ORGANIC LETTERS

2013
Vol. 15, No. 21
5456–5459

N-Heteropolycyclic Compounds from the Formal Intramolecular (4 + 1)-Cycloaddition of Chromium Aminocarbenes

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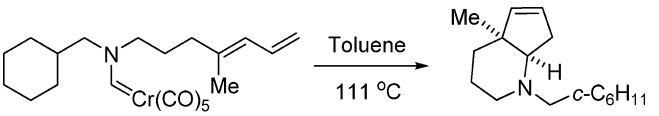
Received September 9, 2013

ABSTRACT



14 **15**

Chromium aminocarbenes tethered to dienes of all three electronic natures undergo an efficient intramolecular (4 + 1)-cycloaddition to give *N*-heteropolycyclic compounds. Ligands on chromium had a profound effect on the course of the reaction.

We have been interested in the (4 + 1)-cycloaddition as a way to synthesize five-membered carbocyclic compounds for some time.[1] We have used dialkoxyoxadiazolines (**1**, X = O) as precursors of free dialkoxycarbenes,[2] which undergo formal (4 + 1)-cycloadditions with electron-poor dienes to give adducts such as **2** (X = O, Scheme 1). However, while aminoalkoxyoxadiazolines (**1**, X = NR) can be prepared this way, they usually give unstable aminal-containing carbopentacycles **2** (X = NR).[3] Moreover, free alkoxycarbenes, bearing only one heteroatom, react with dienes to give only cyclopropanation products, thus limiting the scope of this methodology.[4] We therefore sought alternatives to making such compounds, and chromium alkoxy- and aminocarbenes[5] caught our attention. Chromium alkoxycarbenes (CALC) and chromium aminocarbenes (CAMC) are important reactive intermediates that undergo a plethora of reactions with alkenes, alkynes, and dienes.[6] Yet, they are often stable to air and to chromatographic purification. CALC complexes have been the subject of more studies and applications than their amino counterpart since the first report by Fischer on the synthesis of alkoxychromium complexes.[7] These species can undergo formal cycloaddition reactions with 1,3-dienes including (2 + 1)-,[8,9b] (3 + 2)-,[9,10a,10b] and (4 + 1)-cycloadditions[10] depending on the nature of the carbene and of the diene.[6c] However, the (4 + 1)-cycloaddition observed only in cases involving alkoxy(alkenyl)carbene

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(4) Bélanger, F. M.Sc. Thesis, University of Sherbrooke, Sherbrooke, QC, Canada, 2006.

(5) The first chromium aminocarbenes were synthesized by the group of E. O. Fischer: (a) Klabunde, U.; Fischer, E. O. *J. Am. Chem. Soc.* **1967**, *89*, 7141–7142. (b) Baikie, P. E.; Fischer, E. O.; Mills, O. S. *Chem. Commun.* **1967**, 1199–1200. (c) Connor, J. A.; Fischer, E. O. *Chem. Commun.* **1967**, 1024.

(6) For reviews of both chromium alkoxy- and aminocarbenes, see: (a) Schwindt, M. A.; Miller, J. A.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143–153. (b) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299–307. (c) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259–2283. (d) Dötz, K. H.; Stendel, J., Jr. *Chem. Rev.* **2009**, *109*, 3227–3274. (e) Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *Chem. Commun.* **2010**, *46*, 7670–7687. (f) Fernandez, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res.* **2010**, *44*, 479–490.

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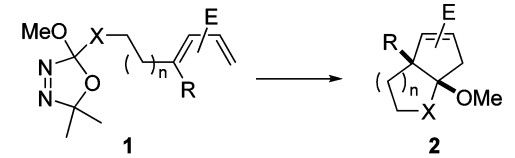
(8) Buchert, M.; Reissig, H.-U. *Liebigs Ann.* **1996**, 2007–2013.

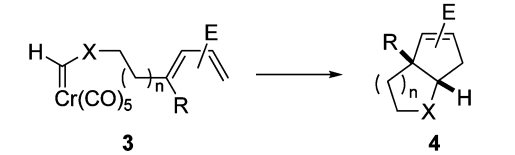
(9) For lead references, see: (a) Kagoshima, H.; Fuchibe, K.; Akiyama, T. *Chem. Record* **2007**, *7*, 104–114. (b) Hoffmann, M.; Buchert, M.; Reissig, H.-U. *Chem.—Eur. J.* **1999**, *5*, 876–882.

