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Authors: Johannes C. L. Walker and Martin Oestreich

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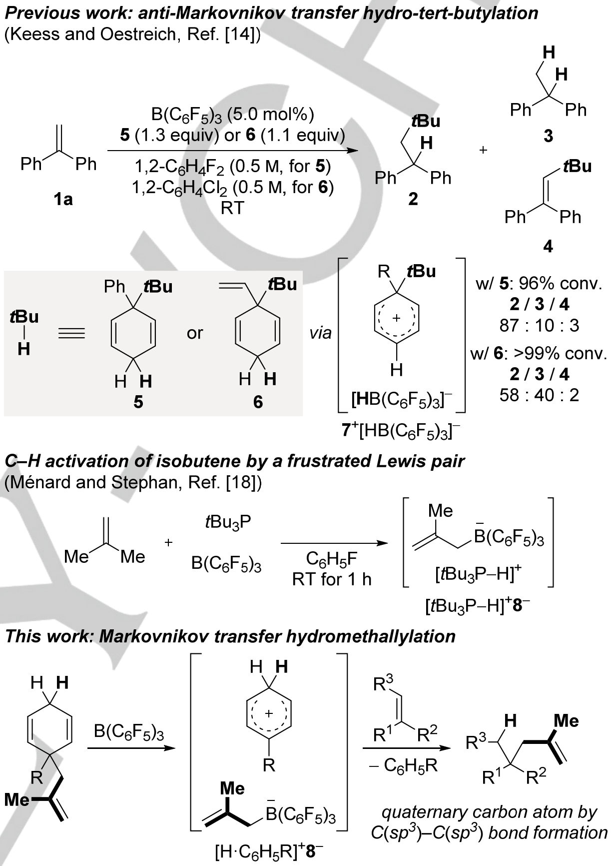
Lewis Acid-Catalyzed Transfer Hydromethallylation for the Construction of Quaternary Carbon Centers

Johannes C. L. Walker and Martin Oestreich*

Abstract: The design and gram-scale synthesis of a cyclohexa-1,4-diene-based surrogate of isobutene gas is reported. Using the highly electron-deficient Lewis acid $B(C_6F_5)_3$, its application in the hydromethallylation of electon-rich styrene derivatives to provide sterically congested quaternary carbon centers was achieved. The reaction proceeds by $C(sp^3)$–$C(sp^3)$ bond formation at a tertiary carbenium ion that is generated by alkene protonation. The possibility of two concurrent mechanisms is proposed on the basis of mechanistic experiments using a deuterated surrogate.

The catalytic preparation of quaternary carbon centers using $C(sp^3)$–$C(sp^3)$ bond-forming reactions has been identified as a key challenge in organic synthesis.[1] Recent progress in this area has mainly centered on transition-metal-catalyzed transformations.[2–4] Metal-free approaches are less common.[5,6] One strategy to achieve $C(sp^3)$–$C(sp^3)$ bond formation is the attack of a carbon nucleophile onto a tertiary carbenium ion.[7,8] Although this has been exploited in the context of carbenium-ion generation by dehydration of tertiary alcohols with catalytic amounts of strong acid,[5,6,9] the complementary process by catalytic protonation of alkenes is far less well explored.[10,11]

Our laboratory has been investigating cyclohexa-1,4-diene-based surrogates of difficult-to-handle compounds for metal-free transfer reactions.[12–15] As part of this programme we previously developed cyclohexa-1,4-dienes **5** and **6** as surrogates of isobutane gas and reported their use in the transfer hydro-*tert*-butylation of alkenes using the strong boron Lewis acid $B(C_6F_5)_3$ (Scheme 1, top).[14,16] Hydride abstraction from the bisallylic position of the surrogates led to formation of the *tert*-butyl-substituted Wheland intermediates $\mathbf{7}^+$ and transfer of the electrofugal *tert*-butyl group to the terminus of 1,1-diaryl-substituted alkenes. Borohydride addition to the resulting benzylic tertiary carbenium ion delivered formally *anti*-Markovnikov alkylation products such as **2**. However, this process was hampered by side reactions to give **3** and **4**, and the substrate scope was quite limited.



