Hydrogen-Atom Donors

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Catechols as Sources of Hydrogen Atoms in Radical Deiodination and Related Reactions

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Abstract: *When used with trialkylboranes, catechol derivatives, which are low-cost and low toxicity, are valuable hydrogen atom donors for radical chain reactions involving alkyl iodides and related radical precursors. The system 4-tert-butylcatechol/triethylborane has been used to reduce a series of secondary and tertiary iodides, a xanthate, and a thiohydroxamate ester. Catechol derivatives are right in the optimal kinetic window for synthetic applications, as demonstrated by highly efficient radical cyclizations. Cyclizations leading to the formation of quaternary centers can be performed in an all-at-once process (no slow addition of the hydrogen atom donor) at standard concentrations. The H-donor properties of catechol derivatives can be fine-tuned by changing their substitution pattern. In slow radical cyclization processes, an enhanced ratio of cyclized/uncyclized products was obtained by using 3-methoxycatechol instead of 4-tert-butylcatechol.*

Radical reactions are becoming an increasingly attractive tool in synthetic organic chemistry, and more particularly in the synthesis of densely functionalized compounds like natural products and biologically relevant molecules.[1] Among all radical reactions, processes involving a final hydrogen atom transfer from a triorganotin hydride have played a unique role in their development towards synthetic applications.[2] Owing to the toxicity of these tin reagents, several alternatives based on molecules possessing a weakly bound hydrogen atom, for example, Si–H,[3] Ge–H,[4] C–H,[5] S–H,[6] B–H,[7] P–H,[8] or O–H,[9] have been developed with variable success depending on the applications.[10] These reagents do not, however, outperform tin hydride in terms of simplicity of use, synthetic efficacy, or price.

A crucial point in the development of good alternatives to tin hydride for a wide range of applications such as simple dehalogenation and cyclization reactions, is to design a hydrogen donor (H-donor) with the right ability to transfer a hydrogen atom. An overview of the rate constants for the hydrogen atom transfer to primary alkyl radicals from various reagents at 25 °C is given in Figure 1. An ideal value for most synthetic applications would be slightly below that of Bu_3SnH ($k_H = 2.7 \times 10^6\,M^{-1}s^{-1}$ at 30 °C),[11] that is, between 1×10^5 and $5 \times 10^6\,M^{-1}s^{-1}$, to ensure an efficient chain process and to provide a sufficient lifetime for the radical to be involved in radical rearrangements before the hydrogen atom is delivered. Among all the possible sources of hydrogen atoms, only a few of them are close to these optimal values (Figure 1, gray region).

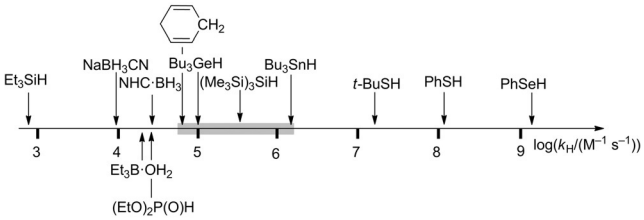

Figure 1. Rate constants for the hydrogen transfer between various hydrogen atom donors and a primary alkyl radical.

Reagents based on O–H hydrogen donors such as alcohols and water are particularly attractive owing to their availability, low toxicity, and low price, but they need to be activated to become hydrogen atom donors. Upon complexation with a boron Lewis acid such as trimethyl- and triethylborane[12] the O–H bonds of water and alcohols is considerably weakened,[13] and such complexes have been used in radical-mediated deoxygenation and deiodination reactions.[12a,b,14] However, this approach gives rise to H-donors that are about two orders of magnitude less potent than tin hydride derivatives.[15] We have reported that catechols can be used as a source of hydrogen atoms in radical reactions involving organoborane radical precursors.[16] For instance, a mild procedure for the protonolysis of organoboranes has been developed based on a highly efficient radical chain process.[16a] Interestingly, catechols are excellent H-donors for alkyl radicals with rate constants in the desired range (gray region in Figure 1). Herein, we report that catechols, in the presence of organoboranes, are becoming a highly attractive source of hydrogen atoms for a variety of transformations such as deiodination, decarboxylation, and deoxygenation reactions.