10.1021/ol4025887
Published on Web 10/11/2013

complexes. It is often a minor pathway in competition with the more prominent (3 + 2)-cycloaddition pathway.[10,11] Five-membered carbocycles[12] have been prepared by the (3 + 2)-cycloaddition of alkynes with β-amino-α,β-unsaturated carbene complexes,[13] alkoxycarbenes,[10,11] and cyclopropyl alkoxycarbenes.[14] With some notable exceptions,[10d] alkenes and dienes react with CALC to give cyclopropane products.[15]

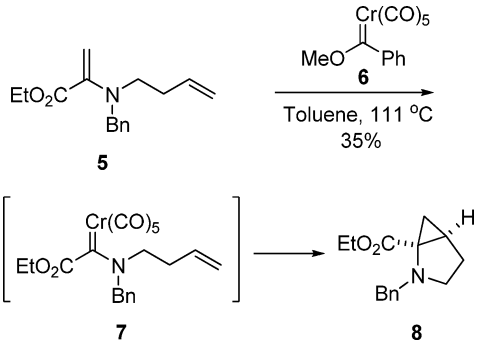
Scheme 1. Oxadiazolines and Chromium Carbenes



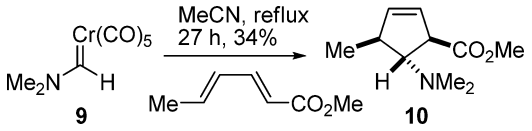


CAMCs are less reactive than their alkoxy counterpart toward alkenes and have thus seen fewer applications. Examples of cyclopropanations with CAMCs are scarcer than ones involving CALCs. One example is shown in Scheme 2.[16] It is believed that the ester substituent on aminocarbene **5** increases its reactivity by depleting the electron density on chromium. There is one example of an intermolecular (4 + 1)-cycloaddition between a dimethylaminocarbene complex and (*E*)-methyl penta-2,4-dienoate giving the cyclopentene product in 34% yield (Scheme 3).[17]

Scheme 2. Intramolecular Cyclopropanation of a Chromium Carboxyaminocarbene



Scheme 3. Formal (4 + 1)-Cycloaddition of Chromium Dimethylaminocarbene and (*E*)-Methyl Penta-2,4-dienoate



This is, in fact, the first and only example of a formal (4 + 1)-cycloaddition involving a CAMC and a diene.

Our initial foray into using CALCs to effect formal (4 + 1)-cycloadditions with dienes met with failure, not unexpectedly. The former gave exclusively cyclopropanation products while chromium dimethoxycarbene[18] was completely unreactive. We decided to explore the potential of CAMCs to give (4 + 1)-cycloadducts, cognizant of their lower propensity to undergo cyclopropanation reactions. However, we were unable to improve on the results obtained by Hegedus and his co-workers for the intermolecular reaction of **9** to give **10** (Scheme 3). On the other hand, when we heated a series of CAMC tethered to a diene (**11**), we were delighted to find that the intramolecular version of this reaction proceeds quite efficiently to give the corresponding (4 + 1)-cycloadducts (Table 1). The first striking observation from the results listed in Table 1 is that the reaction proceeds whether electron-deficient (entries 1 and 5), electron-rich (entry 4), or unactivated dienes (entries 2 and 3) are involved. No other (4 + 1)-cycloaddition methodology we know of, formal or not, displays this highly desirable feature. Esters, ethers, and silyl ethers were compatible with the reaction. The nitro derivative **11f** decomposed upon heating, perhaps owing to the increased acidity of the allylic protons. The *cis* ring junction was obtained in all cycloadducts **12** and **13**, and the major product **12** has the *syn* stereochemistry relative to the other chiral carbons.

Yields were even higher with unactivated dienes, ranging between 60% and 85% (Table 2). Fused 5−5 (**15a**) and 5−6 bicyclic compounds (**15b**) could be prepared

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(13) (a) de Meijere, A. *Pure Appl. Chem.* **1996**, *68*, 61–72. (b) Flynn, B. L.; Funke, F. J.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 1007–1010. (c) Flynn, B. L.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 812–814. (d) Duetsch, M.; Vidini, S.; Stein, F.; Funke, F.; Noltemeyer, M.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1679–1680.

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(16) Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett.* **2002**, *4*, 4273–4276.

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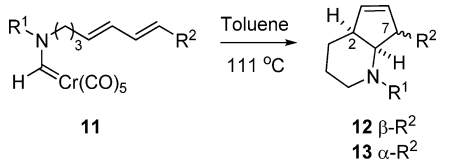
(18) Imwinkelried, R.; Hegedus, L. S. *Organometallics* **1988**, *7*, 702–706.

