Alkene Synthesis

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Stereoselective Synthesis of Tri- and Tetrasubstituted Alkenes by Iron-Catalyzed Carbometalation Ring-Opening Reactions of Cyclopropenes**

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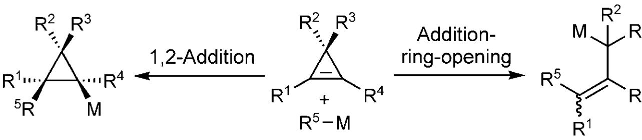
Alkenes are one of the major classes of chemical building blocks for organic synthesis. Although numerous methods exist for the preparation of alkenes, the stereoselective synthesis of tri- and tetrasubstituted[1] alkenes can still pose a significant challenge. One method that has enjoyed considerable success in this respect is the carbometalation of alkynes.[1–5] In this approach, the key issue is regioselectivity, which usually originates either from directing groups present in the substrate,[2] or from significant differences in steric and/or electronic properties between the two groups attached to the alkyne.[3] Although internal alkynes lacking either of these two features are a more challenging class of substrates from both regioselectivity and reactivity standpoints, encouraging progress has been documented in a number of recent publications.[4] These successes notwithstanding, the development of new carbometalation procedures[5] that tolerate an increased range of substrates and organometallic reagents, enabling access to a correspondingly broader array of alkenes, remains an important challenge. In particular, the continued development of methods that employ non-alkyne precursors is an attractive goal. Herein, we describe a carbometalation strategy that employs cyclopropenes as substrates, enabling the preparation of tri- and tetrasubstituted alkenes with excellent control of regio- and stereoselectivity. This process leads to β,γ-unsaturated ester building blocks, which can be difficult to prepare using alternative methods owing to possible migration of the alkene into conjugation.[6]

Owing to their highly strained nature, cyclopropenes exhibit a diverse range of reactivities, which present unique opportunities for organic synthesis.[7] Although cyclopropenes are susceptible to a range of useful carbometalation (and hydrometalation) reactions,[7,8] a significant majority of examples described to date result in preservation of the three-membered ring to provide highly functionalized cyclopropanes (Scheme 1, left).[7,8] We envisaged that development of a cyclopropene carbometalation reaction that is followed by cleavage of a C–C σ-bond could provide a powerful route to multisubstituted alkenes (Scheme 1, right). Within this manifold, critical selectivity issues that would need to be addressed are: a) carbometalation regioselectivity with unsymmetrical cyclopropenes ($R^1 \neq R^4$), and b) *E*/*Z* stereoselectivity of the alkene in the product.



Scheme 1. Addition of organometallic reagents (R^5–M) to cyclopropenes.

Surprisingly, despite the potential utility of such a transformation, relatively few examples have been described.[9] The single existing report of catalytic cyclopropene addition ring-opening reactions using carbon nucleophiles was restricted to active methylene compounds and 3,3-dihexylcyclopropene as the substrates.[9d] Furthermore, issues of regio- and stereoselectivity were not relevant in this case. The only examples of cyclopropene addition ring-opening reactions using hard organometallic reagents as nucleophiles were uncatalyzed, and displayed low efficiencies and limited scope.[9a–c] We speculated that synthetically more useful processes using hard carbon nucleophiles might be realized through the use of a catalyst to facilitate carbometalation, and by the presence of anion-stabilizing substituents at R^2 and R^3 to promote ring-opening.

Our experiments began with a brief survey of reactions of cyclopropenes with various organometallics in the presence of substoichiometric quantities of first-row d-block metal salts. These studies revealed that with cyclopropenes containing two electron-withdrawing groups at C3,[10] [Fe(acac)$_3$] (5 mol%) is able to promote the desired carbometalation ring-opening sequence using trialkylaluminum reagents.[11,12] Under optimized conditions, cyclopropenes **1a–1h**[13] reacted smoothly to provide a variety of trisubstituted alkenes **2a–2r** in good to excellent yields with high stereoselectivities (> 19:1) (Table 1).[6] Tolerated functionality at C3 encompassed a range of esters and a phenylsulfone, while both alkyl and aromatic substitution at the cyclopropene C=C bond were permitted. Regarding the scope of the organometallic reagent, trialkylaluminum moieties ranging from linear