N-tosyl-4-iodopiperidine **1a** was used as a model substrate to find optimal reaction conditions and 4-*tert*-butylcatechol (TBC) was chosen for its commercial availability, low price, solubility in organic solvents, and excellent H-donor properties. The use of 1.0 equiv of TBC and 1.3 equiv of triethylborane (BEt_3) gave the best results. The reaction proceeded equally well in various apolar solvents (hexane, benzene, toluene, 1,2-dichloroethane, or dichloromethane), whereas the use of the hydrogen bond acceptor solvents Et_2O, EtOAc, or *t*-BuOMe led to lower conversions of the iodide, which is

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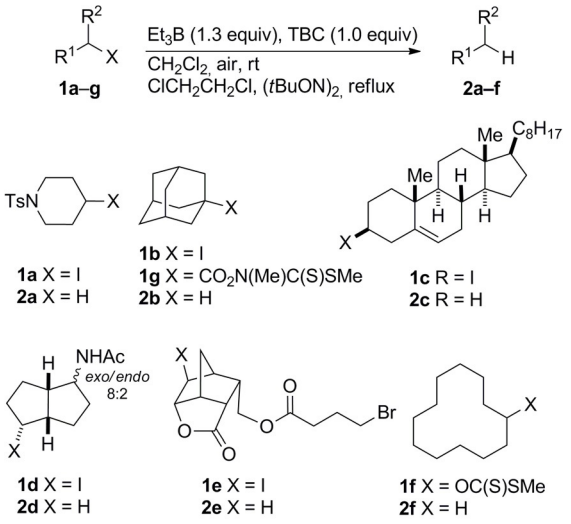
presumably due to a less efficient chain process resulting from the lower rate of hydrogen atom transfer in such solvents.[17] In dichloromethane at room temperature, the reaction afforded the deiodinated product **2a** in 88% yield (Table 1, entry 1). Under these conditions, the reduction of adamantyl iodide **1b** proceeded efficiently, yielding adamantane **2b** in 95% yield (GC) after 6 hours (Table 1, entry 2). A similar result was obtained after only three hours when the reaction was performed at 80°C in 1,2-dichloroethane using di-*tert*-butyl hyponitrite as an initiator (Table 1, entry 3). Cholesteryl iodide **1c** proved to be more defiant, as complete conversion could never be achieved (Table 1, entries 4 and 5). Nevertheless, on a 40 mmol scale, cholest-5-ene **2c** could be obtained in 71% yield after recrystallization (Table 1, entry 6). Secondary iodides **1d** and **1e** were also efficiently deiodinated (Table 1, entries 7 and 8). Remarkably, the iodobromoderivative **1e** was selectively deiodinated in 87% yield. Under the same reaction conditions (room temperature), the deoxygenation of cyclododecyl xanthate **1f** yielded the expected cyclododecane **2f** in 64% yield (Table 1, entry 9). Using di-*tert*-butyl hyponitrite as an initiator in refluxing 1,2-dichloroethane, xanthate **1f** was entirely consumed after 5 hours, providing **2f** in high yield (Table 1, entry 11). The reductive decarboxylation of the adamantyl thiohydroxamate ester **1g**,[18] furnished the corresponding rearranged thioester and adamantane **2b** in circa 1:1 ratio at room temperature. As for xanthate **1f**, increasing the temperature to 80°C dramatically enhanced the formation of adamantane **2b** to 93% (Table 1, entry 11). It is worth mentioning that initiation with air proved to be less efficient than with di-*tert*-butyl hyponitrite in all of the reactions conducted in refluxing 1,2-dichloroethane.

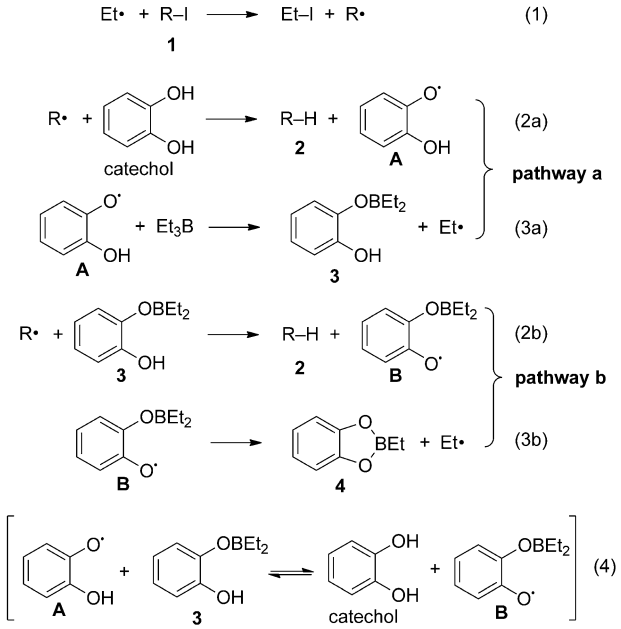
The ^{11}B NMR spectrum of BEt_3 (0.3 M) in a degassed 1.0 M solution of TBC in C_6D_6 displays an identical chemical shift ($\delta = 86.9$ ppm) as in a solution of only C_6D_6 ($\Delta\delta < 0.05$ ppm). Reciprocally, the ^1H NMR spectrum of TBC is not affected by the presence of BEt_3, ruling out any significant complex formation that would enhance the H-donor ability of TBC.[12b,15c] Therefore, we believe that a mechanism closely related to that reported for the protonolysis of organoboranes is operating for this reaction[16a] as depicted in Scheme 1. The

Table 1: Deiodination, deoxygenation, and decarboxylation reactions.



