A Ruthenium-Catalyzed Pyrrolidine and Piperidine Synthesis

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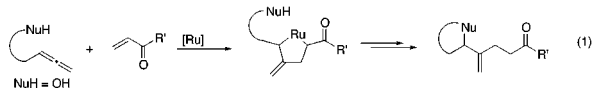
The importance of nitrogen heterocycles, especially pyrrolidine and piperidine types, as subunits of bioactive molecules stimulates the development of new synthetic methods.[1] Our recent success in a ruthenium-catalyzed cycloetherification[2] induced us to question whether such a catalytic system could be extended to nitrogen nucleophiles to create an analogous process as outlined in eq 1. Unfortunately, previous work in our laboratories suggested



(1)

that basic amines served as catalyst poisons in many of our ruthenium-catalyzed reactions.[3] Furthermore, the fact that nitrogen nucleophiles are normally good Michael-type donors in contrast to alcohols raises the question of the direct addition of the nitrogen nucleophile to the vinyl ketone. Nevertheless, the importance of the target stimulated us to investigate whether some class of nitrogen nucleophile might serve in a ruthenium-catalyzed pyrrolidine or piperidine synthesis.[4,5]

Initially, we examined the use of various amide and sulfonamide nucleophiles (eq 1, e.g. NuH = NHTs, NHBoc) to form cyclic nitrogen compounds.[6] However, under a variety of conditions, only 1,3-dienes were formed in analogy to our earlier work.[7] Despite our misgivings, we turned to simple amines. Since β-hydrogen elimination competes with heterocycle formation, according to our working hypothesis, the faster rate of formation of a five-membered ring led to exploration initially of a pyrrolidine synthesis. Surprisingly, we found that the use of secondary amines under our conditions for cycloetherification (1.5 equiv of methyl vinyl ketone (MVK), 10 mol % **1**,[8] 15 mol % $CeCl_3 \cdot 7H_2O$, DMF, 60 °C) led to the desired cyclic amine albeit in low yield. We therefore examined the optimization of the reaction shown in eq 2 as summarized in Table 1, using allene **2** and 1.5 equiv of MVK.

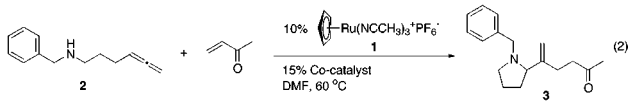
Table 1. Selected Optimization for Equation 2

entry	cocatalyst	isolated yield **3** (%)	entry	cocatalyst	isolated yield **3** (%)
1	$CeCl_3 \cdot 7H_2O$	21	5[a]	$TiCl_4$	73
2[a]	$CeCl_3 \cdot 7H_2O$	42	6[a]	none	0
3[a]	$SnCl_4 \cdot 5H_2O$	59	7[a,b]	$TiCl_4$	0[c]
4[a]	CH_3AlCl_2	69			

[a] Reaction worked up by the addition of pyrrolidine. [b] Run with no catalyst. [c] Approximately 30% of the product resulting from Michael-type addition to MVK was obtained.

Table 2. Selected Optimization for Equation 3

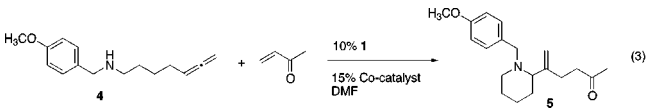
entry	cocatalyst	time (h)	temp (°C)	isolated yield **5** (%)
1	$TiCl_4$	2	60	34
2	CH_3AlCl_2	2	60	37
3	CH_3AlCl_2	1	60	39
4	CH_3AlCl_2	1	40	53
5	CH_3AlCl_2	1	rt	27



(2)

Using our standard conditions for cyclic ether formation (entry 1), a 21% yield of pyrrolidine **3**[9] was obtained. Concerned that coordination (during workup) of **3** to both the ruthenium and cerium led to lower isolated yields, we worked up the reaction by adding pyrrolidine (1 equiv relative to allene). This led to a near doubling in yield (entry 2). We next examined a variety of Lewis acids (entries 3−5). From the Table, we see that the use of stronger Lewis acids leads to much higher yields, that is, Ti versus Sn versus Ce.[10] We therefore settled on the use of 15 mol % $TiCl_4$ as the cocatalyst of choice for pyrrolidine formation. Entries 6 and 7 show the necessity of the cocatalyst and catalyst, respectively. Use of no-cocatalyst (entry 6) led only to recovered starting material. The mandatory use of a cocatalyst is in contrast to our work with an alcohol nucleophile, where the cocatalyst led to only a moderate increase in yield. In the absence of the ruthenium catalyst (entry 7) none of the coupled product was formed. Only small amounts of products arising from Michael-type addition of the amine to the enone were obtained.

