ORGANIC LETTERS

2005
Vol. 7, No. 19
4249−4252

Cobalt-Catalyzed Hydrohydrazination of Dienes and Enynes: Access to Allylic and Propargylic Hydrazides

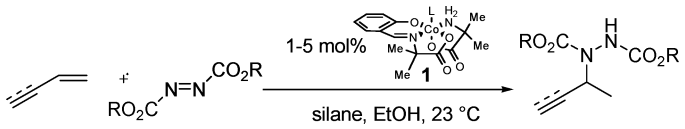
Jérôme Waser, José C. González-Gómez, Hisanori Nambu, Pascal Huber, and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Hönggerberg, HCI H335 8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

Received July 22, 2005

ABSTRACT



The cobalt-catalyzed hydrohydrazination reaction of dienes and enynes is presented. Allylic and propargylic hydrazines were obtained in synthetically useful yields (allylic amines, 60–90%; propargylic amines, 47–83%) and good chemo- and regioselectivity.

Allylic and propargylic amines and their derivatives are useful building blocks for the synthesis of biologically active compounds.[1] Consequently, a number of new methodologies detailing the preparation of these building blocks have recently been disclosed, largely involving the direct addition of alkynyl or alkenyl nucleophiles to imines.[2,3] The introduction of amine functionality via C−N bond formation constitutes a fundamentally different disconnection,[4] and it has been achieved via allylic substitution reactions,[4e−h] ene reactions,[4i] Overman rearrangement,[4j] or the hydroamination reaction of dienes.[4k−m] This latter strategy has been successfully employed for the synthesis of allylic amines, but there are only a few reports for the synthesis of propargylic amines using this approach.[5] During our recent studies on the cobalt-catalyzed hydrohydrazination reaction of olefins,[6] we observed an important accelerating effect of olefin conjugation to an aromatic ring (styrene derivatives) on the reaction rate of the process. We speculated that if a similar effect was present with alkenes and alkynes as substituents (i.e., dienes or enynes as substrates), it would be possible to achieve a monohydrazination of dienes and enynes. Herein, we wish to report the successful realization of this strategy, culminating in a new efficient synthesis of allylic and propargylic hydrazines (Figure 1).

In prior work, we have documented the reaction of olefins and azodicarboxylates in the presence of silanes mediated

(1) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970.

(2) (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (b) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054. (c) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (d) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (e) Knopfel, T. E.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (f) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (g) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (h) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941.

(3) Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493.

(4) (a) DuBois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915. (b) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364. (c) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M.; Day, M. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1645. (d) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. (e) Vonmatt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573. (f) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (g) Shu, C. T.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (h) Yamagishi, T.; Ohnuki, M.; Kiyooka, T.; Masui, D.; Sato, K.; Yamaguchi, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3275. (i) Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261. (j) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (k) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (l) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (m) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.

(5) An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 3737.

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10.1021/ol0517473 CCC: $30.25
Published on Web 08/19/2005

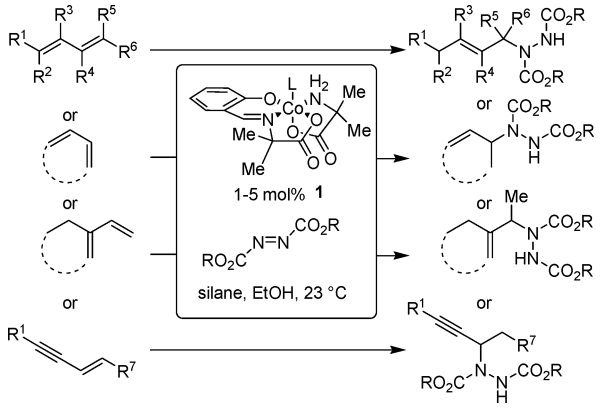
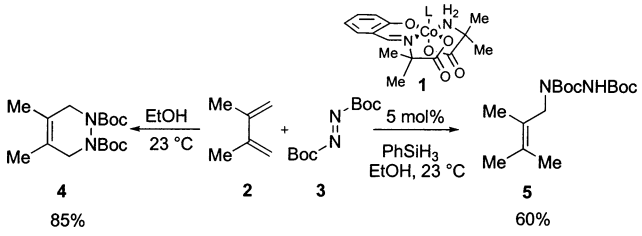


Figure 1. Hydrohydrazination of conjugated olefins.

