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**Authors:** Amir H. Hoveyda, Yucheng Mu, Thach T. Nguyen, Farid W. van der Mei, and Richard R. Schrock



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# Traceless Protection for More Broadly Applicable Olefin Metathesis

*Yucheng Mu,[†] Thach T. Nguyen,[†] Farid W. van der Mei, Richard R. Schrock, and Amir H. Hoveyda**

[*] Prof. R. R. Schrock, Prof. A. H. Hoveyda, Y. Mu, T. T. Nguyen, F. W. van der Mei

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467 (USA)

Prof. R. R. Schrock

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA)

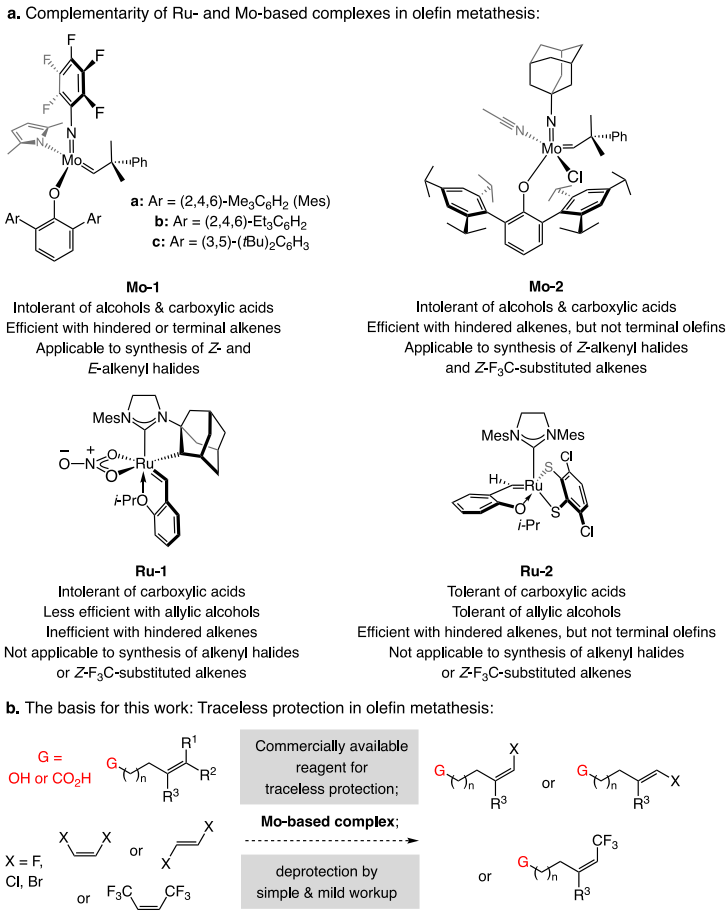
[†] These authors contributed equally.

E-mail: amir.hoveyda@bc.edu

***Abstract:*** *An operationally simple in situ protection/deprotection strategy that significantly expands the scope of kinetically controlled catalytic Z- and E-selective olefin metathesis is introduced. We demonstrate that, prior to the addition of a sensitive Mo- or Ru-based complex, treatment of a hydroxy- or a carboxylic acid-containing olefin with commercially available HB(pin) or readily accessible HB(trip)$_2$ (pin = pinacolato, trip = 2,4,6-tri(iso-propyl)phenyl) for 15 minutes is sufficient for efficient generation of a desired product. Routine workup leads to quantitative deprotection. A range of stereochemically defined Z- or E-alkenyl chlorides, bromides, fluorides, and boronates or Z-trifluoromethyl-substituted alkenes with a hydroxy- or a carboxylic acid group were thus prepared in 51–97% yield and 93% to >98% stereoselectivity. The substrates, HB(pin), and cross-partners were used as received. We also show that, regardless of whether a polar functional unit is present or not, a small amount of HB(pin) (e.g., 10 mol %) may be used to remove residual water, significantly enhancing efficiency (i.e., lower catalyst loading).*