Scheme 1. Cyclohexa-1,4-diene-based surrogates of isobutane and isobutene gas for metal-free transfer hydroalkylation and -allylation, respectively.

We wondered whether an appropriately substituted cyclohexa-1,4-diene would facilitate abstraction of a nucleofugal hydrocarbon group and then lead to the complementary Markovnikov hydroalkylation.[17] In seeking a plausible hydrocarbon unit, we were interested in a report by Ménard und Stephan who had achieved the stoichiometric C–H activation of isobutene with the frustrated Lewis pair $tBu_3P/B(C_6F_5)_3$ (Scheme 1, middle).[18] The methallyl borate $\mathbf{8}^-$ formed represents a potential nucleophilic source of the methallyl group,[19,20] and we hoped that a cyclohexa-1,4-diene surrogate of isobutene gas could be developed to allow for the abstraction of the methallyl nucleofuge by $B(C_6F_5)_3$ to give $\mathbf{8}^-$ and a Brønsted-acidic Wheland intermediate. Interception of this complex by an alkene might then allow for transfer hydromethallylation and the formation of a quaternary carbon center by way of $C(sp^3)$–$C(sp^3)$ bond formation (Scheme 1, bottom).[21–23]

The required surrogate would likely necessitate a quaternary center adjacent to the methallyl group to prevent undesired side

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[*] Dr. J. C. L. Walker, Prof. Dr. M. Oestreich
Institut für Chemie, Technische Universität Berlin
Strasse des 17. Juni 115, 10623 Berlin (Germany)
E-mail: martin.oestreich@tu-berlin.de
Homepage: http://www.organometallics.tu-berlin.de

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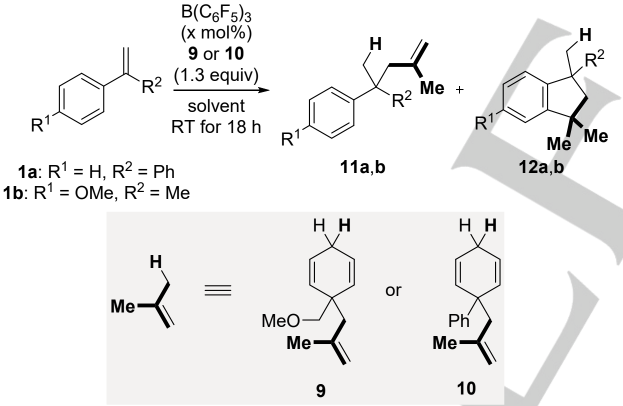
reactions such as transfer hydrogenation,[24] as well as to aid stabilization of the positively charged Wheland intermediate. Surrogates **9** and **10** fulfill this requirement and were easily accessible by Birch alkylation from benzoic acid and biphenyl, respectively (see the Supporting Information for experimental details). We then subjected the surrogates to a model reaction with 1,1-diphenylethene (**1a**) and 10 mol% $B(C_6F_5)_3$ in CH_2Cl_2 (Table 1, entry 1). Benzyl ether-based surrogate **9** did not give any of the desired hydromethallylation product **11a**, instead providing indane **12a** in 6% yield; **12a** presumably results from the intramolecular Friedel–Crafts alkylation of **11a**.[25] Biphenyl-based surrogate **10** was more reactive, forming the intended product **11a** in 3% and indane **12a** in 40% yield (entry 2). Switching the solvent to toluene improved the selectivity for **11a** (entry 3). We eventually established that electron-rich styrene derivatives allowed the reaction to proceed to full conversion, and we could suppress cyclization to indanes **12** by modifying the steric environment of the alkene. Using *para*-anisyl-substituted alkene **1b**, we were initially able to form **11b** in 82% yield with no indane **12b** observed (entry 4). The loading of both surrogate **10** and $B(C_6F_5)_3$ could be reduced with no detrimental impact on the yield, and **11b** was then isolated in 82% yield (entry 5). The reaction could also be scaled up to 1.00 mmol (entry 6). No reaction occurred in the absence of the catalyst (entry 7), but interestingly, $B(C_6F_5)_3$ was able to partially decompose surrogate **10** to biphenyl in the absence of the alkene starting material (entry 8).

