

C–C Bond Formation

International Edition: DOI: 10.1002/anie.201909852
German Edition: DOI: 10.1002/ange.201909852

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

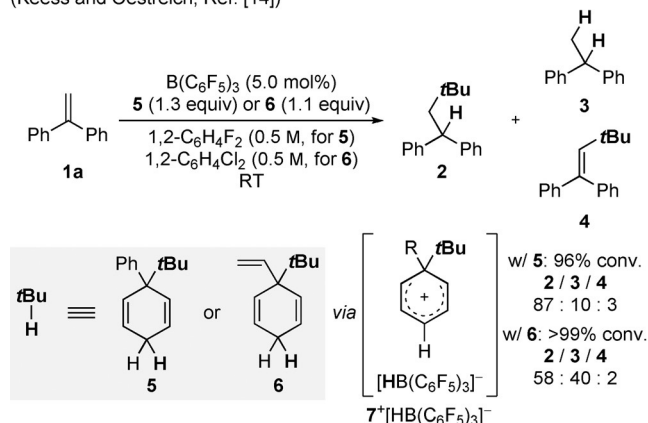
Johannes C. L. Walker and Martin Oestreich*

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 $B(C_6F_5)_3$, application of this surrogate in the hydromethallylation of electron-rich styrene derivatives provided sterically congested quaternary carbon centers. 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.

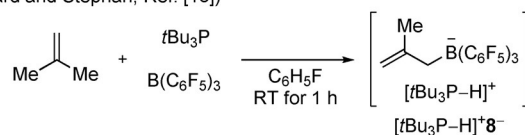
The catalytic preparation of quaternary carbon centers using $C(sp^3)–C(sp^3)$ bond-forming reactions has been identified as a key challenge in organic synthesis.^[1] Recent progress in this area has mainly centered on transition-metal-catalyzed transformations.^[2–4] Metal-free approaches are less common.^[5,6] 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 program 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 **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,

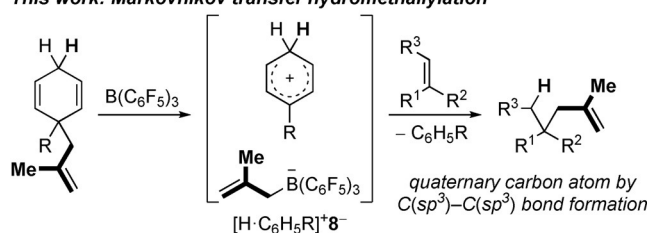
Previous work: anti-Markovnikov transfer hydro-*tert*-butylation (Keess and Oestreich, Ref. [14])



C–H activation of isobutene by a frustrated Lewis pair (Ménard and Stephan, Ref. [18])



This work: Markovnikov transfer hydromethallylation



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

this process was hampered by side reactions to give **3** and **4**, and the substrate scope was quite limited.

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 and 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 **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 **8**[−] and a Brønsted acidic Wheland intermediate. Interception of this complex by an alkene might then allow for transfer

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<https://doi.org/10.1002/anie.201909852>.

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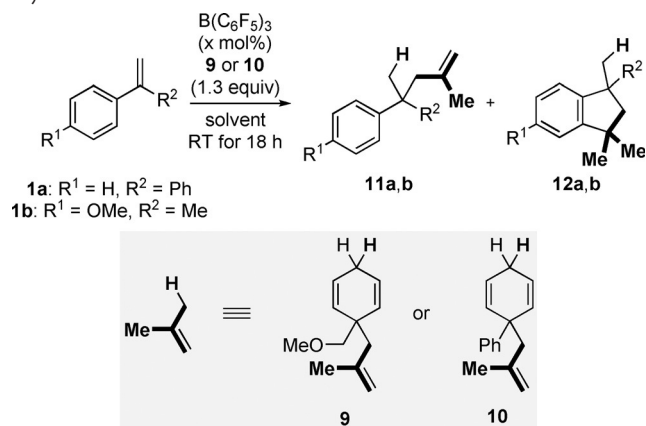
hydromethallylation and the formation of a quaternary carbon center by way of $C(sp^3)-C(sp^3)$ bond formation (Scheme 1, bottom).^[21–23]

The required surrogate would likely necessitate a quaternary center adjacent to the methallyl group to prevent undesired side reactions such as transfer hydrogenation,^[24] as well as to help stabilize 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).