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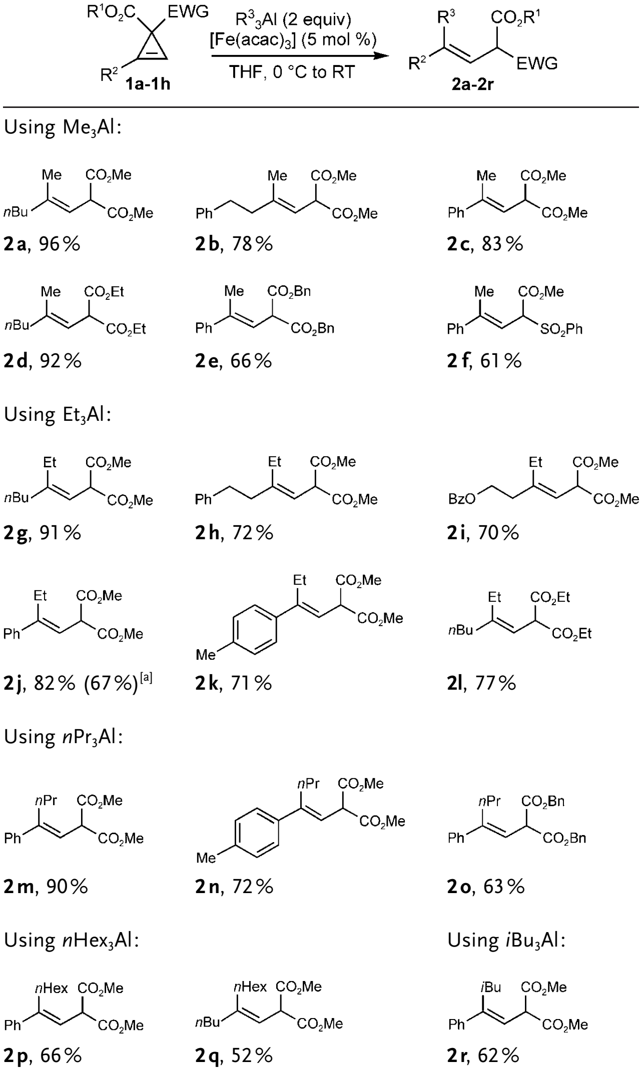
Table 1: Iron-catalyzed carbometalation ring-opening of cyclopropenes **1a–1h** with trialkylaluminum reagents.



Using Me$_3$Al:

2a, 96%
2b, 78%
2c, 83%
2d, 92%
2e, 66%
2f, 61%

Using Et$_3$Al:

2g, 91%
2h, 72%
2i, 70%
2j, 82% (67%)[a]
2k, 71%
2l, 77%

Using nPr$_3$Al:

2m, 90%
2n, 72%
2o, 63%

Using nHex$_3$Al:

2p, 66%
2q, 52%

Using iBu$_3$Al:

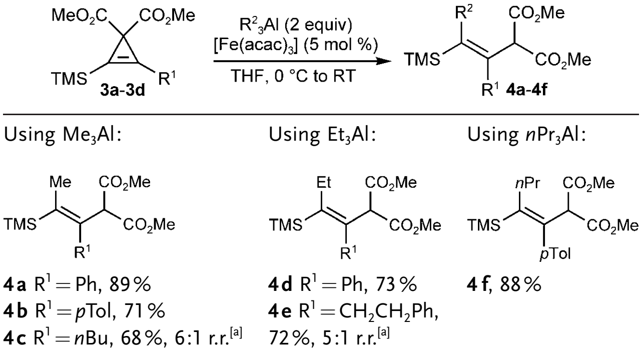
2r, 62%

[a] Yield in parentheses refers to an experiment conducted using 0.5 equivalents of Et$_3$Al.