The colossal impact of olefin metathesis on modern chemistry is largely due to the complementary nature of Mo-based alkylidenes and Ru-based carbenes,[1] an attribute more recently manifested in the recently introduced methods for *Z*- or *E*-selective processes (Scheme 1a).[2] While only monoaryloxide pyrrolide (MAP)[3] **Mo-1** and monoaryloxide chloride (MAC)[4] **Mo-2** can be used to generate *Z*- or *E*-alkenyl halides,[5] and synthesis of *Z*-trifluoromethyl-substituted alkenes is confined to reactions with **Mo-2**,[4] a hydroxy or a carboxylic acid unit decompose the derived catalysts rapidly. Reactions with **Ru-1**[6] can involve hydroxy-containing substrates, but efficiency is lower with an allylic alcohol,[7] and, as with Mo-based catalysts, a carboxylic acid is not tolerated.[7] Unsaturated organic compounds bearing an alcohol and/or a carboxylic acid,[8-9] are suitable substrates for **Ru-2**; however, unlike **Mo-1** and **Ru-1**, and similar to **Mo-2**, monosubstituted alkenes cannot be used.[10]

Unsaturated hydrocarbons with a hydroxy or a carboxylic acid group are an important class of compounds in chemistry.[11] Many are renewable raw materials, including animal fats and vegetable oils, inexpensive and viable substitutes for the dwindling petrochemicals,[11] and others are biologically active. The ability to synthesize stereochemically defined alkenyl halide derivatives[5] of the aforementioned molecules by cross-metathesis without protection/deprotection sequences or rigorous purification would be highly advantageous. In this context, stereochemically defined alkenes with a fluoro or a




***Scheme 1.*** Complexes used for kinetically controlled olefin metathesis and the objectives of this study.

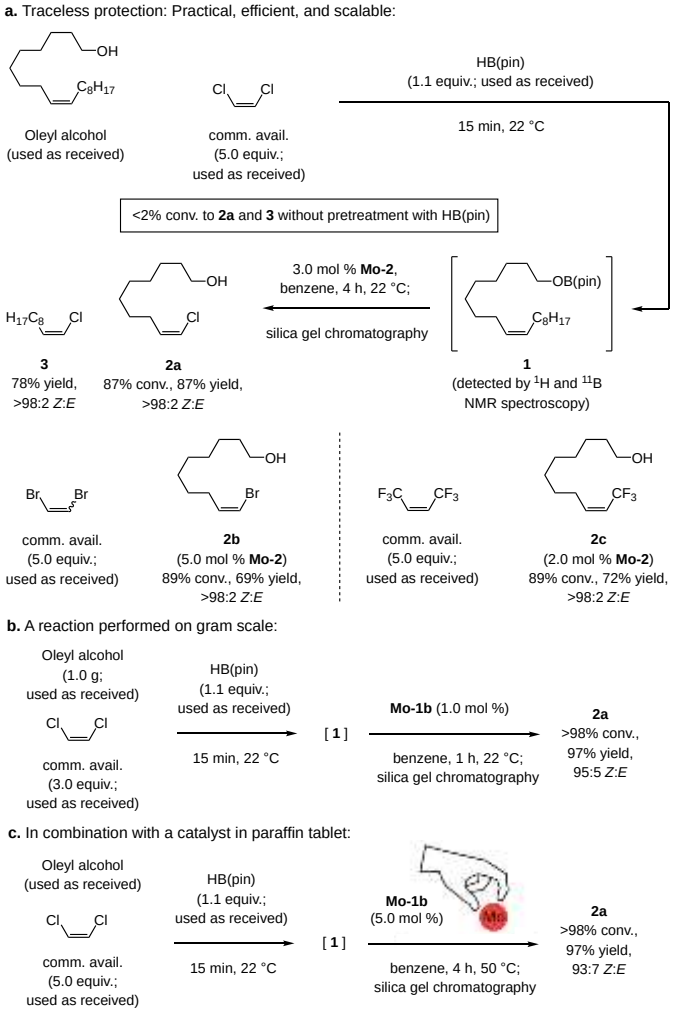
trifluoromethyl substituent would be especially attractive products. Such entities are vital to future advances in medicine,[12] and the corresponding chlorides or bromides may be transformed to many valuable entities with high stereospecificity by catalytic cross-coupling.[13]