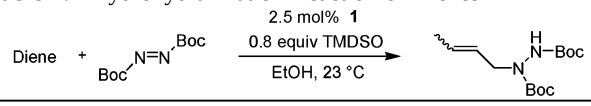
by a simple Co-catalyst to afford alkylhydrazides.[6] Expansion of the scope of the monohydrazination process to include dienes would require that a number of key criteria be met. First, the reactivity difference between the diene starting material and the product monoalkene would have to be sufficiently large to minimize the formation of products corresponding to double hydrohydrazination. Given the lack of reactivity of alkynes under the conditions we have examined, this first concern did not apply to the enyne starting materials. Second, competitive semireduction of the reactive dienes or enynes would need to be prevented. Third, additional side reactions such as Diels−Alder cycloaddition reaction of the azodicarboxylate with dienes, a well-precedented transformation at ambient temperature, would need to be slow relative to the hydrohydrazination process.[7] With respect to the last of these, as a control experiment, treatment of di-*tert*-butyl azodicarboxylate (**3**) with 2,3-dimethyl-1,3-butadiene (**2**) led to the formation of cycloadduct **4** in 85% yield in 24 h (23 °C). By contrast, a mixture of diene **2** and azodicarboxylate **3** in the presence of cobalt catalyst **1** and phenylsilane led to the selective and preferential formation of hydrohydrazination product **5** in 60% yield in the span of 1 h (Scheme 1).

Scheme 1. Test Case for the Hydrohydrazination of Dienes



Subsequent optimization studies highlighted the benefits of TMDSO (tetramethyldisiloxane) and lower catalyst loading (2.5 mol%) in the reaction, allowing the isolation of **5** in 83% yield as a single regioisomer (Table 1, entry 1). The selective formation of the primary hydrazine derivative **5** is

Table 1. Hydrohydrazination Reaction of Dienes



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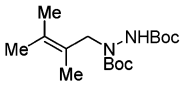
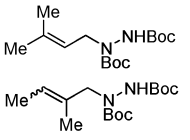
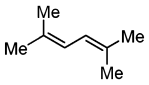
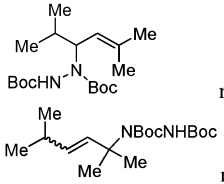
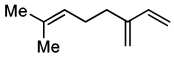
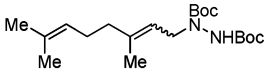
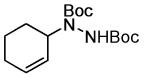
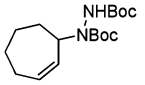
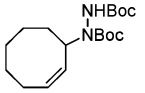
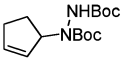
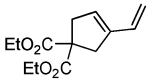
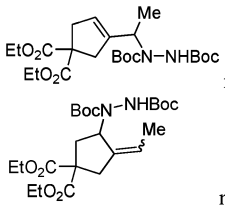
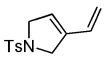
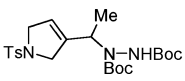
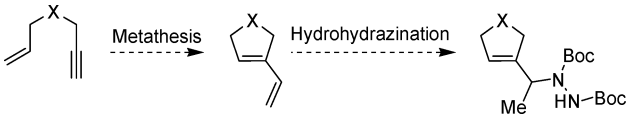
1				83 (69)[b]
2			major minor	60 (4:1)
3			major minor	71 (7:1)
4				65
5				73
6				84
7				81
8				45
9			major minor	75 (5:1)
10				90

[a] Isolated yield after chromatography. [b] 5 mol% of catalyst **1** was used.

rather unexpected, because the results of previous studies with olefins had indicated a strong preference for formation of Markovnikov products.[6] To further assess the scope and the regioselectivity of the reaction, we first examined acyclic olefins (Table 1, entries 2−4). Isoprene (entry 2) gave a 4:1 mixture of products consistent with the preferential hydrocobaltation of the α,α-disubstituted double bond followed

by amination at the primary center. The reaction of 2,5-dimethylhexa-2,4-diene (entry 3) underscores the unusual regioselectivity of the reaction of conjugated dienes, in which formation of the secondary allylic amination product was favored over the tertiary one (7:1). In the case of myrcene (entry 4), the reaction showed impressive regio- and chemoselectivity, allowing the isolation of one major isomer in 65% yield and a small amount (3%) of the Diels−Alder adduct. We then turned to cyclic substrates. These are some of the best substrates for the hydrohydrazination reaction. The desired cyclic allylic hydrazines were obtained in good yields (entry 5−7), even for 1,3-cyclooctadiene, which has proven to be unreactive or much less reactive in other methods.[4k−m] Cyclopentadiene could be converted to the desired hydrazine (entry 8), although in this case background cycloaddition reaction of cyclopentadiene and the azodicarboxylate leads to formation of the Diels−Alder adduct in 23% yield. Finally, we observed the selective formation of an exocyclic hydrazine (entries 9 and 10). Entry 10 is especially interesting, as in this case complete selectivity is observed. As similar dienes are easily accessible via enyne metathesis,[8] the high yield and selectivity observed is promising for further applications of the reaction (Scheme 2).