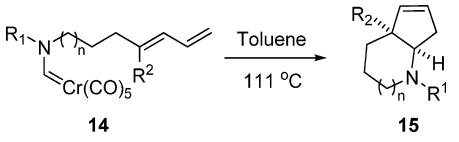
Table 1. Effect of Substituent R^2

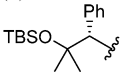


entry	R^1	R^2	11	yield (%)[a]	ratio 12:13
1	Bn	CO_2Me	**a**	43[b]	3:1[c]
2	Bn	$CH_2OTBDPS$	**b**	58	2:1[d]
3	*i*-Bu	Ph	**c**	62	3:2[d]
4	*i*-Bu	*p*-MeOPh	**d**	61	3:2[d]
5	*i*-Bu	*p*-(MeO_2C)Ph	**e**	59	3:2[d]
6	*i*-Bu	*p*-(O_2N)Ph	**f**	0	–

[a] Isolated yield. [b] Includes 21% of the product, in which the double bond has migrated in conjugation with the ester (see Supporting Information). [c] Determined by ^{1}H NMR. [d] Determined by GC.

Table 2. (4 + 1)-Cycloaddition with Nonactivated Dienes



entry	n	R^1	R^2	15	yield (%)[a]
1	0	CH_2-*c*-C_6H_{11}	H	**a**	60
2	1	CH_2-*c*-C_6H_{11}	H	**b**	66
3	1	CH_2-*c*-C_6H_{11}	Me	**c**	72[b]
4	1	CH_2-*c*-C_6H_{11}	Me	**c**	85[c]
5	1	(*S*)-α-MeBn	H	**d,e**	80[d]
6	1		H	**f,g**	64[e]

[a] Determined by ^{1}H NMR. [b] Reaction in refluxing *m*-xylene; *cis*/*trans* ratio was measured at 13:1. [c] 1.05 equiv of PPh_3 added. [d] dr = 60:40. [e] dr = 70:30.

(entries 1 and 2) although the corresponding fused 5−7 system could not be made in this way. Steric hindrance is well tolerated on the nitrogen atom (entries 5 and 6). Asymmetric induction was low in these two cases (60:40 and 70:30 d.r., respectively) but we have not yet studied this aspect in any depth. More importantly, the formation of a quaternary carbon was possible (**15c**) in 72% yield in xylene at 139 °C (entry 3). At that temperature, a small amount of the cycloadduct having the *trans* ring junction was observed (< 8%). Interestingly, the addition of 1.05 equiv of PPh_3 substantially increased the reactivity of the carbene and the cycloadduct **15c** could now be obtained in 85% yield at 111 °C. The significant effect of ligands such as phophines or amines on the reactivity of chromium carbene has already been observed in other reactions.[19]

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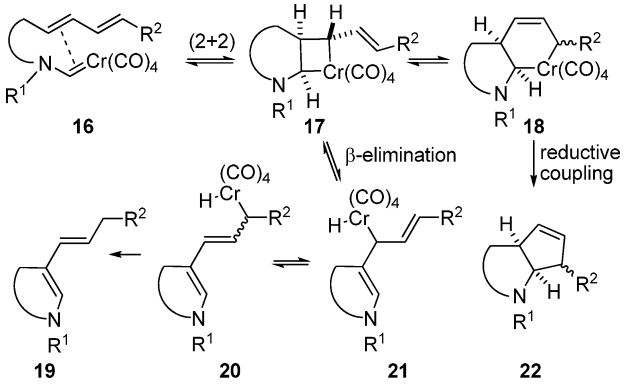
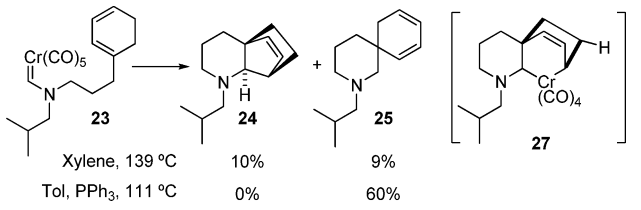
Scheme 4. Mechanistic Portrait of the Reaction



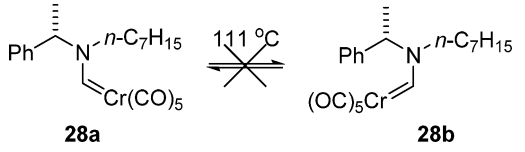
We have observed that, with most substrates, the addition of PPh_3 had a major influence on reaction rate and the nature of the final product. In most cases, an enamine was observed as the major or only product in the crude reaction mixture, though it proved unstable to purification. This enamine (**19**) could come from a β-elimination pathway (Scheme 4). Even though the details of the mechanism are not known, we believe that it should start in a similar fashion to the one proposed for the cyclopropanation of olefins by chromium alkoxycarbenes:[17] after the departure of one carbon monoxide ligand, the alkene nearest to the carbene coordinates the chromium (**16**) and undergoes a (2 + 2)-cycloaddition to form the metallacyclobutane **17**. This species is also an allyl chromium that will be in equilibrium with **18** from which a reductive coupling leads to the desired (4 + 1)-cycloaddition product **22**. However, either intermediate **17** or **18** can undergo β-elimination with one of the hydrogens at the ring fusion to give **21** and **20**, respectively. The two species are likely in equilibrium. Reductive coupling from species **20** gives the observed conjugated enamine **19**. It is not yet clear why triphenylphosphine favors the β-elimination process.