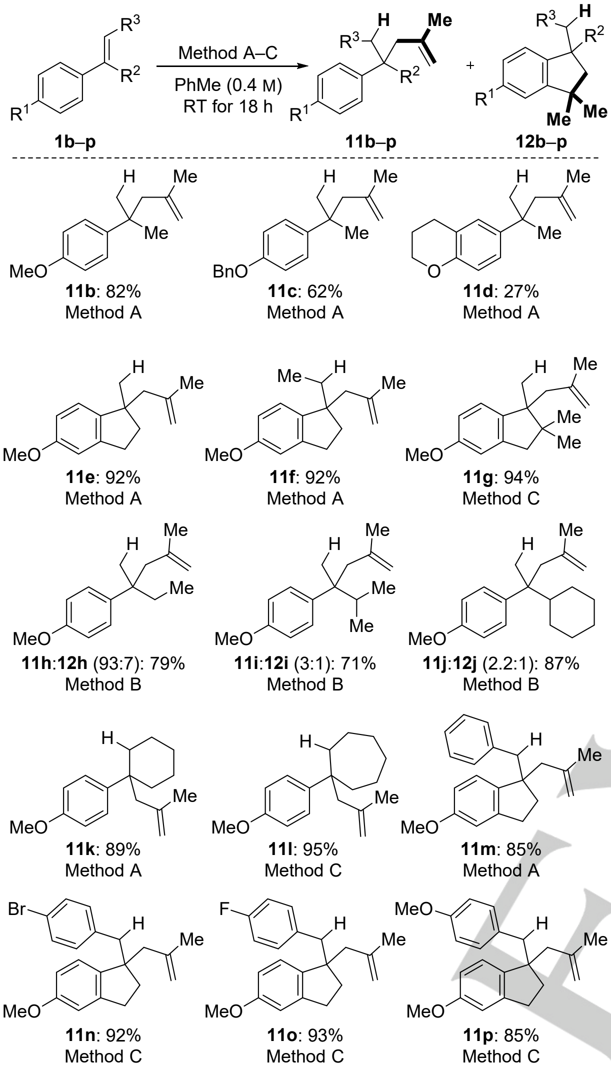
Table 1. Optimization of the $B(C_6F_5)_3$-catalyzed transfer hydromethallylation.[a]



Entry	Alkene	Surrogate	$B(C_6F_5)_3$ [mol%]	Solvent	Yield of **11** [%][b]	Yield of **12** [%][b]
1	**1a**	**9**	10	CH_2Cl_2	<1	6
2	**1a**	**10**	10	CH_2Cl_2	3	40
3	**1a**	**10**	10	PhMe	32	11
4	**1b**	**10**[c]	10	PhMe	82	<1
5	**1b**	**10**	5.0	PhMe	85 (82)[d]	<1
6[e]	**1b**	**10**	5.0	PhMe	74[d]	<1
7	**1b**	**10**	—	PhMe	<1	<1
8[f]	**1b**	**10**	5.0	PhMe	<1[f]	<1