The above considerations led us to envision a traceless protecting group strategy (Scheme 1b) that would offer the following features: a) efficient and rapid protection of an alcohol or a carboxylic acid under mild conditions; b) readily accessible and mild reagent; c) transient derivatives that are not too basic or nucleophilic (e.g., a metal alkoxide); d) easily removable and innocuous byproducts with no adverse influence on catalyst activity; e) umasking by a simple, efficient, and mild protocol. Herein, we disclose the realization of the above objective.

The negative impact of a Lewis basic amide or amine on the efficiency of olefin metathesis reactions with Ru-based catalysts has been formerly addressed by the addition of an appropriate additive (e.g., a Ti-based complex[14] or a Brønsted acid[15]). In 2005 we reported a case where chelation of a Mo alkylidene with a nearby secondary amine may be circumvented by pre-treatment of the substrate with freshly distilled catecholborane (12 h, 22 °C), releasing $H_2$. Ensuing subjection to aqueous NaOH regenerated the product free amine.[16] We thus chose to identify another boron–hydride reagent which,

while readily available and inert towards addition to alkenes, can react with a hydroxy group to afford a boronate[17] more quickly (e.g., ≤1 vs. 12 h) and without the need for initial purification/drying. These deliberations led us to pinacolborane (HB(pin)), a robust, mild and commercially available reagent. Whether the strategy would be applicable to carboxylic acids remained to be established.

To probe the feasibility of the approach, we treated a mixture of oleyl alcohol and *Z*-dichloroethene with 1.1 equivalent of HB(pin) for just 15 minutes at room temperature, affording boronic ester **1** (observable by $^{1}$H and $^{11}$B NMR spectroscopy; Scheme 2a); **Mo-2** (3.0 mol % in benzene) was then added. After four hours and routine silica gel chromatography, we isolated *Z*-alkenyl chlorides **2a** and **3** in 87% and 78% yield, respectively (>98% *Z*). Similarly, we synthesized *Z*-alkenyl bromide **2b** (69% yield, >98:2 *Z*:*E*), and *Z*-$F_3C$-substituted alkene **2c** (72% yield, >98:2 *Z*:*E*). The approach is amenable to gram-scale operations (Scheme 2b) and the use of a complex confined in a paraffin pellet [18] (Scheme 2c). Regardless of the cross-partner or the conditions used, we were able to obtain the alkyl-substituted alkenyl halide

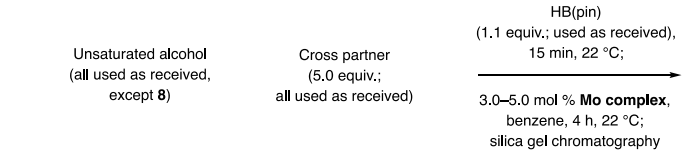


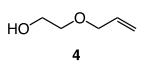
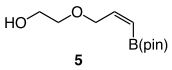
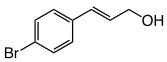
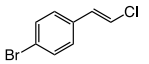
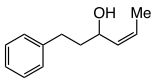
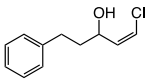
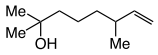
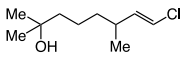
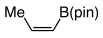
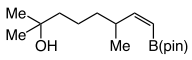
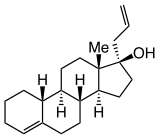
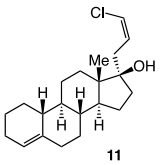

***Scheme 2.*** Traceless protection of an alcohol substrate with HB(pin) is practical, efficient, and scalable. Conversion was determined by $^{1}$H NMR analysis of unpurified product mixtures; see the Supporting Information for details.

