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Benzylic bromination catalyzed by triphenylphosphine selenide via Lewis basic activation

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ABSTRACT

The synthesis of benzyl bromides was achieved under mild reaction conditions using *N*-bromosuccinimide as a bromine source and triphenylphosphine selenide as a catalyst. These conditions were compatible with a variety of substrates including boronic esters, protected amines to give imines, and carboxylic acids (to give phthalides when *ortho* to the benzylic center). A preliminary mechanistic investigation utilizing calculated bond dissociation energies (BDE) is employed to rationalize how a Lewis base can activate a radical mechanism.

Benzylic halides are synthetically useful intermediates in myriad organic processes. They are commonly used as protective groups for diverse functionalities,[1,2] and are key synthetic intermediates[3–5] towards countless pharmaceuticals and agrochemicals.[6,7] Historically, free radical syntheses of benzylic bromides are commonly achieved via the *Wohl-Ziegler* reaction using *N*-bromosuccinimide (NBS).[8] Although many variants have been reported, they often suffer from disadvantages such as harsh reaction conditions, a reliance on radical initiators, and often require prolonged reaction time and high temperatures.[9–12] Recently, Yamamoto has reported a Lewis acid catalyzed *Wohl-Ziegler* variant that utilizes 1,3-dibromo-5,5-dimethylhydantoin and catalytic $ZrCl_4$.[13] Herein we report a conceptually divergent and complimentary approach for the synthesis of benzyl bromides under mild conditions using a Lewis basic triphenylphosphine selenide catalyst to activate NBS and initiate radical bromination at room temperature.

Lewis bases have been frequently demonstrated by Denmark and others to increase the electrophilicity of halide sources.[14–16] Tunge and coworkers have used Lewis basic selenium catalysts to activate *N*-chlorosuccinimide towards formal allylic chlorination,[17] which proceeds through an electrophilic addition process. In previous studies from our group, we found that Lewis bases such as phosphine sulfides were efficient catalysts for electrophilic aromatic halogenation (S_EAr, Fig. 1, A).[18] Additionally, we found catalytic thioureas can act via a Lewis basic mechanism to control the regioselective halogenation of phenols[19] as well as

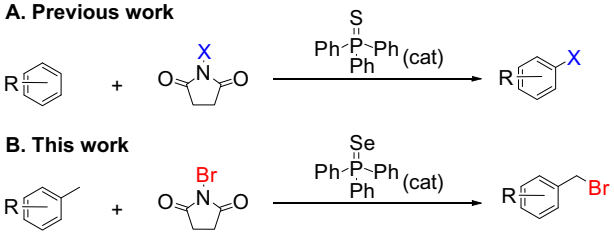

Fig. 1. Halogenations via Lewis base catalysts.

the sulfenylation of heterocycles.[20] During these studies, we occasionally observed minute amounts of benzylic halogenation on less electronically activated arenes. While studying the effect of catalyst structure on similar substrates such as toluene we observed exclusive benzylic bromination with phosphine selenides. Intrigued by this result we decided to further explore the scope and depth of this process.

To begin our investigation, we selected toluene **1a** as the model substrate using 10 mol% catalyst and 1.5 equivalents of NBS as a bromine source (Table 1). Conversions were measured by ^1H NMR in deuterated chloroform using tetramethylsilane as an internal standard. As our preliminary results suggested, catalytic triphenylphosphine selenide **2** led to rapid and exclusive benzylic bromination at room temperature (Table 1, entry 2). In contrast, triphenylphosphine sulfide **3** yielded minimal benzylic bromination (~5%) after 2 h (Table 1, entry 3). Thiourea **4**, which Mukherjee has found to catalyze the oxidation of secondary alcohols in the presence of NBS, [21]possibly in a mechanism similar to the

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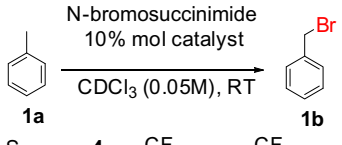
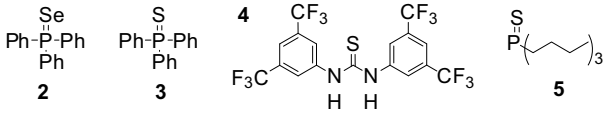
Table 1
Lewis base catalyst screen.[a]





Entry	Catalyst	Mol%	Conversion (%)[b]
1	None	0	0
2	Se = PPh_3 **2**	10	89
3	S = PPh_3 **3**	10	5
4	Catalyst **4**	10	4
5	S = P(*n*-Bu)$_3$ **5**	10	29