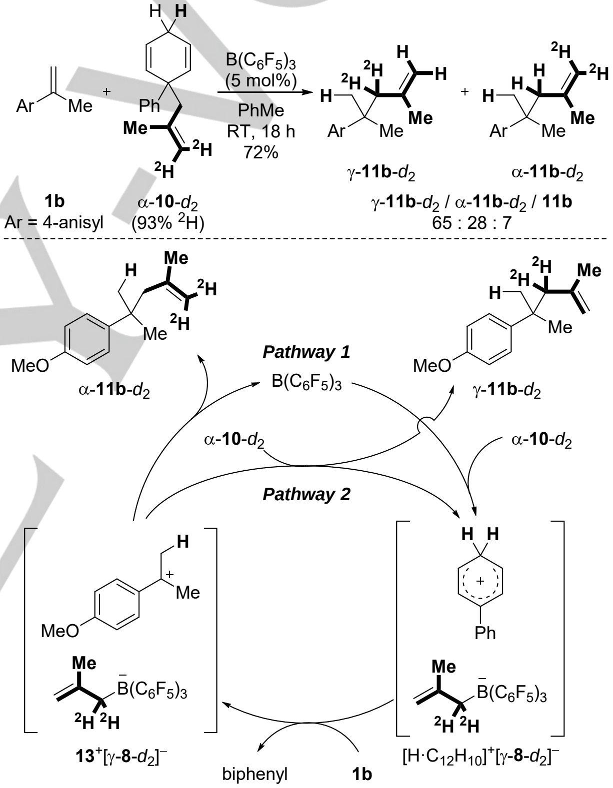
[a] Unless otherwise noted, reactions were performed on a 0.10 mmol scale with 1.3 equiv **9** or **10** in 0.25 mL (0.4 M) of the indicated solvent. [b] Determined by ^1H NMR spectroscopy by the addition of 1,2-dibromomethane as an internal standard. [c] 1.5 equiv surrogate **10** used. [d] Isolated yield. [e] On a 1.0 mmol scale. [f] Alkene **1b** was not added. 22% conversion of surrogate **10** to biphenyl.

With optimized conditions in hand, we proceeded to investigate the substrate scope (Scheme 3). A range of electron-rich α-substituted styrenes could be used with benzyl ethers as in **11c** and cyclic ethers as in **11d** both tolerated. The indane-based alkene **11e** could be prepared in 92% yield and, using this framework, an exocyclic trisubstituted alkene could also be reacted to give **11f** in 92% yield. As previously observed in other transfer reactions, tetrasubstituted alkenes were unreactive.[12,13] Products bearing two contiguous quaternary carbon centers could be accessed, with **11g** formed in 94% yield. Here, slightly higher loadings of $B(C_6F_5)_3$ and surrogate **10** were required to push the reaction to completion. These conditions found further application with other less reactive substrates. Increased substitution at the α-position of the styrene was also tolerated, as in **11h**–**j**, although in these cases cyclization to indanes **12h**–**j** could not be completely suppressed; the proportion of indanes **12h**–**j** increased with the size of the α-substituent. Performing the reaction with two equivalents of surrogate **10** did help to reduce the extent of cyclization; **11h** and **12h** were however formed in a 3:1 mixture with 1.3 equiv surrogate **10**. A substrate bearing the bulky *tert*-butyl group in the α-position was unreactive. Cyclic alkanes containing quaternary carbon centers could also be synthesized using this methodology with cyclohexane **11k** and cycloheptane **11l** being formed in 89% and 95% yield, respectively. Finally, a series of compounds bearing pendant aryl groups was prepared. Phenyl-substituted **11m** was formed in 85% yield, and products with halogen substituents as in **11n** and **11o** as well as an electron-donating methoxy substituent as in **11p** could also be accessed. To illustrate the utility of these products, a selection of these compounds was further derivatized (see the Supporting Information for details).



Scheme 2. Scope of the $B(C_6F_5)_3$ catalyzed transfer hydromethallylation of alkenes. Method A: $B(C_6F_5)_3$ (5.0 mol%), surrogate **10** (1.3 equiv); Method B: $B(C_6F_5)_3$ (5.0 mol%), surrogate **10** (2.0 equiv); Method C: $B(C_6F_5)_3$ (7.5 mol%), surrogate **10** (2.0 equiv).