(cf. **3**) or trifluoromethyl co-products with identical stereochemical purity as the component bearing a primary alcohol but in slightly lower yields (volatile). The oleyl alcohol, the halogen-containing reagents, and HB(pin), all commercially available, were used as received.

Different unsaturated alcohols and cross partners are suitable substrates (Table 1). Kinetically *Z*- or *E*-selective transformations with substrates with a primary aliphatic (entry 1), a primary or secondary allylic (entries 2–3), or a tertiary alcohol (entries 4–6) were efficient, affording 1,2-disubstituted alkenyl boronates (**5** and **10b**) or alkenyl halides (**7**, **9**, **10a**, and **11**) in 59–93% yield and with high stereoselectivity.

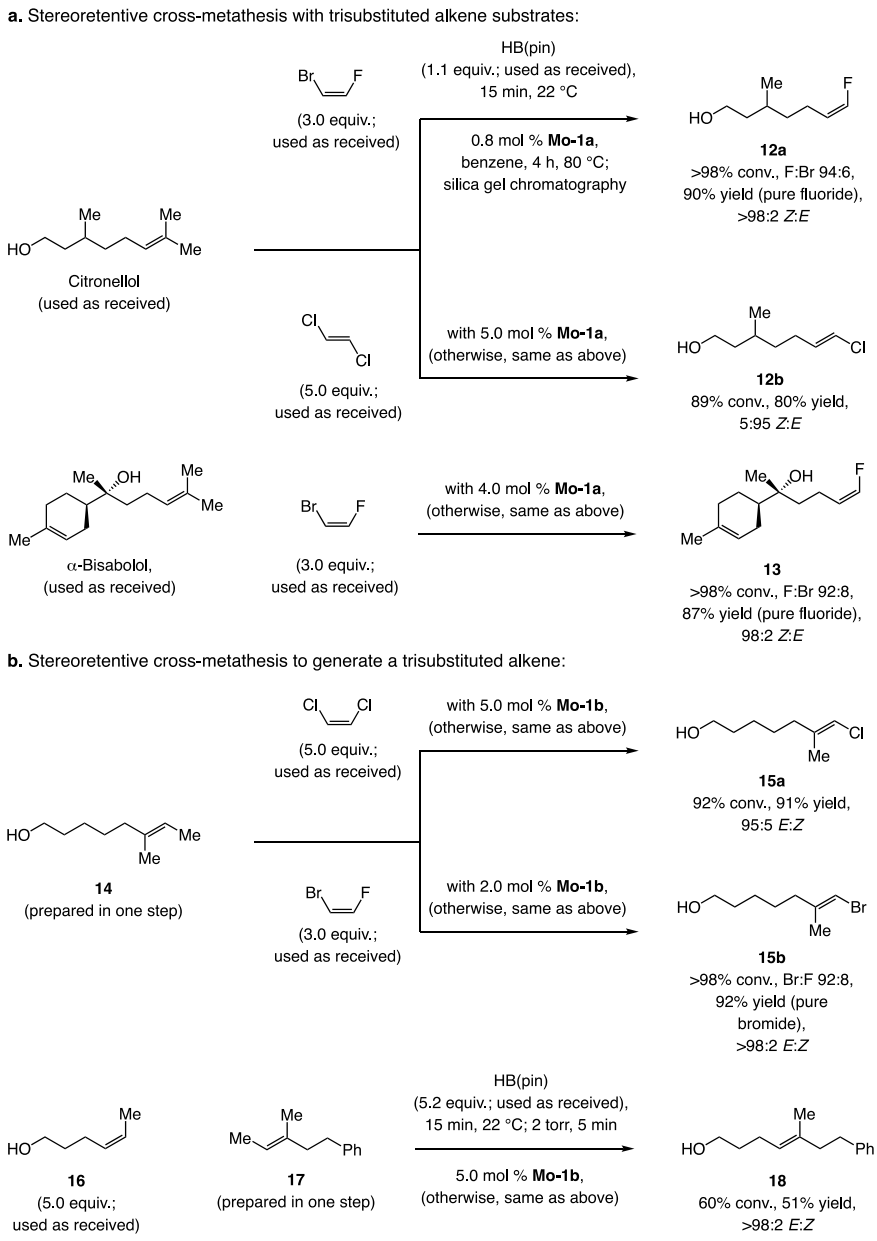
***Table 1:*** Traceless protection for alcohol-containing substrates.[a]




