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Hydroalkylation

3-*tert*-Butyl-Substituted Cyclohexa-1,4-dienes as Isobutane Equivalents in the $B(C_6F_5)_3$-Catalyzed Transfer Hydro-*tert*-Butylation of Alkenes

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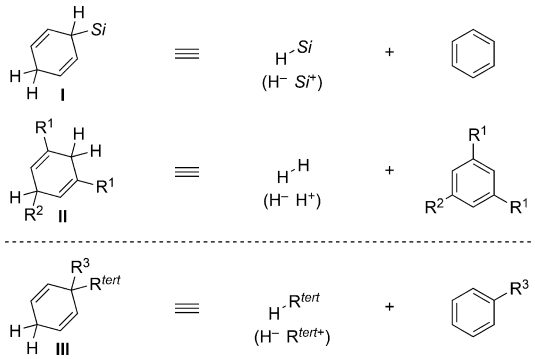
Abstract: Cyclohexa-1,4-dienes with a *tert*-butyl group at C3 are shown to function as isobutane equivalents when activated by the strong boron Lewis acid tris(pentafluorophenyl)borane. The hitherto unprecedented transfer hydro-*tert*-butylation from one unsaturated hydrocarbon to another is achieved with 1,1-diarylalkenes as substrates, thereby presenting itself as a new way of incorporating tertiary alkyl groups into carbon frameworks. Transient carbocation intermediates give rise to competing reaction pathways that could not be fully suppressed.

Our laboratory recently demonstrated that adequately substituted cyclohexa-1,4-dienes **I** and **II** serve as transfer reagents for hydrosilanes[1] and dihydrogen,[2] respectively (Scheme 1, top). The approach hinges on the ability of the strong Lewis acid tris(pentafluorophenyl)borane, $B(C_6F_5)_3$,[3] to abstract a hydride from the bisallylic methylene group of these surrogates,[1e,2b] forming Wheland intermediates either stabilized by a silyl group (for **I**) or alkyl substituents (for **II**) along with borohydride $[HB(C_6F_5)_3]^-$ (not shown).[1e,2b] These eventually release arenes, thereby enabling the (formal) transfer of hydrosilanes or dihydrogen to C=C/C≡C[1b–d,2b] as well as C=O/C=N[1c,2a] groups.

As part of this research program, we entertained the idea of applying the above strategy to the transfer of hydrocarbons, and surrogates **III** containing tertiary electrofuges R^{tert} seemed particularly promising candidates (Scheme 1, bottom). We expected **III** to require additional substitution in the *ipso* position to avoid competing proton release. Our plan was to realize the hydro-*tert*-alkylation of alkenes, examples of which are exceedingly rare.[4,5] The reaction will involve carbocations at the different stages of transfer process and is as such closely related to the difficult Friedel–Crafts-type alkylation of alkenes.[6]

With the *tert*-butyl group as the archetypical tertiary electrofuge, we began to explore the transfer hydro-*tert*-butylation of 1,1-disubstituted alkenes catalyzed by $B(C_6F_5)_3$. We envisaged



Scheme 1. Substituted cyclohexa-1,4-dienes as synthetic equivalents for hydrosilanes and dihydrogen (verified) and hydrocarbons (planned). *Si* = $R_nH_{3-n}Si$ (n = 0–3, R = aryl and/or alkyl). R^1/R^2 = H or Me. R^3 = aryl or alkyl.