The competition between β-hydrogen elimination and cyclization in our working hypothesis suggested that increasing the ring size was not a trivial extrapolation. Indeed, analogous formation of piperidines as outlined in eq 3 under the optimized conditions



(3)

for pyrrolidine formation gave only modest yields of **5**. We therefore reexamined the conditions according to eq 3, with the results summarized in Table 2. Changing the cocatalyst to CH_3AlCl_2 led to an increase in yield, especially at shorter reaction times (entries 2 and 3). Furthermore, lowering the reaction

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(2) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842.
(3) For example: Trost, B. M.; Indolese, A.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615; Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888.
(4) For some examples using tethered nitrogen, oxygen, and carbon nucleophiles in Pd-catalyzed reactions with allenes, see: Larock, R. C.; Veraprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274; Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652; Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88; Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85. Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156.
(5) (a) For some recent methods of cyclic amine syntheses, see: Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169. Jonasson, C.; Karstens, W. F. J.; Hiemstra, H.; Bäckvall, J.-E.*Tetrahedron Lett.* **2000**, *41*, 1619. (b) For a stoichiometric cobalt-mediated process, see: Bates, R. W.; Rama-Devi, T.; Ko, H.-H. *Tetrahedron* **1995**, *51*, 12939. (c) See also: Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.9, pp 397−411.
(6) For some examples of azametalations of allenes with stoichiometric Hg, see: Hodjat-Kachani, H.; Périé, J. J.; Lattes, A. *Chem. Lett.* **1976**, 405. Arseniyadis, S.; Goré, J. *Tetrahedron Lett.* **1983**, *24*, 3997. With Ag: Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand., Ser. B* **1979**, *33*, 309. Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4235. For catalytic Ag, see: Grimaldi, J.; Cormons, A. *Tetrahedron Lett.* **1986**, *27*, 5089; Gallagher, T.; Vernon, P. *J. Chem. Soc., Chem. Commun.* **1987**, 243; Davies, I. W.; Gallagher, T.; Lamont, R. B.; Scopes, D. I. C. *J. Chem. Soc., Chem. Commun.* **1992**, 335; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. For catalytic examples, see: Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633.
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(8) Gill, T. B.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
(9) All new compounds have been satisfactorily characterized spectroscopically, and elemental composition has been established by high-resolution mass spectrometry and combustion analysis.
(10) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley: Cambridge, 2000.

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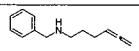
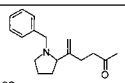
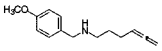
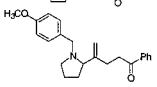
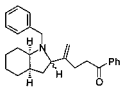
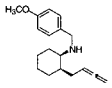
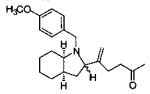
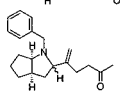
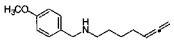
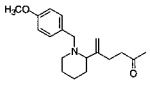
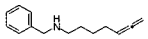
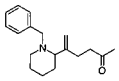
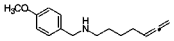
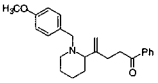
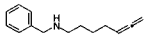
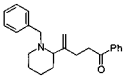
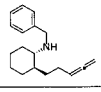
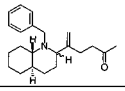
Table 3: Some Examples of Ruthenium-Catalyzed Pyrrolidine and Piperidine Formation[a]

Entry	Allene	R'	Method	Product	Yield (%)
1		-CH_3	A[b]		73
2		-Ph	A		64
3		-Ph	A		76
4		-CH_3	A		90
5		-CH_3	A		60
6		-CH_3	B[c]		53
7		-CH_3	B		67
8		-Ph	B		47
9		-Ph	B		62
10		-CH_3	B		71

[a] All denoted stereochemistry is relative. [b] Method A: 10 mol % **1**, 15 mol % $TiCl_4$, 60 °C, 2 h, workup with pyrrolidine. [c] Method B: 10 mol % **1**, 15 mol % CH_3AlCl_2, 40 °C, 1 h, workup with pyrrolidine.

temperature to 40 °C gave another increase in yield (entry 4). At room temperature, however, the reaction was sluggish and did not go to completion (entry 5).