| Entry | Substrate | Cross partner | Mo complex; mol % | Product | Conv. (%);[b] Yield (%)[c] | *Z*:*E*[b] |
|---|---|---|---|---|---|---|
| 1 |  **4** |  | **Mo-1b**; 3.0 |  **5** | 74; 64 | >98:<2 |
| 2 |  **6** |  | **Mo-1c**; 5.0 |  **7** | >98; 59 | <2:>98 |
| 3 |  **8** |  | **Mo-2**; 5.0 |  **9** | 93; 91 | >98:<2 |
| 4 |  Dihydromyrcenol |  | **Mo-1c**; 5.0 |  **10a** | 97; 93 | 7:93 |
| 5 | |  | **Mo-1b**; 3.0 |  **10b** | 83; 65 | >98:<2 |
| 6 |  Allylestrenol |  | **Mo-1b**; 5.0 |  **11** | 67; 61 | >98:<2 |

[a] Reactions were performed under $N_2$ atm. [b] Determined by analysis of $^1$H NMR spectra of unpurified product mixtures. [c] Yield of isolated and purified product. See the Supporting Information for details.

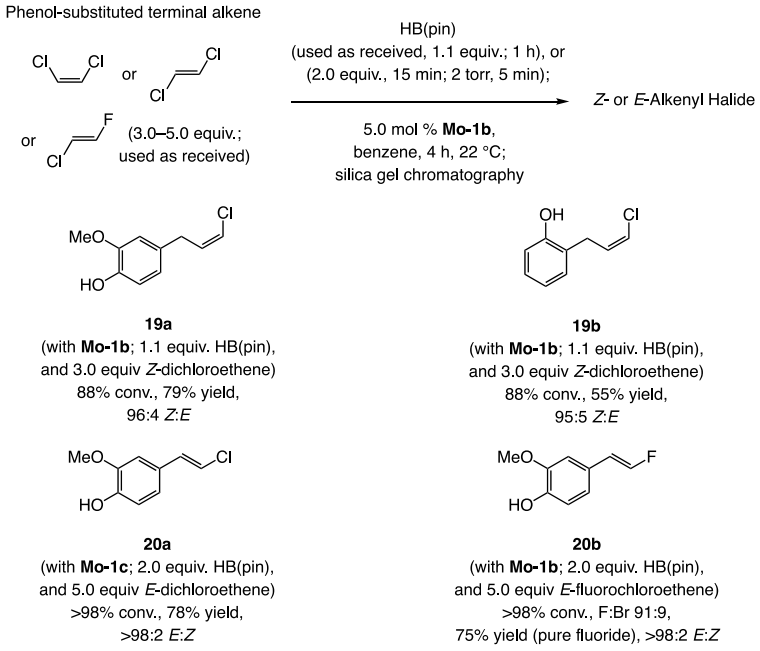
The strategy is applicable to more challenging reactions, involving trisubstituted alkenes (Scheme 3a). Citronellol was converted to *Z*-alkenyl fluoride **12a** with 94:6 fluoro:bromo selectivity, in 90% yield (pure fluoride) and >98:2 *Z*:*E* selectivity. The transformation to *E*-alkenyl chloride **12b** was as efficient and stereoretentive (80% yield, 95:5 *E*:*Z*). *Z*-Alkenyl fluoride **13** was prepared from natural product bisabolol in 87% yield (pure fluoride) and 98:2 *Z*:*E* selectivity. In light of the prevalence of compounds that contain an isoprenyl group along with a polar (e.g., hydroxy) group, the approach provides a cost-effective and