Entry	Substrate	Product	Temp.[a]	Time [h]	Yield of **2** [%][b]
1	**1a**	**2a**	rt	10	88
2	**1b**	**2b**	rt	6	95[c]
3	**1b**	**2b**	83 °C	3	96[c]
4	**1c**	**2c**	rt	10	76
5	**1c**	**2c**	83 °C	4	58
6	**1c**	**2c**	rt[d]	30	71
7	**1d**	**2d**	rt	10	74
8	**1e**	**2e**	rt	5	87
9	**1f**	**2f**	rt	12	64
10	**1f**	**2f**	83 °C	5	87[c,e]
11	**1g**	**2b**	83 °C	4	93[c]

[a] Conditions: Et_3B (1.3 equiv), TBC (1.0 equiv), 0.3 M, in CH_2Cl_2 open to air at rt or in refluxing 1,2-dichloroethane (83 °C) using $(t\text{-BuON})_2$ (6 mol%) as an initiator. [b] Yields of isolated product unless otherwise mentioned. [c] Yields determined from GC. [d] 40 mmol scale. [e] Average yield over three runs.

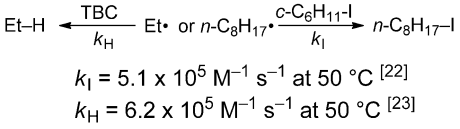


Scheme 1. Proposed mechanism for the deiodination process.

ethyl radical formed in the initiation step enters the chain process by abstracting an iodine atom to generate the desired alkyl radical [Eq. (1)]. Then, the alkyl radical abstracts a hydrogen atom from catechol to deliver the product **2** and the phenoxyl radical **A** [Eq. (2a)]. Reaction of the phenoxyl radical **A** with Et_3B affords the monoborinate ester **3** as well as an ethyl radical that can sustain the chain process [Eq. (2b)]. Interestingly, compound **3** may also act as H-donor in a second chain process (pathway b). Hydrogen transfer from **3** to the alkyl radical gives the product **2** and a new phenoxyl radical **B** [Eq. (2b)] that can undergo an intramolecular homolytic substitution to furnish *B*-ethylcatecholborane **4** and an ethyl radical that propagates further the chain process [Eq. (3b)]. Hydrogen atom exchange between phenoxy radicals is known to take place with high rates,[19] thus pathways **a** and **b** may be closely interlinked through

a rapid equilibrium between radicals **A** and **B** [Eq. (4)]. Preliminary investigations have shown that the monoborinate ester **3** is a better hydrogen atom donor than catechol towards alkyl radicals and it has been assumed that **3** was involved as a repair agent in a recently reported thiol–ene coupling process.[20,21]

The delicate part of the reaction arises from the use of an ethyl radical to sustain the chain since the direct reduction of the ethyl radical by TBC competes with the iodine atom transfer reaction. The rate constant for the iodine atom transfer process between a primary alkyl radical (1-octyl) and a secondary alkyl iodide has been reported by Newcomb to be $5.1 \times 10^5\,M^{-1}s^{-1}$ at 50 °C.[22] This rate constant is about half as large than the one we have reported for the reduction of secondary alkyl radical by 4-*tert*-butylcatechol at 80 °C ($k_H = 1.3 \times 10^6\,M^{-1}s^{-1}$)[16a] and very close to that reported by Villa for the reduction of a primary alkyl radical ($k_H = 6.2 \times 10^5\,M^{-1}s^{-1}$ at 50 °C).[23] As a consequence, at low concentrations of the starting alkyl iodide (near the end of the reaction), most of the ethyl radicals are converted into ethane (Scheme 2) and the

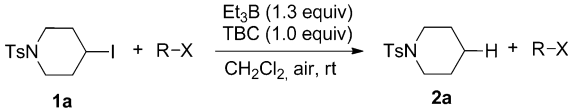


Scheme 2. Competition between iodine atom transfer and reduction for a primary alkyl radical chain carrier.

deiodination cannot reach completion.[24] The presence of the monoborinate ester **3**, possibly present in larger amount at the end of the reaction, may also favor the unproductive reduction of the ethyl radical. Likewise, competition between addition to the thiocarbonyl group and direct reduction of the ethyl radical may account for the limited conversion observed when reactions with xanthate **1f** or thiohydroxamate ester **1g** were conducted at room temperature.

