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N-Heterocycles from Chromium Aminocarbenes

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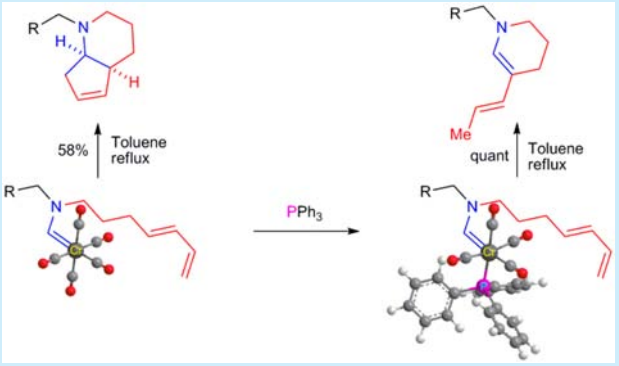
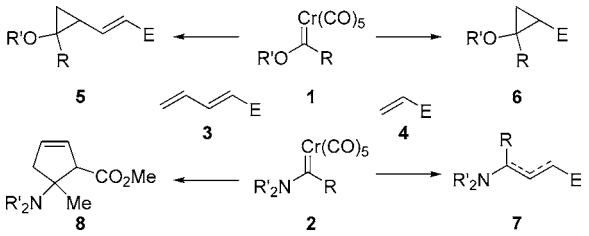
Supporting Information

ABSTRACT: The initial [2 + 2]-cycloadduct between a chromium aminocarbene and a tethered alkene undergoes a β-hydrogen elimination very efficiently when triphenylphosphine is added as a ligand. The reaction gives cyclic enamines or homoenamines depending on the substitution on the alkene.



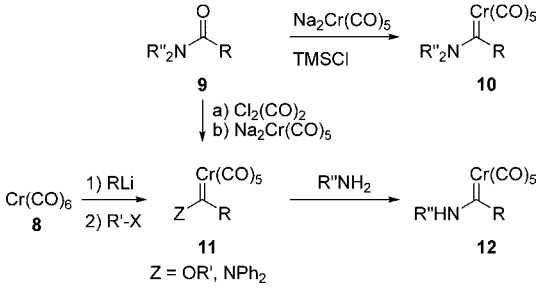
Chromium alkoxycarbenes **1** (CALC) and chromium aminocarbenes **2** (CAMC) are useful reactive intermediates and have been used to make a wide variety of organic compounds.[1,2] Both undergo a photochemically initiated formal [2 + 2]-cycloaddition with imines to give β-lactams, respectively.[3,4] Although both CALC and CAMC resemble each other by their structures and reactions, there are marked differences between these two Fisher carbenes: CAMC tend to be less reactive and are more stable than CALC; cyclopropanation is a main reaction pathway for CALC, not so for CAMC (e.g., **1** → **5** or **6** versus **2** → **7** or **8** Scheme 1).[5]

Scheme 1. Reactions of CALC 1 and CAMC 2



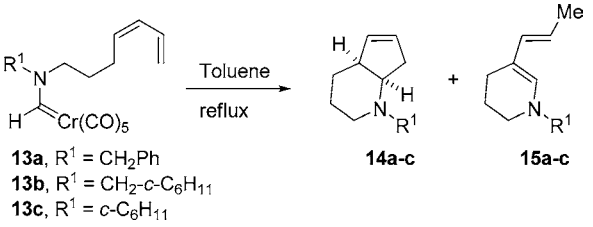
Chromium aminocarbenes have been generally less exploited than their chromium alkoxycarbenes counterpart.[1b,6,7] Reactions involving CAMC where the carbene carbon bears a hydrogen have been even less frequently described.[1d,3d,8] This may stem in part from the availability of methods for their preparation. A general method for CAMC synthesis involves the addition of pentacarbonylchromate ($M_2Cr(CO)_5$) to an amide **9** to give CAMC **10** (Scheme 2)[8b,9] Aminolysis of CALC is possible with primary or unhindered secondary amines (**11** → **12**). However, CALC **11** (Z = OR′) where R = H are not known; thus formamides (**9**, R = H) are, in effect, the only available source of CAMC **10** with R = H.