***Scheme 3.*** Transient protection in cross-metathesis reactions involving trisubstituted alkenes as products or substrates.

stereoselective method for synthesis of an assortment of valuable and/or easily functionalizable derivatives. Traceless protection may be used in reactions that convert readily available trisubstituted alkenes to those that are less easily accessible (Scheme 3b),[19] including alkenyl chlorides, bromides, and olefins that contain three C-based substituents (**15a**-**b**[20] and **18**, respectively). The high yield (80–90%) and stereoisomeric purity (95% to >98% of one isomer) with which **12a**-**b** and **13** (Scheme 3a) are formed is noteworthy because, generally, alkenyl halides bearing an unhindered (linear) alkyl substituent cannot be obtained efficiently from a terminal or a 1,2-disubstituted olefin. Homocoupling and/or isomerization of the 1,2-disubstituted olefin is a complication with these less substituted alkenes, and fluoro:bromo or *E*:*Z* selectivity is typically lower (~70:30).[5]

Commercially available eugenol was converted to alkenyl chloride **19a** in 79% yield and 96:4 *Z*:*E* selectivity (Scheme 4). The reaction generating *ortho*-substituted **19b** (55% yield, 95:5 *Z*:*E*) was somewhat less efficient, perhaps due to internal O→Mo chelation.[21] When we applied the same procedure to synthesis of *E*-styrenyl halides **20a** and **20b**, there was <5% conversion. This might be for two reasons: reduced Lewis basicity of the styrenyl phenol, resulting in slower boronate formation, a scenario that is supported by analysis of the relative rates of boronate formation ($^1$H NMR), [22] and lower rate of olefin metathesis due to the sterically more hindered alkenes. Therefore, with 2.0 equivalents of HB(pin) **20a** and **20b** were isolated in 78% and 75% yield, respectively (>98:2 *E*:*Z*). With more borane present, brief