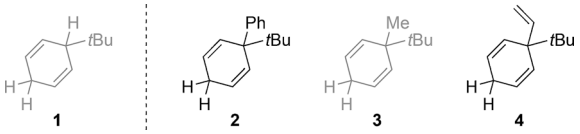


Figure 1. Cylohexa-1,4-dienes **1**–**4** as isobutane equivalents.

cyclohexa-1,4-dienes **2**–**4** as potential transfer reagents (Figure 1) and excluded parent **1**[7] for its assumed tendency to preferentially engage in transfer hydrogenation.[2b]

Transfer reagent **2** was readily obtained in one step by Birch reductive alkylation of biphenyl (not shown).[8] We also pursued the synthesis of surrogate **3** (Scheme 2) to replace difficult-to-remove biphenyl with toluene as the stoichiometric byproduct of the transfer hydro-*tert*-butylation. Birch reduction of benzoate **5** and subsequent treatment with $LiAlH_4$ yielded alcohol **6** (**5**→**6**, Scheme 2, top).[9] However, the deoxygenation of **6** proved to be challenging (**6**→**3**). The delicate combination of steric hindrance (neopentylic primary alcohol) and electronic properties (bishomoallylic position of the hydroxy functionality) creates this demanding setting (Scheme 2, bottom). Transformation of **6** into the corresponding tosylate or mesylate was successful but no reactivity toward $LiAlH_4$ was observed (not shown). The more reactive triflate (not shown) as well as phosphoramidate instantaneously rearranged to furnish cycloheptatriene **7** (**6**→**7**).[10] A similar outcome was obtained when using Et_2SiH_2 as the reductant in the presence of catalytic amounts of $B(C_6F_5)_3$ (**6**→**8**).[11] Conversion of **6** to chloride **9** was achieved with $SOCl_2$/pyridine (**6**→**9**) but reduction with

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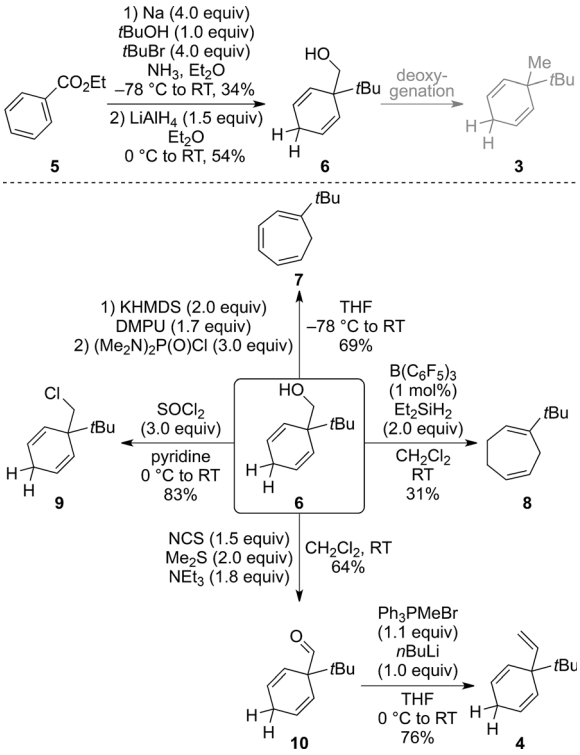
$LiAlH_4$ failed again (not shown). Attempts to prepare the respective bromide by the Appel reaction were again thwarted by ring expansion. We finally succeeded in the "deoxygenation" of the hydroxymethyl group in **6** by Corey–Kim oxidation (**6**→**10**) followed by Wittig olefination (**10**→**4**). While **4** was not what we had initially had in mind, we recognized **4** as an attractive transfer reagent. The liberated styrene could undergo cationic polymerization under the reaction setup of the $B(C_6F_5)_3$-catalyzed hydro-*tert*-butylation, thereby allowing for facile separation of the stoichiometric byproduct.

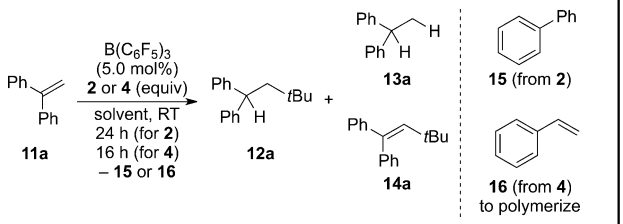


Scheme 2. Planned synthesis of transfer reagent **3** (top) and attempted deoxygenations of alcohol **6**, eventually arriving at surrogate **4** (bottom). KHMDS = potassium bis(trimethylsilyl)amide. DMPU = 1,1-dimethyltetrahydropyrimidin-2(1*H*)-one. NCS = *N*-chlorosuccinimide.