Scheme 2. Main Methods of Preparation of CAMC



We have shown that the latter can undergo a formal intramolecular [4 + 1]-cycloaddition when tethered to a diene, as in **13a**, to give *N*-heterobicyclic product **14a** in good yields (Scheme 3).[10] Dienamine **15a** often accompanied adduct **14a** as a byproduct and is the result of a β-hydride elimination on

Scheme 3. Formal [4 + 1]-Cycloaddition and β-Hydride Elimination of CAMC 13a−c Tethered to a Diene



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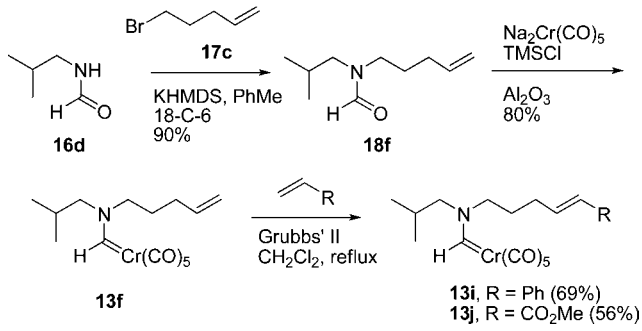
the purported [2 + 2]-metallocyclobutane intermediate (cf. Scheme 6). We have found that when 1 equiv of triphenylphosphine is added as a ligand to chromium, dienamine **15a** becomes the sole product of the reaction. We wondered if this reaction was general and could be performed on simple or substituted alkenes as opposed to dienes. We herein report that this reaction is indeed of wide scope and proceeds with electron-rich, electron-deficient, or unactivated alkenes and dienes, giving rise to a wide range of interesting *N*-heterocyclic structures.

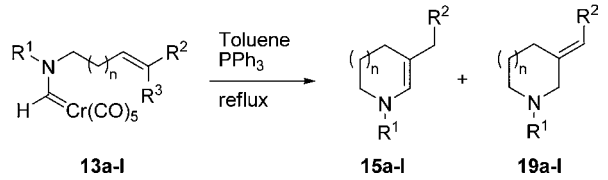
CAMC are stable species that can often be purified by chromatography on normal silica gel. They can tolerate the presence of many functional groups and reagents, with the exception of some oxidants.[1] In many ways, CAMC are amide surrogates and have a similar reactivity pattern.[11] Scheme 4 depicts syntheses of CAMC **13i–j** by the Semmelhack–Hegedus method.[8b] The tolerance of the chromium amino-carbene **13f** to alkene metathesis is remarkable and useful.[12]

Scheme 4. Synthesis of CAMC 13f and 13i–j



Heating CAMC **13a–c**, tethered to a diene, in the absence of triphenylphosphine, gave *N*-heterobicyclic products **14a–c**, respectively (Scheme 3).[10a] Heating CAMC **13a–c** in the presence of triphenylphosphine led to the formation of dienamines **15a**, **15b**, and **15c** as the sole products, respectively (Table 1, entries 1–3). Complete conversion of the CAMC **13a–c** to dienamines **15a–c** was monitored by NMR, but the latter are unstable to silica gel (even impregnated with Et_3N), and they could not be purified. Heating CAMC **13d**, tethered to an isolated alkene (as opposed to a diene), gave a surprising result: 3-methylenepiperidine **19d** was isolated in 69% yield as the only product, instead of the expected tetrahydropyridine **15d** (Table 1, entry 4). Using a shorter tether between the carbene and the alkene, the more volatile pyrrolidine **19e** was formed in 42% yield (Table 1, entry 5). Bulky groups on nitrogen are tolerated. Pyrrolidine **19g** was isolated in excellent yield (Table 1, entry 6). In this particular case, we did not add triphenylphosphine, and though the reaction is slower, the product can be easier to purify (2 h, 90% yield versus 1 h 70% yield with PPh_3). Therefore, the use of triphenylphosphine is not mandatory in the case of isolated alkenes. Substitution on the alkene as in **13h** is tolerated (Table 1, entry 7). However, trisubstituted alkenes were unreactive under these reaction conditions (Table 1, entry 12). Conjugating substituents on the alkene (**13i–k**) (Table 1, entries 8–11) led to the formation of the corresponding unstable enamines **15i–k**. These results are perplexing, but we offer a rationale for their occurrence (*vide infra*). We found that the use of polymer-bound triarylphosphine in these cases helps in the purification of these rather unstable products by sequestering chromium species after the

Table 1. Results of the Thermal Reaction of CAMC Tethered to Different Alkenes and Dienes