Triphenylphosphine increases the overall reaction rate and yield of the (4 + 1)-cycloaddition when a hydrogen at the ring fusion is absent (entry 4). However, in cases where the steric encumbrance is too high, β-elimination at other sites becomes competitive. The reaction of compound **23** illustrates this point (Scheme 5). While the reaction without PPh_3 in refluxing xylene gave 10% of the (4 + 1)-cycloaddition product **24**, in this particular case, the addition of PPh_3 led to a very clean and rapid reaction in refluxing toluene giving diene **25** as the sole product in 60% yield. Presumably, intermediate **27** undergoes β-elimination faster than reductive coupling because of steric hindrance and strain in (4 + 1)-cycloadduct **24**. Also, preliminary investigations of CAMCs that possess a carbon atom attached to the carbene instead of hydrogen show that they require high temperature and/or the addition of triphenylphosphine in order to react and only the dienamine, the product of a β-elimination, was isolated (see Supporting Information, CAMC **76**).

Scheme 5. Effect of the Addition of PPh_3



Scheme 6. Heating CAMC Rotamers **28a** and **28b**



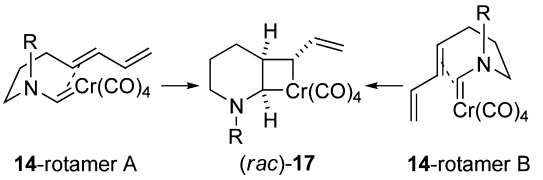
As is the case for formamides, CAMCs have a strong rotation barrier for the N−C bond, estimated to be greater than 25 kcal/mol.[20] The two rotamers do not equilibrate at room temperature and can be separated by chromatography and isolated without any subsequent equilibration. A fully saturated homologue of substrate **14d** was synthesized, and the rotamers **28a** and **28b** were separated by flash chromatography. Heating the major rotamer (we believe it to be **28a**) to 111 °C for 30 min showed no equilibration (^{1}H NMR) (Scheme 6). A mixture of the two rotamers was also heated, and their ratio was shown to be constant over time.

The stereoisomeric ratio of the cycloadducts **12**, **13**, or **15** do not reflect the starting ratio of the corresponding CAMC rotamers. This implies that both CAMC rotamers react independently to give the same final products. By admitting that the first step of the mechanism is a (2 + 2)-cycloaddition, both CAMC rotamers could react with the internal double bound with the linker chain being in a boat conformation. For reasons of orbital alignment, both reactions would result in the formation of **17** with the same relative stereochemistry (Scheme 7).

Our preliminary investigation shows that CAMCs tethered to a diene undergo efficient formal intramolecular (4 + 1)-cycloadditions to give bicyclic *N*-hetereocyclic

(20) Moser, E.; Fischer, E. O. *J. Organomet. Chem.* **1968**, *13*, 387–398.

Scheme 7. Mechanistic Approach for the Two CAMC Rotamers



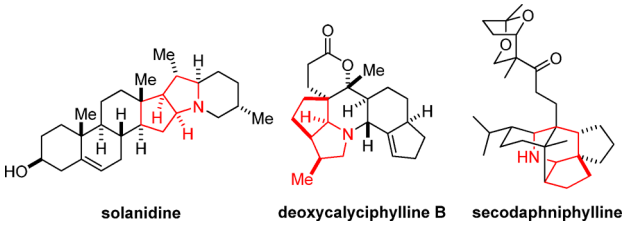


Figure 1. Complex natural products embedding the structural motif from the formal (4 + 1)-cycloadditions of CAMCs.

compounds. The reaction proceeds well with dienes of all electronic natures and more so with unactivated ones. The formation of quaternary centers demonstrates the potential of this reaction for target oriented synthesis. The structural motifs generated by the intramolecular (4 + 1)-cycloaddition of CAMCs is embedded in a large number of natural alkaloids (Figure 1), but it can also be used to construct other motifs thanks to the versatility of the alkene functionality. The addition of PPh_3 was shown to have a strong influence on the rate and outcome of the reaction, and studies are being conducted to better understand the mechanistic details of the reaction.

Acknowledgment. We wish to thank the Natural Sciences and Engineering Research Council of Canada, the Fonds Québécois de Recherche − Nature et Technologie, and the Université de Sherbrooke for financial support.

Supporting Information Available. Experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.