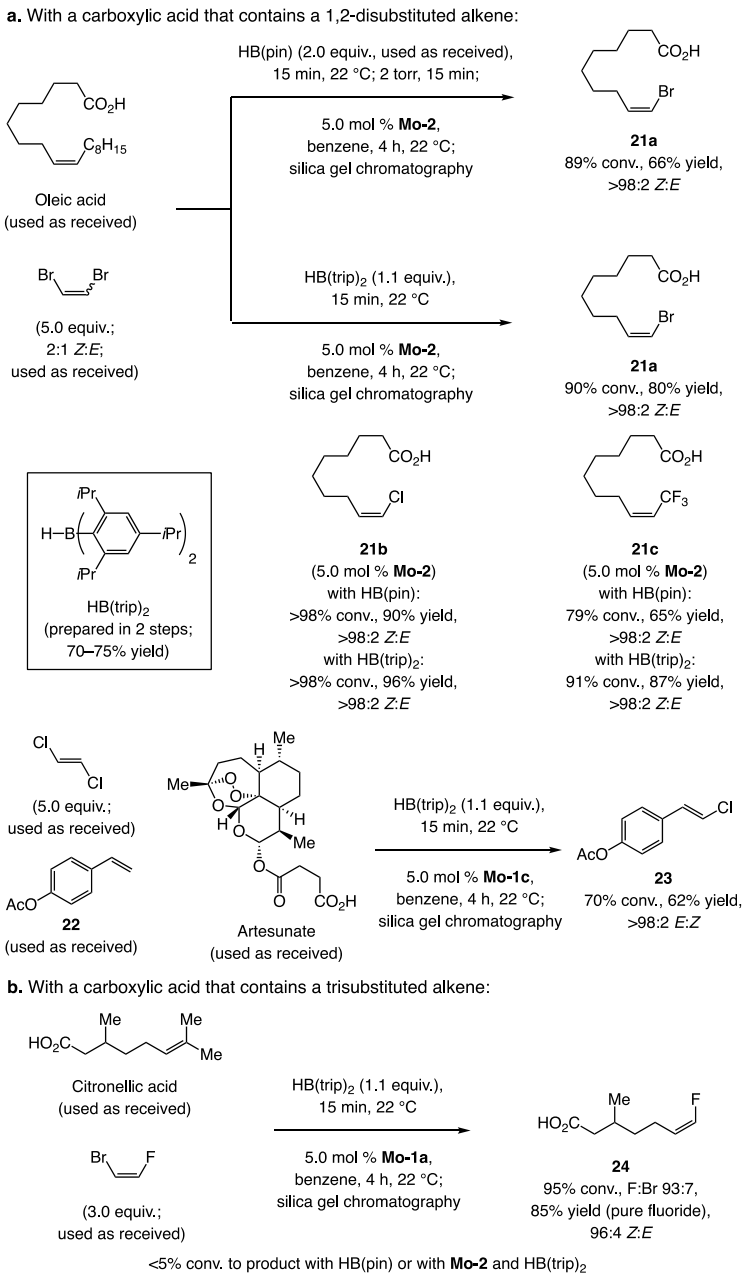



***Scheme 4.*** Traceless protection in cross-metathesis with phenolic alkenes.

subjection of the solution to mild vacuum (5 min, 2 torr) is needed to ensure maximum efficiency (e.g., without vacuum: 40% conv. with natural product eugenol); this shows that excess HB(pin) and/or its long term exposure to a Mo MAP or MAC complex can have an adverse impact (more on this below).

With oleic acid (Scheme 5), 2.0 equivalents of HB(pin) were needed and *Z*-alkenyl bromide **21a** was isolated in 66% yield (>98% *Z*). The need for excess borane was not surprising in light of the earlier data (cf. **20a**-**b**) and the lower Lewis basicity of a carboxylic acid. More disconcerting were the boron containing byproducts; one was confirmed to be (pin)BOB(pin) ($^{11}$B NMR, $\delta$ 21.7 ppm),[23] arising from bimolecular disproportionation of in situ generated carboxyl boryl compounds (to give a carboxylic anhydride).[24]

We therefore examined the effectiveness of HB(trip)$_2$. We surmised that this more sizeable alternative might be less susceptible to disproportionation and react less readily with a Mo alkylidene complex; although, boronate formation could be too slow as well. In the event, we prepared HB(trip)$_2$, a robust reagent that can be accessed in multi-gram quantities in two straightforward steps and 70-75%

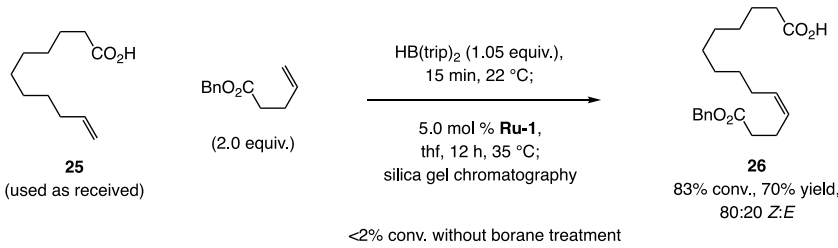



***Scheme 5.*** Transient protection in cross-metathesis with unsaturated carboxylic acids.

overall yield.[22] When pre-treatment with $HB(trip)_2$ was applied (1.1 equiv.), under otherwise identical conditions, we were able to isolate **21a** in 80% yield (vs. 66% with HB(pin); >98% *Z*). There was no byproducts and subjection to mild vacuum was not necessary. Synthesis of *Z*-alkenyl chloride **21b** and *Z*-$F_3C$-substituted alkene **21c** further highlight utility. The smaller difference in yields for alkenyl chloride **21b** might be attributed to the faster pace of this particular reaction, compared to those involving the less reactive *Z*-1,2-dibromoethene (cf. **21a**) or *Z*-1,1,1,4,4,4-hexafluoro-2-butene (cf. **21c**), which in turn implies that, as cross-metathesis rate is reduced, there is stronger likelihood that a borane reacts with a Mo complex.[25] The conversion of aryl olefin **22** to *Z*-alkenyl chloride **23**, carried out in the presence of