13a-l 15a-l 19a-l

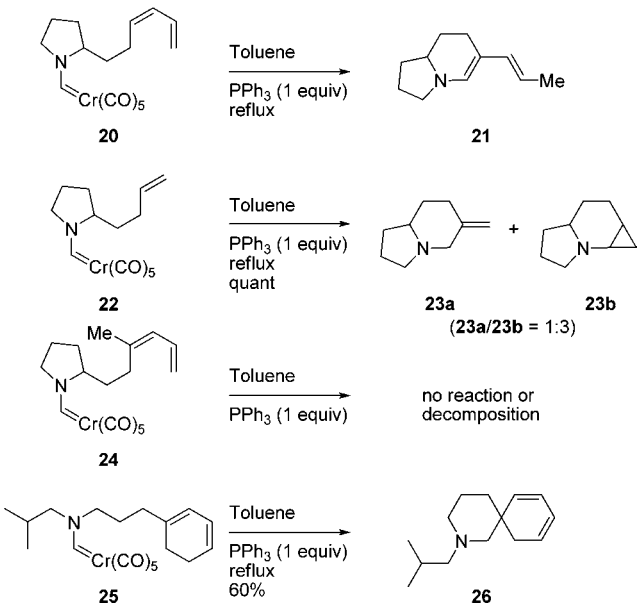
entry	R^1	R^2	R^3	*n*	13	yield (%)[a]	prd
1	Bn	CH=CH$_2$	H	1	**13a**	–[b]	**15a**[c]
2	CH$_2$(*c*-C$_6$H$_{11}$)	CH=CH$_2$	H	1	**13b**	–[b]	**15b**[c]
3	*c*-C$_6$H$_{11}$	CH=CH$_2$	H	1	**13c**	–[b]	**15c**[c]
4	*c*-C$_6$H$_{11}$	H	H	1	**13d**	69	**19d**
5	*c*-C$_6$H$_{11}$	H	H	0	**13e**	42	**19e**
6[d]	*t*-Bu	H	H	1	**13g**	90	**19g**
7	*t*-Bu	Me (*E*,*Z*-mix)	H	1	**13h**	72	**19h**[e]
8[f]	*i*-Bu	Ph	H	1	**13i**	33[b]	**15i**
9	*i*-Bu	CO$_2$Me	H	1	**13j**	–[b]	**15j**
10[f]	*i*-Bu	CO$_2$Me	H	1	**13j**	24[b]	**15j**
11[f]	*i*-Bu	C≡C–SiMe$_3$	H	1	**13k**	34[b]	**15k**
12	*c*-C$_6$H$_{11}$	Me	Me	1	**13l**	0	–

[a]Isolated yield of pure compound. [b]Complete conversion to **15** as monitored by NMR, product unstable to chromatography. [c]See Scheme 3 for the correct structure (double bond has moved into conjugation). [d]No Ph_3P was added. 70% yield with PPh_3 added. [e]*E*-geometry determined from NOE experiments. [f]Polymer-bound $ArPh_2P$ was used.

reaction.[13] For example, we could not purify **15j** properly when using the usual reaction conditions (Table 1, entry 9), but could achieve a 24% isolated yield of pure **15j** using the polymer-bound triarylphosphine (Table 1, entry 10).

More complex polycyclic structures are accessible. CAMC-diene **20** gave the bicyclic dienamine **21** while the analogous CAMC-alkene **22** gave the expected exocyclic double bond in bicyclic amine **23a** along with the unexpected cyclopropane **23b** (Scheme 5). As we alluded to earlier, cyclopropanation is

Scheme 5. Reactions of CAMC 20, 22, 24, and 25



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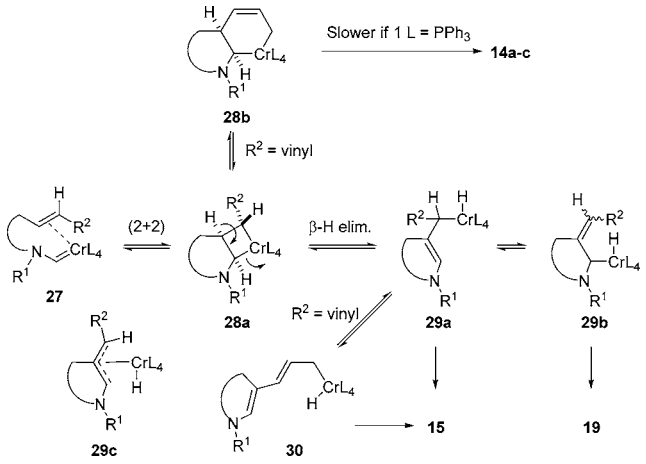
not a frequently encountered reaction with CAMC and the formation of **23b** is both rare and surprising. We do not know exactly why its formation is preferred in this case, but we suspect that a conformational preference in the corresponding metallacyclobutane **28** (Scheme 6) imposes a fast reductive elimination to the cyclopropane **23b**.