We then subjected both surrogates **2** and **4** to the typical protocol of the alkene transfer hydrogenation[2b] with 1,1-diphenylethylene (**11a**) as the model substrate and observed quantitative conversion of **11a** after 24 or 16 h, respectively (Table 1, entries 1 and 14). ^{1}H NMR spectroscopic analysis of the reaction mixtures showed that transfer of the *tert*-butyl cation to alkene **11a** had indeed occurred,[12] and desired **12a** was formed predominantly in both cases (83% for **2** and 58% for **4**) along with **13a** (11% for **2** and 35% for **4**) and **14a** (6% for **2** and 7% for **4**) as byproducts. This product distribution emphasizes the effect of the R group in the *ipso* position on the selectivity of this reaction. Isobutane surrogate **2** with a phenyl group favors the formation of product **12a** to a greater extent than **4** bearing a vinyl group in this position.[13]

As anticipated for isobutane equivalent **4**, the stoichiometric byproduct styrene (**16**) polymerized as the monomer was not

Table 1. Optimization of the reaction conditions.

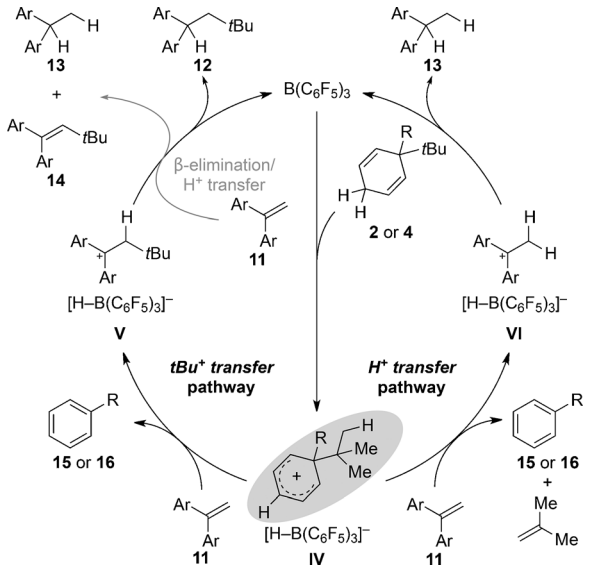


Entry	Surrogate (equiv)	Solvent	Conc. [M]	Conv.[a]	**12a**/**13a**/**14a**[b]
1	**2** (1.0)	1,2-$F_2C_6H_4$	0.50	98%	83:11:6
2	**2** (1.0)	1,2-$Cl_2C_6H_4$	0.50	90%	85:11:4
3	**2** (1.0)	C_6H_6	0.50	traces	n.d.
4	**2** (1.0)	*n*-pentane	0.50	traces	n.d.
5	**2** (1.0)	CH_2Cl_2	0.50	50%	53:24:23
6	**2** (1.3)	1,2-$F_2C_6H_4$	0.10	46%	64:20:16
7	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	96%	87:10:3
8	**2** (1.3)	1,2-$F_2C_6H_4$	1.0	>99%	87:10:3
9[c]	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	98%	85:11:4
10[d]	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	67%	85:10:5
11[e]	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	30%	78:14:8
12[f]	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	>99%	51:34:15
13[g]	**2** (1.3)	1,2-$F_2C_6H_4$	0.50	>99%	89:9:2
14	**4** (1.1)	1,2-$F_2C_6H_4$	0.50	>99%	58:35:7
15	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.50	>99%	58:40:2
16	**4** (1.1)	C_6H_6	0.50	11%	22:50:28
17	**4** (1.1)	*n*-pentane	0.50	14%	35:42:23
18	**4** (1.1)	CH_2Cl_2	0.50	97%	37:44:19
19	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.10	62%	53:42:5
20	**4** (1.3)	1,2-$Cl_2C_6H_4$	0.50	>99%	57:41:2
21	**4** (1.1)	1,2-$Cl_2C_6H_4$	1.0	>99%	60:38:2
22[c]	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.50	>99%	57:41:2
23[d]	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.50	95%	58:39:3
24[f]	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.50	46%	33:46:21
25[g]	**4** (1.1)	1,2-$Cl_2C_6H_4$	0.50	89%	61:39 : <1