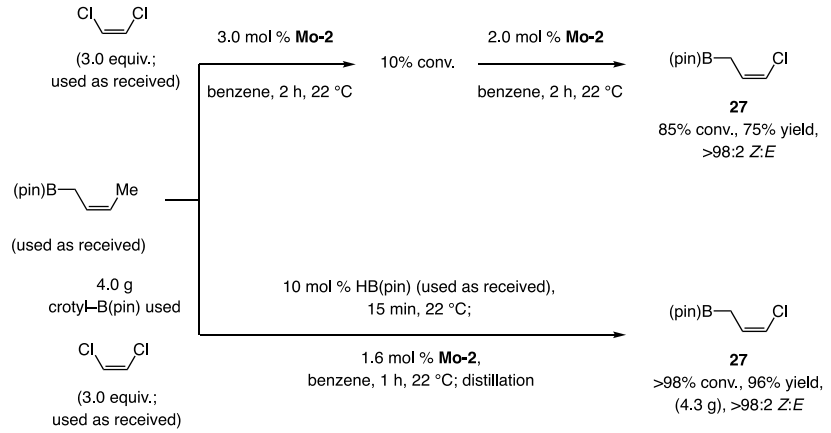
anti-malarial agent artesunate,[26] demonstrates applicability to relatively sensitive functional groups. Whereas trisubstituted alkene of citronellic acid was converted to *Z*-alkenyl fluoride **24** in the presence of 1.1 equivalents of $HB(trip)_2$ (85% yield, 96:4 *Z*:*E*), there was <5% conversion when HB(pin) was used or when the combination of the more sensitive **Mo-2** and $HB(trip)_2$ was employed (<5% conv.).

The present strategy may be used to improve reactions with Ru-based catalysts that, although effective with terminal alkenes (i.e., **Ru-1** vs. **Ru-2**),[10] do not tolerate a carboxylic acid. Whereas there was no conversion to **26** under a typical set of conditions (Scheme 6), the desired product was obtained in 70% yield when the mixture was charged with 5.0 mol % **Ru-1** after brief initial treatment with $HB(trip)_2$. There was <5% conversion with HB(pin), indicating that, similar to Mo-based systems, this class of Ru carbenes is susceptible to decomposition[27] when subjected to a reactive boron hydride. This example underscores a key advantage of the transient protection strategy, as **26** is a type of acid/ester compound, which would be difficult to access efficiently by site-selective hydrolysis of a diester. While stereocontrol is not optimal with **Ru-1**, the strategy should be germane to transformations with the more selective variants.[28]




***Scheme 6.*** The traceless protection strategy expands the scope of reactions catalyzed by Ru-based complexes.

The approach can be applied conveniently to removing residual moisture or other debilitating impurities, allowing for improved efficiency (Scheme 7). Subjection of *Z*-crotyl–B(pin) to *Z*-1,2-dichloroethene and 3.0 mol % **Mo-2** led to minimal conversion; only after the addition of another 2.0 mol % **Mo-2** were we able to isolate **27** in 75% yield (>98:2 *Z*:*E*). In contrast, with 4.0 gram of *Z*-crotyl–B(pin), after initial treatment with just 10 mol % HB(pin) for 15 minutes at room temperature before addition of




***Scheme 7.*** Commercially available HB(pin) may be used to remove residual moisture, allowing for enhanced efficiency.

just 1.6 mol % **Mo-2** for one hour, we obtained 4.3 grams of **27** (96% yield) as a single stereoisomer after distillation.

In closing, we present a practical solution to several key problems in the state-of-the-art in catalytic olefin metathesis, which are likely to have an immediate impact on stereoselective chemical synthesis. Development of additional traceless protection approaches that are applicable to other sensitive functional groups is in progress.

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**Keywords:** alkenes, catalysis, cross-metathesis, stereoselectivity, synthesis

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