Scheme 6. Plausible Mechanism for the Formation of Products 15 and 19



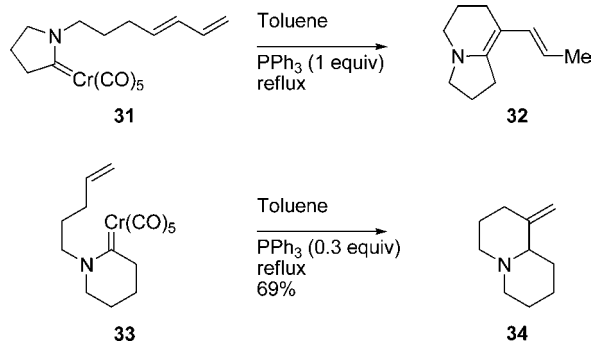
When there is no available hydrogen (CAMC **24**) to allow formation of the β-H elimination intermediates, then no reaction occurs at 110 °C and higher temperatures lead to decomposition. However, hydrogens at other positions may participate (**25** → **26**, Scheme 5).

Scheme 6 summarizes our proposed mechanistic steps that lead to product **15** or **19**.[10b] All intermediates depicted in Scheme 6 are probably under equilibrium. The scrambling of double bond geometry is good evidence for this (cf. Table 1, entry 7). The dependence on conjugation of the selectivity of formation of enamine **15** or compound **19** is difficult to explain. Based on the stability of the double bonds in the intermediate **29a** or **29b**, we could expect the selective formation of **19** when R^2 is conjugating and of the enamine **15** when R^2 is not conjugating. However, we observed the exact opposite. One possible explanation implies a π-allyl complex **29c**, where the hydride might be delivered at the position with the highest positive charge density, away from nitrogen. The cases of dienes **13a–c** and **20** are special because the corresponding stable dienamine intermediates **30** become available via allylic transposition.

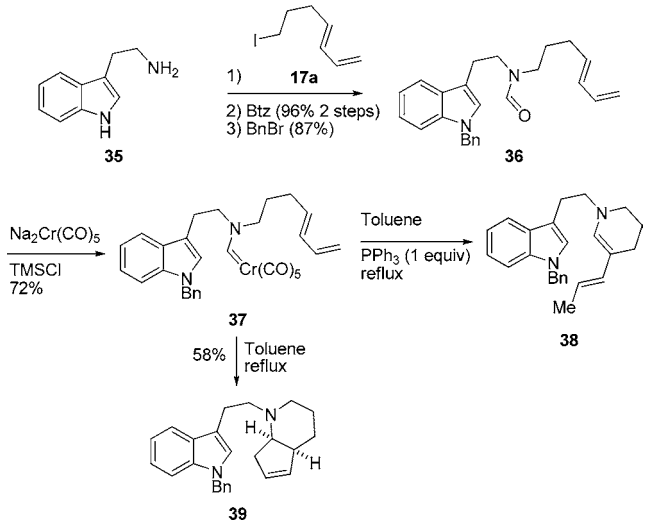
The β-H elimination pathway works well even in the cases of CAMC where the carbene carbon is substituted by a carbon atom (as opposed to a hydrogen). CAMC **31** was converted quantitatively to dienamine **32** while CAMC **33** gave a 69% isolated yield of perhydroquinolizine **34** (Scheme 7). One could imagine using such core structures to make natural alkaloids, and we tested this idea with a yet more complex substrate.

Scheme 8 shows the potential of this strategy in alkaloid synthesis. Tryptamine **35** was alkylated, acylated, and then protected to give formamide **36**. Heating its chromium carbene derivative **37** in the presence of triphenylphosphine gave a quantitative conversion to dienamine **38**. As alluded to earlier, we can control the outcome of the reaction by adding or omitting triphenylphosphine. For example, compound **39** could

Scheme 7. Reaction of CAMC 32 and 34



Scheme 8. Alkaloid-like Structures via Reaction of CAMC 37



be obtained in 58% isolated yield simply by omitting to add triphenylphosphine to the reaction flask. Both compounds are advanced intermediates in the synthesis of cylindrocarine alkaloids[14] or members of the corynanthe group of alkaloids,[15] respectively, which are underway in our laboratories.

Although the role of triphenylphosphine has not been unambiguously ascertained, we believe that it simply makes the metal more electron-rich. This would slow the reductive elimination step to the [4 + 1]-adduct, allowing for the β-H elimination to occur (Scheme 6). Initial results obtained with the use of other ligands (e.g., isonitriles and other phosphines) as well as other experiments support this view. A more complete mechanistic study will be reported in due course in a subsequent article.

From the point of view of the structural transformation, this reaction is related to the nucleophilic addition on activated amides.[16] However, the latter reaction requires electron-rich alkenes (enol ethers and allylsilanes for examples) whereas this new reaction of chromium aminocarbenes, involving a β-H elimination pathway, works well with electron-deficient, electron-rich, or unactivated alkenes. We have shown its scope to be wide, and we have presented examples of its synthetic potential. Control over two competing pathways (β-H elimination versus [4 + 1]-cycloaddition) is also possible for CAMCs tethered to a diene. A full report will be submitted in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Characterization data and copies of ^{1}H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) See ref 1c and 1e.

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