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Transition Metal-Catalyzed Hetero-[5 + 2] Cycloadditions of Cyclopropyl Imines and Alkynes: Dihydroazepines from Simple, Readily Available Starting Materials

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Previous studies in our laboratory on new transition metal-catalyzed [$m + n$] cycloadditions have produced the first [5 + 2] and [6 + 2] cycloadditions of vinylcyclopropanes (VCPs) and vinylcyclobutanes with π-systems.[1−3] More recently, we have explored the extension of these concepts for two-component [$m + n$] cycloadditions to three-component [$m + n + o$] cycloadditions,[2d] leading thus far to the first [5 + 2 + 1] cycloadditions of VCPs, π-systems, and CO. To further enlarge this body of new reactions and expand their synthetic utility, we have started to investigate whether one or more heteroatoms could be introduced into any or all of the [$m + n$ (+ o)] components and report herein the first transition metal-catalyzed hetero-[5 + 2] cycloadditions, leading to a new route to dihydroazepines.[4]

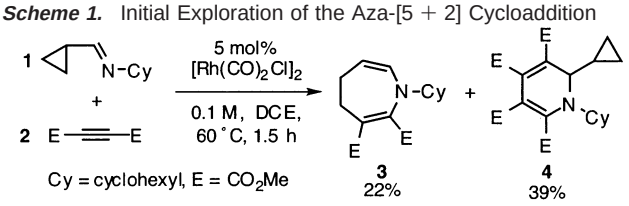
Drawing a connection to our work on VCPs as 5C cycloaddition partners, Murai et al. have recently shown that cyclopropyl imines can be used in a $Ru_3(CO)_{12}$-catalyzed carbonylative cycloaddition to provide a novel [5 + 1] cycloaddition route to six-membered unsaturated lactams.[5] The proposed intermediate in this process, azaruthenacycle **A** (Scheme 2), is analogous to a rhodacyclohexene which we proposed and have identified (NMR) as a possible intermediate or resting state in one mechanism for the [5 + 2] cycloaddition of VCPs.[2a,b] These observations led us to explore whether cyclopropyl imines could be used as hetero five-atom components in metal-catalyzed [5 + 2] cycloadditions.[6]

Our initial attempt at achieving an aza-[5 + 2] cycloaddition involved reaction of **1** and **2** with $[Rh(CO)_2Cl]_2$ as catalyst in dichloroethane (DCE) at 60 °C (Scheme 1). Gratifyingly, the dihydroazepine **3** was obtained, albeit in low yield. Subsequent control experiments demonstrated this cycloaddition did not occur in the absence of a catalyst or with simple Lewis acids.[7] The isolation of dihydropyridine **4**, the product of a [2 + 2 + 2] cycloaddition of alkyne **2** and imine **1**, was key to controlling the selectivity of this process.[8]

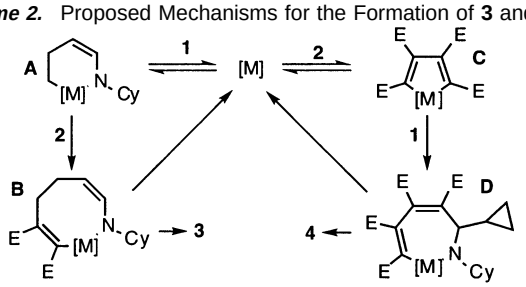
As a working hypothesis, dihydroazepine **3** could arise from the initial formation of metallacycle **A** (Scheme 2). Migratory insertion of dimethyl acetylenedicarboxylate (DMAD) **2** into **A** would generate metallacycle **B**. As we previously proposed for [5 + 2] cycloadditions of VCPs, an alternative path would entail formation of an azametallacyclopentene followed by ring expansion to **B**.[2a] In either case, **B** upon reductive elimination would yield **3** and catalyst. At higher concentrations of DMAD, the formation of **C** would be favored, giving rise to **4** via **D**.