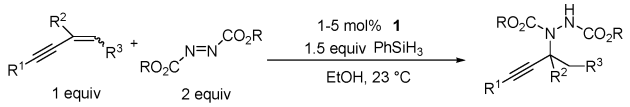
Scheme 2. Application of the Hydrohydrazination Reaction

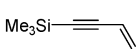
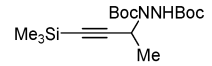
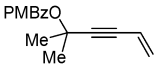
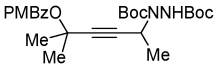
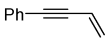
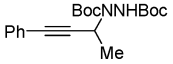
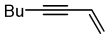
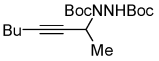
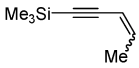
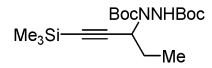
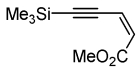
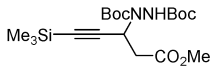
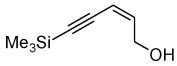
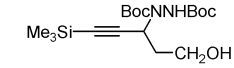
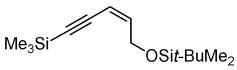
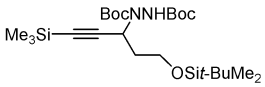
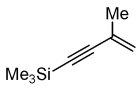
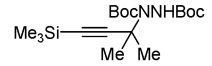
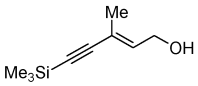
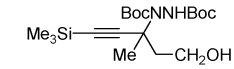
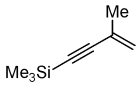
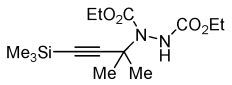
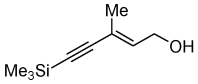
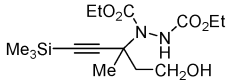


Having successfully developed the hydrohydrazination of dienes, we were interested in examining enynes as substrates. Enynes are interesting substrates because the presence of the alkyne triple bond alleviates any potential difficulties associated with the stereoselective synthesis of dienes and potentially leads to the question of chemoselectivity of the process. Furthermore, advances in the Sonogashira reaction[9] and development of alkyne−alkyne coupling processes[10] provide fast and modular access to these compounds. Yet, the selective functionalization of enynes has proven to be a challenging task.[11] Although there are some reports on the selective functionalization of the triple bond,[2g,11b,c] selective reactions with the double bond are very scarce.[11d,e] To the best of our knowledge, there is only one report of a hydroamination reaction of conjugated enynes; however, under the reaction conditions, multiaminated products are observed.[11f]

We decided to focus initially on enynes bearing an unsubstituted double bond and a bulky protecting group on the alkyne (TMS or an acetone-derived protecting group (Table 2, entries 1 and 2)). It was indeed possible to obtain propargylic hydrazides as the only isolable products in the presence of catalyst **1** (5 mol%), phenylsilane (1.5 equiv), and di-*tert*-butylazodicarboxylate (**3**) (2 equiv). TMS proved to be optimal as a protecting group, furnishing the desired

Table 2. Hydrohydrazination Reaction of Enynes



entry	enyne	product	yield (%)[a]
1			83
2			61
3			56[b]
4			78
5			55
6			47
7			77
8			63
9			42
10			27[b]
11			67[c]
12			66[c]

[a] Isolated yield after chromatography. [b] TMDSO (2.5 equiv) was used instead of phenylsilane. [c] 1 mol% catalyst was used.

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product in 83% yield under these conditions. Phenyl- (entry 3) and butyl-substituted (entry 4) alkynes were also tolerated. However, for these products, quenching of the reaction immediately after full consumption of the starting material was crucial to prevent reduction of the triple bond. In the case of phenyl, this reduction side-reaction could only be suppressed by the use of TMDSO as the silane.

Substrates incorporating alkene substitution were investigated. A methyl (entry 5) and an ester (entry 6) substituent at the β-position of the double bond were tolerated, but the products were obtained in moderate yields (54 and 47% respectively). ^{1}H NMR analysis of the crude reaction mixture showed signals corresponding to allenic side products, but, unfortunately, these compounds could not be isolated. We were pleased to observe that the introduction of an hydroxy (entry 7) or silyl ether group (entry 8) in the β-substituent led to product formation in 77 and 63% yield, respectively.

Enynes with an α-substituted or an α,β-disubstituted double bond were examined next. The products from the hydrohydrazination of these could only be isolated in low yields using the conditions described above (entries 9 and 10). In both cases, we also isolated considerable quantities of product resulting from dimerization at the propargylic position. We reasoned that lower catalyst loadings and the use of sterically less hindered azodicarboxylates would increase the yield of the desired hydrazines. Indeed, using 1 mol% catalyst **1** and diethyl azodicarboxylate allowed us to obtain useful yields (66−67%) with these substrates (entries 11 and 12).

In summary, we have documentated a new approach toward allylic and propargylic hydrazines based on the cobalt-catalyzed hydrohydrazination reaction of dienes and enynes. For dienes, our method is mechanistically distinct from existing approaches and displays useful yields and regioselectivities. For enynes, the selective amination of the double bond is unprecedented and opens a new perspective for the selective functionalization of enynes en route to useful building blocks and biologically active compounds. Further studies are ongoing in our laboratory in order to extend this strategy and to examine the transformation of the obtained hydrazines into other useful compounds.

Acknowledgment. We thank the Swiss National Foundation for support of this research and the Roche Research Foundation for the support of J.W. H.N. thanks the Japan Society for the Promotion of Science (JSPS) for a postdoctoral fellowship. J.C. thanks the Xunta de Galicia for a postdoctoral fellowship.

Supporting Information Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0517473