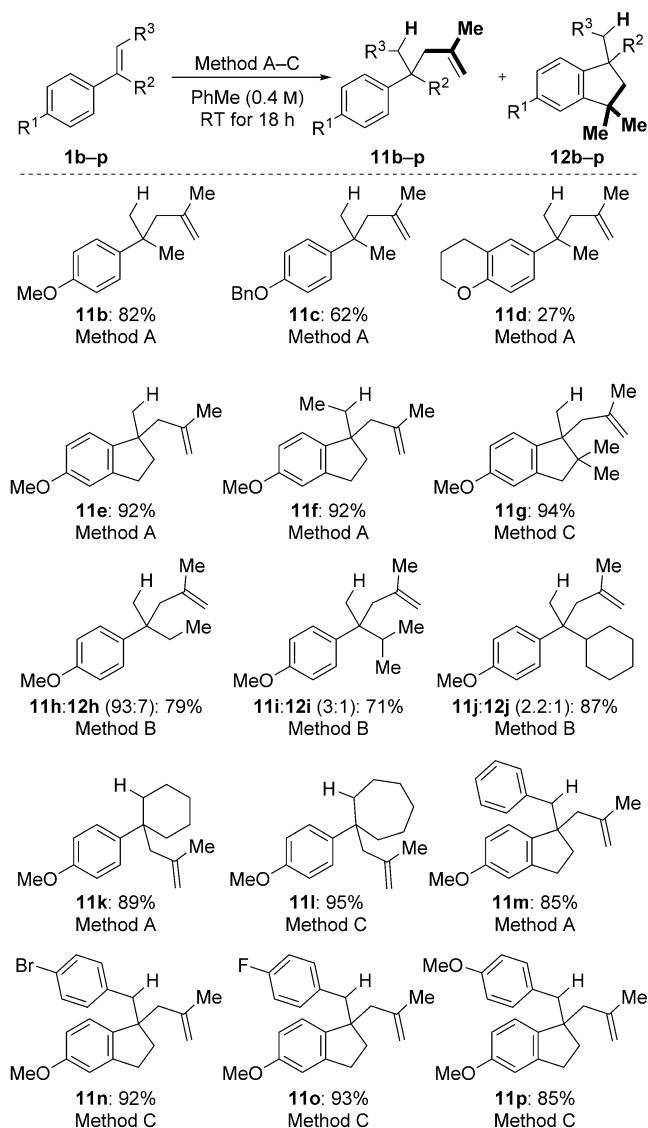
With optimized conditions in hand, we proceeded to investigate the substrate scope (Scheme 2). A range of electron-rich α -substituted styrenes could be used, with benzyl ethers as in **11c** and cyclic ethers as in **11d** both tolerated. The indane-based alkene **11e** could be prepared in 92% yield 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

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



| Entry | Alkene | Surrogate | $B(C_6F_5)_3$ [mol%] | Solv. | 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 |

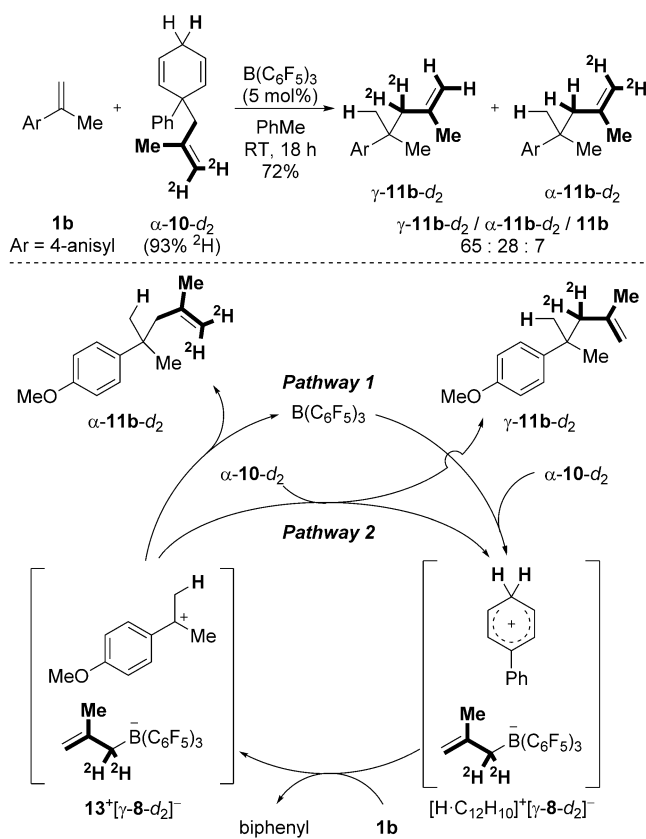
[a] Unless otherwise noted, reactions were performed on a 0.10 mmol scale with 1.3 equiv **9** or **10** in 0.25 mL (0.4 M) of the indicated solvent. [b] Determined by 1H NMR spectroscopy by the addition of 1,2-dibromomethane as an internal standard. [c] 1.5 equiv surrogate **10** used. [d] Yield of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



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).

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 were further derivatized (see the Supporting Information for details).

To gain insight into the reaction mechanism, we prepared deuterated surrogate α -**10-d₂** (Scheme 3; see the Supporting Information for experimental details). Although this surrogate was deuterated solely at the allyl terminus (γ -position), its reaction with alkene **1b** produced **11b-d₂** with deuterium



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

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-d₂** to $B(C_6F_5)_3$ results in abstraction of the methallyl group and formation of α -deuterated methallyl borate complex $[\gamma-8-d_2]^-$ along with protonated biphenyl $[H-C_{12}H_{10}]^+$ (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 $[\gamma-8-d_2]^-$ to **13⁺** then provides γ -deuterated alkene α -**11b-d₂** with formation of a $C(sp^3)-C(sp^3)$ bond. Alternatively, direct transfer of the methallyl fragment from α -**10-d₂** to carbenium ion **13⁺** would result in the formation of the regioisomer γ -**11b-d₂** with deuteration in the α -position (Pathway 2). In this scenario, $B(C_6F_5)_3$ operates as an initiator and methallyl borate $[\gamma-8-d_2]^-$ 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-d₂** 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-d₂**, and attack of the methallyl group onto carbenium ion **13⁺** then provides γ -**11b-d₂**. It has not yet been possible to distinguish between the two possible pathways leading to γ -**11b-d₂**.

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.

Acknowledgements

J.C.L.W. gratefully acknowledges the Alexander von Humboldt Foundation for a Theodor Heuss fellowship (2018–2019). M.O. is indebted to the Einstein Foundation Berlin for an endowed professorship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: boron · carbocations · C–C bond formation · Lewis acids · transfer processes

How to cite: *Angew. Chem. Int. Ed.* **2019**, *58*, –
Angew. Chem. **2019**, *131*, –

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Manuscript received: August 4, 2019

Accepted manuscript online: August 26, 2019

Version of record online: September 12, 2019