On the basis of this analysis and certain rate assumptions, the formation of **3** would be favored by a low concentration of **2**, which in turn could be achieved by slow addition. This procedural change proved to be highly successful. When DMAD was added over 12.5 h to a solution of imine **1** in toluene,[9] the dihydroazepine **3** was

Scheme 1. Initial Exploration of the Aza-[5 + 2] Cycloaddition



Scheme 2. Proposed Mechanisms for the Formation of **3** and **4**



formed in 85% yield (GC) and isolated in 83% yield.[10] Several other imines were also examined (Table 1) and found to react with similar efficiency. The modest yield variation as a function of *N*-alkyl group is thought to be a function of product hydrolysis during purification. Entry 5 is of mechanistic interest, as the imine is flanked by two cyclopropyl rings and therefore could react to give product **8** or a 2*H*-5,6-dihydro regioisomer.[11] Only **8** is observed. In general, dihydroazepines are formed in good to excellent yields.

With the initial success of this hetero-[5 + 2] cycloaddition, we sought to determine whether this new route to dihydroazepines could be further simplified through in situ imine formation, providing effectively a three-component process. Toward this end, the aldehyde and amine were combined in toluene and water was removed azeotropically using a Dean−Stark trap. The reaction temperature was then lowered to 60 °C, after which the catalyst was added. Slow addition of the alkyne in toluene afforded the desired dihydroazepines in good to excellent yields (Table 2). This serial imine formation/aza-[5 + 2] cycloaddition enables a dihydroazepine synthesis from three commercially available starting materials. Attempts at simultaneous imine formation/aza-[5 + 2] cycloaddition with either $MgSO_4$ or molecular sieves were unsuccessful.

To explore the scope and synthetic utility of this reaction, the effect of substituents on the cyclopropane ring was investigated. 2-Methylcyclopropanecarboxaldehyde **11** (Scheme 3) was selected to examine the regiochemical outcome of the cyclopropane cleavage. As observed in our work on [5 + 2] cycloadditions of VCPs, cleavage of the less substituted cyclopropyl bond is observed, leading to dihydroazepine **12** as a single regioisomer.[12,13] Substitution at the 1-position of the cyclopropane is also tolerated, even

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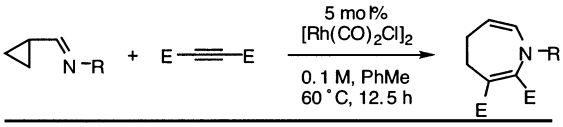
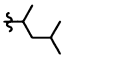
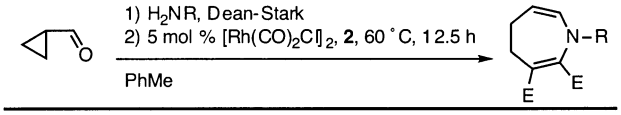
Table 1. Aza-[5 + 2] Cycloadditions with Various Imines



entry	R =	Product	yield[a]
1	Cy	**3**	85% (83%)
2	*n*-hexyl	**5**	95% (91%)
3		**6**	(83%)
4		**7**	(79%)
5		**8**	68% (61%)

[a] GC yield (isolated yield).

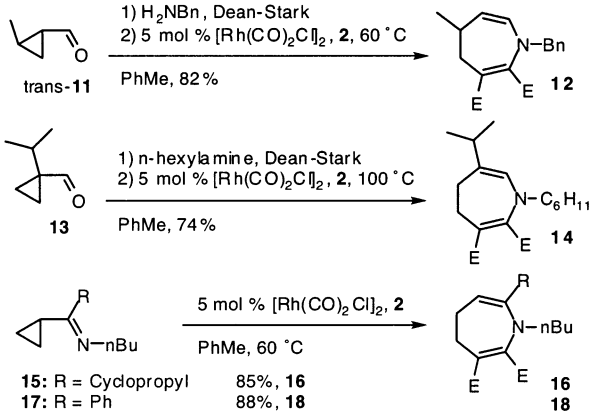
Table 2. Serial Imine Formation/Aza-[5 + 2] Cycloadditions



entry	R =	Product	yield[a]
1	Cy	**3**	94% (91%)
2	Bn	**9**	87% (84%)
3		**10**	99% (95%)

[a] GC yield (isolated yield).