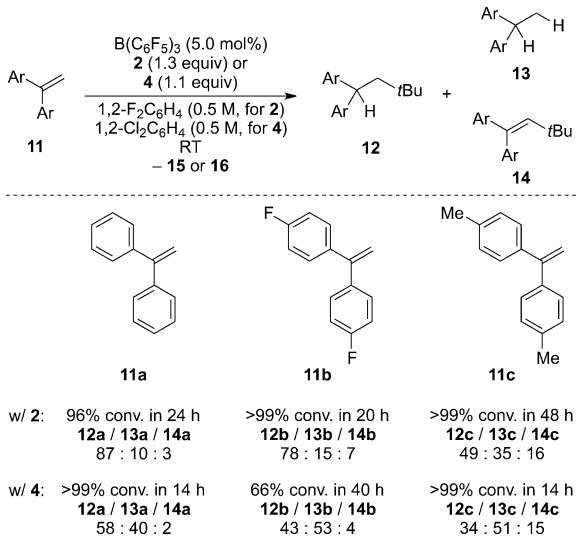
[a] Substrate conversion determined by GLC analysis using mesitylene as internal standard. [b] Determined by ^{1}H NMR analysis. [c] 10 mol% $B(C_6F_5)_3$ were used. [d] 2.5 mol% $B(C_6F_5)_3$ were used. [e] 5.0 mol% B(4-$C_6F_4H)_3$ used as catalyst. [f] 100 °C. [g] 0 °C. n.d. = not determined.

detected by ^{1}H NMR spectroscopic or GLC analysis of the crude reaction mixture. The involvement of carbenium ions inevitably led to side reactions, that is, the generation of byproducts **13** and **14** (Scheme 3). $B(C_6F_5)_3$-triggered hydride abstraction from cyclohexa-1,4-dienes **2** or **4** affords ion pair **IV**. The Wheland complex in **IV** can either transfer the *tert*-butyl cation (**IV**→**V**, left cycle) or a distal proton (**IV**→**VI**, right cycle) to alkene **11**. In the latter case, formation of ion pair **VI** is accompanied by the stoichiometric release of isobutene, likely being the driving force for this pathway. **VI** eventually collapses to close the catalytic cycle, forming byproduct **13**. Intermediate $\mathbf{V}^+$ can either be directly reduced by the borohydride to furnish the desired alkane **12** or can suffer β-elimination concomitant with protonation of another molecule of substrate **11** to yield byproducts **13** and **14** after hydride transfer. The observation that **13** and **14** are not formed in equimolar ratio shows that both cycles are operative.

Further attempts to improve the product distribution were largely unsuccessful. The solvent had a pronounced effect (entries 1–5 and 14–18) but the best selectivity and reactivity was obtained in 1,2-$F_2C_6H_4$ or 1,2-$Cl_2C_6H_4$ (entries 1/2 and 14/15)



Scheme 3. Proposed catalytic cycle with pathways for the formation of by-products **13** and **14**.