To illustrate further the synthetic potential of the TBC/Et_3B system for deiodination reactions, the chemoselectivity of the reaction was investigated by running the deiodination of the secondary iodide **1a** in the presence of functionalized co-substrates known to be reactive under radical processes. The results are summarized in Table 2. The deiodination process of the secondary iodide **1a** is highly selective in the presence of benzyl azide (Table 2, entry 1) and phenyl iodide (Table 2, entry 2). In these two cases, the use of 1.3 equiv of BEt_3 did not lead to any significant consumption of the co-substrates R–X. The selective deiodination of the secondary iodide **1a** in the presence of a primary iodide (*n*-dodecyl iodide) was examined next and proved to be more challenging. When 0.9 equiv of Et_3B was used, consumption of the secondary iodide was four times larger than that of the *n*-dodecyl iodide and **2a** could be isolated in 72% yield. The ratio of consumed **1a** vs. *n*-dodecyl iodide could be increase to 7.4 when 0.5 equiv of BEt_3 was used. For comparison, in entry 4, a reaction with 1.0 equiv of Bu_3SnH lead to a 1.3:1 ratio of consumed secondary vs. primary iodide.

Table 2: Chemoselective deiodination reactions.



1a **2a**

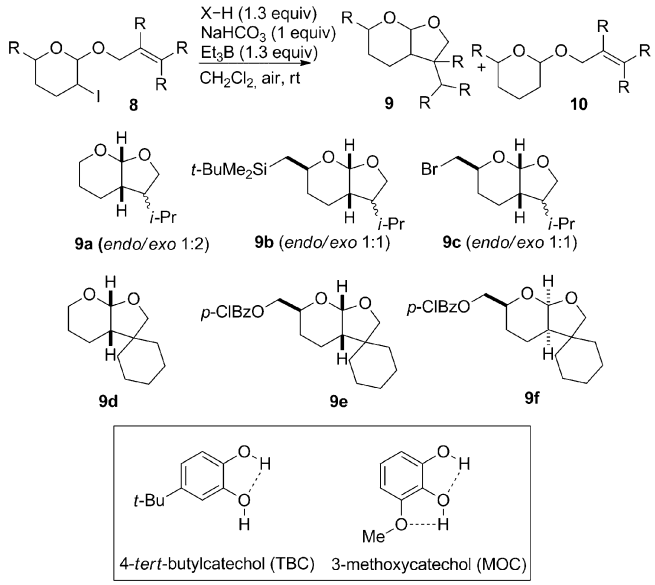
Entry	R–X	Reacted **1a**/R–X	Yield of **2a** [%][a,b]
1	$C_6H_5CH_2$–N_3	≥15	92 (97)
2	C_6H_5–I	≥100	82 (85)
2[c]	n-$C_{12}H_{25}$–I	4.0	72 (83)
3[d]	n-$C_{12}H_{25}$–I	7.4	55 (93)
4[e]	n-$C_{12}H_{25}$–I	1.3	54 (95)

[a] Yields of isolated product. [b] Yields in parenthesis are based on consumed **1a**. [c] Using 0.9 equiv BEt_3. [d] Using 0.5 equiv BEt_3. [e] Using Bu_3SnH (1.0 equiv) and azobisisobutyronitrile (AIBN; 0.2 equiv) in refluxing benzene.

