organomet. Chem.* **1981**, *212*, 145–153; b) Y. Terao, M. Aono, N. Imai, K. Achiwa, *Chem. Pharm. Bull.* **1987**, *35*, 1734–1740; c) J. S. Swenton, M. Plats, L. D. Venham, *J. Org. Chem.* **1988**, *53*, 2764–2768; d) S. Suga, K. Miyamoto, M. Watanabe, J.-I. Yoshida, *Appl. Organomet. Chem.* **1999**, *13*, 469–474; e) M. Shindo, Y. Sato, R. Koretsune, T. Yoshikawa, K. Matsumoto, K. Itoh, K. Shishido, *Chem. Pharm. Bull.* **2003**, *51*, 477–478.

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