(Me$_3$Al, Et$_3$Al, nPr$_3$Al, and nHex$_3$Al) to branched (iBu$_3$Al) were effective. The regioselectivities of these reactions were also uniformly high (> 19:1), the sense of regioselection being consistent with the majority of carbometalations of 1-alkylcyclopropenes described previously,[7b] wherein the alkyl nucleophile is delivered to the more substituted carbon of the alkene. Notably, 1-arylcyclopropenes, which have proven to be problematic substrates with respect to regioselectivity using other carbometalation procedures,[7b,8a,h] also underwent highly regioselective reactions under the present conditions.[14] Although two equivalents of the trialkylaluminum reagent were routinely used in our experiments, smaller quantities are tolerated. For example, alkene **2j** was isolated in 67% yield using only 0.5 equivalents of Et$_3$Al, demonstrating that transfer of more than one alkyl group from aluminum is possible. This finding augurs well for the use of more complex organoaluminum reagents in the future.

The more challenging task of tetrasubstituted alkene synthesis was next addressed. Using conditions identical to those employed in Table 1, a range of 1-trimethylsilylcyclopropenes **3a–3d** [13,15] underwent carbometalation ring-opening to provide α,β,β′-trisubstituted vinylsilanes **4a–4f** (Table 2).[16] Importantly, the sense of regioselectivity obtained in these reactions is opposite to that summarized in Table 1, with the alkyl group delivered preferentially to the TMS-bearing carbon. Regioselectivity was highest (> 19:1) with aryl-substituted cyclopropenes (preparation of **4a**, **4b**, **4d**, and **4f**). With alkyl-substituted cyclopropenes, formation of the regioisomer was detected (preparation of **4c** and **4e**).

Table 2: α,β,β′-Trisubstituted vinylsilane synthesis.



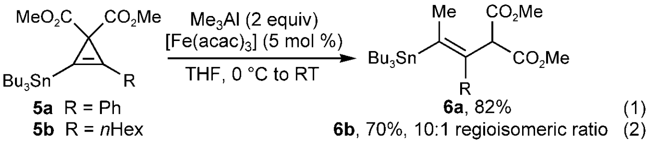
Using Me$_3$Al:
4a R^1 = Ph, 89%
4b R^1 = pTol, 71%
4c R^1 = nBu, 68%, 6:1 r.r.[a]

Using Et$_3$Al:
4d R^1 = Ph, 73%
4e R^1 = CH$_2$CH$_2$Ph, 72%, 5:1 r.r.[a]

Using nPr$_3$Al:
4f, 88%

TMS = trimethylsilyl. [a] r.r. = Regioisomeric ratio.

In similar fashion, the use of 1-stannylcyclopropenes enabled the synthesis of α,β,β′-trisubstituted vinylstannanes [Eq. (1) and Eq. (2)].

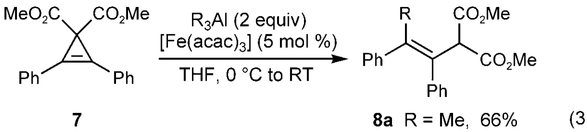


5a R = Ph
5b R = nHex

6a, 82% (1)
6b, 70%, 10:1 regioisomeric ratio (2)

Finally, this methodology was applied to preparation of all-carbon tetrasubstituted alkenes [Equations (3)–(5)].[1] Cyclopropenes **7** and **9** underwent efficient carbometalation ring-opening to provide tetrasubstituted alkenes **8a**, **8b**, and **10**. With unsymmetrical substrate **9**, the alkyl group was delivered preferentially to the methyl-substituted carbon of the cyclopropene [Eq. (5)].