To investigate the application of catechols in radical cyclization processes, the behavior of iodoacetals[25] was next examined. The results are summarized in Table 3. 2-(Alk-2-enyloxy)-3-iodopyran derivatives **8a–f** were prepared by iodoetherification reactions involving 2-*H*-dihydropyranes **5–7**, allylic alcohols and *N*-iodosuccinimide (NIS; see the Supporting Information). The 5-*exo-trig* cyclization of 3-oxahex-5-enyl radicals is known to be faster than the 5-hexenyl carbon analogues.[26] As expected, treatment the iodoacetal **8a** (0.3 M solution in dichloromethane) with 1.3 equiv of BEt_3 and 1 equiv of TBC at room temperature afforded exclusively the cyclized product **9a** in 82% yield.[27] The 2:1 *endo*/*exo* ratio is in accordance with previous reports involving this system.[28] Similarly, the silyl ether **8b** and the bromide **8c** yielded the *cis*-bicyclic products **9b** and **9d** in 82% and 71% yield under the same reaction conditions. Cyclizations involving the formation of quaternary carbon centers were investigated next with substrates **8d–f**. Under our standard reaction conditions (0.3 M in TBC), **8d** gave an 85:15 mixture of cyclized/non-cyclized products **9d**/**10d**. To optimize the formation of the cyclized product, other catechol derivatives were tested. Interestingly, 3-methoxycatechol enhanced the ratio of cyclized/uncyclized products **9d**/**10d** to 95:5 and pure **9d** was isolated in 88% yield. As a comparison, the reaction was also run with tributyltin hydride as a source of hydrogen atoms. Even when the reaction was run under dilute conditions (0.07 M), the reaction afforded a 45:55 mixture of **9d**/**10d,** and pure **9d** could only be isolated in 41% yield. Similar results were obtained with **8e** where radical cyclization was even slower than in the case of **8d**. By using 4-methoxycatechol, the cyclized product was the major product (**9e**/**10e** 75:25) and **9e** was isolated in 67% yield, whereas the tin hydride method (0.008 M) afforded mainly the non-cyclized product **10e** (**9e**/**10e** 23:77). Finally, **9f**, the minor diastereomer obtained during the iodoetherification leading to **9e**, was also examined. Only the bicyclic compound **9f** was obtained in 74% yield of isolated product when using 3-methoxycatechol as a source of hydrogen atom. The formation of a non-cyclized product of type **10** could not be observed in this reaction.

The improvement of the yield of the cyclized product **9d** and **9e** when using 3-methoxycatechol instead of 4-*tert*-

Table 3: Radical cyclization of iodoacetals **8a–f**.



Entry	Iodide	X–H	Product	**9**/**10**[a]	Yield of **9** [%][b]
1	**8a**	TBC (0.3 M)[c]	**9a**	≥95:5[d]	82
2	**8b**	TBC (0.3 M)[c]	**9b**	≥95:5[d]	82
3	**8c**	TBC (0.3 M)[c]	**9c**	≥95:5[d]	71
4	**8d**	TBC (0.3 M)[c]	**9d**	85:15	72
5	**8d**	MOC (0.2 M)[e]	**9d**	95:5	88
6	**8d**	Bu_3SnH (0.07 M)[f]	**9d**	45:55	41
7 g	**8e**	TBC (0.3 M)[c]	**9e**	60:40	n.d.
g[g]	**8e**	MOC (0.1 M)[e]	**9e**	75:25	67
9 g	**8e**	Bu_3SnH (0.008 M)[f]	**9e**	23:77	n.d.
1g[g]	**8f**	MOC (0.2 M)[e]	**9f**	≥95:5[d]	74

[a] Ratio determined by GC, assuming an equal response factor for the isomeric compounds **9** and **10**. [b] Yields of isolated product. [c] TBC (1 equiv, 0.3 M), $NaHCO_3$ (1 equiv), Et_3B (1.3 equiv), CH_2Cl_2, rt, air. [d] The monocyclic product **10** was not detected. [e] 3-Methoxycatechol (MOC; 1 equiv, 0.2 M), $NaHCO_3$ (1 equiv), Et_3B (1.3 equiv), CH_2Cl_2, rt, air. [f] Bu_3SnH (1.3 equiv), Et_3B (0.1 equiv), benzene, rt, air. [g] *p*-ClBz = *p*-chlorobenzoyl.

butylcatechol is in full agreement with the work of Villa, who reported that 3-methoxycatechol reduces primary alkyl radicals five times slower than 4-*tert*-butylcatechol.[23] This difference of reactivity can be rationalized by the fact that both hydrogen atoms of 3-methoxycatechol are involved in intramolecular hydrogen bonds,[29] whereas only one hydrogen is involved in hydrogen bonding for 4-*tert*-butylcatechol.[30]

In summary, we have demonstrated that simple catechol derivatives can be used with trialkylboranes as hydrogen atom donors for radical chain reactions. For instance, excellent results have been obtained with 4-*tert*-butylcatechol, a well-established antioxidant, stabilizer, and polymerization inhibitor for various alkenes.[31,32] These reagents are not only commercially available and cheap, but they possess also a very moderate toxicity.[33] Interestingly, the hydrogen atom donor properties of catechol derivatives are right in the optimal kinetic window for synthetic applications as demonstrated here by highly efficient radical cyclizations leading to the formation of quaternary centers. Finally, the H-donor properties of catechol derivatives can be fine-tuned by playing with the substitution pattern. This particular aspect of their chemistry has been demonstrated by using 3-methoxycatechol, a slower H-donor reagent than 4-*tert*-butylcatechol, to optimize slow radical cyclization processes.

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Keywords: catechols · cyclizations · hydrogen atom donors · phenols · radicals

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