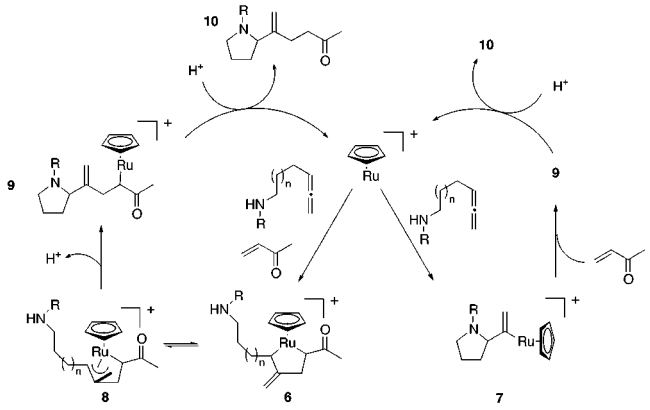
With the two sets of optimized conditions in hand, we examined a range of substrates as shown in eq 4 and Table 3. As shown, a


(4)

range of pyrrolidines (entries 1−5) and piperidines (entries 6−10) can be formed. In general, good yields are obtained for pyrrolidine formation, and both benzyl (entries 1, 3, and 5) and PMB groups (entries 2 and 4) can be tolerated on the nitrogen. Both 6,5-*cis* (entries 3 and 4) and 5,5-*cis* (entry 5) ring systems can be formed. A similar range of piperidines can be synthesized, including a 6,5-*trans* bicyclic system (entry 10). In general, somewhat lower yields were obtained with PMB groups (entries 6 and 8 vs entries 7 and 9), most likely due to the lower stability of such groups toward strong Lewis acids.[11] Indeed, some decomposition was observed when resubmitting the piperidine from entry 6 to the reaction conditions. This did not appear to be as much of an issue with the pyrrolidines. Replacing MVK by other vinyl ketones is illustrated by the successful use of phenyl vinyl ketone (entries 2, 3, 8, and 9). The products are readily characterized in the ^{1}H NMR spectra by the absorptions for the terminal methylene unit ($\sim\delta$ 5) and the allylic methine next to nitrogen ($\sim\delta$ 3).

Although definitive mechanistic data has not been obtained, two pathways, as outlined in Scheme 1, appear reasonable. One possibility is coordination of both the allene and the enone to

Scheme 1. Mechanistic Possibilities



form ruthenacycle **6**,[12] which could also exist as the π-allyl species **8**.[13] Internal attack of the nitrogen would then lead to Ru enolate **9**,[14] which would be protonated to provide product. This pathway generates support from the simple addition of allenes and vinyl ketones. In addition, a cobalt-mediated process invokes a carbametalation−cyclization sequence involving nitrogen attack on a π-allylcobalt intermediate.[5b] However, the compatibility of secondary amines in this reaction in contrast to other ruthenium-catalyzed processes, which involve ruthenacycles, and the absence of any competition of Michael-type addition products to the vinyl ketones leads us to question whether an alternative path may exist. One possibility envisions initiation of the reaction by a ruthenium-catalyzed azametalation[6] of the allene to give **7**. The resultant vinylruthenium species would then insert into the enone and proceed in the same fashion. At this point, conclusive mechanistic information to favor either pathway is absent.

In conclusion, substituted pyrrolidine and piperidines are accessed in a catalytic, atom-economical fashion.[15] The reaction is distinguished from all of the previously developed ruthenium-catalyzed reactions involving **1** and related catalysts in its compatibility with basic amines. Its obvious tolerance of other functionalized groups, notably carbonyl groups, suggests a good breadth of chemoselectivity. The juxtaposition of functionality also allows for further elaboration by debenzylation and cyclization involving a reductive amination. Current work is examining mechanistic issues as well as extending the range of nucleophiles.

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Supporting Information Available: Typical experimental procedures and characterization for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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