Scheme 2 illustrates a possible catalytic cycle for these reactions. Reaction of [Fe(acac)$_3$] with the trialkylaluminum most likely generates a low-valent iron species **11**. *Syn*-carbometalation of the substrate **12** with **11** would generate cyclopropyl iron species **13**. β-Carbon elimination[17] of **13**



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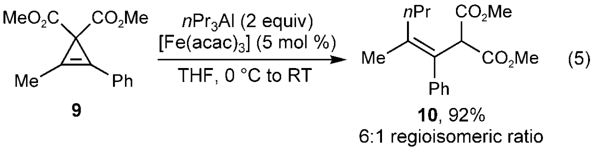
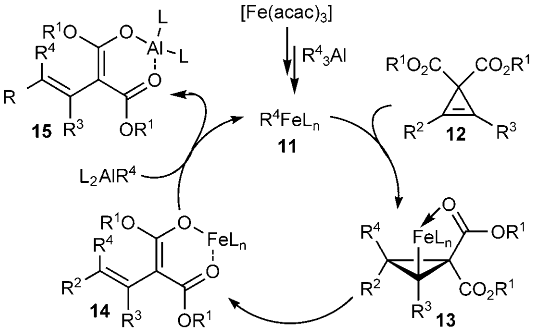
8a R = Me, 66% (3)
8b R = Et, 87% (4)

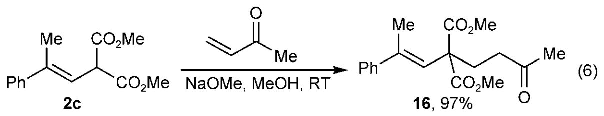


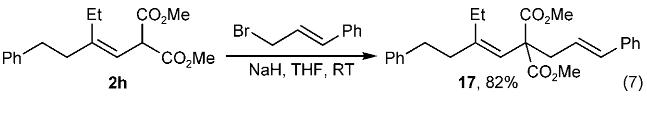


Scheme 2. Possible catalytic cycle. L = ligand.

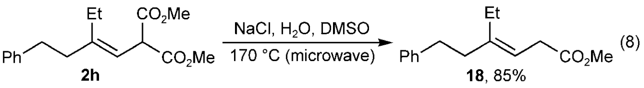
with conservation of the *cis*-relationship between R^2 and R^3 would then provide iron enolate **14**, which can undergo transmetalation with an alkylaluminum species (L_2AlR^4) to provide aluminum enolate **15** and regenerate **11**. The assistance of β-carbon elimination of **13** by Lewis acid coordination of the trialkylaluminum to the malonate to provide enolate **15** directly is a possibility that should also be considered.

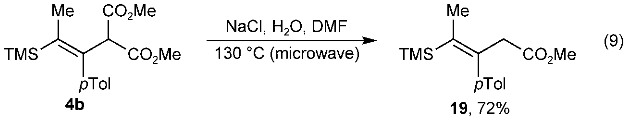
Although in situ functionalization of the aluminum enolates **15** was an attractive possibility for obtaining other compounds of interest, we found these species to be rather unreactive,[18] and attempted trapping with various electrophiles was unsuccessful. Therefore, our attention turned to elaboration of the isolated ring-opened products. A major concern with this approach was the potential sensitivity of these compounds towards isomerization of the alkene into conjugation with the esters, or scrambling of the *E*/*Z* stereochemistry of the alkene. However, we have not found these issues to be problematic. For example, Michael addition or alkylation of the ring-opened products was accomplished efficiently without compromising the integrity of the alkene [Eq. (6) and Eq. (7)].





Furthermore, Krapcho decarboxylation[19] of both tri- and tetrasubstituted alkenes proceeded smoothly under microwave irradiation to provide β,γ-unsaturated esters in good yields [Eq. (8) and Eq. (9)].





In summary, an iron-catalyzed cyclopropene carbometalation ring-opening sequence that enables the efficient synthesis of tri- and tetrasubstituted alkenes has been developed. The reactions proceed with high levels of regio- and stereocontrol to produce a range of multisubstituted alkenes that may be difficult to access by other means, including α,β,β′-trisubstituted vinylsilanes, α,β,β′-trisubstituted vinylstannanes, and all-carbon tetrasubstituted alkenes. In addition, the ring-opened products may be manipulated without affecting the alkene. Further investigations into the interesting reactivity of cyclopropenes will be reported in due course.

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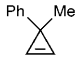

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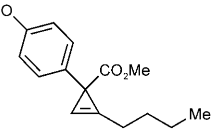

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