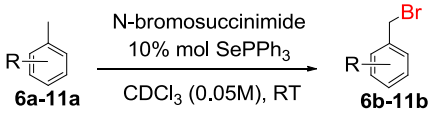
[a] Reactions were performed at room temperature on a 0.03 mmol substrate with 10% mol of catalyst and 600 μL of $CDCl_3$ washed with basic alumina in an NMR tube, followed by addition of 4.5 mmol NBS.
[b] Conversions were determined by ^{1}H NMR with TMS as internal standard

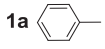
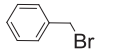
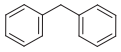
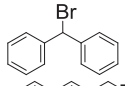
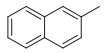
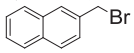
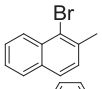
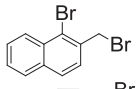
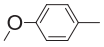
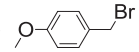
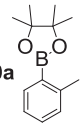
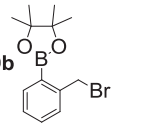
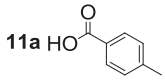
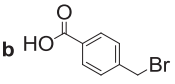
chemistry reported here, also yielded minimal benzylic bromination (Table 1, entry 4). Finally, it should be noted that more electron rich sulfide catalysts such as **5** yielded a significant amount of benzylic bromination (29%), yet still trailed far behind selenides. While this reactivity trend would be expected to transfer to selenides, we felt the commercial availability of **2** represented a major advantage over other potential catalysts that would need to be synthesized and thus chose to further characterize **2** for this study.

We next examined **2** across a range of substrates using the same conditions in Table 2 with varying NBS amounts when necessary. In the absence of catalyst, little to no reaction was observed in each case, however **2** led to rapid and clean benzylic bromination. For example, we obtained comparable results for the benzylic bromination of diphenylmethane and different methyl containing naphthalenes observing conversions to **6b** in 80% conversion, **7b** in 73% conversion and **8b** in 90% conversion (Table 2, entries 2–4). We found that *p*-methoxy methyl benzene **9a** also undergoes primarily benzylic bromination, yielding 53% conversion of *p*-methoxy benzyl bromide **9b**; the lower conversion is attributed to a small amount (~8%) of S_EAr (Table 2, entry 5). Finally, we evaluated **10a** which possesses a Lewis acidic boron pinacol ester that could in theory hinder the catalyst via adduct formation, however this concern proved unfounded as we observed clean benzylic bromination to yield **10b** in 83% conversion (Table 2, entry 6) in deuterated acetone. To test the scalability of this chemistry we brominated **10a** on an intermediate preparative scale and isolated **10b** in 69% yield. These results are comparable to those reported by Yamamoto using a completely different and comparable manifold of activation. Finally, although substrate **11a** contains a Brønsted acidic functional group, we found bromination of carboxylic acids can also be achieved, converting **11a** to **11b** in 44% isolated yield (Table 2, entry 7). We also ran this substrate on a larger scale and found in this case the isolated yields outperformed the observed NMR conversion.

We next utilized these conditions on substrates that possessed a functionality that could further react with the introduced bromide. For example, we found that substrates containing a carboxylic acid *ortho* to the benzylic center (**12a–14a**) yielded the corresponding phthalide lactone in good conversion and isolated yield (Table 3, entries 1–3). These lactones are most likely formed through an intramolecular S_N2 on a benzylically brominated intermediate. This hypothesis is supported by **12a** and **13a** (Table 3, entry 1–2) in which the benzylically brominated intermediate is

Table 2
Benzylic bromide synthesis.[a]



Entry	Substrate	Eq NBS	Conversion (%)[b]		Time (h)	Product
			Catalyst	No Catalyst		
1	**1a** 	2.0	89	2	2.0	**1b** 
2	**6a** 	2.0	80	2.5	2.0	**6b** 
3	**7a** 	1.8	73	0	5.0	**7b** 
4	**8a** 	2.0	90	0	2.0	**8b** 
5	**9a** 	1.4	53	10	3.0	**9b** 
6	**10a** 	3.0	83(69)[c]	0	2.0	**10b** 
7	**11a** 	2.0	44(67)[c]	0	2.0	**11b** 

[a] Reactions were performed at room temperature on a 0.03 mmol substrate with 10% mol of **2**, and 600 μL of $CDCl_3$ or $(CD_3)_2CO$ washed with basic alumina into an NMR tube, followed by addition of NBS.
[b] Conversions were determined by ^{1}H NMR with TMS as an internal standard.
[c] Parenthesis indicate isolated yield on 50mg scale.