To gain insight into the reaction mechanism, we prepared deuterated surrogate α-**10**-d_2 (Scheme 3; see the Supporting Information for experimental details). Despite this surrogate being deuterated solely at the allyl terminus (γ-position), its reaction with alkene **1b** produced **11b**-d_2 with deuterium incorporation in both the α- and γ-positions. This suggests the presence of at least two concurrent mechanisms (see the Supporting Information for more elaborate catalytic cycles). First, based on the work of Ménard and Stephan,[18] we propose that alkene attack from surrogate α-**10**-d_2 to $B(C_6F_5)_3$ results in abstraction of the methallyl group and formation of α-deuterated methallyl borate complex [γ-**8**-d_2]$^-$ along with protonated biphenyl $[H{\cdot}C_{12}H_{10}]^+$ (Scheme 3, Pathway 1). Protonation of alkene **1b** by the Brønsted-acidic Wheland complex yields the tertiary carbenium ion **13**$^+$ with concomitant aromatization of the surrogate core to biphenyl. Transfer of the methallyl group from methallyl borate [γ-**8**-d_2]$^-$ to **13**$^+$ then provides γ-deuterated alkene α-**11b**-d_2 with formation of a $C(sp^3)$–$C(sp^3)$ bond. Alternatively, direct transfer of the methallyl fragment from α-**10**-d_2 to carbenium ion **13**$^+$ would result in the formation of the regioisomer γ-**11b**-d_2 with deuteration in the α-position (Pathway 2). In this scenario, $B(C_6F_5)_3$ operates as an initiator and methallyl borate [γ-**8**-d_2]$^-$ as a spectator counteranion. The dual role of $B(C_6F_5)_3$ as catalyst and initiator in transfer chemistry has previously been discussed on the basis of computational calculations.[26] Another pathway to arrive at γ-**11b**-d_2 is the transfer of the methallyl group between two boron centers (see Pathway 3 in the Supporting Information). This would lead to γ-deuterated α-**8**-d_2, and attack of the methallyl group onto carbenium ion **13**$^+$ then provides γ-**11b**-d_2. It has not yet been possible to distinguish between the two possible pathways leading to γ-**11b**-d_2.



Scheme 3. Mechanistic experiment with deuterated surrogate and proposed mechanism.

To summarize, a cyclohexa-1,4-diene-based surrogate of isobutene gas has been developed and utilized in the transfer hydromethallylation of electron-rich styrene derivatives. The method enables the catalytic formation of sterically congested quaternary carbon atoms and represents a rare example of the formation of $C(sp^3)$–$C(sp^3)$ bonds from carbenium ions that have been formed by the protonation of an alkene. A range of different scaffolds could be incorporated, and the utility of the products was demonstrated by their derivatization.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boron • carbocations • carbon–carbon bond formation • transfer processes • Lewis acids

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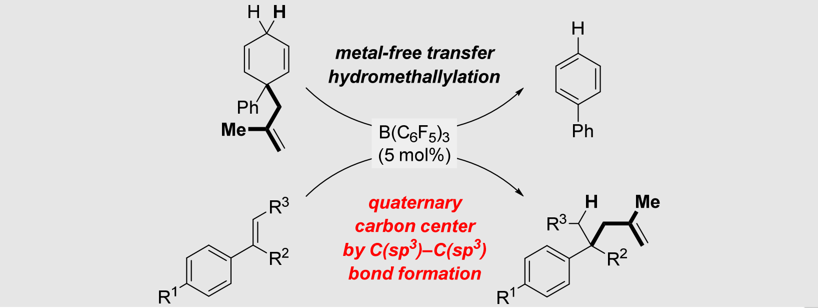

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Lewis Acid-Catalyzed Transfer Hydromethallylation for the Construction of Quaternary Carbon Centers

Quat a wonderful world. A surrogate of isobutene gas based on cyclohexa-1,4-diene has been designed that enables the transfer hydromethallylation of alkenes under Lewis-acidic conditions. The method allows for the construction of a congested quaternary carbon center and a C(sp^3)–C(sp^3) bond by way of a tertiary carbenium ion generated by alkene protonation.