Scheme 3. Aza-[5 + 2] Cycloadditions with Substituted Substrates

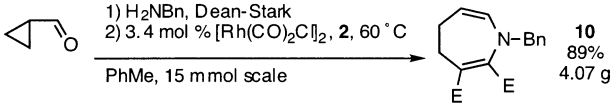


though such systems are sterically encumbered. For example, 1-isopropylcyclopropanecarboxaldehyde **13** is smoothly converted to dihydroazepine **14**, albeit at a slightly higher temperature (100 °C). Of further note is the finding that the reaction also works for ketimines, with **15** and **17** reacting to provide the highly functionalized dihydroazepines **16** and **18**. It is interesting that the VCP subunit of **16** does not engage in a second [5 + 2] cycloaddition under these conditions.

Aza-[5 + 2] cycloadditions enable rapid assembly of dihydroazepine building blocks useful in the synthesis of more complex molecules. To explore the preparative potential of this process, an *N*-benzyl imine was selected for study since the benzyl group could be removed in the dihydroazepine cycloadduct. Gratifyingly, we were able to conduct the aza-[5 + 2] cycloaddition on a 15 mmol scale, generating 4.07 g (89% isolated yield) of the expected dihydroazepine **10** (Scheme 4).

In summary, the first transition metal-catalyzed hetero-[5 + 2] cycloadditions and a new method for dihydroazepine synthesis are

Scheme 4. Preparative Scale Aza-[5 + 2] Cycloaddition



described. This new cycloaddition works well with a Rh(I) catalyst (other catalysts are being screened). The dihydroazepine cycloadducts are readily derived from either preformed or in situ generated cyclopropyl imines. The serial imine formation/aza-[5 + 2] cycloaddition enables dihydroazepine synthesis from three commercially available starting materials in one operation, effectively a three-component cycloaddition. This reaction works with aldimines, ketimines, and substituted cyclopropanes. Single regioisomers are obtained. These reactions are also readily scaled, generating multigram quantities of the substituted dihydroazepines, compounds of use as synthetic building blocks and as scaffolds for combinatorial synthesis. Further studies are in progress.

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Supporting Information Available: Spectroscopic data and experimental details for cycloadducts **3**−**10**, **12**, **14**, **16**, and **18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) For a general review, see: Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25−31.

(2) For the initial examples, see the following. Intramolecular [5 + 2] cycloadditions: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. Intermolecular [5 + 2] cycloadditions: (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. [6 + 2] cycloadditions: (c) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815−7816. [5 + 2 + 1] cycloadditions: (d) Wender, P. A.; Gamber G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876−2877.

(3) For recent examples, see the following. Intramolecular [5 + 2] cycloadditions: (a) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323−2326. Intermolecular [5 + 2] cycloadditions: (b) Wender, P. A.; Gamber G. G.; Scanio, M. J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3895−3897.

(4) For a review of azepine natural products, see: O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637−651.

(5) (a) Kamitani, A.; Chatani, N.; Morimoto, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 9230−9233. For a review of carbonylative cycloadditions, see: (b) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414−422.

(6) Examples of heteroatom variants of the five-carbon VCP include vinylaziridines, vinyl epoxides, *C*-cyclopropyl imines, *N*-cyclopropyl imines, and cyclopropanecarboxaldehydes.

(7) In a limited screening of catalysts, $[Rh(CO)_2Cl]_2$ gave the best results in the unoptimized cyclization of **1** and **2** to **3**. $Ir(Cl)(CO)(PPh_3)_2$ and $RhCl(PPh_3)_3$ gave 6% and 5% isolated yields of **3**, respectively, and >50% isolated yield of **4**. $Ru_3(CO)_{12}$ or $MgSO_4$ was ineffective as a catalyst.

(8) (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 6844−6845 and references therein. (b) For a review of [2 + 2 + 2] cycloadditions, see: Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915.

(9) Toluene proved to give the highest yields. Other solvents (e.g., THF, EtOAc, Et_2O, acetone) gave yields which were generally lower.

(10) The current reaction conditions work best with acetylene diesters. Acetylene monoesters, phenyl acetylene, and propargyl alcohol derivatives were unreactive. Further studies on alkyne variations are in progress.

(11) A previous attempt on use of *N*-cyclopropyl benzaldimine as substrate for a hetero-[5 + 2] cycloaddition was unsuccessful.

(12) (a) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442−10443. (b) Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089−2092.

(13) The regiochemical outcome was determined by decoupling NMR experiments detailed in the Supporting Information.

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