Scheme 4. Different 1,1-diarylalkenes for the isobutane transfer.

while other solvents such as C_6H_6, *n*-pentane, and CH_2Cl_2 led to significantly lower conversions and selectivities (entries 3–5 and 16–18). A slight excess of **2** or **4** was beneficial in terms of reaction rate but did not affect the selectivity (entries 7 and 20). A more dilute reaction mixture was detrimental, favoring byproduct formation (entries 6 and 19). Conversely, higher concentration merely influenced the reaction rate (entries 8 and 21). We expected the concentration of the borohydride to have an influence on the selective formation of **12a** over **13a** and **14a**. However, no effect was seen when using either 10 or 2.5 mol% $B(C_6F_5)_3$ (entries 9/10 and 22/23). Moreover, less Lewis-acidic borane $B(4\text{-}C_6F_4H)_3$[14] even led to a decreased amount of desired **12a** (78%, entry 11 versus 87%, entry 7). The borohydride emerging from $B(4\text{-}C_6F_4H)_3$ is the slightly better hydride donor than $[HB(C_6F_5)_3]^-$,[15] and that could have favored reduction ($\mathbf{V}^+ \rightarrow$**12**) over β-elimination/proton transfer ($\mathbf{V}^+ \rightarrow$**14**). Elevated reaction temperatures favored the formation of **13a** (entries 12 and 24), and running the transfer hydro-*tert*-butylation at 0 °C had no effect (entries 13 and 25).

We then compared **11a** with electronically modified 1,1-diarylalkenes **11b** and **11c** in the isobutane transfer (Scheme 4). Both **11b** and **11c** with electron-withdrawing and -donating substituents, respectively were also converted quantitatively following the standard protocol. However, **11c** reacted significantly less selective than parent **11a**, favoring transfer hydrogenation over alkylation. Slightly better stabilization of intermediate $\mathbf{V}^+$ reducing its hydride-accepting ability is likely to account for this behavior. An electron-withdrawing substituent as in **11b** turned out to be less problematic when reacted with surrogate **2** but hydrogenation prevailed with **4**. As for the related transfer hydrogenation,[2b] other alkene motifs such as α-olefins, 1,2-disubstituted alkenes, α-alkyl-substituted styrenes as well as trisubstituted alkenes resulted in intractable mixtures.

We disclosed here a rare example of an alkene hydroalkylation involving carbocation intermediates.[4] The approach, that is the formal transfer of isobutane from one unsaturated hydrocarbon to another, was in fact unprecedented before. However, the work is conceptual rather than synthetically useful at this stage. The reagent preparation is challenging, and selectivity issues arising from the intermediacy of carbocations have not been overcome yet. Nevertheless, the present hydro-*tert*-butylation reveals itself as a new strategy to install tertiary alkyl groups at an alkene terminus.

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Keywords: alkenes · boron · carbocations · hydroalkylation · Lewis acids

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[13] We also subjected **9** to our standard setup but neither *tert*-butyl-group nor proton transfer to alkene **11a** was observed. Instead, **9** ring-expanded to **7** and **8**.
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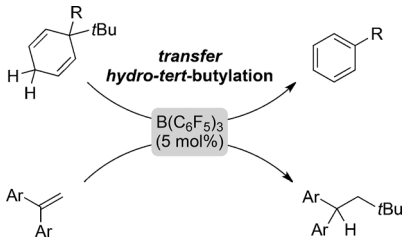
Jump! $B(C_6F_5)_3$-triggered hydride abstraction from 3-*tert*-butyl-substituted cyclohexa-1,4-dienes facilitates the formal transfer of isobutane to 1,1-diarylalkenes. Although side reactions of the carbocation intermediates limit the synthetic utility of this conceptually new methodology, the present transfer hydro-*tert*-butylation is a new way to introduce tertiary alkyl groups into carbon frameworks.



Hydroalkylation

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3-*tert*-Butyl-Substituted Cyclohexa-1,4-dienes as Isobutane Equivalents in the $B(C_6F_5)_3$-Catalyzed Transfer Hydro-*tert*-Butylation of Alkenes